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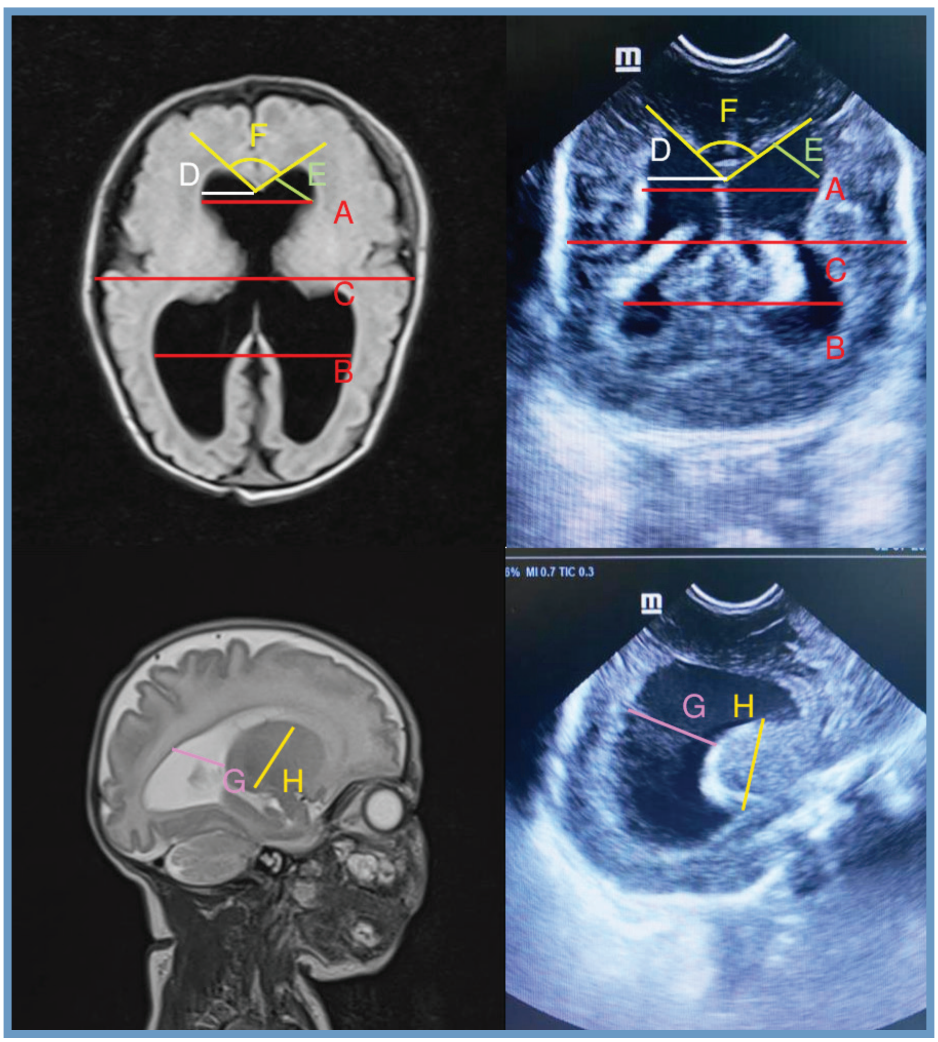
Official Journal of the Turkish Neurosurgical Society



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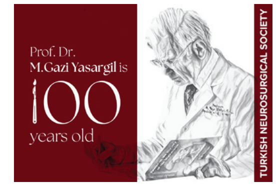

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B. Book chapter

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D. Example of thesis

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E. Software

Epi Info [computer program]. Version 6. Atlanta: Centers for Disease Control and Prevention, 1994

F. Online journals

Friedman SA. Preeclampsia: A review of the role of prostaglandins. Obstet Gynecol [serial online]. January 1988;71:22-37. Available from: BRS Information Technologies, McLean, VA. Accessed December 15, 1990

G. Database

CANCERNET-PDQ [database online]. Bethesda, MD: National Cancer Institute, 1996. Updated March 29, 1996

H. World Wide Web

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CONTENTS

Turkish Neurosurgery

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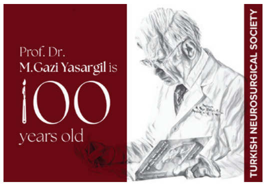
ORIGINAL INVESTIGATIONS

CASE REPORT

Turk Neurosurg 35(5):677-683, 2025
DOI: 10.5137/1019-5149.JTN.49213-25.1



Original Investigation

General Neurosurgery and Miscellaneous-Others

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A Bibliometric Analysis of the Contributions of Turkish Female Authors to "Turkish Neurosurgery"

Ismail Ertan SEVIN[1], Safiye HATIPOGLU[2], Busranur GENYUZ[1], Eralp SEVIN[1], Mohtaram GASIMOVA[2], Selin BOZDAG[1], Hasan Kamil SUCU[1]

[1]Izmir Katip Celebi University, Faculty of Medicine, Department of Neurosurgery, Izmir, Türkiye
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ABSTRACT

AIM: To assess the contributions of Turkish female authors to the field of neurosurgery through "Turkish Neurosurgery", the only neurosurgery journal in Türkiye indexed by The Science Citation Index Expanded (SCIE).

MATERIAL and METHODS: A bibliometric analysis was conducted on articles published in "Turkish Neurosurgery" from 2019 to 2023. Data were gathered on authorship, gender distribution, article types, topics, and institutional affiliations. Statistical analyses included chi-square tests, the Cochran–Armitage test, and logistic regression to evaluate the association between female senior and first authorship.

RESULTS: Of the 751 articles reviewed, 505 featured contributions from at least one Turkish author, comprising 2,601 Turkish contributors (24.8% female, 74.4% male). Turkish female authors appeared in 292 of these publications (57.8%), serving as first authors in 103 (20.4%) and senior authors in 92 (18.2%). The proportion of Turkish female first authorship increased significantly over the study period, peaking at 31.2% in 2022 ($p=0.049$). Logistic regression analysis revealed that the presence of a Turkish female senior author significantly increased the likelihood of female first authorship ($OR = 3.96$, $p<0.001$). Only 16.2% of Turkish-authored articles included female neurosurgeons. Of all Turkish female authors, 23.6% of first authors and 19.6% of senior authors were neurosurgeons. Most publications by Turkish female authors (59.7%) were original research articles, primarily focusing on neuro-oncology, spine, and functional neurosurgery.

CONCLUSION: This study highlights encouraging progress in the representation of Turkish female authors, particularly neurosurgeons, who exhibit strong academic engagement relative to their workforce proportion in neurosurgical academic publishing. Mentorship plays a crucial role in increasing female first authorship. To strengthen this effect, academic institutions could implement structured mentorship programs, fund collaborative research, and establish platforms to connect senior and junior female researchers.

KEYWORDS: Neurosurgery, Female authorship, Gender disparity, Bibliometric analysis, Academic publishing

ABBREVIATIONS: WFNS: World Federation of Neurosurgical Societies, **SCIE:** Science Citation Index Expanded, **EANS:** European Association of Neurosurgical Societies, **FIENS:** International Education in Neurological Surgery

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INTRODUCTION

In 2005, at the World Federation of Neurosurgical Societies (WFNS) Congress, Romanian neurosurgeon Sofia Ionescu was recognized as the world's first female neurosurgeon for successfully performing surgery on a living patient in 1944 (5). Similarly, Diana Beck from the United Kingdom emerged as one of the pioneering women in neurosurgery, with her first documented operation performed in 1952 (8). Historically, Türkiye witnessed the early inclusion of women in neurosurgery, beginning with Aysima Altınok, who completed her training in 1959 (2). Since then, the number of female neurosurgeons has steadily increased worldwide, including in Türkiye (4,12). Despite this upward trend, women in neurosurgery continue to face limited academic visibility in the field (6,20).

Publishing in a peer-reviewed journal not only secures a study's place in the literature but also serves as a benchmark of its validity. Moreover, it plays a vital role in career development and academic advancement within the profession. This study aimed to assess the representation of Turkish female authors in articles published in *Turkish Neurosurgery*, the only neurosurgery journal from Türkiye indexed in the Science Citation Index Expanded (SCIE).

MATERIAL and METHODS

Ethical approval was obtained from the Ethics Committee of Izmir Katip Celebi University (Date: 19.12.2024, Decision Number: 0280). This bibliometric study analyzed articles published in *Turkish Neurosurgery* over the past five years (2019–2023). The journal's archival information was retrieved from its official website (https://turkishneurosurgery.org.tr/archive.php).

The articles were categorized by type into "original research," "case reports," "meta-analyses or systematic reviews," and "letters to the editor." Additionally, the articles were further classified by topic into subgroups, such as spinal, neurovascular, neuro-oncological, pediatric, trauma, peripheral nerves, neurocritical care, radiosurgery, neuroanatomy, cerebrospinal fluid circulation, and others.

For each article, data were recorded on the total number of authors; the number of Turkish female and male authors; the number of Turkish female first and senior authors; the number of Turkish male first and senior authors; the affiliated institutions; and the region of the institution where the study was conducted. The final listed author was designated as the senior author. In cases where the gender of an author could not be confidently determined based on their name, an internet search was performed.

All statistical analyses were performed using IBM SPSS Statistics for macOS, Version 27.0 (IBM Corp., Armonk, NY, USA) with R integration through R Syntax for advanced procedures (R Core Team, 2023; https://www.R-project.org/). Comparisons were conducted using the chi-square test. The Cochran-Armitage trend test was employed to assess the proportion of female authors over the years. The association between female senior authorship and the probability of female first authorship was also examined using a binary logistic regression model. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Turkish female author participation

This study included 751 publications from *Turkish Neurosurgery*, published between 2019 and 2023. Among the 751 publications reviewed, 505 included contributions from at least one Turkish author, irrespective of gender. Out of the 2,601 individual Turkish contributors identified, 644 (24.8%) were female and 1,935 (74.4%) were male. Of these, 292 (57.8%) included contributions from at least one Turkish female author, while 492 (97.4%) featured at least one Turkish male author. The Cochran-Armitage test showed no statistically significant change in the proportion of publications with Turkish female authorship relative to the total number of Turkish-contributed publications between 2019 and 2023 (p=0.917) (Table I).

Turkish female authors served as first authors in 103 (20.4%) of the 505 publications that included contributions from at least one Turkish author, while Turkish male authors held the first author position in 397 publications (78.6%) (χ^2, p<0.001). The proportion of Turkish female first authorship among Turkish-contributed publications increased from 12.9% in 2019 to a peak of 31.2% in 2022, before declining to 23.4% in 2023. This upward trend was found to be statistically significant (Cochran–Armitage test, p=0.022).

Turkish female authors were senior authors in 92 (18.2%) of the Turkish-contributed publications reviewed in this study, while Turkish male authors held the senior author position in 410 (81.2%) of these publications. The proportion of Turkish female senior authorship remained relatively stable over the years, ranging from 15.8% in 2019 to 19.1% in 2023. No statistically significant trend was observed (Cochran-Armitage test, p=0.872).

A total of 38 publications featured both a Turkish female first author and a Turkish female senior author. Logistic regression analysis revealed that the presence of a Turkish female senior author significantly increased the likelihood of Turkish female first authorship (OR=3.63, p<0.001), suggesting a strong mentorship effect.

Participation of Turkish female neurosurgeon authors

Of the 505 Turkish-contributed publications reviewed, 411 included contributions from at least one Turkish neurosurgeon, irrespective of gender. Turkish male neurosurgeon authors were identified in 403 publications (98.1%), while Turkish female neurosurgeon authors were identified in 75 publications (18.2%) (χ^2, p<0.001).

The rate of first authorship among Turkish neurosurgeons was higher in males (71.8%, 285 out of 397) than in females (21.9%, 23 out of 105) (χ^2, p<0.001). Among Turkish senior authors, 273 (66.6%) males and 15 (16.2%) females were neurosurgeons. The proportion of neurosurgeons was significantly higher among male authors (χ^2, p<0.001).

Of the 75 publications featuring a Turkish female neurosurgeon author, 20 listed her as the first author (26.7%) and 15 as the senior author (20.0%). In contrast, Turkish female authors from other medical specialties contributed to 260 publications, serving as first authors in 83 (31.9%) and as senior authors in 77 (29.6%) (χ^2, p=0.008; 0.038). A total of 43 publications included both a Turkish female neurosurgeon and a Turkish female author from another specialty.

Article types and locations

The majority of the analyzed publications were original research papers (84.95%, 638 articles). Among the 505 publications with Turkish contributions, 457 (90.5%) were original articles. Turkish female authors contributed to 59.7% of these (273 articles), serving as first authors in 21.4% (98 articles) and as the senior authors in 18.6% (85 articles). The distribution of Turkish female authorship across other article types is presented in Table II.

The most prevalent research areas in the overall dataset were spine, neuro-oncology, and neurovascular. Among articles authored by Turkish female researchers, the most frequent topics were neuro-oncology, spine, and functional neurosurgery. Similarly, articles led by a Turkish female first author most

Table I: The Proportion of Publications with Turkish Female Authors Relative to the Total Number of Publications Involving Either Turkish Female or Male Authors by Year

Publication Year	Total Publications	Publications Contributed Turkish Authors	Publications Contributed Turkish Female Authors, n (%)	Publications Contributed Turkish Female Neurosurgeon Authors, n (%)	Turkish Female First Author, n (%)	Turkish Female First Neurosurgeon Author, n (%)	Turkish Female Senior Author, n (%)	Turkish Female Senior Neurosurgeon Author, n (%)
2019	149	101	60 (59.4)	12 (11.9)	13 (12.9)	3 (3.0)	16 (15.8)	4 (4)
2020	148	110	60 (54.5)	21 (19.1)	19 (17.3)	6 (5.5)	23 (20.9)	4 (3.6)
2021	149	104	59 (56.7)	15 (14.4)	21 (20.2)	6 (5.8)	17 (16.3)	0 (0)
2022	150	96	56 (58.3)	11 (11.5)	30 (31.2)	3 (3.1)	18 (18.8)	3 (3.1)
2023	155	94	57 (60.6)	19 (20.2)	22 (23.4)	5 (5.3)	18 (19.1)	4 (4.3)
Total	**751**	**505**	**292 (57.8)**	**78 (15.4)**	**105 (20.8)**	**23 (4.5)**	**92 (18.2)**	**15 (3)**

Table II: Distribution of Article Types and the Proportion of Publications with Turkish Female Authors Relative to the Total Number of Publications Involving Either Turkish Female or Male Authors by Article Types

Article Type	Total Publication	Total Publications with Turkish Contribution	Turkish Female Author Contribution, n (%)	Turkish Female Neurosurgeon Author Contribution, n (%)	Turkish Female First Author, n (%)	Turkish Female First Neurosurgeon Author, n (%)	Turkish Female Senior Author, n (%)	Turkish Female Senior Neurosurgeon Author, n (%)
Original Investigation	638	457	273 (59.7)	72 (15.8)	98 (21.4)	22 (4.8)	85 (18.6)	14 (3.1)
Case Report	62	32	16 (50)	4 (12.5)	5 (15.6)	1 (3.1)	6 (18.8)	0
Meta-analyses/ Systematic reviews	19	4	2 (50)	1 (25)	2 (50)	0	1 (25)	1 (25)
Letters to the Editor	32	12	1 (8.3)	1 (8.3)	0	0	0	0
Total	**751**	**505**	**292 (57.8)**	**78 (15.4)**	**105 (20.8)**	**23 (4.6)**	**92 (18.2)**	**15 (3)**

commonly focused on neuro-oncology, functional neurosurgery, and spine. In studies where a Turkish female researcher was the last author, the predominant research areas included functional neurosurgery, neuro-oncology, and spine, respectively. The comparative distribution of research topics is illustrated in Figure 1.

Of the 292 publications involved the participation of Turkish female authors. The vast majority of these studies were conducted in Türkiye (n=286), with a few originating from other countries, including the United States (n=4), Germany (n=1), and Iran (n=1). Of the 105 publications with Turkish female first authors, 104 were conducted in Türkiye, with the remaining one originating from the United States. Similarly, among the 92 publications with Turkish female senior authors, 91 were affiliated with studies conducted in Türkiye, and one originated from Germany.

DISCUSSION

Historically, Türkiye was among the first countries to integrate women into the field of neurosurgery on a global scale (9). Aysima Altınok completed her training in 1959, becoming Türkiye's first female neurosurgeon. In 1968, Altınok was one of the 21 founding members of the Turkish Neurosurgical Society (2). The second female neurosurgeon in Türkiye was Yıldız Yalcınlar, who was certified in 1965 (4). Several other pioneering female neurosurgeons followed, including Nilgün Alp, Dilek Könü-Leblebicioğlu, Hamiyet Camuşçu, and Nurperi Gazioğlu (12). A study published by Kuzucu et al. in 2022 reported that between 1960 and 1980, there were only four female neurosurgeons in Türkiye (12). The same study also stated that, according to the year-end 2020 data from the Turkish Neurosurgical Society, 94 (5.5%) of the 1,699 registered neurosurgery specialists in Türkiye were women. Among them, 10 were full professors (10.6%), 16 were associate professors (17%), five were assistant professors (5.3%), and 63 were neurosurgery specialists (67%). Additionally, the study reported that nine female academic neurosurgeons (9.5%) had an h-index greater than 10. Nurperi Gazioğlu became Türkiye's first female professor of neurosurgery and, in 2013, was elected the first female president of the Central Nervous System Surgery Society (12). Despite having appointed 23 presidents over 38 years, the Turkish Neurosurgical Society elected its first female president, Emel Avcı, in 2021 (15). Prof. Dr. Pınar Akdemir Özışık became the first female neurosurgeon to be appointed as dean in 2021 (12). Prof. Dr. Melike Mut Aşkın was a co-founder of the Turkish Society of Neuro-Oncology (14). In addition to holding the titles FAANS, FAAP, and FACS, Eylem

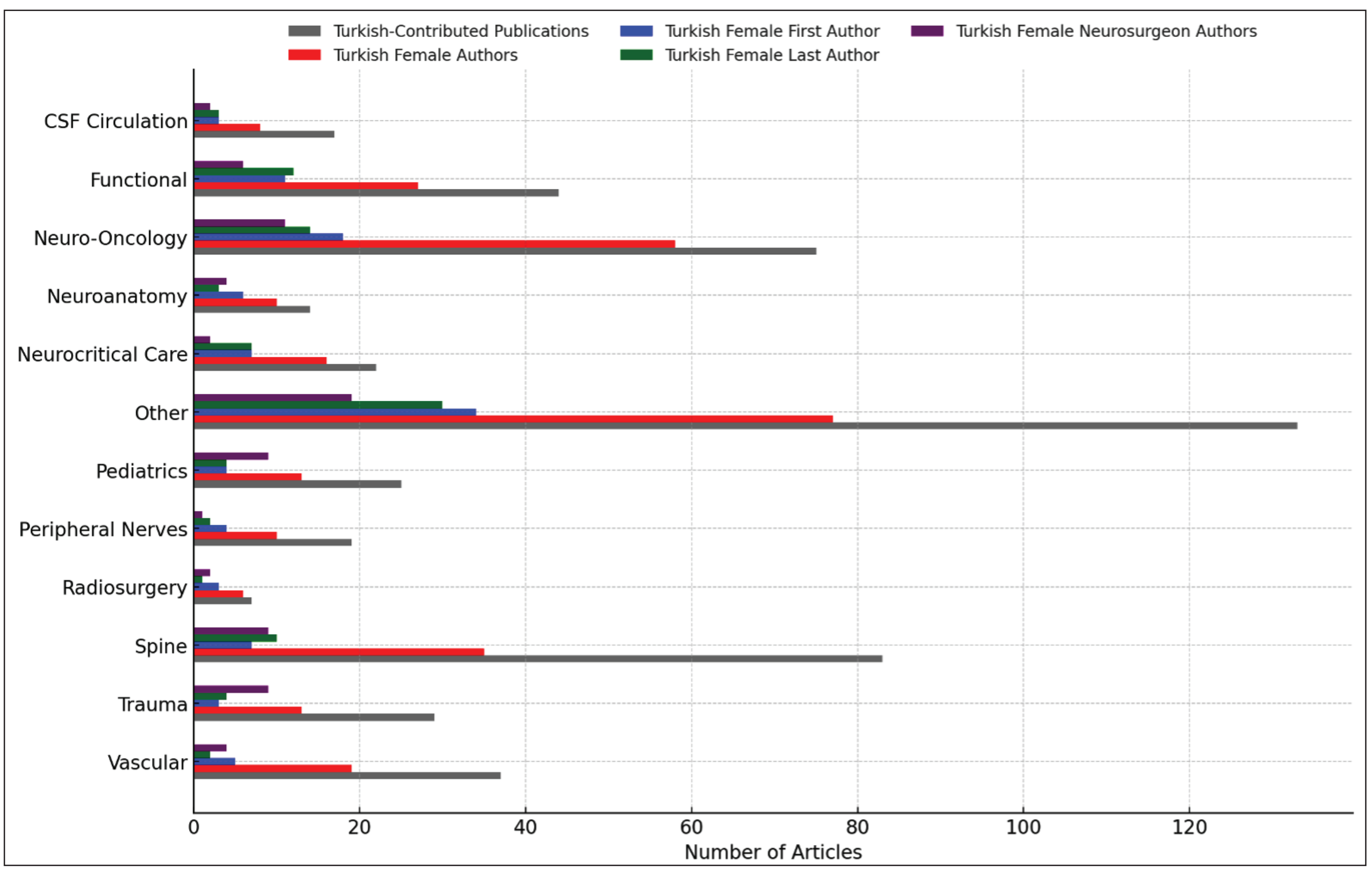

Figure 1: Comparative bar chart illustrating the topic distribution of general articles with Turkish author contributions and those authored by Turkish female researchers in *Turkish Neurosurgery*. The chart displays all Turkish-contributed publications (gray), those involving Turkish female authors (red), Turkish female first authors (blue), Turkish female last authors (green), and Turkish female neurosurgeon authors (purple).

Ocal was awarded the title of Professor in 2022, becoming the first Turkish female neurosurgeon to attain an academic rank abroad. In 2024, Ayşegül Esen Aydın was elected to the Individual Membership Committee of the European Association of Neurosurgical Societies (EANS), becoming the first Turkish female neurosurgeon to hold an administrative position within the international organization. The number of women entering the field of neurosurgery in Türkiye is increasing, reflecting global trends. A 2017 study surveying neurosurgeons across 39 EANS member countries found that 12% (1,565 out of 12,985) were women (19). Similarly, 2016 data showed that only 6.1% (259 out of 4,178) of board-certified neurosurgeons in the United States were women (17).

In 2021, the study titled “Female Participation in Academic European Neurosurgery” reported that female authors comprised 17.5% (670 out of 3,821) of all contributors to European neurosurgical publications (6). Another study analyzing 66,546 articles across 16 major neurosurgical journals found that the proportion of female first authorship increased from 5.8% in 2002 to 17.2% in 2019 ($p<0.001$) (20). In comparison, our findings reveal a notably higher level of female representation (24.8%) among Turkish-contributed studies published in *Turkish Neurosurgery*. These results suggest that Turkish female neurosurgeons contribute to academic publishing at rates comparable to those of their European counterparts. In our study, the rate of Turkish female first authorship is 20.4%, which falls between the previously reported rates (13.3% and 15.7%) (1,6,16,20). These findings suggest that Turkish female researchers contribute to scientific publishing at rates comparable to—even exceeding—those of their international peers.

The number of female senior authors in publications was examined as an indirect representation of leadership in academic neurosurgery. Previous studies have reported female senior authorship rates in neurosurgical literature ranging from 7.3% to 10.8% (1,6,16,20). In contrast, our study found a higher proportion of female senior authors (18.2%), indicating a comparatively stronger presence of Turkish female neurosurgeons in senior academic roles compared to international averages. This finding demonstrates the notable progress women in Turkish neurosurgery are making in their academic careers. The literature has reported an increase in female senior authorship from 5.5% in 2002 to 12.0% in 2019 ($p<0.001$) (20). Regional analysis of female authorship trends in neurosurgical research suggests that Europe has reached a plateau, with women accounting for approximately 20% of first (junior) authors and 10% of last (senior) authors (6,16,20). In contrast, in the US and Canada, although the percentages of first and senior female authors were lower in early 2009, they have increased in the years since (16). However, researchers have expressed concerns that this trajectory mirrors the trend observed in Europe a decade earlier, suggesting that the US and Canada may likewise approach a plateau in the coming years (10,16,20). Similarly, our findings from the past five years in Türkiye indicate a potential plateau phase, suggesting that if this mirroring trend continues, Türkiye may also experience stagnation in the growth of female authorship over the next decade.

Previous studies across various fields—not limited to neurosurgery—have shown that the presence of a female senior author significantly increases the likelihood of female first authorship (7,13). One study reported that articles were 2.69 times more likely to have a female first author when the senior author was also female (20). Another study found that female first authorship increased to nearly 30% when the senior author was a woman, compared to just 12% when the senior author was a man (16). Our findings further reinforce this mentorship effect, demonstrating that in *Turkish Neurosurgery*, the presence of a Turkish female senior author was significantly associated with a higher likelihood of female first authorship ($OR=3.63$, $p<0.001$). Despite the growing presence of women in surgery, they remain underrepresented on editorial boards, which may contribute to unconscious bias and the lower proportion of female authors (11). A study of high-impact general surgery journals found that female editorial board membership increased from 5% to 19% over two decades (11), while another study reported that women comprised only 9% of the editorial boards of leading neurosurgery journals (3). Further research is needed to assess the evolution of editorial boards and their impact on female faculty publishing, particularly in the field of neurosurgery.

While most Turkish male authors in the journal were neurosurgeons, the majority of Turkish female authors belonged to non-neurosurgical specialties. These results are consistent with previous studies highlighting the underrepresentation of women in neurosurgical authorship and leadership roles (1,6,16). This disparity highlights a potential gender gap in neurosurgery-specific academic contributions and underscores the need for targeted initiatives to support and retain women in neurosurgical academia. Although women comprise only 5.5% of the 1,699 registered neurosurgeons in Türkiye (94 female), no statistically significant difference was observed between male and female neurosurgeons in first authorship or senior authorship, despite the lower female representation (χ^2, $p=0.133$; 0.902)

Most of the Turkish-contributed publications in Turkish neurosurgery were original investigations, with Turkish female authors contributing to 59.9% of these articles. In contrast, an international study reported a higher female authorship rate of 66.2% in original investigations (6). Among articles authored by Turkish female researchers, the most frequently studied topics were neuro-oncology, spine, and functional neurosurgery. Similarly, previous studies have reported that these research areas are also among the most common for female authors in neurosurgery (16). This consistency suggests that women in neurosurgical research tend to engage in similar subspecialties worldwide. Our findings indicate that the vast majority of publications involving Turkish female authors originated from institutions within Türkiye, with minimal contributions from international affiliations. Multiple factors may contribute to this pattern, including limited opportunities for global academic collaboration among Turkish female researchers. These limitations—such as language barriers, funding constraints, and restricted access to international research networks—can hinder their visibility and career advancement. As a potential solution, similar efforts, such as global education initiatives by the Society of Neurological Surgeons and the Foundation for International Education in Neurological Surgery (FIENS), could be implemented to support young female researchers (3,18). However, another explanation is that Turkish female neurosurgeons affiliated with international institutions may prefer to publish in other SCIE-indexed journals rather than in *Turkish Neurosurgery*.

Limitations

Our study has several limitations that need to be acknowledged. First, it focuses exclusively on the proportion of Turkish female authors in Turkish-contributed publications in *Turkish Neurosurgery*. Second, the analysis was limited to a five-year period, which may have contributed to the apparent plateau in female authorship trends.

CONCLUSION

This bibliometric analysis reveals encouraging progress in the representation of Turkish female authors in neurosurgical academic publishing. The overall proportion of female authorship in *Turkish Neurosurgery* remains below that of their male counterparts. However, Turkish female researchers—particularly neurosurgeons—demonstrate a noteworthy level of academic engagement, especially given their limited representation in the national workforce. Furthermore, the presence of a Turkish female senior author was associated with a 3.63-fold increase in the likelihood of Turkish female first authorship compared to publications without a female senior author. This highlights the crucial role of female mentorship in advancing female authorship in neurosurgical research. To further strengthen this effect, academic institutions could implement structured mentorship programs, allocate funding for collaborative research, and establish platforms to connect senior and junior female researchers. Nevertheless, the underrepresentation of women in neurosurgical subspecialties, leadership roles, and international collaborations indicates that structural and systemic barriers persist. Identifying barriers or the absence of key facilitators in this advancement process is essential for developing targeted strategies to enhance academic visibility and leadership opportunities for female neurosurgeons.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: IES, SB, HKS
Data collection: IES, SH, BG, ES, MG, SB
Analysis and interpretation of results: IES, SH, BG, ES, MG, SB
Draft manuscript preparation: IES, SB
Critical revision of the article: HKS
Other (study supervision, fundings, materials, etc...): HKS
All authors (IES, SH, BG, ES, MG, SB, HKS) reviewed the results and approved the final version of the manuscript.

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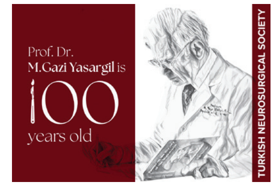

Factors Affecting the Development of Hydrocephalus in Patients with Spinal Neural Tube Defects

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ABSTRACT

AIM: To identify the factors that could prevent the formation of spina bifida, and to determine the causes of hydrocephalus.

MATERIAL and METHODS: We retrospectively evaluated the data of 51 patients with neural tube defects (NTDs) who were surgically treated at Sanliurfa Training and Research Hospital between December 2021 and October 2022.

RESULTS: The mean maternal folate level was 7.02 ± 3.66 µg/L. Of the 51 mothers, 14 (27.5%) had low folate levels and 37 (72.5%) had normal folate levels. The mean maternal vitamin B12 level was 287.29 ± 91.64 ng/L. Of the 51 mothers, 9 (17.6%) had low vitamin B12 levels and 42 (82.4%) had normal vitamin B12 levels. Ventriculoperitoneal shunt (VPS) surgery was performed in 19 (37.3%) of 51 patients. The area of NTD was significantly higher in infants who underwent VPS surgery due to hydrocephalus than in infants without hydrocephalus. The risk of developing hydrocephalus increased as the severity of NTD type increased. Furthermore, the risk of developing hydrocephalus increased in patients with NTDs at higher anatomical levels.

CONCLUSION: Although the optimum blood folate level for preventing MMC remains uncertain, the upper limit of the normal reference should be targeted. Hydrocephalus is an important cause of morbidity and mortality in patients with SB and its incidence is higher in patients with an anatomical higher NTD, a more severe type of NTD, and a large defect diameter. Furthermore, hydrocephalus is more common in patients with SM and female patients.

KEYWORDS: Folate, Defect area, Meningomyelocele, Hydrocephalus

ABBREVIATIONS: MMC: Meningomyelocele, **MS:** Myeloschisis, **MC:** Meningocele, **SB:** Spina bifida, **VP:** Ventriculoperitoneal, **CM:** Chiari malformation, **DIAM:** Diastematomyelia, **DST:** Dermal sinus tract, **LCL:** Low conus localization, **SM:** Syringomyelia, **CCA:** Corpus callosum agenesis, **CSF:** Cerebrospinal fluid, **USG:** Ultrasound, **ECHO:** Echocardiogram, **MR:** Magnetic resonance, **ASD:** Atrial septal defect, **PDA:** Patent ductus arteriosus, **VSD:** Ventricular septal defect

INTRODUCTION

Meningomyelocele (MMC) is type of spina bifida in which the spinal neural tube does not close during embryonic development (11,28). Its frequency range between 0.2 and -10 per 1000 across different geographical regions (5). The etiology of MMC includes common genetic mutations, inadequate nutrition, low blood folate level, family history of SB, history of radiation, history of diabetes in the parents, maternal history of seizure and low socioeconomic status. Furthermore, MMC is more common in low socioeconomic status countries (11,24). MMC can present as weak-

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ness in the extremities, urinary and bowel dysfunction, orthopedic problems, structural abnormalities, postural problems, and cosmetic problems below the level of the defect (11).

Cranial and spinal imaging for neuropathological screening in patients with MMC revealed the presence of Chiari malformation (CM), diastematomyelia (DIAM), low conus localization (LCL), syringomyelia (SM) and corpus callosum agenesis (CCA) (26,29). Infants with MMC may also develop hydrocephalus. Hydrocephalus is an abnormal progressive accumulation of cerebrospinal fluid (CSF) in the ventricles and an important cause of morbidity and mortality in individuals with MMC (19). Currently, the recommended treatment for patients with MMC is closure of the defect at the earliest (28).

Our clinic is a referral hospital in our region and in close proximity to a war zone. Thus, we frequently encounter MMC in our practice. In this study, we aim to describe the etiological, clinical, radiological and surgical characteristics of patients with MMC and share our experience regarding the causes of hydrocephalus and methods to prevent MMC.

MATERIAL and METHODS

Study Design

We retrospectively analyzed the data of 51 patients with SB who underwent surgical treatment at Sanlıurfa Training and Research Hospital between December 2021 and October 2022. Ventriculoperitoneal (VP) shunt surgery was performed in patients who developed hydrocephalus in the postoperative period. Patients who required revision surgery for complications such as CSF fistula and wound closure defect after the SB operation were revised. Patients were followed up during their admission to the neonatal intensive care unit or ward. Data of mothers who were referred to the neurosurgery outpatient clinic after the prenatal diagnosis in the gynecology outpatient clinic were also obtained.

The following patient data were analyzed: age, sex, birth weight, birth week, type of delivery, head circumference, APGAR score, presence of additional systemic anomalies, interval between birth and operation for MMC, defect diameter, need for VP shunt surgery, postoperative complications, and revision surgery for postoperative complications. The systemic ultrasound (USG), echocardiogram (ECHO) and magnetic resonance (MR) images of the patients were evaluated. The mothers' age, blood folate and vitamin B12 levels, number of children, family history, and history of antiepileptic use were also evaluated.

The study was approved by the Clinical Research Ethics Committee of the Faculty of Medicine, Harran University (No: HRU /22.23.14, date: 11.28.2022), and conducted in accordance with the principles of the Declaration of Helsinki (30).

Statistical Analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, version 26.0 (IBM Corp., Armonk, NY, USA). Descriptive statistical methods (mean and, standard deviation and, median and, frequency, as well as percentage and, minimum - maximum) were used to evaluate the study data. The suitability of the quantitative data to normal distribution was evaluated using the Shapiro -Wilk test and graphical analyses. The Student's t-test was used for the comparisons of normally distributed quantitative variables between two groups, and The Mann-Whitney U test was used for the comparisons of nonnormally distributed quantitative variables between two groups. Qualitative data were compared using the Pearson chi-square test, Qualitative data were compared using Fisher's exact test and the Fisher-Freeman-Halton test. Statistical significance was set at $p<0.05$.

RESULTS

The mean age of the mothers was 27.18 ± 5.37 years and the median age was 27 years (range: 16-40). A family history of SB was present in 9 patients (17.6%) and absent in 42 patients (82.4%). Only one mother had a history of antiepileptic drug use. Of the 51 mothers, only 40 (78.4%) were administered antenatal folate supplement. The mean maternal folate level was 7.02 ± 3.66 µg/L (median, 7 µg/L [range: 2-20]. Although 14 (27.5%) mothers had low folate levels, 37 (72.5%) had normal folate levels. The mean vitamin B12 level was 287.29 ± 91.64 ng/L (median, ng/L 277 [range: 144-590]. Although nine mothers (17.6%) had low vitamin B12 levels, 42 (82.4%) had normal vitamin B12 levels. Among the infants, 4 (7.8%), 16 (31.4%), 7 (13.7%), 10 (19.6%) were first, second, third, fourth-born children, respectively. The remaining infants (n=14) (27.5%) were the fifth or later child of their mothers (Table I).

Of the 51 infants, 22 (43.1%) were female and 29 (56.9%) were male. The mean gestational age was 37.84 ± 2 weeks (median, 39 years [range: 30-40] weeks. The mean birth weight was 3055.49 ± 503.24 g, (median, 3020 g [range: 1670-4270]. The mean head circumference at birth was 35.27 ± 19.4 cm (median, 35 cm [range: 30-47]. Of the 51 infants, 8 (15.7%) were born by normal vaginal delivery and 43 (84.3%) were born by cesarean section. The mean APGAR scores at 1 and 5 min were 8.14 ± 1.06 and 9.45 ± 0.83, respectively, The median APGAR scores at 1 and 5 min were 8 (range: 4-10) and 10 (range: 6-10), respectively. The systemic USG yielded a normal study in 39 (76.5%) patients. However, renal abnormalities were detected in 12 (23.5%). The thyroid function test yielded a normal result in 41 (80.4%) patients, Hypothyroidism was detected in 10 (19.6%) patients. An orthopedic anomaly was present in 25 (49.0%) patients. ECHO revealed normal findings in 48 (94%) patients, ASD (atrial septal defect) in one patient and PDA (patent ductus arteriosus) in one patient, VSD (ventricular septal defect) in one. No motor deficit was observed in 23 (45.1%) patients. However minimal deficit, minimal movement and, paraplegia was observed in 2 (3.9%), 6 (11.8%), 18 (35.3%) patients, respectively (Table II).

The mean area of the defect was 33.55 ± 22.21 cm² (median, 29 cm² [range: 4-80]. Of the 51 patients, 18 had a meningocele (MC), 10 had a myeloschisis (MS) and 23 had a MMC (Table III). The SB defect was located in the lumbar region, sacral and

Table I: Descriptive Characteristics of Mothers

Maternal Age	Mean ± SD Median (Min-Max)	27.18 ± 5.37 27 (16-40)
Family history, n (%)	No Yes	42 (82.4) 9 (17.6)
Antiepileptic Use, n (%)	No Yes	50 (98.0) 1 (2.0)
Taking Folate Supplements, n (%)	No Yes	40 (78.4) 11 (21.6)
Folate level (μg/L)	Mean ± SD Median (Min-Max) Low, n (%) Normal, n (%)	7.02 ± 3.66 7 (2-20) 14 (27.5) 37 (72.5)
Vitamin B12 level (ng/L)	Mean ± SD Median (Min-Max) Low, n (%) Normal, n (%)	287.29 ± 91.64 277 (144-590) 9 (17.6) 42 (82.4)
Number of children, n (%)	1 2 3 4 ≥5	4 (7.8) 16 (31.4) 7 (13.7) 10 (19.6) 14 (27.5)

Table II: Birth Characteristics of the Patients

Gender, n (%)	Female Male	22 (43.1) 29 (56.9)
Birth week (weeks)	Mean ± SD Median (Min-Max)	37.84 ± 2.47 39 (30-40)
Birth weight (grams)	Mean ± SD Median (Min-Max)	3055.49 ± 503.24 3020 (1670-4270)
Birth Head Circumference (cm)	Mean ± SD Median (Min-Max)	35.27 ± 1.94 35 (30-47)
Type of Birth, n (%)	Normal C/S	8 (15.7) 43 (84.3)
APGAR 1st Minute	Mean ± SD Median (Min-Max)	8.14 ± 1.06 8 (4-10)
APGAR 5th Minute	Mean ± SD Median (Min-Max)	9.45 ± 0.83 10 (6-10)
Systemic USG, n (%)	Normal Kidney anomaly	39 (76.5) 12 (23.5)
Thyroid function test result, n (%)	Normal Hypothyroidism	41(80.4) 10 (19.6)
Orthopaedic anomaly, n (%)	No Yes	26 (51.0) 25 (49.0)
Echocardiography, n (%)	Normal ASD PDA VSD	48 (94.0) 1 (2.0) 1 (2.0) 1 (2.0)
Motor function, n (%)	No deficit Minimal deficit Minimal movement One leg Immobile Paraplegia	23 (45.1) 2 (3.9) 6 (11.8) 2 (3.9) 18 (35.3)

Table III: Operation-Related Characteristics of Infants

Defect Area (cm^2)	Mean ± Sd Median (Min-Max)	33.55 ± 22.21 29 (4-80)
Spina Bifida Types, n (%)	Meningocele Meningomyelocele Myeloschisis	18/51 (35.29) 23/51 (45.09) 10/51 (19.6)
Spina Bifida Type and Treated Hydrocephalus Rates, n (%)	Meningocele Meningomyelocele Myeloschisis	3/18 (16.6) 9/23 (39.13) 7/10 (70.0)
Spina Bifida Localization and Additional Pathology Localization, n (%)	Thoracal Lumbar Sacrum Cervical (MMC) - Lumbar (DST) Lumbar (MMC) - Thoracal (DST) Lumbar (MMC) – Thoracal (MMC) - Cervical (DST)	5/51 (9.8) 26/51 (50.98) 17/51 (33.33) 1/51 (1.96) 1/51 (1.96) 1/51 (1.96)
Level of spina bifida and Treated Hydrocephalus Rates, n (%)	Thoracal Lumbar Sacrum Cervical (MMC) - Lumbar (DST) Lumbar (MMC) - Thoracal (DST) Lumbar (MMC) - Thoracal (MMC) – Cervical (DST)	4/5 (80.0) 9/26 (34.61) 3/17 (11.0) 1/1 (100.0) 1/1 (100.0) 1/1 (100.0)
MR Finding, n (%)	Normal CM VM LCL CCA DIAM SM	2 (3.9) 36 (70.6) 36 (70.6) 21 (41.2) 21 (41.2) 2 (3.9) 5 (9.8)
Operation time (hours)	Mean ± Sd Median (Min-Max)	26.96 ± 17.80 24 (5-72)
Postoperative complication, n (%)	None CSF leaking CSF leaking-wound necrosis Wound necrosis	44 (86.2) 3 (5.8) 1 (2.0) 3 (5.9)
VP shunt operation, n (%)	No Yes	32 (62.7) 19 (37.3)
Re-operation, n (%)	No VP shunt revision Wound Debridement - VP shunt revision Wound Debridement	45 (88.2) 2 (4.0) 1 (2.0) 3 (5.9)
Length of Hospital Stay (days)	Mean ± Sd Median (Min-Max)	21.82 ± 17.31 14 (5-70)

***CM:** Chiari Malformation, **VM:** Ventriculomegaly, **LCL:** Low Conus Localisation, **CCA:** Corpus Callosum Agenesia, **DIAM:** Diastometamyelia, **SM:** Syringomyelia, **DST:** Dermal Sinus Tract, **MMC:** Meningomyelocele, **MS:** Myeloschisis, **MC:** Meningocele, **CSF:** Cerebrospinal Fluid, **VP:** Ventriculoperitoneal*

the thoracic regions in 26 (51.0%), 17 (33.3%), and 5 (9.8%) patients, respectively (Figure 1). Furthermore, one patient (2%) exhibited a dermal sinus tract (DST) in the thoracic region and an MMC in the lumbar (Figure 2), and another patient (2%) exhibited an MMC in the cervical region and a DST in lumbar region. In one patient (2%), there was a DST in the cervical region and an MMC in the thoracic and lumbar regions (Table III).

The rates of treated hydrocephalus according to SB types, were as follows; meningocele,16.6% (n=3), MMC 39.13% (n=9), and myeloschisis 70% (n=7) (Table III). The rates of treated hydrocephalus according to the level of SB were as

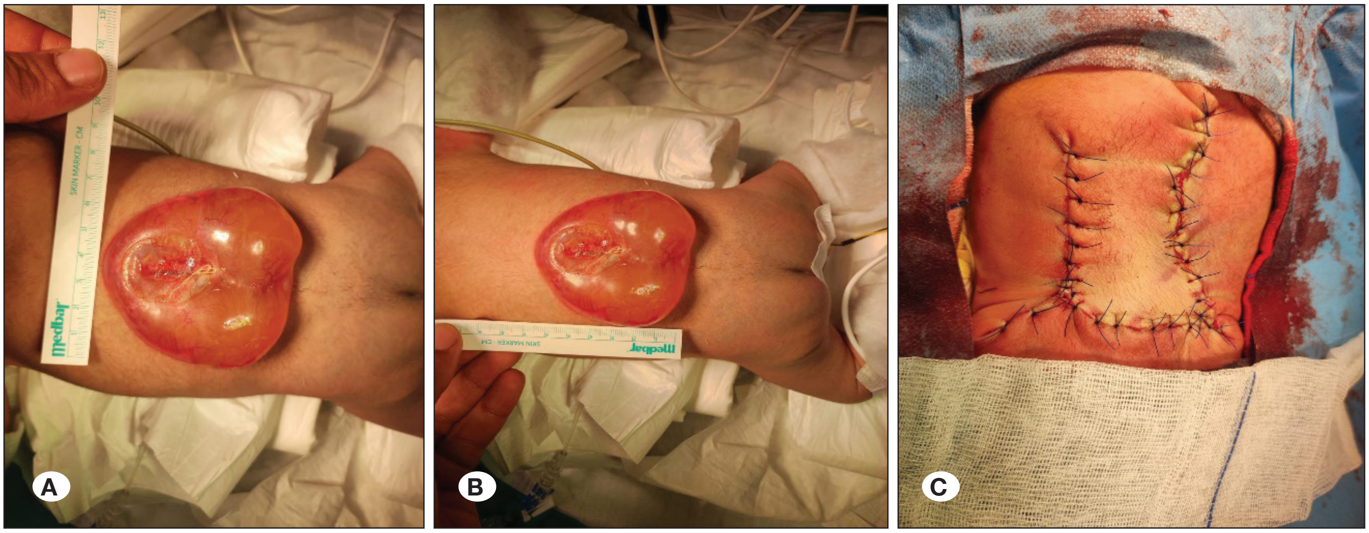

Figure 1: Preoperative **(A, B)** and postoperative **(C)** pictures of a case with lumbar meningomyelocele.

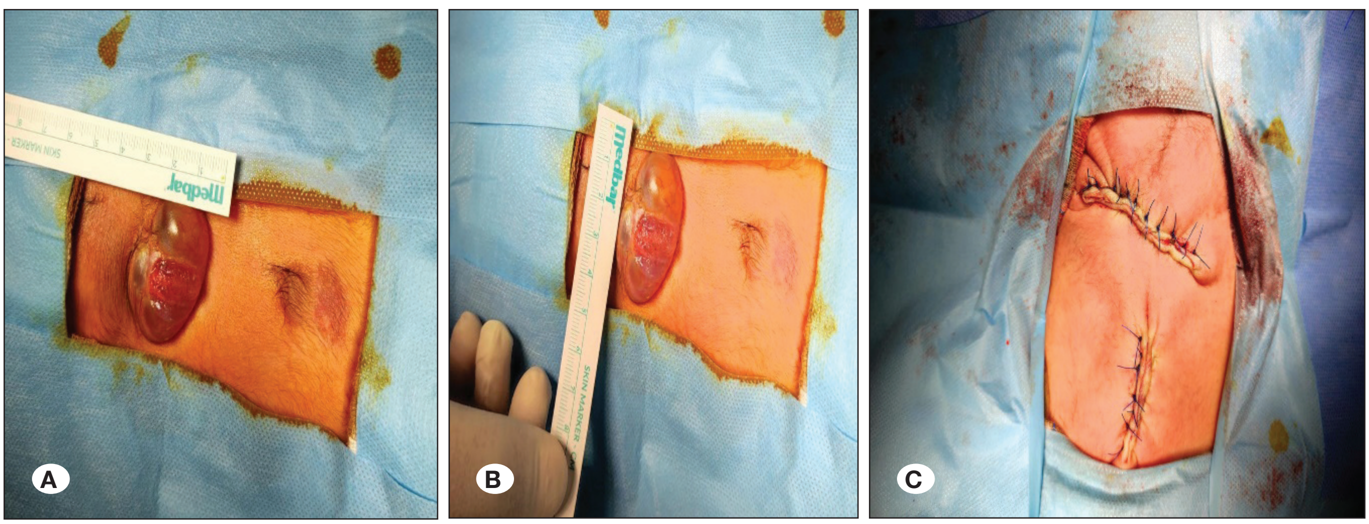

Figure 2: Preoperative **(A, B)** and postoperative **(C)** pictures of the case with lumbar meningomyelocele and thoracal DST.

follows: thoracic region, 80% (n=4), lumbar region, 34.61% (n=9) and sacral region, 11% (n=3) (Table III).

The mean operative time was 26.96 ± 17.80 h (median, 24 h [range: 5-72]. No complication developed in the postoperative period in 44 (86.2%) patients. However, a CSF fistula, CSF leakage with wound necrosis, and wound necrosis alone developed in three (5.8%), one (2.0%), three (5.9%) patients, respectively. Hydrocephalus developed in 19 (37.3%) patients and it was treated by VP shunt insertion. Hydrocephalus did not develop in 32 (62.7%) patients (Figure 3). The incidence of hydrocephalus according to the SB type was as follows: MMC (39.13%), meningocele (16.6%), and myeloschisis (70%) (Table III). VP shunt revision surgery was performed in two (4.0%) patients. Wound debridement and VP shunt revision were performed in one (2.0%) patient. Wound debridement alone was performed in three (5.9%) patients. The mean hospitalization duration of the patients was 21.82 ± 17.31 days, median, 14 days [range: 5-70] (Table III).

Female patients required VP shunt operation significantly more frequently than male patients (p=0.001). However, there was no statistically significant correlation between VP shunt operation and the other patient characteristics such as maternal age, family history, folate supplementation, folate level, vitamin B12 level, number of children, head circumference at birth, defect location and surgical timing. Furthermore, there was no correlation between hydrocephalus and the presence of neurologic deficit. However, there was a statistically significant correlation the area of the defect and VP shunt surgery (p=0.001). The defect area was larger in patients who underwent the VP shunt operation than in those who did not undergo surgery. Additionally, the duration of hospitalization was statistically significantly longer in these patients (Table IV). There was also a statistically significant correlation between SB type and hydrocephalus. The more severe SB type, the higher the risk of developing hydrocephalus. Moreover, higher levels of SB lesions exhibited an increased risk of developing hydrocephalus.

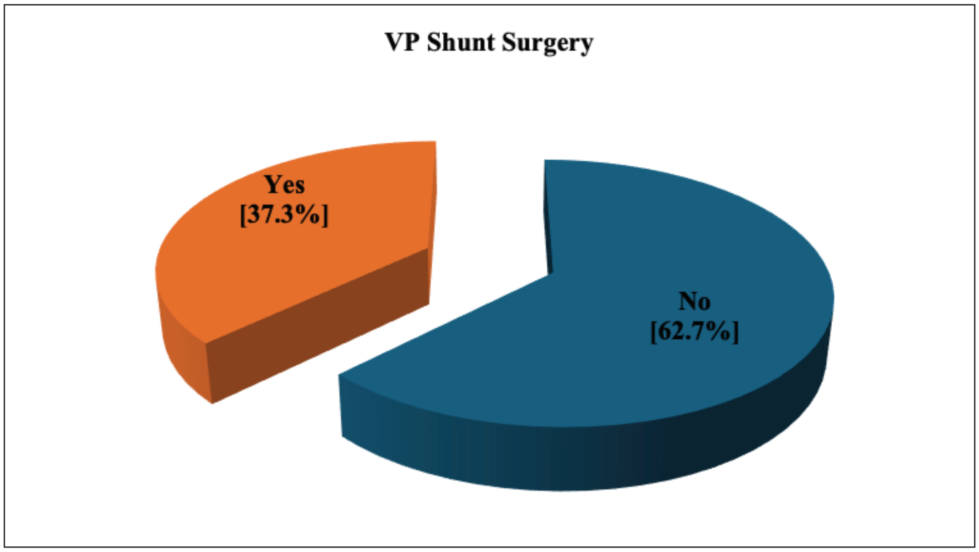

Figure 3: Percentage of meningomyelocele patients who underwent ventriculoperitoneal shunt surgery.

Tablo IV: Evaluation of the Presence of V/P Shunt Surgery According to the Characteristics of Mothers and Babies

		VP Shunt (-) (n=32)	VP Shunt (+) (n=19)	p-value
Infant gender, n (%)	Female Male	8 (36.4) 24 (82.8)	14 (63.6) 5 (17.2)	**[b]0.001****
Maternal age	Mean ± SD Median (Min-Max)	26.97 ± 5.36 26.5 (16-40)	27.53 ± 5.52 27 (19-37)	[a]0.724
Family history, n (%)	No Yes	28 (66.7) 4 (44.4)	14 (33.3) 5 (55.6)	[c]0.266
Taking folate supplements, n (%)	No Yes	25 (62.5) 7 (63.6)	15 (37.5) 4 (36.4)	[c]1.000
Folat, n (%)	Low Normal	9 (64.3) 23 (62.2)	5 (35.7) 14 (37.8)	[b]0.889
Vitamin B12, n (%)	Low Normal	5 (55.6) 27 (64.3)	4 (44.4) 15 (35.7)	[c]0.711
Number of children, n (%)	1. child 2. child 3. child 4. child ≥5. child	4 (100.0) 10 (62.5) 3 (42.9) 7 (70.0) 8 (57.1)	0 (0.0) 6 (37.5) 4 (57.1) 3 (30.0) 6 (42.9)	[d]0.465
Birth Head Circumference (cm)	Mean ± SD Median (Min-Max)	34.50 ± 1.27 34 (32-38)	36.58 ± 4.29 35 (30-47)	[e]0.103
Type of Birth, n (%)	Normal C/S	6 (75.0) 26 (60.5)	2 (25.0) 17 (39.5)	[c]0.694
Defect Area (cm^2)	Mean ± SD Median (Min-Max)	24.81 ± 16.81 16 (4-80)	48.26 ± 22.80 49 (9-80)	**[e]0.001****
Surgery Time (hours)	Mean ± SD Median (Min-Max)	26.53 ± 17.99 24 (6-72)	27.68 ± 17.94 24 (5-72)	[e]0.746
Length of Hospital Stay (days)	Mean ± SD Median (Min-Max)	13.56 ± 9.13 12 (5-40)	35.74 ± 19.05 40 (6-70)	**[e]0.001****

*[a]Student-t Test, [b]Pearson Chi-Square Test, [c]Fisher's Exact Test, [d]Fisher Freeman Halton Test [e]Mann Whitney U Test. **p<0.01.*

Table V: Logistic Regression Results of Factors Affecting VP Shunt Surgery

	odds	95% Confidence Interval odds (Lower)	95% Confidence Interval odds (Upper)	p-value
Chiari Malformation	2.803	0.335	23.436	0.342
Ventriculomegaly	1.084	0.229	5.123	0.919
Low Conus Localisation	1.280	0.267	6.130	0.758
Corpus Callosum Agenesia	0.726	0.147	3.578	0.694
Syringomyelia	12.885	1.175	141.243	**0.036***
Defect Area	1.063	1.026	1.103	**0.001****

**p<0.05, **p<0.01.*

We found that the existence of CM, LCL and CCA in addition to MMC on MR imaging was statistically significantly more common in patients who underwent VP shunt surgery than in those who did not undergo surgery. Furthermore, there was a statistically significant association between the presence of SM and VP shunt operation (p=0.036) (Table V).

DISCUSSION

Morbidity and mortality in patients with MMC vary according to age, sex, ethnicity, level and severity of the lesion, presence of multiple birth defects and the treatment method. Low birth weight, higher levels of spinal cord involvement and the presence of congenital anomalies are considered to be poor prognostic factors. Although a maternal age of less than or more than 40 years is reportedly a risk factor for MMC, data regarding mother's age in association with MMC are limited in literature. In our study, the average maternal age was 27 years (range, 16-40) (15,31). No study has reported a relationship between the number of children and MMC. However, in our study, 7.8% of patients with MMC were first-born children, and 27.5% of the patients were born the fifth-born child or later. No parallelism was found a higher number of children and the incidence of MMC. Cesarean delivery prevents the tearing of the MMC pouch. Previous studies have reported a varying cesarean birth rate of 69% to -80% (3). In our study, this rate was higher (84.3%).

Surgical timing may prevent further deterioration of motor functions, contribute to the well-being of the genitourinary system, and reduce the risk of infectious complications. However, an analysis of a national database showed no significant difference in the infection rates between the same day and next day surgery for MMC. However, performing MMC surgery 48 h after delivery increased the infection rates. Furthermore, infections are associated with a 54% increase in the duration of hospitalization. Therefore, if the closure of MMC is delayed beyond the first 24 h after birth, there is a significant increase in the infection and hospitalization rates (22). The mean interval between birth and MMC surgery in our study was 26.9 hours and all patients were operated within 72 hours of delivery.

MMC is an important public health challenge that can affect systems such as neurological, genitourinary, orthopaedic and circulatory systems and the organs such as the skin. Thus, a multidisciplinary approach is required for the management of this disease. Yorulmaz et al. reported orthopedic complications, urinary system complications, congenital heart diseases and hypothyroidism in 31.1%, 23.1%, 27.5%, 7.5% of the patients, respectively (31). Similarly in our study, orthopedic complications, urinary system complications, congenital heart diseases and hypothyroidism were observed in 49%, 23.5%, 6% and, 19.6% of the patients, respectively.

In this study, the neurological examination yielded normal results in only 45.1% of the patients. Similarly, Rehman et al. reported that 42% of their study participants did not exhibit any neurological deficit (23). Patients with neurological deficits were included in physical therapy program after discharge. In the same study, the authors observed that the defect was frequently (86%) located in the lumbosacral (23). Similarly, we found that 90.8% of the patients had lumbar or sacral involvement.

No complications developed after the MMC surgery in 86% of the patients. However, a CSF fistula, wound necrosis, and a combination of CSF fistula and wound necrosis developed in 5.8%, 5.8%, and 2% of patients, respectively. In the study by Khan, CSF fistula and wound problems developed in 23.7% and 13.5% of their patients, respectively (12). Therefore, the rate of postoperative complications in our study was lower than that reported in the literature.

Folate deficiency is a vital risk factor for the development of MMC, especially in low socioeconomic regions. Its prevalence reduced by 5 - 6 per 10,000 and 19% after implementation of a folic acid enriched dietary supplementation program in China and in the USA, respectively (6,9). Furthermore, supplementation with 0.4 µg of folate per day reduces the occurrence of neural tube defects by 70% (6). Only 21% of patients in our study were administered antenatal folate supplementation. Furthermore, the median maternal folate level in our study was 7 (range: 2-20) which is slightly higher than the minimum value of the normal range (normal range: 3-34 µg/L in our laboratory. Nevertheless, to prevent the development of neural tube defects, we need to target the upper limit of the normal range, because none of our patients exhibited a folate value level of > 20 µg/L. The maternal vitamin B12 levels in our study were within the normal range. Only one mother had a history of antiepileptic drug use.

Hydrocephalus is one of the most common coexisting condition in patients with MMC. Its incidence varies between 65% and 85% in the literature (1,10,14,16,25,27). And it may become symptomatic after pouch repair. Shunt insertion is commonly performed to treat hydrocephalus. In our study, 37.3% of the patients underwent VP shunting. Data regarding the incidence of hydrocephalus according to SB type and anatomic level of SB are lacking. Kim et al. demonstrated that the more rostral lesions are associated with higher rates of treated hydrocephalus (13), which is similar to our study's findings. Dysfunction and infections may develop after shunt surgery. In our study, the shunt was revised in 9.3% of the patients which is consistent with the findings in the literature. The mean head circumference in our study was 35.27 cm, which is lower than that reported in another study conducted in our country (21,31). Hydrocephalus plays a crucial role in increasing the morbidity and mortality in patients with MMC. It prolongs hospitalization and causes a significant financial burden. In our study, we examined patients who developed hydrocephalus. In our study, maternal age, family history, head circumference, operative time, defect area, maternal folate and vitamin B12 levels, folate supplementation status, mode of delivery and number of children were not statistically significantly correlated with the incidence of hydrocephalus. However, the incidence of hydrocephalus was statistically significantly higher in patients with a larger defect diameter, patients with SM and female patients. The incidence of hydrocephalus according to sex in previous reports has varied across countries and regions (20). In our study, the incidence of hydrocephalus was higher in female patients than in male patients.

