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Predictive Role of Posterior Communicating Artery Spasm on Axonal Degeneration in Oculomotor Nerve Root Following Subarachnoid Hemorrhage: Experimental Study

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Abstract: The oculomotor nerve root's medial aspect in the cisternal space is closely associated with the posterior communicating artery and receives blood supply from it. This study investigates whether ischemic damage to oculomotor nerve roots results from posterior communicating artery spasm in subarachnoid hemorrhages. A total of 18 rabbits participated in this study. Baseline pupil diameters were measured using sunlight and ocular tomography. Rabbits were divided into control (GI, n=5), SHAM (GII, n=5; 0.75 cc serum physiologic injection), and subarachnoid hemorrhage-induced groups (GIII, n=8; 0.75 cc autologous blood injection). Pupil diameters were re-measured after the experiment and daily for three weeks. The animals were observed for one week before euthanasia. The posterior communicating artery vasospasm index (VSI) was determined using the wall surface/lumen surface ratio. Stereological methods were employed to examine the normal and degenerated axon densities of the oculomotor nerves. The Kruskal-Wallis and Mann-Whitney U tests were used to evaluate degenerated axon density (n/mm^2) and VSI values. A p-value of less than 0.005 was considered significant. The degenerated axon numbers in per square millimeter (n/mm2) of posterior communicating artery and average equatorial diameter of lens (mm) were 3±1/0.936±0.212 in GI; 18±4/1.578±0.235 in GII; and 212±34/2.515±0.347 in GIII. The p-values were $p<0.005$ for GI/GII, $p<0.0005$ for GII/GIII, and $p<0.001$ for GI/GIII. The posterior communicating artery vasospasm plays a significant role in oculomotor nerve root injury. ©2023 NTMS.

Keywords: Subarachnoid Hemorrhage; Oculomotor Nerve; Vasospasm; Ischemic Demage.

1. Introduction

The basilar, posterior cerebral, superior cerebellar (SCA), and posterior communicating arteries (PCom) are responsible for providing nourishment to the oculomotor nerve (OcN) network. According to Zhang et al [1], the PCom predominantly supplies blood to the nerve roots. Additionally, the cisternal segment of the OcN is often supplied by the mesencephalic perforators [2].

Clamping the PCom can lead to third nerve palsy due to inadequate blood flow to the third cranial nerve root and mechanical harm to the nerve [3]. The primary cause of third nerve palsy is PCom aneurysm [4]. Blunt head injuries can result in widespread axonal damage and OcN detachment [5]. Localized subarachnoid hemorrhage may contribute to delayed oculomotor palsy [6].

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Facial nerves cause vasodilation in cerebral arteries [7]. Facial ischemia can worsen PCom spasms, increasing the risk of OcN ischemia. The ciliary ganglia regulate light and accommodation reflexes by causing miosis. According to Onen et al, it is not only the degenerated neuron density of the ciliary ganglion caused by parasympathetic pupilloconstrictor palsy that leads to pupil dilation, but also the high neuron density present in the pupillodilatory superior cervical sympathetic ganglia must be taken into account as a significant contributing factor [8]. Subarachnoid hemorrhage and aneurysmal compression of PCom can result in axonal degeneration in OcN's and denervation degeneration in ciliary ganglions [9-11]. Facial and trigeminal nerves contribute to vasodilation in cerebral arteries [7]. In the presence of facial ischemia, PCom spasms can worsen, increasing the risk of OcN ischemia.

2. Material and Methods

This study was carried out with the approval of the ethics committee (E-45361945-000-2200224815) from Atatürk University, Faculty of Medicine. In this study, 18 rabbits weighing between 2.5-3 kg were divided into three groups: baseline controls (Group I, n=5), SHAM (Group II, n=5), and the experimental group (Group III, n=8). The researchers initially measured the pupil diameters of all rabbits using natural light and ocular tomography, and these measurements were used as control data for the study. The rabbits belonging to both the experimental and SHAM groups were subjected to anesthesia through subcutaneous injection drugs in proper doses. After preparing the occipito-cervical region, subarachnoid hemorrhage (SAH) was induced in the experimental group by injecting 0.75 cc of blood obtained from the auricular arteries into the cisterna magna. In contrast, the SHAM group was administered 0.75 cc of saline solution instead. Rabbits were monitored for a week with daily pupil diameter measurements and were given a standard diet and unrestricted water access. After the observation period, the rabbits were euthanized, and their OcN roots were collected and examined histologically.

