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Sudden Death in Adults Caused by Intracranial Pathology: A Systematic Review

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ABSTRACT

AIM: To review the literature, and to identify the main intracranial pathologies that cause sudden deaths in adults.

MATERIAL and METHODS: The systematic review was carried out in concordance with the PRISMA checklist.

RESULTS: Epilepsy and intracranial hemorrhage have been found to be the two main causes of sudden and unexplained deaths in adults due to intracranial pathologies. Intracranial neoplasms are not among the two main causes of SD, as they are usually discovered before fatality, so their rate of SD is not so extensive. It is noticed that the highest incidence of this type of death is also related to the abusive use of alcohol and other drugs, such as cocaine, heroin and nicotine. There is a possibility that the actual incidence of SD in adults due to intracranial pathologies is even greater, since there is a lack of reliability in autopsies and the fact that most SD in adults are not witnessed.

CONCLUSION: The most recurrent etiologies of SD in adults are epilepsy, intracranial hemorrhage, meningitis or purulent abscess and tumors. Thus, it represents real challenge for neurosurgeons, since their understanding, accurate diagnosis and adequate treatment of these pathologies, in addition to healthy lifestyle habits by people can reduce the possibility of SD.

KEYWORDS: Sudden death, Intracranial pathology, Intracranial findings, SUDEP, Forensic medicine

INTRODUCTION

The sudden death (SD) of a hospitalized or not adult, causes major distress to family members and health teams. Verification of the aetiology of this type of death is crucial, and in most cases it is essential to perform an autopsy. However, a high number of SD cases remain unexplained, since the causes of such death are multifactorial (4,50).

Sudden death can be conceptualised as a non-violent death, which happens in an improbable and fast way - from minutes to a few hours - in people with good or apparent good health, or even with an acute or chronic pathology, whose fatal outcome is highly surprising. This type of death can be subclassified as: sudden death in unexamined cases which is characterized by the affected individual having been seen in regular shape and alive in less than 24 hours before being pronounced dead. In addition to this subtype, there is witnessed cases of sudden death that is characterised as an quick change in cardiovascular status with a time interval of death being less than 1 hour. SD is also used to refer to cases of unexplained deaths, unexpected deaths, or unexplained sudden deaths (4,50).

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It is noteworthy that regardless of the type of sudden death, there are several different causes, each with its own particularity, however, all converge to an alteration in the cardiovascular and/or neurological condition, which in turn lead to SD (4,50).

Many doctors misdiagnose their patients, which may explain the greater proportion of adults who become victims of unexpected death. Although the main cause of SD are cardiovascular diseases, intracranial pathologies are its second leading cause in adults, as such, in the context of sudden unexplained deaths in adults, neuropathologies have a significant rate of co-occurence that deserves to be highlighted. The epidemiological profiles in both developed and developing countries are similar, with variables depending on genetic, demographic and lifestyle habits (4,19,42,43,50,64).

This study aimed to systematically review the literature, present knowledge and identify the main intracranial pathologies that cause sudden death in adults, as well as their relationship with this type of fatality.

MATERIAL and METHODS

Study Design and Identification

This is a systematic review, according to the preferred reporting item guidelines for systematic reviews and meta-analyses (PRISMA) (40,46,52), being a literature review with a synthesis of the scientific evidence found. Based on the guiding question: "what are the intracranial pathologies that cause sudden death in adults and their scientific evidence related to SD in this age group?". A systematic and comprehensive literature review was performed in Cochrane Central Register of Controlled Trials, MEDLINE, Web of Science, SciELO and EMBASE, using the following keywords: "sudden death", "neuropathology", "pathology", " epilepsy", "intracranial hemorrhage", "adults", "cancer", "tumor", "neoplasm", "etiology", "cause", "physiopathology", "diagnosis", "treatment", "outcome", "accident cerebral vascular", "cranioplasty", "cerebral aneurysm", "infection", "cerebral" and "intracranial". Combinations were performed with Boolean operators: "AND", "OR" and "NOT". The keywords were searched in the modality "all fields". Each article and its respective references were obtained and carefully analysed.

Eligibility Criteria

Articles presenting scientific evidence of adult individuals affected by a diagnosed SD. Only studies that clearly presented the diagnosis of sudden death caused by a certain intracranial pathology, being in adults. In addition, these articles had to include the following infomation: characteristics of the intracranial disease, age, medical history, diagnostic procedures used, treatment for the pathology (if performed before the fatality) and the neurological results, which were adequately reported, being well carried out works methodologically and adequately developed were included in this study. And also studies with major findings and updates in the medical literature on the subject.

