Spinal Subarachnoid Hemorrhage Induced Intractable Miotic Pupil. A Reminder of Ciliospinal Sympathetic Center Ischemia Based Miosis: An Experimental Study

Mehmet Dumlu AYDIN1, Ayhan KANAT2, Coskun YOLAS3, Celalettin SOYALP4, Mehmet Resid ONEN5, Ilhan YILMAZ6, Nuh Cagri KARAAVCI1, Muhammet CALIK7, Orhan BAYKAL8, Leyla RAMAZANOGLU9

1Ataturk University, Faculty of Medicine, Department of Neurosurgery, Erzurum, Turkey
2Recep Tayyip Erdogan University, Faculty of Medicine, Department of Neurosurgery, Rize, Turkey
3Erzurum Education and Research Hospital, Department of Neurosurgery, Erzurum, Turkey
4Yuzuncu Yil University, Faculty of Medicine, Department of Anesthesiology, Van, Turkey
5Umranliye Education and Research Hospital, Department of Neurosurgery, Istanbul, Turkey
6Sisli Hamidiye Etfal Education and Research Hospital, Department of Neurosurgery, Istanbul, Turkey
7Ataturk University, Faculty of Medicine, Department of Pathology, Erzurum, Turkey
8Ataturk University, Faculty of Medicine, Department of Ophthalmology, Erzurum, Turkey
9Fatih Sultan Mehmet Education and Research Hospital, Department of Neurosurgery, Istanbul, Turkey

Corresponding author: Mehmet Dumlu AYDIN nmda11@hotmail.com

ABSTRACT

AIM: To examine ischemic neurodegeneration of the ciliospinal center on permanent miosis following subarachnoid hemorrhage (SAH).

MATERIAL and METHODS: Nineteen rabbits were examined in this study. The animals were divided into three groups, as control (GI, n=5), sham (GII, n=5) and study group (GIII, n=9). Pupil diameters were measured after giving 0.5 mL physiological saline for sham and autologous arterial blood for the study group into the cervico-thoracic subarachnoid space. After three weeks of follow up, the cervico-thoracic cord and bilateral superior cervical sympathetic ganglia were removed. The pupil diameter values were compared with degenerated neuron volumes of sympathetic ganglia and degenerated neuron densities of thoracic sympathetic nuclei which were studied by stereological methods.

RESULTS: The mean pupil diameter was 5180 ± 370µm and the mean degenerated neuron density of the ciliospinal center was 4 ± 1/mm³ in animals of the control group (GI). These values were 9850 ± 610 µm, 10 ± 3/mm³ in sham (GII), and 7.010 ± 440 µm and 98 ± 21/mm³ in the study (GIII) groups. There was an inverse relationship between degenerated neuron density of the ciliospinal nuclei and pupil diameters.

CONCLUSION: Although there is a widespread belief that the main cause of miosis is oculomotor nerve injury during SAH, we showed and reported for the first time that ciliospinal sympathetic center ischemia-induced neurodegeneration may have been responsible for permanent miosis following SAH.

KEYWORDS: Subarachnoid hemorrhage, Miotic pupil, Ciliospinal sympathetic center, Mydriasis, Miosis, Rabbit
INTRODUCTION

An intracranial aneurysm occurs in 5% to 6% of the general population (10). Its rupture leads to subarachnoid hemorrhage (SAH), which is a devastating condition (17). SAH accounts for approximately 5-10% of strokes (20), and currently, neurosurgery has gone through moments of great renewal (8). However, SAH has the highest mortality and morbidity among all types of stroke (23). Despite major improvements in surgical techniques for aneurysmal SAH, 30-day mortality from SAH has been shown to have changed very little from what it was 40 years ago (1,11).

Multiple ocular functions are controlled by the autonomic nervous system (21). Both parasympathetic and sympathetic nervous system disorders appear to be important factors in pupillary diameter changes (21). Although the basic mechanism of mydriasis is well known, the effects of denervative degeneration injury of cerebral sympathetic ganglia induced by the spinal sympathetic center have not been investigated following subarachnoid hemorrhage (SAH). One of the most common external physical signs of SAH is pupillary diameter abnormalities (21). Postganglionic fibers of the ciliary ganglia (CG) influence pupillopapillary parasympathetic innervation, and postganglionic fibers coming from the superior cervical ganglion (SCG) command the sympathetic innervations (21).

Statistical Analysis

The data were analyzed using the Kruskal-Wallis and non-parametric Mann-Whitney U tests. Differences were considered statistically significant at p<0.005.

RESULTS

The pupil diameter was 5180 ± 370 µm, and the mean degraded neuron volume of the thoracic sympathetic center was 2 ± 1/mm³ in animals of the control groups (Figure 1). These values were 9850 ± 610 µm, and 9 ± 3/mm³ in the sham group (Figure 2) and 7010 ± 440 µm and 98 ± 77/mm³ in the study group (Figure 3). The macroscopic appearance of the brains and spinal cords of the study group showed subarachnoid hemorrhage-induced brain and spinal cord edema, and clot formation in the subarachnoid spaces and nerve roots. The basal view of a subarachnoid hemorrhage in rabbit brain and extension of the spinal cord (base) (Figure 4A, B), and a horizontal section of the cervicothoracic spinal cord and sympathetic ciliospinal center neurons are shown in Figure 4A, B, respectively.

