



Original Investigation

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

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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 $5180 \pm 370 \mu\text{m}$ and the mean degenerated neuron density of the ciliospinal center was $4 \pm 1/\text{mm}^3$ in animals of the control group (GI). These values were $9850 \pm 610 \mu\text{m}$, $10 \pm 3/\text{mm}^3$ in sham (GII), and $7.010 \pm 440 \mu\text{m}$ and $98 \pm 21/\text{mm}^3$ in the study (GIII) groups. There was an inverse relationship between degenerated neuron density of the ciliospinal nuclei and pupil diameters.

CONCLUSION: 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

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■ 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 cervical sympathetic ganglia induced by the spinal sympathetic center have not been investigated following SAH. One of the most common external physical signs of SAH is pupillary diameter abnormalities (21). Postganglionic fibers of the ciliary ganglia (CG) influence pupilodilatory parasympathetic innervation, and postganglionic fibers coming from the superior cervical ganglion (SCG) command the sympathetic innervations (21). Postganglionic fibers of the SCG are under control of the cilio-spinal center located in the cervicothoracic region. SCG neurons are responsible for accommodation and pupil constriction. However, pupil dilation is realized via SSG neurons. The sympathetic preganglionic pupil-dilation neurons are located at the C8-T1 segmental part of the spinal cord. While coming into the eye, these axons visit the choroid and innervate the dilator muscle of the iris (16). Neurodegeneration in the CG, as a result of SAH, induces indirect mydriasis (3). Vessels of cisternal segments of the oculomotor nerve are affected and parasympathetic preganglionic denervation of the CG may result in mydriasis due to plegia of the pupil-constrictor muscles (2). Highly degenerated neuron density of the CG and/or high neuron density of pupilodilatory superior cervical sympathetic ganglia play an important role in pupil dilatation (19). SAH-induced ischemic degradation in the oculomotor nerve can result in indirect mydriasis because the presynaptic supply of CG via the preganglionic fibers fails to maintain its trophic effect (4). Although Onen et al. declared that spinal cord ischemia can be responsible for sympathetic center ischemia-related miosis (19), the main neuropathological mechanism of cilio-spinal center ischemia-based miosis is not yet known. Nevertheless, Kanat et al. showed that spinal SAH results in severe spinal cord ischemia causing neurodegeneration in the dorsal root ganglion (DRG) via vasospasm of DRG-supplying arteries (12). Cerebral vasospasm is one of the most challenging complications following SAH (22). Vasospastic blood vessels of the spinal cord come across to subarachnoid blood and the vasospasm of DRG blood vessels may cause ischemic neurodegeneration in the DRG, while diminished normal neuron density (NND) or increased degraded neuron density (ND) of DRGs may play an essential role on the modulation of spinal cord blood flow. Low ND of DRG should be considered an essential factor in the pathogenesis of severe neurodegeneration in cilio-spinal

center ischemia in SAH. A previous experimental study exhibited that degenerated ND of the DRG play a role in vasospasm of the anterior spinal artery in SAH. The objective of this study was to evaluate whether there was an association between cilio-spinal center injury and miosis development after SAH.

■ MATERIAL and METHODS

Nineteen rabbits were used in this study. They were randomly separated into 3 groups of control (GI, n=5), SHAM (GII, n=5) and the study group (GIII, n=9). Experiments were done according to the procedures set by the ethics committee of Ataturk University Faculty of Medicine (B.30 .2.ATA.0.23.85-41/28.6.2010). The pupil diameters of all the animals were measured in sunlight using ocular tomography on the first day of the experiment (Figure 1). These results were accepted as the baseline control values. Pupil diameters were measured again after the injection of 0.5 mL saline to the sham group and autologous arterial blood into the cervicothoracic subarachnoid space of the study group. After a 3-week follow-up period, the cervicothoracic cord was extracted. The pupil diameter values were compared with the degenerated neuron densities of the cilio-spinal center which were examined using stereological methods.

All animals were followed up for 3 weeks with daily pupillary diameter measurements. Thoracic sympathetic nuclei were examined histopathologically as described by Onen et al. (19). The physical dissector method was applied to estimate the number of degraded neurons in cilio-spinal sympathetic nuclei as was described by Aydin et al (2).

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 $5180 \pm 370 \mu\text{m}$, and the mean degraded neuron volume of the thoracic sympathetic center was $2 \pm 1/\text{mm}^3$ in animals of the control groups (Figure 1). These values were $9850 \pm 610 \mu\text{m}$, and $9 \pm 3/\text{mm}^3$ in the sham group (Figure 2) and $7010 \pm 440 \mu\text{m}$ and $98 \pm 77/\text{mm}^3$ 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 a rabbit brain and extension of the spinal cord (base) (Figure 4A, B), and a horizontal section of the cervicothoracic spinal cord and sympathetic cilio-spinal 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).