Moreover, other inclusion criteria were the selection of qualitative and quantitative primary research (such as randomised controlled trials and observational studies) and secondary research (such as meta-analyses and patient review reports); which were available online in full as an article in the languages: English, Spanish or Portuguese. Controlled vocabulary/MeSH terms and free text words and were combined without any limitations during the search period. The MEDLINE search terms were adapted for each database.

Additional relevant studies were found in the references section of the included articles and by a manual search (''snowball" method) was conducted to also include relevant and reliable grey literature, applying the described criteria above. Narrative and integrative review articles, letters to the editor, monographs, and any studies with animal models were excluded. Studies involving people with SD due to cardiac causes were excluded.

Population Data

Population selection was based on articles that addressed adult individuals with SD due to any intracranial pathology. No restrictions on sex, race, colour or socioeconomic status were imposed.

Mapping, Analysis, Validation and Data Extraction Process

Following the PRISMA guidelines and the Population, Intervention, Comparison and Result (PICO) structure (57) the titles were examined two by individuals independently and abstracts identified in the research. Articles considered relevant were selected and downloaded for full text review. Two researchers independently reviewed the full texts and selected the articles to be included in the review based on inclusion and exclusion criteria (Figure 1).

Relevant study characteristics, including sample size, study type/design, characteristics of intracranial pathology, diagnostic procedures, and treatment (if performed before the fatality), were collected, analysed, and extracted later. Disagreements in data collection were discussed with the third researcher until agreement was reached. Finally, a third independent researcher checked the extracted data in order to resolve disagreements and verify consistency. When the relevant data available was limited, an attempt was made to contact the authors of the respective article in order to obtain potentially available additional data, as well as information and clarification in this regard (Figure 1).

The quality of each article was evaluated and the level of evidence was qualified according to the Oxford Centre for Evidence-Based Medicine classification (33).

Bias Risk Assessment

The assessment of the risk of bias of each study was performed according to the following criteria: selection bias (allocation concealment, random sequence generation); performance bias (blind process for participants and research staff); reporting bias (selective reporting); detection bias (blind outcome assessment); attrition bias (incomplete outcome data) and others (30). According to the Cochrane database,