To conduct light microscopic analysis, the samples were prepared as paraffin blocks. Hematoxylin & eosin and GFAP techniques were used to stain the sections. Before the analysis, all brain samples had their cranial nerves and vascular structures removed as much as possible. The Cavalieri method was implemented to evaluate the normal and degenerated axon numbers in both OcN's. Furthermore, the vasospasm index of the PCom, which supplies the OcN, was determined using a previously described calculation method. The vasospasm index is determined by the value of vessel wall surface area divided by lumen area volume and can be formulated as VSI = (R2-r2)/r2). The Cavalieri volume estimation method was utilized to determine the total number of axons in each OcN. Total axon numbers were calculated by multiplying the number of 45-degree portions of OcN's by [8]. The numerical density of axons in each OcN is depicted. The pupil diameter measurement method is summarized in Figure 11. Specific findings are detailed in figure legends, with axon counts presented as mean±SD.

Lens diameters were measured by ocular tomograthy devices. They were followed three weeks and decapitated. The normal and degenerated axon densities of oculomotor nerves were examined by Stereological methods. Lens diameters and degenerated axon density (n/mm2) of oculomotor nerves were evaluated by the Kruskal-Wallis and Mann-Whitney U test. Differences were significant at $p< 0.005$. Data were analyzed using nonparametric statistics with the Mann-Whitney U Test.

3. Results

The number of degenerated axons per square millimeter (n/mm2) and VSI values of the PCom were 3±1/0.936±0.212 for the control group, 18±4/1.578±0.235 for the SHAM group, and 212±34/2.515±0.347 for the experimental group. A negative correlation was found between the degenerated axon density in OcN's and the PCom VSI values.

Anatomical analysis of the brain samples revealed swelling, pink-purple subarachnoid spaces, adhesions, clotted degenerations, cortical injury, and periarterial adhesions. OcN sections were conducted 3 mm after the nerve's origin (Fig 1). Figure 2 shows the typical histological features of OcN's and PCom in a healthy rabbit. The brain histopathological examinations revealed the presence of subarachnoid blood accumulations, inflammations, thickening, pia-arachnoid adhesions, arterial spasms and narrowings, endothelial damage, inner elastic membrane convolutions, muscular hypertrophy, thrombosis, and intimal edema in the arteries that supply OcN roots.

Researchers conducting macroscopic brain examinations on the experimental group identified the presence of brain edema caused by subarachnoid hemorrhage, clot formation, displacements, and leakage of bloody material into the OcN roots and basal brain arteries. They also observed the occurrence of microembolism in the basilar artery and arachnoid pia adhesions. However, due to the presence of meningeal adhesions, they were unable to observe the basal cisterns and subarachnoid spaces of the OcN's. Microscopic brain examinations of the experimental group yielded similar findings. Upon histopathological evaluation of the OcN's, uneven surfaces and axons with noticeable indentations in some nerves were observed. Axonal displacement to the periphery, axonal thinning, and the formation of a peri-axonal halo resulting from axonal regression were identified as degenerated axons. Using the GFAP method, researchers were able to identify axonal degeneration in OcN's in the experimental group. All histopathological examinations are demonstrated in Figure 1-10.

This study has revealed that the ischemia of the radicular OcN and the resulting axonal degeneration

play critical roles in the development of mydriatic pupils. It is noteworthy that the high density of degenerated axons present in OcN's can be considered as a significant contributing factor in the development of mydriatic pupils. This phenomenon can occur in both normal individuals and in various neurological pathologies that affect the light reflex.

The degenerated axon numbers in per square milimeter (n/mm^2) of posterior communicating artery and average equatorial diameter of lens (mm) were 3±1/0.936±0.212 in Group I, 18±4/1.578±0.235 in Group II, and 212±34/2.515±0.347 in Group III. The p-values were $p<0.005$ for Group I/Group II, $p<0.0005$ for Group II/Group III, and $p<0.00001$ for Group I/Group III.