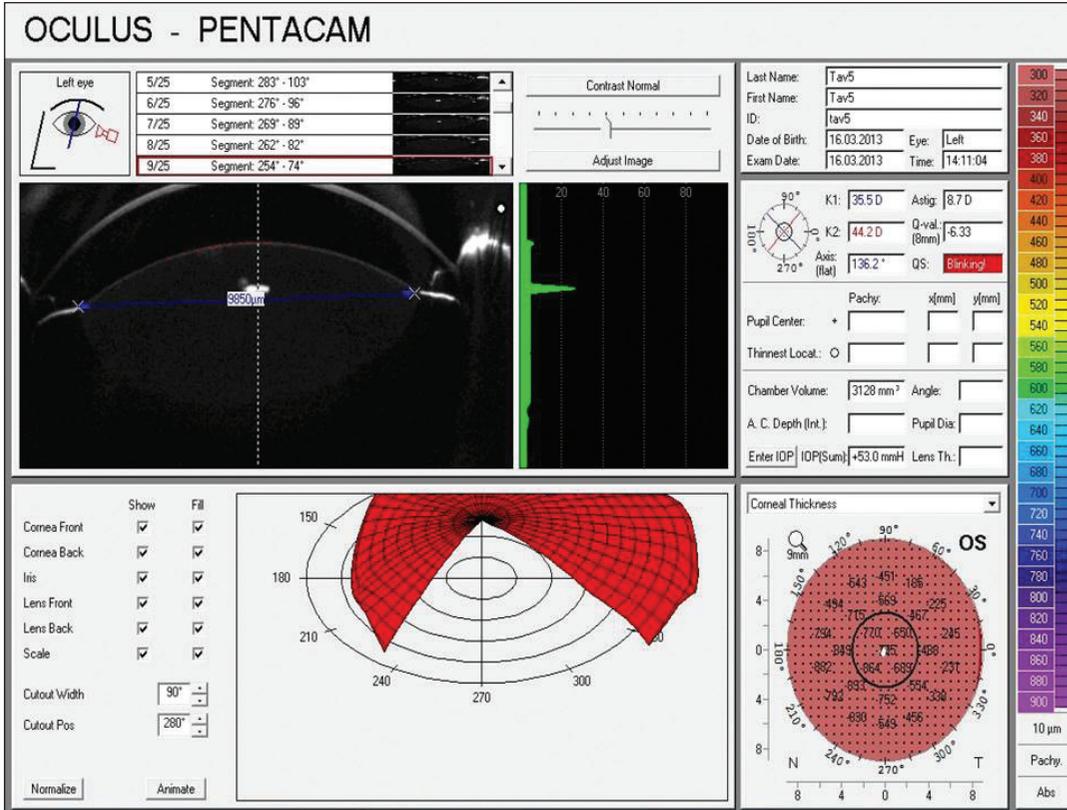


Figure 1: Pupil diameter values were measured as $9850 \pm 610 \mu\text{m}$ with the ocular tomography device in all groups before the experiment.