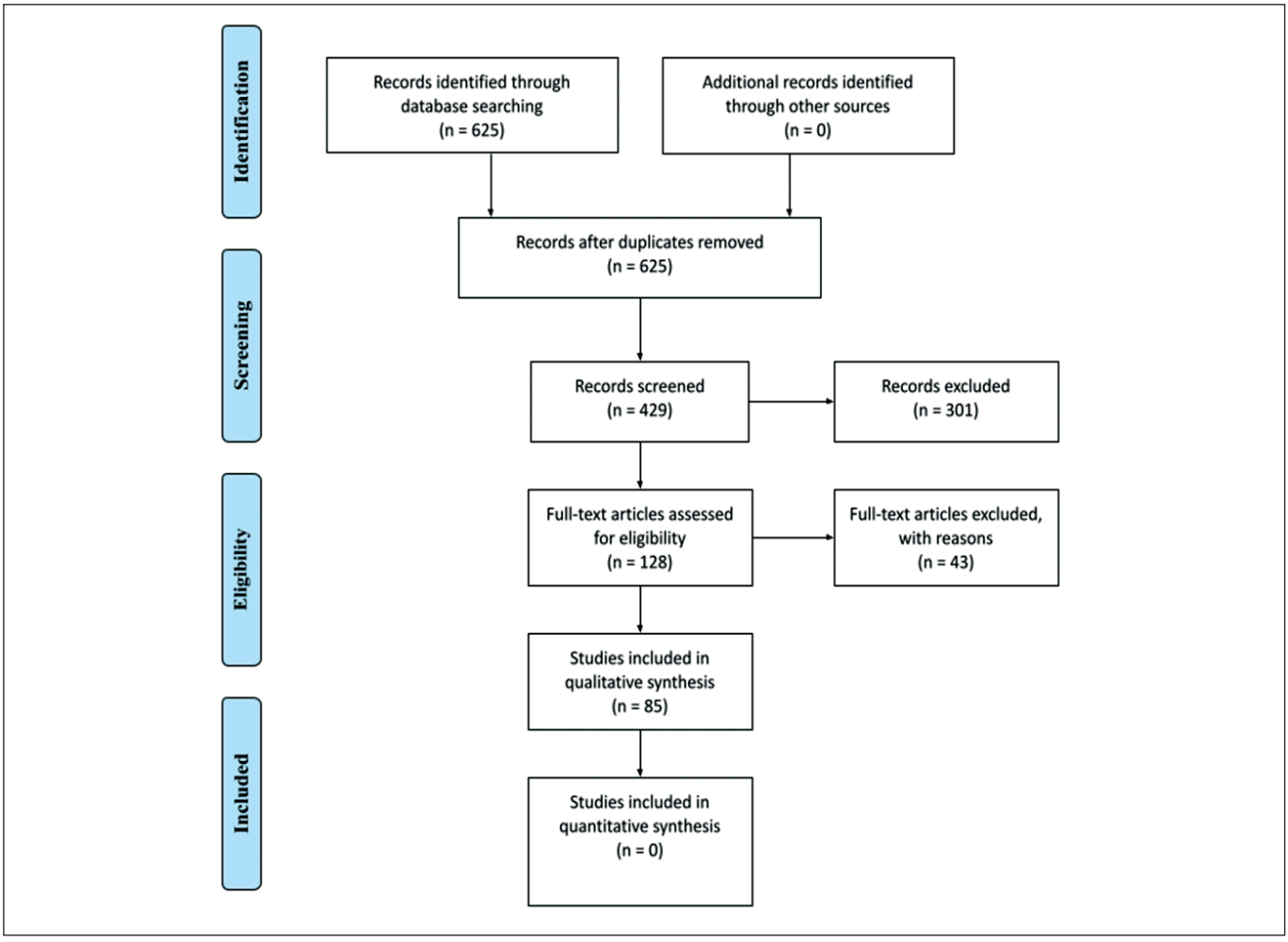

Figure 1: Flowchart representing the identification, screening, eligibility and inclusion and exclusion criteria of this systematic review.

the risk of bias can be categorised as high, low or uncertain, with high risk of bias being determined whenever jobs do not meet any of the assessment criteria described above. The risk of bias was rated as low when these criteria were properly determined. Whenever the available information was insufficient to categorise the risk of bias for each item as low or high, or when it was not correctly described in the article, the risk of bias was classified as uncertain (20).

RESULTS

Intracranial pathologies causing sudden deaths in adults are: epilepsy; spontaneous meningeal haemorrhages: subdural, subarachnoid, ruptured aneurysms (especially saccular), vascular malformations; arterial hypertension and intraparenchymal haemorrhage; meningoencephalitis; complications of neoplasms of the central nervous system, such as primary metastases; thromboembolism; neurocysticercosis; hydrocephalus; Reye's syndrome; brain abscess, viral encephalitis; colloid cyst of the third ventricle; meningioangiomatosis, cerebral venous thrombosis, epidermoid cyst, pituitary stroke, cerebral aspergillosis; malaria; hypoglycaemia; necrotizing encephalitis by Naegleria sp; bacterial meningitis; cerebral amyloid angiopathy (CAA) or congophilic angiopathy; thrombosis of the dural sinuses; cerebral oedema; encephalopathy due to hyperbilirubinemia; central myelinolysis of the alcohol bridge; porencephalic cyst; blood dyscrasia; recent cerebral infarction; occasional haemorrhages from the superior colliculus; and lobar holoprosencephaly with corpus callosum and olivopontocerebellar atrophy (3,6,7,35,44,55,65,68,70,71) (Table I).

DISCUSSION

Epilepsy

SUDEP defined as the sudden unexpected death of a person with epilepsy without a reasonable anatomical or toxicological justification. Here, death is classified into three types: defined, probable or possible. Definitive SUDEP is characterised when the following criteria are met: history of epilepsy, death or cardiorespiratory impairment is sudden and is not generated by status epilepticus, death is unpredictable (without life-threatening circumstances), and death after a review of all the evidence, including the autopsy, remains unexplained. Probable SUDEP is characterised by the following criteria:

Table I: Reference List with the Main Intracranial Disease that Cause Sudden Death in Adults