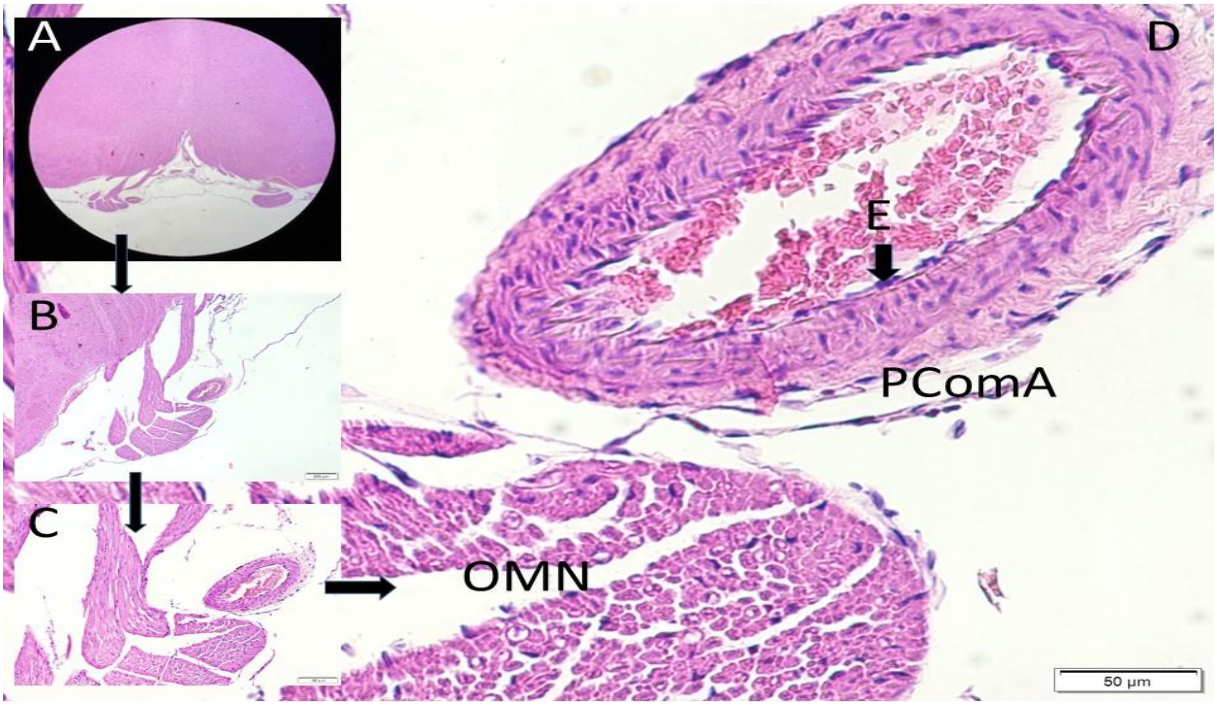

Figure 1: Posterior communicating artery (PComA) and oculomotor nerve (OMN) in normal animal (LM, H&E, x4/AB; x10/C; xx20/D).