A crucial challenge of MMC surgery is the closure of the skin defect, A larger defect is more challenging to repair. Various repair methods have been described in the literature, including skin grafts, skin flaps, and muscle or musculocutaneous flaps (18). Clinical practices regarding defect closure may vary, in some clinics, the entire may be repaired by neurosurgeons, whereas in some other clinics a plastic surgeon may repair it, in other clinics small defects may be repaired by neurosurgeons and large defects may be repaired by plastic surgeons. In our study, we requested the assistance of a plastic surgery in only five patients (9.8%). As the size of the defect increases, the amount of affected neural tissue also increases. Thus, the size of the defect is a vital prognostic factor. However, studies on this aspect are limited, and in these limited studies the defect was correlated with the patient's neurological status (4,7,8,18). In our study, there was a significant difference between the defect size and development of hydrocephalus. The mean defect area was 48.26 cm² in patients with hydrocephalus and 24.81 cm² in patients without hydrocephalus. This difference in defect area between the two groups was statistically significant ($p=0.001$). No study till date has demonstrated a relationship between the defect area and hydrocephalus incidence. We hypothesize that the higher incidence of hydrocephalus in patients with a larger defect area may be explained by the simple rules of physics. After the defect repair, CSF volume equivalent to the volume of the defect will enter into the normal CSF circulation. This increased CSF load will result in hydrocephalus. As the area for CSF circulation decreases, the head circumference will increase and hydrocephalus will become clinically apparent.

In our study, only two (2.9%) patients did not exhibit any additional neurological pathology on MR imaging. In the rest of our patients, a CM, VM, LCL, CCA, DIAM or SM was detected. A CM and VM was detected in 70.6 % of our patients. VP shunt surgery was performed in 19 of the patients with VM. Previous studies have reported a CM incidence of 67% to 95% in patients with MMC, and 10-30% of these patients are symptomatic (2,17,26). The incidence of CM has decreased after the recent introduction of intrauterine fetal MMC operations. However, according to MOMS, the procedure involves serious risks (up to 30%) for the fetus and mother (20). CCA is another anomaly observed in patients with MMC, with an incidence of 30% to 50% (17). In our study, the incidence of CCA, LCL and DIAM were 41 %, 41.2%, 3.9%, respectively. The incidence of SM in patients with MMC is reportedly 30% - 75% (29). However, in our study, it was 9.8%. This is similar to the findings (8.5) of another study (31). Hence, we hypothesize that the incidence of SM varies according to the geographical region. We observed that our neurological imaging were consistent with those in the literature. Furthermore, more VP shunt surgeries were performed in patients with SM than in patients with other coexisting conditions. As there is no information on this aspect in the literature, we believe that this result may be incidental.

CONCLUSION

MMC is a neural tube defect that may develop despite normal maternal folate levels, making it difficult to define the optimum protective threshold. In our study, no maternal blood folate level exceeded 20 µg/L, suggesting that the upper limit of the normal range may be a reasonable target. Hydrocephalus frequently accompanies MMC and often requires shunt placement, which carries risks such as infection and malfunction. We found that hydrocephalus is more common in patients with higher-level or severe spinal defects, larger lesions, spinal meningoceles, and in female patients. The limited sample size is a study limitation, and further validation is needed.

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: BE, YB

Data collection: BE, YB, MK

Analysis and interpretation of results: BE, BU, MK, HA

Draft manuscript preparation: BE, YB, HA

Critical revision of the article: BE, YB

Other (study supervision, fundings, materials, etc...): BE, HA, YB, BU, MK

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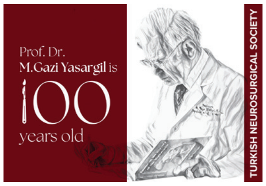

Original Investigation

Pediatrics

Correlation of Transfontanel Ultrasonography and Brain Magnetic Resonance Imaging Measurements in Neonates with Hydrocephalus

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This study has been presented as an oral presentation at the 67th National Pediatric Congress, October 2023, Cyprus, and were awarded the best research prize.

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ABSTRACT

AIM: To evaluate whether transfontanel ultrasonography could serve as a practical and less complex alternative to brain magnetic resonance imaging in infants with hydrocephalus.

MATERIAL and METHODS: In this prospective study, 54 infants diagnosed with hydrocephalus underwent both transfontanel ultrasonography and brain magnetic resonance imaging. A neonatologist and a radiologist independently assessed ventricular measurements, including the Evans index, frontooccipital horn ratio, bilateral ventricular index, anterior horn width, thalamooccipital distance, callosal angle, and corpus callosum length.

RESULTS: Among the 54 infants, 48 (88.9%) received a ventriculoperitoneal shunt. A strong correlation was found between transfontanel ultrasonography and magnetic resonance imaging for most ventricular measurements: Evans index (r=0.875, p=0.0001), frontooccipital horn ratio (r=0.867, p=0.0001), callosal angle (r=0.868, p=0.0001), bilateral ventricular index (left r=0.937, right r=0.944; p=0.0001 for both), bilateral anterior horn width (left r=0.918, right r=0.908; p=0.0001 for both), and bilateral thalamooccipital distance (left r=0.956, right r=0.919; p=0.0001 for both). The correlation for corpus callosum length was statistically significant but weaker (r=0.386, p=0.004).

CONCLUSION: Our study emphasizes that transfontanel ultrasonography—which achieves better results in experienced hands—should be widespread and an excellent alternative to unnecessary and repeated imaging methods.

KEYWORDS: Hydrocephalus, Magnetic resonance imaging, Transfontanel ultrasonography, Infant, Neuroimaging

ABBREVIATIONS: AHW: Anterior horn width, **CA:** Callosal angle, **CT:** Computed tomography, **EVD:** External ventricular drain, **FOHR:** Frontal occipital horn ratio, **MRI:** Magnetic resonance imaging, **TFUS:** Transfontanel ultrasonography, **TOD:** Thalamooccipital distance, **USG:** Ultrasonography, **VI:** Ventricular index, **VPS:** Ventriculoperitoneal shunt

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INTRODUCTION

Hydrocephalus results from obstruction, impaired absorption, or overproduction of the cerebrospinal fluid pathways due to several developmental, genetic, and inherited abnormalities. It can damage the neurodevelopmental outcome of affected newborns (13,31). Its incidence ranges from 0.3 to 2.5 per 1,000 live births, and it is one of the most common congenital anomalies of the nervous system (13). Hydrocephalus in infants can be congenital or acquired, with congenital forms being either syndromic—involving conditions such as neural tube defects, craniosynostosis, and X-linked inheritance—or nonsyndromic (31).

Measuring ventricular size is essential in pediatric patients with hydrocephalus because the severity of ventricular dilatation is related to an enhanced risk of adverse neurodevelopmental outcomes in fetuses with isolated ventriculomegaly (7). In the diagnosis and treatment of newborns, ultrasonography (USG), computed tomography (CT), or magnetic resonance imaging (MRI) are frequently carried out. Transfontanel ultrasonography (TFUS) is a highly effective, cost-effective, and noninvasive diagnostic tool for rapidly evaluating the anatomy of the infant's brain and detecting normal and abnormal findings in detail (23). It also has limitations in assessing complex malformations, vascular pathologies, and obstetric trauma, detecting small parenchymal pathologies and cerebral infarction, and evaluating white matter injury. TFUS enables evaluating supratentorial structures in more detail, whereas the evaluation of infratentorial structures is relatively restricted (11). Definitions have been determined according to the measurements of the ventricles (3), and studies comparing MRI/CT with USG measurements are minimal.

With the development of technology and the diversification of imaging methods for hydrocephalus and ventriculomegaly, diagnosis and post-treatment follow-up can be performed with a large number of linear measurements. Reference values for ventricular index (VI), anterior horn width (AHW), and thalamooccipital distance (TOD) have been established for neonatal lateral ventricles, which might enable the early identification of posthemorrhagic ventricular dilatation and the accurate timing of interventions in infants with ventricular dilatation (3). USG-derived frontal occipital horn (FOHR) and frontal temporal horn are reliable indices for clinically monitoring infantile ventriculomegaly in infants younger than six months (25). It is a valuable tool for following pediatric hydrocephalus patients (24). In the last decade, studies have shown that callosal angle (CA) measurement correlates with the Evans index, which has been used for years in the diagnosis of ventriculomegaly and hydrocephalus in both adult and pediatric patients (17,32). With the expansion of the lateral ventricles, the corpus callosum primarily exhibits elevation of its body and—to a lesser extent—an increase in length (15).

This study aims to compare linear USG with MRI measurements in hydrocephalus because USG can be used at the bedside and has no radiation risk. Moreover, it seeks to ascertain whether USG can be utilized as a more straightforward imaging method in hydrocephalic infants.

MATERIAL and METHODS

Participants

This study was conducted in line with the principles of the Declaration of Helsinki. After obtaining approval from the Yuzuncu Yil University Clinical Research Ethics Committee (Decision no: 15/11/2023-05), 60 newborn infants with hydrocephalus who were admitted to the neonatal intensive care unit of our hospital in 2023–2024 were included in the study. Demographic features (sex, gestational age, birth weight, type of delivery, consanguineous marriage, maternal age, and type of surgery required for hydrocephalus) and additional anomalies were recorded. Patients with hydrocephalus whose measurements could not be performed due to massive hydrocephalus were excluded. The legal parents of the patients were informed about the study. Informed consent was obtained from all individual participants enrolled in the study.

Measurements

Evans index, FOHR, bilateral TOD, bilateral AHW, bilateral ventricular index, CA, and corpus callosum length measurements were performed on the same day by a radiologist experienced in brain MR imaging recommended by neurosurgical consultation, and by a neonatologist with TFUS.

The Evans index is the ratio of the frontal horns' maximum width to the skull's maximum internal diameter.

FOHR is determined by adding the largest diameter of the frontal and occipital horns and dividing by twice the biparietal diameter.

VI is the distance between the most lateral side of the ventricles and the interhemispheric fissure in the coronal section, showing the third ventricle.

AHW is the widest distance between the ventricular walls in the coronal section through the third ventricle.

TOD is measured between the farthest posterior points of the thalamus and the lateral ventricle in the sagittal section, where the lateral ventricle is seen in its entirety. Ventricular index, anterior horn, and thalamo-occipital distance were measured independently for the right and left.

CA was measured on coronal sections at the point where the vertical line descending from the anterior commissure and posterior commissure planes—90° from the posterior commissure line—crossed the lateral ventricles.

Corpus callosum length measurements were performed on the best midsagittal sections from the most anterior to the most posterior view. Figure 1 shows representative TFUS and cranial MRI measurements.

Image Analysis

A senior neonatologist with fifteen years of experience conducted cranial ultrasound measurements with a bedside ultrasound device (Mindray, Diagnostic Ultrasound System, DC-N3 PRO, 2022). Standard coronal and sagittal section images were collected through the anterior fontanelle. For MRI protocol, a Siemens Altea 1.5 tesla MR was used to obtain

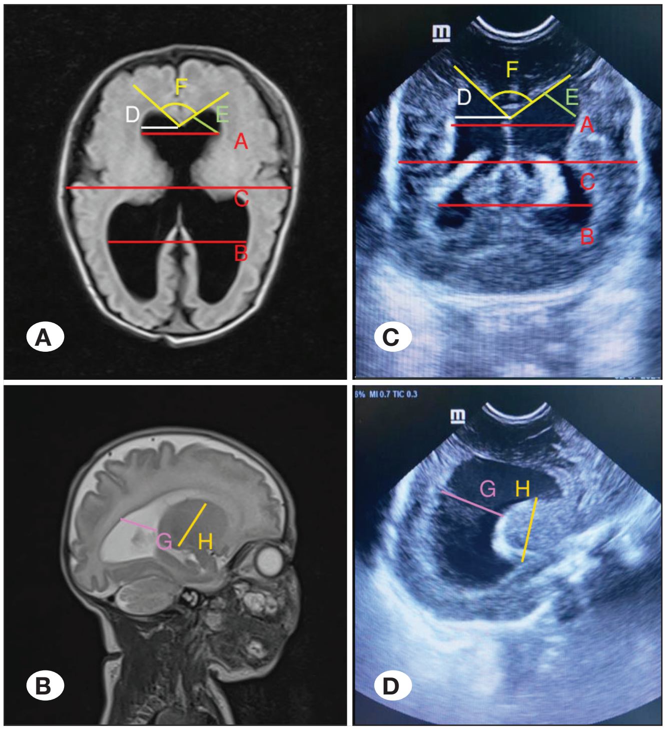

Figure 1: Representative images for MRI **(A,B)** and TFUS **(C,D)** measurements. Evans index=A/B; FOHR=A+B/2C; bilateral ventricular index=D; bilateral anterior horn width=E; callosal angle=F; bilateral thalamooccipital distance=G; corpus callosum length=H.

two-dimensional T1AG, T2AG and flair sequences with 5×5 cm contiguous axial and sagittal scans, and 3 mm sections were obtained. The sonogram neonatologist and senior radiologist for the MRI scans were blinded to infant history and previous radiology reports, and both methods were measured on the same postnatal day.

Statistical Analysis

Descriptive statistics for continuous variables are expressed as the mean, standard error, minimum, and maximum values, while descriptive statistics for categorical variables are expressed as numbers and percentages. The independent t-test was used to compare continuous variables according to categorical variables. Pearson correlation coefficients were calculated to evaluate the relationships between continuous variables. For Pearson correlation coefficients, values greater than 0.4 and up to 0.69 were classified as low correlations, those between 0.7 and 0.89 were considered moderate, and coefficients exceeding 0.9 were interpreted as indicating strong to very strong correlations (28). The statistical significance level was set at 0.05, and SPSS (version: 26) statistical package software was utilized for calculations.

RESULTS

Sixty newborns with hydrocephalus were hospitalized in our hospital unit during the study period. Six patients whose radiologic measurements could not be performed due to massive hydranencephaly were excluded from the study. Therefore, ultimately the researchers could measure 54 newborns with hydrocephalus. Table I provides demographic characteristics of the hydrocephalic newborns included in the study.

No statistically significant difference was found between the measurements in binary comparisons (Table II). After comparing the correlations of brain MRI and TFUS measurements, Evans index (r=0.875, p=0.0001), FOHR (r=0.867, p=0.0001), CA (r=0.868, p=0.0001), bilateral VI (left r=0.937, p=0.0001; right r=0.944, p=0.0001), bilateral AHW (left r=0.918, p=0.0001; right r=0.908, p=0.0001), and bilateral TOD (left r=0.956, p=0.0001; right r=0.919, p=0.0001) were found to be significantly correlated. Although the corpus callosum length was statistically significant between different imaging modalities, the correlation between the analyses was not as strong as the other measurements (r=0.386, p=0.004; Figure 2).

DISCUSSION

Transfontanelle ultrasonography is a valuable tool for detecting intracranial lesions in infants. Hydrocephalus is the most common indication for performing the scan, as well as the most frequently observed abnormality (12).

In the literature, there are many studies on TFUS, including a large number of cases. However, there are few studies for newborns in which many cranial parameters are measured and MR-CT measurements are compared. In the study of neonatal neuroanatomy and disease, TFUS—which is widely used—offers many advantages, including the lack of ionizing radiation and its portability, wide availability, and low cost (21), and it might also provide volumetric measurements (1). The potential disadvantages of the technique are that it is operator-centered and requires a suitable acoustic window (11). MRI has become widespread as a promising imaging tool since 2007, especially for the central nervous system (22). In method comparison research, studies comparing USG with MRI (10,25)—which is often not available in every center and requires sedation—and CT—which carries radiation risk—have been conducted in many diseases (16,24).

Transfontanelle ultrasonography (TFUS) was used to detect intraventricular hemorrhage in preterm neonates by scanning through the anterior fontanel in both coronal and sagittal sections at multiple time points within the first two weeks of life. The findings were classified based on severity, and TFUS is the imaging modality used for early detection and grading of intraventricular hemorrhage in preterm neonates (8). Cross-sectional and longitudinal reference curves were generated for VI, AHW, and TOD according to USG measurements for early definition and measurement of ventriculomegaly due to either posthemorrhagic ventricular dilation or loss of periventricular white matter (3). AHW is a linear measurement in a single plane that is easy to measure and consistent for ventriculomegaly with a reliable cut-off value of 6 mm, independent of postmenstrual age (20). Likewise, although there are curves for AHW as defined by (5), moderate ventricular dilatation should be considered above 6 mm and severe ventricu-

Table I: Demographic Characteristics of Hydrocephalic Newborns

Variables (n=54)		Mean ± Standard Error	Minimum - Maximum
Gestational age (week)		37.48 ± 0.34	(27-40)
Birth weight (grams)		2985.83 ± 99.2	(900-4835)
Maternal age (years)		26.15 ± 1.03	(18-44)
		n (%)	
Sex	Male	29 (53.7)	
	Female	25 (46.3)	
Type of delivery	Caesarian Section	43 (80)	
	Natural Delivery	11 (20)	
Surgery for hydrocephalus	VPS	48 (88.9)	
	EVD	3 (5.6)	
	None	3 (5.6)	
Neural tube defect		48 (88.9)	
Consanguineous marriage		12 (22.2)	
Mortality		3 (5.5)	

***VPS:** Ventriculoperitoneal shunt, **EVD:** External ventricular drain.*

Table II: Comparison of Measurements with TFUS and Cranial MRI (Mean ± Standart Error)

Measurements	TFUS	MRI	t-test	p-value
Evans index	0.43 ± 0.007	0.42 ± 0.008	0.981	0.329
Frontooccipital horn ratio	0.48 ± 0.01	0.48 ± 0.01	-0.087	0.931
Ventricular index- L (mm)	16.77 ± 0.8	16.14 ± 0.74	0.57	0.56
Ventricular index- R (mm)	16.11 ± 0.72	16.95 ± 0.81	-0.77	0.44
Anterior horn width- L (mm)	13.45 ± 0.64	13.63 ± 0.68	-0.185	0.85
Anterior horn width- R (mm)	13.23 ± 0.7	13.29 ± 0.73	-0.058	0.95
Thalamooccipital distance- L (mm)	36.23 ± 1.0	37.54 ± 0.99	-0.925	0.35
Thalamooccipital distance- R (mm)	37.81 ± 1.2	38.18 ± 1.3	-0.205	0.83
Corpus callosum length (mm)	45.09 ± 0.66	44.28 ± 0.71	0.83	0.406
Callosal angle (°)	81.45 ± 2.03	80.77 ± 1.7	0.256	0.79

***TFUS:** Transfontanel ultrasonography, **MRI:** Magnetic resonance imaging.*

lar dilatation above 10 mm (6). Similarly, while curves exist for TOD, approximately 25 mm is generally accepted as the upper standard limit (5). Treatment approaches for posthemorrhagic hydrocephalus according to baby age in weeks have recently been reported as protocols based on these measurements. The fact that these VI, AHW, and TOD measurements can be measured with both MRI and TFUS shows the importance of USG in the treatment approach and follow-up of the patient over the weeks (9). Left-right ventricular asymmetry was noted both at birth and at term-equivalent age. The absolute differences from side to side exceeded 3 mm for VI and AHW and 7 mm for TOD. Male newborns had a moderately larger ventricle size than female newborns (3). AHW is a reliable ultrasound measure of ventricular enlargement that strongly correlates with intracranial pressure measured noninvasively. This combined assessment can help in managing elevated intracranial pressure in preterm infants with posthemorrhagic hydrocephalus by guiding cerebrospinal fluid removal interventions (2).

It has been reported that shunting decisions can be made with curves created using VI, AHW, and FOHR (20). A recent study has shown that while AHW and VI only provide information

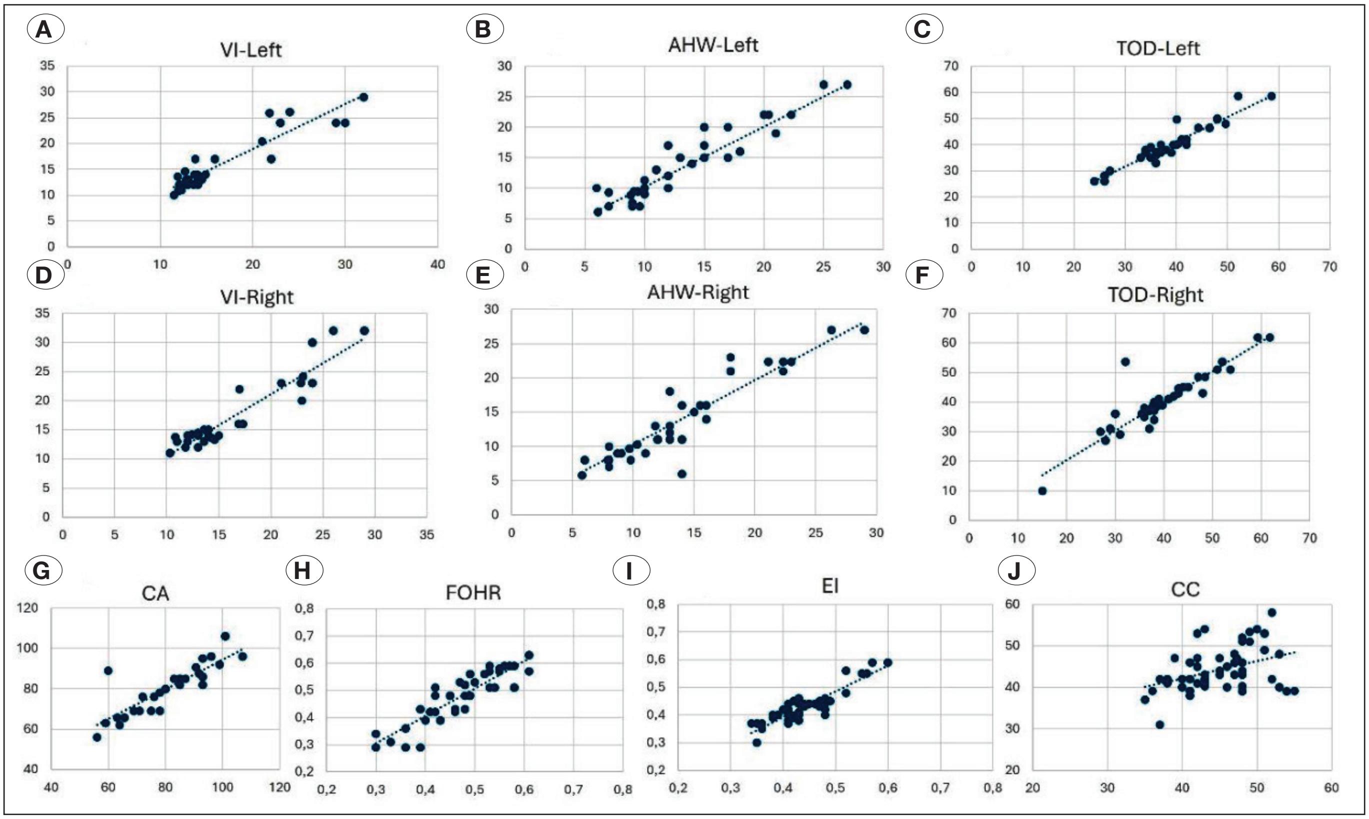

Figure 2: Correlations of TFUS and brain MRI measurements in hydrocephalic neonates. **A, D)** Bilateral ventricular index (left r=0.937, p=0.0001; right r=0.944, p=0. 0001); **B, E)** Bilateral anterior horn width (left r=0.918, p=0.0001; right r=0.908, p=0.0001); **C, F)** Bilateral thalamooccipital distance (left r=0.956, p=0.0001; right r=0.919, p=0.0001); **G)** Callosal angle (r=0.868, p=0.0001); **H)** FOHR (r=0.867, p=0.0001); **I)** Evans index (r=0.875, p=0.0001); **J)** Corpus callosum length (r=0.386, p=0.004).

about the anterior structures, FOHR enables evaluating both posterior and anterior structures together (19). FOHR was also measured on CT, MRI, and US scans in 44 normal children, including premature children aged 0–17 years, and the effect of age was evaluated by linear regression. A close correlation has been found between ventricular/brain area ratio and ventricular volume, as well as between ventricular volume and FOHR (24). The high sensitivity (100%) of TFUS in differentiating ventriculomegaly with the FOHR clinical threshold of 0.55 is one of the most prominent findings of the current study. A strong correlation has also been observed between the mean FOHR obtained from US and the mean FOHR obtained from MRI (25). It has been reported that ventricle/brain volume ratios are categorized into mild and severe hydrocephalus stages based on FOHR by volumetric MRI examinations (14). In a study among children compared with a matched age-matched control group, although the Evans index, Frontal horn index, and Bicaudate index also had statistically significant associations with ventricle size indices, FOHR recorded the most significant association with actual ventricle size (26). Infants with adverse composite outcomes had higher FOHR, and increased ventricular volumes were linked to lower Bayley cognitive and motor scores, regardless of group assignment (4).

A study involving 517 children aged 0–18 years and retrospective cranial MRI scans measured third and fourth ventricular widths and the Evans index, which has held diagnostic importance for years. The Evans index was <0.3 and demonstrated a minimal age-related decline. Normative data on ventricles in childhood could be helpful for early diagnosis of hydrocephalus or follow-up of shunt treatment. As data for both sexes and all age groups has been provided, it offers excellent advantages for objective evaluations (27). In a recent study evaluating the clinical value of classification in treating children with suprasellar arachnoid cysts, MRI/CT with Evans index and FOHR measurements were used to assess hydrocephalus follow-up after surgery (34).

In adult patients with hydrocephalus, it was found that surgical treatment and postoperative follow-up in patients with idiopathic normal pressure hydrocephalus can be determined with CA and Evans index measurements, which are preferred in cranial MRI imaging because they can be performed quickly without the need for a radiologist (17). The callosal angle—which has both diagnostic and prognostic value and has recently been frequently used in patients with normal pressure hydrocephalus—significantly increased after endoscopic third ventriculostomy in patients with childhood hydrocephalus on MRI. In the same study, the Evans index, FOHR, and lateral ventricular horn width decreased after successful surgery (30). However, pre-operative radiological markers did not correlate with the response to shunt treatment (18). To our knowledge, no study in the literature has monitored hydrocephalus by CA measurements with TFUS.

In patients with hydrocephalus, alterations in the corpus callosum might take place with or without shunting. Elevation of the corpus callosum by enlarged ventricles can cause the falx cerebri to strike the middle and posterior third of the corpus callosum in the midline, causing notch-like deformities (29). The mechanism is considered mechanical ischemia, and an animal model has demonstrated a reduction in capillary number (33). One study observed that with enlargement of the lateral ventricles, the corpus callosum is elevated mainly in its body and—to a lesser degree—in length. It also suggests that the corpus callosum might resist the deterioration in hydrocephalus to some extent, due to its plasticity (15).

The position of the head might cause differences between the ventricles. On the other hand, it is necessary to visualize some critical anatomical structures to perform the planned measurements. Measurements could not be performed for cases with hydranencephaly, where these structures could not be seen.

CONCLUSION

In infants with hydrocephalus and anterior fontanelle patency, various measurements performed with TFUS by experienced physicians are highly effective. For neurosurgeons, among radiologic examinations for ventriculoperitoneal shunt indication, TFUS has considerable advantages over cranial CT and MRI given that it has no radiation risk. Moreover, it can be performed at the bedside effectively and rapidly. The radiation risk and cost of CT—which are particularly important in children—the fact that MRI cannot be performed in every center, the need for sedation and intubation for MRI in the neonatal period, and its cost make TFUS more critical. Our study emphasizes that TFUS—which achieves better results in experienced hands—should be widespread and an excellent alternative to unnecessary and repeated imaging methods.

Declarations

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AUTHORSHIP CONTRIBUTION

Study conception and design: NA, OT, HA

Data collection: NA, HA, OT

Analysis and interpretation of results: SK, AAt, AAy, NA

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Critical revision of the article: OT, HA

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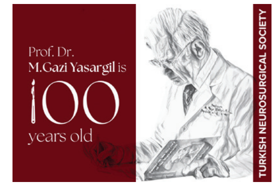

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Embryotoxic Effects of Sunset Yellow in Congenital Neural Tube Defect Formation in Early-Stage Chick Embryos: A Histopathological Study

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ABSTRACT

AIM: To investigate the embryotoxic effects of Sunset Yellow (SY) exposure on neural tube development in an experimental model of chicken embryos.

MATERIAL and METHODS: Sixty fertilized special pathogen-free (SPF) Leghorn genus chick embryos were used. Three experimental groups were determined, comprising the control group (0.1 ml saline), daily intake dose [2.5 mg/kg Sunset Yellow FCF E110 (SY)], and high dose [5 mg/kg SY] groups (n=20). SPF status was determined on day 0 when eggs were placed in the incubator. Eggs were injected at the 30th hour of incubation, and incubated for the following 72 hours.

RESULTS: Upon light microscope examination, in the control group the surface ectoderm was intact, the neural tube was closed, and the neuroepithelium, basement membrane surrounding the neuroepithelium, notochord, and somites were all normal. In the daily intake dose SY group, four examples of neural tube defects (NTDs) were observed. Six instances of NTDs were observed in the high-dose SY group. The high-dose group had a statistically significant increase in the number of embryos with NTDs compared to other groups (p=0.0004).

CONCLUSION: These results suggest that SY consumption can cause irregular neural tube development. SY should not be ingested in high doses for extended periods of time, should be regulated even when used as an additive, and should be avoided during pregnancy. Further studies are needed in a wider range of dose groups to observe the embryotoxic effects of SY on neuronal development.

KEYWORDS: Food coloring agents, Spinal dysraphism, Neural tube defects, Sunset yellow, Chick embryo

ABBREVIATIONS: FA: Food additives, **FAO:** Food and Agriculture Organization of the United Nations, **H&E:** Hematoxylin and eosin, **HH:** Hamburger-Hamilton, **NaB:** Sodium benzoate, **NT:** Neural tube, **NTD:** Neural tube defect, **SPF:** Special pathogen-free, **SY:** Sunset Yellow FCF E110, **WHO:** World Health Organization

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INTRODUCTION

The use of various substances as food additives (FA) is common to color products, prevent their deterioration, and boost their nutritional value (29). Food dyes are used to enhance the appeal of foods and beverages by altering their appearance and aroma. With the increased consumption of certain products, an individual's exposure to processed food dyes increases daily. Certain additives used in the food industry, such as Sunset Yellow FCF E110 (SY), tartrazine, azorubin, and ponceau-4R, are known to have negative effects on human health (2,3). SY is a synthetic azo dye used in the food, pharmaceutical, and cosmetic industries. It is widely utilized in the food industry for sweet and savory products, frozen foods, alcoholic and non-alcoholic beverages, cosmetics, and pharmaceutical food supplements (11,22). Some azo dyes have been linked to allergic reactions such as contact dermatitis, angioneurotic edema, asthma, rhinitis, anaphylaxis, and immunosuppression. In sensitive individuals, this can result in immune responses such as allergies and hypersensitivity. SY has been reported to cause bronchial contractions in patients with chronic asthma, food intolerance and behavioral hyperactivity disorder in children, cancer, birth defects, genetic disorders, and brain damage (2,7,22).

Neural tube defects (NTDs), caused by aberrant tissue movement during neural crest cell migration and neurulation, are the second most common birth defect after congenital cardiac disease and represent a significant public health issue from both a sociological and economic perspective (9,10). The first three weeks of pregnancy are essential for the embryo's neural development. Many chemicals can be transmitted from mother to infant through the placenta. Exposure to synthetic chemicals, even in low amounts, can have a negative impact on embryonic development and, by extension, the newborn. The neural development of a human embryo during its first month is similar to that of a chicken embryo during its first seventy-two hours. Moreover, the low cost and replicability of the chicken embryo experimental model are important advantages for neural development studies (20,21,23). While the in ovo toxic effects of various compounds on neural tube development have been studied (8,12,24,27), an evaluation of the link between SY and NTDs in a chicken embryo model has not been reported (12,21).

In this study, we aimed to investigate the histopathological and embryotoxic effects of SY exposure on neural tube development in a chicken embryo model.

MATERIAL and METHODS

Experimental Embryos and Study Design

Sixty, 65 ± 2 g, Leghorn genus fertilized special pathogen-free (SPF) chicken embryos were used from eggs obtained from The Ministry of Agriculture and Rural Affairs, Bornova Veterinary Control Institute, Izmir, Turkey. Animal experiments in this study were performed with ethical approval from the Local Animal Experiments Ethics Council of Marmara University (approval number and date: 83.2021mar, 09/11/2021). Sample numbers and doses were determined according to data obtained from previous studies and considering the 0–2.5 mg/kg dose recommended by the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) as a daily allowable maximum. The SPF eggs were randomly divided into three groups of twenty eggs each. Groups were determined as control (0.1 ml saline), daily intake dose (2.5 mg/kg SY), and high dose (5 mg/kg SY) (2,7,8,28). Due to potential losses from physical damage and infertile eggs during the experiment, each group utilized forty extra SPF eggs. Fertilized SPF eggs were placed in a CT60S incubator (Cimuka, Turkey) with their pointed edges pointing downward (Figure 1). The day on which the eggs were placed in the incubator was recorded as day 0. The eggs were kept at 37.2 ± 0.1°C and 60–70% humidity for 30 hours in an incubation system with an automated air cycle feature and were rotated every two hours to vary their positions. Stage 9 of the Hamburger-Hamilton (HH) staging series (HH 9; 30th hour of incubation) coincides with the development of the neural plate (24).

Preparation of Sunset Yellow FCF E110

Pure SY (Cas No. 2783-94-0; 90% purity, IFC, Turkey) in powdered form was dissolved in 0.9% isotonic sodium chloride. A main stock was prepared for each group. Powdered SY was weighed at 12.8 mg for a daily dose and 26.4 mg for a high dose. The main stocks were prepared using 8 ml of physiological serum (Polifarma, Turkey) in 15 ml Falcon containers. The main stocks were wrapped in foil and stored in the refrigerator at 4°C for later use. The solutions were vortexed (BioCote, United Kingdom) before application. A 0.22 μm filter (Minisart nonpyrogenic hydrophilic filter unit, USA) was used to prepare solutions for use.

In Ovo Administration, Evaluation and Sample Collection

At HH 9, infertile and fertile eggs were separated according to their injection status. Fertilized SPF eggs were removed from the incubator and sterilized with 70% ethyl alcohol. To expose the ring-shaped embryonic discs, apertures of 0.5–1 cm in diameter were cut into the eggshell membranes. This process was performed using a new technique on all eggs used in the experiment (8,12,24). The SY solution was carefully injected subblastodermically into the chicken embryonic disc using an insulin injector attached to a 26 G 1/2 needle. Since excessive injection could damage the embryonic disk, the amount of substance did not exceed 0.1 ml. The openings in the eggs were then covered with a band, and the eggs placed in the incubator for 72 hours (Figures 2A–C). At the end of the incubation period, the SPF eggs were removed from the incubator, the egg windows were expanded, and the egg yolk was placed in a glass container with serum physiologic water. Afterward, the embryonic membranes and vitellin membranes were cut with surgical scissors over the yolk sac (Figures 3A–D). Both the vitellin membrane and the membrane-attached blastoderm were dissected from the yolk sac. The samples were then placed in an embryo container with 10% neutral buffered formalin for histological analysis.

Histopathological Analysis

Embryos from all groups were fixed in a 10% neutral buffered formalin solution for 72 hours at ambient temperature for light

Figure 1: The arrangement of special pathogen-free (SPF) eggs within the incubator. The pointed edges of SPF eggs project downwards.

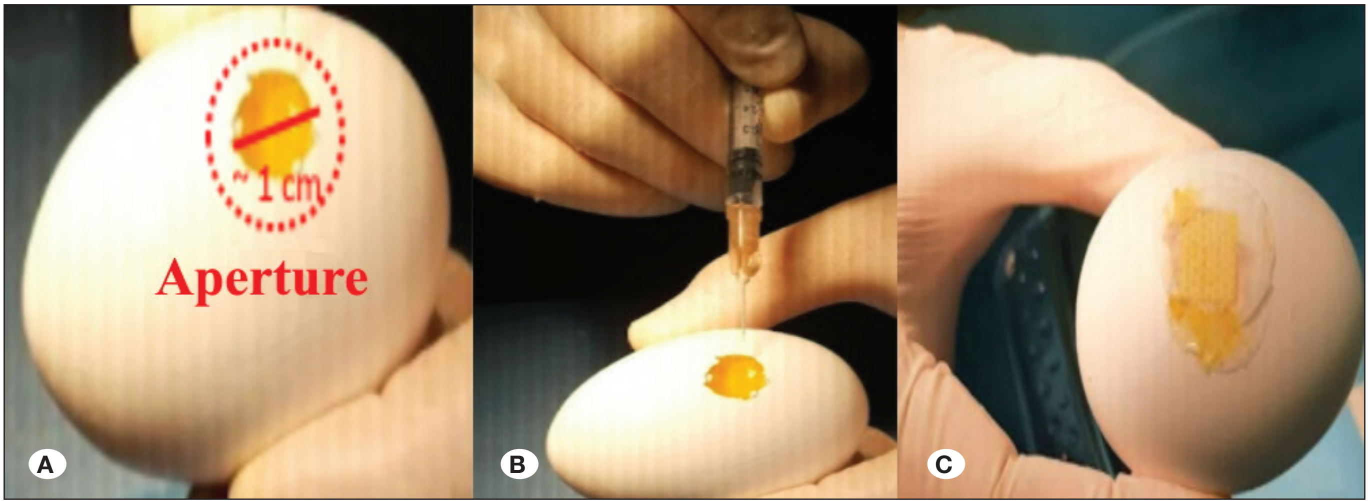

Figure 2: Demonstration of the injection technique in chicken embryos. **A)** The aperture opens to a diameter of about 0.5–1 cm. **B)** Subblastomeric injection is performed through a small aperture. **C)** The openings in the special pathogen-free eggs are covered with point injection bands.

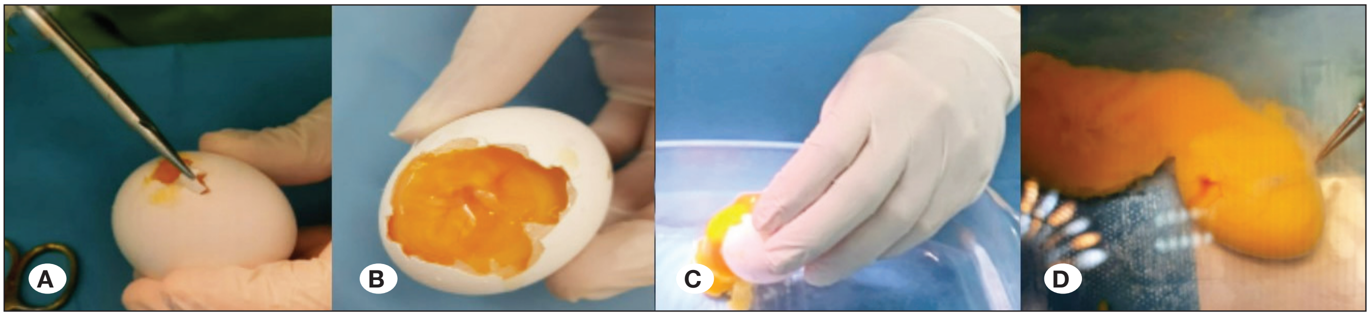

Figure 3: Chicken embryo collection from special pathogen-free eggs**. A)** Picture demonstrating the expansion of the previously opened aperture. **B)** Early chicken embryo from the expanded window at 72 hours. **C)** The placement of the chicken embryo in the glass container with serum physiological water. **D)** Cutting the embryonic membrane, vitellin membrane, and yolk sac using surgical scissors.

microscopic examination. The embryos were dehydrated using an increasing series of ethyl alcohol (70%, 80%, 90%, and 96%). Samples were then cleared with xylene and embedded in paraffin blocks. The blocks were cut into 4 μm thick sections with a rotary microtome (Medite M530, Germany), placed on the glass sides, and deparaffinized in an incubator. The sections were stained with hematoxylin and eosin (H&E) for histomorphological evaluation and covered with mounting medium (Entellan). Morphological changes in the neural tube, notochord, and neuroepithelium were examined and photographed under a computer-equipped CCD camera (Olympus DP 72, Tokyo, Japan) and attached photo-light microscope (Olympus BX51, Tokyo, Japan).

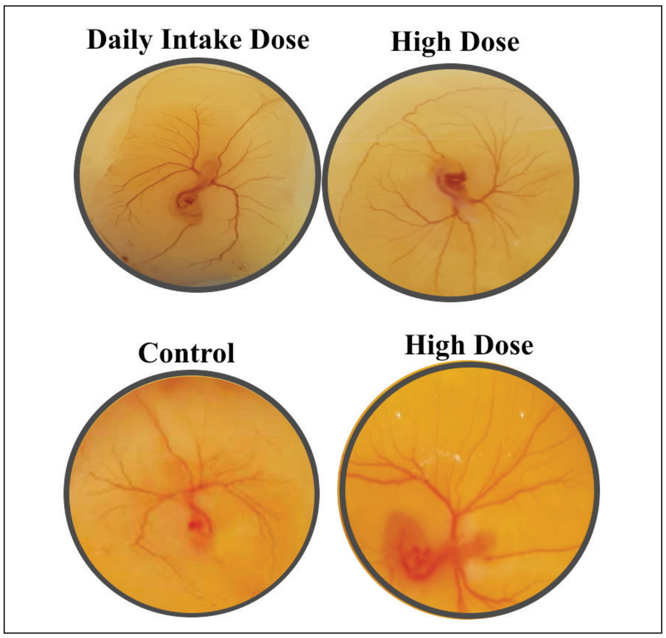

Figure 4: Macroscopic images of the samples after 72 hours of incubation**.** The embryonic disc and vascular structure of the yolk sac are more advanced in the control group, but the embryos in the daily and high-dose groups have weaker vascular structures.

Statistical Analysis

Data were analyzed with the chi-squared test using Graphpad Prism 9. Probability values of $p<0.05$ were considered statistically significant. The independent Student's t-test was used to determine whether changes were random in comparisons between the experimental groups.

RESULTS

Macroscopic Analysis

Following the completion of the injection procedures for the experimental groups, the number of dead and viable embryos was recorded in the 72nd hour of incubation. In the control group, 90% of embryos were alive and 10% were dead; in the daily intake group, 89% of embryos were alive and 11% were dead; and in the high dose group, 81% of embryos were alive and 19% were dead. The ratio of dead samples in the was significantly higher in the groups administered SY than in the control group, and was higher in the high-dose compared to the daily dose group (p=0.006). Compared to the SY groups, the vascular structure of the embryonic disc and yolk sac was observed to be more prominent in the control group (Figure 4). At the 72nd hour, all experimental groups were found to be compatible with HH 19.

Histopathological Analysis

The neural tube and notochord were observed in the transverse and sagittal planes in all groups. In the control group, the surface ectoderm was intact, the neural tube was closed, and the notochord, somites, neuroepithelium, and basal membrane surrounding the neuroepithelium were normal (Figure 5A). NTDs were detected in four embryos in the daily dose SY group (Figure 5B). In one additional sample from the same group, the neural tube was intact, but the width of the lumen was remarkable. In another embryo, neuroepithelial tissue was observed to have thickened, but the neural tube and notochord were intact. In addition, the caudal region of the neural tube was enlarged, and the lumen was not observable. In other embryos from the same group, the neural tube

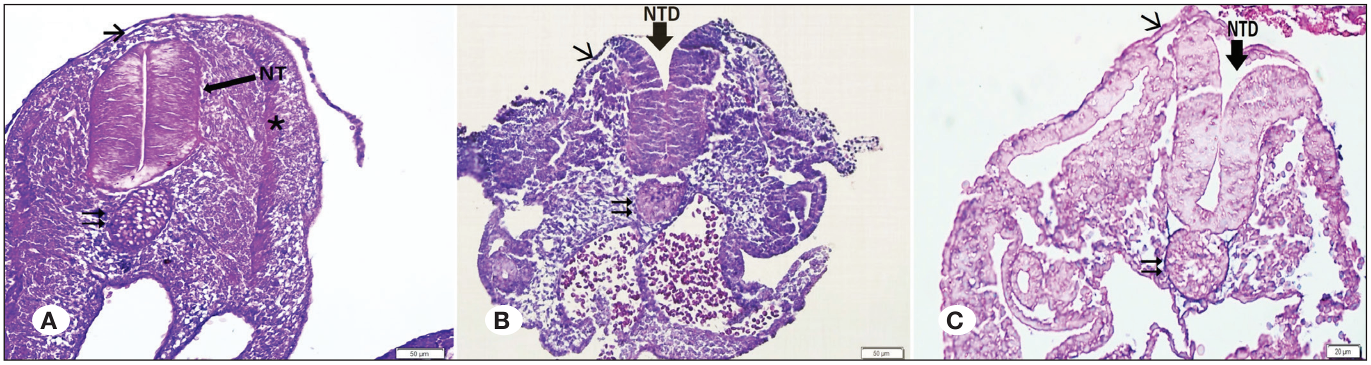

Figure 5: Hematoxylin and eosin-stained light micrographs showing the neural tube, notochord, and surface ectoderm in the transverse plane in all groups. **A)** Neural tube (NT), notochord (⇉), somite (*), and surface ectoderm (→) are intact in the control group (Scale bar: 50 μm). **B)** Neural tube defect (NTD) as observed in the 2.5 mg/kg Sunset Yellow FCF E110 (SY) group. **C)** NTD as observed in the 5 mg/kg SY group (Scale bars: B: 50 μm, C: 20 μm).

structure was similar to that of the control group. In the high-dose SY group, NTD was observed in six embryos (Figure 5C). In addition to NTD cases, extensive vacuoles were observed in the notochord of another embryo, and abnormal neural tube boundaries and neuroepithelial tissue were observed in a further sample. No evidence of NTD was observed in the remaining embryos of this group. 75% of embryos developed normally in the daily SY dose group, with 25% developing with NTD. In the high-dose SY group, 45% of embryos developed healthy, while 55% of embryos developed NTDs. As expected, a higher proportion of embryos with NTD was observed in the high-dose group compared to the other groups. The chi-squared test for independence yielded a p-value of 0.0004. The experimental groups were compared using the Student's t-test, indicating a statistically significant ($p<0.05$) relationship between the variables (Figures 6A–C) (Table I).

DISCUSSION

In humans, the development of the neural tube coincides with the third week of gestation; this period is particularly sensitive to external factors (3,21). Determining the effects of short- and long-term consumption of FA and adjusting the dosages of these substances accordingly is crucial (15,17,18). FA are commonly used chemicals present in our daily lives to extend the shelf life of foods, satisfy nutritional requirements, and improve the flavor, appearance, and quality of nutrients (6,16). SY is a synthetic azo dye used in numerous industries, particularly the food industry (15,22,28).

The first 72 hours of neural and spinal development in the chicken embryo are very similar to the first month of the human embryo (5,8,23). The minimal cost and repeatability of the chicken embryo experimental model are significant benefits. The use of numerous chicken embryos provides a statistical advantage for the evaluation of toxicity when compared with mammalian species studies. For this reason, we utilized chicken embryos in our study.

It has previously been reported that no adverse effects are observed when food coloring limits are not exceeded. However, in certain developing countries, the average consumption of SY exceeds the permissible daily ingestion

Table I: Dispersion of Neural Tube Defect Development and Statistical Evaluation in Chicken Embryos in All Groups

Groups	Sunset Yellow FCF E110 (SY)		p-value ($p<0.05$)
	Intact	NTD	
Control Group, (0.1 ml saline) (n=20)	20	0	**0.0004**[1]
Daily Intake Dose Group (2.5 mg/kg SY) (n=20)	16	4	Control vs Daily Intake dose groups **0.002**[2]
High Dose Group (5 mg/kg SY) (n=20)	14	6	Control vs High dose groups **0.0002**[2]

[1]Chi-square test; [2]Student's t-test.

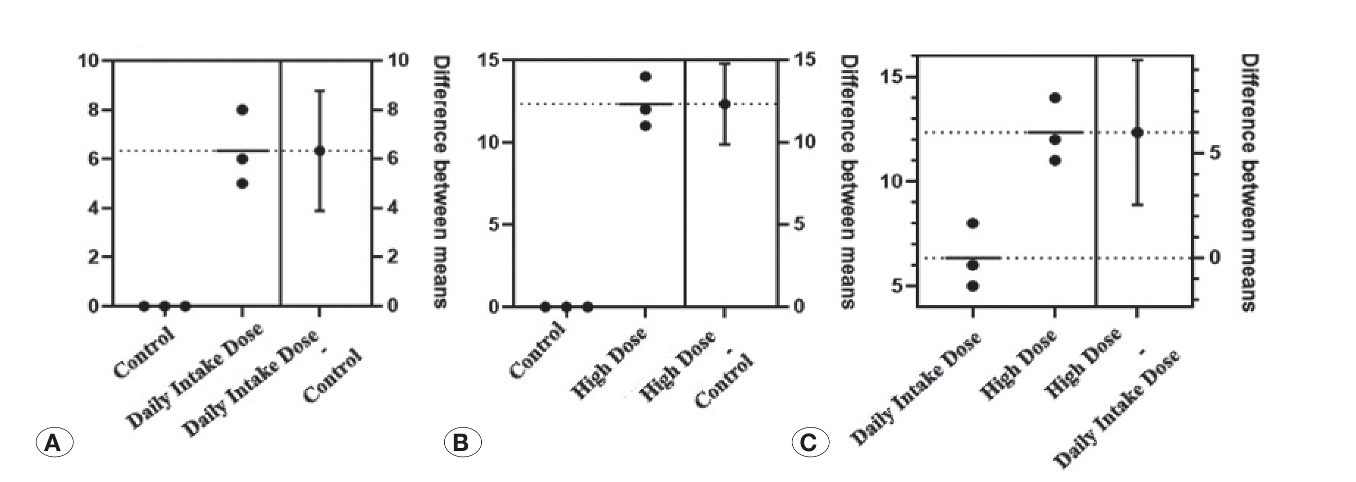

Figure 6: Graphs showing student t-test results of experimental groups. **A)** Comparison between the control and daily intake dose groups (p=0.002); **B)** Comparison between the control and high dose groups (p=0.0002); **C)** Comparison between the daily and high dose groups (p=0.0086).

value by 88%, whereas in Europe and the United States, this value varies between <0.2 and 12% (6,16,25,29). In nearly all relevant age groups, the consumption of food dyes exceeds the recommended daily allowance. Considering the body mass of children, this calculated value is disproportionately high. This is a factor that should raise alarms and concerns in terms of public health in many developing countries. Amplifying these concerns, we found NTDs in every group to which SY was applied in our study.

Previous studies have suggested that consuming SY in food can result in various adverse effects. However, it is unknown whether this was a result of the toxic effects of SY or a dose-related effect. The findings of this study contribute to the overall understanding of these circumstances. Changes in developmental rate, morphological abnormalities, other induced deformities, and altered survival/mortality rates of embryos in experimental groups have been previously observed (1,2,25,28). In one study, pregnant rats were exposed to food dyes including SY; learning and memory difficulties were observed in the newborn rats, reportedly due to changes in expression of nicotinic acetylcholine receptors (1,2). In our study, the majority of embryonic deaths during the incubation period occurred in the SY groups, particularly the high-dose group. During microscopic examinations of high-dose group embryos, neural tube fragility was prominent, its boundaries were often abnormal, and the neuroectoderm was generally thin. These findings suggest that food dye affected the development of the embryos.

SY has also been associated with certain behavioral changes, with reports of hyperactive behavior disorder in children, certain allergies, and side effects caused by effects on the immune system (18). Sweeney et al. demonstrated that azo dyes, including SY, could directly initiate oxidative genotoxicity (26). In a study with chicken embryos, necrosis developed in the hepatocyte and renal tubule cells of all SY-treated groups as a result of structural alterations to organelles. Histopathological alterations, such as hydropic degeneration and renal tubules in hepatocytes, indicated that intracellular edema developed as a consequence of toxicity or immune response. It was concluded that SY had a significant cytotoxic effect on cells (8,22,25). In our study, the 2.5 mg/kg daily dose SY group exhibited vacuolization at the rostral end of the caudal neural tube region. In addition, the neuroepithelial tissue was intertwined, the neural tube exhibited hydropic alterations, and the lumen was inaccessible due to edema. In the 5 mg/kg SY group, the notochord was severely vacuolated and adhered to the neural tube, and the cell nuclei were heterochromatic. In addition, neural tube boundaries were irregular, and neuroepithelial tissue was abnormal. Ali et al. observed that in vivo combinations of SY and sodium benzoate (NaB) in rats caused structural abnormalities associated with genotoxicity through DNA damage and abnormal serum protein distribution (1). McCann et al. suggested that dietary food colorings such as SY, food preservatives such as sodium benzoate, or combinations of the two, caused increased hyperactivity in 3-year-old and 8/9-year-old children (18). Studies have shown that tartrazine administration in rats causes neuronal loss, vacuolar degeneration, and several other histopathological changes in the cellular layers of both the cerebellar and cerebral cortex (4,13,14,19). These findings suggest that it can induce neuro-degenerative changes, chromatolysis, pyknosis, and apoptotic cell death in the rat brain. These changes were attributed to aromatic amines that increase reactive oxygen species production (17,22,26,29). In our study, in the histopathologic evaluation of both SY groups, the notochord was densely vacuolated and swollen in the caudal region of the neural tube, and the cell nuclei had a heterochromatic appearance. In addition, the neural tube borders were irregular, and abnormal neuroepithelial tissue was present. Since both food dyes belong to the azo group, they share final degradation products. Therefore, the histopathologic results of the two studies are thought to be parallel to each other.

We believe that SY may cause malformations in spinal cord development in human embryos due to its negative effects on neural tube development in chicken embryos. While the data obtained from studies using the chicken embryo model cannot be directly translated to human embryo developmental stages, they may indicate future evaluations to be made in this field.

CONCLUSION

In conclusion, although SY was applied at dosages within the upper limits of the daily recommended intake dose, we have demonstrated its degenerative effects on the neural tube development of chicken embryos. In our study, we detected statistically significant incidence of NTD in all groups in which SY was administered. Based on these data, the reference values for food dyes could be reevaluated. We believe that SY should not be ingested in high doses for an extended period of time, and its use should be controlled, particularly during pregnancy. Further studies are needed to investigate the NTD-inducing potential of SY in chicken embryos through specific molecular pathways, and using a broader range of groups and doses.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: STE, FT, DA
Data collection: FT, DSA
Analysis and interpretation of results: FT, DA, DSA
Draft manuscript preparation: FT, EA
Critical revision of the article: FT, STE, EA
Other (study supervision, fundings, materials, etc...): FT, STE, EA
All authors (FT, DSA, DA, EA, STE) reviewed the results and approved the final version of the manuscript.

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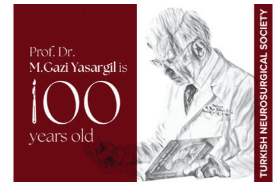

Original Investigation

Pediatrics

Incidence and Factors of Tethering After Sectioning the Filum Terminale

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ABSTRACT

AIM: To assess the incidence of retethering in patients who underwent surgery for tethered cord in our clinic.

MATERIAL and METHODS: We included patients who underwent surgical intervention for tethered cord in our clinic between 2010 and 2020, and were subsequently diagnosed with retethering during follow-up. Only those with available postoperative clinical follow-up data were included. The study analyzed the timing of surgery, gender, presenting symptoms, intraoperative findings, postoperative outcomes—including complications—and follow-up duration.

RESULTS: Over a 10-year period, 59 patients underwent surgery for tethered cord. Among them, 11 patients required reoperation for retethering at a median age of 5 years. The median interval between the initial and retethering surgeries was 47.6±43.20 months. Two patients were asymptomatic at the time of their initial surgery. Among the 11 patients with retethering, 3 (27.2%) presented with bladder or bowel dysfunction, 4 (36.3%) with neuro-orthopedic symptoms, and 4 (36.3%) with pain. Two patients experienced a second episode of retethering and required a third surgery, which occurred approximately 2 years after the second procedure.

CONCLUSION: The risk of retethering should be carefully monitored in patients with tethered cord, particularly during growth periods.

KEYWORDS: Tethered cord, Retethering, Filum terminale syndrome

ABBREVIATIONS: LSL: Lumbosacral lipomas

INTRODUCTION

Tethered cord syndrome occurs when the spinal cord fails to develop in coordination with the spinal column, leading to tension. This condition can result in bladder or bowel dysfunction, gait disturbances, orthopedic abnormalities, sensory deficits, and scoliosis (9,19,22). To prevent these complications, it is recommended to surgically release the thickened or fatty filum terminale responsible for the tension, even in asymptomatic children. However, early surgical intervention carries a risk of subsequent retethering. Therefore, long-term follow-up is necessary until the completion of growth.

The prevalence of retethered cord and the optimal follow-up strategy for patients at risk of retethering remain subjects of debate. This study aims to evaluate the incidence of retethering in patients who underwent surgery for tethered cord in our clinic.

MATERIAL and METHODS

This study was approved by the Clinical Research Ethics Board of Istanbul Yeni Yüzyıl University (2025/03-1503). A retrospective review was conducted on the medical records of 59 children who underwent surgery for a thickened filum

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terminale between 2010 and 2020 at Bursa Uludag University and Medicabil Hospital. Patients who required reoperation due to tethering were also examined. Those with radiological evidence of a tethered cord but no clinical findings were excluded. Patient records were analyzed for age at the time of surgery, gender, presenting symptoms, intraoperative findings, postoperative outcomes—including complications—and follow-up duration. For patients who experienced one or more episodes of tethering, the age at tethering, time to retethering, presenting symptoms, type of dural repair, and surgical outcomes were documented.

Statistical Analysis

The Shapiro–Wilk test was used to assess whether age and follow-up duration followed a normal distribution across patient groups. Since the variables did not exhibit a normal distribution, they were presented as median, minimum, and maximum values. Categorical variables were reported as frequencies and corresponding percentages. The Mann–Whitney U test was used to compare continuous variables between groups, while Fisher's exact test and the Fisher–Freeman–Halton exact test were applied for intergroup comparisons of categorical variables. Logistic regression analysis was conducted to identify factors associated with recurrence in patients with spinal dysraphism. All statistical analyses were performed using SPSS (IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY, IBM Corp.), with a significance threshold of $\alpha = 5\%$.

RESULTS

Over a 10-year period, 59 patients underwent surgery for tethered cord. Gender distribution did not significantly differ between the retethered and non-tethered groups (p=0.187), whereas patient age showed a significant difference (p=0.039). The median age at surgery was 14 months in the retethered group and 9 months in the non-tethered group. The average diameter of the filum terminales in retethering group was 2.35 ± 0.6 mm. Although of the 11 patients who underwent reoperation, 6 had lipomyelomeningocele at the initial operation, 4 had fatty filum terminale and one had dermoid cyst, no significant differences were observed between the groups regarding pathology and detailed pathology findings (p=0.055 and p=0.185, respectively) (Figure 1). Similarly, neurological examination results, presenting symptoms, and postoperative complication rates did not show significant differences between groups (p>0.05). However, a significant difference was found in follow-up duration (p<0.001), with a longer follow-up period in the retethered group. The median follow-up duration was 72 months in the retethered group and 24 months in the non-tethered group (Table I).