Study	Type of study	Etiology of death	Total number of cases reviewed	Date	Number of etiology cases cited
Krohn, 1963 (38)	RS	SUDEP	107	NR	14
Freytag and Lindenberg, 1964 (23)	RS	SUDEP	294	NR	294
Freytag and Lindenberg, 1966 (22)	RS	Rupture of intracranial aneurysms	250	NR	250
Zielinski, 1974 (72)	RS	SUDEP	218	NR	19
Hauser et al., 1980 (29)	RS	Epilepsy	618	1935-74	NR
DiMaio et al., 1980 (17)	RS	Intracranial neoplasms	10995	NR	10995
Silver et al., 1984 (59)	RS	Stroke	1073	NR	212
Graham et al., 1987 (25)	RS	High intracranial pressure (ICP)	434	NR	434
Klenerman et al., 1993 (36)	RS	Epilepsy	3992	NR	≥239
Cockerell et al., 1994 (10)	RS	Epilepsy	1091	1984-87	NR
Milroy and Smith, 1996 (45)	RS	Glial cyst of the pineal gland	1	NR	1
Nilsson et al., 1997 (51)	RS	SUDEP	9000	1980-92	NR
Leestma, 1997 (40)	RS	SUDEP	45	NR	≥18
Tokgözoglu et al., 1999 (63)	RCT	Stroke	62	NR	5
Dolinak et al., 2000 (18)	RS	Hypoglycemia causing axonal injury	13	NR	13
Ficker, 2000 (21)	RS	SUDEP	100	NR	≤17
Diener et al., 2000 (16)	RCT	Ischemic stroke	1786	NR	NR
Orlandi et al., 2000 (52)	RCT	Intracranial pathology	44	NR	NR
Yapo Ette et al., 2002 (71)	RS	Cerebral malaria	12	NR	12
Huang et al., 2002 (34)	MA	Aneurysmal SAH	3832	1965-2001	578
Black and Graham, 2002 (7)	RS	Epilepsy	131	1991–6	131
Black and Graham, 2002 (7)	RS	Intracerebral hemorrhage	15	1995–8	15
Black and Graham, 2002 (7)	RS	Spontaneous subarachnoid hemorrhage	41	1995–8	41
Black and Graham, 2002 (7)	RS	Subdural hematoma	24	1995–8	24
Black and Graham, 2002 (7)	RS	Extradural hematoma	2	1995–8	2
Black and Graham, 2002 (7)	RS	Bacterial meningitis	4	1995–8	4
Black and Graham, 2002 (7)	RS	Brain tumors	11	1995–8	11
Matschke et al., 2002 (44)	RS	Epidermoid cysts of the brain	1	NR	1
Eckart et al., 2004 (19)	RS	Intracerebral hemorrhage	126	1977-2001	5
Dickerman et al., 2004 (15)	RS	Fulminant intracranial aspergillosis	1	NR	1
Wixom et al., 2005 (68)	RS	Meningioangiomatosis	1	NR	1
Yadav et al., 2005 (70)	RS	Cerebral venous thrombosis	1	NR	1
Colivicchi et al., 2005 (11)	RS	Ischemic stroke	48	NR	6

Table I: Cont.

Study	Type of study	Etiology of death	Total number of cases reviewed	Date	Number of etiology cases cited
Colivicchi et al., 2005 (11)	RCT	Ischemic stroke	208	NR	NR
Reis et al., 2006 (55)	RS	Hemorrhagic stroke	750	1993-2002	≥39
Reis et al., 2006 (55)	RS	Ischemic stroke	750	1993-2002	≥22
Meulen et al., 2006 (6)	RS	Colloid cyst of the 3rd ventricle	1	NR	1
Warwar et al., 2006 (67)	RS	Hemorrhage within a pituitary macroadenoma	1	NR	1
Prosser et al., 2007 (54)	MA	Ischemic stroke	846	NR	NR
Prosser et al., 2007 (54)	RS	Ischemic stroke	846	NR	NR
Rincon et al., 2008 (56)	RS	Intracranial pathology	655	NR	NR
Rincon et al., 2008 (56)	RS	Intracranial pathology	655	NR	NR
Alencar et al., 2010 (3)	RS	Colloid cyst of the 3rd ventricle	1	NR	1
Honeybul and Ho, 2011 (32)	RS	Cerebral swelling (after cranioplasty)	164	2004-2009	≥3
Honeybul, 2011 (31)	RS	Cerebral swelling (after cranioplasty)	3	NR	3
Nichols and Chew, 2012 (50)	RS	Brain stem compression	175	NR	NR
Sörös and Hachinski, 2012 (60)	RS	Ischemic stroke	814	NR	125
Wang and Hu, 2013 (66)	RS	Medullary infarction	1	NR	1
Broughton et al., 2014 (8)	RS	Cerebral swelling (after cranioplasty)	87	2004 - 2011	2
Na et al., 2014 (49)	RS	Glial cyst of the pineal gland	1	NR	1
Sviri, 2015 (62)	RS	Cerebral swelling (after cranioplasty)	4	01/2005 - 08/2010	4
Tseng et al., 2018 (64)	RS	Intracranial pathology (sudden death and non-sudden)	20440	02/01/2011 - 03/01/2014	≥1124
Robles and Cuevas-Solorzano, 2018 (57)	RS	Intracranial pathology	26	NR	NR
Barranco et al., 2018 (5)	RS	Glial cyst of the pineal gland	1	NR	1
Akgunduz et al., 2018 (2)	RS	Spontaneous subdural hematoma	1	NR	1
Anastasakis et al., 2018 (4)	RS	Non-cardiovascular causes	349	2002-10	63