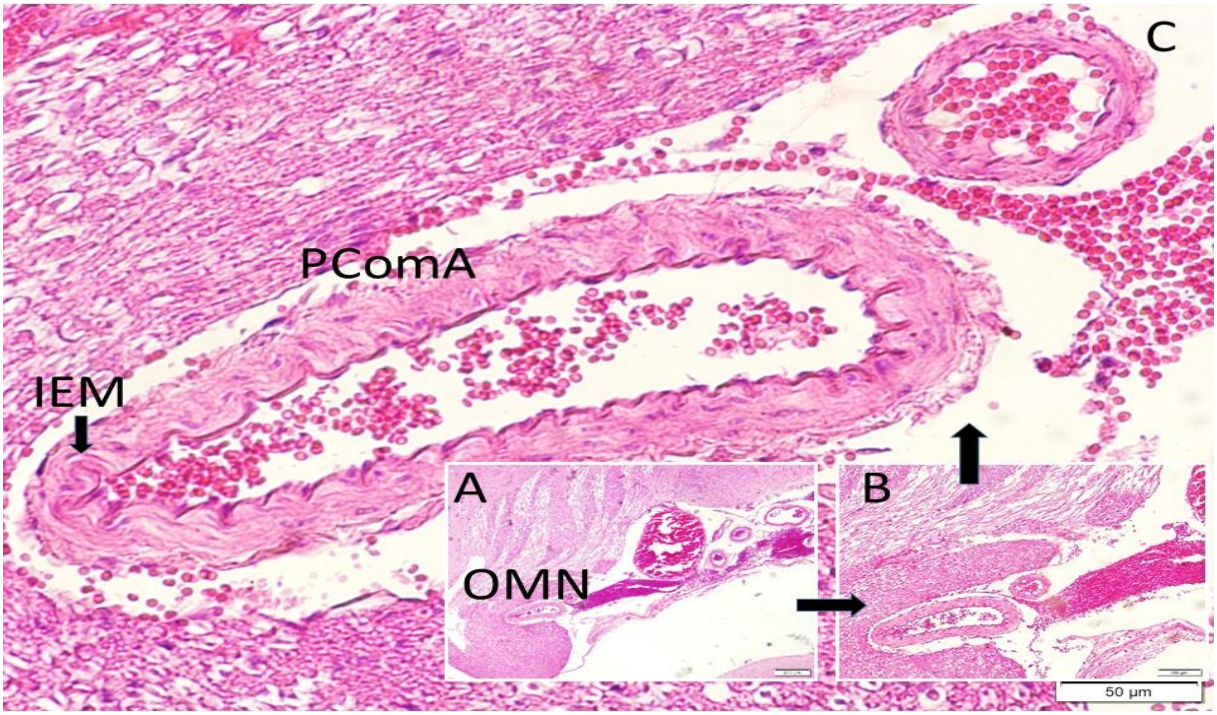

Figure 2: Posterior communicating artery (PComA), internal elastic membrane (IEM) and oculomotor nerve (OMN) is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, H&E, x4/AB; x10/C; xx20/D).