Apoptotic neuronal degradation was detected using the TUNEL method in ciliary ganglia (34%), but apoptotic degeneration was not significant in the thoracic sympathetic center as it is supplied by external spinal arteries which are rarely affected by SAH-related vasospasm (Figure 5A, B).
Figure 1: Pupil diameter values were measured as $9850 \pm 610 \mu m$ with the ocular tomography device in all groups before the experiment.

Figure 2: Pupil diameter values were measured as $7010 \pm 440 \mu m$ with the ocular tomography device in the study group just after the experiment.
There was an inverse relationship between the neuron density of the thoracic sympathetic center and pupil diameters (p<0.005). Highly degenerated neuron density of the thoracal sympathetic center should also be considered an important factor in the development of a miotic pupil in both normal conditions and in various neurological pathologies that affect the light reflex (Figures 1, 2).

**DISCUSSION**

The timely detection of neurological deterioration is important for patients with SAH. The most meaningful way to follow a traumatic or nontraumatic brain-injured patient in the intensive care unit is to perform serial bedside neurological examinations (26). In these examinations, pupil diameters should be checked daily in patients with SAH. Patients with central, preganglionic, or postganglionic lesions consistently show differences in pupil functions. The sympathetic system takes a role in the pupil-dilating phase of the edge-light pupil cycle time, presumably by exerting a tonic mydriatic effect. Since this tonic effect is lost in Horner's syndrome, leading to slower redilatation, the edge-light pupil cycle time becomes prolonged (5).

**Anatomo-Pathological Causes of Sympathetic Disorders of the Pupil:**

Horner's syndrome, which is seen when there is disruption of the oculosympathetic pathway, includes an injury influencing the ocular sympathetic nerve causing miosis, palpebral ptosis and enophthalmos, and is accompanied by hemifacial anhidrosis in its complete forms. Syringomyelia is a disorder of the spinal cord in which a cyst formation occurs within the cord. This is a significant reason of Horner's syndrome as a result of a lesion of the cervical sympathetic nerve fibers (13). Untreated contused cervicothoracic cords cause permanent sympathetic injury and result in Horner's syndrome, with the lesion localized to cranial to C5 cervical intumescence at the levels of C6-T2 (7,15). Acute SAH surrounding the brain and spinal cord is an important cause of undiagnosed Horner's syndrome. SAH results in denervation injury-related neurodegeneration in the CG which induces indirect mydriasis (2). Highly degenerated neuron density of the CG and high neuron density of pupil-dilatory superior cervical sympathetic ganglia should be thought an essential factor for pupil dilatation (19). The loss of trophic effect from the presynaptic supply of the CG via the preganglionic fibers of the oculomotor nerve could potentially change the structure of the ganglion through the anterograde transneuronal degradation process in SAH-induced ischemic degradation in the oculomotor nerve in the brainstem (4). Although Onen et al. reported that spinal cord ischemia could be responsible for sympathetic center ischemia-related miosis, the main neuropathological mechanism of ciliospinal center ischemia-based miosis is not yet known (19). Nevertheless, Kanat et al. showed that spinal SAH resulted in severe spinal cord ischemia causing neurodegeneration in the DRG via vasospasm of dorsal root ganglion-supplying arteries (12). Vasospastic blood vessels of the spinal cord come across to subarachnoid blood and
Vasospasm of DRG blood vessels may cause ischemic neurodegeneration in the DRG, while diminished normal neuron density or increased degraded neuron density of DR ganglia may play an essential role in the modulation of spinal cord blood flow. Low neuron density of DR ganglia should be considered an essential factor in the pathogenesis of severe neurodegeneration in ciliospinal center ischemia in SAH (12). Lee et al. reported that cervical spinal cord stimulation increases global cerebral and spinal blood flow (14). This information may prove that DR ganglia could have a vasodilatory effect through the electrical impulses on the spinal cord supplying arteries following SAH. Neuroprosthetic stimulations relieve volitional control of paretic eyes (16).

Limitations:
SAH results in bloody cerebrospinal fluid and the bloody or highly proteinous CSF may lead to neural degeneration (18). Spinal arachnoiditis may develop after SAH and intrathecal drug applications (18), and affects the spinal cord and nerve roots, and can also lead to spinal cord dysfunction (18). In this study, the saline injection by itself led to a slight to moderate diameter changes of the pupils. Those changes were prominent in animals of the SAH group. Saline injection in the sham group can be harmful, and lead to some changes in the subarachnoid space. In a study, saline injection directly into the sciatic nerve caused nerve damage (6).

CONCLUSION
The management of SAH requires a comprehensive understanding of the pathophysiology, which is paramount to define treatment strategies and algorithms (21). During the past 2 decades, neuroscientists have gained an improved understanding of the pathophysiological events that occur after SAH (9). Although there is widespread belief that the main cause of miosis is oculomotor nerve injuries during SAH,
this study demonstrates that SAH-induced ciliospinal center neurodegeneration may have been responsible for permanent miosis following SAH and has not been mentioned in the literature so far. Further studies are needed.

REFERENCES