RS: *Retrospective study,* ***RCT:*** *Randomized controlled trial,* ***MA:*** *Meta-analysis,* ***NR:*** *Not reported.*

history of epilepsy, cardiorespiratory impairment or death are immediate and are not caused by status epilepticus and death is unexpected (without life-threatening chances), however, the data are not sufficient due to the lack of autopsy and there is no elucidation of other possibilities (21,40).

Epilepsy is widely recognised, particularly in patients with epilepsy uncontrolled. According to most authors, epilepsy is the main intracranial pathology causing SD. In addition, it is emphasised that SUDEP is responsible for approximately 2- 17% of the total unexpected and unexplained deaths, with this value being variable in different populations. About one in 1000 patients with chronic epilepsy dies suddenly, even with a post-mortem examination. Many studies have shown that the rate of sudden deaths from epilepsy exceeds 24 times the rate of SD among the general population. It was also noticed that the mortality rate in cases of symptomatic epilepsy (acute) is higher than in cases of idiopathic epilepsy. Mortality may be directly linked to the seizure frequency (10,21,23,29,36,38,51,72).

Acute Stroke

Notably, patients with cerebrovascular diseases have cardiovascular risk factors similar to patients with peripheral arterial occlusive disease or occlusive coronary artery, including arterial hypertension, smoking and diabetes mellitus. Furthermore, in many patients with stroke there are high risk factors for recurrence, such as, preexisting atrial fibrillation and coronary artery disease (27,52,63,69).

It has been concluded that patients with stroke and a history of congestive heart failure, diabetes or kidney failure are more likely to progress to SD due to cardiac changes, compared to patients who do not manifest these problems. Particular predictors of SD are: the magnitude, as well as the location and extent of the stroke, acute markers of myocardial injury, abnormalities in cardiac conduction and the lengthening of the QTc interval (11,16,54,69).

Non-traumatic Intracranial Haemorrhage

Subarachnoid haemorrhage is one of the main causes of SD.

Around 12% of the fatality victims die before receiving medical care (8,55). In one study, autopsies were performed on 165 adults hospitalised patients from the University of Pittsburgh Medical Center (UPMC) Health System, who experienced SD after the onset od symptoms. The study found that the most frequent cause was immediate death was cardiac arrhythmia, representing 58 cases (33,1%). The second most common was haemorrhage, with an index of 38 cases (21,7%). Brainstem compression caused only two cases of SD (4).

Ruptured Saccular Aneurysm

According to a research with a large number of patients who died before arriving at a hospital, 60% of the victims of an aneurysm rupture died immediately. The mean age of those patients was 46 years. In addition, necropsies that 96% of the cases corresponded to massive subarachnoid haemorrhage, 22% of the cases were equivalent to subdural hemorrhage and 43% to intracerebral haemorrhage. Patients with saccular aneurysms in the posterior part of the Willis Polygon (Willis Circle) or of the internal carotid artery showed a higher probability of dying during the period of rupture than individuals with aneurysms in other arteries (7,23,34).

Intracerebral Hematoma

Massive haemorrhage in brain substance has immediate onset and rapid evolution. According to a study based on medicolegal practice, cases (393) of intracerebral haematomas were investigated, of which, 40% were formed in the basal ganglia, 15% in the thalamus, 16% in the pons, 10% in the brain and 12% in the cerebellum. In approximately 35% of cases, individuals were found dead or died during the time of arrival at a hospital. According to records from the department of forensic medicine, 15 documented cases of SD from intracerebral haemorrhage occurred from 1995 to 1998 (7).

The incidence of sudden death caused by intracerebral haematoma, due to aneurysm rupture is higher in middle-aged men with hypertension or in the elderly, since such rupture is usually caused by an increase in blood pressure or by vasculitis. Intracerebral and subarachnoid haemorrhage are increasingly correlated with drug abuse, such as ecstasy, cocaine and other amphetamines, and excessive alcohol intake. There are also reports of intracerebral haematomas with minor incidences caused by related to blood dyscrasia or by rupture of a vascular malformation, sickle cell disease or antithrombotic treatment. Last, a less frequent situation is massive haemorrhage in a pre-existing tumour (7).