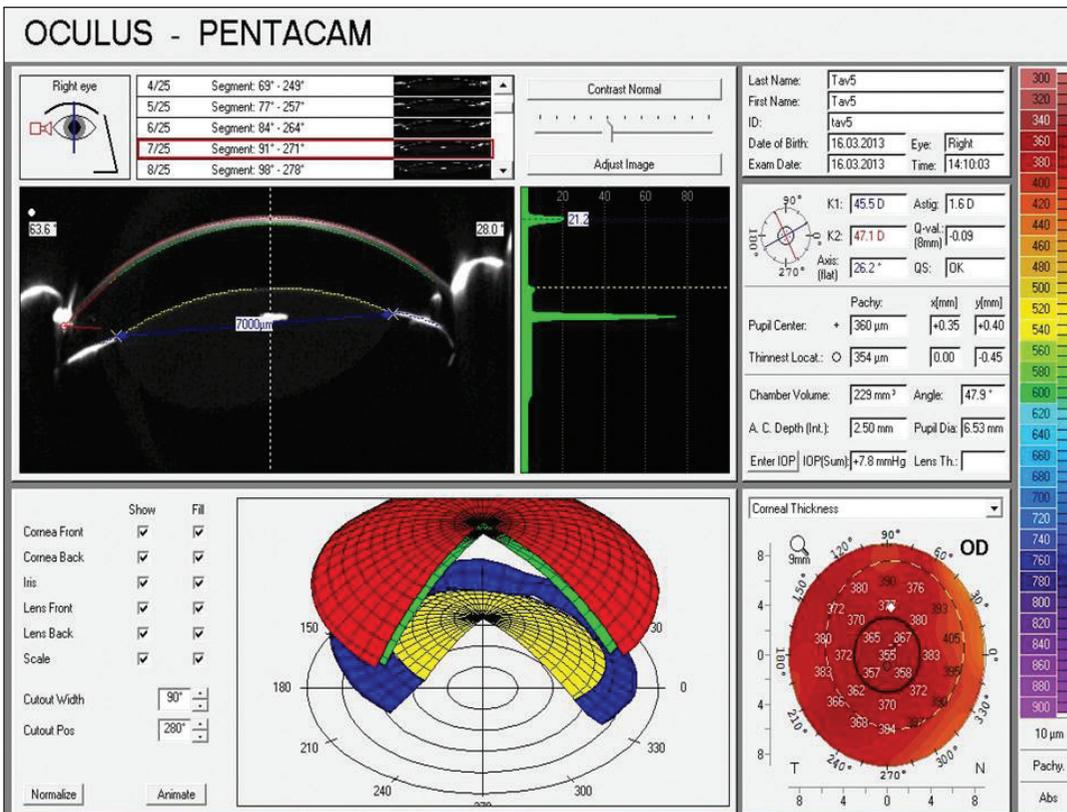


Figure 2: Pupil diameter values were measured as $7010 \pm 440 \mu\text{m}$ with the ocular tomography device in the study group just after the experiment.

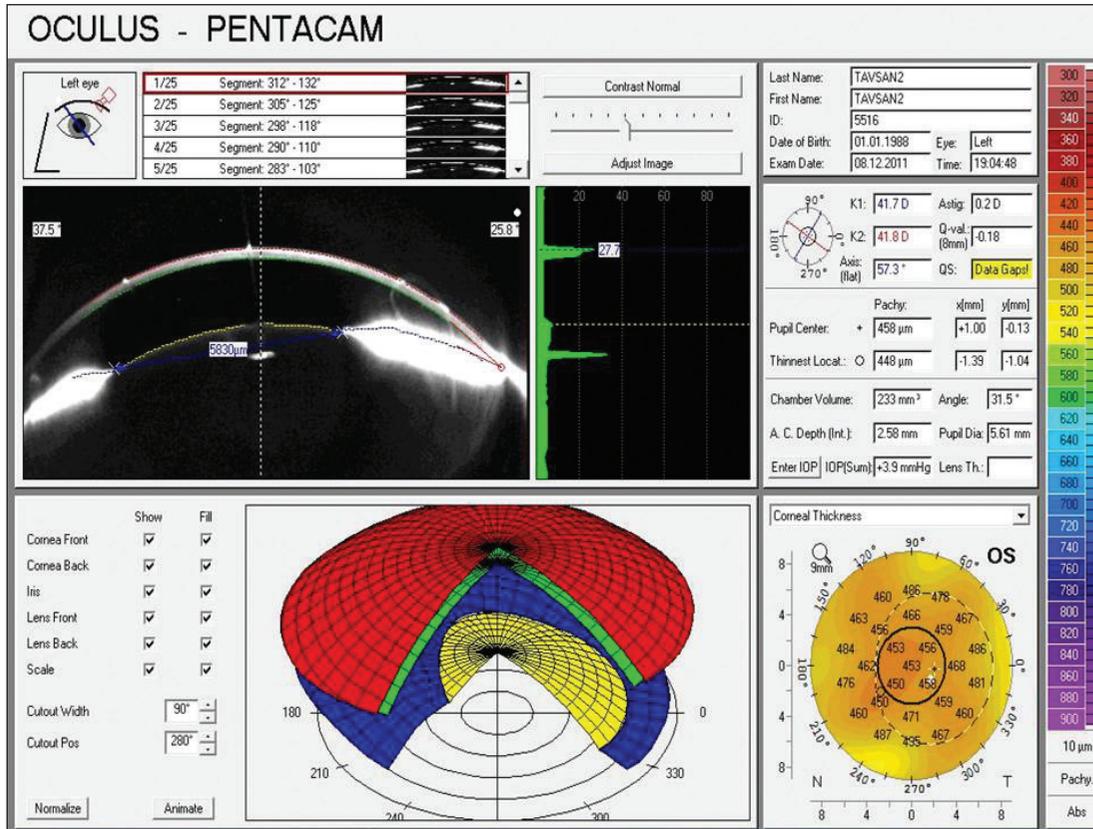


Figure 3: Pupil diameter values were measured as 5180 ± 370 µm with the ocular tomography device in all animals with SAH.