A total of 11 patients underwent surgery for retethering at a median age of 5 years. The median interval between the initial surgery and the retethering operation was 47.6±43.20 months. Two patients were asymptomatic at the time of their first surgery. Among the 11 patients who developed retether-

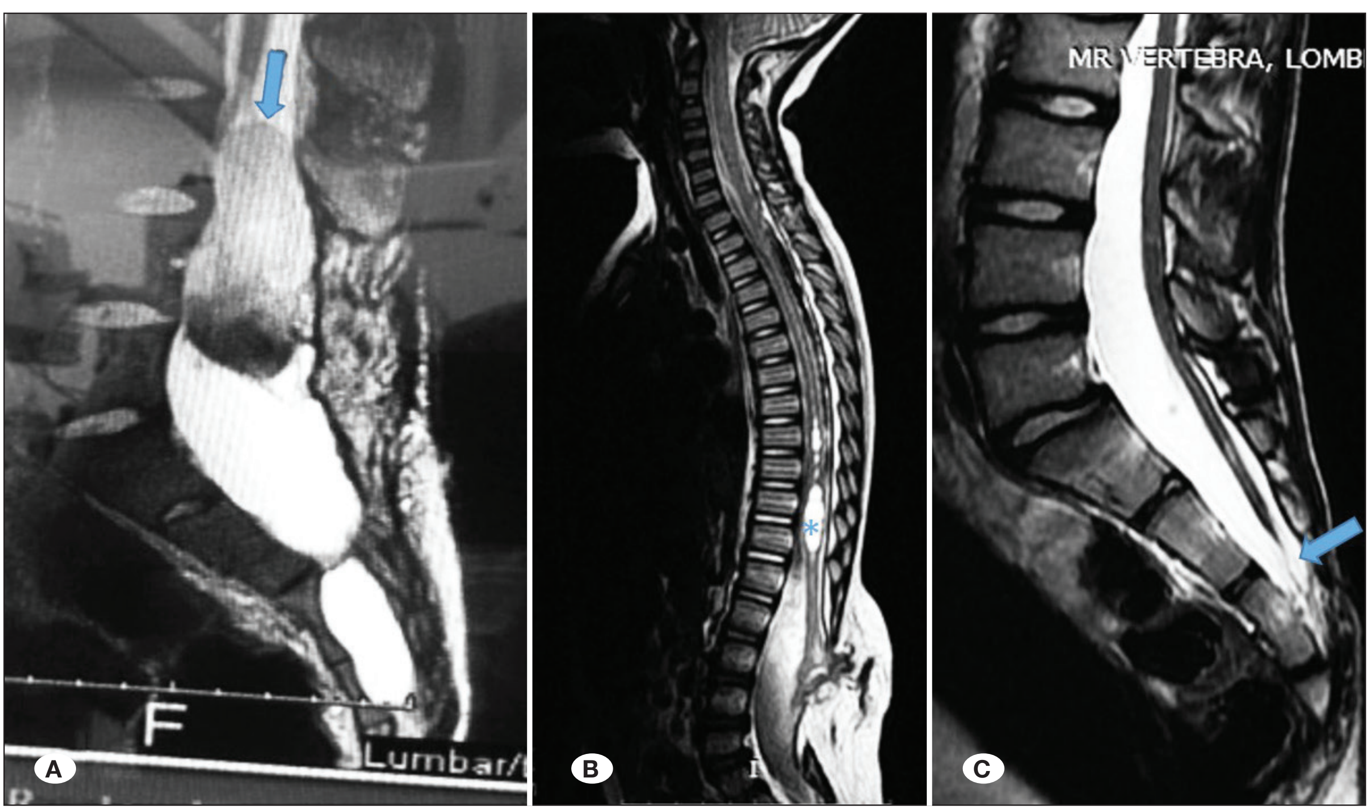

Figure 1: A) T2-weighted images showes an intradural dermoid cyst at L3-4 levels and tethered cord sticking to cyst (arrow); **B)** T1-weighted sagittal MRI revealed an appearance compatible with tethered spinal cord and syringomyelia (asterisk) secondary to lipomyelomeningocele. **C)** In the T2-weighted sagittal MRI section, fatty filum terminale ending at the S3 level is observed (arrow)

Table I: Demographic and Clinical Characteristics of Spinal Dysraphism Patients with and without Retethering

	Retethered (n=11)	Non-tethered (n=48)	p-value
Gender, n (%)			
Female	4 (36.40)	29 (60.40)	0.187[a]
Male	7 (63.60)	19 (39.60)	
Age (years), n (%)	14 (5–25)	9 (1–25)	**0.039[b]**
Pathology			
MMC	1 (9.10)	2 (4.20)	0.055[c]
MC	3 (27.30)	3 (6.30)	
Tethered	7 (63.60)	43 (89.60)	
Detailed pathology, n (%)			
Lipoma	6 (54.50)	34 (70.80)	0.185[c]
Fatty filum	1 (9.10)	8 (16.70)	
Dermoid-epidermoid	4 (36.40)	6 (12.50)	
Neurological examination, n (%)			
No deficit	7 (63.60)	30 (62.50)	>0.999[a]
Deficit	4 (36.40)	18 (37.50)	
Complaint, n (%)			
Urinary and gait incontinence	3 (27.30)	7 (14.60)	0.927[c]
Paraparesis	1 (9.10)	7 (14.60)	
Scoliosis	5 (45.50)	24 (50)	
Low back pain	1 (9.10)	4 (8.30)	
Hypertrichosis in the lumbar region	1 (9.10)	4 (8.30)	
No complaint	0	2 (4.20)	
Postop complication, n (%)	3 (27.30)	4 (8.30)	0.112[a]
Follow-up (months)	72 (36–132)	24 (1–84)	**<0.001[b]**

***MMC:** Myelomeningocele, **MC:** Myeloschisis.*

ing, 3 (27.2%) presented with bladder or bowel dysfunction, 4 (36.3%) with neuro-orthopedic symptoms, and 4 (36.3%) with pain. Two patients experienced a second episode of retethering and required a third surgery, which occurred 2 years after their second operation. All dural repairs were performed with primarily; no dural graft was used. All of the patients were lumbosacral tethered cords. There were no any bony spicules in the affected segments.

To identify factors associated with recurrence in patients with spinal dysraphism, the variables listed in Table I were first analyzed using univariate logistic regression. Variables meeting the p<0.25 threshold were then included in a multivariate logistic regression model (2). Based on univariate logistic regression analysis, the factors that met this criterion were gender, age, detailed pathology, presence of postoperative complications, and follow-up duration (Table II).

The analysis indicated that the multivariate logistic regression model was a good fit for the data (Hosmer–Lemeshow test, p=0.973) and was statistically significant (p<0.001). The results showed that each additional unit increase in follow-up duration increased the risk of developing retethering in patients with tethered cord by 1.06 times. No significant effect was observed for the other variables included in the analysis.

A total of seven postoperative complications occurred across all tethered cord surgeries. No patients experienced lower extremity paresthesias or urinary incontinence. One patient developed a wound infection (1.7%), while five had cerebrospinal fluid (CSF) leakage (8.4%). A patient whose drain had been sutured was reoperated for removal of the drain. Among those with CSF leaks, two belonged to the retethered group.

Table II: Factors Linked to the Development of Tethering

	Univariate logistic regression analysis				Multivariate logistic regression analysis			
	Crude OR	95% CI		p	Adj. OR	95% CI		p
		Lower	Upper			Lower	Upper	
Gender (female)								
Female (Reference)	1	-	-	**-**	1	-	-	**-**
Male	2.67	0.69	10.39	**0.156**	3.54	0.54	23.25	0.188
Age (months)	1.14	1.02	1.28	**0.022**	1.03	0.88	1.21	0.685
Detailed pathology				**0.187**				0.782
Lipoma (Reference)	1	-	-	**-**	1	-	-	**-**
Fatty filum	0.71	0.07	6.74	**0.764**	0.53	0.01	>100	0.844
Dermoid-epidermoid	3.78	0.82	17.52	**0.090**	2.18	0.22	22.06	0.509
Neurological Examination								
Normal (Reference)	1	-	-	**-**	1	-	-	**-**
Deficit	0.95	0.24	3.71	0.944				
Postop complication								
No (Reference)	1	-	-	**-**	1	-	-	-
Yes	4.13	0.77	22.04	**0.097**	0.45	0.02	9.30	0.445
Complaint				0.961				
Urinary and gait incontinence (Reference)	1	-	-	**-**	1	-	-	**-**
Paraparesis	0.33	0.03	4.04	0.388	-	-	-	-
Scoliosis	0.49	0.09	2.56	0.395	-	-	-	-
Low back pain	0.58	0.04	7.66	0.682	-	-	-	-
Hypertrichosis in the lumbar region	0.58	0.04	7.66	0.682	-	-	-	-
No complaint	0.01	0.01	0.01	0.999	-	-	-	-
Follow-up duration	1.06	1.02	1.09	0.001	1.06	1.02	1.10	**0.005**

DISCUSSION

There are limited studies in the literature that investigate the long-term outcomes of tethered cord surgery. Both the management and treatment of retethering remain subjects of debate, and available research on the topic is scarce. In this study, we observed that the likelihood of detecting retethering increases with prolonged follow-up in patients who underwent surgery for tethered cord.

The reported incidence of retethering ranges from 2.7% to 15% (4,11). Some studies indicate that this rate rises as the follow-up period extends (14,17). A meta-analysis by Goodrich et al., which reviewed 608 patients from 13 studies, identified a significant positive linear correlation between follow-up duration and the incidence of retethering, showing an annual increase of 3.2%. No cases of retethering were detected within the first 2.1 years, whereas 57% of patients exhibited retethering during an 18-year follow-up period (5). In our series, the retethering rate was 18.6%. This higher incidence compared to previous studies may be attributed to an extended follow-up period or more rigorous patient monitoring made possible by advancements in technology.

Some studies have suggested that age is a risk factor for retethering. Bowman et al. reported that the tethering rate decreased from 7.4% at age 15 to 1.8% at age 20, though this may also be related to the cessation of spinal growth in their patient population (3). Retethering is generally observed to occur within 5 years after the initial surgery (12). In our study, we also followed our patients until they were transferred to the adult group at the age of 16, and the follow-up period was longer in the retethered group.

The retethering rate is reported to be lower in cases of filar lipomas, and higher retethering rates have been noted in lumbosacral lipomas (LSLs) compared to myelomeningoceles (MMCs) (1). Lee et al. found that symptomatic retethering was more commonly observed in lower-level MMCs (8). In cases of complex lesions, Samuels et al. reported a lower retethering rate in patients who underwent duraplasty compared to those who had primary closure (15), while Mehta et al. found no significant difference (10). Pang et al. emphasized the importance of the cord/sac ratio as a prognostic factor in their multivariate analysis (13). In our series, we did not find a significant relationship between the underlying pathology and retethering, which differs from the findings in the literature.

When retethering occurs, patients typically present with neurological symptoms, with urological and motor symptoms being more common than others (10,18). Abnormal urodynamic studies can be a sign of retethering. Tarcan et al. reported urological deterioration in 32% of patients during follow-up (21). In our series, neuro-osteopathic symptoms were the most frequent complaint in the retethering group. Urodynamic testing is performed preoperatively and during annual follow-ups in our series.

Retethering is diagnosed by excluding other potential causes, rather than being identified through radiological imaging. Prone magnetic resonance imaging and spinal sonography are recommended for diagnosing retethering (16,20). However, neurosurgeons should be cautious during follow-up, as the dentate ligaments prevent the filum terminale from moving upward after surgery. Close monitoring of patients with clinical assessments and evoked potentials, along with radiological evaluation based on symptoms, is necessary. In particular, the width of the P37 response is a useful parameter for detecting tethering but we could not get this data in our hospital.

Spinal column shortening is a surgical approach used for recurrent tethering, but we did not perform this procedure on any of our patients.

Complete untethering has been achieved in 93%–100% of tethered cord patients (6). All operetions were performed with neuromonitorisation. This high success rate may be due to surgeons opting for more aggressive surgical interventions in symptomatic patients.

The results of retethered cord surgery are generally reported to be favorable, with 26%–93% of patients showing improvement or stabilization of symptoms (7,14). In our series, in line with the literature, no deterioration was noted in patients who underwent surgery for retethering. Nine patients experienced a reduction in symptoms, and two patients' symptoms remained stable.

A key limitation of this study is that we did not assess the level of retethering, and radiologically confirmed retethered cases were excluded. Additionally, as not all patients had somatosensory evoked potential data during follow-up, we were unable to analyze and interpret this parameter in relation to retethering. All surgeries and follow-ups were performed by the same surgical team, which may have created a higher retethering rate in patients operated on the begining of the learning curve.

CONCLUSION

Retethering presents a significant clinical burden for both patients with tethered cord and their families. The literature reports highly variable data regarding the incidence rate, and severity of surgical complications, as well as long-term outcomes. During the follow-up of tethered cord patients, the possibility of retethering should be considered, particularly while the patients are still growing.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: MOT

Data collection: DB

Analysis and interpretation of results: DB

Draft manuscript preparation: DB, MOT

Critical revision of the article: MOT, DB

All authors (DB, MOT) reviewed the results and approved the final version of the manuscript.

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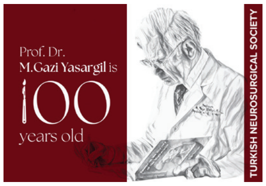

Original Investigation

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Assessment of the Prevalence of Paediatric Spondylolysis

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ABSTRACT

AIM: To determine the frequency of spondylolysis (SLi) in children examined due to trauma, which has not been reported before in Turkey, and to discuss the demographic features of these cases together with accompanying secondary pathologies.

MATERIAL and METHODS: Between January 2013 and June 2023, lumbar computed tomography (CT) scans performed due to trauma for children aged between 0 and 18 years were evaluated. Demographic data of the patients, the unilateral or bilateral occurrence of SLi, and additional findings detected on CT scans were recorded. Differences between Turkish citizens and Syrian immigrants were also assessed.

RESULTS: From lumbar CT scans performed for children aged 0-18 years, the prevalence of SLi was found to be 5.8%. The prevalence was significantly higher in boys and it increased with age, with significantly higher rates in the age group of 11-18 years compared to younger children. Although the difference between Turkish and Syrian children was not statistically significant, Syrian children showed a numerically higher incidence of SLi. Among SLi cases, the rate of spondylolisthesis was 33.3%, and it was significantly more prevalent in cases of bilateral SLi than cases of unilateral SLi. Spina bifida was significantly more common among patients with SLi than those without.

CONCLUSION: The prevalence of SLi in children is affected by some demographic characteristics. However, the rate did not differ between Turkish and Syrian children. Spondylolisthesis and spina bifida were significantly more common in patients with SLi than in the normal paediatric population.

KEYWORDS: Epidemiology, Paediatric spondylolisthesis, Spondylolysis

INTRODUCTION

Spondylolysis (SLi) involves the presence of a defect between the posterior elements of vertebrae and their vertebral bodies, most often in the pars interarticularis. It commonly occurs at the L5 and L4 vertebrae and can be unilateral or bilateral (1). Various theories exist regarding its aetiology. Stress fractures due to repetitive minor trauma and loading are frequently implicated, supported by the higher prevalence of SLi among athletes involved in sports requiring repetitive lumbar extension such as gymnastics, Olympic lifting, American football, and pole vaulting, as well as among individuals engaged in heavy lifting (1,5). However, the varying reported frequencies in different populations suggest that genetic factors also play a role (2).

Spondylolysis is a common condition in children and adolescents with back pain, but it can also be incidentally detected in asymptomatic children (5). The prevalence of SLi in children is largely established through radiological studies. The reported prevalence rates in the general paediatric population range from 0% to 7% across different countries (4,7,11,12,14,15).

There are no studies on the prevalence of SLi in children in Turkey. This study was designed to determine the prevalence of SLi in this country.

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MATERIAL and METHODS

Ethical Approval

This study received approval from the institutional review board of the Health Sciences University, Bagcilar Health Application and Research Center, Istanbul, Türkiye (2024/02/08/022).

Patient Population

All records of lumbar spine computed tomography (CT) scans performed for children aged 0-18 years between January 2013 and June 2023 were identified using our hospital's digital imaging archive system. To ensure that the study group represented the general paediatric population, only examinations conducted due to trauma were included, while the records of children identified in the imaging archive system who underwent CT scans for non-traumatic reasons such as non-specific back pain were excluded from the study.

Evaluation

Axial and sagittal sections of the analysed lumbar CT scans were reviewed by an experienced author for the presence of SLi, spondylolisthesis (SL), spina bifida (SB), and other congenital or traumatic abnormalities (Figure 1). SB was recorded for occurrences at the most common levels of SLi (L4 and L5) for patients without SLi and for occurrences at the same level as SLi occurrence for patients with SLi. All findings were documented. Patient age, gender, nationality, and clinical data were recorded from the hospital records.

Data Analysis

Patients were divided into two groups based on the presence or absence of SLi. The groups were compared regarding age, gender, nationality, and the presence of SL, SB, and other abnormalities. Additionally, the entire patient cohort was stratified into four age groups of 0-5, 6-10, 11-14, and 15-18 years and the prevalence of SLi was compared among these age groups.

Statistical Analysis

Data were analysed using the E-PICOS program. Categorical variables were presented as percentages. The normality of numerical data was assessed using the Kolmogorov-Smirnov test. Normally distributed numerical data were expressed as mean ± standard deviation, while non-normally distributed and ordinal data were presented as median values with minimum and maximum values. Categorical variables were compared between groups using chi-square or Fisher exact tests according to patient numbers. Normally distributed

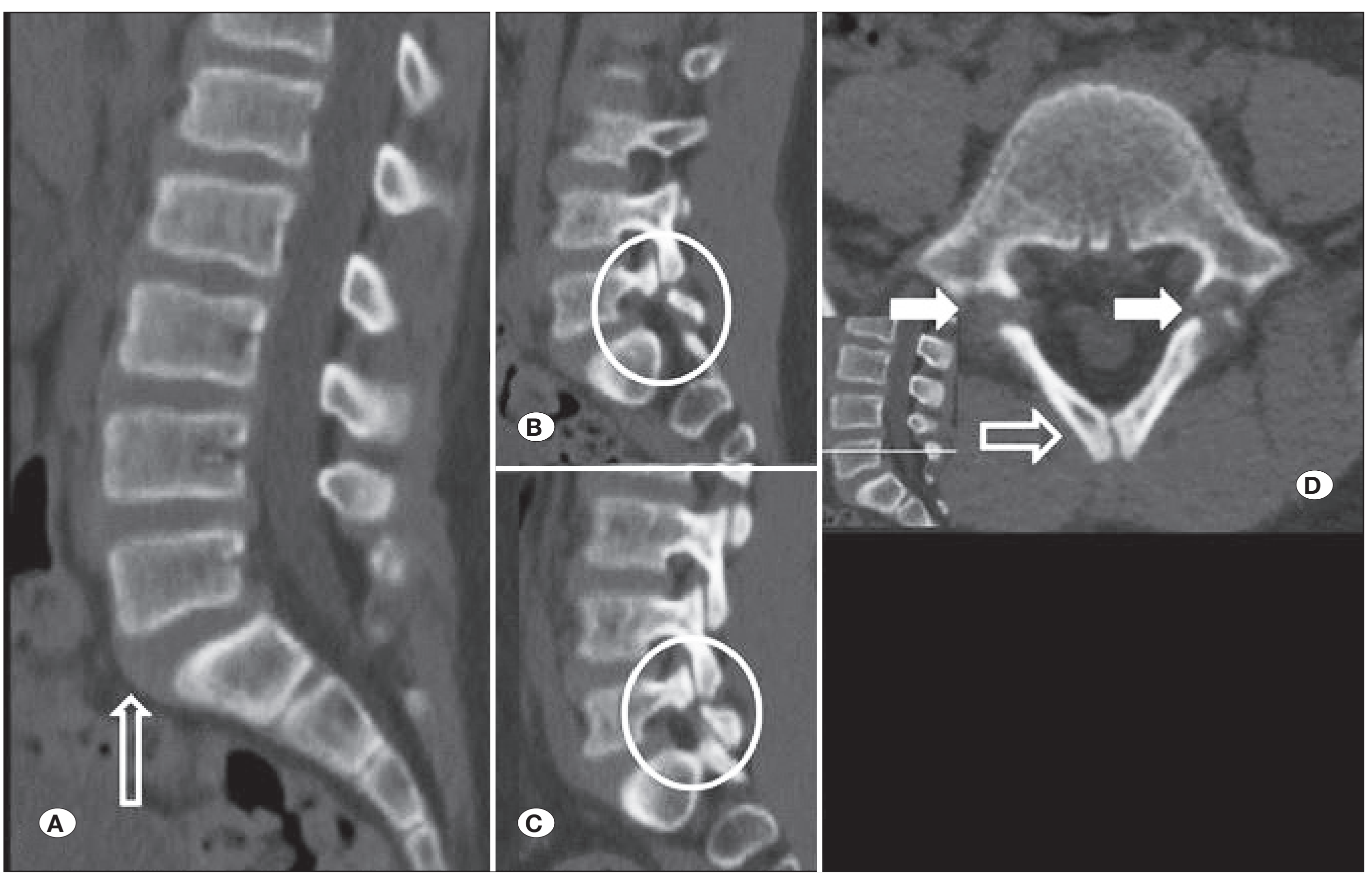

Figure 1: An 8-year-old boy **A)** showing grade 1 spondylolisthesis at L5-S1 in the midline sagittal reconstruction of lumbar CT (*white arrow*) and **B)** demonstrating bilateral spondylolysis at the L5 level on the right and **C)** in the left parasagittal sections (*white circles*). **D)** An axial section passing through the L5 level reveals spina bifida (*hollow white arrow*) and defects of bilateral spondylolysis (*solid white arrows*).

numerical data were compared using t-tests and non-normally distributed or ordinal data were compared using Mann-Whitney U tests. Values of p<0.05 were considered statistically significant.

RESULTS

A total of 2368 lumbar spine CT scans were identified within the target age group. After removing duplicate scans obtained for the same patient, 2337 scans remained. Two patients were excluded due to significant motion artifacts that hindered clear evaluation of their CT scans. Additionally, 117 patients whose scans were performed for non-traumatic reasons were excluded from the study, resulting in 2218 patients being included in the analysis (Figure 2).

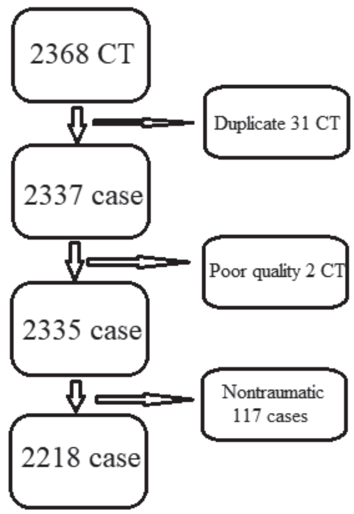

Figure 2: Flowchart showing the numbers of cases included and excluded from the study.

Demographic Data

The distribution of the genders, ages, and nationalities of the patients is presented in Table I. Of all patients, 63% were male and the median age was 13 years (range: 0-18 years). While 94% of the patients were of Turkish nationality, 6% (133 cases) were Syrian.

Prevalence of SLi

From among the total of 2218 patients, 129 (5.8%) were diagnosed with SLi. The prevalence of SLi was 6.7% in boys and 4.2% in girls, with a statistically significant difference (p=0.015). Patients with SLi were significantly older compared to those without SLi (p<0.001). Furthermore, it was observed that the prevalence increased with age, being significantly higher in the age groups of 11-14 and 15-18 years (prevalence rates of 1.8%, 4%, 8.7%, and 9.3% for the age groups of 0-6, 6-10, 11-14, and 15-18, respectively; p<0.001) (Table I). The frequency of SLi was numerically higher among Syrian nationals compared to Turkish nationals, but this difference was not statistically significant (9% vs. 5.6%, respectively; p=0.104).

Location and Side of SLi

The distribution of SLi levels and sides is presented in Table II. Bilateral SLi was observed in 72.1% of cases and L5 was involved in 88.3% of cases. There were no cases of multi-level SLi. Among the 117 patients excluded due to non-traumatic reasons for the performance of lumbar CT scans, 17.1% (20 cases) had SLi (Figure 3).These 20 cases were not included in the analysis.

Associated Abnormalities

The rate of cases with SL accompanying SLi is presented in Table III. Among cases with SLi, 33.3% had SL, whereas only 2 out of 2089 cases without SLi exhibited SL. Excluding one case, all instances of SL were located at the L5-S1 level. In one case ofbilateral L4 SLi, there was also grade 1 SL. The

Table I: Demographic Data and Prevalance of Spondylolysis

	Total	SLi (-)	SLi (+)	p-value
Total, n (%)	2218	2089 (94.2)	129 (5.8)	
Gender M, n (%)	1393 (63)	1299 (62)	94 (73)	**0.015***
Age (median/min.-max.) (years)	13 (0-18)	12 (0-18)	14 (2-18)	**<0.001[a]**
Age groups distribution, n (%) (years)				
0-6	492	483 (98.2)	9 (1.8)	**<0.001***
7-10	371	356 (96.0)	15 (4.0)	
11-14	472	431 (91.3)	41 (8.7)	
15-18	883	819 (92.7)	64 (9.3)	
Nationality, n (%)				
Turkish	2081	1964 (94.4)	117 (5.6)	0.104*&
Syrian	133	121 (91.0)	12 (9.0)	
Others	4	4 (100.0)	0 (0.0)	

:** *Chi^2 test;* ***a: *Mann-Whitney U test;* ***&:*** *between Turkish and Syrian; significant p values were given in italic characters.* ***M:*** *Male,* ***min:*** *Minimum,* ***max:*** *Maximum.*

prevalence of SL was significantly higher in cases of bilateral SLi compared to unilateral cases (44% vs. 5.5%, Fisher exact test, p<0.001). Among these cases, one was classified as grade 2 according to the Meyerding system, while the others were grade 1.

The prevalence of SB was 24% among patients with SLi and 13.7% among patients without SLi, reflecting a statistically significant difference (p=0.0011) (Table III). The presence of other spinal congenital anomalies and spinal traumatic lesions did not differ significantly between patients with and without SLi (Table III).

DISCUSSION

The development of SLi has been associated with genetic factors, with studies reporting significantly higher rates of SLi among first-degree relatives of affected individuals compared to the general population (16). This is further supported by varying prevalence rates reported across different ethnic groups. Studies have documented notably higher SLi prevalence among Eskimos and Native Americans compared to other populations (5,10). Fredrickson et al., in a prospective study with 500 children in the United States, reported SLi prevalence of 4.4% at age 6, increasing to 6% in adulthood (4). In France, Lemoine et al. found a 4.7% prevalence rate of SLi among asymptomatic children (7). Suzue et al. reported SLi prevalence of 0.005% among children and adolescents playing soccer in Japan (12). Studies from Chile by Urrutia et al., Korea by Song et al., and the Netherlands by van den Heuvel et al. reported SLi rates of 3.5%, 2.5% in a symptomatic children, and 0% in non-sporting and pain-free children, respectively (11,14,15). A study from the United States indicated varying SLi prevalence across different races and genders, with the highest rate of 6.4% observed in white males and lower rates among black children (2.8% in boys and 2.3% in girls) (8).

No studies regarding the prevalence of SLi in children or adults have been conducted in Turkey. Therefore, our study is the first of its kind for this country. We found a prevalence rate of 5.8% for SLi among children younger than 18 years who underwent lumbar CT scans due to trauma. Excluding patients for whom lumbar CT scans were performed for reasons other than trauma likely allowed us to reflect the general paediatric population more accurately. Our findings generally align with prevalence rates reported in studies conducted in the United States and European countries (4,7,8).

Consistent with other studies, our study found that SLi prevalence increased with age and was significantly higher in the age groups of 11-14 and 15-18 years compared to younger children. This is expected as older children engage more frequently in physically demanding sports and play activities, increasing the likelihood of SLi. In the literature, SLi prevalence in adults is reported to be about 5-6% (3,4,6). The rates of 8.7% in the 11-14 age group and 9.3% in the 15-18 age group observed in our study are higher than those reported for adult populations in other countries, but direct comparisons with adult rates in the Turkish population cannot be made due to the lack of studies to date on adult prevalence in Turkey.

In our study, SLi prevalence was significantly higher in boys than girls (6.7% vs. 4.2%, respectively). This male predominance is consistent across nearly all studies conducted in

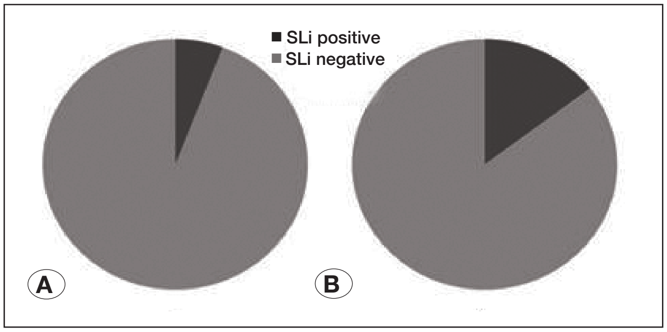

Figure 3: Rate of spondylolysis in patients undergoing CT scans for **A)** trauma-related and **(B)** non-trauma-related reasons.

Table II: Level and Side of Spondylolysis

	n (%)
Level	
L2	1 (0.8)
L3	2 (1.6)
L4	12 (9.3)
L5	114 (88.3)
Multiple	0 (0)
Site	
Right	18 (13.9)
Left	18 (13.9)
Bilateral	93 (72.1)

Table III: Associated Abnormalities on Computerized Tomography

	Total	SLi (-)	SLi (+)	p-value
Spondylolisthesis, n (%)	45 (2)	2 (0.001)	43 (33.3)	**<0.001&**
L4-5 Spina bifida, n (%)	317 (14.3)	286 (13.7)	31 (24)	**0.0011***
Spinal traumatic lesions, n (%)	105 (4.7)	102 (4.8)	3 (2.3)	0.28&
Spinal other congenital lesions, n (%)	17 (0.7)	16 (0.7)	1 (0.7)	1&

*&: Fisher exact test; *: Chi^2 test;* ***a:*** *Mann-Whitney U test;* ***&:*** *between Turkish and Syrian; significant p values were given in italic characters.*

both adult and paediatric age groups. This phenomenon may be attributed to higher physical exertion experienced by boys compared to girls and could also involve anatomical differences. Zehnder et al. reported significantly reduced interpedicular distances at lower lumbar levels in children with SLi, suggesting potential anatomical variations, although gender was not specifically evaluated in their study (17). Further studies are needed to assess whether such anatomical differences exist between boys and girls.

Previous series have reported that SL accompanies SLi in 5-68.4% of patients with SLi (4,7,11,13). In our study, SL was present in 33.3% of cases of SLi, and the rate of SL was significantly higher in cases ofbilateral SLi compared to unilateral cases (44% vs. 5.5%). Only two patients without SLi had grade 1 SL.

The presence of SB at the same level has been reported as a risk factor for developing SLi (6). Urrutia et al. evaluated SLi and SB prevalence in children and adults, reporting the SLi and SB prevalence as 3.5% and 41.2% in children and as 3.8% and 7.7% in adults, respectively, and attributing the higher prevalence in children to incomplete ossification (14). Another study comparing SLi rates between patients with and without SB did not find a significant difference (13). On the other hand, Sakai et al. concluded that the SLi rate in patients with SB was 3.7 times higher than that in the general population (9). Consistent with the findings of Sakai et al., our study demonstrateda significantly higher prevalence of SB at the same level in patients with SLi compared to those without SLi.

Our hospital serves a relatively high number of Syrian immigrants, and particularly in the emergency departments. Therefore, we compared the SLi prevalence in Turkish and Syrian children to evaluate whether there was an ethnic difference. The prevalence in Syrian children was found to be numerically higher compared to Turkish children (9% vs. 5.6%), but this difference was not statistically significant.

Limitations

Our study focused exclusively on lumbar CT scans performed due to trauma, excluding those performed for other reasons such as back pain. Therefore, we believe our results reflect the general paediatric population well. However, the lack of standardization in lumbar CT scans and the use of thicker slices, particularly for younger children to reduce radiation exposure, may have led to some cases of SLi being missed. This could potentially explain why SLi prevalence was found to be lower in the age group of 0-10 years compared to older children. Nonetheless, similar studies evaluating SLi prevalence in paediatric age groups consistently report lower rates in younger children, which supports the accuracy of our study's results.

CONCLUSION

We identified a prevalence rate of 5.8% for SLi among children aged 0-18 years who underwent lumbar CT scans due to trauma. The prevalence was significantly higher in boys. We also observed an increase in prevalence with age, with significantly higher rates in the age group of 11-18 compared to younger children. Although the difference was not statistically significant, Syrian children had a higher prevalence of SLi compared to Turkish children. Among patients with SLi, the rate of accompanying SL was 33.3%, and that rate was significantly higher when SLi was bilateral compared to unilateral cases.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: AO, FKG

Data collection: AO, AAT

Analysis and interpretation of results: FKG, IG, BE

Draft manuscript preparation: FKG, AO, AAT

Critical revision of the article: FKG, AO, AAT, IG, BE, NSB

Other (study supervision, fundings, materials, etc...):

All authors (AO, AAT, IG, BE, NSB, FKG) reviewed the results and approved the final version of the manuscript.

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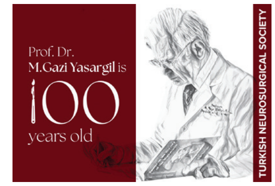

Endoscopic or Microscopic Discectomy: Which One Do Neurosurgeons Prefer for Their Own Lumbar Disc Surgery?

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ABSTRACT

AIM: To examine the factors influencing neurosurgeons' preferences between microscopic discectomy (MD) and endoscopic discectomy (ED) for the treatment of lumbar disc herniation (LDH) in Türkiye.

MATERIAL and METHODS: A cross-sectional survey was administered to 229 active neurosurgeons in Türkiye. The 23-item questionnaire assessed various factors influencing the preference for ED or MD, including training, surgical experience, demographic characteristics, and institutional factors. Data analysis was performed via ANOVA, multivariate logistic regression, chi-square tests, t tests, and descriptive statistics. A thematic analysis was conducted on the open-ended responses.

RESULTS: The results revealed that while traditional MD remained the preferred technique among older and more experienced neurosurgeons, 62.9% of surgeons with endoscopic training favored ED. Surgical preferences are significantly influenced by hands-on experience and institutional support for endoscopic procedures. Although younger surgeons preferred ED, MD was favored in complex and emergency situations ($p < 0.05$).

CONCLUSION: Younger surgeons increasingly opt for ED because of their familiarity with minimally invasive techniques, although MD remains the predominant approach among more experienced surgeons. Surgical decisions are heavily influenced by institutional support and practical experience. Continuous education and support for endoscopic methods will be essential for enhancing patient outcomes and integrating new technologies into clinical practice as surgical practices evolve.

KEYWORDS: Endoscopic discectomy, Microscopic discectomy, Lumbar disc herniation, Neurosurgeons, Surgical preferences

ABBREVIATIONS: ED: Endoscopic discectomy, **MD:** Microscopic discectomy, **LDH:** Lumbar disc herniation

INTRODUCTION

Lumbar disc herniation (LDH) is a common spinal condition that often requires surgical intervention when conservative treatments fail (11). Surgical techniques have evolved from traditional open procedures to less invasive options, with microscopic discectomy (MD) and endoscopic discectomy (ED) emerging as popular options (9). MD was first used in the 1970s and is still considered the gold standard for treating LDH, largely because of its proven safety record and consistent surgical outcomes (8). A magnifying view is possible with MD due to the smaller incision sizes required versus those used for open surgery (13). Precise handling of the dura and nerve roots can be accomplished with less muscle damage, a quicker recovery, reduced opioid use, and lower total treatment costs due to magnification surgery performed under the muscles (11). More recently, the development of ED has provided an even less invasive alternative. Unlike MD, ED uses highly specialized instruments and extremely small incisions—sometimes only approximately 10 mm^2—to access the herniated disc material (11). This technique aims to preserve paraspinal muscle integrity by avoiding large muscle dissections, potentially reducing postoperative discomfort and ac-

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celerating recovery (9). Despite sharing similarities, MD and ED differ notably in their technical demands, required equipment, and learning curve (4). Many surgeons continue to favor MD, given its long track record and the reliability of its outcomes. However, interest in ED has been increasing, particularly among surgeons seeking to minimize tissue trauma and shorten patient rehabilitation times (12). Thus, understanding what drives neurosurgeons' choice between MD and ED is becoming increasingly relevant.

This study examined how factors such as professional experience, the availability of institutional resources, and patient-specific considerations influence decision-making in lumbar spine surgery (3,11). By highlighting these dynamics, this research contributes to more personalized surgical planning and helps shape future training and clinical practice directions.

MATERIAL and METHODS

This study was approved by the ethics committee of the Istinye University (23.11.2024 -24/226).

This study employed a cross-sectional survey design to investigate neurosurgeons' preferences between ED and MD for LDH. The study included 229 actively practicing neurosurgeons across Türkiye. Participants were recruited from all types of healthcare institutions to ensure a diverse and representative sample. A tailored 23-question survey was developed to evaluate factors influencing surgeons' preferences for ED or MD, including demographics (age, years of experience, and practice setting), surgical training, and familiarity with ED and MD techniques. Additional factors assessed were the perceived advantages and disadvantages of each approach, patient selection criteria, expected outcomes, institutional factors (such as equipment availability and cost considerations), personal preferences, and comfort levels with each technique. The survey also included a hypothetical scenario based on an LDH diagnosis. The survey incorporated a blend of multiple-choice, Likert scale, and open-ended questions to collect quantitative and qualitative data. The survey was pilot-tested with a small group of neurosurgeons before distribution to ensure clarity and validity. The survey was administered electronically via a secure online platform (Survey Monkey), and potential participants received an email invitation containing study information and a link to the survey. Reminder emails were sent one and two weeks after the initial invitation to increase response rates. The survey was open for two weeks. Quantitative data were analyzed via descriptive statistics, including frequencies, percentages, means, and standard deviations. Chi-square tests were employed to examine relationships between categorical variables, whereas *t* tests or ANOVA were used for continuous data analysis. Multivariate logistic regression analysis was conducted to identify independent ED or MD preference predictors. The open-ended responses were subjected to thematic analysis. Two researchers independently coded the data, resolving discrepancies through discussion to ensure reliability. The study received ethical approval from Istinye University's Institutional Review Board. Informed consent was obtained from all participants prior to survey initiation. All the data were collected anonymously and stored securely to maintain confidentiality. This methodology facilitated a comprehensive examination of neurosurgeons' preferences and decision-making processes regarding ED and MD, offering valuable insights into current practices in LDH surgery management.

RESULTS

We investigated the factors influencing the surgical preferences of 229 neurosurgeons in treating LDH (Table I). The effects of demographics, clinical experience, institutional environments, and training on surgical decisions were evaluated via chi-square tests.

Surgery Preferences and Demographics

Age and sex were not significantly associated with the selection of techniques for LDH surgery ($p>0.05$). The male sex predominated in the cohort (92.6%; n=212). Younger neurosurgeons exhibited a greater inclination toward minimally invasive procedures; however, this difference was not significant. In contrast, more experienced neurosurgeons, particularly those with more than 20 years of practice (29.3%; n=67), tended to prefer traditional methods (Table II).

Previous Experience and Method Selection

Years of experience alone did not significantly influence surgical preference when the participants were grouped into categories of less than 10 years versus more than 10 years ($p>0.05$). However, experience with endoscopic surgeries significantly impacted decision-making. Surgeons with specialized endoscopic training were significantly more likely to choose minimally invasive techniques (62.9%, n=144; $p<0.05$), highlighting the importance of hands-on experience in building confidence with these methods. Moreover, surgeons working in institutions with established endoscopic practices (71.2%, n=163) more frequently favored endoscopic procedures than those who did not have such institutional support ($p<0.01$), suggesting that organizational infrastructure and familiarity with the methods contribute to the preference for endoscopic techniques.

Preferences Based on Scenarios

Emergency Situations

In urgent cases, traditional methods were significantly preferred over endoscopic treatments ($p<0.001$), indicating a tendency to favor techniques that offer greater control and visualization in life-threatening situations. Additionally, patients with recurrent LDH were significantly more likely to be treated with traditional surgery ($p<0.05$). This preference likely reflects the perceived reliability and effectiveness of traditional methods in addressing complex and recurrent issues. In situations requiring additional treatments, such as complex decompression or fusion, open surgery was the preferred approach ($p<0.001$). This trend suggests that traditional techniques are favored when broader access and direct visualization are necessary for multistep procedures (Table II). The chi-square analysis revealed that the observed difference between ED and MD was

Table I: Characteristics of the Responders to the Survey

Variable	Category	n (%)
Age (years)	< 30	5 (2.2)
	31–40	81 (35.4)
	41–50	71 (31.0)
	51-60	43 (18.3)
	>60	29 (12.7)
Gender	Female	17 (7.4)
	Male	212 (92.6)
Years of experience	< 5	62 (27.1)
	6–10	35 (15.3)
	11–15	38 (16.6)
	16-20	27 (11.8)
	>20	67 (29.3)
Type of institution	University Hospital, Training and research Hospital	45 (19.7)
	Goverment Hospital	59 (25.8)
	Private Hospital	30 (13.1)
	Private Practice	79 (34.5)
Previous history of lumbar spinal surgery	No	210 (91.7)
	Yes	19 (8.3)
Endoscopic training	Yes	144 (62.9)
	No	85 (37.1)
Institutional endoscopic practice	Yes	163 (71.2)
	No	66 (28.8)

Table II: Comparison of Groups in Various Clinical Scenarios

Factor	Category	Preferred Surgical Method	Significance (p-value)
Age (years)	< 40 vs. ≥ 40	No significant difference	> 0.05
Gender	Male vs. Female	No significant difference	> 0.05
Years of experience	< 10 vs. ≥ 10 years	Minimal trend toward open	> 0.05
Endoscopic training	Yes vs. No	Endoscopic favored with training	**< 0.05**
Institutional Endoscopic Practice	Yes vs. No	Endoscopic favored in endo-supported clinics	**< 0.01**
Emergency Surgery Need	Urgent vs. Routine	Traditional favored in emergencies	**< 0.001**
Recurrent Disc Herniation	Yes vs. No	Traditional favored in recurrence	**< 0.05**
Combined Interventions Required	Yes vs. No	Traditional preferred for complex cases	**< 0.001**

Table III: Multivariate Logistic Regression Analysis of Factors Affecting Surgical Preferences in Lumbar Disc Herniation Surgery

Independent variables	OR	95% CI		p-value
		Lower	Upper	
Age	1.498	0.493	4.548	0.476
Gender	0.277	0.027	2.831	0.279
Years as a specialist	1.006	0.467	2.164	0.988
Institution type	0.877	0.527	1.458	0.613
History of LDH surgery	6.187	0.145	263.658	0.341
Close relative with LDH surgery in the last 5 years	0.717	0.225	2.284	0.574
Institution performing endoscopic lumbar disc surgery	0.280	0.060	1.303	0.105
Preferred method for LDH surgery	3.470	0.492	24.490	0.212
Training in endoscopic spinal surgery	1.304	0.287	5.920	0.731
Number of microscopic LDH surgery performed	1.800	0.893	3.631	0.100
Preference method for recurrent LDH surgery	112.837	7.075	1799.683	**0.001**
Preference for discectomy with spinal stenosis	6.658	1.016	43.640	**0.048**
Preference for urgent LDH surgery	28.042	2.969	264.817	**0.004**
Preference for upper lumbar region disc surgery	0.179	0.047	0.674	**0.011**

***OR:** Odds ratio, **CI:** Confidence intervals, **LDH:** Lumbar disc herniation.*

primarily linked to insufficient training and experience in ED. In contrast, logistic regression analysis revealed no significant associations between the choice of ED or MD and the absence of adequate endoscopic surgical training (Table III). Our chi-square and logistic regression analyses also highlighted that traditional surgical techniques are significantly preferred in cases involving discectomy for spinal stenosis, emergency LDH surgery, and upper LDH procedures.

DISCUSSION

Either MD or ED are typically performed in LDH surgeries. Our nationwide survey of 229 neurosurgeons in Türkiye revealed that access to surgical equipment and years of professional experience significantly influenced technique selection. Notably, surgeons with longer career durations demonstrated a marked preference for MD, consistent with the findings of previous studies identifying MD as the most effective treatment for LDH (8,11). Longstanding existence with MD combined with the comprehensive training provided for this technique in residency programs explains this preference. ED is gaining popularity among patients and surgeons because of its minimally invasive nature. However, many neurosurgeons consider ED to be a less familiar and more difficult method to perform than MD (2,6). The prominence of minimally invasive techniques in surgical training programs has increased the tendency toward ED among young surgeons, leading to generational changes. Studies have shown that young surgeons demonstrate a greater ability to adapt to new technologies and benefit more from modern training methods (1,5). Considering that young surgeons will play a greater role in their clinics in the future, ED is expected to be applied more widely. Practical experience plays an important role in determining surgical preferences. Similarly, in our study, surgeons who received training in endoscopic techniques tended to prefer ED. Surgeons working in institutions where endoscopic equipment is easily accessible demonstrate a greater preference for ED (15,17). The microscopic method provides direct visualization, a wider working area, and the ability to perform extensive decompression (10). ED has the advantages of a shorter hospital stay and less postoperative pain. In addition, our study evaluated preferences in different scenarios, such as urgent discectomy, recurrent discectomy, multiple-level disc herniations, and lumbar stenosis. Neurosurgery specialists still prefer MD as the first choice, which aligns with the literature (9). The results support the belief that ED has a narrow indication among surgeons. Obtaining optimal treatment results requires incorporating patient preferences into the decision-making process. The increasing emphasis on shared decision-making has made it important to inform patients about treatment options and ensure their active participation in the process. In this context, neurosurgeons must balance their technical preferences with patients' expectations and comfort levels and include patients in decision-making by properly informing them (7). Studies comparing the long-term results of MD and ED methods in different patient groups will provide important information about the long-term effectiveness of these methods. In addition, determining the factors that prevent the wider use of ED will provide valuable insights for surgical education and infrastructure improvements (16). Importantly, neurosurgeons receive continuous education to enable them to perform minimally invasive spine surgery safely and effectively. Creating uniform standards for identifying patients most appropriate for ED or MD would promote more reliable, evidence-based choices (14). A lack of technical support, restricted access to endoscopic systems, and insufficient opportunities for practical training in EDs are some of the main reasons why MD is still preferred. By the way, endoscopic procedures are anticipated to become more widely accepted for spinal pathologies in the future, particularly as more long-term research data become available, even though traditional surgical methods are still the recommended choice for more complicated and recurring cases.

Limitations

Since our study relied on a survey, the limited number of neurosurgeons performing ED and the underrepresentation of female neurosurgeons led to nonhomogeneous groups. The inability to reach a larger number of neurosurgeons is another limitation.

CONCLUSION

This study underscores the multifaceted nature of surgical decision-making in managing LDH, particularly when selecting between the ED and MD approaches. While MD continues to be the preferred method among more experienced surgeons owing to its proven reliability and familiarity, younger surgeons trained in minimally invasive techniques are increasingly favoring ED. As surgical practices evolve, it is essential to cultivate an environment of ongoing learning and adaptation to ensure the best patient outcomes across various clinical situations.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: HK, ASA

Data collection: HK, ASA

Analysis and interpretation of results: HK, ASA

Draft manuscript preparation: HK, ASA

Critical revision of the article: HK, ASA

Other (study supervision, fundings, materials, etc...): HK, ASA

All authors (HK, ASA) reviewed the results and approved the final version of the manuscript.

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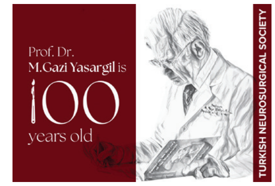

Cervical Fusion Techniques Unmasked: Plating vs. Cage-Only

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ABSTRACT

AIM: To compare the effect of fusion with anterior plating and cage (PLATE) versus cage-only (CAGE-O) technique on postoperative cervical sagittal alignment parameters, clinical outcome, and complication profiles after two-level anterior cervical discectomy and fusion (ACDF).

MATERIAL and METHODS: Clinical and radiological data of 42 patients who underwent two-level ACDF with either cage-only or anterior plating were retrospectively analyzed. Sagittal alignment parameters, including cervical lordosis, C0-C2 angle, T1 slope, and cervical sagittal vertical axis (cSVA), were evaluated preoperatively and postoperatively. Clinical outcomes were analyzed using the visual analog scale (VAS) and Neck Disability Index (NDI) scores.

RESULTS: Both groups showed significant clinical improvement in VAS and NDI scores over a 2-year follow-up period. Postoperatively, the CAGE-O group exhibited a significant increase in T1 slope and C0-C2 angles, whereas the PLATE group did not. Cervical lordosis and cSVA values showed no significant change postoperatively in both groups. Complication rates were similar between both groups.

CONCLUSION: Both anterior plating and cage-only techniques in two-level ACDF demonstrated comparable outcomes in terms of sagittal alignment, clinical improvement, and complication rates. The decision to utilize anterior plating should be based on individual patient factors and surgeon preference rather than differences in outcomes.

KEYWORDS: Cervical discectomy, Plate, Cage, Alignment, Disc degeneration

INTRODUCTION

The anatomy and biomechanics of the cervical region are remarkably complex (4). It is more mobile than the other parts of the spine (17). The primary function of the cervical region is to support the head, allowing a wide range of movements. This feature makes the cervical region susceptible to degenerative diseases (3). One of the most commonly applied surgical treatment methods for cervical problems is anterior cervical discectomy and fusion (ACDF), which provides successful outcomes and has low complication rates (9). There are several studies on the effect of changes in sagittal alignment parameters after surgery on clinical results, among which some studies have reported a relationship between sagittal alignment parameters and clinical outcomes (1,12,14). Conversely, some studies also argue that the alignment exerts limited effect on clinical outcomes (10,11,15).

Although the inclusion of an anterior plate can provide the benefit of instant stability, it also presents potential limitations, including the possibility of plate or screw malfunction, loosening, incorrect placement, and an increased risk for degen-

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eration in the segments adjacent to it, especially in multilevel surgery (21).

Elucidating the changes in sagittal alignment parameters after ACDF with polyetheretherketone cages, which is one of the most common surgical interventions in neurosurgery, and the effect of plating on them will help determine the aspects to be considered in the surgical technique, contribute to the accumulated knowledge on the subject, and pave the way for future studies.

This retrospective study was conducted to investigate the effect of anterior plating compared with the cage-only technique on clinical outcomes and postoperative cervical sagittal alignment parameters after two-level ACDF.

MATERIAL and METHODS

This retrospective study was conducted in two tertiary healthcare and spine centers and was approved by the local ethics committee (Decision number: TUTF-BAEK 2023/67). Due to the retrospective and anonymous nature of the study, written informed consent was waived.

Study Design

Data of patients who underwent two-level ACDF with polyetheretherketone cages in the participating study centers between January 1, 2014, and December 31, 2021, were retrospectively examined. Clinical and radiological data of the patients were accessed through 1. Hospital Information Systems, 2. Patient files (Neurosurgery and Spine Center Clinical Archives), and 3. Picture Archiving and Communication Systems.

The predefined study inclusion criteria were as follows: 1) ACDF performed in the participating study centers between January 1, 2014, and December 31, 2021, 2) First time and two levels, 3) ACDF performed with polyetheretherketone cages with or without anterior cervical plate and screw fixation, and 4) Diagnosis of cervical degenerative disc disease or/and cervical spondylotic myelopathy.

The predefined exclusion criteria were as follows: 1) ACDF performed on dates other than between January 1, 2014, and December 31, 2021, or in nonparticipating study centers, 2) Except for the first time or other than two levels, 3) Operated with other techniques, and 4) Operation due to tumor, trauma, or infection.

Data Acquirement

Patients' data were extracted from all existing written and electronic medical records, which included age, gender, duration of pain in months, and level of the relevant spine. Demographic, clinical, and radiological data were extracted by scanning patients' electronic and written documents. The following variables were used in this study: age, gender, operated spine levels, duration of pain in months, preoperative and postoperative cervical sagittal vertical axis (cSVA) values, cervical lordosis angle, occipito-C2 angles, and T1 slopes. All patients were evaluated using the visual analog scale (VAS) and Neck Disability Index (NDI) scores in the preoperative period, early postoperative period, and at the 6-, 12-, and 24-month postoperative follow-up. Furthermore, all patients underwent anteroposterior and lateral cervical X-ray examinations during the preoperative period and throughout all postoperative follow-ups.

Statistical Analysis

Results were expressed as mean ± SD for normally distributed numerical variables and as median (interquartile range) or percentages where appropriate. Average or median values were calculated for continuous variables, and frequency numbers and percentages were calculated for categorical variables. Statistical analysis of categorical variables was performed using the chi-square test. For continuous variables, the ordinary one-way ANOVA was performed to compare multiple groups, and t-test was used for the comparison of two groups.

$p \leq 0.05$ was accepted as the threshold for statistical significance. Statistical analyses were conducted using the Jamovi Statistics version 2.4 package program (12). An *a priori* power analysis was conducted for a two-tailed Wilcoxon signed-rank test [$\alpha = 0.05$, power $(1 - \beta) = 0.80$, and effect size = 0.5], which yielded a required sample size of 35. Power analysis was performed using the G*Power software version 3.1.

RESULTS

Participant Demographics and Baseline Characteristics

This study enrolled 42 participants, of whom 21 (50%) were women. The mean age was 47.8 ± 10.3 years, with a range of 20–68 years. The median duration of pain before intervention was 6.5 (IQR = 7.5) months. A total of 23 (54.8%) patients were stabilized with only cages (CAGE-O), and 19 (45.2%) were stabilized with plates and screws in addition to cages (PLATE) (Table I). The distribution of surgical etiologies and the analysis results of patients' preoperative values are presented in Tables II and III, respectively. Regarding the preoperative characteristics of the patients, only the preoperative number of days with pain before admission (higher in the cage-only group) was different. Other parameters (radiological parameters, age, sex, etiology, and operated levels) showed no differences between the groups.

Radiological Outcomes

Sagittal alignment of the cervical spine was evaluated using preoperative and postoperative cervical lordosis, C0-C2 angle, T1 slope, and cSVA values. Both cSVA and cervical lordosis values remained significantly unchanged after the operation (p=0.5900 and p=0.2163, respectively). The T1 slope of patients in the CAGE-O group significantly increased (preoperative: 11.10 ± 2.98, postoperative: 14.52 ± 3.66, p=0.0035), whereas it remained significantly unchanged in the PLATE group (preoperative: 10.30 ± 4.09, postoperative: 12.38 ± 3.70, p=0.2976). Similarly, the C0-C2 angle significantly increased in only the CAGE-O group (preoperative: 33.47 ± 5.44, postoperative: 38.95 ± 7.16, p=0.0171), whereas the PLATE group showed almost no change (preoperative: 30.25 ± 5.87, postoperative: 30.22 ± 5.85, p>0.9999). Table V summarizes the radiological outcomes of the patients.

Table I: Patient Characteristics

Characteristic		n (%)
Age, Mean ± SD (years)		47.8 ± 10.3 (20-68)
Gender	Female	21 (50)
	Male	21 (50)
Operation	CAGE-O	23 (54.8)
	PLATE	19 (45.2)
Level of Operations	C3-C5	1 (2.4)
	C4-C6	14 (33.3)
	C5-C7	27 (64.3)

***CAGE-O:** Fusion with only cage, **PLATE:** Fusion with cage and plates.*

Table II: Distribution of Etiologies

	Etiology	n (%)
CAGE-O	Degenerative disc disease	8 (42.1)
	Cervical spondylotic myelopathy	7 (36.84)
	Mixed	4 (21.05)
PLATE	Degenerative disc disease	9 (39.13)
	Cervical spondylotic myelopathy	11 (47.83)
	Mixed	3 (13.04)

***CAGE-O:** Fusion with only cage, **PLATE:** Fusion with cage and plates.*

Table III: Analysis of Preoperative Age, Pain Duration and Radiological Values

	Group	Mean	Median	SD	p-value*
Preop C0-2 (º)	CAGE-O	33.47	34.0	5.438	0.088
	PLATE	30.25	31.00	5.868	
Preop CL (º)	CAGE-O	9.67	10.0	4.207	0.288
	PLATE	8.26	8.00	5.046	
Preop T1 Slope (º)	CAGE-O	11.10	11.0	2.979	0.469
	PLATE	10.30	9.50	4.093	
Preop cSVA (mm)	CAGE-O	12.73	11.0	6.311	0.389
	PLATE	11.42	10.00	7.305	
Age (years)	CAGE-O	49.04	49.0	9.979	0.418
	PLATE	46.37	46.00	10.673	
Pain Duration (days)	CAGE-O	12.17	10.0	9.238	**<0.001**
	PLATE	5.42	4.00	3.220	

Mann-Whitney U test was performed. **N: Number, **SD:** Standard Deviation, **CAGE-O:** Fusion with only cage, **PLATE:** Fusion with cage and plates.*

Clinical Outcomes

Both the PLATE and CAGE-O groups showed significant improvement in VAS and NDI scores over the 2-year follow-up period ($p<0.001$) (Table IV). Significant improvements in the mean VAS and NDI scores were observed at all time points in both groups. All patients in the CAGE-O and PLATE groups showed fusion as evaluated by lateral cervical graphs and cervical CT scans. No instrument failure or pseudoarthrosis was observed in the follow-ups for both groups. All patients showed satisfactory neurological recovery levels and clinical improvements. The mean operating time was 92.23 ± 9.45 min in the CAGE-O group and 107.48 ± 12.38 min in the PLATE group. The estimated blood loss volume in the CAGE-O group was 105.43 ± 23.51 mL and 132.54 ± 19.62 mL in the PLATE group. Among the cases analyzed, 1 (5.26%) subcutaneous hematoma and 1 (5.26%) temporary hoarseness were detected in the PLATE group. Furthermore, 1 (4.34%) new-onset

Table IV: Clinical Parameters of the Patients

Clinical parameters	Preoperative	Postoperative				
		3 months	6 months	12 months	2 years	p-value*
CAGE-O						
VAS	7.83 ± 2.39	4.77 ± 1.38	4.06 ± 1.29	3.12±1.21	2.67 ± 0.91	**<0.001**
NDI	35.41 ± 8.71	24.12 ± 6.04	20.43 ± 5.72	20.05 ± 4.19	17.25 ± 3.92	**<0.001**
PLATE						
VAS	8.02 ± 2.15	3.94 ± 1.25	3.22 ± 1.08	2.90 ±1.02	2.82 ± 1.05	**<0.001**
NDI	33.25 ± 7.38	22.15 ± 6.11	20.71 ± 5.53	19.37 ± 4.66	18.41 ± 4.18	**<0.001**

*Repeated measures ANOVA (Friedman) test was applied. **CAGE-O:** Fusion with only cage, **PLATE:** Fusion with cage and plates, **VAS:** Visual Analog Scale, **NDI:** Neck Disability Index.*

Table V: Radiological Parameters of the Patients

Radiological Parameters	Preoperative		p-value*	Postoperative		p-value*
	CAGE-O	PLATE		CAGE-O	PLATE	
cSVA (mm)	12.73 ± 6.31	11.42 ± 7.31	0.389	13.91 ± 4.91	12.53 ± 4.43	0.509
C0-C2 (°)	33.47 ± 5.44	30.25 ± 5.87	0.088	38.95 ± 7.16	30.22 ± 5.85	**<0.001**
T1 Slope (°)	11.10 ± 2.98	10.30 ± 4.09	0.469	14.52 ± 3.66	12.38 ± 3.70	0.072
Cervical Lordosis (°)	9.67 ± 4.21	8.26 ± 5.05	0.288	11.25 ± 4.77	11.63 ± 7.98	0.595

*Mann Whitney U test was applied. **CAGE-O:** Fusion with only cage, **PLATE:** Fusion with cage and plates*

disc in the adjacent segment in the CAGE group and 1 (5.26%) adjacent segment degeneration and consequent new-onset disc formation in the PLATE group were observed in the follow-ups. The new-onset disc in both patients was radiological only, and both patients did not require intervention. Moreover, 4 (21.19%) patients in the PLATE group and 2 (8.69%) patients in the CAGE group reported dysphagia. However, no statistically significant differences were observed in early dysphagia occurrences (p=0.255). Patients did not require treatment for dysphagia, and the symptoms resolved after 1 month in both groups. There were no cases of subsidence in this cohort. Figure 1-2 represents selected cases from this cohort.

DISCUSSION

ACDF, initially described by Smith and Robinson in 1958 (18), is a commonly performed surgical intervention for degenerative cervical spine conditions and radiculopathies, providing successful outcomes with low complication rates (7). This procedure involves removing a damaged disc or bone spurs from the cervical spine and fusing the adjacent vertebrae to stabilize the spine. However, there is still a lack of consensus on the utilization of anterior plating on two-level ACDF. In this study, we investigated the effect of fusion with cage and anterior plating (PLATE) compared with the cage-only (CAGE-O) technique on postoperative cervical sagittal alignment parameters, clinical outcomes, and complication profiles after two-level ACDF. Our findings contribute to the ongoing debate concerning the need and implications of adding anterior plates in two-level ACDF procedures.