Intracranial Infection

The incidence of intracranial infections is higher in children than in adults. A previous study showed that acute bacterial meningitis and meningitis related to a large brain abscess are the most frequent infectious causes of sudden death. However, meningitis is not a recurrent aetiology of sudden death compared to other intracranial pathologies, such as epilepsy and haemorrhages, since in the 1995–8 forensic medicine archives only two cases of SD related to meningitis were revealed (7).

Brain Tumours

Brain tumors are a rare cause of sudden and unexplained deaths in adults. Approximately 8% of non-traumatic intracerebral haemorrhages are caused by intracranial tumours, with less than half of these cases progressing to death. Furthermore, only a very small proportion of cases result in sudden deaths (19,69,70). From 1995 analyzed the 1998, the archives of the department of forensic medicine that only found one SD caused by intracranial tumours (7,17).

Glial Cyst of the Pineal Gland

Glial custs of the pineal gland are benign, normally, they are asymptomatic and consequently of this cyst are identified in most cases, by means of magnetic resonance imaging or by autopsy. Rarely, such injury can cause loss of consciousness, chronic headache, sensory and corticospinal impairment and even sudden death (13,45,49).

SD caused by compression by a pineal gland cyst is very rare, and there are few cases described in the literature. In one study, case reports on SD resulting from a glial cyst of the pineal gland were analysed and it was found that in most cases, an additional neuropathology was generated: intracranial hypertension; brainstem compression, consequently causing a nervous impairment of cardiorespiratory activity; neuro-ophthalmological symptoms; cerebellar involvement, headache (the most recurrent symptom); hydrocephalus; corticospinal and sensory impairment; loss of consciousness; Parinaud's syndrome. The less frequent clinical consequences were ataxia and mental and/or emotional disorders (56,58,60,61,69).

Cranioencephalic Trauma

Acute subdural haematoma (ASDH) is considered one of the causes of SD, and often caused by rupture of pontine veins during a CTE. Approximately 2% to 6.7% of ASDH cases are considered spontaneous (64). The mortality rate ranges from 60% to 76.5% (9,14,15). It usually occurs in aged men and those with a previous history of arterial hypertension (63). Cases of spontaneous ASDH without precipitating factors such as alcohol abuse or CTE, manifested clinically with: headache, nausea and vomiting (12).

Cranioplasty

Cranioplasty is often performed after certain neurological conditions such as: CTE, cerebral infarction, cerebral haemorrhage and subarachnoid haemorrhage, recently massive cerebral oedema and SD have been reported after cranioplasty (27,44).

The risk of MS for massive brain swelling after a cranioplasty ranges between 2.2% and 7% in previous studies (8,32,62). Little has been reported about the fatal complications resulting from this neurosurgical procedure, and case reports presented in the literature, mostly result in SD as an outcome of massive brain swelling, with some exceptions, in which disability has been found to be the outcome of the condition (32,48,57,69).

CONCLUSION

Intracranial pathologies are the second leading cause of death sudden in adults, after cardiovascular causes. The most common aetiologies of SD in adults are epilepsy, intracranial haemorrhage, meningitis or purulent abscesses and tumours. However, the lack of records, safe necropsies and reliable witnesses of SD can hinder the real increase in the reported incidence of this type of SD. Furthermore, this fatality is real challenge for neurosurgeons, since it encompasses several pathologies that, when well understood, diagnosed and properly treated, can prevent SD. In summary, this study qualitatively and quantitatively highlights the main neuropathologies that lead to SD in adults. One limitation of this review is the lack of high-quality articles on this subject. In this sense, novel qualitative and quantitative studies are vital for performing more accurate meta-analysis and gaining insight into the main intracranial pathologies that cause sudden deaths in adults.

AUTHORSHIP CONTRIBUTION

Study conception and design: MGSB, NNR
Data collection: MGSB, JFSJ, ACSE, CUP
Analysis and interpretation of results: MGSB, NNR, MCGP, EGF
Draft manuscript preparation: MGSB, NNR, MCGP, EGF
Critical revision of the article: MGSB, NNR, MCGP, EGF, CUP
All authors (MGSB, JFSJ, ACSE, CUP, MCGP, EGF, NNR) reviewed the results and approved the final version of the manuscript.

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