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 thoracic 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

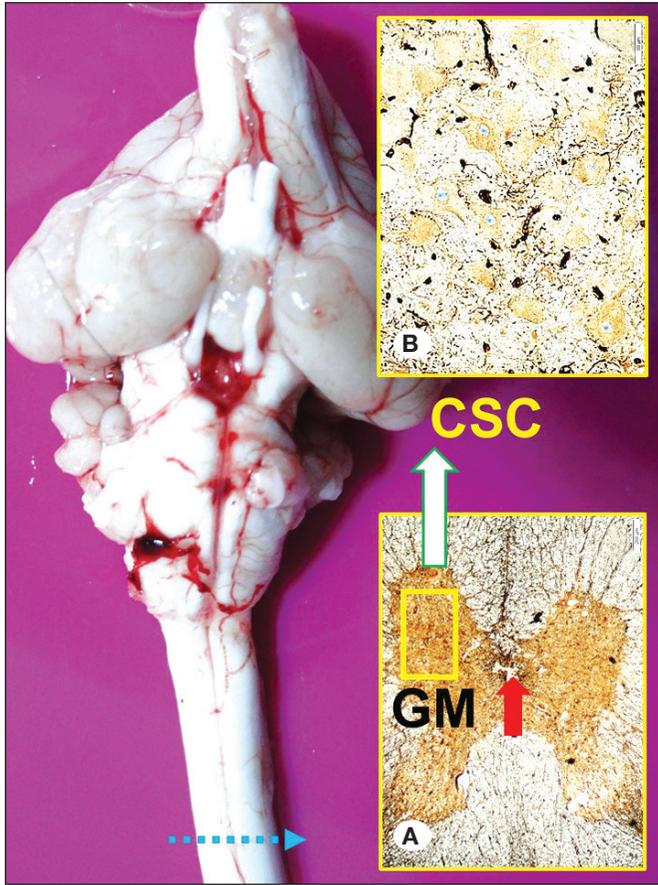


Figure 4: Macroscopical appearance of brain with cervicothoracic spinal cord to Th3 level (Base). Inlet; **A:** Horizontal section of spinal cord at Th1-level, central canal (red arrow), gray matter of spinal cord (GM), cilio-spinal center (CSC-Yellow Square) (light microscopy, GFAP, x10). Inlet; **B:** Cilio-spinal center neurons (light microscopy, GFAP, x 20) (B) are seen in a normal rabbit.

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 cilio-spinal 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). This study demonstrates that SAH-induced cilio-spinal center neurodegeneration may have been

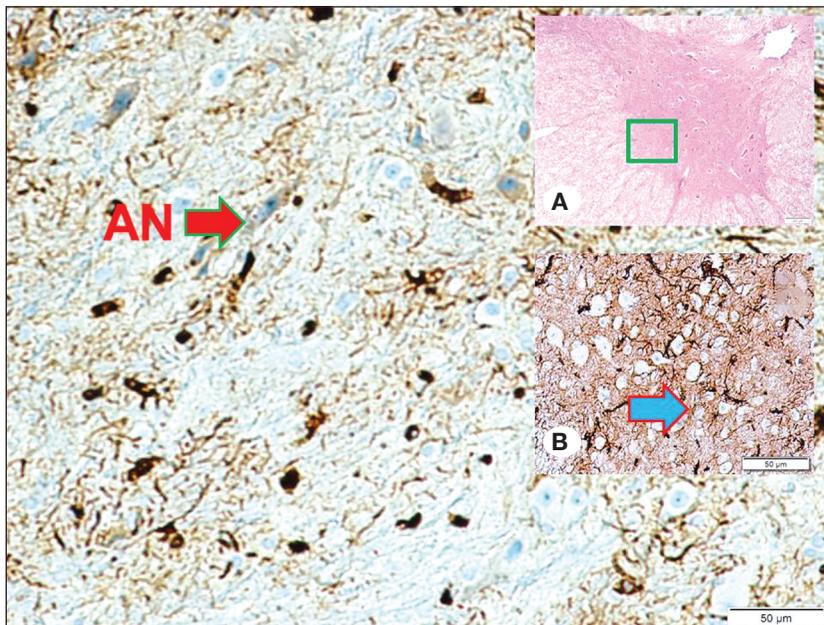


Figure 5: The apoptotic neurons (AN) of the cilio-spinal center (Base) (light microscopy, TUNEL, x 20). Inlet; **A:** histological appearances of the spinal cord at the level of Th-1 (light microscopy, Hematoxylin & Eosin, x10). Inlet; **B:** the deformed neurons labeled with a blue arrow (light microscopy, GFAP, x10).

responsible for permanent miosis following SAH and has not been mentioned in the literature so far. Further studies are needed.

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