Both the CAGE-O and PLATE groups exhibited comparable radiological outcomes regarding spinal alignment. For two-level ACDF, both techniques caused no significant changes in cSVA values and cervical lordosis, although the mean values improved in both groups, which may be due to either the low sample size or the preoperative characteristics of the patients. Furthermore, most patients had accompanying cervical degenerative changes in addition to the disc herniation, and hence pain-related loss of lumbar lordosis might explain the lower postoperative cervical lordosis values than those reported in the literature (5,19). Zavras et al. observed no significant change in sagittal alignment followed by T1 slope, cSVA value, and cervical lordosis between the cage-only and anterior plating techniques in ACDF (21). Similarly, Akgun et al. observed no significant change in sagittal alignment followed by laminoplasty or laminectomy with fusion (2). Interestingly, in our cohort, only the CAGE-O group showed a significant increase in T1 slope and CO-C2 angles, whereas these values remained stable in the PLATE group. This difference may be related to better stability of the fused segment by anterior plating and consequent changes in adjacent vertebrae. Conversely, Lau et al. reported that cSVA values, cervical lordosis, and T1 slope showed no correlation with pain outcomes in patients who underwent ACDF (13). Similarly, in our cohort, both the CAGE and PLATE groups showed significant improvement in pain outcomes irrespective of differences in radiological differences between the groups.

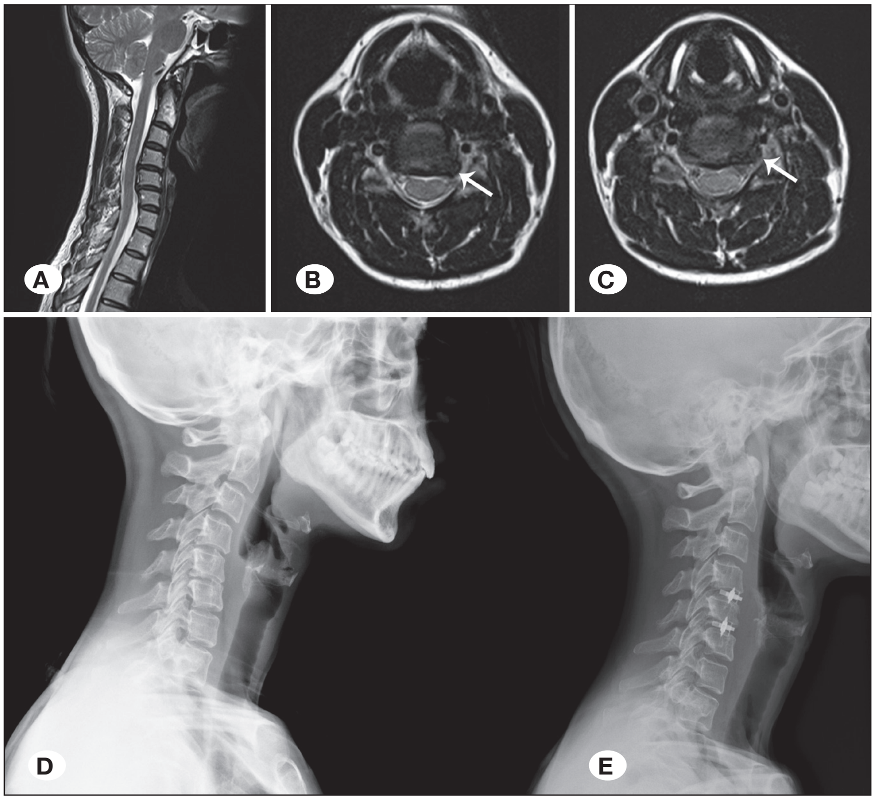

Figure 1: Radiographic images of the patient treated with anterior cervical discectomy and fusion with cage-only technique.
A) Preoperative T2W sagittal magnetic resonance imaging (MRI).
B, C) Preoperative T2W axial MRIs showing C4-C5 and C5-C6 disc herniations respectively (arrows indicate disc herniations).
D) Preoprative and **E)** postoperative lateral cervical X-Rays.

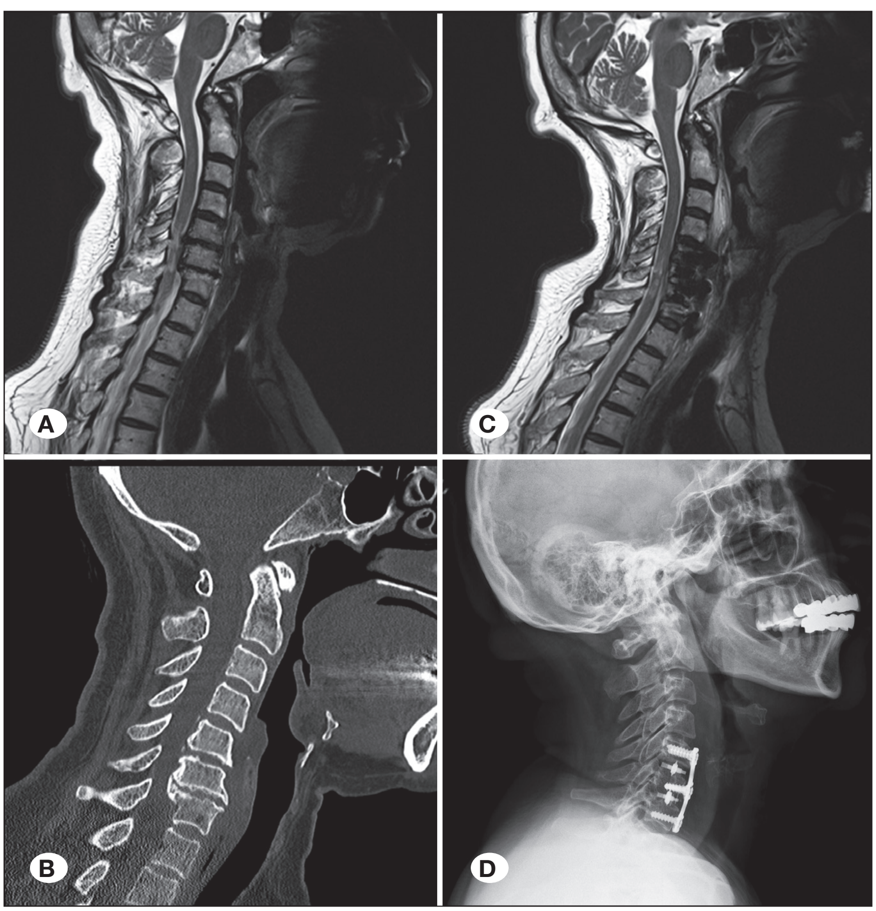

Figure 2: Radiographic images of the patient treated with anterior cervical discectomy and fusion with cage and anterior plating technique. Preoperative sagittal **(A)** T2W magnetic resonance imaging (MRI) and **(B)** Computerized tomography showing osteophyte formation and myelomalacia. Postoperative **(C)** sagittal T2W MRI and **(D)** lateral X-Ray showing anterior cervical plate at C5-C7 levels.

When we compared the clinical outcomes of patients who underwent ACDF with either anterior plating or cage-only techniques, we observed similar and significant improvements in both groups over the 2-year follow-up period. The VAS and NDI scores exhibited substantial improvements with no significant differences between the CAGE-O and PLATE groups. These results suggest that both techniques effectively alleviate symptoms and improve functional status in patients with two-level cervical radiculopathy. Oh et.al. observed that both anterior plating and cage-only techniques provide comparable clinical outcomes in patients who underwent two-level ACDF (16). Similarly, Cheung et al. conducted a meta-analysis and reported no significant difference in VAS, JOA, or NDI scores between anterior plating and cage-only techniques in ACDF (6). Our clinical findings comparing these two techniques also support the interchangeable characteristics of these anterior plating and cage-only techniques, in terms of alleviation of pain, in two-level ACDF.

Regarding complication profiles, both the PLATE and CAGE-O groups exhibited similar rates of adverse events, with no significant difference in hardware-related complications or postoperative morbidity. Dysphagia is one of the most common complications of ACDF surgery (8). In our cohort, a higher number of patients reported early postoperative dysphagia in the PLATE group than in the CAGE-O group; however, this difference did not reach statistical significance. Moreover, no patients' symptoms persisted for more than 1 month. New-onset adjacent segment pathology was rare and occurred at similar rates in both groups. Nevertheless, Ji et al. reported a higher incidence of adjacent segment disease (ASD) with anterior plating and construction than with the cage-only technique in two-level ACDF (20). Similarly, Cheung et al., in their meta-analysis, observed a higher rate of ASD (6). Our findings of low incidence and similar rate of ASD among the groups may be related to our preoperative planning. Regarding possible disc bulging and apparent degenerative changes in adjacent segments, we opted for a longer three-level ACDF. This emphasizes the importance of careful consideration of factors such as the extent of disc pathology and the presence of adjacent segment degeneration, which can mitigate the risk of developing postoperative complications. Regarding perioperative findings, assuming that additional hardware such as plates and screws are not used in the cage-only technique, it reduces the risk of hardware-related complications, including implant failure, loosening, and malpositioning. This simplification of the surgical procedure may result in shorter operative times and reduced intraoperative blood loss, thereby contributing to improved surgical outcomes and patient recovery. Moreover, the cage-only technique may provide cost savings compared with anterior plating, as it eliminates the costs associated with implanting additional hardware.

The limitations of our study include its retrospective design and the relatively small sample size. Furthermore, the 2-year follow-up duration may not capture the long-term outcomes and complications associated with ACDF. In addition, the decision to utilize anterior plating or cage-only technique was based on surgeon preference and patient characteristics. This variability in the selection of the surgical approach could limit the generalizability of our findings. Prospective studies with larger cohorts with broader patient characteristics and longer follow-up periods are required to further clarify the comparative effectiveness and long-term outcomes of cage-only versus plating techniques in two-level ACDF procedures.

CONCLUSION

This retrospective study comparing anterior plating versus cage-only techniques in two-level ACDF demonstrated comparable outcomes in terms of sagittal alignment, clinical improvement, and complication rates over a 2-year follow-up period. Both the anterior plating and cage-only groups showed significant postoperative clinical improvement in VAS and NDI scores. Complication rates were also similar between the two groups, except for short-term dysphagia that was detected more in the anterior plating group. Our findings contribute to the increasing evidence that ACDF without anterior plating is a feasible technique for maintaining the desired cervical sagittal alignment. The decision to utilize anterior plating should be based on individual patient factors and surgeon preference rather than differences in clinical outcomes.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: ATA, MYA, TO, OA, AFO

Data collection: CG, BC, ATA

Analysis and interpretation of results: MYA, EAU, SOG, BC, ATA, TO

Draft manuscript preparation: MYA, CG, ATA

Critical revision of the article: MYA, ATA, TO, OA, AFO

All authors (CG, MYA, EAU, BC, ATA, SOG, TO, OA, AFO) reviewed the results and approved the final version of the manuscript.

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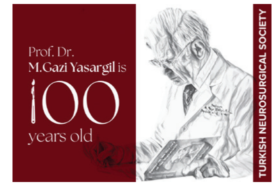

Comparison of Preoperative and Postoperative Clinical and Electrophysiological Results of Patients with Carpal Tunnel Syndrome Presenting a Positive Scratch Collapse Test

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ABSTRACT

AIM: To examine the correlation between clinical outcomes and electrophysiological findings following open carpal tunnel release (CTR) surgery in patients with a positive scratch collapse (SC) test, and to the postoperative course of the SC test.

MATERIAL and METHODS: The study included 29 patients who had a positive SC test and a confirmed diagnosis based on nerve conduction study (NCS) findings. The findings of Boston Carpal Tunnel Questionnaire (BCTQ), visual analog scale (VAS), NCS, and SC test were assessed preoperatively and postoperatively at the 2nd and 8th weeks. The correlations between NCS findings and BCTQ and VAS scores were analyzed.

RESULTS: Significant postoperative improvements were observed in BCTQ and VAS scores at the 2nd and 8th weeks. In the 8th week, NCS findings also showed significant improvement; however, no correlation was found between NCS findings and functional scores. The SC test became negative in 89.6% (n=26) of patients postoperatively.

CONCLUSION: In the early period following open CTR surgery, there is no correlation between improvements in NCS findings and functional scores. However, in 90% of patients with a positive preoperative SC test, the test became negative early after the open CTR surgery. Therefore, the SC test can be used to evaluate postoperative treatment results because it is easily applicable, repeatable, and cost-effective compared with NCS.

KEYWORDS: Carpal tunnel, Scratch collapse, Nerve conduction study, Boston carpal tunnel questionnaire, Postoperative period

ABBREVIATIONS: SC: Scratch collapse, **NCS:** Nerve conduction study, **VAS:** Visual analog scale, **BTCQ:** Boston carpal tunnel questionnaire, **CTS:** Carpal tunnel syndrome, **CTR:** Carpal tunnel release, **EMNG:** Electroneuromyography, **DML:** Distal motor latencies, **CMAP:** Combined muscle amplitude potential, **AAEM:** American Association of Electrodiagnostic Medicine, **SCV:** Sensory nerve conduction velocity, **SSS:** Symptom severity scale, **FSS:** Functional status scale

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INTRODUCTION

Carpal tunnel syndrome (CTS) is the most common compression neuropathy. Although entrapment neuropathies affect a localized portion of the nerve, they can lead to significant physical, psychological, and economic consequences. Although physical examination alone is often sufficient for diagnosis, electroneuromyography (ENMG) is used to confirm the diagnosis and assess disease severity (22). Demyelination is the primary pathological mechanism in compression neuropathies; however, axonal damage may also develop in advanced stages (27). Several studies have shown that electrophysiological findings may not improve postoperatively, even when patients experience symptomatic and functional relief (15,24). Although various studies have compared conservative and surgical treatments for CTS, there is no proven scale to evaluate the treatment results of these entrapment neuropathies except for clinical assessments (4,18).

The scratch collapse (SC) test is a physical examination technique used in entrapment neuropathies, offering high sensitivity and specificity compared to other diagnostic maneuvers (5). In this test, the examiner gently scratches the skin over the nerve compression site for a few seconds while the patient resists external shoulder rotation. Following scratching, a sudden loss of muscle resistance occurs. The exact mechanism of the SC test remains unclear. However, it is believed that either the cutaneous silent period (CSP) or elevated levels of substance P, a neurotransmitter, may cause a sudden decrease in muscle strength as a protective mechanism against pain (3).

Postoperative clinical evaluations, ultrasonographic measurements, and nerve conduction study (NCS) findings often yield inconsistent results when assessing surgical outcomes (4,16,18). Additionally, there is no consensus on the optimal timing for these assessments.

This study aimed to investigate the postoperative electrophysiological and clinical outcomes in patients with moderate to severe CTS who did not benefit from conservative treatment and to analyze the change in nerve conduction velocities after surgery. It further aimed to determine the role of NCS and SC test in postoperative follow-up.

MATERIAL and METHODS

This retrospective, observational clinical study was approved by the Ankara Etlik City Hospital, Local Institutional Ethics Committee (decision no:2024-635, date: 17/07/2024). The study was conducted jointly at two care centers: secondary and tertiary.

Between January 2022 and 2024, patients aged 18–75 years who had NCS findings consistent with CTS, a positive SC test, and who underwent open carpal tunnel release (CTR) surgery were included. During retrospective screening, the following were excluded: 392 patients owing to missing study parameters [Boston Carpal Tunnel Questionnaire (BCTQ), postoperative NCS, visual analog scale (VAS)], 3 patients with revision surgeries, 13 patients with polyneuropathy, 27 patients with diabetes mellitus, 2 patients with thyroid disease, and 4 patients with cervical radiculopathy. Of the remaining 65 patients, 35 had a negative SC test and were excluded. As a result, 29 patients were included in the study. All surgeries were performed by two surgeons using a standard open incision technique under local anesthesia. Patients were discharged the same day and followed up postoperatively at the 2nd and 8th weeks. Preoperative and 8-week postoperative ENMG evaluations were performed by two neurologists.

Parameters Analyzed in the Study

ENMG: Distal motor latency (DML), combined muscle amplitude potential, motor conduction velocity, and sensory conduction velocity were evaluated during the preoperative and 8th-week postoperative ENMG evaluations. NCS findings were classified by neurologists according to the recommendations of the American Association of Electrodiagnostic Medicine (AAEM) during the preoperative and postoperative periods (26). NCS was performed using a Neuropack S1 MEB-9400K (Nihon Kohden, Tokyo, Japan), with filter settings between 20 and 2000 Hz. The median nerve compound muscle action potential, DML, and motor nerve conduction velocity were measured by orthodromically stimulating the median nerve at the wrist, with recording electrodes placed on the abductor pollicis brevis muscle. Sensory nerve conduction velocity was recorded at the wrist using antidromic stimulation with ring electrodes placed around the proximal and middle phalanges of the second finger. The skin temperature of the hand was maintained between 32°C and 34°C.

BCTQ: It is the most commonly used test for evaluating and standardizing treatment outcomes in entrapment neuropathies. This scale provides symptomatic and functional assessment. It consists of two subscales. The symptom severity scale (SSS) contains 11 questions; each question is scored from 1 (mildest) to 5 (most severe). The mean score (sum of scores/11) is calculated. The functional status scale (FSS) contains eight questions assessing difficulty with performing daily tasks, each scored from 1 to 5. The mean score (sum of scores/8) is calculated. In both scales, the maximum score is 5, and the magnitude of the score determines the severity of symptoms and disability. This score was evaluated preoperatively and postoperatively at the 2nd and 8th weeks.

SC test: This test evaluates for a sudden decrease in muscle strength after scratching the nerve compression site. This test was performed preoperatively and postoperatively at the 2nd and 8th weeks, with all evaluations conducted by the same surgeon. A positive test response is characterized by a momentary loss of voluntary strength in a specific muscle group in the limb, and it has been associated with CSP. CSP refers to the withdrawal response of a limb to a noxious stimulus, functioning as an inhibitory spinal reflex mediated by A-delta fibers. This reflex has also been demonstrated using EMG (9,17). Another theory suggests that substance P plays a role in the effectiveness of the test. In normal tissues, the scratching stimulus does not evoke a response; however, in areas of nerve damage, it triggers an allodynic response, potentially leading to excessive release of substance P. Histopathological studies have documented increased levels of substance P in nerve and surrounding tissues obtained from patients undergoing open CTR surgery (23). Furthermore, substance P levels are known to increase in peripheral nerve endings following nerve damage or in chronic inflammatory conditions (7). This correlation between elevated substance P and nerve damage may help explain the reflexive muscle collapse observed in a positive SC test (14).

VAS: This was used to assess pain intensity. It consists of a 10 cm line with endpoints representing 0 (no pain) and 10 (worst imaginable pain).

Statistical Analysis

All analyses were conducted using the Jamovi Project (2022, Jamovi Version 2.3, Computer Software). The findings of this study are expressed as frequencies and percentages. Normality analysis was assessed using the Shapiro–Wilk test, skewness, kurtosis, and histograms. Categorical variables were presented as absolute numbers with percentages. Continuous variables were compared between responders and nonresponders using the Mann–Whitney U-test and Kruskal–Wallis H-test, and are presented as medians with interquartile ranges. Categorical data were compared using the chi-squared test or Fisher's exact test, as appropriate. Changes in VAS, BCTQ-SSS, and BCTQ-FSS scores were analyzed using the Friedman test, and ENMG findings were compared using the Wilcoxon signed-rank test. Spearman's correlation was used to investigate associations among BCTQ, VAS, and electrophysiological findings. A p-value of <0.05 was considered statistically significant.

RESULTS

Overall, 70% of the patients were females, with a mean age of 50 years (range: 36–65 years). The preoperative VAS score was 5 (3–6), BCQT-SSS was 3.6 (1.8–4.5), and BCQT-FSS was 3.9 (2.0–4.6). In the postoperative evaluation, the SC test remained positive in 3 patients at the 2nd week, while it became negative in 26 patients (89.6%; Table I).

Analysis of the clinical outcomes revealed that the preoperative VAS, BCTQ-SSS, and BCTQ-FSS scores were significantly higher than the postoperative scores at the 2nd and 8th weeks (Table II, Figure 1). Furthermore, scores at the 2nd week were also higher than those at the 8th week. In short, all clinical outcomes showed significant improvements at the 2nd postoperative week compared with the preoperative period, and these improvements continued through the 8th week.

Table III presents the preoperative and postoperative ENMG findings. Assessment of electrophysiological findings revealed significant improvements were observed across all parameters at the 8th postoperative week compared with the preoperative period (Table III, Figure 2).

Table IV summarizes the severity of CTS in the preoperative and postoperative periods based on the AAEM criteria. None of the patients had severe CTS. Of the 10 patients with severe CTS preoperatively, only 5 (50%) showed a reduction in disease severity by the 8th week postoperatively. The remaining five patients were still classified as having severe CTS at that time. All patients who experienced a reduction in severity were reclassified as having moderate CTS.

Among the 19 patients with moderate CTS preoperatively, 42% (n=8) showed regression to mild CTS during the postoperative period. However, 57.9% (n=11) of the patients did not experience any reduction in disease severity. According to the NCS findings, no patient was considered healthy at the8th postoperative week.

In the analysis of postoperative VAS and BCTQ scores in correlation with NCS findings at the 8th postoperative week, no correlation was observed between the 2nd and 8th week measurements (Table V).

Table I: Demographics and Clinical Characteristics of Study Participants

Variables	Results
Age, median (min-max), years	50 (36-65)
Sex, female/male, n (%)	20 (68.9) / 9 (31.1)
Side of pain, n (%)	
Right	15 (51.7)
Left	14 (48.3)
Baseline scratch collapse test, n (%)	29 (100.0)
Baseline BCTQ-SSS score (median, min-max)	3.6 (1.8-4.5)
Baseline BCTQ-FSS score (median, min-max)	3.9 (2.0-4.6)
Postoperative scratch collapse test, n (%)	
Positive	3 (10.4)
Negative	26 (89.6)

***BCTQ:** Boston carpal tunnel questionnaire, **SSS:** Symptom severity scale, **FSS:** Functional status scale.*

Table II: The Time Main Effect on VAS, BCTQ-SSS, and BCTQ-FSS Scores

		Mean SD	Median (min-max)	Mean Rank	p-value
VAS	Pre-operative	4.93±0.96	5 (3-6)	2.98	**<0.001***
	Post-operative 2nd week	2.69±0.85	3 (1-5)	1.86	
	Post-operative 8th week	1.52±0.78	2 (0-3)	1.16	
BCTQ-SSS	Pre-operative	3.53±0.72	3.6 (1.8-4.5)	2.97	**<0.001***
	Post-operative 2nd week	1.81±0.51	1.9 (0.9-3.2)	1.91	
	Post-operative 8th week	1.31±0.23	1.3 (1.0-1.9)	1.14	
BCTQ-FSS	Pre-operative	3.65±0.77	3.9 (2.0-4.6)	3.00	**<0.001***
	Post-operative 2nd week	1.82±0.53	1.8 (1.0-3.5)	1.91	
	Post-operative 8th week	1.31±0.23	1.3 (1.0-1.9)	1.09	

***:** *Friedman test*
VAS: *Visual analog scale,* ***BCTQ:*** *Boston carpal tunnel questionnaire,* ***SSS:*** *Symptom severity scale,* ***FDS:*** *Functional status scale.*

Table III: The Time Main Effect on Electroneuromyography Results

		Mean SD	Median (min-max)	Mean Rank	p-value
Motor Latency	Pre-operative	5.39±1.44	4.9 (4.02-9.28)	11.5	**<0.001***
	Post-operative 8th week	4.36±1.16	4.1 (3.06-8.28)		
CMAP	Pre-operative	5.61±3.17	5.96 (0.5-10.8)	43.1	**<0.001***
	Post-operative 8th week	6.82±2.66	6.9 (0.7-11.9)		
Motor Velocity	Pre-operative	43.4±6.54	45.0 (30.1-54.8)	40.9	**<0.001***
	Post-operative 8th week	48.9±7.27	50.4 (32.1-58.4)		
Sensory Velocity	Pre-operative	27.2±5.62	27.4 (20.1-36.5)	39.8	**<0.001***
	Post-operative 8th week	35.5±7.34	33.2 (21.7-53.3)		

***:** *Wilcoxon Test*
CMAP: *Combined muscle amplitude potential.*

Table IV: Patients' Pre- and Post-Operative Severity Levels according to American Association of Electrodiagnostic Medicine Recommendations

	Severity level		
	Mild	Moderate	Severe
Pre-operative	-	19	10
Post-operative	8	16	5

DISCUSSION

This study demonstrates that the SC test is feasible for evaluating surgical success in the early postoperative period following open CTR surgery. Although NCSs collectively indicated postoperative improvement, no significant change in disease severity was observed. Furthermore, individual analysis of NCS findings failed to reliably reflect clinical improvement. Notably, no correlation was found between early postoperative NCS findings (at the 8th week) and the BCTQ scores.

The clinical success rate following open CTR surgery is reported to range between 75% and 90% (6). Various parameters have been used to assess treatment outcomes, including NCS, symptom-based questionnaires, grip strength measurements, complication rates, pain and dexterity assessments, return-to-work times, and overall functional capacity (2). Although some authors advocate for the use of NCS as a standardized tool in evaluating CTS diagnosis and treatment efficacy, others argue that it is not essential. For instance, Heybeli et al. reported improvements in BCTQ scores following open CTR surgery without a corresponding correlation with NCS findings at 3 and 6 months postoperatively (11). However, some studies have found inconsistent and heterogeneous correlations between NCS and clinical outcomes in the postoperative period (1,12,25). Our study found no correlation

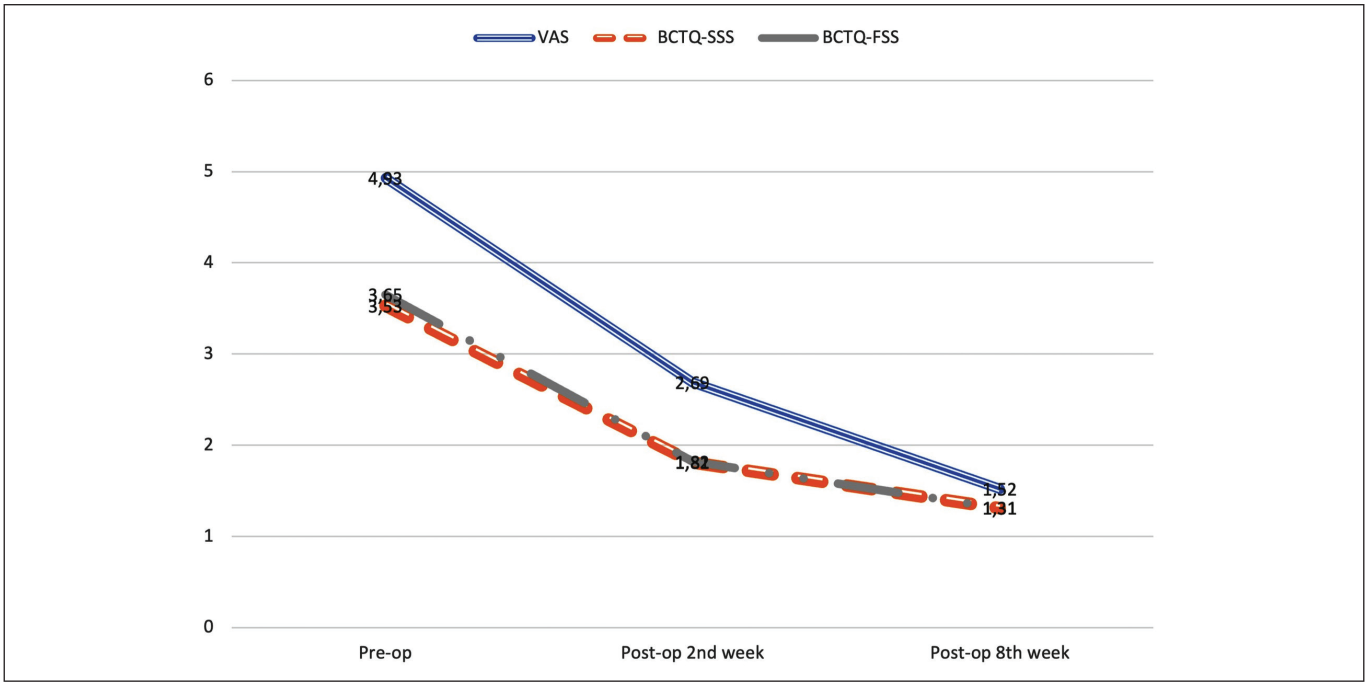

Figure 1: Time based functional scores (**VAS:** Visual analog scale, **BCTQ:** Boston carpal tunnel questionnaire, **SSS:** Symptom severity scale, **FDS:** Functional status scale).

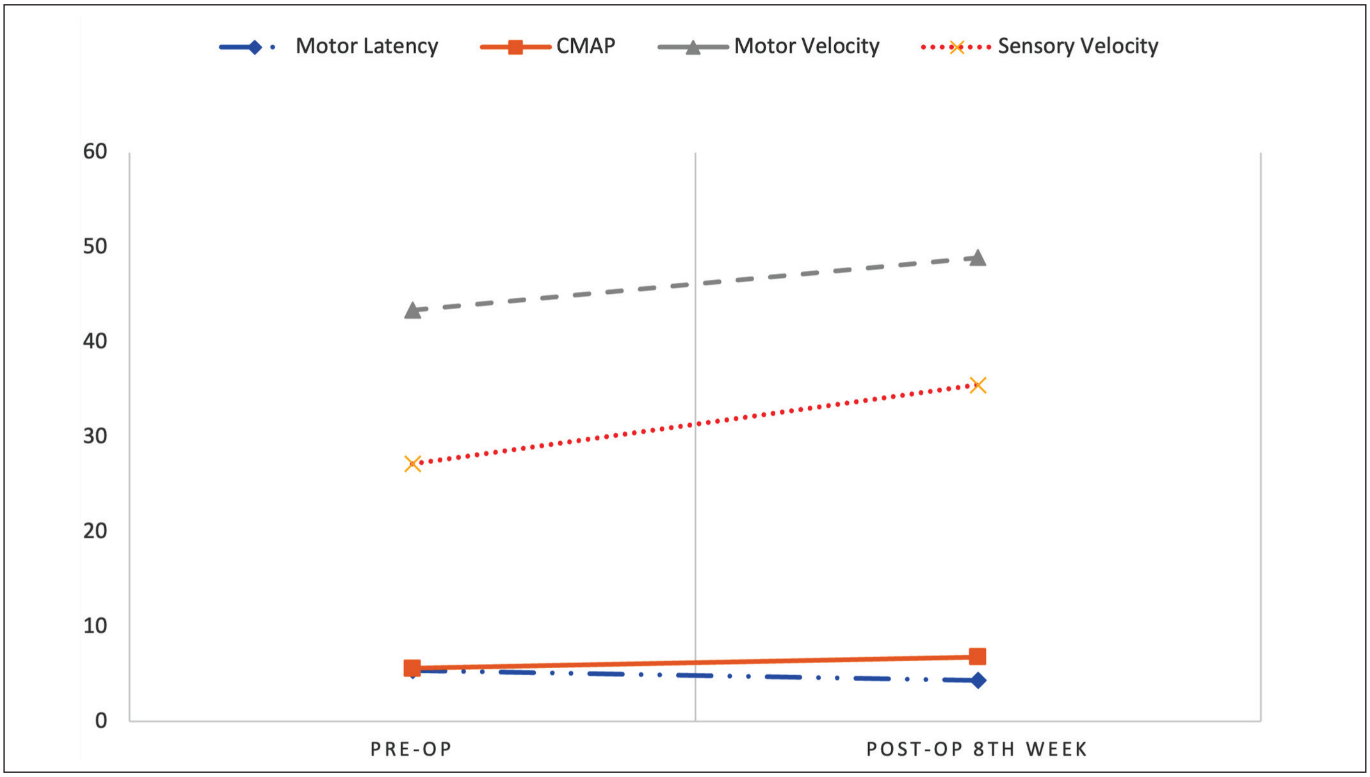

Figure 2: The time main effect on electroneuromyography results (**CMAP:** Combined muscle amplitude potential).

Table V: Spearman's Correlation Coefficients Between 8th Week Postoperative Nerve Conduction Measures and Difference in BCTQ and VAS

Instrument Scale (Post-operative 8th week)	Postoperative 2nd week			Postoperative 8th week		
	VAS	BCTQ SSS	BCTQ FSS	VAS	BCTQ SSS	BCTQ FSS
Motor latency	0.360	-0.178	-0.097	0.256	0.242	0.238
CMAP	-0.354	0.116	0.025	-0.084	-0.060	-0.022
Motor velocity	-0.321	0.282	0.107	0.009	-0.019	-0.146
Sensory velocity	-0.337	0.186	0.024	-0.212	-0.053	-0.236

**p<0.05*
***BCTQ:** Boston carpal tunnel questionnaire, **VAS:** Visual analog scale, **CMAP:** Combined muscle amplitude potential, **SSS:** Symptom severity scale, **FSS:** Functional status scale.*

between postoperative NCS findings and clinical outcomes, including BCTQ-SSS, BCTQ-FSS, and VAS scores. Although NCS findings and clinical outcomes are not correlated, using them together may offer a more comprehensive understanding of postoperative recovery

The SC test is more sensitive and specific in diagnosing CTS and peroneal nerve compression than traditional examination techniques (e.g., Tinel's sign and compression testing) (5,10). Furthermore, the SC test has utility in detecting additional sites of compression and localizing multiple levels of compression along a nerve pathway (8). In our study, the SC test was positive in 29 (45.3%) of 64 patients preoperatively. At the postoperative evaluation, the test became negative in 26 of these 29 patients (89.6%) by the 2nd week, with no further changes noted at the 8th week. Although the electrophysiological findings did not show remarkable improvement by the 8th week, the SC test showed approximately 90% improvement at the 2nd week. This discrepancy may be attributed to persistent nerve impingement at different anatomical sites or inadequate surgical decompression in the three patients whose SC tests remained positive postoperatively. Two main hypotheses have been proposed to explain SC test mechanism: excessive substance P release and the CSP. Regardless of the underlying mechanism, it is possible that the SC test normalizes earlier than EMG findings due to the resolution of excessive substance P or the disappearance of CSP following surgical decompression.

The clinical parameters, including VAS, BCTQ-FSS, and SSS, improved by the 2nd postoperative week compared to the preoperative period, with continued improvement observed through the 8th week. Although some prior studies have failed to show significant improvements in VAS scores after open CTR surgery, the present study demonstrated otherwise (21). The discrepancy in earlier studies was likely due to the subjective nature of pain assessments (21). Like the current study, Okumura et al. found significant improvements in VAS and BCTQ scores for up to 3 months following endoscopic CTR (20).

The literature presents conflicting results regarding postoperative NCS findings. Kim et al. reported improvements in DML, distal motor amplitudes, distal sensory latency, and distal sensory amplitudes at the 3rd week and 3rd month following open CTR surgery (16). Similarly, Mondelli et al. observed electrophysiological improvements between 1st and 6th months postoperatively (19). However, other studies have not demonstrated statistically significant improvements in postoperative NCS values (13). In our study, although all NCS parameters showed some degree of improvement at 8 weeks postoperatively, none returned to normal levels.

In a study by Aksekili et al., among the seven patients with very severe CTS based on AAEM criteria, none demonstrated electrophysiological improvement at 3 months (1). Furthermore, of the 19 patients in the severe CTS group, 9 improved to a moderate level and 7 to a mild level. Among four patients with moderate CTS, two remained at a moderate level and two improved to a mild level. Similarly, in our cohort, half of the patients with severe CTS improved to a moderate level postoperatively, while the other half showed no change. Among those with moderate CTS, 42% improved to a mild level, and the remainder exhibited no change in disease severity. Consequently, none of the patients in our study exhibited a return to normal NCS values based on AAEM criteria in the postoperative period.

This retrospective study has several limitations. While our sample size was comparable to previous studies, it could have been expanded, given the high prevalence of CTS in the population. However, the number of patients with a positive SC test in the preoperative period, along with their postoperative electrophysiological parameters and clinical outcomes, provides valuable preliminary data that can inform future studies. Another limitation is the relatively short follow-up period. Longer follow-up period could have provided insights into whether further electrophysiological and functional improvements occur over time. For instance, Okamura et al. found that improvements continued during the first 3 months but plateaued between the 3rd and 6th postoperative months (20). Nevertheless, as our study aimed to assess early postoperative outcomes, the current follow-up period was appropriate. A further limitation is the omission of other physical examination findings (e.g., two-point discrimination and opposition strength) in the postoperative assessment. Despite this, our study is the first known in the literature to evaluate the SC test following open CTR surgery, and it may serve as a foundation for future research.

CONCLUSION

In this study, no correlation was observed between improvements in NCS findings and functional scores during the early postoperative period following open CTR surgery. However, in 90% of patients with a positive preoperative SC test, the test became negative two weeks after open CTR surgery. Although demyelination and axonal damage caused by nerve compression in CTS did not improve during the early period following open CTR surgery, the SC test results showed an improvement in that period, likely due to the normalization of neurotransmitter flow after decompression of the nerve. Therefore, the SC test can be used to evaluate postoperative treatment results because it is easily applicable, repeatable, and cost-effective compared with NCS.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: ED, AA

Data collection: OT, ABA

Analysis and interpretation of results: EC, HBC, ED

Draft manuscript preparation: ED, AA, OT

Critical revision of the article: EC, HBC

Other (study supervision, fundings, materials, etc...): ED, ABA

All authors (ED, AA, ABA, EC, OT, HBC) reviewed the results and approved the final version of the manuscript.

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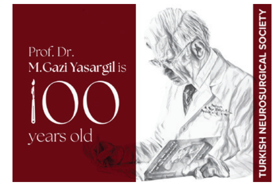

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Original Investigation

Cerebrovascular-Endovascular

The Prognostic Value of Serum ET-1, MCP-1, and Lactic Acid Levels in Patients with Ruptured Intracranial Aneurysm After Interventional Embolization

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ABSTRACT

AIM: To evaluate the prognostic value of serum endothelin-1 (ET-1), monocyte chemotactic protein-1 (MCP-1), and lactic acid (LA) levels in patients with ruptured intracranial aneurysm (IA) after interventional embolization.

MATERIAL and METHODS: Patients with ruptured IA were divided into mild, moderate, and severe groups according to Hunt-Hess grades, and the correlation between serum parameters and disease severity was analyzed. Multivariate logistic regression was employed to analyze the influence of serum ET-1, MCP-1, and LA levels on the prognosis of patients, and ROC curves were plotted to analyze the predictive value of these parameters.

RESULTS: There were 29 cases in the mild group (grade I), 49 cases in the moderate group (grade II-III), and 25 cases in the severe group (grade IV-V). In the severe group, serum ET-1, MCP-1, and LA were elevated compared to the moderate and mild groups, with the moderate group showing higher levels than the mild group. Serum ET-1, MCP-1, and LA levels were positively correlated with the severity of IA ($p<0.05$). The Hunt-Hess grade, Fisher grade, and serum ET-1, MCP-1, and LA levels in patients with poor prognosis were higher than those with good prognosis. Hunt-Hess grade IV-V, Fisher grade 3 to 4, ET-1 ≥ 41.78 pg/mL, MCP-1 ≥ 229.05 ng/L, and LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization. The AUC values of serum ET-1, MCP-1, and LA levels to evaluate the prognosis of patients were 0.772, 0.871, and 0.791, respectively.

CONCLUSION: Serum ET-1, MCP-1, and LA levels correlate with disease severity in patients with ruptured IA and have predictive values for the prognosis of patients after interventional embolization. They are risk factors for poor prognosis of patients after interventional embolization.

KEYWORDS: Intracranial aneurysms, Interventional embolization, Endothelin-1, Monocyte chemotactic protein-1, Lactic acid, Prognosis

INTRODUCTION

Intracranial aneurysm (IA), or intracranial aneurysms, are localized pathological dilatations on cerebral arteries, identified by weakened vessel walls (9). In individuals free from comorbidities, unruptured IA has a prevalence of about 3.2%, typically emerging at the mean age of 50 (22). Unruptured IA generally presents no symptoms and may remain hidden until a rupture happens. Upon rupture, it frequently results in aneurysmal subarachnoid hemorrhage (SAH) with potentially severe outcomes. The mortality rate for aneurysmal SAH continues to be about 30-40%, despite advances in neurosurgical intensive care (16), and close to half of the survivors encounter disabilities or persistent cognitive difficulties (3,4). The level of lactic acid (LA) in cerebrospinal fluid of patients with IA was increased (20). LA in cerebrospinal fluid is produced by anaer-

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obic glycolysis in neurons and neuroastrocytes. The pyruvate formed by glycolysis is reduced to LA under hypoxia conditions. The use of serum LA levels to predict postoperative outcomes of IA still requires more investigation. Endothelin-1 (ET-1) has a contractile effect on blood vessels (23). ET-1 is involved in vascular dysfunction associated with cardiovascular diseases, including arterial spasms after cerebral aneurysm rupture and hemorrhage, atherosclerosis, hypertension, and cardiac hypertrophy. Monocyte chemoattractant protein-1 (MCP-1) has a strong chemoattractant effect on monocyte macrophages, which can infiltrate the damaged brain parenchyma. As a result, MCP-1 present in the serum can indirectly signify the severity of brain tissue damage (7,14). Therefore, the purpose of this study was to explore the prognostic value of serum ET-1, MCP-1, and LA levels of patients with ruptured IA after interventional embolization.

MATERIAL and METHODS

Clinical Data

This was a prospective study that followed STROBE guidelines. The study was approved by The Affiliated Hospital of Guangdong Medical University (No.202105ZJ-3) ethics committee and informed consent was obtained from all patients. A total of 103 patients with ruptured IA with SAH were studied, including 62 males and 41 females. There were 58 patients aged ≥ 60 years and 45 patients aged < 60 years, 45 cases with hypertension, and 39 cases with diabetes. Hunt-Hess classification identified 29 cases of grade I, 49 cases of grade II- III, and 25 cases of grade IV-V. There were 50 cases with anterior communicating artery aneurysms, 24 cases with internal carotid aneurysms, 4 cases with middle cerebral aneurysms, 14 cases with posterior communicating aneurysms, and 11 cases with vertebrobasilar aneurysms.

Inclusion Criteria

1) Spontaneous SAH was diagnosed by computed tomography (CT) (25); 2) Patients met the diagnostic criteria for IA; 3) Patients had complete clinical data; 4) Patients underwent interventional embolization.

Exclusion Criteria

1) Patients had severe cardiac, liver, and renal dysfunction; 2) Patients did not undergo embolization or craniotomy; 3) Patients had multiple aneurysms; 4) Patients had incomplete clinical data.

Ethical Statement

The present study was approved by the Ethics Committee of The Affiliated Hospital of Guangdong Medical University (No.202105ZJ-3) and written informed consent was provided by all patients prior to the study start. All procedures were performed in accordance with the ethical standards of the Institutional Review Board and The Declaration of Helsinki, and its later amendments or comparable ethical standards.

Interventional embolization

The patients underwent a routine examination before surgery and femoral artery puncture using the Seldinger technique after general anesthesia. Angiography was conducted on both the vertebral and internal carotid arteries. Thompson and lateral photographs were taken, and oblique photographs at appropriate angles were selected. After being diagnosed, the catheter was replaced and patients were administered heparin. The microcatheter was guided into the aneurysm. Using coils, the aneurysm was embolized while keeping the artery open. The catheter was slowly withdrawn once it was confirmed that there was no contrast agent left in the aneurysm. The catheter sheath was removed 6 h after interventional embolization, and the femoral artery was compressed about 15 mm at about 1 cm above the puncture point. Once bleeding had ceased, a compression bandage was administered, and the lower limb of the puncture site was immobilized for 24 hours after the interventional embolization.

Serum ET-1, MCP-1 and LA levels

Fasting peripheral venous blood samples of 5 mL were taken from all patients before and one week after surgery, then centrifuged at 3000 rpm for 10 min. Serum ET-1 level was measured by radioimmunoassay with the detection kit (Beijing Purevalley Biotechnology Co., Ltd.). Serum MCP-1 level was detected by ELISA kits (R&D Company, USA). Serum LA level was detected by Abbott C8000 automatic biochemical analyzer.

Severity

According to Hunt-Hess classification (13), the patients were divided into the mild group (grade I, 29 cases), moderate group (grade II-III, 49 cases), and severe group (grade IV-V, 25 cases).

Outcome Measures

The prognosis was assessed using the Glasgow Outcome Scale (GOS) six months post-operation (12). The scoring system assigned 1 point for death, 2 points for a vegetative state with minimal responses, 3 points for clear consciousness accompanied by severe disability or inability to live independently, 4 points for mild disabilities capable of independent living and work, and 5 points for recovery with slight defects. In 35 cases, a score of 1 to 3 points was indicative of a poor prognosis, while in 68 cases, a score of 4 to 5 points indicated a good prognosis.

Statistical Analysis

All data were evaluated by SPSS 22.0 software. Enumeration data (%) were subjected to comparative analysis using χ^2 test, and measurement data (mean ± standard deviation) after normal tests were compared by *t*-test. Spearman test was applied to analyze the correlation between serum parameters and disease severity. Multivariate logistic regression was conducted to analyze the effects of serum ET-1, MCP-1, and LA levels on the prognosis of patients, and ROC curves were plotted to analyze the prognostic value of each index. $P<0.05$ emphasized a significant statistical difference.

RESULTS

Changes in preoperative and 1-week postoperative serum ET-1, MCP-1, and LA levels Serum ET-1, MCP-1, and LA levels decreased at 1 week postoperatively compared with preoperatively ($p<0.05$, Table I). Serum ET-1, MCP-1, and LA levels in patients with different severity

In the severe group, serum ET-1, MCP-1, and LA levels were elevated compared to the moderate and mild groups, with the moderate group showing higher levels than the mild group ($p<0.05$, Figure 1).

Correlation analysis

Serum ET-1, MCP-1, and LA levels were positively correlated with disease severity ($p<0.05$, Figure 2).

Univariate analysis of prognosis

The Hunt-Hess grade, Fisher grade, and serum ET-1, MCP-1, and LA levels were higher in patients with poor prognosis than those with good prognosis ($p<0.05$, Table II).

Multivariate analysis of prognosis

Hunt-Hess grade IV-V, Fisher grade 3-4, ET-1 ≥ 41.78 pg/ml, MCP-1 ≥ 229.05ng/L, LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization ($p<0.05$, Table III).

Evaluation value of serum ET-1, MCP-1, and LA levels for prognosis of patients

The AUC values of serum ET-1, MCP-1, and LA levels for the prognosis of patients were 0.772, 0.871, and 0.791, respectively (Table IV and Figure 3).

Table I: Serum ET-1, MCP-1 and Lactate Levels in Patients

Factors	Before operation	1st week after operation	t	p-value
ET-1 (pg/ml)	38.87 ± 13.50	30.12 ± 8.36	5.593	**<0.001**
MCP-1 (ng/L)	213.91 ± 44.40	175.45 ± 20.94	7.951	**<0.001**
Lactic acid (mmol/L)	6.64 ± 1.68	5.69 ± 2.03	3.659	**<0.001**

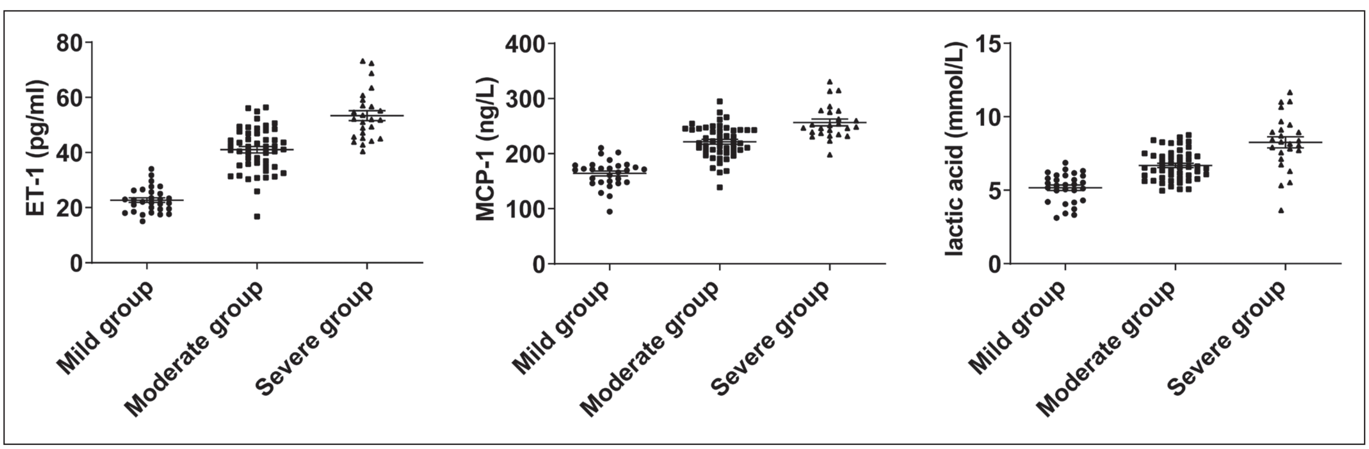

Figure 1: Serum ET-1, MCP-1, and LA levels in patients with different severity.

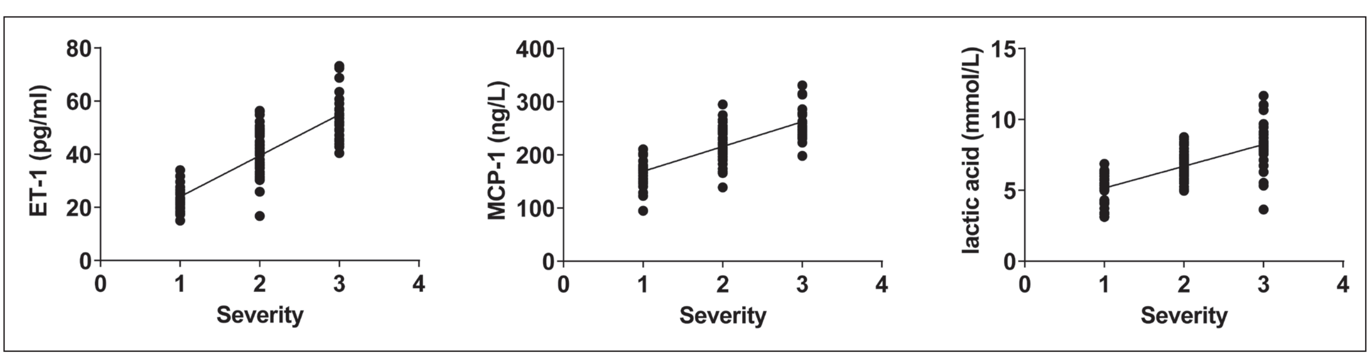

Figure 2: Correlation analysis of serum ET-1, MCP-1, LA levels and severity of disease.

Table II: Univariate Analysis of Prognosis After Interventional Embolization

Factors		Poor prognosis (n=35)	Good prognosis (n=68)	χ^2/t	p-value
Gender	Male	20	42	0.206	0.650
	Female	15	26		
Age (years)	≥ 60	19	39	0.088	0.766
	< 60	16	29		
Combined hypertension		15	30	0.015	0.903
Combined diabetes		13	26	0.012	0.914
Hunt-Hess grade	I	5	24	21.698	**<0.001**
	II-III	12	37		
	IV-V	18	7		
Location	Anterior communicating aneurysm	19	31	1.751	0.781
	Internal carotid aneurysm	8	16		
	Middle cerebral aneurysm	1	3		
	Posterior communicating aneurysm	5	9		
	Vertebrobasilar aneurysm	2	9		
Operation timing	Early stage	16	30	0.104	0.949
	Middle stage	2	5		
	Late stage	17	33		
Tumor diameter	< 15 mm	16	29	0.088	0.766
	≥ 15 mm	19	39		
Ratio of tumor length diameter to width	< 0.5	13	27	0.064	0.800
	≥ 0.5	22	41		
Fisher grade	1-2	12	42	6.996	0.008
	3-4	23	26		
ET-1 (pg/ml)		52.81 ± 10.37	30.08 ± 6.52	13.615	**<0.001**
MCP-1 (ng/L)		263.85 ± 42.21	189.52 ± 30.19	10.296	**<0.001**
Lactic acid (mmol/L)		8.72 ± 1.28	5.75 ± 1.03	12.742	**<0.001**

Table III: Multivariate Analysis of Prognosis After Interventional Embolization

Factors	β	SE	wald χ^2	OR	95%CI	p-value
Hunt-Hess grade	0.583	0.134	18.929	1.791	1.378~2.329	**< 0.001**
Fisher grade	0.819	0.257	10.156	2.268	1.371~3.754	**0.002**
ET-1	0.673	0.291	5.349	1.96	1.108~3.467	**0.021**
MCP-1	0.438	0.201	4.748	1.55	1.045~2.298	**0.030**
Lactic acid	0.749	0.228	10.792	2.115	1.353~3.306	**0.001**

Assignment: *Hunt-Hess grade (1 for grades IV to V, 0 for grades I to III); Fisher grade (1 for grades 3 to 4, 0 for grades 1 to 2); ET-1 (≥ 41.78 pg/ml was 1, < 41.78 pg/ml was 0); MCP-1 (≥ 229.05 ng/L was 1, < 229.05 ng/L was 0); Lactic acid (≥ 7.13 mmol/L was 1, < 7.13 mmol/L was 0).*

Table IV: Prognostic Value of Serum ET-1, MCP-1 and Lactate Levels in Patients

Factors	Cut-off value	AUC	SE	95%CI	p-value
ET-1	41.78 pg/ml	0.772	0.056	0.662~0.883	**<0.05**
MCP-1	229.05 ng/L	0.871	0.037	0.799~0.942	**<0.05**
Lactic acid	7.13 mmol/L	0.791	0.051	0.691~0.890	**<0.05**

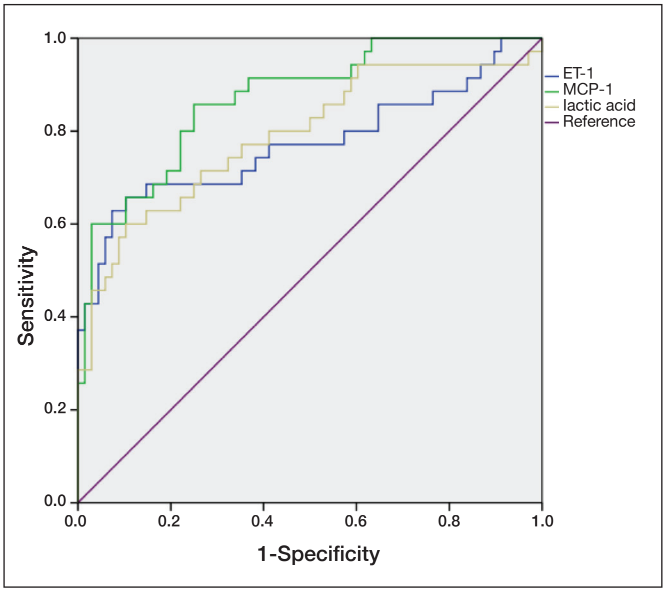

Figure 3: ROC curve of serum ET-1, MCP-1, and LA levels.

DISCUSSION

IA poses a significant public health challenge, impacting 3.2%-7.0% of adults (8). Aneurysm rupture and bleeding are major threats to IA, clinically manifested as severe subarachnoid hemorrhage, rapid onset, and severe headache. Patients might experience symptoms like projectile vomiting due to elevated intracranial pressure, and in severe instances, they may lose consciousness or fall into a coma. Surgical intervention is the mainstay of IA treatment, and DSA-guided aneurysm embolization has become the predominant treatment for most IA patients. MCP-1 acts as a chemotactic agent for mononuclear macrophages, being a specific inflammatory cytokine, and is expressed at low levels in healthy human brain tissue. In the event of brain tissue damage, macrophages and neurons release significant amounts of MCP-1, attracting mononuclear macrophages to infiltrate the brain parenchyma and contribute to brain injury. Therefore, MCP-1 level can indirectly reflect the severity of brain tissue injury (19,26). ET-1 is involved in vascular dysfunction related to cardiovascular diseases (1,4). As a potent vasoconstricting active substance released after blood vessel damage, ET-1 can stimulate the enhancement of platelet activity, aggravation of microcirculation disorders, vasospasm, and damage of neurons (21). It is currently believed that when brain activity is intensifies, the energy needed goes up, enhancing glycolysis and increasing LA production. LA can accumulate in traumatic brain injury as it is produced by glycolysis, especially when brain neurons are damaged (15,24). Hydrocephalus and intracerebral hemorrhage are related to the change in LA levels (5), suggesting that LA is related to the severity of cerebrovascular diseases. Further analysis showed that serum ET-1, MCP-1, and LA were positively correlated with the severity of patients' disease.

IA might rupture unexpectedly, resulting in subarachnoid hemorrhage, a swift increase in intracranial pressure, severe headache, and irritation of the meninges. IA treatment aims to stop blood flow in the diseased artery, prevent tumor rupture, and limit damage to the patient's normal functions (6). Endovascular interventional embolization is one of the main methods for IA, but some patients have poor prognosis after surgery (11). In this study, it was found that Hunt-Hess grade IV-V, Fisher grade 3-4, ET-1 ≥ 41.78 pg/mL, MCP-1 ≥ 229.05 ng/L, and LA ≥ 7.13 mmol/L were risk factors affecting the prognosis of patients after interventional embolization.

Even with a successful aneurysm surgery, patients can experience nerve function defects, and many postoperative complications may follow. Therefore, finding effective indicators to predict the prognosis of IA and formulating reasonable treatment plans have clinical values for postoperative outcomes of IA. Increased serum LA concentrations are largely attributed to tissue hypoxia and/or oxygen debt resulting from inadequate perfusion (10,18). Elevated serum LA is associated with the prognosis of patients with aneurysmal SAH (2,17). This study showed that the AUC values of serum ET-1, MCP-1, and LA levels in evaluating the prognosis of patients were 0.772, 0.871, and 0.791, respectively, all greater than 0.75, suggesting that all indexes have predictive values for the prognosis of patients.

CONCLUSION

In summary, serum ET-1, MCP-1, and LA levels correlate with disease severity in patients with ruptured IA and have predictive value for the prognosis of patients after interventional embolization. They are also risk factors for poor prognosis of patients after interventional rembolization. However, there are limitations to our study. The foremost issue is the small sample size, potentially leading to biased outcomes; second, this was a single-center study, and the findings may reflect only local characteristics. Therefore, we hope that a multicenter study with a larger sample size can be conducted in the future to validate these findings.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: HL

Data collection: HL, ZBL, QWY

Analysis and interpretation of results: TW, ZXH

Draft manuscript preparation: HL

Critical revision of the article: ZXH

All authors HL, ZBL, QWY, TW, ZXH) reviewed the results and approved the final version of the manuscript.

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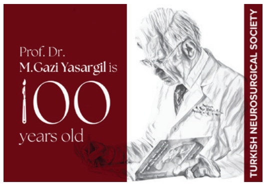

Original Investigation

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Therapeutic Effects of tDCS on Calcium and Glutamate Excitotoxicity in a Cerebral Ischemia–Reperfusion Rat Model

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ABSTRACT

AIM: To investigate the therapeutic effects of transcranial direct current stimulation (tDCS) on calcium and glutamate excitotoxicity caused by ischemia–reperfusion (IR).

MATERIAL and METHODS: The IR model was generated by transient middle cerebral artery occlusion. tDCS treatment was applied at 1 mA for 30 min daily at the 2nd, 24th, and 48th h of IR. The motor and cognitive functions and the concentrations of Ca^{2+}, glutamate, and N-methyl-D-aspartate receptor (NMDAR) in the hippocampus tissues were evaluated.

RESULTS: Results showed a reduction in motor and cognitive functions in the IR group compared with that in the sham group, whereas these functions increased in the IR+tDCS group compared with those in the IR group. Ca^{2+}, glutamate, and NMDAR concentrations were higher in the IR group than in the sham group but lower in the IR+tDCS group than in the IR group.

CONCLUSION: These results suggest that tDCS treatment improves motor and cognitive dysfunctions after IR and exerts therapeutic effects on learning and memory through the regulation of Ca2+ and glutamate excitotoxicity.

KEYWORDS: Excitotoxicity, Glutamate, Ischemia–reperfusion, tDCS

ABBREVIATIONS: IR: Ischemia/reperfusion, **tDCS:** transcranial direct current stimulation, **NMDAR:** N-methyl-D-aspartate receptor

INTRODUCTION

The brain, which accounts for approximately 2% of our body weight, consumes 25% of glucose, 20% of blood flow, and 25% of total oxygen. The primary energy source of our brain is adenosine triphosphate (ATP) (2). Blockage of the cerebral artery supplying the brain causes insufficient blood flow to the center and surrounding area supplied by the artery (2). Ischemia in the brain causes disruption

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of Na^+/K^+ ATPase activity due to ATP deficiency, change in membrane potential, depolarization of neurons, and release of neurotransmitter substances from neurons. Consequently, there occurs an excessive release of glutamate and aspartate into the extracellular space (2). However, the reuptake of glutamate and aspartate into the cell does not occur because the involved mechanism is energy-dependent, which exerts an excitotoxic effect. Furthermore, this situation triggers the continuous stimulation of neurons and Ca^{2+} uptake into the cell. Increased glutamate concentrations in the synaptic gap causes overstimulation of postsynaptic glutamate receptors, especially N-methyl-D-aspartate receptors (NMDARs) (35). Overactivation of NMDARs intakes more calcium ions into the cell and activates enzymes such as protease, nuclease, and caspase, leading to neuronal death in the postsynaptic region (35).

It is essential to treat stroke because of its adverse effects on the individual, family, and society in terms of psychology, community, and economy. The primary purpose of stroke treatment is to ensure that the brain region that cannot be supplied with blood is resupplied with blood and receives the essential nutrients to prevent secondary damage that may occur after ischemia and to accelerate treatment (2). In the clinic, antiaggregant, anticoagulant, thrombolytic, antiedema, and neuroprotective medications are frequently used for stroke treatment. Antiaggregants are drugs that inhibit the aggregation of platelets. Although there are studies on drug treatment for cognitive impairment after cerebral ischemia, neuromodulation by transcranial direct current stimulation (tDCS) has recently been widely used. tDCS is a noninvasive technique that causes changes in membrane potential through the modulation of Na^+ and Ca^{2+} channels by transmitting subthreshold electrical activity to the brain. tDCS is effective on voltage-gated calcium channels, AMPA, and NMDA (23-25). tDCS modulates the membrane potential mediated by the GABAergic and glutamatergic pathways (2). Regulation of these ion channels occurs through the regulation of Na^+ and Ca^{2+} ion transients involved in processes such as cell stimulation, cell death, and apoptosis (2,4). This study was conducted to investigate the therapeutic effects of tDCS on motor and cognitive function impairment caused by calcium and glutamate excitotoxicity in an ischemia–reperfusion model. In addition, cognitive function was evaluated.

MATERIAL and METHODS

All animal use and experimental protocols were approved and implemented by Erciyes University (22/212). A total of 30 male Wistar albino rats weighing 290–300 g were divided into sham, IR, and IR+tDCS groups (Figure 1). The IR model was generated through a 90-min middle cerebral artery occlusion (MCAO), which was used in our previous study and that of Longa et al. (2,18). tDCS treatment was administered as anodal 1 mA for 30 min and 2 days under isoflurane anesthesia (Figure 2) using the Gün medical device. Motor function

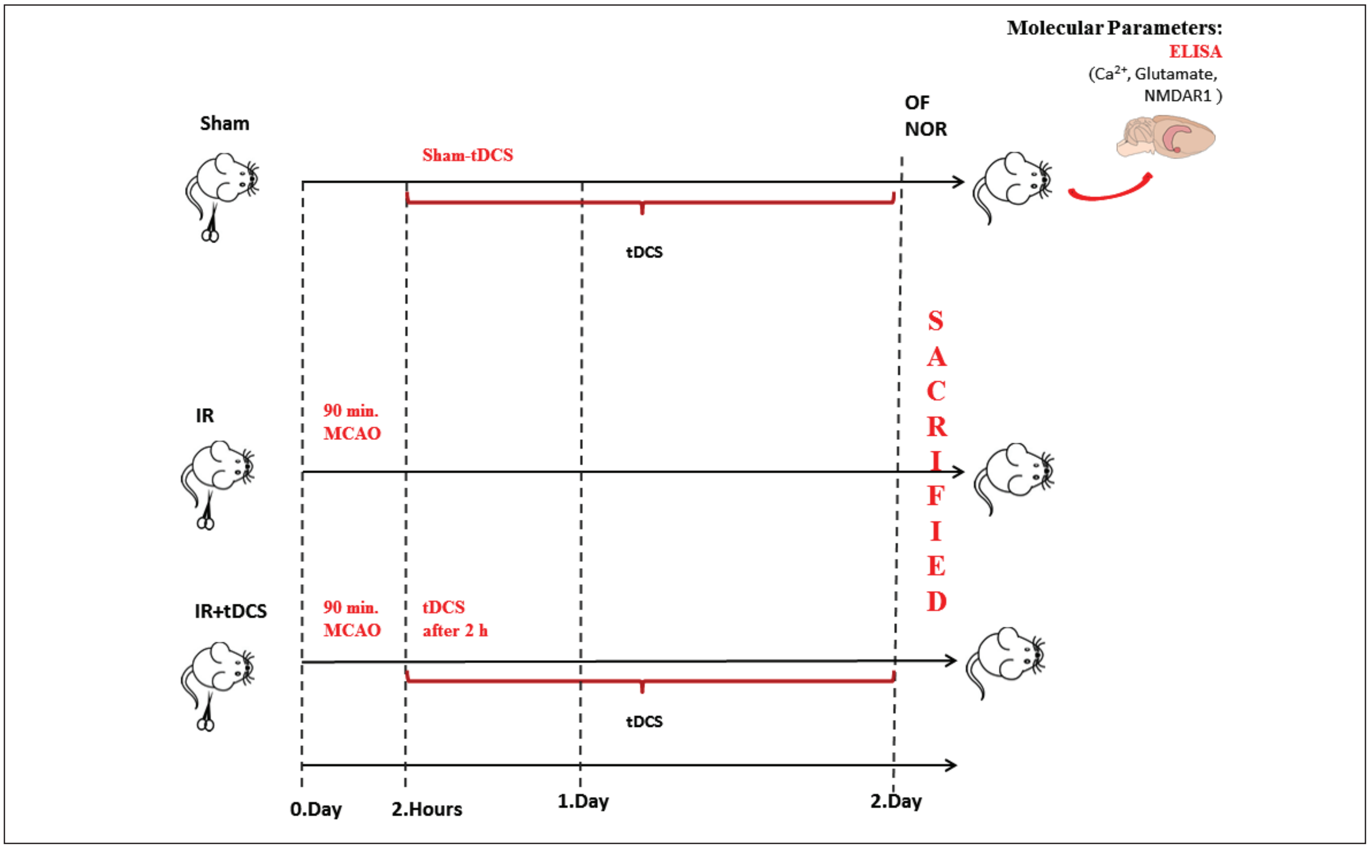

Figure 1: Experimental protocol.

Table I: Behavior Results of Experimental Groups

	Sham		IR		IR+tDCS	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Body weight (gr)	298.00	5.60	275.00	4.80	281.00	5.00
mNSS test score	3.80	0.40	**9.30****	0.90	**7.40#**	**0.70#**
Total Distance (cm)	1289.79	91.97	**786.84****	30.84	**1052.53#**	**38.34#**
Velocity (cm/s)	4.25	0.22	**2.96****	0.10	**3.75#**	**0.16#**
Discrimination index (%)	72.00	1.69	**41.00****	4.60	**60.00#**	**2.32#**
Exploration time of the novel object (s)	40.67	1.18	**29.00****	2.51	**34.00#**	**1.84#**

***p<0.01 compared to sham, #p<0.05, ## p<0.01 compared to IR, one-way ANOVA test, followed by Tukey post hoc test. All data are presented as means ± SEM, n=10 for each group)*

Figure 2: tDCS treatment application.

and cognitive function were evaluated using the open field (OF) and novel object recognition (NOR) tests, respectively. The concentrations of Ca^{2+}, glutamate, and NMDAR1 in the hippocampus tissue were analyzed by ELISA.

Assessment of Neurological Severity Score (NSS)

Rats were subjected to a modified NSS test, which is similar to the sensory, motor, reflex, and balance tests conducted on humans. The experimental protocol was performed according to our previous study (2).

Assessment of Motor Function

The OF test is a behavioral experiment in which locomotor activity is evaluated. Motor function was evaluated using the total distance (cm) and velocity (cm/s) (3).

Assessment of Cognitive Function

The NOR test evaluates attention or short-term memory activities. We used an experimental protocol as described previously (1). The discrimination index (DI) and the duration spent with the novel object (seconds) were evaluated.

Biochemical Analysis

Protein measurements

Homogenization of hippocampus tissues and measurements of protein concentrations were performed according to our previous research (4).

ELISA

The concentrations of Ca^{2+}, glutamate, and NMDAR1 were measured by ELISA as described previously (4).

Statistical Analysis

Data were subjected to one-way ANOVA followed by Tukey's post hoc test. Results are expressed as mean ± SEM and considered significant only when p<0.05.

RESULTS

Table I shows the results of the behavioral tests. Body weights that were measured on day 2 (Figure 2A) showed a nonsignificant reduction in the IR and IR+tDCS groups compared with those in the sham group. Motor behavior indices that were measured on day 2 of ischemia–reperfusion (Figure 2B) showed considerable increases in the IR and IR+tDCS groups compared with those in the sham group; however, the indices in the IR+tDCS group showed a decrease compared with those in the IR group. The motor function, analyzed using the OF test (Figures 2C, D), showed significant reductions in the IR group compared with that in the sham group (p<0.01). tDCS treatment significantly increased the motor function in the IR+tDCS group compared with that in the IR group (p<0.05) (Figures 2C, 2D). Short-term memory was analyzed using the NOR test (Figures 2E, 2F), which revealed a substantial reduction in learning in the IR group compared with that in the sham group (p<0.01); however, there was a substantial increase in the IR+tDCS group compared with that in the IR group (p<0.05). The mean ± SEM concentrations of Ca^{2+}, glutamate, and NMDAR1 are shown in Table II, revealing a substantial increase in the IR group compared with those in the sham group; however, there was a substantial increase

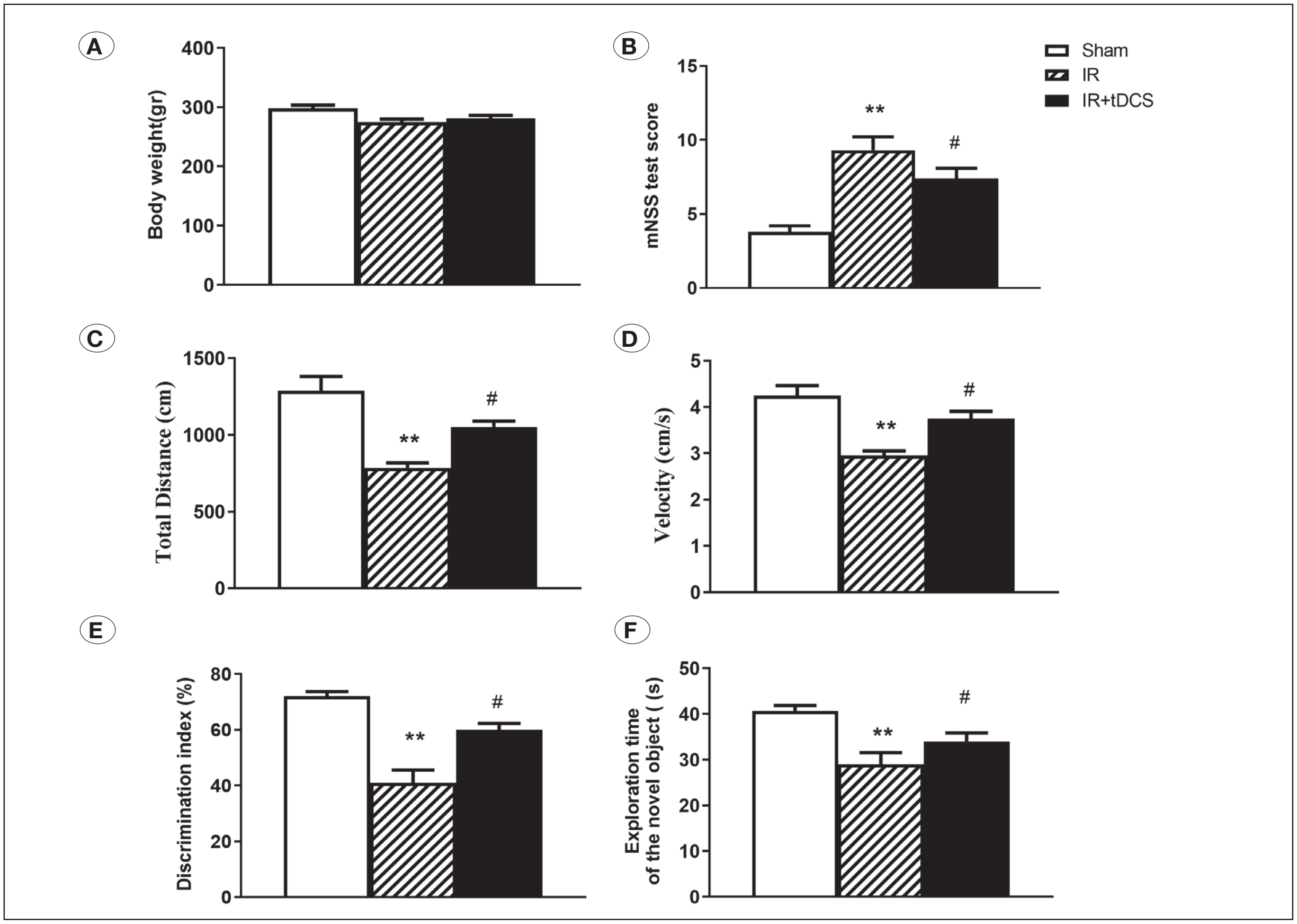

Figure 3: Behavioral results of experimental groups. **A)** 2nd-day body weights of rats, **B)** 2nd-day motor behavior indexes of the groups, **C)** Total distance (cm) in the OF test, **D)** Velocity (cm/s), **E)** Discrimination index (%), and **F)** Exploration time of the novel object (seconds) (*p<0.05, **p<0.01, vs. sham, #p<0.05, vs. IR, n=10, for each group).

Table II: ELISA Results

	Sham		IR		IR+tDCS	
	Mean	**SEM**	**Mean**	**SEM**	**Mean**	**SEM**
Ca^{2+} (µg/ml/g protein)	1.30	0.05	**1.63****	0.04	**1.45#**	0.03
Glutamate (µg/ml/g protein)	0.67	0.05	**1.07****	0.07	**0.87#**	0.02
NMDAR1 (µg/ml/g protein)	1.18	0.05	**2.07****	0.20	**1.61#**	0.12

***p<0.01 compared to sham, #p<0.05, ##p<0.01 compared to IR, one-way ANOVA test, followed by Tukey post hoc test. All data are presented as means ± SEM, n = 10for each group)*

in these concentrations in the IR+tDCS group compared with those in the IR group after tDCS treatment (Figure 3).

DISCUSSION

Cerebrovascular diseases cause bleeding of blood vessels due to changes in the blood vessels supplying the brain or in the properties of blood. Cerebrovascular diseases account for >80% of neurological disorders requiring hospital treatment, of which 87% are ischemic and 13% are hemorrhagic strokes. Improvements in diagnosis and treatment methods in developed countries have led to a decrease in the mortality rates caused by stroke. Therefore, it is important to develop treatment methods that will accelerate the recovery of patients by preventing reperfusion damage after ischemia in stroke (7,33).

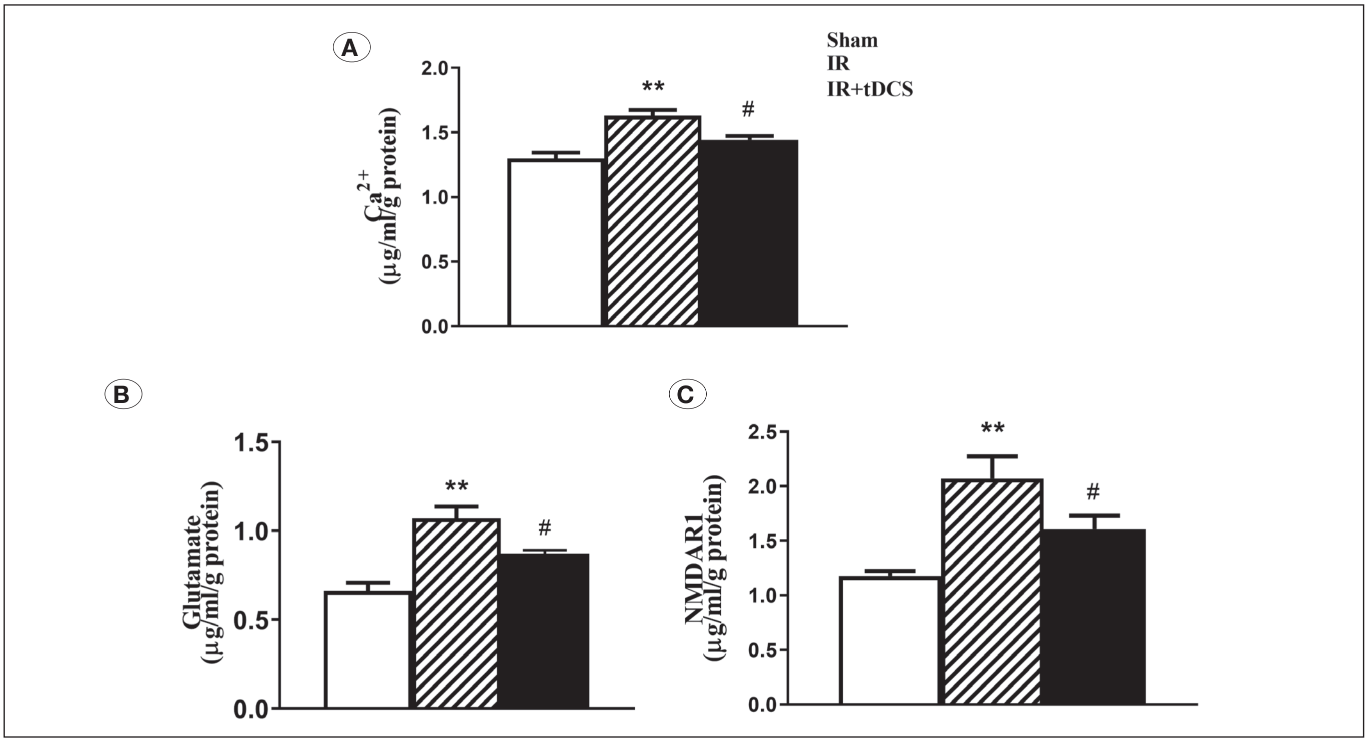

Figure 4: Results of ELISA. **A)** Ca^{2+} concentrations in the hippocampus, **B)** Glutamate concentrations in the hippocampus, and **C)** NMDAR1 concentrations in the hippocampus (******p<0.01, vs. sham, **#**p<0.05, vs. IR, n=10, for each group).

Studies have shown that tDCS therapy improves motor and cognitive functions in patients with Parkinson's disease (4), modulates brain activity in patients with stroke (5), and improves working memory performance in patients with Alzheimer's disease (19). Jiang et al. demonstrated that 0.1-mA anodal stimulation of rats using the MCAO model improved motor activity and increased neuronal plasticity (12). In our study also, we investigated the efficacy of tDCS treatment after MCAO and showed that tDCS reduces cell damage and improves learning and memory loss (2). We have earlier reported that tDCS treatment is especially by the regulation of AMPAR1, NMDAR1, and NMDAR2A receptors (2). In the present study, our aims were to increase the current value by decreasing the duration of treatment and to increase the efficacy of treatment more rapidly. Accordingly, we explored whether tDCS treatment exerts therapeutic efficacy in rats with focal ischemia induced by MCAO. Compared with the other groups, the IR group showed decreased body weight, hemiplegia, balance, and poster impairment. Stroke-related motor and cognitive dysfunction was observed after the stroke; however, tDCS treatment improved the motor and cognitive dysfunction.

Glutamate is the most important excitatory neurotransmitter in the mammalian brain. Glutamate stimulates Ca^{2+} channel receptors such as NMDARs and triggers ischemic neuronal damage and intracellular Ca^{2+} increase, leading to enzymatic cellular death (17,27). In animal stroke models, high concentrations of extracellular amino acids such as glutamate, aspartate, and glycine have been detected after focal cerebral ischemia (20,34). An 80-fold increase in glutamate levels occurs, especially in the ischemic area of stroke (10). Glutamate and its receptors play a vital role in the pathology of ischemia because the excessive increase in glutamate levels in the extracellular space during ischemia and the excessive activation of glutamate receptors in the postsynaptic region cause glutamate–calcium toxicity. Pascual et al. demonstrated an increase in glutamate level in neurons and astrocytes after 60 min of focal MCAO (26). Goldberg et al. also demonstrated that hypoxic injury increased the concentrations of glutamate and glutamine (6). In the present study, we found increased levels of Ca^{2+}, glutamate, and NMDAR1 in the hippocampus tissue of the IR group, which is consistent with the literature. The amount of glutamate increases in the first 4 h after stroke (11,22); however, in our study, tDCS application was applied to the IR+tDCS group 2 h after ischemia. Decreased glutamate levels reduce neuronal damage and infarct volume, thus playing a protective role for glutamate transporters in stroke (13). When we evaluated our data in the light of this information, we observed that the decrease in Ca^{2+}, glutamate, and NMDAR1 levels after tDCS treatment contributed to the neuronal damage and behavioral improvements. The binding of glutamate to ionotropic NMDA and AMPA receptors results in increased Ca^{2+} entry during ischemia (21,32). The activation of NMDA and AMPA receptors plays a critical role in Ca^{2+} toxicity leading to ischemic brain damage (2). Several studies have demonstrated that the stimulation of NMDARs causes cell death (14,30,37). Increased glutamate release or impaired glutamate reuptake in the ischemic region results in an excessive accumulation of glutamate in the extracellular space, causing excessive activation of NMDARs and cell death by excessive Ca^{2+} entry (28,31). However, when overactivated in ischemic stroke, NMDARs initiate toxic pathways that cause neuronal death (8,9,15,16,29). NMDARs are especially effective in brain damage associated with acute ischemic stroke. Another study on rats showed that NMDA gene and protein expression increased after transient MCAO (2). Zaric et al. demonstrated that 15 min of transient global cerebral ischemia caused a significant increase in the hippocampal NMDAR1 protein level (36). Our NMDAR1 findings are similar to the results reported in the literature, wherein we observed an increase in NMDAR1 levels after IR, which might be related to the excessive stimulation of NMDARs by glutamate after IR. After ischemia, tDCS treatment decreased the NMDAR1 level. tDCS regulates membrane potential by modulating AMPA and NMDA receptors (2). Na^{+} and Ca^{2+} ion transients occur through these ionotropic glutamate receptors. Because Na^{+} and Ca^{2+} ions play a role in processes such as cell stimulation, cell death, and apoptosis, tDCS treatment after ischemia may reduce NMDAR activation and reduce Na^{+} and Ca^{2+} ion transients into the cell, which may reduce cell stimulation and prevent cell death and loss of motor and cognitive functions (2,4). We also observed that tDCS treatment decreases the increased glutamate and Ca^{2+} activation after ischemia, which can be achieved by reducing NMDAR activation.

tDCS treatment may exert a neuroprotective effect against cognitive and motor dysfunctions by reducing ischemia-induced calcium and glutamate excitotoxicity. We also concluded that tDCS treatment acts as an antagonist on NMDARs, which plays a critical role in ischemic damage.

In summary, this study demonstrated that early tDCS treatment after cerebral ischemia is effective in the treatment of motor and cognitive dysfunction by regulating glutamate and calcium excitotoxicity.

CONCLUSION

Although we investigated the therapeutic efficacy of tDCS on the glutamatergic pathway after cerebral ischemia–reperfusion, it is known that the excitatory and inhibitory balance plays a vital role in brain damage. In this context, we investigated only the excitatory pathway, i.e., the glutamatergic pathway, and did not investigate the GABAergic pathway, which is considered a limitation of our study. In future studies, we intend to explore the effectiveness of tDCS treatment on the GABAergic pathway.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: GA, DK
Data collection: GA, YME, CC
Analysis and interpretation of results: GA, DK, TG
Draft manuscript preparation: GA, DK, AY, FD, TG
Critical revision of the article: GA
All authors (GA, FD, DK, TG, AY, YME, CC) reviewed the results and approved the final version of the manuscript.

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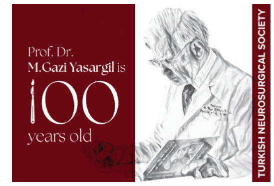

Investigation of the Effects of Dexpanthenol on Brain Tissue in Experimental Global Cerebral Ischemia-Reperfusion Injury

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ABSTRACT

AIM: To investigate the protective and therapeutic effects of dexpanthenol in experimental global cerebral ischemia-reperfusion injury.

MATERIAL and METHODS: Thirty-two female Wistar-Albino rats were used, and the rats were divided into four groups (sham, sschaemia reperfusion [IR], IR+dexpantol [IR+DXP] and DXP+IR), with eight animals in each group. At the end of 72 hours of reperfusion, the rats were decapitated after performing the rotarod and accelerrod tests, their brain tissues were removed and histopathologically examined, and superoxide dismutase (SOD), catalase (CAT), glutathione peroxidase (GPx), glutathione (GSH), and malonyldialdehyde (MDA) levels were evaluated.

RESULTS: In this study, motor skill functions deteriorated in the ischemia-reperfusion (IR) group compared to the sham group, while significant improvements were observed in both the IR+DXP and DXP+IR groups ($p<0.05$). There were no notable differences in CAT, SOD, and GPx enzyme levels among the groups ($p>0.05$); however, malondialdehyde (MDA) levels increased in the IR group and decreased significantly in the IR+DXP group ($p<0.05$). Similarly, glutathione (GSH) levels were lower in the IR group but higher in the IR+DXP group ($p<0.05$). Neuronal degeneration also significantly increased in the IR group but decreased in the IR+DXP group ($p<0.05$).

CONCLUSION: Overall, these findings suggest that dexpanthenol has a neuroprotective effect, particularly when administered during reperfusion, effectively improving motor skills and reducing neuronal damage.

KEYWORDS: Dexpanthenol, Cerebral ischemia, Reperfusion injury, Rat brain

ABBREVIATIONS: CAT: Catalase, **DXP:** Dexpanthenol, **GPx:** Glutathione peroxidase, **GSH:** Glutathione, **IR:** Ischemia-reperfusion, **MDA:** Malonyldialdehyde, **SOD:** Superoxide dismutase

INTRODUCTION

Cerebral ischaemia is a leading cause of disease-related deaths and disabilities globally (24). The World Health Organisation (WHO) defines stroke as a condition causing sudden onset, focal, or global cerebral dysfunction in the cerebrum, spinal cord, or retina, lasting 24 hours or more, leading to disability or death without any cause other than a vascular one (34). In Western societies, around 85% of strokes are ischaemic and 15% are haemorrhagic, making stroke the most common neurological disease and the leading cause of mortality (18).

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Stroke is the third leading cause of death worldwide, following coronary artery disease and malignant diseases. With the growing elderly population, stroke-related deaths and complications are increasing. Stroke not only causes neurological issues but also psychiatric and various medical complications, including cardiopulmonary and metabolic disorders, anxiety, depression, gastrointestinal bleeding, infections, venous thromboembolism, pressure sores, and malnutrition (31). The economic impact of stroke, including treatment, rehabilitation, and decreased productivity, is substantial, accounting for 2–4% of global health expenditures and over 4% of such expenditure in developed Western countries (33).

Cerebral ischaemia can be focal or global, depending on the underlying cause. Global cerebral ischaemia may result from acute brain oedema after cardiac arrest or subarachnoid haemorrhage, while focal ischaemia can occur due to embolic occlusion or local vasospasm following trauma or haemorrhage (36,37). It begins with the depletion of oxygen, ATP, and glucose due to decreased or ceased cerebral blood flow and ends with neural tissue destruction (36). Reperfusion damage, caused by the rapid entry of free oxygen and free oxygen radicals (FOR), is more severe than ischaemia-related damage (27,47). Antioxidant enzymes, such as superoxide dismutase (SOD), glutathione peroxidase (GPx), and catalase (CAT), help prevent damage from free oxygen radicals during oxidative metabolism (19).

Dexpanthenol (D-panthenol; [+]-2, 4-dihydroxy-N-3-hydroxypropyl 3, 3 dimethylthiamide) (DXP) is an alcoholic analogue of pantothenic acid (PA), also known as provitamin B5, which is oxidized to PA in tissues (9). PA and its derivatives enhance intracellular reduced glutathione (GSH), coenzyme A (Co A), and ATP synthesis, particularly in mitochondria (5). PA also increases epithelialisation, anti-inflammatory responses, and antioxidants, all of which play a key role in cellular defence and repair against oxidative stress and inflammation (43).

This study aimed to investigate the neuroprotective effects of dexpanthenol on ischaemia reperfusion injury by inducing global brain ischaemia in rats, using motor skill tests (rotarod and accelerod), histopathology, and biochemical analyses (MDA, SOD, CAT, GPx, GSH). The simultaneous clipping of both arteria carotis communis and the reduction or cessation of cerebral flow is a common method to study cerebral ischaemia pathophysiology (14), and was chosen for its ease of application and lack of need for craniectomy.

MATERIAL and METHODS

This study was approved by the Inonu University Experimental Research Unit and Experimental Animals Ethics Committee on 09.01.2020 with protocol number 2020/01-3.

In the study, 32 female Wistar-Albino rats weighing between 200 and 250 grams and aged 3–4 months old, which had not previously been used in any experiment, were used. The rats were obtained from the Inonu University Experimental Animals Application and Research Centre laboratory. An accelerod device in the laboratory of Inonu University Faculty of Medicine, Department of Pharmacology was used in the study. Biochemical analyses were performed in the research laboratory of the Department of Biochemistry, and histopathological analyses were performed in the research laboratory of the Department of Histology and Embryology.

Rats were housed in polycarbonate cages with a maximum of four animals in each cage, at constant room temperature and humidity (22 ± 3°C temperature and 60 ± 7% humidity), with daily cage cleaning and nutrition (standard animal feed and sufficient water) and appropriate light during the study period.

The rats were divided into four main groups:

Group 1 - Sham Group (n=8): This group underwent only cervical midline incision and paratracheal dissection without cerebral ischemia, followed by surgical closure.

Group 2 - Ischemia-Reperfusion (IR) Group (n=8): In this group, the carotid arteries were bilaterally clamped to induce 30 minutes of cerebral ischemia, followed by 72 hours of reperfusion after surgical closure. No medication was administered.

Group 3 - Post-Ischemia Dexpanthenol Treatment (IR+DXP) Group (n=8): In this group, the carotid arteries were bilaterally clamped to induce 30 minutes of cerebral ischemia, followed by the administration of 500 mg/kg of dexpanthenol intraperitoneally (I.P) at the 1st hour, 2nd, and 3rd days. The group was then subjected to 72 hours of reperfusion.

Group 4 - Pre-Ischemia Dexpanthenol Treatment (DXP+IR) Group (n=8): Starting three days before cerebral ischemia, this group received 500 mg/kg of dexpanthenol intraperitoneally (I.P.) at 08:00–10:00 AM on the 1st, 2nd, and 3rd days. On the 3rd day, the carotid arteries were bilaterally clamped to induce 30 minutes of cerebral ischemia, followed by 72 hours of reperfusion.

The rats were decapitated 72 hours after the induction of ischemia following rotarod and accelerod tests, and the experiment was then concluded.

Anesthesia

Before the surgical procedure, all rats were administered 10 mg/kg of xylazine (Bayer, Leverkusen, Germany) and 50 mg/kg of ketamine hydrochloride (Parke-Davis, Detroit, MI, USA) intraperitoneally (I.P.). If needed, additional doses were given intermittently, not exceeding 20% of the initial doses.

Rotarod, Accelerod Test

This test, conducted to measure motor skills in experimental animals, consists of special rotating rod setups on which the animals (usually rats or mice) try to maintain their balance. The rat is forced to walk on a system programmed to rotate at predetermined speeds. The time until the rat loses its balance and falls off the rotating system is measured. The test provides insight into the extent of brain damage induced in the experiment, the effectiveness of the treatment given, and the rat's sense of fatigue (6). The device was adjusted according to the purpose of the experiment, with the rods rotating at a constant speed (RPM) or at varying speeds over a certain period. In this study, the Rotamex 4/8 system (Columbus Instruments) was used to detect balance and coordination loss in experimental cerebral ischemia at speeds of 5, 10, 20, 30, and 40 RPM and within 4 and 10 minutes at 1-79 accelerating RPM, with a maximum duration of 300 seconds.

Cerebral Ischemia Model and Application

The rats were fasted for 24 hours before surgery, with only water provided. To induce anesthesia, 10 mg/kg of xylazine hydrochloride and 50 mg/kg of ketamine hydrochloride were administered intraperitoneally (I.P.). The anesthetized rats were placed in the supine position, and the surgical area on the cervical region was shaved and painted with a 10% povidone-iodine solution to ensure asepsis. After a midline cervical skin incision, a retractor was placed, and the bilateral paratracheal areas were bluntly dissected. The common carotid arteries were exposed and separated from the vagus nerve, and Yasargil aneurysm clips were placed on both arteries. After 30 minutes, the clips were removed, arterial blood flow was checked, and the incision site was sutured closed once blood flow was observed to be sustained. All subjects were then allowed free access to food and fluids.

Collection of Tissue Samples for Histopathological and Biochemical Analyses

Xylazine and ketamine hydrochloride were used to induce deep anaesthesia in all groups of rats following a predetermined procedure. After deep anaesthesia had been induced, the brain tissue of the rats was removed without any damage. For histological and biochemical analysis of brain tissue, the brain was divided into two hemispheres and one of the hemispheres was placed in 10% formol solution for histological examination. The other hemisphere was placed in previously prepared and numbered containers for each subject and kept at -70ºC for biochemical analysis.

Tissue Reduced Glutathione (GSH) Measurement

GSH levels of tissue samples were measured according to the method described by Ellman (15).

Tissue Malondialdehyde (MDA) Measurement

MDA levels of tissue samples were measured according to the method described by Ohkawa (28).

Measurement of Tissue Superoxide Dismutase (SOD) Activity

SOD enzyme activity levels of tissue samples were measured according to the method described by Sun and Oberley (42).

Measurement of Tissue Catalase (CAT) Activity

CAT enzyme activity levels in tissue samples were measured according to the method of analysis described by Aebi (1).

Measurement of Tissue Glutathione Peroxidase (GPx) Activity

Measurement of GPx enzyme activity levels in tissue samples was performed according to the method of analysis described by Pagli et al. (30).

Statistical Analysis

Statistical analyses were performed with the SPSS package program version 20.0. The Kruskal-Wallis H Test, a non-parametric test, was used for general comparison of groups in terms of all variables, and the Mann-Whitney U test was used for pairwise comparisons between groups. $p<0.05$ was considered statistically significant.

RESULTS

Since there was no statistically significant difference since all groups completed the course at 5 rpm by remaining in balance for 300 s, the balance times at 5 rpm were not included in the comparison. Comparisons were made between the balance times at 10, 20, 30, and 40 rpm. When compared with the IR group, the sham group completed the course by staying in balance for a longer time at all minute cycle speeds (10, 20, 30, 40 rpm), and the differences between the balance times at all rpm speeds were found to be statistically significant ($p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$, $p<0.001$). Although the sham group completed the course by staying in balance for a longer time at all rotation speeds (10, 20, 30, 40 rpm) compared to the IR+DXP group, the results were not statistically significant ($p=0.214$, $p=0.172$, $p=0.103$, $p=0.082$). The sham group completed the course by staying in balance for a longer time at all rotation speeds (10, 20, 30, 40 rpm) compared to DXP+IR group and the balance times at 20, 30,4 0 rpm were statistically significant ($p=0.084$, $p=0.001$, $p=0.002$, $p=0.003$). Compared to the IR+DXP group, the IR group completed the course with a shorter balance time at all minute rotation speeds (10, 20, 30, 40 rpm), and the times at all rpm speeds were statistically significant ($p=0.001$, $p=0.001$, $p=0.001$, $p=0.001$). Compared to the DXP+IR group, the IR group completed the course by staying in balance for a shorter time at all minute rotation speeds (10, 20, 30, 40 rpm), and the balance times at 10, 30, 40 rpm were statistically significant ($p=0.005$, $p=0.031$, $p=0.004$, $p=0.002$). The IR+DXP group completed the course by staying in balance for a longer time at all minute rotation speeds (10, 20, 30, 40 rpm) and the balance times at 20, 30 rpm were statistically significant when compared with the DXP+IR group ($p=0.452$, $p=0.001$, $p=0.009$, $p=0.130$) (Table I).

The sham group, compared to the IR group, completed the course by staying in balance for a longer time in both accelerations from 0 to 79 rpm, lasting 10 min and 4 min, and the difference between the time to stay in balance during the acceleration in both groups was statistically significant ($p=0.001$ and $p=0.001$). When compared with the IR+DXP group, the sham group completed the course by remaining in balance for a longer time in both acceleration tests lasting 10 min and 4 min, from 0 to 79 rpm, but the difference between the time to remain in balance during the acceleration test lasting only 4 min was found to be statistically significant ($p=0.462$ and $p=0.011$). When compared with the DXP+IR group, the sham group completed the course by remaining in balance for a longer time in both acceleration tests, lasting 10 min and 4 min from 0 to 79 rpm, but only the acceleration test lasting 4 min was found to be statistically significant ($p=0.248$ and $p=0.023$). Compared to the IR+DXP group, the IR group completed the course for a shorter time in both acceleration tests lasting 10 min and 4 min, from 0 to 79 rpm and both acceler-

Table I: Rota-Rod Test Results Between Groups

	5rpm Med. ± SD (Min-Max)	10rpm Med. ± SD (Min-Max)	20rpm Med. ± SD (Min-Max)	30rpm Med. ± SD (Min-Max)	40rpm Med. ± SD (Min-Max)
Sham	300 ± 0 (300-300)	293.75 ± 17.6 (250-300)	198.88 ± 59.7 (123-300)	156.75 ± 73.3 (85-300)	46 ± 40.7 (15-140)
IR	300 ± 0 (300-300)	131.63 ± 30.8 (85-80)	45.75 ± 25.3 (12-85)	11.75 ± 4.9 (5-17)	6.25 ± 2.3 (5-10)
IR+DXP	300 ± 0 (300-300)	273.75 ± 38.8 (200-300)	162.88 ± 37.3 (122-240)	108.38 ± 41.5 (62-180)	23.12 ± 16.7 (10-58)
DXP+IR	300 ± 0 (300-300)	246.25 ± 68.2 (120-300)	78.38 ± 25.6 (35-110)	51.12 ± 29.9 (10-105)	13.13 ± 4.5 (10-23)

Table II: Accelerod- Test Results Between Groups

	0-79 rpm (10 min.) Med. ± SD (Min-Max)	0-79 rpm (4 min.) Med. ± SD (Min-Max)
Sham	169.88 ± 72.8	86.5 ± 29.8
	(94-274)	(65-140)
IR	66.87 ± 19.4	34.25 ± 9.2
	(39-90)	(20-51)
IR+DXP	128.25 ± 27.9	59.38 ± 10.2
	(84-162)	(45-73)
DXP+IR	116.50 ± 58.3	57.50 ± 14.5
	(39-188)	(30-72)

ation tests were found to be statistically significant (p=0.002 and p=0.002). Compared to the DXP+IR group, the IR group completed the course by remaining in balance for a shorter time in both acceleration tests lasting 10 min and 4 min, from 0 to 79 rpm, but only the acceleration test lasting 4 min was found to be statistically significant (p=0.128 and p=0.010). Compared to the DXP+IR group, the IR+DXP group completed the course by remaining in balance for a longer time in both acceleration tests, lasting 10 min and 4 min from 0 to 79 rpm, but no statistically significant difference was found between the groups in both tests (p=0.753 and p=0.958) (Table II).

No statistically significant difference was found between the groups in terms of tissue CAT, GPx, and SOD results; therefore, pairwise comparisons were made only between GSH and MDA. When the sham group was compared with the IR group, GSH levels were higher in the sham group than in the IR group (p=0.007), MDA levels were higher in the IR group than in the sham group (p=0.001), and the difference between both results was statistically significant. When the sham group was compared with the IR+DXP group, it was found that GSH levels were lower in the IR+DXP group than in the sham group (p=0.598) and MDA levelx were higher in the IR+DXP group than in the sham group (p=0.527), although the difference between both results was not statistically significant. When the sham group was compared with the DXP+IR group, GSH levels were found to be lower in the DXP+IR group than in the sham group; however, the difference between the results was not found to be significant (p=0.156). MDA levels were found to be higher in the DXP+IR group than in the sham group (p=0.001) and the difference between the results was found to be statistically significant. When the IR group was compared with the IR+DXP group, GSH levels were higher in the IR+DXP group than in the IR group (p=0.031), and MDA levels were lower in the IR+DXP group than in the IR group (p=0.015). When the IR group was compared with the DXP+IR group, it was found that GSH levels were higher in the DXP+IR group than in the IR group and MDA levels were higher in the DXP+IR group than in the IR group, although the difference between both results was not significant (p>0.05). When the IR+DXP group was compared with the DXP+IR group, it was found that GSH levels were higher in the IR+DXP group than in the DXP+IR group (p=0.248) and the difference between these values was not statistically significant, while MDA levels were lower in the IR+DXP group than in the DXP+IR group (p=0.013) (Table III).

Brain tissue samples taken for histopathological examination were fixed with 10% formaldehyde for 48 hours. After fixation, brain tissue samples were subjected to routine histological tissue follow-up procedures and embedded in paraffin blocks. Sections of 6 μm thickness were prepared from the paraffin blocks using a microtome. The sections taken on slides were stained with haematoxylin-eosin (H-E) and examined and photographed with a Leica DFC 280 light microscope and the Leica QWin image analysis system (Leica Microsystems Imaging Solutions, Cambridge, UK). Cerebrum tissues removed at the end of the experiment were fixed in 10% formaldehyde. After tissue tracing, 4–5 μm thick sections were taken from the prepared paraffin blocks. The sections were stained with the haematoxylin-eosin staining method to determine their general morphological structure. The cerebral cortex was evaluated for neuronal degeneration. The severity of neuronal degeneration was ascertained by determining the number of degenerated neurons (neurons with shrunken hypereosinophilic cytoplasm and pyknotic nuclei) in 10 randomly selected areas under x40 magnification (35).

In the sections belonging to the sham group, neurons with normal morphological characteristics with round, large, and euchromatic nuclei and a small number of degenerated neurons were found (Figure 1A). There was a significant increase in the number of degenerated neurons with shrunken, hypereosinophilic cytoplasm and pyknotic nuclei in the IR group, and this increase was statistically significant when compared with the sham group (p=0.0006) (Figure 1B). It was observed that the number of degenerated neurons decreased with DXP application before and after IR. However, the decrease in the number of degenerated neurons in the DXP+IR group was not statistically significant when compared with the IR group (Figure 1C). On the other hand, the decrease in the number of degenerated neurons in the IR+DXP group was statistically significant compared to both IR and DXP+IR groups (p=0.0006) (Figure 1D). The number of degenerated neurons in each group is detailed in Table IV.

Table III: Tissue GSH, SOD, MDA, GPx and CAT Results Between Groups

	CAT (K/g Protein) Med. ± SD (Min-Max)	GPx (U/g protein) Med. ± SD (Min-Max)	SOD (U/g protein) Med. ± SD (Min-Max)	GSH (nmol/g wet tissue) Med. ± SD (Min-Max)	MDA (nmol/g wet tissue) Med. ± SD (Min-Max)
Sham	56.7 ± 16.8 (25.7-87.1)	33.43 ± 9.6 (17.15-45.4)	250.2 ± 33 (234.5-336.6)	744.6 ± 60 (673-836)	135 ± 33.9 (101.3-202.6)
IR	37.7 ± 26.3 (27.3-90.6)	26.2 ± 13.7 (19.1-60.2)	251.5 ± 19.2 (221.5-280.4)	657.9 ± 37.7 (622-734)	229.16 ± 18.4 (206.7-269.2)
IR+DXP	54.8 ± 18.9 (38.2-91.6)	32.4 ± 27.4 (21.07-96.87)	246.9 ± 45.2 (216.9-348.4)	724.2 ± 83 (633-887)	159,2 ± 51.4 (110-225)
DXP+IR	59.6 ± 17.1 (36.5-86.08)	34.7 ± 20.4 (22.5-86.2)	278.4 ± 41.9 (224.3-362.2)	708.9 ± 54.2 (622.2-775.2)	234.9 ± 42.8 (206-327.7)

***CAT:** Catalase, **GPx:** Glutathione peroxidase, **GSH:** Glutathione, **MDA:** Malonyldialdehyde, **SOD:** Superoxide dismutase, **IR:** Ischemia-reperfusion, **DXP:** Dexpanthenol.*

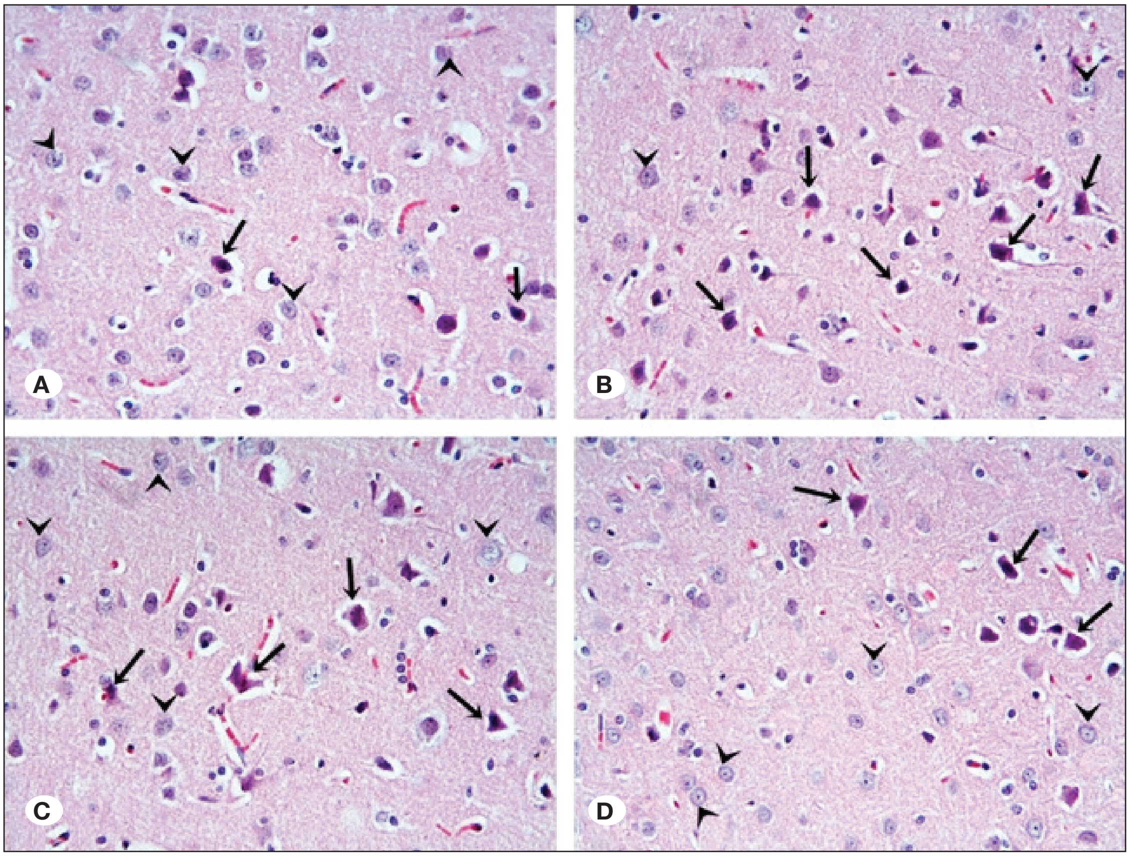

Figure 1: Appearance of the cerebral cortex according to the groups. **A)** Sham group; **B)** IR; **C)** DXP+IR; **D)** IR+DXP. Long arrow heads indicate normal neurons with large, round, and euchromatic nuclei; short arrow heads indicate degenerated neurons with shrunken, hypereosinophilic cytoplasm and pyknotic nuclei. Hematoxylin and eosin, x40.

Table IV: Number of Degenerated Neurons Between Groups

Group	Degenerated neurons Med. (Min-max)
Sham	1.5 (0.0-8.0)
IR	5.0 (0.0-31.0)
IR+DXP	2.0 (0.0-11.0)
DXP+IR	3.5 (0.0-19.0)

***IR:** Ischemia-reperfusion, **DXP:** Dexpanthenol.*

DISCUSSION

Some amount of free oxygen radicals (FORs) is continuously produced in tissues, but these can be neutralised by antioxidant enzyme systems such as CAT, SOD, and GPx (2). The molecules that initiate pathophysiological events in cerebral ischemia are activated by the energy deficit resulting from decreased cerebral blood flow. When glucose metabolism is affected, a state of metabolic imbalance occurs in which ATP and phosphocreatine levels decrease and lactate levels increase. Decreased ATP causes an increase in intracellular calcium, sodium, and chlorine and extracellular potassium levels by disrupting membrane permeability and depolarisation (11). In tissue damage resulting from ischaemia, the duration and depth of ischaemia are the two most important determinant factors (10). In the case of re-oxygenation of ischaemic tissue as a result of reperfusion, a high amount of FOR is formed by the reduction of molecular oxygen by oxidative enzymes in the cell, and these free oxygen radicals play the most important role in the formation of ischaemia reperfusion injury. Superoxide radical (O_2^-), hydroxyl ion (OH^-) and hydrogen peroxide (H_2O_2) are the most important free oxygen radicals. Free oxygen radicals cause damage in the cell membrane by causing lipid peroxidation, and disruption of membrane permeability leads to excessive calcium (Ca^{+2}) accumulation in the cell (25). Increased intracellular calcium activates the apoptosis pathway, resulting in cell death (23). In addition, increased free oxygen radicals and lipid peroxides exert chemotactic effects on neutrophils and cause inflammation and cell damage in reperfused tissue (11).

Dexpanthenol (provitamin B5) is a synthetic alcohol form of pantothenic acid with antioxidant and anti-inflammatory effects (29). It enhances reduced glutathione (GSH), coenzyme A (CoA), and ATP synthesis in cells (12). GSH and glutathione-dependent peroxidases protect against oxidative stress and lipid peroxidation in ischaemia-reperfusion injury and are used in various conditions, including hepatotoxicity, wound healing, and nephropathy, without significant side effects (22,40). To date, although dexpanthenol is a very cheap and easily obtainable substance, there are not many studies in the literature showing its effects on cerebral ischaemia-reperfusion injury.

This study aimed to investigate the protective effect of dexpanthenol in experimental cerebral ischaemia-reperfusion injury. While ischaemia-reperfusion durations vary, studies show 10 minutes is sufficient for cerebral ischaemic damage and 15 minutes for reperfusion damage (20,46). Here, 30 minutes of bilateral carotid artery clamping followed by 72 hours of reperfusion induced cerebral tissue damage. Dexpanthenol was administered prophylactically (DXP+IR group) for 3 days, with 1x500 mg/kg being therapeutically administered before ischaemia (IR+DXP group) for 3 days and 1x500 mg/kg being administered immediately after ischaemia during reperfusion.

In the rotarod test, the sham group balanced the longest at all rpm speeds, while the IR group balanced the shortest. The IR+DXP group outperformed the DXP+IR and IR groups but was shorter than the sham group, and the DXP+IR group balanced longer than the IR group (all comparisons were statistically significant at all rpm speeds). These results reflect brain damage and exhaustion levels in the rats (6). Similarly, in the accelerod test, the balance times were ranked as sham, IR+DXP, DXP+IR, and IR groups (the accelerod 4 min test was significant, while the 10-minute test was not in many comparisons). A study by Korkmaz et al. showed that dexpanthenol improved rotarod and accelerod results in sciatic nerve damage (21). In this experiment, dexpanthenol administered before or after cerebral ischaemia significantly prolonged balance times compared to the untreated ischaemia group.

In ischaemia-reperfusion injury, cells activate antioxidant enzymes like SOD, CAT, and GPx to protect against excessive free oxygen radicals (3). Ucar et al. found lower SOD levels in the ischaemia-reperfusion group compared to the sham group (45), while Soylu Karapinar et al. observed lower GPx and CAT levels in ovarian ischaemia-reperfusion (41). Many studies show that ischaemia-reperfusion increases free radical levels, depleting antioxidant enzymes. Both studies reported increased SOD, GPx, and CAT levels in dexpanthenol-treated groups. Slyshenkov et al. showed that dexpanthenol scavenges free radicals and boosts antioxidant enzyme synthesis (38). In our study, CAT and GPx were lower in the IR group compared to the sham group, while SOD levels were similar in both groups. In the IR+DXP and DXP+IR groups, all three enzymes were higher than the IR group, but the increase was not statistically significant ($p>0.05$).

Malondialdehyde (MDA) is a lipid peroxidation product and an indicator of oxidative damage in tissues, causing cell damage by interacting with membrane lipids (13). Previous studies show increased MDA levels due to ischaemia-reperfusion injury (8), and our study also found a significant increase in MDA levels in the IR group compared to the sham group. Dexpanthenol is thought to reduce lipid peroxidation-induced cell damage by boosting glutathione (GSH) synthesis and GPx enzyme activity (17). Ermis et al. and Tutun et al. reported that dexpanthenol treatment decreased MDA levels in various injury models (16,44). In our study, the MDA level was significantly lower in the IR+DXP group compared to the IR group ($p<0.05$), but no decrease was observed in the DXP+IR group.

Glutathione, an essential tripeptide, is an important endogenous antioxidant involved in the final detoxification of free oxygen radicals (32). Besides working as a scavenger for free oxygen radicals, glutathione is known to be involved in DNA repair, activation of transcription factors, regulation of cell cycle, calcium homeostasis, and enzymatic activities. In oxidative stress, reduced glutathione (GSH) acts as a substrate for free oxygen radicals and GSH levels in tissue decrease (4). In a study conducted by Mukherjee et al. (26), it was shown that the level of GSH in brain tissue decreased significantly as a result of 24 hours of cerebral reperfusion. Previous studies have shown that dexpanthenol increases GSH activity and balances endogenous antioxidants. In a study by Ucar et al.evaluating the effects of dexpanthenol in renal ischaemia-reperfusion injury (45), it was reported that GSH decreased significantly in the ischaemia group compared to the sham group, and GSH levels increased significantly in the dexpanthenol-treated groups compared to the IR group (45). Slyshenkov et al. (39) showed that pantothenic acid supplementation increased hepatic GSH and made liver cells more resistant to radiation. In a study by Cagin et al. investigating the protective effects of dexpanthenol in experimentally induced mesentery ischaemia-reperfusion injury in rats (7), GSH levels were significantly higher in the dexpanthenol-treated group. In our study, results parallel to the studies in the literature were obtained and GSH levels were found to be significantly lower in the IR group compared to the sham group (p=0.007). A statistically insignificant increase in GSH level was found in the DXP+IR group in which dexpanthenol was administered before ischaemia-reperfusion compared to the IR group (p=0.187), and GSH levels were found to be significantly higher in the IR+DXP group treated with dexpanthenol after ischaemia-reperfusion compared to the IR group (p=0.031).

CONCLUSION

Considering that dexpanthenol is a good oxygen free radical scavenger and its antioxidant effects are have been well documented in previous studies, when the results of histopathological, motor skill tests, and biochemical parameters of cerebral tissue obtained in our study were evaluated together, it was thought that dexpanthenol may have a neuroprotective effect in the IR+DXP group treated with dexpanthenol after ischemia and during reperfusion. Although the DXP+IR group, in which dexpanthenol treatment was administered before cerebral ischaemia, caused a relative improvement in the results, this improvement was not statistically significant, and it was concluded that dexpanthenol given before cerebral ischaemia had no neuroprotective effect. Additional experimental and clinical studies are needed to clarify the role of dexpanthenol in the treatment of cerebral ischaemic stroke.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

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AUTHORSHIP CONTRIBUTION

Study conception and design: SS, SCO
Data collection: RE, SS, DEK
Analysis and interpretation of results: SS, RE, II
Draft manuscript preparation: SS, II, DEK
Critical revision of the article: RE, SCO
Other (study supervision, fundings, materials, etc...): SS, RE, DEK II, SCO
All authors (SS, RE, DEK, II, SCO) reviewed the results and approved the final version of the manuscript.

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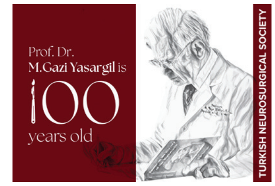

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Assessing Dexmedetomidin's Efficacy in Traumatic Brain Injury Treatment Using a Rat Experimental Model

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ABSTRACT

AIM: To elucidate the effects of nasal and intraperitoneal dexmedetomidine (DexN and DexP, respectively) administration in an animal model, and to explore the underlying action mechanisms on the treatment of traumatic brain injury (TBI).

MATERIAL and METHODS: A total of 31 Wistar albino rats served as a weight-drop model to induce experimental TBI. The two treatment groups received DexN and DexP on the day of the trauma and then after 5 days. The Garcia test was performed for the neurological evaluation along with histopathological and biochemical analyses.

RESULTS: The rats in the treatment group displayed better neurological outcomes, as evidenced by a higher Garcia test score ($p<0.001$). DexP group presented with increased anti-inflammatory and neuroprotective effects in comparison to DexN ($p<0.001$). DexN group demonstrated a reduction in the neuron specific enolase (NSE) levels ($p=0.023$), indicating that it inhibited the neuronal destruction.

CONCLUSION: The present study support the hypothesis that a psychoactive drug, Dex, which has been conventionally used for sleep disorders and is also known for its cognitive-enhancing properties, may have beneficial effects after TBI owing to its anti-inflammatory, anti-oxidative, and neuroprotective properties.

KEYWORDS: Traumatic brain injury, Dexmedetomidine, Neuroprotective agents, Anti-inflammatory agents, Rats

ABBREVIATIONS: BBB: Blood-brain barrier, **CASP3:** Caspase-3, **Den N:** Dexmedetomidine nasal, **DEX:** Dexmedetomidine, **DexP:** Dexmedetomidine peritoneal, **GSH-PX:** Glutathione peroxidase, **H&E:** Hematoxylin and eosin, **Hpf:** Highpower field, **NSE:** Neuron-specific enolase, **S100B:** S100 calcium-binding protein B, **TBARS:** thiobarbituric acid reactive substances, **TBI:** Traumatic brain injury

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INTRODUCTION

Traumatic brain injury (TBI) is an acute biomechanical brain injury caused by an abrupt trauma, often resulting from falls, accidents, or direct impacts. The associated symptoms range from mild ones, such as headaches and brief confusion, to severe ones, including neurological deficits, coma, or even death. TBI involves complex pathological processes, including white matter degeneration, neuronal loss, abnormal protein formation, neurotransmitter imbalances, and chronic neuroinflammation (3). It is a major public health concern affecting all age groups. Despite the advancements made in diagnostics and clinical care domains, the underlying pathological process remains poorly understood, which hinders the development of effective treatments. In addition, co-occurring external injuries often complicate TBI assessments. Understanding the mechanisms of brain injury and recovery is thus crucial for therapeutic advancements.

Dexmedetomidine (DEX), a selective α-2 adrenergic agonist, exhibits sedative, analgesic, and neuroprotective properties via reduction in the sympathetic activity and enhancement of neuroprotection. Recently, DEX has gained attention for its anti-inflammatory and antioxidant effects in TBI models (6). This study evaluated the potential neuroprotective benefits of DEX and compared the efficacy of intranasal versus systemic administration in experimental TBI.

MATERIAL and METHODS

Study Approval

Appropriate Institutional Review Board approval was obtained prior to conducting the study (Ankara Research and Training Hospital Ethics Committee, no: 0019/23102014/317), and the study was conducted in accordance with the "Principles of Laboratory Animal Care" (NIH publication 82-23, revised in 1985 and further updated in 1996). The ARRIVE Essential 10 checklist (available at https://arriveguidelines.org/resources/author-checklists) was applied as the reporting guideline. Thirty-one healthy adult male Wistar rats (n=31) weighing 250–300 g were housed in a temperature-controlled environment (24 ± 2°C) with a 12-hour (h) photophase and administered with an *ad libitum* access to standard chow and water. The rats were randomly assigned into four groups: control (n=7), trauma (n=8), DEX nasal (DexN) (n=8), and DEX peritoneal (DexP) (n=8).

Animal Preparation and Experimental Protocol

Marmarou et al. initially established a model of diffuse cortical injury (8), which was subsequently modified in the present study by the integration of a steel plate, so as to reduce the incidence of post-traumatic seizures. To induce anesthesia, the rats were administered intraperitoneally with 60 mg/kg of ketamine hydrochloride (Alfamine 10%, Egevet Veterinary Services) and 5 mg/kg of xylazine (Alfazyne 2%, Egevet Veterinary Services).

In order to reveal the coronal and lambdoid sutures, a vertical scalp incision was created. Thereafter, a circular aluminum plate (approximately 10-mm diameter, 3-mm thickness) was affixed to the cranium by using bone wax. Subsequently, a 450 g cylindrical lead weight was dropped onto the exposed bony surface from a height of 70 cm through a tube.

No additional intervention was performed in the control group from this point onward and this group only received 2 mL of saline on the day of trauma and then a day later. The DEX group was administered DEX at a dosage of 25 mcg/kg/day immediately following the trauma and then on the following day via intranasal and intraperitoneal routes. In a previous study, equivalent doses of IV and IN showed equally effective outcomes and fewer side effects in the IN administration group. Accordingly, in this study, the same dosage was used (11).

Neurological Examination

An 18-point scale proposed by Garcia et al. was used for neurological evaluation (5). This assessment involved the following six parameters: spontaneous activity, symmetry in four limb movements, forepaw outstretching, climbing, body proprioception, and response to vibrissae touch.

Brain Tissue Extraction and Histological Analysis

A week after the TBI, the brain tissues were extracted *en bloc* under anesthesia, thereby ensuring no additional trauma. The specimens for histological and biochemical analyses were collected from the right frontal lobe close to the interhemispheric fissure. The tissue samples were fixed in 10% phosphate-buffered formaldehyde for 24 h. Subsequently, the specimens were sliced vertically into sections of 4-mm thickness and then placed in cassettes. These sections remained in an ethanol bath for 24 h for fixation, followed by infiltration with paraffin wax. Finally, the samples were sectioned into 5-μm-thick horizontal sections.

Before staining with hematoxylin and eosin (H&E), the sections were kept in 10% buffered formaldehyde for 24 h. A pathologist (blinded to the treatment and control groups) evaluated the sections under a light microscope (Nikon Eclipse 80i) focusing on neuron loss, inflammation, congestion, and gliosis. Anti-inflammatory and neuroprotective analyses served as the main focus, as evidenced by the histopathological scoring system given in Table I. Congestion was analyzed by counting the number of congested vascular structures per high-power field (hpf), whereas the number of inflammatory cells was used for inflammation analysis.

The parameters employed in this analysis were specifically selected for their reproducibility and low susceptibility to bias. The loss of neurons and the presence of gliosis were used to quantify the neuroprotective effect. The number of neurons was considered as 100% in healthy control rats under 5 hpf. Thereafter, quartiles were used to grade the amount of neurons in the test subjects. Similarly, no gliosis was detected in the healthy subjects, and this effect was compared with that observed in the TBI rats. The scoring system was composed of 12 points, with "12" indicating a healthy subject and "0" indicating the most severe injury. Congestion and inflammation points made up for the anti-inflammatory analysis, whereas neuron loss and gliosis made up for the neuroprotective effect.

Table I: Scoring System Used in the Pathological Analysis

Histopathological analysis		Value			
		0	1	2	3
Anti-inflammatory	Congestion[1]	>3	2-3	1	None
	Inflammation	Small groups of inflammatory cells within the parenchyma	Few inflammatory cells within the parenchyma	Perivascular inflammatory cells	No inflammation
Neuroprotective	Neuron loss[2]	>75%	50-75%	25-50%	<25%
	Gliosis[3]	Extended	Limited	Mild	None

[1]*The number of congested vascular structures observed per 1 high-power field (hpf).*
[2]*The specimens obtained from the control group underwent evaluation at the 5 hpf stage. In comparing with other groups, the average number of neurons was taken into account at 60 neurons, expressed in percentage terms as 100%.*
[3]*The control group was evaluated as normal at 3 points. The maximum gliosis was scored as 0. 1-2 points were scored in between.*

Biochemical Analysis

Biochemical analyses were performed by blinded biochemists. The levels of neuron-specific enolase (NSE), S100 calcium-binding protein B (S100B), caspase-3 (CASP3), thiobarbituric acid reactive substances (TBARS), and glutathione peroxidase (GSH-PX) were determined. Tissue samples were mixed with an isotonic solution (0.9% NaCl) and then centrifuged. A commercially available solid-phase enzyme immunoassay kit (Shang Hai Yehua Biological Technology Co., Ltd.) was used for the measurements.

Statistical Analysis

Shapiro–Wilk normality test was applied to determine the normality of the data, whereas Mann–Whitney U-test was used for comparison between the groups. Normally distributed groups were analyzed with one-way ANOVA and non-parametric ANOVA (Kruskal–Wallis) for non-parametric values. P<0.05 was considered to indicate statistical significance. After the Kruskal–Wallis test, the Dwass–Steel–Critchlow–Fligner method was employed for post-hoc analysis. All statistical analyses were conducted using the Jamovi program (version 2.3.21).

RESULTS

One rat in control group died on the night after the intervention, necessitating the omission of all subsequent analyses.

The mean values and standard deviation results for all four groups are detailed in Table II. Table III presents the Garcia Score Test, along with the anti-inflammatory and neuronal protective impacts, as well as the overall histopathological score.

The trauma group exhibited statistically significant ($p \leq 0.001$) poorer outcomes compared to the control group across all four parameters (i.e., Garcia score, anti-inflammatory, neuroprotective, and total histopathologic effect).

The evaluation of the Garcia score via the DexP method and the DexN method yielded identical outcomes. The DexP method demonstrated a more pronounced anti-inflammatory effect relative to the DexN method. With regard to the total histopathological score, the DexP method was more efficacious than the DexN method. In all histopathological analyses (i.e., inflammation, congestion, neuronal loss, gliosis, and overall histopathologic score), the results demonstrated statistically significant better outcomes when compared to those of the trauma group (Table IV). In consideration of the neuroprotective effect, an analysis of the results of additional biochemical markers indicated that DexN demonstrated a more favorable outcome. Biochemical analysis indicated a significant increase in the NSE, S100B, CASP, and TBARS and a decrease in the GSH-PX levels in the trauma group when compared to both the control and trauma groups (Table II). The p-values for S100B, TBARS, and GSH-PX levels among the control, trauma, and pharmacologically treated (DexN and DexP) groups were >0.05, indicating the absence of statistically significant differences between the groups for these variables (S100B: p=0.212, CASP3: p=0.085, TBARS: p=0.160, and GSH-PX: p=0.149, respectively). The non-parametric ANOVA results for the groups with non-parametric distributions (i.e., NSE, CASP3, and GSH-PX) were analyzed. The Kruskal–Wallis test for the NSE levels revealed statistically significant differences between the groups ($\chi^2(3) = 9.56$, p=0.023). This finding supports the hypothesis about the presence of significant differences in the NSE levels among the control, trauma, and pharmacologically treated (Groups 3 and 4) groups. The Kruskal–Wallis test for the GSH-PX and CASP3 levels indicated no significant differences between the groups ($\chi^2(3)= 5.34$, p=0.149 and $\chi^2(3)=6.61$, p=0.085, respectively). Pairwise comparisons were conducted using Dwass–Steel–Critchlow–Fligner tests. The results of the pairwise comparisons for NSE indicated a statistically significant difference between the control and trauma groups (p=0.010). The differences among the other groups were not statistically significant (Dex N vs Trauma: p=0.392; Dex P vs Trauma: p=1.000; DexN vs Control: p=0.967; DexP vs Control: p=0.124; DexN vs DexP: p=0.456).

DISCUSSION

This present study aimed to assess the effects of DEX in an experimental TBI model by using the Marmarou method (8), with the addition of a steel plate to prevent cranial fractures

Table II: Descriptive Values of Biochemistry Markers and Comparison Between Groups (*nonparametric ANOVA Test was Performed For Non-Normal Distributions)

Biochemical markers	Group name	n	Mean	SD	ANOVA/ Non parametric ANOVA*	
					df2/χ^2	p-value
NSE (ng/ml)	Control	7	6.29	1.46	9.56	0.023*
	Trauma	8	9.77	2.25		
	Dex N	8	7.54	4.74		
	Dex P	8	9.91	8.37		
CASP3 (ng/ml)	Control	7	10.54	3.82	6.61*	0.085*
	Trauma	8	11.93	2.12		
	Dex N	8	9.84	3.74		
	Dex P	8	13.06	3.46		
TBARS (pg/ml)	Control	7	128.68	49.29	13.6	0.160
	Trauma	8	184.40	83.34		
	Dex N	8	139.99	28.16		
	Dex P	8	176.77	90.70		
GSH-PX (U/ml)	Control	7	79.06	68.55	5.34*	0.149*
	Trauma	8	100.69	41.79		
	Dex N	8	114.06	22.55		
	Dex P	8	127.25	80.83		
S100B(pg/ml)	Control	7	162.92	63.10	13.8	0.212
	Trauma	8	182.16	53.98		
	Dex N	8	179.13	73.55		
	Dex P	8	187.29	107.24		

Non-parametric values are presented as median ± interquartile range (IQR) and subjected to statistical analysis using the Kruskal–Wallis test.* ***NSE:* *Neuron-specific enolase,* ***CASP3:*** *Caspase-3,* ***TBARS:*** *Thiobarbituric acid reactive substances,* ***GSH-PX:*** *Glutathione peroxidase, and* ***S100B:*** *S100 calcium-binding protein B.*

Table III: Distribution of Garcia score, Anti-Inflammatory Effect, Neuroproductive Effect and Total Histopathologic Scores according to Groups

Groups	Anti-Inflammatory	Neuroprotective	Histopathological score	Garcia Test	Garcia score* p-value
Control	Min: 5.90 Max: 6.00 Median: 6.00	Min: 5.90 Max: 6.00 Median: 6.00	Min: 11.90 Max: 12.00 Median: 12.00	Min: 17.90 Max: 18.00 Median: 18.00	**<0.001**
Trauma	Min: 1.00 Max: 2.00 Median: 2.00	Min: 2.00 Max: 4.00 Median: 2.50	Min: 4.00 Max: 6.00 Median: 2.00	Min: 14.90 Max: 15.00 Median: 15.00	-
DexN	Min: 1.00 Max: 4.00 Median: 3.00	Min: 2.00 Max: 4.00 Median: 4.00	Min: 4.00 Max: 8.00 Median: 6.50	Min: 17.90 Max: 18.00 Median: 18.00	**<0.001**
DexP	Min: 3.00 Max: 4.00 Median: 4.00	Min: 3.90 Max: 4.00 Median: 4.00	Min: 7.00 Max: 8.00 Median: 8.00	Min: 17.90 Max: 18.00 Median: 18.00	**<0.001**

***Mann Whitney U test for comparison with trauma group.*

Table IV: Comparison Between Groups according to Histopathological Parameters

Histopathological parameters	Dex N Control	Dex N Trauma	Dex N Dex P	Trauma Control	Control DexP	Trauma DexP	Kruskal-Wallis	
							χ^2	p-value
Inflammation	0.064	0.001	0.156	0.001	0.954	0.001	23.2	**<0.001**
Congestion	0.001	0.001	0.245	<0.001	<0.001	<0.001	29.5	**<0.001**
Neuronal loss	0.962	0.001	0.245	0.001	0.114	<0.001	23.3	**<0.001**
Gliosis	0.019	<0.001	0.750	<0.001	0.004	<0.001	27.6	**<0.001**
Total score	0.109	0.002	0.070	0.001	0.002	0.001	26.6	**<0.001**

linked to increased mortality and seizures. The rats received either nasal or intraperitoneal DEX, while the control groups were not treated. Three comprehensive analyses focusing on the neurological status, histological evaluation, and biomarker assessment were performed to elucidate the neuroprotective and anti-inflammatory effects of DEX.

The secondary neuroinflammatory phase of TBI is complex and lays the foundation for long-term effects. NSE, S100B, CASP3, TBARS, and GSH-PX have been previously demonstrated to help assess the level of severity of TBI and prognosis (2,3,10). Hence, these biomarkers are valuable in providing insight into the pathophysiology of TBI while shedding light on potential therapeutic agents. However, the NSE levels were lower in the DexP group, with a statistically significant difference (p=0.023). This result advocates the neuroprotective effect of Dex when administrated nasally.

A glycolytic enzyme specific for neurons is NSE, which has been proven to be a reliable biomarker for neuron damage. Elevated NSE levels have been correlated with worse outcomes after TBI (4). Our results suggested reduced levels of NSE after DexN when compared with the control group (Figure 1).

S100B, a glial protein primarily released by astrocytes after CNS trauma, rises rapidly following TBI, peaking within hours, and then normalizing within 24 h. Its elevated levels are correlated with injury severity and neuroinflammation, which makes it a potential therapeutic target (9). In this study, the DexN group exhibited lower S100B levels compared to the trauma group (179.13 ± 73.55 vs. 182.16 ± 16), albeit the intergroup differences were not statistically significant (p=0.212).

CASP3, a key enzyme in apoptosis, is markedly activated following TBI, indicating neuronal cell death. Elevated CASP3 levels have been associated with poor neurological outcomes, highlighting its value as a predictive biomarker (4). In this study, the CASP3 levels were lower in the DexN group than in the control group (9.84 ± 3.74 vs. 10.54 ± 3.82), while the DexP group showed higher levels (13.06 ± 3.46). Although intergroup differences were not statistically significant (p=0.085), the findings suggest that intranasal DEX may help reduce apoptosis.

Considering the significant alterations in the NSE and CASP3 levels observed in DexN, this treatment exhibited neuroprotective properties.

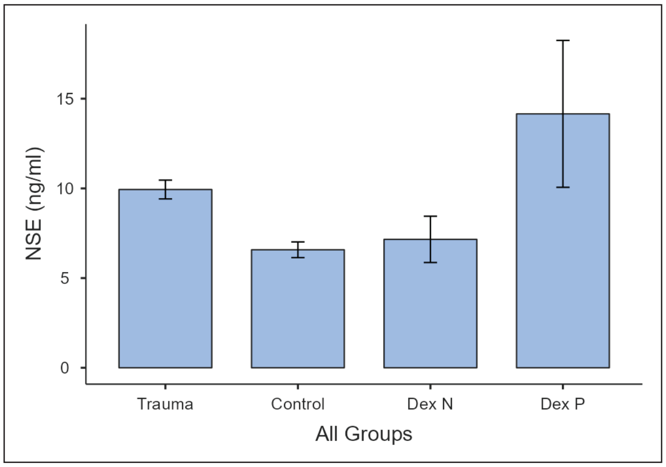

Figure 1: Bar plot showing the level of the neuron-specific enolase (NSE) among all the groups.

TBARS are markers of lipid peroxidation induced by oxidative stress following TBI, with elevated levels associated with worsening neuronal injury and poorer outcomes (1,4). In this study, the TBARS levels in the DexN group were similar to those in the control group (139.99 ± 28.16 vs. 128.68 ± 49.29), while the DexP group exhibited higher levels (176.77 ± 90.70). Although intergroup differences were not statistically significant (p=0.160), the results imply that DexN may help mitigate lipid peroxidation and prevent any secondary neuronal damage.

GSH-PX is an antioxidant enzyme that plays a role in reducing oxidative stress by decreasing hydrogen peroxide levels. In the context of TBI, diminished GSH-PX activity has been demonstrated to indicate a disruption in the antioxidant defense system. Decreased GSH-PX levels have been associated with elevated oxidative stress and adverse outcomes in TBI patients, underscoring the potential importance of maintaining antioxidant balance for neuroprotection. In the groups treated with pharmacological agents, both DexN and DexP were increased in comparison to that in the control group (114.06 ± 22.55 and 127.25 ± 80.83 vs 100.69 ± 41.79, respectively) (Figure 2). However, the Kruskal–Wallis analysis did not yield any statistically significant results (p=0.149). Despite the lack of any statistical significance, the increased GSH-PX level could contribute to reduced morbidity and mortality related

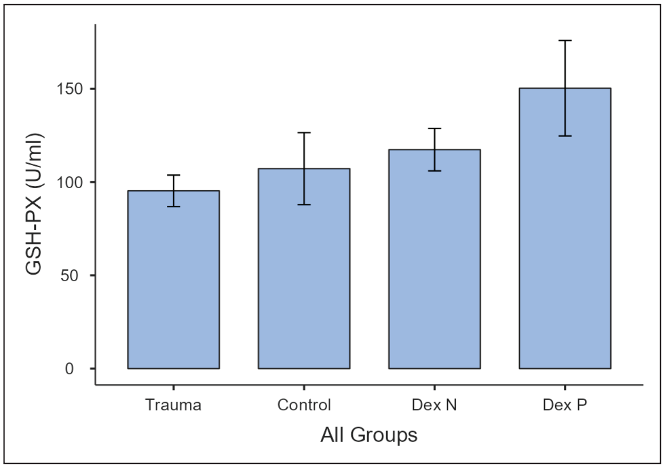

Figure 2: Bar plot showing the level of the glutathione peroxidase (GSH-PX) among all the groups.

to trauma. These findings could be interpreted to suggest that DEX plays a primary role in oxidative stress. Furthermore, the antioxidant effects of DexN are superior to those of DexP.

Histopathological analysis of the brain following a TBI revealed significant pathological changes related to congestion, inflammation, neuronal loss, and gliosis. Each of these factors plays a pivotal role in the comprehensive pathological response to TBI and can affect the outcomes and the clinical course of the injury.

To assess the anti-inflammatory effects of treatment, congestion, and inflammation served as indicators. Similarly, to evaluate the neuroprotective effect, neuron loss and gliosis were employed as markers. The anti-inflammatory effect of DexP was found to be more pronounced than that of DexN. With regard to the neuroprotective and antioxidant effects, an examination of the results of other biochemical markers revealed that DexN exhibited a more favorable outcome.

In terms of the total histopathological score, the DexP drug demonstrated a superior outcome compared to DexN. Our findings are similar to that of a past study in which Dex was used IP after cortical injury in the experimental mice. Dex alleviated early neurological impairment and brain swelling while reducing inflammation, enhancing tight junction protein expression, and mitigating secondary blood–brain barrier (BBB) damage and cell death. These neuroprotective effects have been linked to the suppression of NF-κB and NLRP3 pro-inflammatory pathways. These findings highlight Dex's potential in reducing acute post-traumatic inflammation within 3 days of the injury (11). A recent review article concluded that Dex's neuroprotective effects primarily stem from its ability to suppress inflammation, reduce apoptosis and autophagy, protect the BBB, and stabilize cellular structures. These mechanisms when considered alongside the results of the present study demonstrate significant benefits for neurological recovery in brain injury patients (7).

These results demonstrated that the peritoneally administered DEX drug exhibited a more pronounced anti-inflammatory effect, outperforming the nasally administered DEX drug in terms of histopathological examination. The latter drug, when administered nasally, demonstrated a reduction in the NSE and CASP3 levels, indicating the inhibition of neuronal destruction. Furthermore, an increased level of GSH-PX was recorded, which plays a role in activating the antioxidant system. The drugs administered via both routes exhibited varying degrees of positive outcomes, with a statistically significant difference observed in their Garcia scores, specifically in the neurological assessment ($p<0.001$).

Strengths and Limitations

This study is limited by several factors. The study's limited sample size restricts the generalizability and statistical significance of the findings. Furthermore, the evaluation of dose-response was not feasible owing to the small sample size. However, the use of two different routes of administration represents a strength of this study considering that this study aimed to assess the efficacy of DexP and DexN treatment and to identify the precise mechanism by which Dex exerts its effects. Nonetheless, further investigation is necessary to achieve this goal.

CONCLUSION

The results demonstrated that, following nasal administration, a reduction was noted in the NSE and CASP3 levels, which indicates that the drug inhibited neuronal destruction. In addition, increased levels of GSP-PX were noted, which play an important role in preventing oxidative stress. In contrast, peritoneal administration resulted in a superior outcome in terms of histopathological score when compared to nasal administration. Furthermore, a neurological examination revealed that both routes were associated with positive outcomes.

The present results support the hypothesis that a psychoactive drug, DEX, may impart beneficial effects following TBI through its anti-inflammatory, antioxidant, and neuroprotective effects.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: YO, IB, YG, SS

Data collection: IB, YG, SS

Analysis and interpretation of results: OM, GG, OG

Draft manuscript preparation: OM

Critical revision of the article: OM, IB

Other (study supervision, fundings, materials, etc...): IB, OM, MDJER, YG, SS, OG

All authors (YO, IB, OM, YG, SS, GG, MDJER, OG) reviewed the results and approved the final version of the manuscript.

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Technical Note

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Identification of Decompressive Craniectomy Patients with Refractory ICP using Burst Suppression Ratio and Novel Subgaleal qEEG: A Technical Note

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ABSTRACT

Decompressive hemicraniectomy (DHC) can improve outcome in patients with elevated intracranial pressure (ICP) refractory to medical therapy. However, this transition point for treating refractory ICPs with DHC is unclear as ICPs can often be controlled with escalating doses of medical management. A more individualized and precise way to monitor and define medically "refractory ICP" may be achieved with the utilization of a quantitative electroencephalography (EEG) parameter called burst suppression ratio (BSR). This technical note describes a novel device to continuously gather EEG data from subgaleal electrodes. We present two cases where BSR (i.e. an EEG-derived marker) was associated with maximal cortical suppression, indicating refractory ICP and indication for decompression. Two patients [severe traumatic brain injury (sTBI) and ruptured arteriovenous malformation (AVM)] had BSRs measured through placement of novel subgaleal EEG electrodes. Although both patients had ICPs controlled by a combination of sedation, hyperosmolar therapy, and hypothermia, the BSR over a 20-24 hour period quickly reached almost-complete EEG suppression (BSR > 90%). Each case had different reasons for delaying DHC, however both reached maximal medical therapy. Given the limit of ICP control was reached, DHC was conducted in both cases. Patient 1 failed to recover and was compassionately extubated. Patient 2 clinically recovered and was discharged to acute rehabilitation. These cases illustrate that utilization of a novel subgaleal EEG system to continuously monitor BSR in patients who are being medically managed for ICP control may be used to select appropriate candidates for surgical decompression. In our two cases, a threshold BSR value >90% (induced by medical therapy) was associated with the indication for DHC. This can be used in the future as another tool to define the limit of cortical suppression by medical therapy, thereby, indicating decompression.

KEYWORDS: Burst suppression ratio, Continuous electroencephalography, EEG, Decompressive craniectomy, ICP

ABBREVIATIONS: BSR: burst suppression ratio, **DHC:** Decompressive hemicraniectomy, **ICP:** intracranial pressure, **EEG:** Electroencephalography, **sTBI:** Severe traumatic brain injury, **AVM:** Ruptured arteriovenous malformation, **PRx:** Pressure reactivity index, **CTH:** Computed tomography head

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INTRODUCTION

Severe traumatic brain injury (sTBI) is associated with increased intracranial pressure (ICP) due to multifactorial etiologies (4). Current best-practice guidelines recommend monitoring ICPs with target goals ≤ 22 mmHg (1). However, increased therapeutic intensity level often is insufficient to control ICPs (3). In such cases of “ICP refractory to medical management (ICPref)”, decompressive craniectomies can be offered as a last-tier rescue intervention (7,9).

Offering decompressive craniectomy in this setting requires a better identification of ICPref, whose definition is often opaque due to the diffuse and heterogeneous injury patterns found in sTBI. Although algorithms for medically treating ICPs exist, individualized patient physiology, metabolic clearance of drugs, and underlying brain activity make standardization of medical sedating drip rates impossible (12).

Standard scalp electroencephalography (EEG) and quantitative EEG (qEEG) can quantify background frequencies and detect early-onset ischemia (5). However, scalp qEEG is often insufficient to evaluate background rhythms in patients with ICPref given the suppressed backgrounds in the setting of high doses of sedation required to control ICPs. Using an FDA-approved, novel, neuromonitoring device that uses subgaleal electrodes, we quantified ICPref in sedated patients using a qEEG marker called “burst suppression ratio” (BSR). BSR ranges from 0 to 100% with 100% indicating full suppression of cortical activity.

We describe two patients who had subgaleal electrodes placed and developed ICPref. In these two patients, higher BSR (> 90%) due to escalating doses of medical management was associated with ICPref aiding the decision for decompression.

MATERIAL and METHODS

We describe a novel subgaleal EEG system, iCEWav (iCEWav Neuromonitoring Platform, iCE Neurosystems, Washington, DC, USA).

Subgaleal EEG via iCEWav

One subgaleal electrode consists of eight leads with electrical charge differences measured over leads 1-5, 2-6, 3-7, and 4-8. Each electrode is inserted via a tunneled trochar into the subgaleal space over a parasagittal plane located at the level of the outer conjunctiva. This parasagittal site is thought to best approximate the watershed zone between the middle cerebral and anterior cerebral arteries.

Raw EEG patterns in left side (L1-L5, L2-L6, L3-L7, L4-L8) and right side (R1-R5, R2-R6, R3-R7, R4-R8) (Figure 1) are then converted into qEEG (Figure 2) that incorporate similar quantitative variables as used in traditional scalp EEG—BSR, compressed spectral array (CSA), alpha-delta-ratio (ADR), TPW (total power)—and can incorporate traditional hemodynamic variables—cerebral perfusion pressure (CPP), mean arterial pressure (mART), ICP, brain oxygen (P4).

Patient Treatment Protocol

The treatment regimen adhered to standard, tiered protocols for managing elevated ICP (6). Parenchymal ICP monitors (i.e. bolt) were used (Neurovent-PTO, Raumedic, Mills River, NC, USA). In both cases, medical management for ICP control was initiated. The customized clinical decision – incorporating data from this subgaleal qEEG – for surgical decompression was made by the treating neurosurgical and neurocritical teams.

RESULTS

Clinical presentation

Case 1

A 67-year-old man with hypertension, chronic kidney disease, atrial fibrillation on anticoagulation was transferred from an outside hospital for sTBI after an unwitnessed fall (Figure 3A). The patient had a Glasgow Coma Scale of 12 on admission but quickly deteriorated and was intubated. A left frontal bolt and subgaleal EEG electrodes were placed for monitoring.

Given his bihemispheric contusions, conservative management was deemed reasonable. However, over the next 20

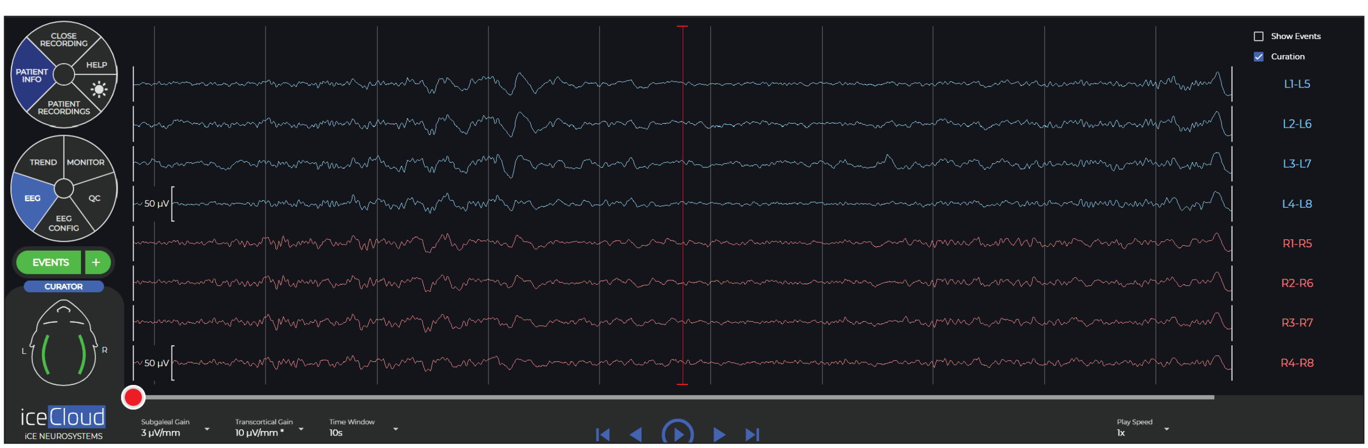

Figure 1: Image from iCEWav demonstrating an example of the raw electroencephalography (EEG) patterns in left side (L1-L5, L2-L6, L3-L7, L4-L8) and right side (R1-R5, R2-R6, R3-R7, R4-R8).

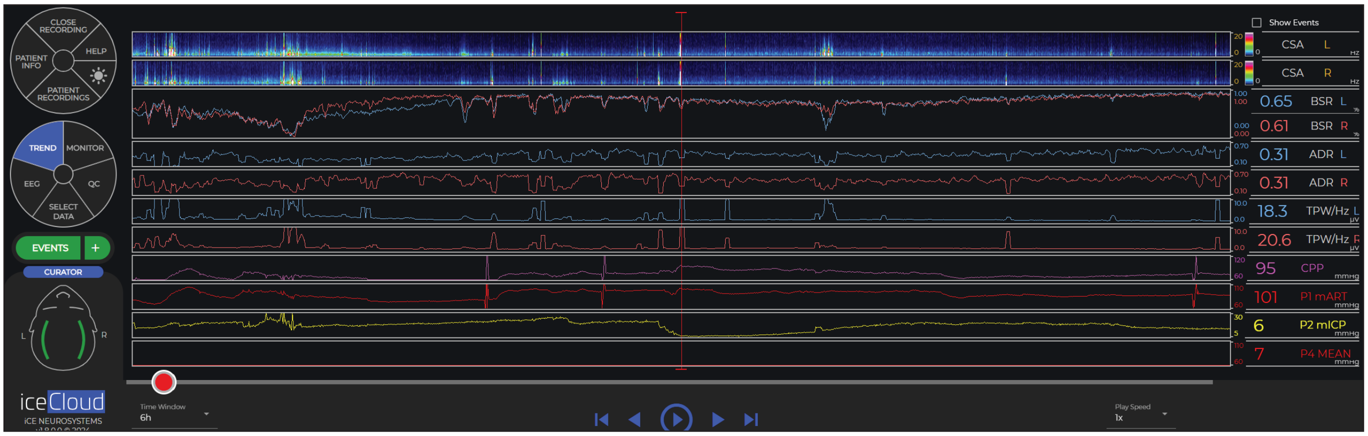

Figure 2: Image from iCEWav demonstrating an example of the quantitative electroencephalography (EEG) values converted from the raw EEG patterns that the system collects. These incorporate similar quantitative variables as used in traditional scalp EEG. **BSR:** Burst suppression ratio, **CSA:** Compressed spectral array, **ADR:** Alpha-delta-ratio, TPW (total power)—and can incorporate traditional hemodynamic variables— **CPP:** Cerebral perfusion pressure, **mART:** Mean arterial pressure, **ICP:** Intracranial pressure, **P4:** Brain oxygen.

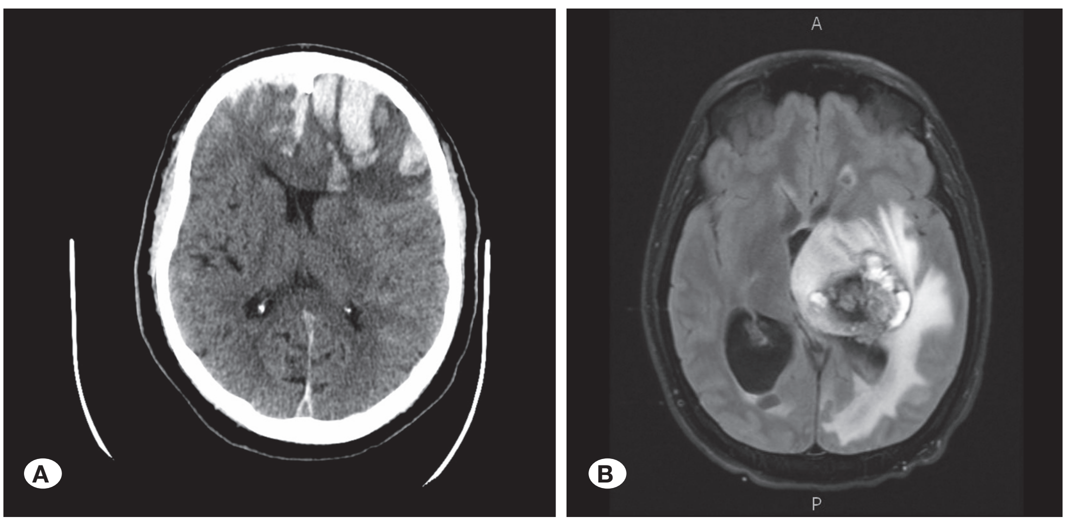

Figure 3: Imaging of **A)** case 1 severe traumatic brain injury demonstrating bifrontal traumatic contusions (left greater than right) and **B)** case 2 demonstrating vasogenic edema and mass effect occurring after a subacutely ruptured arteriovenous malformation.

hours, escalating doses of medical therapy were given for ICP control. He arrived with a body temperature of 32-33°C and this temperature was initially maintained. His medical management included versed drip at 10mg/hr, ketamine drip at 40mg/hr, propofol drip at 50mcg/kg/min, hypertonic saline at 30ml/hr (several boluses were given with a goal serum Na > 160), fentanyl drip at 200mcg/hr, and several vecuronium pushes. His subgaleal electrodes demonstrated extreme burst suppression with a BSR 0.95. On exam, his HR was 49 bpm and sinus rhythm on low-dose levophed to maintain a goal cerebral perfusion pressure (CPP) > 60 mmHg; his pupils remained sluggishly reactive. Despite these treatments, the patient's ICP remained elevated at 22 mmHg. The subgaleal EEGs also demonstrated a steady increase in BSR to 90-100% concurrently with the escalating doses of medication required for ICP control-likely indicating ICPref (Figure 4A). Given the persistently elevated ICPs, the neurosurgical team performed a left-sided decompressive hemicraniectomy.

Post-decompression, he remained comatose. A right-frontal bolt was placed post-decompression to evaluate for further blossoming. Despite the decompression, he remained sedated to control his elevated ICPs until post-operative day 6. His exam would unfortunately remain comatose despite achieving adequate ICP control. After discussion between the treating teams and family, a decision for compassionate extubation was made, and he passed away on hospital day 15.

Case 2

A 27-year-old man with a remote known history of a left-sided arteriovenous malformation (AVM), embolized nine years prior and followed by radiosurgery, had been doing well until presenting with headache, nausea, vomiting, and right-side weakness. He remained awake with a Glasgow Coma Score of 14. Outside hospital computed tomography head (CTH) demonstrated a left thalamic hemorrhage, measuring 4.3 x 3.2 cm, with surrounding vasogenic edema and associated ventriculomegaly. Cerebral angiography on hospital day

1 showed no recurrent aneurysm or underlying AVM. The etiology was unclear with a differential of delayed radiation necrosis or malignancy.

He remained clinically intact until hospital day 10 when he was intubated secondary to seizures. He had hydrocephalus and an external ventricular device (EVD) was placed. Despite CSF drainage, his ICPs continued to escalate. Imaging (Figure 3B) showed a stable lesion and extensive vasogenic edema. However, due to persistent and more frequent ICP elevations, a bolt and subgaleal leads were placed. An initial sedation regimen consisting of versed drip, propofol drip, and fentanyl drip was initiated for more consistent ICP control.

The patient continued to have intermittent, but manageable, ICP spikes until he developed a Cushing reaction. His bradycardia persisted, accompanied by worsening shock, requiring intermittent atropine pushes. While he hemodynamically deteriorated, his ICPs continued to increase; he eventually required versed drip at 15mg/hr, propofol drip at 100 mcg/kg/min, fentanyl at 200mcg/hr, targeted temperature goal of 32-33°C, and hypertonic saline at 100ml/hr (intermittent boluses were given with a goal serum Na > 155). Low-dose pentobarbital infusion was also started. BSR increased to 90-100% (Figure 4B). His BSR demonstrated possible ICPref. Due to the persistently elevated ICPs, the neurosurgical team performed a hemicraniectomy on hospital day 15.

Post-decompression, the sedation was weaned and the patient was rewarmed. On hospital day 35, the patient had a tracheostomy and percutaneous gastrostomy tube placed. He underwent right parieto-occipital ventriculoperitoneal shunt placement on hospital day 45. Slowly his exam improved and on hospital day 87, the patient discharged to acute rehabilitation.

DISCUSSION

Our findings suggest that utilization of BSR may provide a quantitative, functional measure that neurosurgeons can utilize to evaluate for necessity of surgical craniectomy in patients with ICPref. BSR, as a functional marker that evaluates cortical suppression, is important because ICP has more subtle meanings than simply being a targeted number (10). By targeting ICP thresholds with protocolized, medical management but ignoring individualized, cortical activity, clinicians may introduce severe levels of sedation that introduce an irreversible, iatrogenic coma and subsequent shock leading to multi-organ failure while offering little improvement in cortical suppression. The precision-based, individualized evaluation of cortical activity via BSR is also important, particularly in sTBI, because oftentimes the neurological injury is diffuse, and, therefore, the benefits of surgical decompression without a targeted mass lesion is less certain.

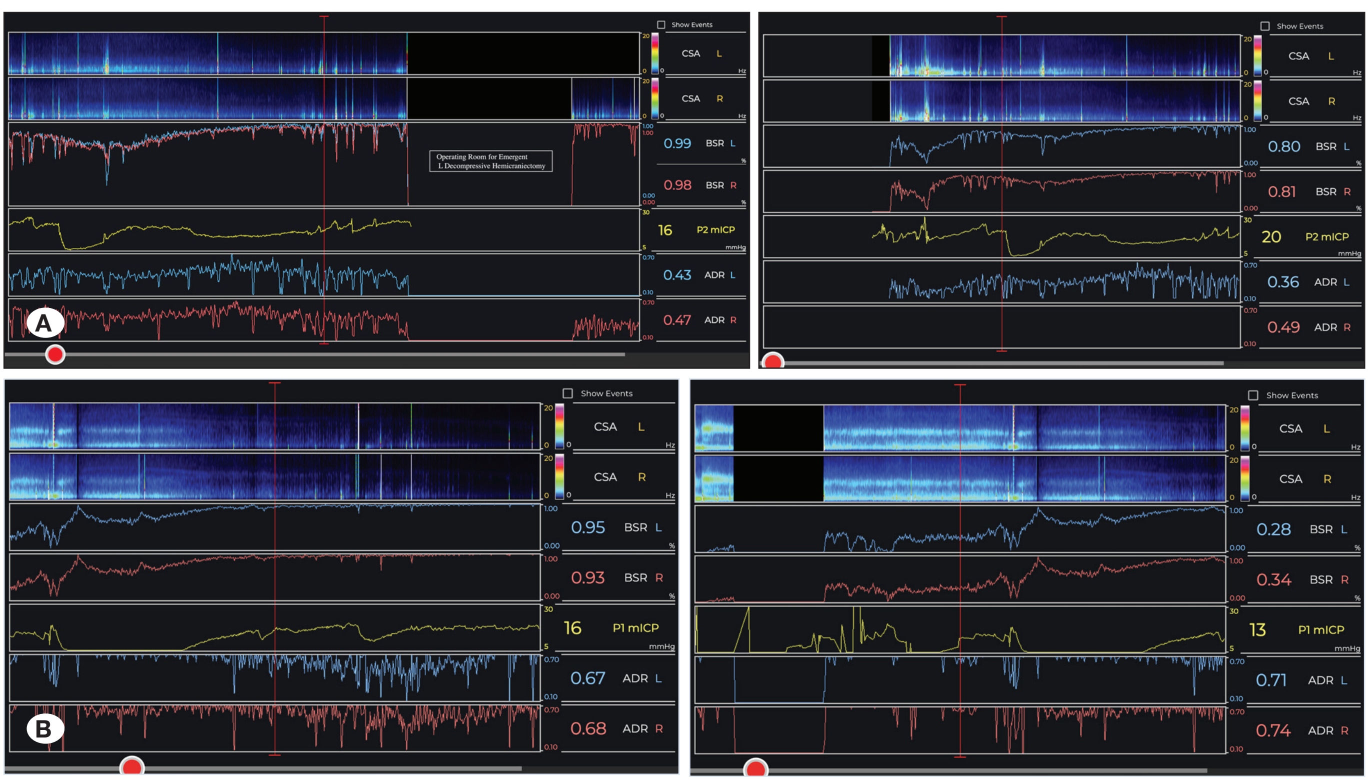

Figure 4: (A) Patient 1: Escalating sedation regimen for increasing intracranial pressure (ICP) correlates with burst suppression ratio (BSR). During this time, patient was on versed drip, propofol drip, fentanyl drip, vecuronium drip, and low-dose norepinephrine drip to achieve a BSR of 0.99 on the left, 0.98 on the right, and intracranial pressure (ICP) of 16 mmHg. **(B) Patient 2:** Escalating sedation regimen for ICP controlled correlated with increasing BSR. During this time, patient was on propofol drip, fentanyl drip, vecuronium drip, low-dose norepinephrine drip to achieve a BSR of 0.95 on the left, 0.93 on the right, and ICP of 16 mmHg. On the figure, **CSA** = compressed spectral array, **BSR** = burst suppression ratio, **P2mICP** = ICP (mmHg), **ADR** = alpha-delta ratio.

In our two cases, we utilized qEEG and BSR – derived from a novel device utilizing continuous subgaleal EEG monitoring – to identify futile levels of sedation and ICPref. This allowed us to identify the time point when medical management had become exhausted and when surgery would need to be offered to prevent further herniation.

A literature search in PubMed does not show any peer-reviewed publication clinically using subgaleal EEG monitoring for evaluation of BSR.

Several limitations exist before considering BSR more routinely as a functional marker for ICPref. First, there is a lack of precision when defining and measuring "BSR", including how these models capture mechanistic versus phenomenological aspects of burst suppression (2,11). Furthermore, BSR as defined in the clinical literature always refers to traditional scalp EEG and not the novel subgaleal EEG that we utilized. We found scalp EEG consistently more suppressed due to the greater distance separating scalp electrodes from cortex. Third, the etiology of burst-suppression is debatable: sedation-induced or due to disease burden (8). We would argue Figure 4 shows that BSR rapidly increased and its sustained elevation (>90%) within a 24-hour span correlated with the escalating sedation regimen. Fourth, the utilization of BSR to quantify "refractory ICP" and initiation of surgical intervention is not necessarily associated with improved functional outcome. However, this limitation really underlies the problem with the multifactorial etiologies that influence clinical outcome and has prevented any surgical decompression trial from demonstrating improved functional outcome (1,3,4). In fact, a more precise definition of "refractory ICP" as aided by subgaleal BSR may help future trials dissect out criteria for when surgical decompression should be offered.

CONCLUSION

We conclude the pathophysiology of BSR and its association with medically refractory ICP needs further study. Once BSR is further characterized, neurosurgeons may use BSR to better define medically "refractory ICP" enabling a better discussion of the risks and benefits of introducing salvage, surgical interventions.

Declarations

Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethical Considerations: The study protocol did not need any IRB approval.

AUTHORSHIP CONTRIBUTION

Study conception and design: AK, JC
Data collection: AK, JC
Analysis and interpretation of results: AK, JC
Draft manuscript preparation: AK, JC
Critical revision of the article: AK, DF, JM, JC
Other (study supervision, fundings, materials, etc...): JC
All authors (AK, DF, JM, JC) reviewed the results and approved the final version of the manuscript.

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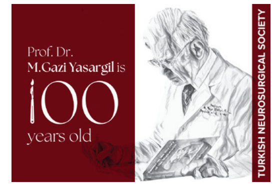

Is C1 Asymmetric Laminectomy Safer? A Cadaver Study

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ABSTRACT

AIM: To investigate the difference in the length of C1 laminectomy between the right and left sides and to determine the importance of considering the dominant vertebral artery in reducing complication risks.

MATERIAL and METHODS: Five caucasian male cadavers were studied. The distance of the C1 posterior tubercle to the vertebral groove (A), the length of the vertebral groove (B), and the diameter of the vertebral artery were measured and statistically investigated. Computed tomography scans were also obtained from all cadaver specimens.

RESULTS: The mean distance of the C1 posterior tubercle to the vertebral groove (A) on the right side was 20.20 ± 2.16 mm and on the left side was 16.40 ± 2.88 mm. The mean distance of the vertebral groove (B) on the right side was 13.80 ± 0.83 mm and on the left side was 17.60 ± 0.89 mm. The mean diameter of the vertebral artery on the right side was 3.58 ± 0.83 mm and on the left side was 3.70 ± 0.10 mm.

CONCLUSION: The vertebral groove was longer on the dominant artery side. Therefore, the dominant and nondominant sides have different lengths of safe C1 laminectomy areas. The length of the laminectomy area to be performed on the dominant artery side is shorter than that on the nondominant side. In cases in which the C1 posterior arcus must be removed for decompression, asymmetric decompression should be performed to reduce the risk of vertebral artery injury.

KEYWORDS: C1, Laminectomy, Vertebral groove, Vertebral artery, Injury

INTRODUCTION

C1 (axis) laminectomy is performed by removing the posterior arcus of axis during surgery. The anatomy of the has a complex structure. For this reason, it differs from other laminae of the spinal region in laminectomy application. C1 laminectomy is usually indicated for spinal cord compressions such as spinal stenosis, trauma, congenital conditions (Chiari malformation, etc.), inflammatory diseases (rheumatoid arthritis, etc.), and infections (1). Insufficient decompression leads to continued pressure on the spinal cord and thus clinical symptoms. Excessive laminectomy increases the risk of complications. Previous studies have reported various complications associated with C1 laminectomy, including infection, bleeding, and nerve damage.

Few studies in the literature have addressed C1 laminectomy, and the length of decompression surgery has been rarely discussed (7). In general, the length of C1 laminectomy is performed symmetrically, like other levels of the spinal column. Despite the known risks of C1 laminectomy, there is limited research on the optimal length of the procedure to minimize complications.

In this study, we aimed to investigate the difference in length of C1 laminectomy between the right and left sides and to determine the importance of considering the dominant vertebral artery in reducing complication risks.

MATERIAL and METHODS

We studied five caucasian male cadavers. Ethical approval for the study was obtained from the local ethics committee

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(No. 09.2021.1130). Dissection was performed on all cadavers through a midline skin incision extending from the occiput to the level of the C3 vertebra at the nuchal line. We performed bilateral dissection from the C1 posterior arch to to reveal the vertebral groove and transverse process. The artery was exposed from where the vertebral artery exits from the C1 transverse process to the vertebral groove and dura mater.

We measured and statistically investigated the distance of the C1 posterior tubercle to the vertebral groove (A) and the length of the vertebral groove (B) (Figure 1). For the statistical analysis, we conducted a paired *t* test using GraphPad Prism version 10.0.0 for Windows (GraphPad Software, Boston, MA, USA; www.graphpad.com).

Radiology

We obtained computed tomography (CT) scans from all cadaver specimens. CT imaging was performed on a 256-channel (2 x 128) or 128-channel multidetector CT scanner (Somatom Definition Flash or Somatom Definition AS+, respectively; Siemens Healthcare, Erlangen, Germany). Images were obtained in the axial plane with 0.6-mm collimation and 120 kVp (kilovolt peak). We adjusted the milliamperes per second for each patient via tube current modulation. The images were reconstructed with 1-mm thickness in all three planes. We determined the dominant and nondominant vertebral artery sides using CT scan measurements from the cadavers.

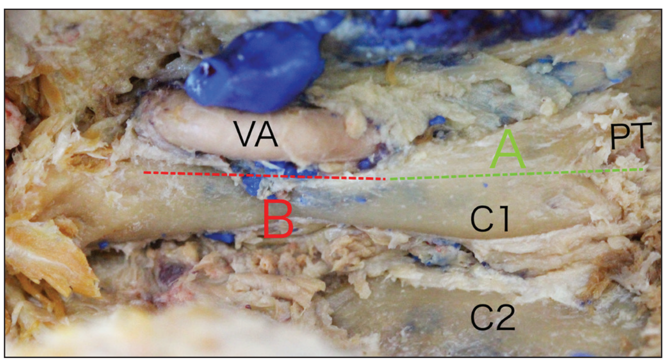

Figure 1: The distance of the C1 posterior tubercle to the vertebral groove (A-green line) and the length of the vertebral groove (B-red line) were measured in all cadavers. C1, first cervical vertebrae; C2, second cervical vertebrae; PT, posterior tubercule; VA, vertebral artery.

RESULTS

We performed dissections on all cadaver specimens. Anatomical distances were physically measured on the cadavers, in addition to the CT scan measurements of the identical specimens (Figure 1; Table I). CT scans were performed on the cadavers to demonstrate the relationship between the vertebral groove and laminectomy. The C1 lamina was measured from the right and left of the midline. The vertebral groove was measured separately on the right and left sides. We determined the dominant and nondominant sides of the vertebral artery in the cadaver tomography sections. According to the vertebral artery (VA) diameter measurements on the CT scans, we determined the left side of all cadavers as the dominant side (Figure 2A; Table II). In Figure 2A, the magenta-colored bar represents the left side of the VA diameter measured on the widest aspect of the artery in the coronal section of the CT image of cadaver 1. In Figure 2B, the magenta-colored bar represents the right-side VA diameter measured on the widest aspect of the artery in the coronal section of the CT image of cadaver 1. We attempted three-dimensional (3D) reconstruction to show the anatomical differences in the posterior–superior and posterior views of the vertebral groove. The 3D reconstructions of the CT images of the cadaver from a posterior–superior aspect of the cranium (Figure 2C). We digitally removed certain parts of the cranium to demonstrate the C1 anatomy. The magenta-colored shades represent the VA grooves on both sides (Figure 2C). The blue shade represents the left lamina, and the green shade represents the right lamina (Figure 2C). The 3D reconstructions of the CT images of the cadaver from a posterior aspect of the cranium (Figure 2D). We digitally removed certain parts of the cranium to demonstrate the C1 anatomy. The magenta-colored shades represent the VA grooves on both sides. The

Table I: Measurements Made on the Posterior Arcus, Vertebral Groove and Vertebral Artery in Cadavers

Cadaver	C1 Length (mm)				VA		
	A		B		Diameter (mm)		Dominant Side
	Right	Left	Right	Left	Right	Left	
1	19	15	13	17	3.5	3.6	L
2	21	18	14	17	3.6	3.7	L
3	22	19	14	17	3.6	3.8	L
4	17	12	13	18	3.5	3.6	L
5	22	18	15	19	3.7	3.8	L
Mean	20.20	16.40	13.80	17.60	3.580	3.70	
SD	2.168	2.881	0.8367	0.8944	0.08367	0.100	

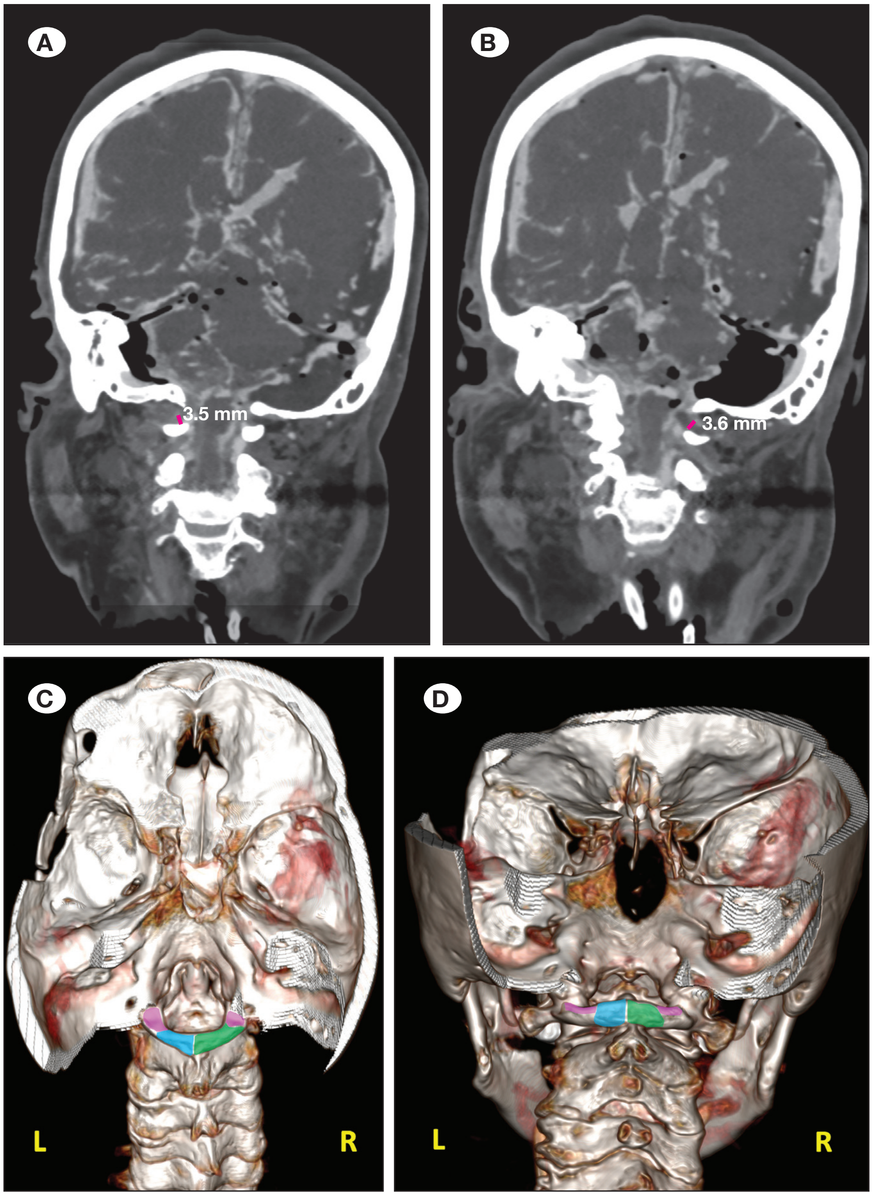

Figure 2: A) Coronal section of the CT image of cadaver 1. The magenta-colored bar represents the diameter of the left-side vertebral artery measured on the widest aspect of the artery. **B)** Coronal section of the CT image of cadaver 1. The magenta-colored bar represents the right-side vertebral artery diameter measured on the widest aspect of the artery. **C)** The 3D reconstructions of the CT images of cadaver 1 from the postero-superior aspect of the cranium. Certain parts of the cranium were digitally removed to demonstrate the C1 anatomy. Magenta shades represent the vertebral artery grooves on both sides. The blue shade represents the left lamina. The green shade represents the right lamina. **D)** The 3D reconstructions of CT images of cadaver 1 from the posterior aspect of the cranium. Certain parts of the cranium were digitally removed to demonstrate the C1 anatomy. Magenta shades represent the vertebral artery grooves on both sides. The blue shade represents the left lamina. The green shade represents the right lamina. L, left; R, right.

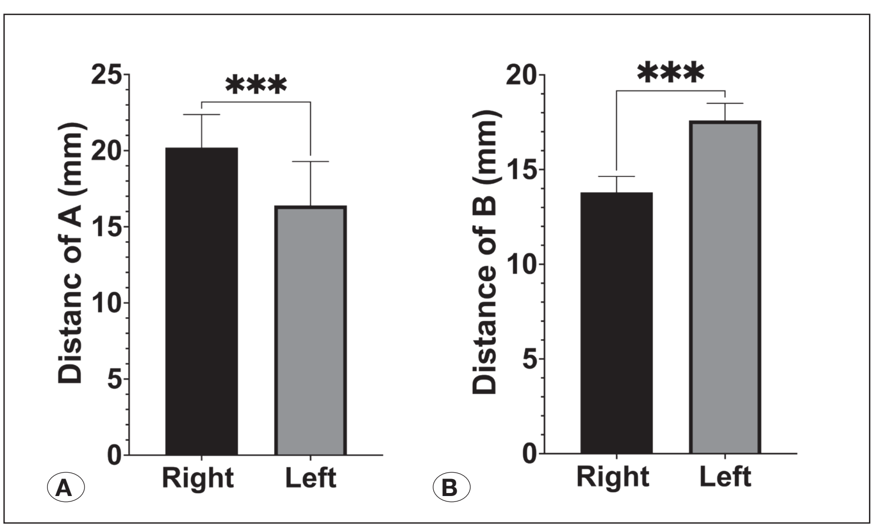

Figure 3: A) The comparison of the right and left posterior tubercle to vertebral groove (A) length measurement showed a significantly greater measurement on the right side ($p<0.05$). **B)** In comparing the length of the vertebral groove (B) on both sides, measurements of the left side were substantially greater ($p<0.05$).

blue-colored shade represents the left lamina, and the green-colored shade represents the right lamina (Figure 2D).

Table I shows the results of the anatomical properties of the C1, C2, and VA measurements of all cadavers. We calculated the means and standard deviations for the parameters based on the left and right measurements, respectively (Table I). The comparison of the right and left posterior tubercle to vertebral groove (A) length measurement showed that the measurement was significantly greater on the right side ($p<0.05$) (Figure 3A). In addition, when comparing the vertebral groove length (B) on both sides, the measurements of the left side were substantially greater ($p<0.05$) (Figure 3B).

In the first cadaver specimen, the distance of the C1 posterior tubercle to the vertebral groove (A) on the right side was 19 mm, whereas the distance on the left side was 15 mm. In the second cadaver specimen, the exact distance (A) was 21 mm on the right side and 18 mm on the left side. The measurements of A in the third cadaver specimen were 22 mm and 19 mm on the right and left sides, respectively. The fourth cadaver specimen had measurements of 17 mm and 12 mm on the left and right sides, respectively, for the same distance (A). Finally, in the fifth cadaver, the distance of A was 22 mm on the right side and 18 mm on the left side. The mean distance of the C1 posterior tubercle to the vertebral groove (A) on the right side was 20.20 ± 2.16 mm whereas it was 16.40 ± 2.88 mm on the left side.

In the first cadaver specimen, the distance of the vertebral groove (B) on the right side was 13 mm and on the left side was 17 mm. In the second cadaver specimen, the exact distance was 14 mm and 17 mm on the right and left sides, respectively. Measurements for the distance of B obtained in the third cadaver specimen were 14 mm and 17 mm on the right and left sides, respectively. In the fourth cadaver, the distance for B was 13 mm on the right and 18 mm on the left. The fifth cadaver specimen demonstrated measurements of 15 mm on the right and 19 mm on the left for the same measurement (B). The mean distance of the vertebral groove (B) on the right side was 13.80 ± 0.83 mm and on the left was 17.60 ± 0.89 mm.

The mean diameter of the VA was 3.58 ± 0.83 mm on the right side and 3.70 ± 0.10 mm on the left side. We accepted the left VA as the dominant artery in all cadavers.

DISCUSSION

C1 laminectomy without fusion is indicated in some cases, especially in patients without spinal instability (3). C1 laminectomy is frequently performed as a surgical intervention for Arnold–Chiari malformation, intraspinal tumors, craniovertebral junction stenosis, trauma, and infections. In this study, our aim was to investigate the difference in C1 laminectomy length between the right and left sides and to determine the importance of considering the dominant VA in reducing the risk of complications.

C1 laminectomy is a well-known surgical procedure. However, it is important to be aware that complications may occur during surgery, and to avoid such complications, careful consideration of the anatomy of the VA is required. According to previous studies, the incidence of VA injury is 5.4% during laminectomy and ranges from 8% to 32.4% during C1–2 fixation (4,5,8). There is also a high risk of VA injury during craniocervical surgical procedures. Complications that occur during C1 laminectomy include VA injury and spinal cord injury. Among these, injury to the VA is a life-threatening complication. Complications of VA injury include bleeding, infection, blood clots in the legs or lungs, spinal cord or nerve root injury, and cerebral infarcts. Studies have demonstrated a risk of VA injury, especially during laminectomy. The C1 anatomy must be well identified to prevent catastrophic complications after VA injury.

The vertebral groove widens anteriorly as it progresses on the posterior arch. From the information we obtained in our previous studies, we noted differences between the measurements of the vertebral groove from the superior–anterior to the posterior regions (2,6). In the current study, we obtained measurements from the posterior region; thus, our surgical view was also posterior. The length of the vertebral groove from the posterior region was shorter than that of the superior region (2). Our study results show that the vertebral groove has a specific anatomical shape. It is understood that the course of the VA continues a few millimeters anteriorly and medially at the superior surface of the C1 arcus, and the length of this part is longer than the length of the vertebral groove of the posterior view. Because of these anatomical differences, it should be kept in mind that the risk of arterial injury is high where the medial border of the vertebral groove begins. It is essential to stop at the medial edge of the vertebral groove, where it is observed from the posterior. As shown in this study, laminectomy should be completed when the medial border of the vertebral groove is reached. Figure 4 shows the free space between the lateral border of the spinal cord and the vertebral

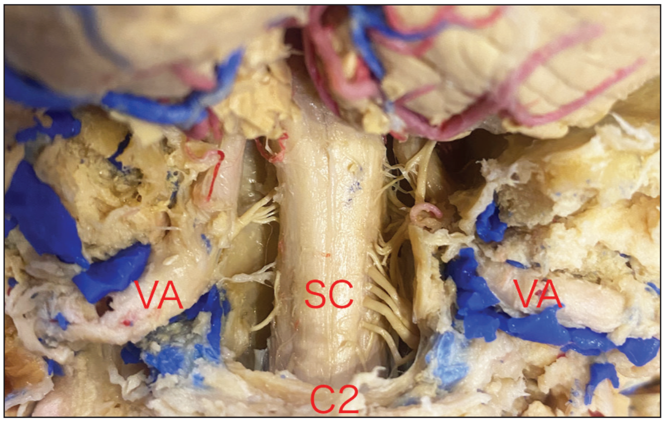

Figure 4: The spinal cord and VA are seen after removal of the C1 posterior arcus, posterior part of the foramen magnum, and part of the occipital bone. The medial border of the vertebral groove is located at the point where the VA artery turns from posterior to anterior. It can be seen in the figure that there is a free distance between the VA and the dura, although the lack of CSF is also taken into account. C2, second cervical vertebrae; SC, spinal cord; VA, vertebral artery.

groove. As seen in the figure, the spinal cord is covered with the dura in a fixed cadaver. Because there is no cerebrospinal fluid (CSF), the distance between the VA and the dura is greater in cadavers than expected in living tissue. Even when CSF is present, there is a free distance between the dura and VA due to the unique feature of the C1 lateral mass. Decompression at the border of the vertebral groove is known to be sufficient. Extending beyond the medial border of the vertebral groove and reaching more laterally is unnecessary for spinal cord decompression (Figure 4). The thickness of the vertebral groove has been studied in the literature, but studies on its length are limited. The length and diameter measurements we obtained for the vertebral groove of the VA are compatible with those reported in the literature (1,6).

This study shows that the length of C1 laminectomy on the dominant side is significantly different from that on the nondominant side. To reduce complication risks, the decision regarding the extent of laminectomy should be based on the dominant VA. This study addresses the difference in laminectomy areas on the right and left sides of the axis posterior arcus. C1 laminectomy is a commonly performed surgical procedure, and in general, the decision regarding the extent of laminectomy is assumed to be similar on both sides. According to our results, the extent of laminectomy should be asymmetric, because VA damage can significantly affect the outcome of the surgery and the patient's recovery. The data in our study showed that the C1 posterior arch and vertebral groove were different in each cadaver. In addition, in our research, we observed that the VA measurements were different in each cadaver. We also noted that the lengths of the vertebral groove on the dominant and nondominant sides were different in each cadaver. The data obtained in this research guide us in clinical studies. It should be known that the length of the dominant artery differs among patients; therefore, the lengths of the vertebral grooves are also different. Thus, it is useful to evaluate the vertebral groove using preoperative CT in patients planning to undergo C1 laminectomy.

This study has significant implications for surgical planning and decision-making in C1 laminectomy procedures. The findings of our study can be applied to improve the outcomes of C1 laminectomy procedures and reduce the risk of complications during surgery. Our study provides new insights into the importance of considering the dominant VA when determining the length of C1 laminectomy. To ensure the best outcomes for patients, preventing complications during C1 laminectomy is vital. Because the C1 anatomy is complex, laminectomy procedures require careful planning and execution to minimize the risk of complications.

In our previous C1–2 anatomy study, we found that the C1–2 CT measurements and dissection measurements were similar to each other (2). In the current study, we performed CT scans on cadavers to demonstrate the relationship between the vertebral groove and laminectomy. Therefore, we advocate taking preoperative CT studies into consideration. Because there is a possibility of not entering the section during the CT scanning procedure in the vertebral groove, the scans should be performed with thin (1-mm) sections. Radiologic examinations should be carefully examined preoperatively, the course of the VA should be evaluated, and the length of the laminectomy on the right and left sides should be calculated preoperatively. This cadaver study emphasizes the importance of measuring the C1 posterior arch and vertebral groove by performing preoperative CT in clinical cases where the C1 posterior arch must be removed.

The artery was filled with silicone in this study; however, the diameters of the vertebral arteries vary in clinical practice. In addition, to reveal the existence of anatomical variations, large-series clinical studies are needed as well as clinical studies that include patients who have undergone surgery and studies that involve CT scans.

CONCLUSION

In this study, we observed that the C1 posterior arcus had different characteristics in each cadaver sample. Our findings contradict the common belief that the length of C1 laminectomy should be the same on both sides. Our study provides supporting data for the importance of considering the dominant VA in determining the extent of C1 laminectomy. The vertebral groove was longer on the dominant artery side and shorter on the nondominant artery side. Thus, the dominant and nondominant sides have different lengths of safe C1 laminectomy areas. The extent of the length of the laminectomy area to be performed on the dominant artery side was shorter than that on the nondominant side. In cases in which the C1 posterior arcus must be removed for decompression, asymmetric decompression should be performed to reduce the risk of VA injury.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: YG, UV
Data collection: YG,UV
Analysis and interpretation of results: UV, YG
Draft manuscript preparation: YG, UV
Critical revision of the article: YG,UV
Other (study supervision, fundings, materials, etc...): UV, YG
All authors (YG, UV) reviewed the results and approved the final version of the manuscript.

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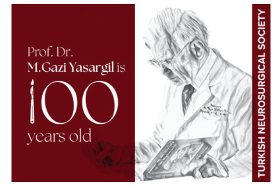

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Investigating the Role of Biomarkers Using Liquid Biopsy in the Diagnosis of Meningiomas

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ABSTRACT

AIM: To evaluate the diagnostic potential of c-MYC, FABP7, GATA4, and MAOB in meningioma patients by analyzing their expression in serum samples.

MATERIAL and METHODS: The study included 20 patients who underwent surgical resection for intracranial meningiomas. Tumor and serum samples were collected during the surgical procedure. Real-time polymerase chain reaction (RT-PCR) was performed to measure the expression of FABP7, GATA4, c-MYC, and MAOB in both tumor tissues and serum samples.

RESULTS: The expression levels of MAOB, c-MYC, and GATA4 were significantly higher in grade 2 meningioma tumor tissues compared to grade 1 tumors ($p=0.031$, $p=0.041$, and $p=0.003$, respectively). Similarly, patients with grade 2 meningiomas had significantly higher MAOB expression in their serum compared to patients with grade 1 meningiomas ($p=0.032$). In addition, the serum levels of FABP7 and MAOB were significantly higher in meningioma patients compared to healthy controls ($p<0.05$).

CONCLUSION: The findings of this study suggest that FABP7 and MAOB expression in serum may serve as diagnostic markers for meningiomas. However, additional studies with larger cohorts are necessary to validate these results.

KEYWORDS: Meningioma, Cancer biomarker, Liquid biopsy, Diagnosis

ABBREVIATIONS: MRI: Magnetic Resonance Imaging, **NF2:** Neurofibromatosis Type 2, **TRAF7:** TNF Receptor-Associated Factor 7, **SMO:** Smoothened, Frizzled Class Receptor, **AKT1:** AKT Serine/Threonine Kinase 1, **KLF4:** Krüppel-Like Factor 4, **POLR2A:** RNA Polymerase II Subunit A, **PIK3CA:** Phosphatidylinositol-4,5bisphosphate 3-Kinase Catalytic Subunit Alpha, **MAOB:** Monoamine Oxidase B, **FABP7:** Fatty Acid Binding Protein 7, **GATA4:** GATA Binding Protein 4, **c-MYC:** Cellular-Myc, **WHO:** World Health Organization, **RT-PCR:** Reverse Transcription Polymerase Chain Reaction

INTRODUCTION

Meningiomas account for approximately 30% of all primary intracranial tumors and originate from arachnoidal cells of the leptomeninges (33). These tumors can grow asymptomatically for long periods, making early detection a significant challenge (16). Advances in research have shed light on the molecular profile of meningiomas. In addition to the previously established association between meningiomas and mutations in the tumor suppressor gene neurofibro-

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matosis type 2 (NF2), several other genes with recurrent mutations have been identified. These include TNF receptor-associated factor 7 (TRAF7), smoothened receptor (SMO), AKT serine/threonine kinase 1 (AKT1), Krüppel-like factor 4 (KLF4), RNA polymerase II subunit A (POLR2A), and phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha (PIK3CA) (1,3,7,40,44).

Research has also indicated that certain genes, such as monoamine oxidase B (MAOB), fatty acid binding protein 7 (FABP7), GATA binding protein 4 (GATA4), and cellular-Myc (c-MYC), are associated with meningiomas and various other tumor types (9). The current diagnostic approaches for meningiomas primarily rely on histopathological analysis and magnetic resonance imaging (MRI). However, radiology-based methods have limitations, as tumors are typically detected only after reaching a certain size. This delay in detection increases the risk of progression from benign to malignant forms, ultimately worsening patient outcomes. High-grade meningiomas are also associated with higher recurrence rates, further complicating management. Additionally, radiologically mimicking tumors can pose challenges to accurate diagnosis (30).

The difficulty in distinguishing tumor grades is another critical issue, as it directly influences treatment decisions. Aggressive surgical resection is recommended for high-grade meningiomas to reduce recurrence, whereas low-grade meningiomas may not require such extensive intervention. Determining the tumor grade prior to treatment is essential. Histological evaluation from surgical tissue sampling remains the gold standard for grading meningiomas. However, surgical procedures carry risks such as hemiparesis and speech problems, making non-invasive diagnostic methods highly desirable (6).

Liquid biopsy has emerged as a promising non-invasive alternative for identifying tumor markers. This method provides valuable information about the molecular and genetic characteristics of malignancies (2,6). Potential biomarkers for meningioma diagnosis include the transcription of genes such as c-MYC, GATA4, MAOB, and FABP7. While previous studies have explored their expression in tumor tissues, little is known about their expression in serum. The aim of this study was to evaluate the use of liquid biopsy by investigating the serum expression of these genes in patients with meningiomas.

MATERIAL and METHODS

Patients

This retrospective study included 20 patients who underwent surgical resection for intracranial meningiomas between May 2017 and March 2021 at our clinic. Approval for the study was obtained from the Ethical Committee (No: 05/110), and the research was conducted in accordance with the principles outlined in the Helsinki Declaration (45). All participants provided informed consent before enrollment. Histopathological evaluation confirmed the diagnosis of meningiomas. Clinical data, including patient age, sex, imaging results, histopathological findings, World Health Organization (WHO) grade, Simpson grade, post-surgical complications, and recurrence status, were collected retrospectively.

Tissue and Serum Sampling

Blood samples were collected prior to surgical intervention, and tumor tissues were obtained during surgery. Serum was separated from blood samples by centrifuging at 2100 rpm for 25 minutes. The isolated serum was stored in Eppendorf tubes at -80 °C until further analysis. Tumor tissues were immediately stored at -80 °C following collection.

RNA Isolation from Tumor and Serum Samples

RNA was extracted from tumor tissues using a total RNA purification kit (EcoTech, Australia), while serum samples were processed with a total RNA purification kit (Jena Bioscience, Germany). Complementary DNA (cDNA) was synthesized using a cDNA synthesis kit (Quantabio qScript cDNA, USA). The concentration of cDNA was measured with a NanoDrop spectrophotometer. Expression levels of FABP7, GATA4, c-MYC, and MAOB were quantified using real-time polymerase chain reaction (RT-PCR) with the SensiFAST SYBR No-ROX Kit (Bioline, USA) on the Rotor-Gene Q system (QIAGEN, USA).

Statistical Analysis

Data analysis was conducted using GraphPad Prism 10.13.0 software. Differences between healthy controls and patient samples were evaluated with the Student's t-test. ANOVA was performed to analyze variance among healthy controls and patients with different tumor grades. Mann-Whitney tests were used to compare gene expression levels in tumor samples. Correlations between gene expression in tumor and serum samples, as well as clinical data, were assessed using Pearson's correlation test. A p-value of less than 0.05 was considered statistically significant.

RESULTS

Patient Characteristics

The study included 20 patients who underwent surgical resection for intracranial meningiomas. Histopathological analysis classified 11 patients (55%) as having WHO grade 1 meningiomas and 9 patients (45%) as having WHO grade 2. The median age of the participants was 53 years, ranging from 43 to 75 years. Patient characteristics are summarized in Table I. Figure 1 presents the distribution of data for meningioma patients and healthy controls (n=15).

Gene Expression Analysis

To assess whether the expression of FABP7, GATA4, c-MYC, and MAOB is elevated in meningioma patients, serum samples were analyzed. FABP7, GATA4, c-MYC, and MAOB expression levels were higher in the serum of meningioma patients compared to healthy controls. However, only FABP7 and MAOB showed statistically significant differences (p=0.036 and p=0.042, respectively) (Figure 2).

When expression levels were analyzed by tumor grade, MAOB expression in serum significantly increased with tumor grade (p=0.032). Although serum levels of c-MYC, FABP7, and GATA4 also showed an upward trend with tumor grade, these differences were not statistically significant (Figure 3).

Table I: Characteristics of Patients Who Underwent Surgical Resection for Meningiomas

Characteristic	Value
Cases total, n (F/M)	20 (12/8)
Median age (range), years	53 (41-75)
Histological type, Grade	
Atypical /Clear cell, Grade 2, n	9
Transitional, Grade 1, n	8
Angiomatosis, Grade 1, n	1
Fibrous, Grade 1, n	1
Meningothelial, Grade 1, n	1

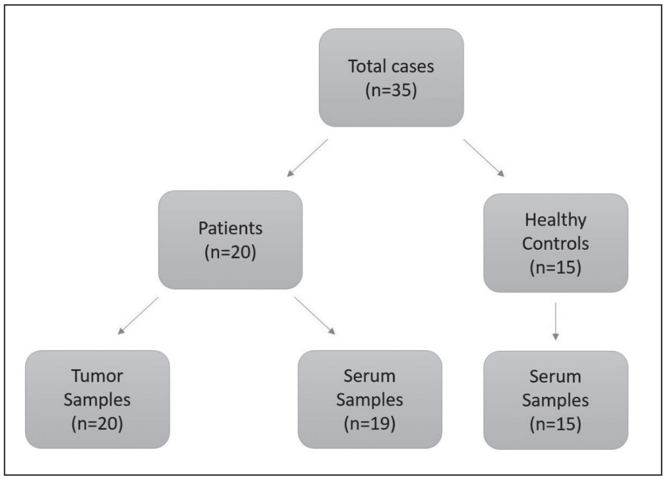

Figure 1: Data stratification.

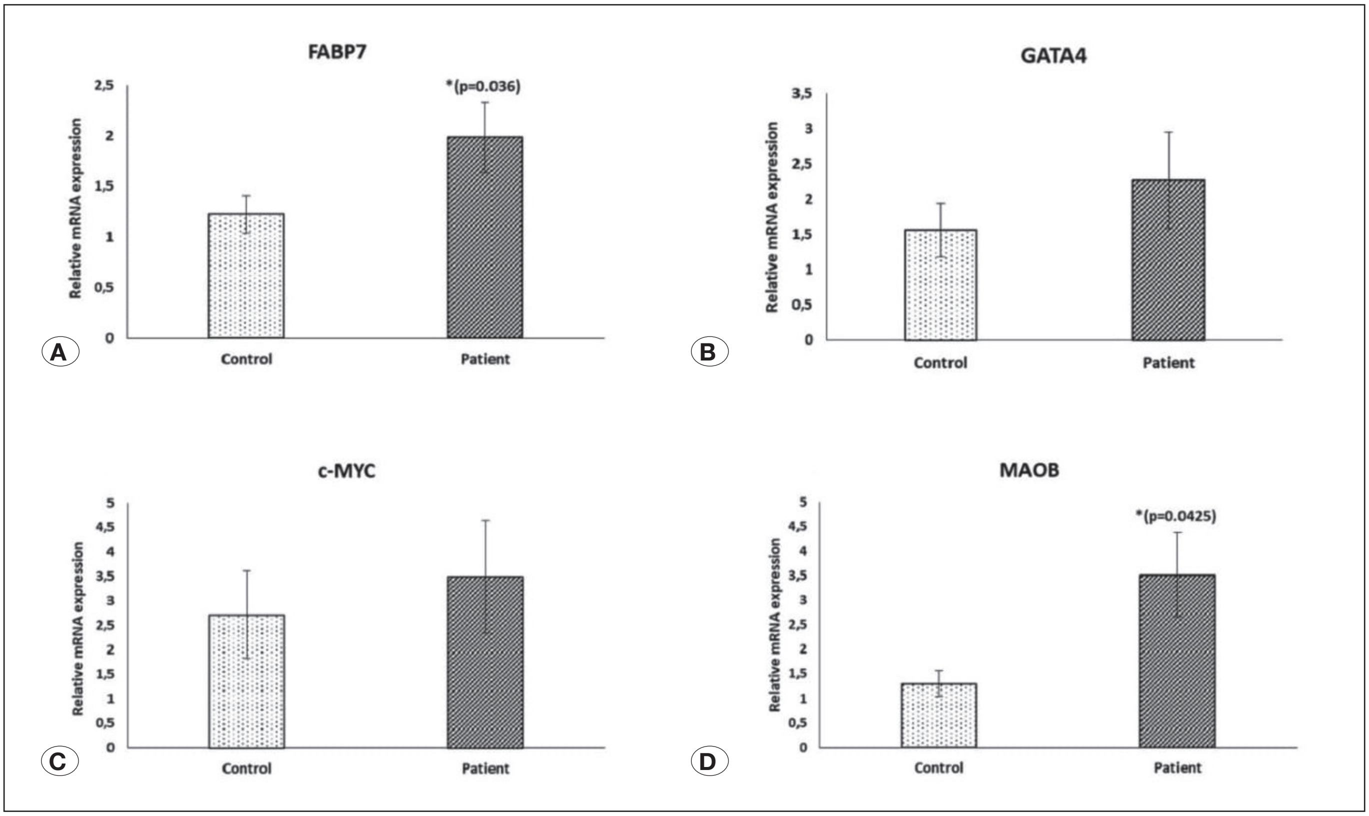

Figure 2: mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB in serum samples of patients with meningioma and healthy controls. FAB7 and MAOB were found to be significantly higher in meningioma patients compared to healthy controls (p=0.036 and p=0.042, respectively).

In tumor tissues, MAOB, c-MYC, and GATA4 expression levels were significantly higher in WHO grade 2 meningiomas compared to WHO grade 1 (p=0.03, p=0.04, and p=0.003, respectively) (Figure 4). No correlation was observed between the gene expression levels and clinical data, such as local tumor control or recurrence rates.

DISCUSSION

The 2021 WHO classification system divides meningiomas into three grades with a total of 15 histopathological subtypes (25). Nine of these subtypes fall under grade 1, while clear cell and chordoid histology are classified as grade 2. Rhabdoid and papillary histologies are no longer used as criteria for

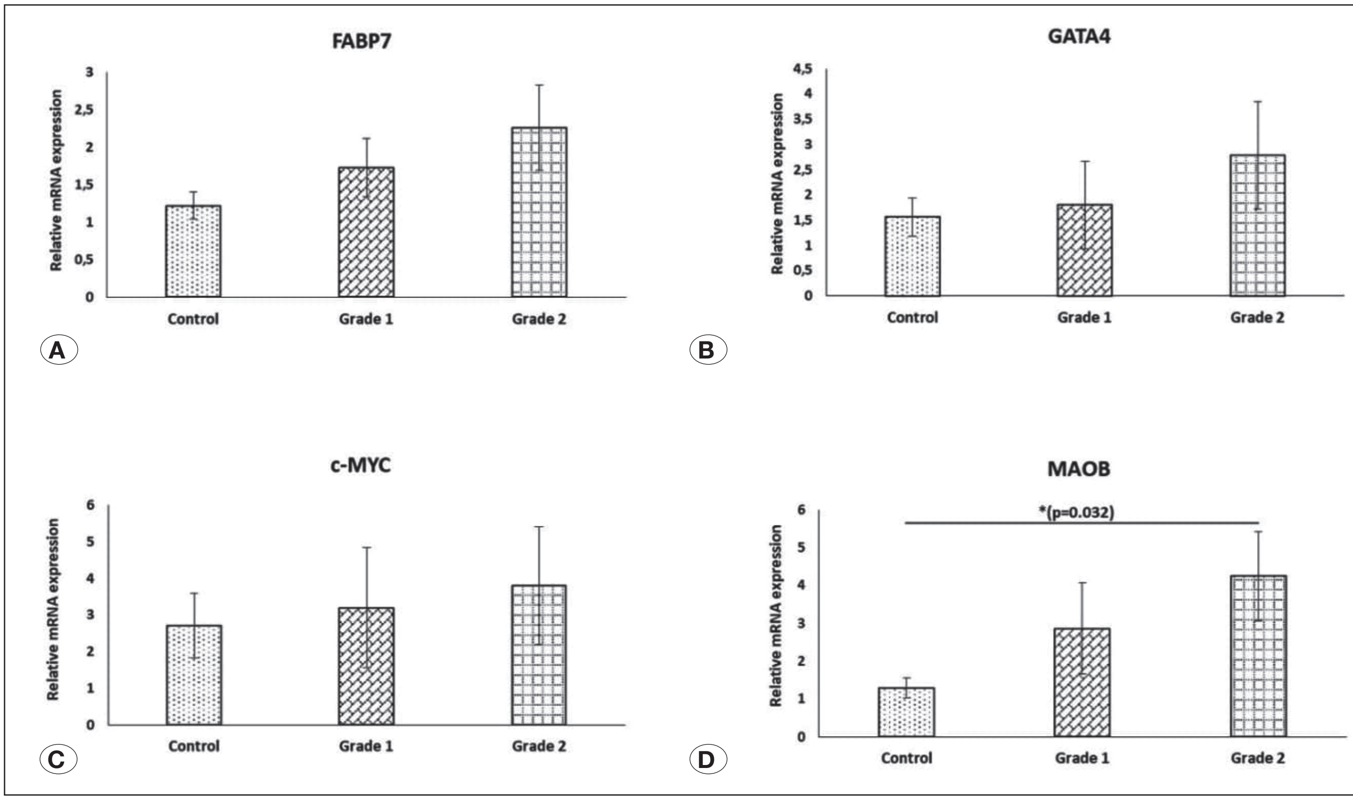

Figure 3: Comparison of mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB between WHO grade 1 meningioma patients' serum samples and WHO grade 2 samples. Only MAOB gene expression in the serum was significantly increased in correlation with an increase in meningioma grade (p=0.032).

grade 3 classification. Most meningiomas are categorized as WHO grade 1, with an 86% five-year progression-free survival (PFS) rate regardless of the extent of resection (EOR) and a 96% PFS following gross total resection (GTR) (15,24,34,36). However, long-term studies indicate that up to 38% of grade 1 meningiomas recur even after gross total resection, highlighting that WHO grade alone may not be sufficient for predicting clinical outcomes (18,20,26,34,36). In contrast, WHO grade 2 (atypical) and grade 3 (anaplastic) meningiomas exhibit more aggressive clinical behavior. These higher-grade tumors are associated with recurrence rates ranging from 20% to 70% within five years, despite surgical resection and adjuvant radiotherapy (5,24). These findings are comprehensively reviewed in a study by Trybula et al. (43).

In this study, we examined whether FABP7, GATA4, c-MYC, and MAOB could be used as diagnostic biomarkers in serum samples from patients with meningiomas through liquid biopsy. We conducted a thorough literature review to identify genes involved in the pathogenesis of meningiomas. Among the many genes studied, we focused on FABP7, GATA4, c-MYC, and MAOB, which have previously been investigated in meningioma tumor tissues and other tumors, particularly gliomas. Moreover, the expression of these genes has been found to differ between malignant and benign forms, suggesting they could serve as potential biomarkers for early detection and diagnosis of meningiomas.

Four genes, c-MYC, FABP7, GATA4, and MAOB, have been implicated in meningioma grades using tumor tissue samples, but their roles in diagnosis, staging, and prognosis of meningiomas are still not fully understood (9,29,31). Additionally, this correlation has not been explored in serum samples. To our knowledge, this is the first study to investigate the diagnostic potential of liquid biopsy for c-MYC, FABP7, GATA4, and MAOB in patients with meningiomas. Our findings showed that FABP7 and MAOB levels were significantly higher in the serum of meningioma patients compared to healthy controls.

The c-MYC protein is a regulator of cellular growth and metabolism. Mutations in c-MYC can lead to cancer development. Overexpression of c-MYC has been observed in glioblastomas, anaplastic meningiomas, atypical meningiomas, and medulloblastomas (19,28,41). This protein promotes cellular changes that can result in neoplasia, contributing to poor clinical outcomes (31). A study by Nagashima et al. examined c-MYC expression in tumor tissues from 20 patients with meningioma, including 17 grade 1, two grade 2, and one grade 3 tumors. Their results showed no c-MYC expression in grade 1 meningiomas, while higher expression levels were associated with tumor recurrence, malignancy, and aggressive progression. However, c-MYC-expressing cells were found to be distinct from proliferating cells, suggesting alternative roles such as involvement in apoptosis rather than direct tumor growth (28). Cai et al. found that in meningiomas, c-MYC

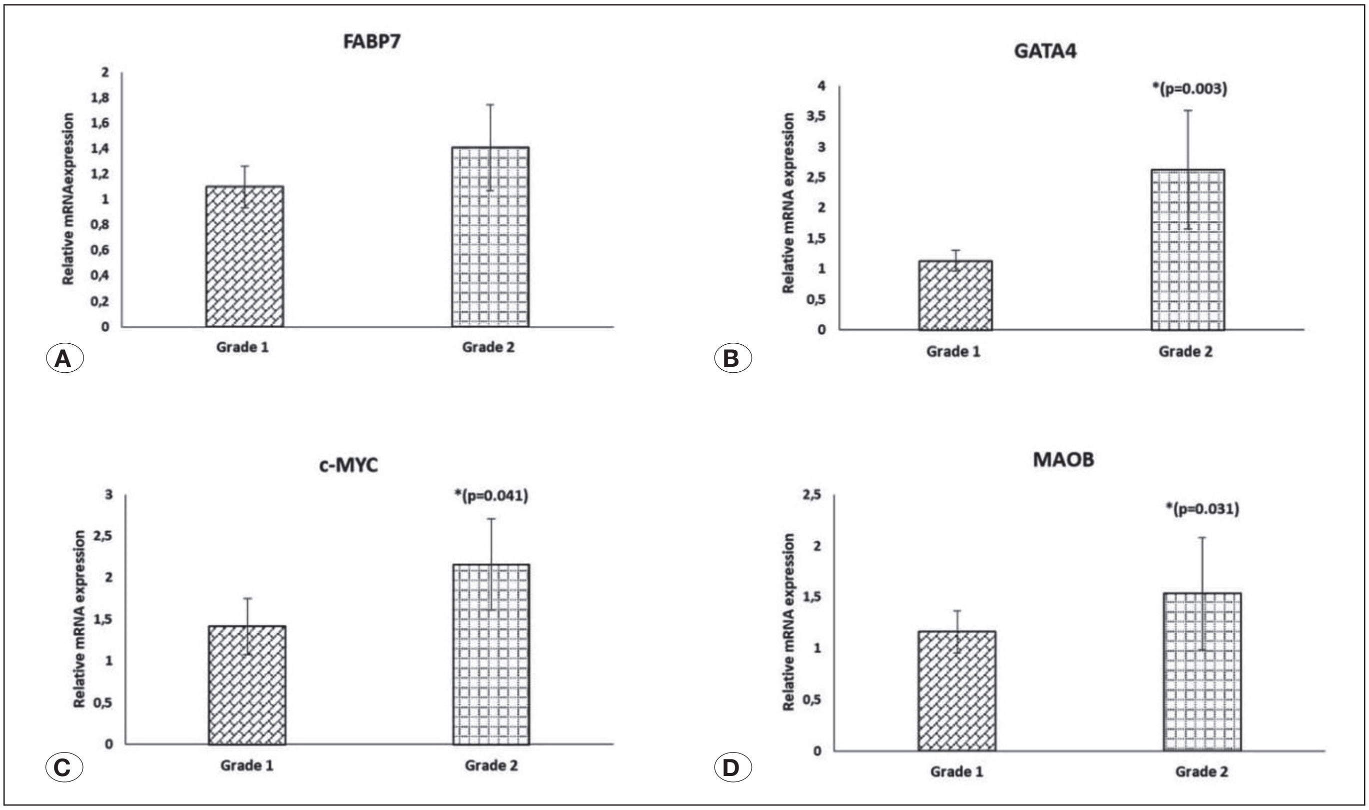

Figure 4: Comparison of mRNA expression levels of **A)** FABP7, **B)** GATA4, **C)** c-MYC, and **D)** MAOB in meningioma tumor samples between WHO grade 1 and WHO grade 2 tumors. The MAOB, c-MYC, and GATA4 genes were significantly higher in WHO grade 2 meningiomas compared to WHO grade 1 (p=0.03, p=0.04, and p=0.003, respectively).

is targeted by RIZ1, which acts as a negative regulator of the ubiquitin-binding enzyme E2C/UbcH1 (4). RIZ1, also known as PRDM2 or KMT8, is a tumor suppressor that functions in transcriptional repression by methylating histone H3 at lysine 9 (47). In our cohort, we found that c-MYC expression was significantly elevated in the tumor tissues of WHO grade 2 meningiomas compared to WHO grade 1 meningiomas (p=0.04). However, no statistically significant differences were observed in c-MYC expression between serum samples from meningioma patients and healthy controls. Additionally, while serum c-MYC levels were higher in patients with WHO grade 2 meningiomas than those with grade 1, this difference was not significant.

FABP7 is a small cytoplasmic protein with a molecular weight of 15 kDa and is highly expressed in astrocytes (9). The fatty acid binding protein (FABP) family facilitates the uptake, transport, metabolism, and storage of long-chain fatty acids within cells. In various cancers, FABP7 expression can increase up to 20-fold and is typically associated with a poor prognosis (14). This protein, widely recognized as a marker for neural stem cells, is predominantly found in glioma stem cells cultured using the sphere method (8). In glioblastoma samples, the FABP7 promoter undergoes hypomethylation, leading to overexpression of FABP7 mRNA, which is linked to reduced survival and greater tumor invasiveness (10,21,23). In meningiomas, FABP7 expression is notably higher in grade III and grade II tumors compared to grade I (9,22). Additionally, it is upregulated in atypical meningiomas compared to benign forms. Markers such as Ki67, PCNA, mitotic index (MI), microvessel density (MVD), BFABP, and COX2 are significantly associated with both FABP7 expression and tumor grade. These correlations between fatty acid transport, eicosanoid metabolism, and proliferation markers like Ki67 and mitotic index suggest that fatty acids play a role in meningioma progression (32). A study by Dunn et al. (9) found FABP7 levels to be eight times higher in grade 3 meningiomas compared to grade 1. Our findings indicated that serum FABP7 levels were notably higher in meningioma patients compared to healthy controls. While serum FABP7 levels were elevated in patients with WHO grade 2 meningiomas compared to those with WHO grade 1, this difference did not reach statistical significance. Furthermore, FABP7 expression in tumor tissue samples did not show any significant difference between WHO grade 2 and WHO grade 1 meningiomas.

Monoamine oxidase (MAO) catalyzes the deamination of compounds in the brain and peripheral tissues, producing hydrogen peroxide (H_2O_2) as a byproduct (39,42). MAO-B activity was found to be significantly higher in glioblastoma tissues compared to postmortem control brains (p<0.01) and meningiomas (p<0.001). No significant differences were observed in MAO-B activity between glioblastomas (n=11), low-grade astrocytomas (n=3), and anaplastic astrocytomas (n=6) (12).

Studies have shown that, compared to normal brain tissue, MAOB activity is markedly elevated in glioblastomas, low-grade astrocytomas, and anaplastic astrocytomas. However, meningioma tissue does not exhibit increased MAOB activity relative to control brain tissue (27). In their study, Sharpe et al. highlight these findings (38). On the other hand, a study by Dunn et al. reported that grade 3 meningiomas displayed approximately 37 times more MAOB expression than grade 1 meningiomas. Minimal or no MAOB expression was detected in grade 1 meningiomas, whereas grade 3 meningiomas showed a significant increase, consistent with western blotting results (9). Consistent with their findings, our study demonstrated that serum MAOB levels were significantly elevated in meningioma patients compared to healthy controls. Furthermore, serum MAOB expression was notably higher in patients with WHO grade 2 meningiomas compared to those with WHO grade 1 tumors. Additionally, MAOB expression in tumor tissue samples was significantly greater in WHO grade 2 meningiomas compared to WHO grade 1 meningiomas.

The transcription factor GATA4 suppresses the expression of the miR-497-195 cluster in stem cells, which helps maintain cellular function. Studies have shown that GATA4 is overexpressed in malignant meningiomas, where it inhibits miR-497-195 expression and promotes cell viability (13,29), as discussed in the review by Halabi et al. (17). Negroni et al. reported that in patients with high-grade meningiomas, serum extracellular vesicles (EVs) exhibited reduced miR-497 levels due to elevated GATA4 expression in these tumors. GATA4 upregulation in high-grade meningioma samples leads to an increase in cyclin D expression (29). Treatment with NSC140905, a small molecule inhibitor of GATA4, reduced cyclin D1 expression and decreased meningioma cell viability in vitro (46). These findings suggest that GATA4 could serve as a biomarker for meningiomas, especially in more aggressive cases (29).

In our study, GATA4 expression in tumor tissue samples was significantly higher in patients with WHO grade 2 meningiomas compared to those with WHO grade 1 meningiomas. However, we did not observe significant differences in GATA4 expression in serum samples between meningioma patients and healthy controls. Although serum GATA4 levels were elevated in WHO grade 2 patients compared to WHO grade 1, the difference was not statistically significant.

Different WHO grades of meningiomas exhibit distinct protein profiles, which can help identify potential protein-based biomarkers (18), as reviewed by Halabi et al. (17). Liquid biopsy is a non-invasive technique for detecting tumor markers in body fluids like blood and cerebrospinal fluid (CSF) (35). This method can identify circulating tumor cells (CTCs) and circulating tumor DNA (ctDNA). Recent developments have shown its effectiveness in diagnosing cancers such as lung, breast, and colorectal cancers (37). Despite these advancements, the blood-brain barrier complicates the use of liquid biopsy for brain tumors by limiting the detection of tumor markers. Nevertheless, liquid biopsy remains a promising tool for brain tumor diagnosis, early detection, and recurrence monitoring (11).

We also examined potential correlations between gene expression and clinical data. However, no significant associations were found, likely due to the limited number of patients in our cohort. Our study has several limitations. First, the sample size was relatively small. Second, because we included consecutive patients, there were no patients with WHO grade 3 meningiomas, which may have influenced the results. Third, we used RT-PCR as the sole method for gene detection in this preliminary study. Some of our findings also differed from previously published data, which may be attributable to the small cohort size. Moving forward, we plan to expand the study by including more patients and performing additional confirmatory analyses.

CONCLUSION

Our findings indicate that FABP7 and MAOB serum expression levels have the potential to serve as diagnostic biomarkers for meningiomas. Despite these promising results, further research with larger cohorts and additional confirmatory analyses is essential to validate the clinical utility of these biomarkers.

Declarations

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AUTHORSHIP CONTRIBUTION

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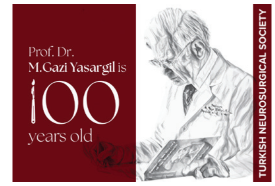

Three-Dimensional Dissection of the Bed Nucleus of the Stria Terminalis and Its White Matter Connections: A Surgical and Neuropsychiatric Perspective

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ABSTRACT

AIM: To provide an in-depth anatomical description of the bed nucleus of the stria terminalis (BST) and its structural affiliations, with an emphasis on its surgical and neuromodulatory relevance.

MATERIAL and METHODS: We conducted stepwise fiber dissections on 14 formalin-fixed human brains prepared using the Klingler method. Under high magnification, dissections were performed lateral to medial and medial to lateral directions, enabling detailed visualization of the BST's relationship with adjacent fiber tracts and nuclei such as the anterior commissure, fornix, stria terminalis, nucleus accumbens, and septal area.

RESULTS: The BST was consistently located anterosuperior to the anterior commissure and medially bordered by the septal nuclei, forming a compact yet integrative structure. Dense projections were identified between the BST and limbic-hypothalamic targets via the stria terminalis, fornical fibers, and the diagonal band of Broca. These connections emphasize the BST's pivotal position in coordinating limbic output with neurovegetative centers.

CONCLUSION: This study refines the topographic and connectional map of the BST, offering structural insight into its role as a limbic hub. Such clarity may assist in tailoring neuromodulatory interventions—such as deep brain stimulation—by improving anatomical precision in disorders involving fear, compulsion, and affect regulation.

KEYWORDS: Bed nucleus of the stria terminalis, White matter, Fiber dissection, Limbic system, Deep brain stimulation

ABBREVIATIONS: AC: Anterior commissure, **BST:** Bed nucleus of the stria terminalis, **CdN:** Caudate nucleus, **DBB:** Diagonal band of Broca, **NAc:** Nucleus accumbens; **OCD:** Obsessive–compulsive disorder, **SI:** Substantia innominata, **ST:** Stria terminalis, **VAFP:** Ventral amygdalofugal pathway

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INTRODUCTION

The bed nucleus of the stria terminalis (BST) is a compact yet anatomically and functionally complex cluster of neuronal nuclei located within the basal forebrain, maintaining close structural and functional associations with the limbic system (12,27). These nuclei are conventionally divided into a narrow dorsolateral segment positioned dorsally to the amygdaloid complex, an intermediate zone extending along the stria terminalis (ST), and a ventromedial expansion situated near the crossing fibers of the anterior commissure (AC) (26,27). Anatomically, the BST forms extensive connections with structures such as the fornix, ST, AC, nucleus accumbens (NAc), and septal nuclei. These connections facilitate neuroanatomical integration with major limbic components including the hippocampus, amygdala, hypothalamus, and prefrontal cortex (2,8,27).

Experimental and clinical studies have consistently demonstrated the pivotal role of the BST in stress response, anxiety-related processes, social behaviors, and sustained emotional regulation (19,32,33). Moreover, in progressive neurodegenerative conditions such as Alzheimer's disease, it has been proposed that disruptions in the BST's connectivity with key limbic pathways—such as the ST and fornix—may contribute to the deterioration of cognitive and emotional functions (11,28). Consequently, the BST has emerged as a neuromodulatory target in a variety of neuropsychiatric conditions, including obsessive–compulsive disorder (OCD), major depressive disorder, anorexia nervosa, and Alzheimer's disease (4,9,10,21-23,25,36).

The BST is surrounded by dense white matter pathways, and the complexity of its internal organization has recently garnered increased attention through cadaveric dissections and advanced neuroimaging techniques (1,19,31). However, the limited volume of this region and the indistinct boundaries with neighboring gray matter structures pose challenges for achieving precise anatomical resolution using noninvasive methods (31).

The present study, aimed to systematically investigate the white matter connectivity of the BST in the human brain through cadaveric dissection, and to evaluate the clinical implications of the findings in light of current literature. These anatomical insights are anticipated to support the refinement of BST-targeted interventions, particularly in the context of neuropsychiatric disorders.

MATERIAL and METHODS

Cadaveric Dissection

This study designed to investigate the three-dimensional anatomical organization of the BST and its surrounding white matter pathways, was based on cadaveric dissection techniques. Fourteen postmortem human brain specimens prepared according to the Klingler method were utilized (15). The specimens were fixed in 10% formaldehit solution for a minimum of eight weeks, then frozen at −16°C for two weeks to facilitate fiber dissection. After thawing in running water, stepwise layer by layer dissections were performed from lateral to medial and medial to lateral directions. All dissections were carried out under a stereomicroscope, and the white matter pathways were meticulously exposed with preservation of anatomical integrity. Special emphasis was placed on identifying the AC, fornix, ST, and septal areas surrounding the BST, and each stage of the dissection was documented with high-resolution three-dimensional imaging in accordance with the protocol described by Shimizu et all. (30).

Ethical Considerations

Since the cadavers were used solely for educational and scientific observational purposes, no additional institutional review board approval was required.

RESULTS

Lateral to Medial Dissection

The dissection process was initiated at the central core of the insula and advanced systematically in a lateral to medial direction. In this sequence, the external capsule, putamen, globus pallidus, internal capsule, thalamic peduncles, thalamus, and caudate nucleus (CdN) were identified from superficial to deep layers (Figure 1A). Upon removal of the putamen and globus pallidus, the posterior limb of the AC projecting posterolaterally and the anterior limb extending anterolaterally were clearly distinguished beneath these structures (Figure 1A). The substantia innominata (SI), including the anterior perforated substance, was identified in the region between the anterior commissural fibers and the uncinate fasciculus. The anteromedial boundary of this region was defined by the anterior limb of the AC, the posterolateral boundary by its posterior limb, and the lateral boundary by the uncinate fasciculus (Figure 1A).

Following the removal of the internal capsule fibers, the thalamus located at the medial core and the CdN arching around it in a C-shaped configuration became clearly visible. The inferolateral segment of the ST originated from the amygdala, coursed medial to the CdN, and traversed posteriorly beneath Meyer's loop. Ascending along the striothalamic sulcus, ST encircled the thalamus dorsally and turned anteriorly along its superior border. As it turned inferiorly in the anterior thalamic region, it terminated on the posterolateral surface of the BST, in close anatomical relation to the NAc and the AC (Figure 1C, 1D).

In lateral to medial dissections, the BST was identified anterosuperior to the AC, posterosuperior to the NAc, anteromedial to the thalamus, and posteroinferior to the CdN (Figure 1D).

Medial to Lateral Dissection

Prior to initiating the medial to lateral dissection, the corpus callosum and cingulum fibers were removed. This step clearly revealed the CdN along the lateral wall of the lateral ventricle, forming a C-shaped arc surrounding the thalamus (Figure 2A). The crus of the fornix extended anteriorly to the level of the AC, situated adjacent to the head of the CdN and the anterior border of the thalamus—an area overlapping with the BST (Figure 2B, 2C, 2D). Just above the AC, the fornix divided into two branches: the postcommissural fornix, descending posteroinferiorly along the posterior hypothalamus toward the mammillary bodies, and the precommissural fornix, projecting anteroinferiorly to approach the rostral portion of the BST medially, in close association with the diagonal band of Broca (DBB) and the septal area (Figure 2B, 2C, 2D).

Positioned superior to the posterior commissure and adjacent to the dorsal aspect of the pineal gland, the habenular commissure gives rise to the stria medullaris thalami, which courses along the medial surface of the thalamus within the lateral wall of the third ventricle. The stria medullaris thalami receives projections from the preoptic and hypothalamic regions as well as the septal area, and it travels anteriorly along the mediobasal thalamus, passing close to the inferior margin of the BST (Figure 2A).

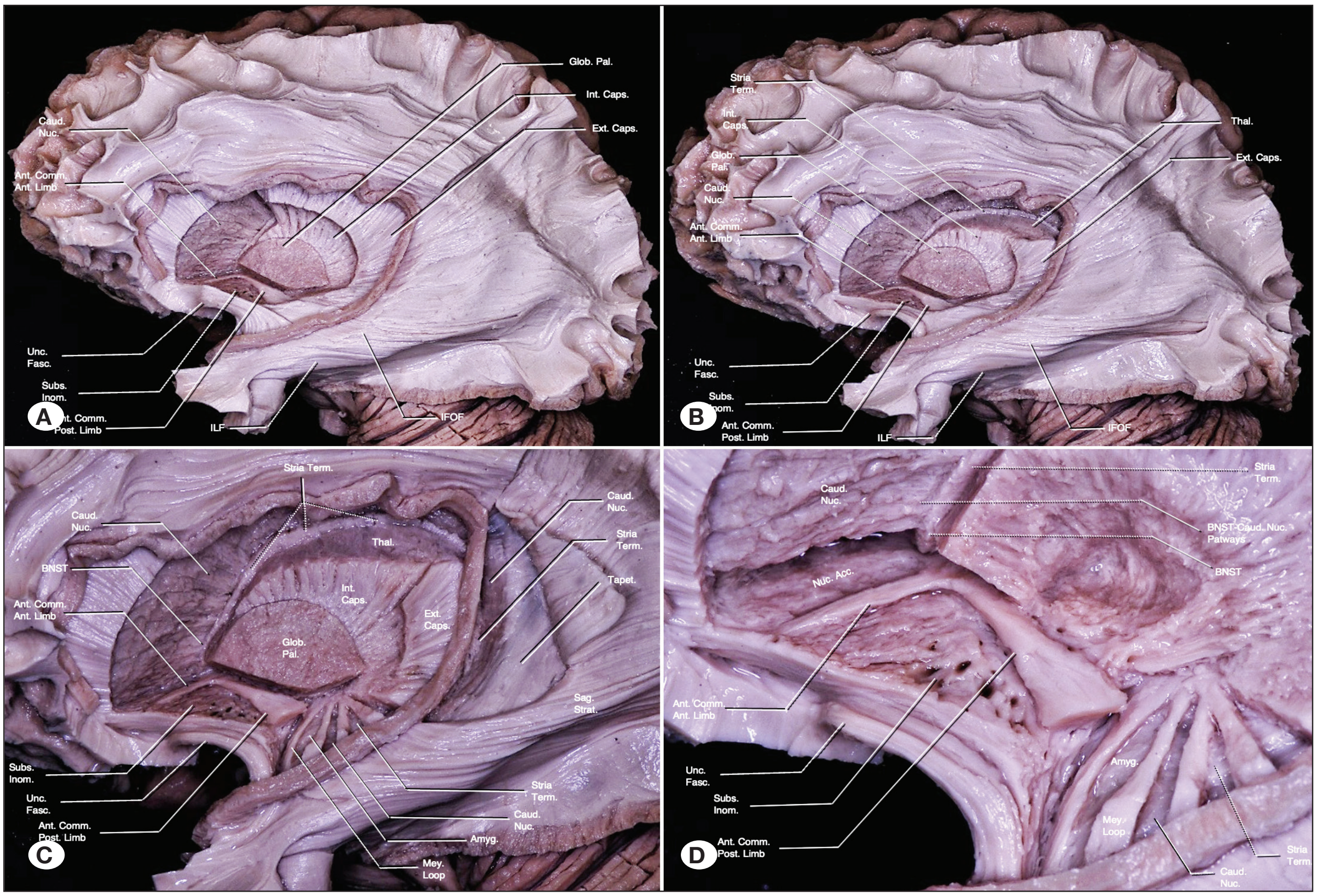

Figure 1: Demonstration of the anatomical relationships of the BNST through lateral to medial dissection. **A)** A central core dissection was performed from the lateral aspect of the brain. Removal of the putamen reveals the underlying globus pallidus and internal capsule fibers. At the base of the putamen lie the substantia innominata and the anterior commissure. When the anterior limb of the internal capsule and the anterior thalamic peduncle fibers are removed, the head of the caudate nucleus becomes visible. **B)** Deep to the internal capsule and the superior thalamic peduncle fibers lie the thalamus and the superior extension of the caudate nucleus. The stria terminalis courses along the striatal-thalamic sulcus located between the thalamus and the caudate nucleus. **C)** Removal of the posterior limb of the internal capsule reveals the tail of the caudate nucleus and the medially positioned stria terminalis. By creating windows among the fibers forming Meyer's loop, the anatomical relationship among the amygdala, the caudate nucleus tail, and the stria terminalis was demonstrated. **D)** Closer view. The stria terminalis, originating from the amygdala, traverses medially to the caudate nucleus, proceeds posteriorly, ascends dorsally beneath Meyer's loop, and curves anteriorly following the superior margin of the thalamus. Upon reaching the anterior thalamic region, it turns inferiorly to reach the posterolateral surface of the BST. This segment of the stria terminalis is in close proximity to the nucleus accumbens and the anterior commissure. The BST was anatomically localized anterosuperior to the anterior commissure, posterosuperior to the nucleus accumbens, posteroinferior to the caudate nucleus, and anteromedial to the thalamus. **Amyg.:** amygdala; **Ant. Comm. Ant. Limb:** anterior limb of the anterior commissure; **Ant. Comm. Post. Limb:** posterior limb of the anterior commissure; **BNST:** bed nucleus of the stria terminalis; **Caud. Nuc.:** caudate nucleus; **Ext. Caps.:** external capsule; **Glob. Pal.:** globus pallidus, **IFOF:** inferior fronto-occipital fasciculus; **ILF:** inferior longitudinal fasciculus; **Int. Caps:** internal capsule; **Mey. Loop:** Meyer's Loop, **Nuc. Acc.:** nucleus accumbens; **Sag. Strat.:** sagittal stratum; **Stria Term.:** stria terminalis; **Subs. Inom.:** substantia innominata; **Tapet.:** tapetum; **Thal.:** thalamus; **Unc. Fasc.:** uncinate fasciculus.

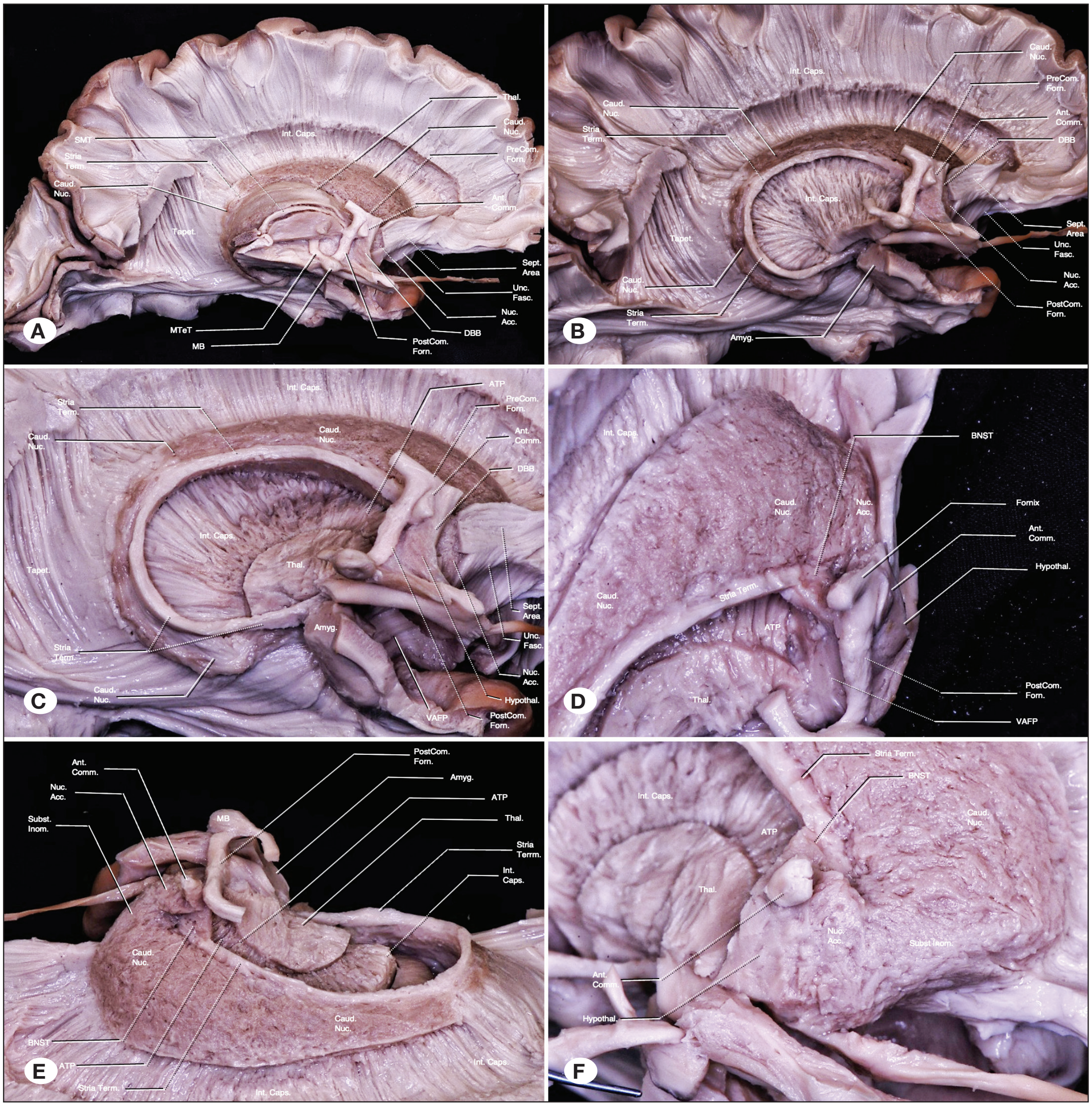

Figure 2: Demonstration of the anatomical relationships of the BNST through medial to lateral dissection. **A)** After removal of the corpus callosum and cingulum fibers, the caudate nucleus extending along the medial wall of the lateral ventricle becomes visible. The caudate nucleus exhibits a C-shaped configuration encircling the thalamus. The stria medullaris thalami, arising from the habenular commissure, courses anteriorly along the dorsomedial surface of the thalamus toward the hypothalamic area. The crus of the fornix projects toward the anterior commissure and is adjacent to both the head of the caudate nucleus and the anterior thalamic nuclei. At this level, the fornix is located in a plane overlapping the BNST. **B)** Following removal of the thalamus, fibers of the internal capsule were exposed. **C)** Closer view. The thalamus is partially removed, with the anterior thalamic peduncle preserved; elsewhere, the internal capsule is revealed. The anterior thalamic peduncle obliquely traverses the BNST from the lateral side. Just above the anterior commissure, the fornix splits into precommissural and postcommissural components. The precommissural fibers of the fornix cross the medial surface of the BNST in close relation to the diagonal band of Broca. The C-shaped course of the stria terminalis, along with the caudate nucleus, originating from the amygdala, was observed. **D–F)** Oblique posteromedial (**D**), superomedial (**E**), and anteromedial (**F**) views depict the anatomical relationships of the BNST. The nucleus accumbens, substantia innominata, and the caudate nucleus were observed to encircle the BNST from the anterior aspect. **Amyg.:** amygdala; **Ant. Comm.:** anterior commissure; **ATP:** anterior thalamic peduncle; **BNST:** bed nucleus of the stria terminalis; **Caud. Nuc.:** caudate nucleus; **DBB:** diagonal band of Broca; **Hypothal.:** hypothalamus; **Int. Caps:** internal capsule; **MB:** mamillary body; **MTeT:** mamillotegmental tractus; **Nuc. Acc.:** nucleus accumbens; **PostCom. Forn.:** postcommissural fornix; **PreCom.Forn.:** precommissural fornix; **Sept. Area:** septal area; **SMT:** stria medullaris thalami; **Stria Term.:** stria terminalis; **Subs. Inom.:** substantia innominata; **Tapet.:** tapetum; **Thal.:** thalamus; **Unc. Fasc.:** uncinate fasciculus; **VAFP:** ventral amygdalofugal pathway.

Upon removal of the thalamus and lateral mesencephalon, the medial surface of the temporal lobe was exposed, revealing the amygdala (Figure 2B). Fibers originating from the amygdala formed the dorsal amygdalofugal pathway, which coursed inferomedially around the CdN and followed the striothalamic sulcus as the ST. This bundle curved dorsally over the thalamus and terminated in the BST, situated at the anterosuperior aspect of the AC. Before reaching the BST, the ST passed medially between the postcommissural fornix and the anterior thalamic peduncle. As it passed superior to the AC, it reached the BST in association with the precommissural fornix, the DBB, and the anterior hypothalamic area (Figure 2C, 2D, 2E, 2F).

The anterior portion of the BST was bordered by the head of the CdN and the NAc. Fibrous continuity was observed between the posterosuperomedial portion of the NAc and the BST. Anteroinferiorly, the BST was in close anatomical relation with the SI.

Anatomical Neighborhood and Fiber Connections of the Bed Nucleus of the Stria Terminalis

Dissections revealed that the BST is located on the anterolateral wall of the third ventricle and is in direct anatomical continuity with several neighboring structures, including the AC, NAc, CdN, SI, septal area, and gyrus paraterminalis (Table I). The AC was observed along the dorsal border of the BST, while the NAc was situated anteroinferiorly and the SI anteroinferiorly and laterally. The septal area was located medially to the BST, and the gyrus paraterminalis occupied a rostral position.

Examination of fiber pathways demonstrated that projections to the BST course through the ST, pre- and postcommissural fornix, AC, DBB, and stria medullaris thalami (Table II). Fibers of the ST, originating from the amygdala, formed a posterior, superior, and anterior arch before reaching the posterolateral surface of the BST. Precommissural fornix fibers approached the rostral BST medially, whereas postcommissural fornix fibers coursed medially to the caudal BST and continued toward hypothalamic structures. Fibers of the DBB were observed along the inferomedial border of the BST, and the posterior limb of the AC passed adjacent to its dorsal margin.

DISCUSSION

This study aimed to revisit the anatomical localization and white matter connectivity of the BST in the human brain through detailed cadaveric dissections, thereby elucidating its position within the broader limbic network. The findings demonstrated that the BST is structurally interconnected with adjacent regions such as the AC, NAc, CdN, and thalamus (Table I, Figures 1-2), and that its afferent and efferent pathways—most notably the fornix, ST, and ventral amygdalofugal pathway (VAFP) —position the BST not as an isolated structure, but rather as a central node within a highly integrated connectional system. This comprehensive network architecture suggests that the BST is not merely a relay station, but an active modulator in processes such as emotional regulation, stress response, and autonomic control (1,7,8,19,33).

The connectivity pattern of the BST exhibits a bidirectional organizational model through both long-range projections (along the anteroposterior axis) and short-range local projections (Table II). Through major pathways such as the ST, VAFP, and the fornix, the BST maintains structural continuity with key limbic centers including the hippocampus, amygdala, and hypothalamus, thus actively participating in emotional information processing, stress regulation, and memory-related functions. In contrast, its short-range projections with structures such as the NAc, septal complex, and SI suggest a modulatory role in region-specific autonomic and affective responses (5,6,8,13, 14,18-20,31).

Our dissections revealed that the ST approaches the BST from a posterolateral trajectory to establish connections with the amygdaloid complex (Figures 1C, 1D, 2B, 2C), supporting its role in the transmission of emotional information (5,8). In this context, the C-shaped course of the ST between the thal-

Table I: Anatomical Neighborhood of the Bed Nucleus of the Stria Terminalis (BST)

Structure	Anatomical Relationship with the BST
Anterior Commissure	Located anterosuperior to the BST; closely associated with its dorsal border.
Nucleus Accumbens	Positioned anteroinferior to the BST; maintains short-range reciprocal connections.
Caudate Nucleus (Head)	Situated anterolateral to the BST; together with the NAc, forms the anterior border.
Anterior Thalamic Peduncle	Extends anterosuperiorly from the posterolateral aspect of the BST.
Substantia Innominata	Located anteroinferior to the BST; provides short fiber connections and receives projections via the VAFP.
Third Ventricle	The BST is located on the anterolateral wall of the third ventricle..
Fornix	Passes posterior and medial to the BST.
Gyrus Paraterminalis	Forms the rostral anterior neighborhood of the BST.
Hypothalamic Region	Situated caudally to the BST.
Septal Area	Located medially to the BST; establish dense structural connections.

Table II: Fiber Connections of the Bed Nucleus of the Stria Terminalis

Fiber	Source	Course	Relation to the BST
Stria Terminalis	Amygdala	Arches posteriorly, superiorly, anteriorly, and inferiorly around the CdN	Terminates at the posterolateral surface of the BST; conveys strong amygdaloid projections
Precommissural Fornix	Hippocampus	Passes anterior to the AC in an anteroinferior direction	Reaches the rostral BST medially; structurally interacts with the DBB and septal areas
Postcommissural Fornix	Hippocampus	Projects inferoposteriorly after passing posterior to the AC	Approaches the caudal BST medially; continues toward the posterior hypothalamus and mammillary bodies
Anterior Commissure	Contralateral hemisphere	Fibers pass near the posteroinferior margin of the BST via the posterior limb	Lies adjacent to the dorsal border of the BST; some BST fibers may cross hemispheres via this structure
Stria Medullaris Thalami	Habenular commissure	Courses anteriorly along the mediobasal thalamus	Passes near the inferior margin of the BST; provides projections to septal and hypothalamic areas
Diagonal Band of Broca	Fibers diverging from the VAFP	Ascends superomedially beneath the AC	Closely related to the medial and inferior borders of the BST
Hypothalamic Projections	Originating from the BST	Extend caudally and inferiorly	Project to the preoptic region and anterior hypothalamus; form caudal efferent connections of the BST

amus and CdN has been previously documented in the literature, and our anatomical findings align structurally with these descriptions (Figure 2A, 2B, 2C) (8,14,18,20,35). Furthermore, the points of contact with the DBB suggest that the BST maintains bidirectional communication with the amygdala via the VAFP.

Our dissection data also demonstrated that the BST establishes particularly robust structural relationships with the septal areas, predominantly in its medial and ventral aspects (Figure 2A, 2B, 2C). The division of the fornix into precommissural and postcommissural branches, each approaching the BST from dorsal and medial directions, respectively, indicates that this nucleus maintains bidirectional connectivity with both anterior limbic structures (such as the septal region and prefrontal cortex) and posterior components (including the hypothalamus and mammillary bodies). Notably, the observation that precommissural fornix fibers reach the dorsal portion of the BST and proceed toward the medial septal and hypothalamic regions supports the notion that the BST serves as a critical transitional station between cortical and limbic systems (Figure 2C, 2D).

The close anatomical relationship between the AC and the BST was clearly observed in our dissections and may indicate a potential role for these structures in interhemispheric regulation of emotional processes (Figure 1C, 1D) (1,27). In their detailed fiber dissection of the septum verum, Barany et al. also demonstrated that projections passing around the AC facilitate information transfer between the BST and septal areas (1). These findings suggest that the BST is not only a component of the limbic system but may also function as a dynamic interface governing bidirectional information flow between cortical and subcortical regions.

Our dissection findings also revealed a distinct anatomical relationship between the BST and the SI in the anteroinferior plane (Figures 1D, 2F). This close spatial association may serve as a structural bridge between the BST and subcortical centers involved in arousal, attention, and visceral regulation within the basal forebrain (27,32). Accordingly, the BST can be considered not only as a conduit for afferent–efferent information transfer but also as a functionally active structure contributing to the maintenance of emotional stability.

Consistent with current literature, our study demonstrated that the stria medullaris thalami courses along the inferior margin of the BST, projecting to septal and hypothalamic regions (Figure 2A) (1,16,29). This anatomical connection may represent a component of an integrated system supporting the neural basis of emotional signal processing, impulse regulation, and autonomic coordination among the dorsal thalamus, habenular complex, and hypothalamus (27,29).

The BST has recently emerged as a key target in deep brain stimulation (DBS) research, particularly in treatment-resistant OCD (4,24,25). In their study involving 11 patients, Naesström et al. reported that DBS targeting the BST generated an electrical field extending beyond the nucleus itself to adjacent structures such as the internal capsule, AC, fornix, and globus pallidus—resulting in clinically significant improvements (25).

The anatomical proximity and connectivity of the BST suggest that it functions as a bidirectional regulatory hub capable of modulating affective and compulsive symptom domains (4,24,25). Its spatial relationship with the AC and NAc further supports its potential role in emotional decision-making and impulsivity regulation via the ventral striatal circuitry (25,34). Based on these observations, our dissection results closely align with the proposed therapeutic targets, reinforcing the functional significance of the BST as a viable intervention site in the treatment of OCD.

Considering the BST as a surgical target highlights the critical importance of anatomical precision in neuromodulation techniques such as DBS. Our findings support the view that even milimeter deviations in electrode placement relative to surrounding structures such as the AC, internal capsule, NAc, SI, fornix, and globus pallidus may significantly influence clinical outcomes, based on the anatomical data obtained in this study (22,24,25). Accordingly, comprehensive mapping of the BST and its neighboring structures is essential not only for accurate targeting but also for maximizing therapeutic efficacy.

The pivotal role of the BST in emotional regulation has led to its consideration as an alternative DBS target not only in OCD but also in treatment-resistant depression and generalized anxiety disorder (3,10,34). Several long-term studies have reported that bilateral DBS targeting the BST yields clinically meaningful improvements in both anxiety and depressive symptoms (3,10,23,34). These findings underscore the BST's importance as a neuromodulatory center interacting not only with the limbic system, but also with regulatory components such as the prefrontal cortex, medial septal region, and hypothalamus (3,7,17,19). The medial approach of the fornix fibers identified in our dissections, as well as the connections with the underlying SI and the anteroinferiorly situated DBB, support the BST's integrative role within the hypothalamo-septal and cortico-limbic networks.

Limitations

Despite the significance of the findings, this study carries several methodological limitations. The use of postmortem human brain specimens restricted the analysis to anatomical connections only, precluding the direct observation of physiological functions or dynamic interactions. Additionally, technical challenges encountered during the dissection of fine fiber bundles may have led to the omission or underrepresentation of certain connections. However, these limitations were mitigated as much as possible by conducting meticulous dissections and continuously validating the findings against existing literature.

CONCLUSION

Our study contributes to both neuroscience and neuromodulation by thoroughly delineating the fiber connectivity of the BST and its anatomical relationships with surrounding structures. By identifying its connections with the AC, fornix, ST, NAc, SI, thalamus, hypothalamus, and amygdala, the present findings support previous studies concerning the role of the BST in emotional regulation, stress response, and the pathophysiology of affective disorders. We consider that these anatomical results provide a significant basis for improving the accuracy of surgical targeting in neuromodulatory interventions. Furthermore, these findings suggest that the BST should be considered a key target in the neuromodulation-based treatment of clinical conditions such as depression, OCD, and generalized anxiety disorder.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

AUTHORSHIP CONTRIBUTION

Study conception and design: OB, SSB, NT
Data collection: OB, OMC, SSB
Analysis and interpretation of results: OB, YED
Draft manuscript preparation: OB, YED, OMC, SSB
Critical revision of the article: OB, SSB, CC, NT
Other (study supervision, fundings, materials, etc...): NT
All authors (OB, YED, OMC, SSB, CC, NT) reviewed the results and approved the final version of the manuscript.

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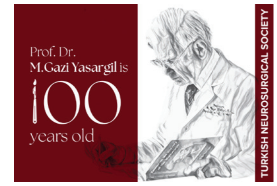

Treatment of a Pediatric Recurrent Dissecting Middle Cerebral Artery Aneurysm with a Flow Diverter: A Case Report

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ABSTRACT

Intracranial aneurysms are rare in the pediatric population, while fusiform middle cerebral artery (MCA) aneurysms are more common. Although surgical clipping is the generally preferred treatment strategy for aneurysms, occasional recurrence may still occur after successful clipping. As expertise in the use of flow diverters in adults has developed, they have also been applied in the management of aneurysms in children. This study aims to report a case of recurrence of MCA aneurysm after clipping, which was effectively treated using the Tubridge flow diverter. In the event of a recurrently clipped aneurysm, the implementation of a flow diverter treatment may be considered. Furthermore, we investigated the use of dual antiplatelet protocols during the perioperative period in children.

KEYWORDS: Case report, Flow diverter, Pediatric, Intracranial aneurysm, Recurrence

ABBREVIATIONS: MCA: Middle cerebral artery, **CTA:** Computed tomography angiography, **DSA:** Digital subtraction angiography, **TEG:** Thromboelastography

INTRODUCTION

Intracranial aneurysms in pediatric patients tend to be infrequent lesions, and their genuine occurrence remains unknown. Children commonly represent less than 5% of patients with aneurysms in most published studies (3,11,14). However, the aneurysm morphology and pathogenesis may differ from that of adults. Fusiform MCA aneurysms are more prevalent in adolescents (2-4). Previous studies have reported that open surgery may be more durable and effective, but occasional recurrence may still occur after successful clipping (4,8). Endovascular treatment is a frequently used treatment method for recurrent aneurysms in adults. Pipeline flow diverters were initially approved for use in patients aged 21 years and above. However, similar to adults, the application of flow diverters in children has been considered an attractive treatment option for aneurysms, especially fusiform and dissecting aneurysms (9,11,13). In this study, we present a case of recurrent dissecting MCA aneurysm in a pediatric patient who was effectively treated using the Tubridge flow diverter.

CASE REPORT

This study included a 5-year-old boy who presented with intermittent headaches without a trigger and was found to have a large complex aneurysm on the right MCA based on the computed tomography angiography (CTA) results (Figure 1). Subsequent digital subtraction angiography (DSA) has revealed a large (14.6 mm × 10.8 mm) MCA aneurysm, with a neck width of 3.3 mm (Figure 2). Shortly after the DSA, the patient and family agreed that he should undergo elective clip reconstruction of the diseased section of the MCA. Moreover, the aneurysm was successfully clipped and the parent artery was remodeled.

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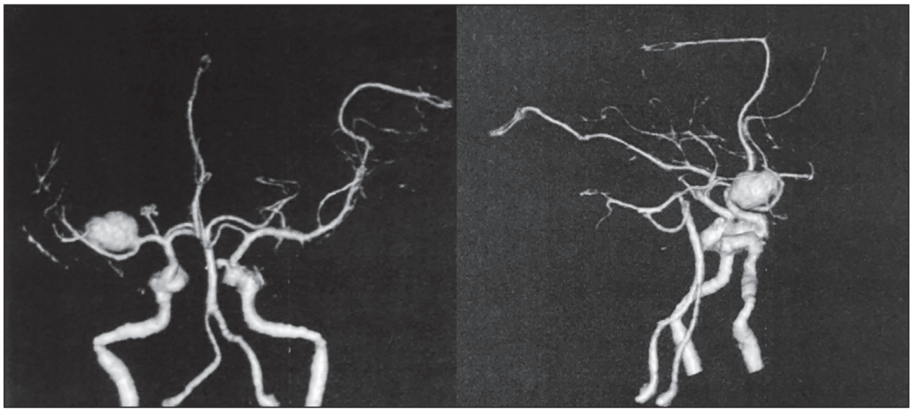

Figure 1: The computed tomography angiography examination on admission. It shows a right MCA aneurysm.

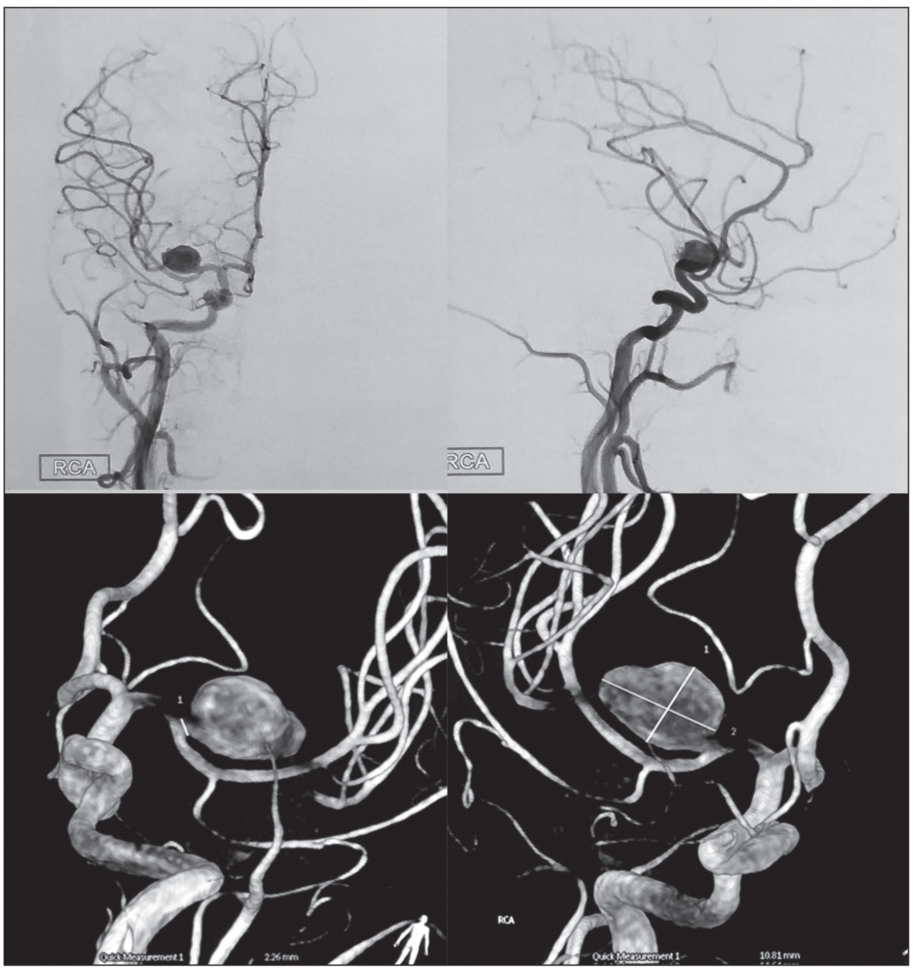

Figure 2: A preoperative digital subtraction angiography reveals a giant (14.6 x 10.8 mm) MCA aneurysm.

Three months after surgical clipping, he presented to the neurosurgery department with a severe headache, and the imaging studies revealed a recurrent aneurysm (Figures 3A, B). Notably, a new aneurysm had developed adjacent to the previously treated aneurysm (Figure 3C). Thus, various treatment options have been considered, including surgical and endovascular procedures. The application of the Tubridge flow diverter was selected as the best treatment option to achieve complete aneurysm obliteration with acceptable risk among other endovascular treatment options.

Since he had a body weight of 30kg, he was pretreated with 60 mg of aspirin and 30 mg of clopidogrel daily for 5 days. Subsequently, we refined the light transmission aggregometry and thromboelastography (TEG) platelet mapping, suggesting that both aspirin and clopidogrel were effective at reducing the platelet aggregation rate to 20% of the normal levels. The procedure was performed under general endotracheal anesthesia, and the patient was systemically heparinized. A bilateral femoral approach was applied to enable the simultaneous navigation of the two microcatheters. Under general anesthe-

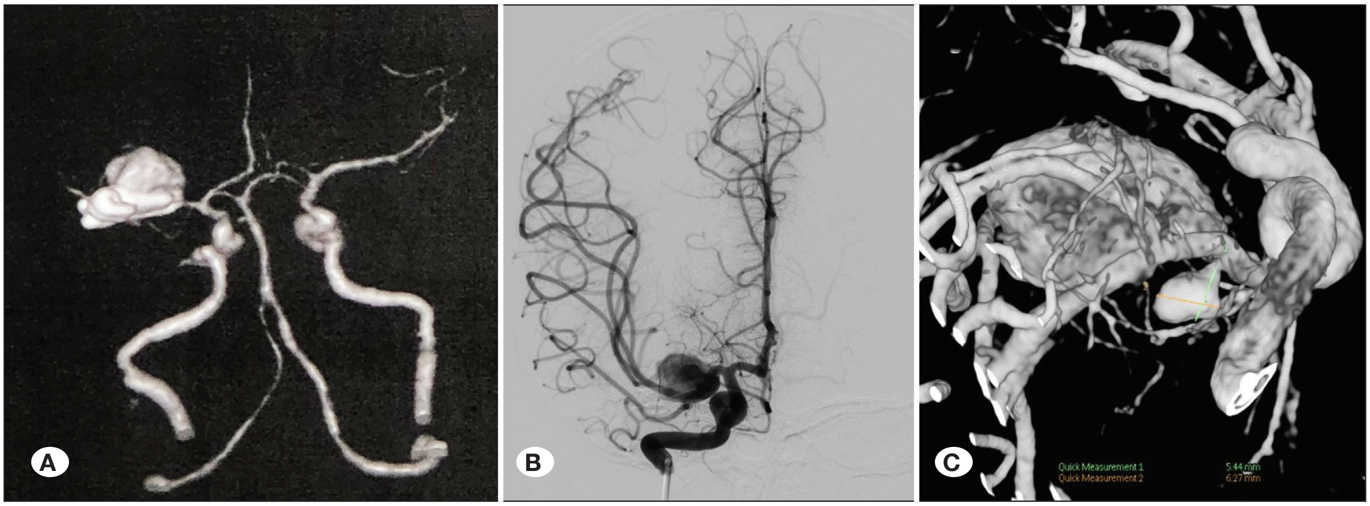

Figure 3: Right internal carotid angiogram 3 months after surgery show a recurrent MCA aneurysm. **A)** Computed tomography angiography. **B)** Digital subtraction angiography. **C)** A reconstructed 3D DSA confirms a new aneurysm has developed near the recurrent aneurysm.

sia and anticoagulation, a 6F 90-cm-long sheath introducer and 5F Envoy guiding catheter were placed into the proximal right internal carotid artery. Moreover, a 5F DAC support catheter was guided through the long sheath and positioned within the right cavernous segment of the internal carotid artery. Subsequently, a T-track microcatheter was navigated via the DAC catheter into the right MCA M2, whereas an Echelon10 microcatheter was navigated coaxially into the small aneurysm sac via the Envoy guiding catheter. Three coils were inserted to embolize the aneurysm. The super-selective catheterization of the large aneurysm revealed a vessel branch arising from the aneurysm wall during angiography. Considering the possibility of acute aneurysm occlusion leading to vascular blockage and subsequent neurological dysfunction, we decided not to insert a coil into the large aneurysm. Finally, the Tubridge flow diverter (3.0 × 25 mm) was advanced into the microcatheter, which was deployed uneventfully and crossed the entirety of the aneurysm neck. The intraprocedural arteriograms revealed successful stent placement with a stagnation of blood flow in the aneurysm (Figure 4A).

The procedure was otherwise uneventful, and the patient was discharged after 4 days. The results of the follow-up catheter angiography, which was conducted 11 months after the Tubridge flow diverter procedure was performed, revealed complete exclusion of the aneurysm and reconstruction of the artery (Figure 4B, C). The Vaso CT indicated good apposition of the stent margins to the arterial wall (Figure 4D). The administration of clopidogrel was discontinued at 11 months, and the patient continued treatment with aspirin on a daily basis.

Written informed consent was obtained from the patient's family for publishing this clinical report.

DISCUSSION

This study presents a case of recurrent aneurysm in the right MCA of a pediatric patient who underwent successful endovascular reconstruction using a flow diverter. Although several studies have reported cases of flow diverter placement in patients with MCA aneurysms, research on the use of the Tubridge flow diverter at this site among pediatric patients under the age of 10 years is limited (7). Moreover, this study aims to contribute significant findings to help develop additional therapeutic approaches for the potential management of recurrent aneurysms after pediatric aneurysm clipping.

Cerebral aneurysms tend to be rare in children, and only a few centers have extensive experience in their treatment (1, 11). Pediatric aneurysms differ from adult aneurysms in terms of sex, morphology, size, and location (13). Upon the re-evaluation of the child three months later, it was observed that not only did the previously clipped aneurysm recur but a new aneurysm also appeared adjacent to the recurrent aneurysm. It was suspected as a dissecting aneurysm, wherein an abnormality in the vessel wall led to the rapid recurrence of the clipped aneurysm and the formation of a new one. Unfortunately, the parents declined the MRI scan due to concerns about its effect on the aneurysm clips. This prevented us from completing the high-resolution MRI and other tests to produce a conclusive diagnosis. Based on the clinical manifestations alone, we can infer that it may be a dissecting aneurysm. Dissecting aneurysms involving the MCA during childhood are uncommon. The review conducted by Lasjaunias et al. on 59 patients younger than 15 years old reported 33 (45%) patients with dissecting aneurysms (only four involving MCA) having a mean age of 6 years (6).

Over the last two decades, a significant shift in the approach to vascular neurosurgery has been observed, wherein the emphasis has shifted from invasive surgical methods for treating intracranial aneurysms to the adoption of minimally invasive endovascular techniques (8). The emergence of flow diverters has facilitated this shift, leading to the treatment of aneurysms through the reconstruction of the parent artery. The Tubridge flow diverter has shown favorable outcomes in treating recurrent and dissecting aneurysms in adult patients

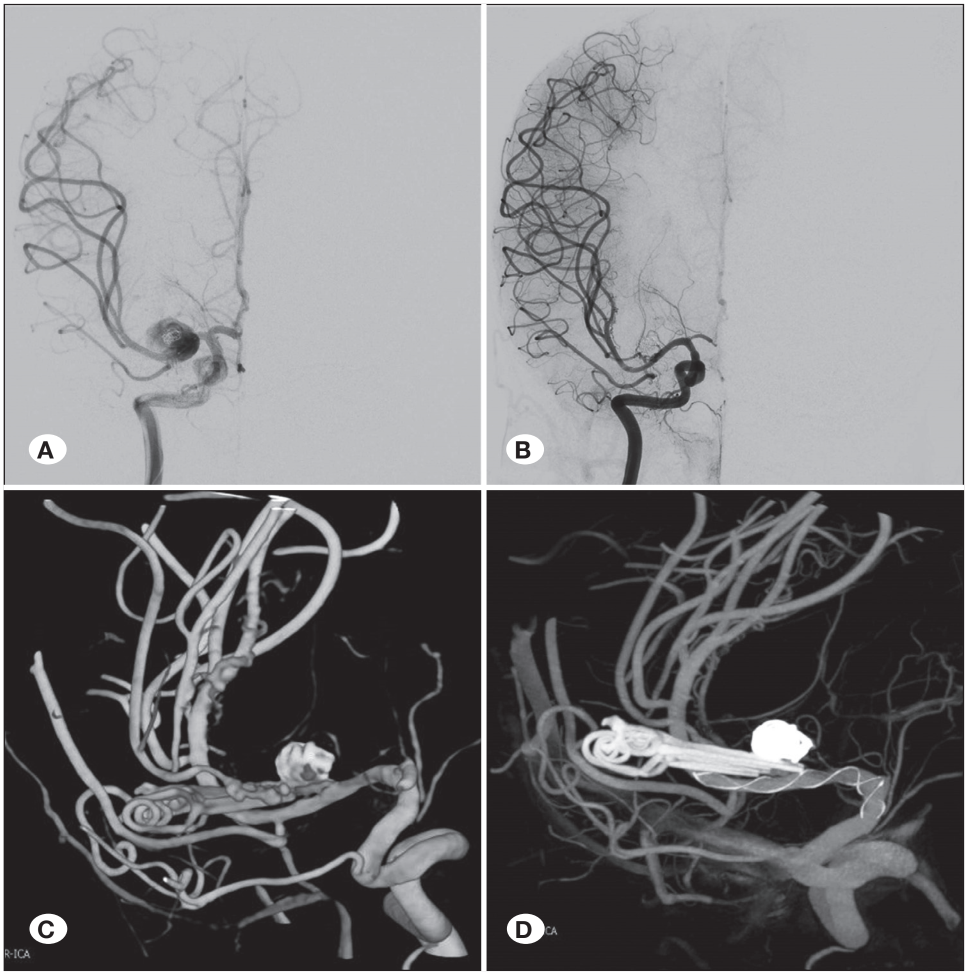

Figure 4: A) Intraprocedural angiogram reveals the contrast stasis within the aneurysm. **B)** The 11-month follow-up digital subtraction angiography (DSA). **C)** A reconstructed 3D image from DSA. **D)** Vaso CT.

(5,15). To our knowledge, the present case is the youngest patient who had received treatment for a recurring aneurysm using a Tubridge flow diverter.

Another issue that should be considered is the growth of the arteries. Arat et al. have assessed the intracranial vessels in adults and children via digital subtraction angiography. They revealed that the internal carotid artery and anterior cerebral artery reach near their maximum diameter by four years of age, while the MCA reaches its approximate adult diameter at six months of age (10). The MCA forms during the early stages of embryonic development, appearing before most other blood vessels and providing a relatively large volume of blood flow. Further research has also shown comparable outcomes related to cerebrovascular growth in children. These studies revealed that the currently available intracranial stents or flow diverters come in a range of sizes suitable for use in the pediatric population, while the intracranial arterial diameters in children do not undergo significant growth, especially after early childhood (1).

More importantly, the antiplatelet protocols used during the perioperative period for flow diverters should be considered. At present, no standard antiplatelet therapy for children undergoing intracranial vascular device placement has been established. Moreover, no published guidelines on antiplatelet therapy for children with cerebrovascular diseases nor any definitive trials on pediatric antiplatelet therapy regimens have been implemented (1). The use of antiplatelet regimens varies among institutions. Some institutions have applied the identical antiplatelet protocol for adults (2), while some institutions administered a lower dose of medication with no definitive explanation (4). In this report, a dual antiplatelet agent was administered at approximately half of the adult dose. Regardless of the regimen, the drug dose should be adjusted based on light transmission aggregometry and TEG platelet mapping. Dual antiplatelet therapy with the administration of aspirin and ticagrelor has been applied in endovascular procedures in adults; however, its utilization in children has not been investigated (12).

CONCLUSION

Further research is needed to better evaluate the use of a dual antiplatelet regimen during the perioperative period for flow diverters in pediatric patients.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Institutional Review Board Statement: Ethical review and approval were waived for this study due to the fact that this is a single-case report.

AUTHORSHIP CONTRIBUTION

Study conception and design: WZ

Data collection: ZL, YF

Analysis and interpretation of results: TZ

Draft manuscript preparation: ZL, YF

Critical revision of the article: TZ

Other (study supervision, fundings, materials, etc...): WZ

All authors (ZL, YF, TZ, WZ) reviewed the results and approved the final version of the manuscript.

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Case Report

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Bilateral Thinning of the Temporal Bone: A Case Report

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ABSTRACT

Bone mass is maintained by a balance between bone formation by osteoblasts and resorption by osteoclasts. Calvarial thinning can occur because of various factors. However, no previous studies have described bilateral temporal thinning (BTT) of the skull. This report presents a case of a squamous part of the bilateral temporal bone in a patient with alcohol-induced liver cirrhosis. This is the first case of BTT exhibiting an appearance similar to that of bilateral parietal thinning (BPT) in a patient with osteoporosis caused by liver cirrhosis. Although the precise pathogenic mechanism underlying thinning of the squamous part of the temporal bone remains unclear, osteoporosis associated with diploë is presumed to have contributed to its development in this patient, and BTT is considered a variant of BPT.

KEYWORDS: Bone formation, Liver cirrhosis, Osteoporosis

INTRODUCTION

Bone mass is meticulously maintained by a delicate balance between bone formation by osteoblasts and bone resorption by osteoclasts. Disruption of this tightly regulated equilibrium maintained by the intricate crosstalk between osteoblasts and osteoclasts can lead to bone thickening and thinning (5). Calvarial thinning can arise from various factors, including bilateral thinning of the parietal bones, osteogenesis imperfecta, hypophosphatasia, achondrogenesis, Menkes syndrome, craniofacial syndromes, arachnoid cyst, mega cisterna magna, and peripherally located tumors (4). However, no previous studies have documented bilateral temporal thinning (BTT) of the skull. To our knowledge, this is the first documented case of BTT in a patient with alcohol-induced liver cirrhosis. The author also proposes a possible mechanism to explain this rare case.

CASE REPORT

A 49-year-old male patient presented to the hospital with noticeable depression of the bitemporal region of his head, which gradually worsened over the prior few years. He denied having a history of head trauma. Despite complaints of dull sensations in both legs, neurological examination revealed no abnormalities. Physical examination revealed significant depression in the temporal areas bilaterally. The patient's medical history included liver cirrhosis, esophageal and gastric cardiac varices, and splenomegaly, all of which were attributed to long-term alcohol consumption. The patient's medical history included liver cirrhosis, esophageal and gastric cardiac varices, and splenomegaly, all of which were diagnosed three years prior and were attributed to long-term alcohol consumption. Under these conditions, the patient was continuously taking ursodeoxycholic acid, silymarin, and spironolactone. Laboratory tests related to bone metabolism and hormone levels were within normal limits, including serum calcium at 9.1 mg/dL (normal range: 8.5–10.2 mg/dL), phosphate at 3.5 mg/dL (2.5–4.5 mg/dL), alkaline phosphatase at 83 IU/L (44–147 IU/L), parathyroid hormone at 42 pg/mL (10–65 pg/mL), 25-hydroxyvitamin D at 79 ng/mL (30–100 ng/mL), and rheumatoid factor at 1.2 IU/mL (0–15 IU/mL). Laboratory test results for bone metabolism and hormone levels were within normal limits. The patient's bone mineral density T-score was -3.5, indicating osteoporosis. A cranial computed tomography (CT) scan revealed focal thinning of the bilateral temporal bones, measuring only 0.7 mm in thickness (Figure 1). Cranial CT performed six years earlier showed no thinning or abnormalities (Figure 2). A whole-body bone scan did not reveal any focal areas of abnormal radiotracer uptake in the cranial bones (Figure 3).

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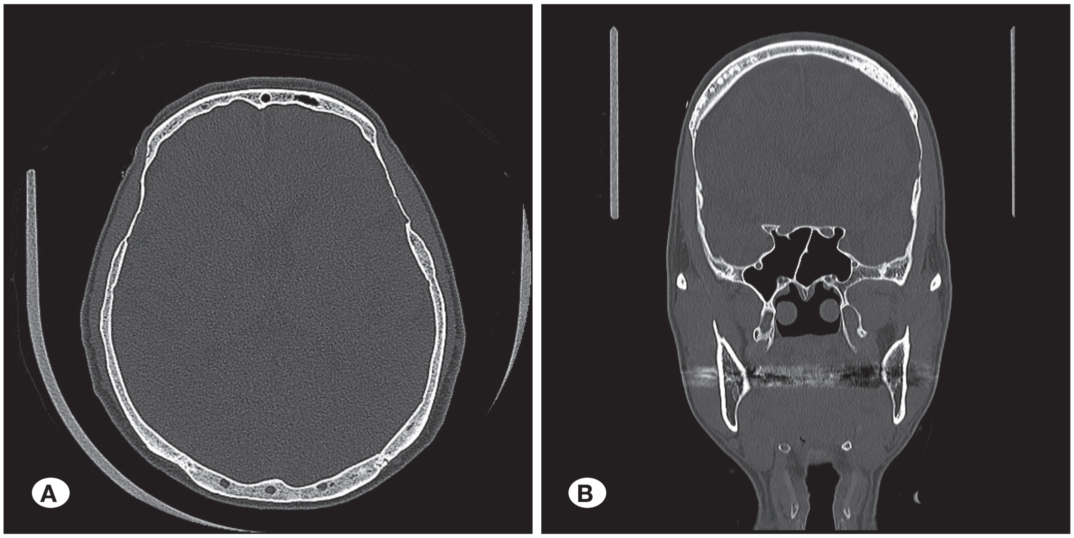

Figure 1: Axial **(A)**, and coronal **(B)** cranial computed tomography scans showing focal thinning of the bilateral temporal bones, with a thickness of 0.7 mm.

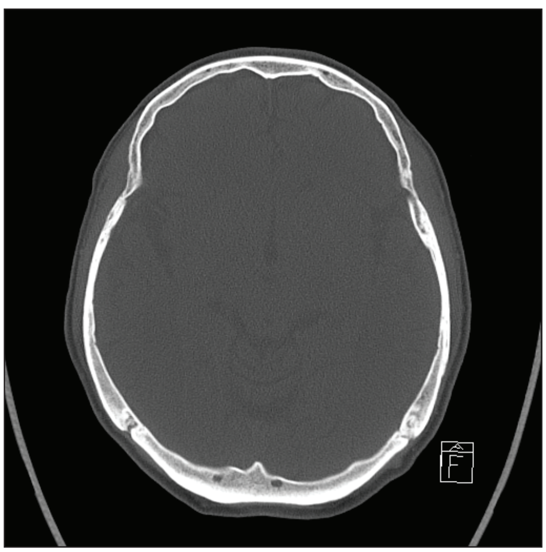

Figure 2: Axial cranial computed tomography obtained six years before the patient's complaints showing no thinning or abnormalities.

DISCUSSION

Calvarial lesions can be classified into the following three categories: 1. single or multiple lytic lesions, 2. focal or multiple diffuse sclerotic lesions, and 3. focal or diffuse calvarial thinning. Common causes of calvarial thinning include neoplastic or transdiploic lesions and osteomyelitis, whereas uncommon causes include Parry-Romberg syndrome (facial hemiatrophy), flap osteonecrosis, Gorham disease, and bilateral parietal thinning (BPT). Diffuse calvarial thinning may be caused by convolutional markings, copper-beaten skulls, lacunar skulls, and craniosynostosis (4). BPT exhibited a pattern of local calvarial thinning similar to that of the patient in this case. BPT of the skull was first described in the 18th century (2). It is a rare acquired disease, affecting an estimated 0.25%–0.8% of the population and is more prevalent in women than in men (2,7). BPT is typically characterized by the thinning of the bilateral parietal bones between the midline sagittal suture and the lateral parietal eminence (5). Cranial radiographs of BPT demonstrate symmetrical thinning of the bilateral parietal bones involving the outer table and diploë of the skull, resulting in a scalloped appearance (2,7,8).

In the present case, the patient experienced bilateral symmetrical thinning of the squamous portion of the temporal bone, resembling BPT. Although both the temporal and parietal bones are classified as flat bones, the temporal bone is more complex in structure, and its histological organization is slightly different because of its involvement in both hearing and cranial protection (3). The temporal bone is composed of several parts: the petrous, squamous, tympanic, and mastoid parts (3). The petrous part contains highly dense, compact bone with few spaces, reflecting its role in protecting delicate structures such as the cochlea and vestibular apparatus. The squamous part forms the lateral walls of the cranium, is relatively thin, and has a flatter bone structure. This part has a larger amount of diploë between the outer and inner layers of the compact bone, making it less dense than the petrous part. The mastoid part is characterized by the presence of mastoid air cells, which are air-filled cavities. These are lined with a thin layer of bone that forms trabeculae, a characteristic not observed in the parietal bone (3). The parietal bone is a typical flat bone, more uniform in structure, consisting of compact bone layers with a diploë. There are no specialized air cells or extremely dense regions, such as in the temporal bone. In the present case, the patient exhibited bilateral calvarial thinning in the squamous part of the temporal bone, which contained the parietal bone diploë. Baek et al. reported two cases of idiopathic calvarial thinning occurring bilaterally in the frontal squama with a pattern similar to that of BPT (1). Frontal squama shares the same structure as the parietal bones. Therefore, the author speculates that idiopathic calvarial thinning occurs in the flat bone containing diploë. Histological examinations in previous studies supported this conjecture (1,8). The diploë is particularly susceptible to the effects of osteo-

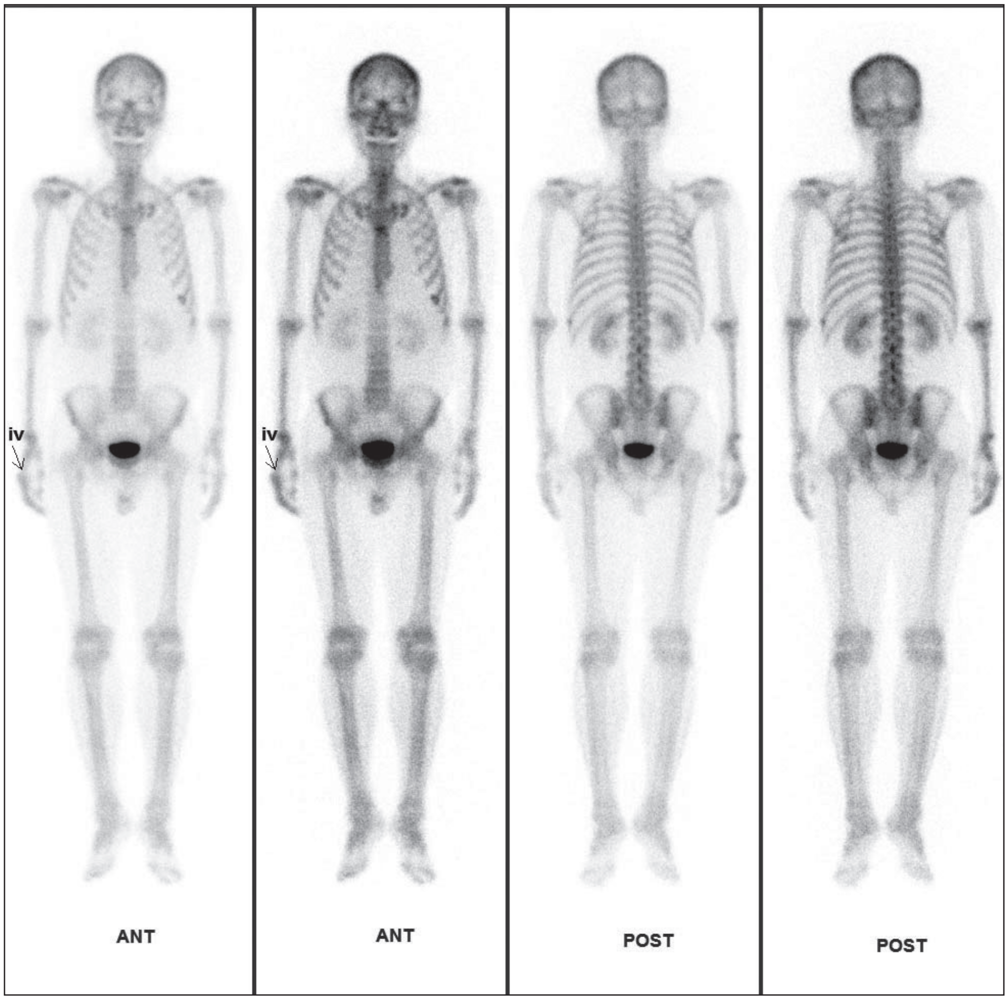

Figure 3: Whole body bone scan showing no focal areas of abnormal radiotracer uptake in the cranial bones.

porosis because of its trabecular structure and large surface area for bone turnover. Osteoporosis weakens the diploë by reducing the strength and number of trabeculae, leading to an increased risk of fractures, especially in bones rich in diploë, such as the vertebrae and pelvis (6). Osteoporosis, a major cause of bone thinning, is more common in women, which may explain why BPT occurs more frequently in women (2,7).

While the exact pathogenesis of BPT remains elusive, various theories have been proposed to explain the pathogenesis of this rare condition. One hypothesis suggests an association between postmenopausal age and senile osteoporosis (2,7,8). Histopathological studies have demonstrated a lack of osteoclasts, implying that BPT may be linked to osteoporosis resulting from decreased bone formation rather than increased bone destruction (2). In the present case, the patient presented with liver cirrhosis, secondary alcohol consumption, and concomitant osteoporosis. Undeniably, osteoporosis in this patient contributed to the development of BTT. Laboratory findings related to bone metabolism and hormone levels were within the normal limits. Zheng et al. reported an osteoporosis prevalence of 20.3% in patients with cirrhosis, which was attributed to liver viruses and alcohol abuse (9). Previous studies have shown that individuals with alcoholic liver disease exhibit a higher propensity for developing osteoporosis or osteopenia than those with chronic viral hepatitis (9). This may be attributed to the detrimental effects of alcohol consumption on osteoblast number and activity, along with its potential to impair nutrition and hormone secretion for bone remodeling. Furthermore, the activation of inflammatory cells in patients with liver cirrhosis can promote the production of pro-inflammatory factors such as tumor necrosis factor and interleukin-1, which can contribute to bone mass reduction. In the present case, thinning of the squamous part of the temporal bone closely resembled BPT both radiologically and histologically. Although the exact pathophysiology remains unknown, it is believed to be related to the diploë, which is most abundant in the parietal bones, as nearly all cases of calvarial thinning affect the parietal bones bilaterally. Therefore, the patient's condition is considered a variant of BPT.

CONCLUSION

To our knowledge, this is the first documented case of BTT with a presentation similar to that of BPT in a patient with osteoporosis caused by liver cirrhosis. Although the precise pathogenic mechanism underlying thinning of the squamous part of the temporal bone remains unclear, osteoporosis associated with diploë is presumed to have contributed to its development in this patient, and BTT is considered a variant of BPT. Further studies are needed to elucidate the clinical, radiological, and histopathological characteristics of this rare disease.

Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The author declare no competing interests.

Ethical Considerations: This study was approved by the ethics committee of Wonkwang University Hospital (approval No. 202311065).

AUTHORSHIP CONTRIBUTION

The author (KSE) confirm responsibility for the following: study conception and design, data collection, analysis and interpretation of results, and manuscript preparation.

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Case Report

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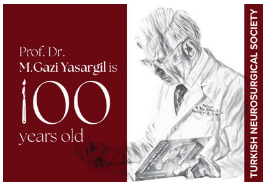

Intracranial Sewing Needles as Foreign Bodies: A Report of Two Cases

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ABSTRACT

Penetrating brain injuries are usually the result of high-velocity accidents. However, intracranial foreign bodies can also rarely occur as a result of child abuse. Inserting a sewing needle into the brain through the sutures before the closure of fontanelles represents a particularly intriguing and relatively unknown form of attempted infanticide. In this study, we analyzed two adults who presented with an intracranial foreign body. Case 1: A 36-year-old woman presented with complaints of headache. Radiographic evaluation revealed a sewing needle lodged in her brain. Case 2: A 62-year-old man was admitted with seizures. Radiographic examination revealed three sewing needles in his brain. Both patients were managed conservatively due to the non-threatening nature of their symptoms. Several victims of needle insertion incidents go unreported. Survivors of such incidents may present with late complications. The needle is often incidentally detected during adulthood. A limited number of publications indicate that authors tend to refrain from treating asymptomatic patients. Furthermore, the related ethical concerns pose significant challenges for the physicians

KEYWORDS: Infanticide, Sewing needle, Intracranial, Foreign body, Adulthood

ABBREVIATIONS: AF: Anterior fontanel, **LS:** Lambdoid suture, **AED:** Anti-epileptic drugs, **ABT:** Antibiotherapy, **MRI:** Magnetic resonance imaging

INTRODUCTION

Intracranial foreign bodies are usually reported secondary to a traumatic event, especially following penetrating brain injuries. In under-developed countries, the insertion of a sewing needle through the cranial sutures before the closure of fontanelles, a method of attempted infanticide, is a very rare cause of intracranial foreign bodies (1). This entity represents a special class of intracerebral foreign bodies and a method of homicide. Because numerous victims die within several days without a diagnosis, this condition is usually reported incidentally in survivors in childhood or adulthood or due to symptoms from late complications (3).

We have observed a concentration of these cases, particularly in Türkiye and its neighboring countries. Thus, we conducted an analysis of the cases reported from Türkiye to understand the prevalence in the country, approach of clinicians, and clinical characteristics of the patients. Additionally, we have presented two of our cases within this study. We believe that this legal issue is also important in countries with an immigrant population.

CASE REPORTS

Case 1

A 36-year-old woman was admitted to the neurology department with complaints of a headache for 10 years. There was no history of vomiting or seizures. The headache was characterized as a tension-type headache. Her general physical and neurological examinations yielded normal results. Cranial computed tomography revealed a foreign object in the cranium (Figure 1). Radiograph of the skull revealed a sewing needle in the right frontal region, extending from the right frontal convexity to the deeper areas of the right brain (Figure 1). She

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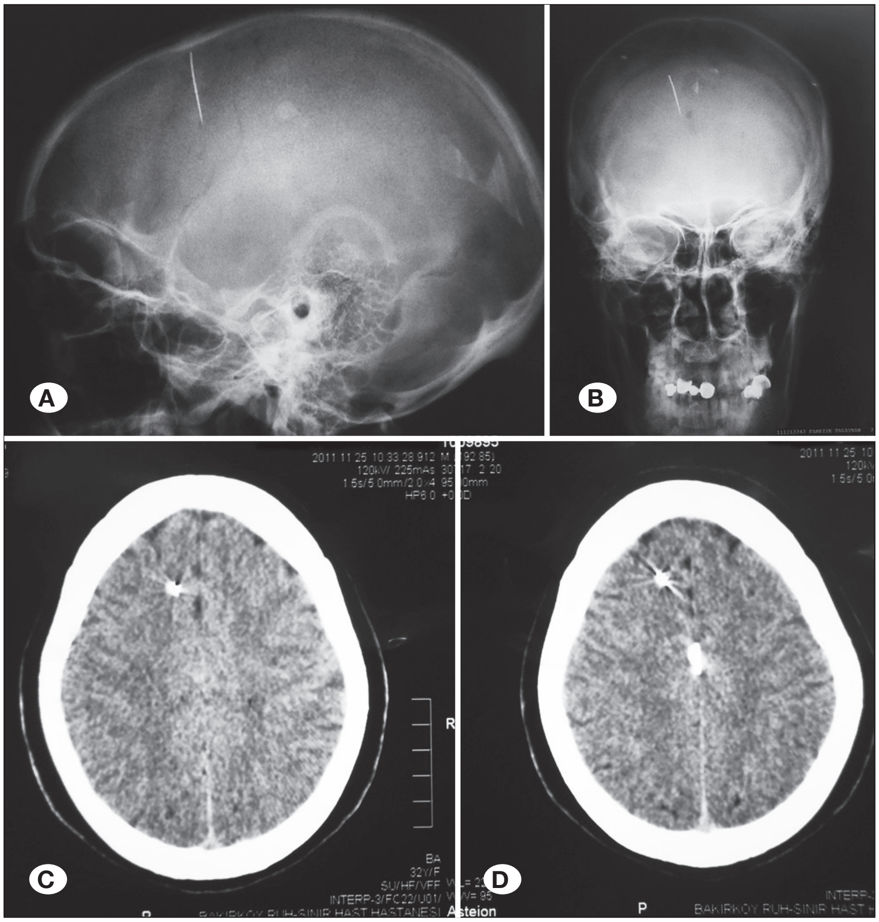

Figure 1: A 36-year-old woman. Plain X-rays of the skull (**A:** lateral, **B:** posteroanterior) and cranial computed tomography scans **(C, D)** reveal a sewing needle in the right frontal region, extending from the right frontal convexity into the deeper areas of the right brain.

was diagnosed with "tension-type headache." She was discharged and advised to follow up.

Case 2

A 62-year-old man with a headache and history of two generalized convulsions in the past week was admitted to the emergency unit. He had no significant medical history except for systemic hypertension for which he was consuming medications. The seizures were of the generalized tonic-clonic type, and his neurological examination yielded normal results. Cranial computed tomography revealed three sewing needles extending from the frontal convexity to the left ventricle (Figure 2). A plain radiograph of the skull was obtained to identify skull defects (Figure 2). The patient and his family did not report a history of needle insertion. The seizures were controlled with carbamazepine (800 mg/day) for a year. However, subsequently, he began to experience intentional tremors and rigidity of movements.

DISCUSSION

Objects traveling at a low velocity may cause penetrate the natural calvarial foramina such as the orbit, ears, and foramen magnum, typically resulting in isolated traumas (6). The presence of an isolated intracranial sewing needle following trauma is highly unusual.

Intracranial foreign bodies, although a rare occurrence, can result from child abuse. In developing countries, illiterate parents or relatives are often the main perpetrators. However, in well-developed countries, stepmothers, stepsisters, and babysitters may be involved (1). Infanticide is an extreme form of abuse, manifesting differently across cultures. One particularly unusual method involves inserting sewing needles into the brain before the fontanelles close. This form of infanticide was first described in Germany in 1914. Since then, fewer than 50 cases have been reported (3,18,19,20,22-24). The majority of these reports are from Iran and Türkiye, with significant series published by Abbasioun and Amirjamshidi in 1979 and 2009, respectively (1,3). Notably, the Iranian writer Sadegh Hedayat (1902-1951) described a case in which a child died following the insertion of a pin into the open fontanelles, indicating that this method of infanticide is known in the northwestern region of Iran.

Victims are often unwanted children or stepchildren, with girls being particularly vulnerable in some cultures. Other risk factors include being illegitimate, hyperactive, or mentally challenged children. The perpetrators are usually mothers or stepmothers. However, stepsisters, babysitters, and relatives may also be involved. Most victims die shortly after pin insertion due to complications. Survivors may suffer from late complications such as seizures, brain abscesses, and movement

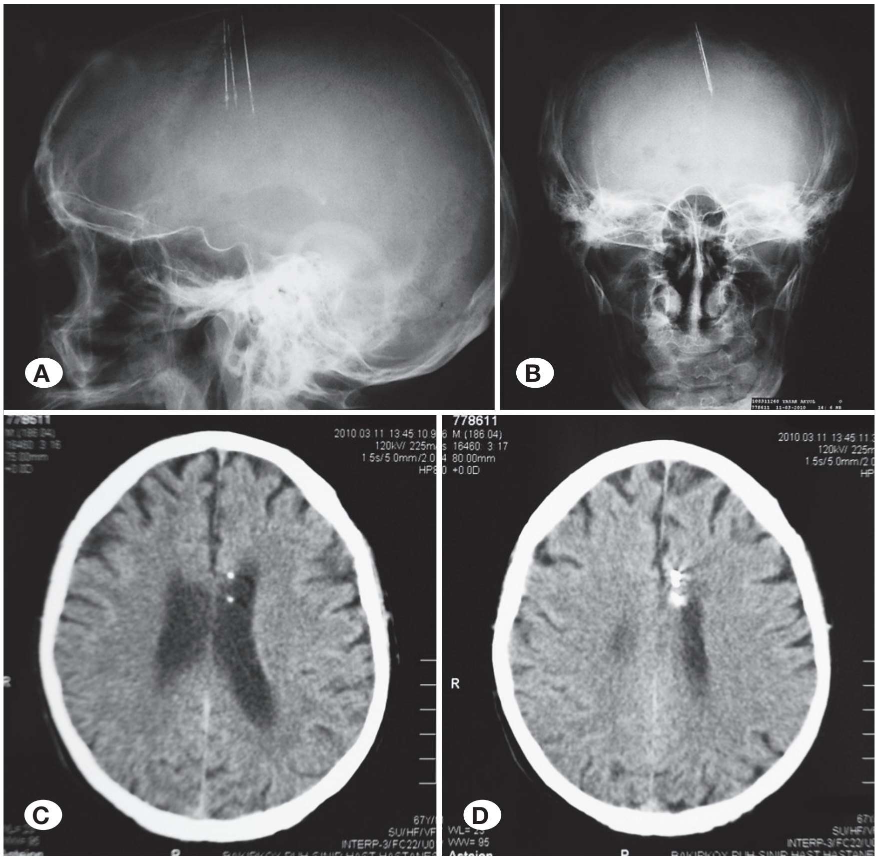

Figure 2: A 62-year-old man. Plain X-rays of the skull (**A:** lateral, **B:** posteroanterior) and cranial computed tomography scans **(C, D)** show three sewing needles extending from the frontal convexity into the left lateral ventricle.

disorders (1,3,16,20,23,24). Seizures and headaches are common symptoms, whereas motor weakness is rarely reported in the late phase. Several patients are incidentally found to have foreign bodies during the evaluation of non-specific symptoms (1,18,19,22). Our first patient was found to have a sewing needle in the brain during the evaluation of a non-specific headache. She was diagnosed to have a tension-type headache, which resolved after 2 weeks of appropriate medical treatment.

Surgical removal of the needles via craniotomy, endoscopic, or stereotactic methods is recommended if diagnosed early. However, this decision is more complex in asymptomatic patients or those with minor symptoms. Asymptomatic patients are often managed conservatively, with clinical and radiological follow-up (18,19,20,22). Amirjamshidi's report on six patients, four of whom underwent surgery, demonstrated mixed outcomes (3).

A significant number of cases involving intracranial foreign bodies have been reported from Türkiye (Table I). In addition to our two patients, 19 cases of suspected infanticide by intracranial needle insertion have survived until adulthood. Most of the cases reported from Türkiye have been male patients (14 males, 5 females, and 3 not specified). Although unwanted children, particularly girls, are generally undesirable, the predominance of male cases is noteworthy. In patients that reach adulthood, needles are often incidentally detected, with headaches being the most common complaint. However, it is difficult to attribute the headaches to the presence of needles, as headaches are common in the general population. In six of the 22 patients, seizures were the presenting symptom. Intracranial needles can cause seizures because of they are foreign in nature. Although electrophysiological evidence is insufficient to confirm this in every case, the needles are most likely the cause of seizures. Two patients presented with an intracranial abscess and involuntary movements. The presence of needles raises a debate regarding the appropriate treatment approach. The needles typically start superficially, but they extend deep into the brain tissue. In patients with incidentally found foreign bodies, there may be a long-term risk of infection or seizures. However, it is challenging to predict this risk in asymptomatic patients, and surgery is not typically preferred in these patients. Only four of the 22 patients underwent surgery. These patients had presented with refractory epileptic seizures. Seizure control was achieved after resection of the foreign body. In patients in whom the needle was retained, diagnostic magnetic resonance imaging (MRI) poses a risk. Thus, patients should be cautioned regarding this.

When an intracranial foreign body is discovered in an adult, the legal process should be promptly initiated, and the findings reported to the relevant authorities. The process typically involves forensic examination, documentation of radiological evidence, and a thorough investigation into the patient's medical and familial history. Legal authorities may involve law enforcement officials to conduct an investigation, because such cases often fall under statutes related to child abuse, even if

Table I: Distribution of Cases Reported in Turkey According to the Literature. We Conducted Comprehensive Searches in PubMed, Cochrane Library, Google Scholar, and Trdizin Databases Using the Search Terms 'Intracranial', 'Sewing', 'Needle', 'Fontanel', 'Insertion', 'Infanticide', 'Foreign Body', 'Dikiş Iğnesi', 'Intrakraniyal', 'Yabancı', 'Cisim', and 'Infantisid'. Studies Not Uploaded by Academic Institutions in Turkey were Excluded, and Duplicate Reports were Omitted to Ensure the Uniqueness of Each Case

Authors	Publication Year	No. of Patients	Age	Gender	No. of Needles	Clinical History	Neurological Examination	Insertion Way	Treatment	Outcome
Barlas and Gokay (5)	1983	2	29 y; 4 mo.	N/A; N/A	1; 1	Headache; Acute accidental insertion	Normal; Normal	AF; AF	No; ABT	good after 8 y; good after 6 mo.
Sener (15)	1997	1	20 y	N/A	3	Incidental	Normal	AF	No	
Unal et al. (21)	2005	1	10 y	F	1	Incidental	Normal	LS	No	
Tun et al. (19)	2006	1	45 y	M	1	Incidental	Normal	AF	No	
Sucu and Gelal (17)	2006	1	29 y	M	1	Incidental	Normal	AF	No	
Tuncer et al. (20)	2007	1	32 y	M	1	Seizure	Normal	LS	AED	No Seizure
Yilmaz et al. (23)	2007	1	10 y	M	5	Abscess	Papillar edema, Meningeal irritation	AF	ABT	No symptom
Yolas et al. (24)	2007	1	9 y	M	1	Seizure	Normal	AF	Surgical Resection	No seizure with AED
Balak et al. (4)	2008	1	10 y	F	1	Seizure	Normal	AF	Surgical Resection	No Seizure
Guven et al. (9)	2008	2	20 y; 21 y	M; M	1; 1	Seizure; Headache	Normal; Normal	AF; AF	Surgical Resection; No	No Seizure (?);
Alp et al. (2)	2009	1	20 y	F	2	Hemichorea	Choreiform movements (Left arm, leg)	AF	No	
Ilbay et al. (10)	2011	1	16 y	M	4	Headache	Normal	AF	No	
Kazanci et al. (13)	2012	1	37 y	M	2	Incidental	Normal	AF	No	
Pelin and Kaner (14)	2012	1	22 y	M	3	Headache	Normal	AF	No	
Karadas et al. (12)	-	-	-	-	-	-	-	-	-	Article Removed
Kahveci and Hamamcioglu (11)	2013	1	20 y	M	2	Headache	Normal	AF	No	
Gencpinar et al. (8)	2014	1	14 y	M	1	Seizure	Normal	AF	Surgical Resection	No Seizure with AED
Ucler and Yucetas (21)	2016	1	48 y	M	1	Headache	Normal	AF	No	
Erdogan et al. (7)	2022	1	78 y	F	1	Incidental	Normal	AF	No	
Present study	2024	2	36 y; 62 y	F; M	1; 3	Headache; Seizure	Normal; Normal	AF; AF	No; AED	No Seizure with AED

***AF:** Anterior Fontanel, **LS:** Lambdoid Suture, **AED:** Anti-Epileptic Drugs, **ABT:** Antibiotherapy, **y:** years, **mo:** months.*

the incident occurred several years ago. Given the sensitive nature of these cases, healthcare professionals play a key role in initiating this process. They are obligated to provide a forensic report, which includes all the medical findings, as well as details about the patient's current condition. In several countries, these types of cases may also require mandatory reporting under child protection laws, regardless of the patient's age at the time of diagnosis.

Providing psychological support for the patient is essential, because informing them of the historical abuse can have significant emotional and psychological impacts. Therefore, a multidisciplinary approach involving legal, medical, and psychological professionals is recommended in managing such cases.

CONCLUSION

Insertion of a needle into the cranium of infants is a rare and unusual form of homicide. The literature suggests that the reported cases are just the tip of the iceberg. Ethical challenges exist in informing patients with late complications regarding the potential abuse, where legal action may be futile. However, informing patients about intracranial foreign objects is crucial, particularly regarding the risks associated with MRI scans.

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Declarations

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Availability of data and materials: The datasets generated and/or analyzed during the current study are available from the corresponding author by reasonable request.

Disclosure: The authors declare no competing interests.

Ethical Considerations: Signed informed consents were obtained from the patients included in the study. Ethical approval was not required for this study as it is a case report.

AUTHORSHIP CONTRIBUTION

Study conception and design: OH, BE

Data collection: BE

Analysis and interpretation of results: OH, BE, BT

Draft manuscript preparation: BE, BT

All authors (OH, BE, BT) reviewed the results and approved the final version of the manuscript.

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