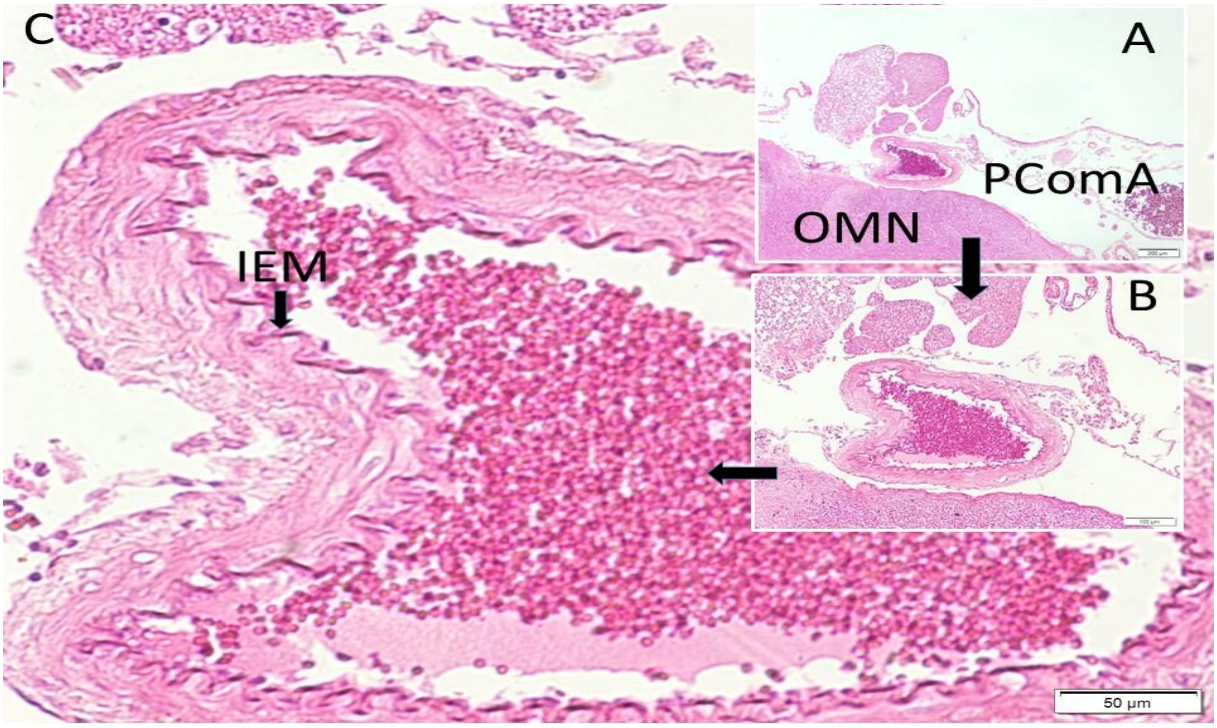

Figure 3: Posterior communicating artery (PComA), convoluted internal elastic membrane (IEM) and edematous nerve oculomotor nerve (OMN) is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, H&E, x4/A; x10/B; x20/C).

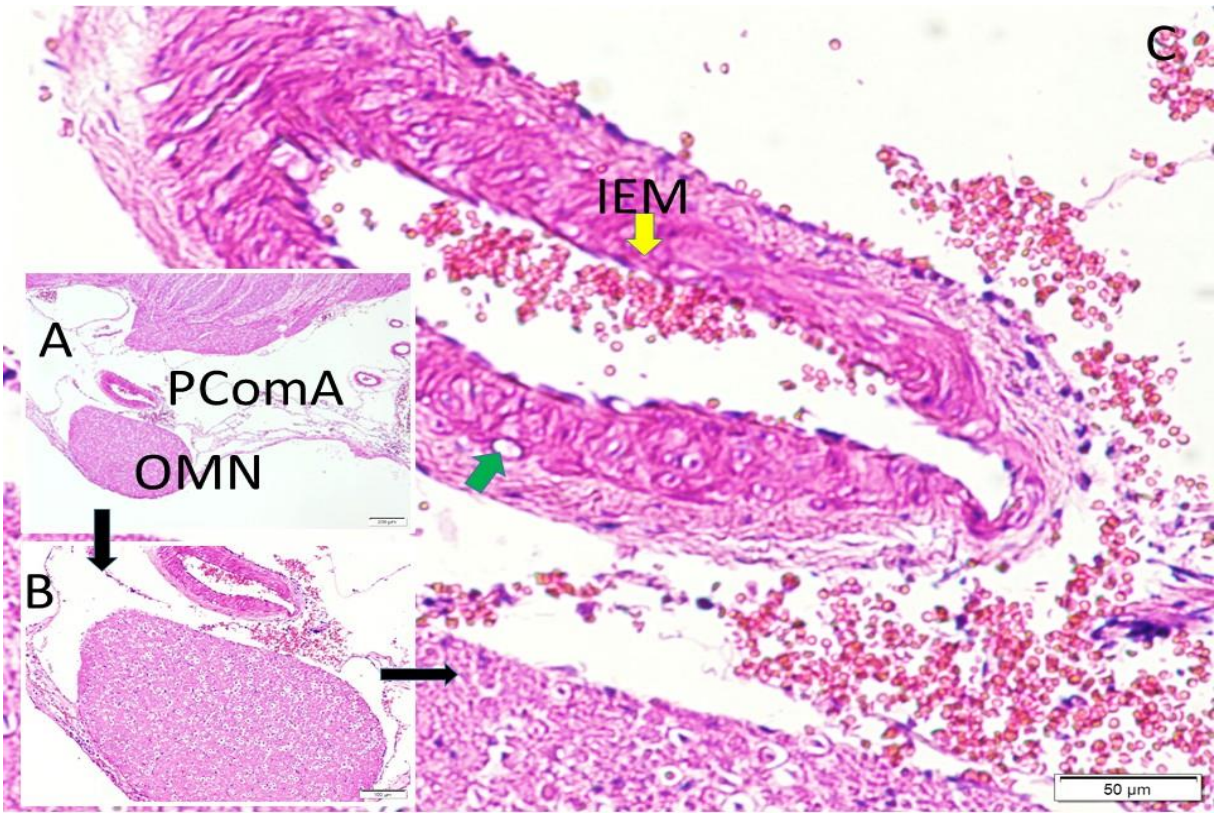

Figure 4: Posterior communicating artery (PComA), convoluted internal elastic membrane (IEM) and significsntly edematous and water collected (Green arrow) in nerve oculomotor nerve (OMN) is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, H&E, x4/A; x10/B; x20/C).

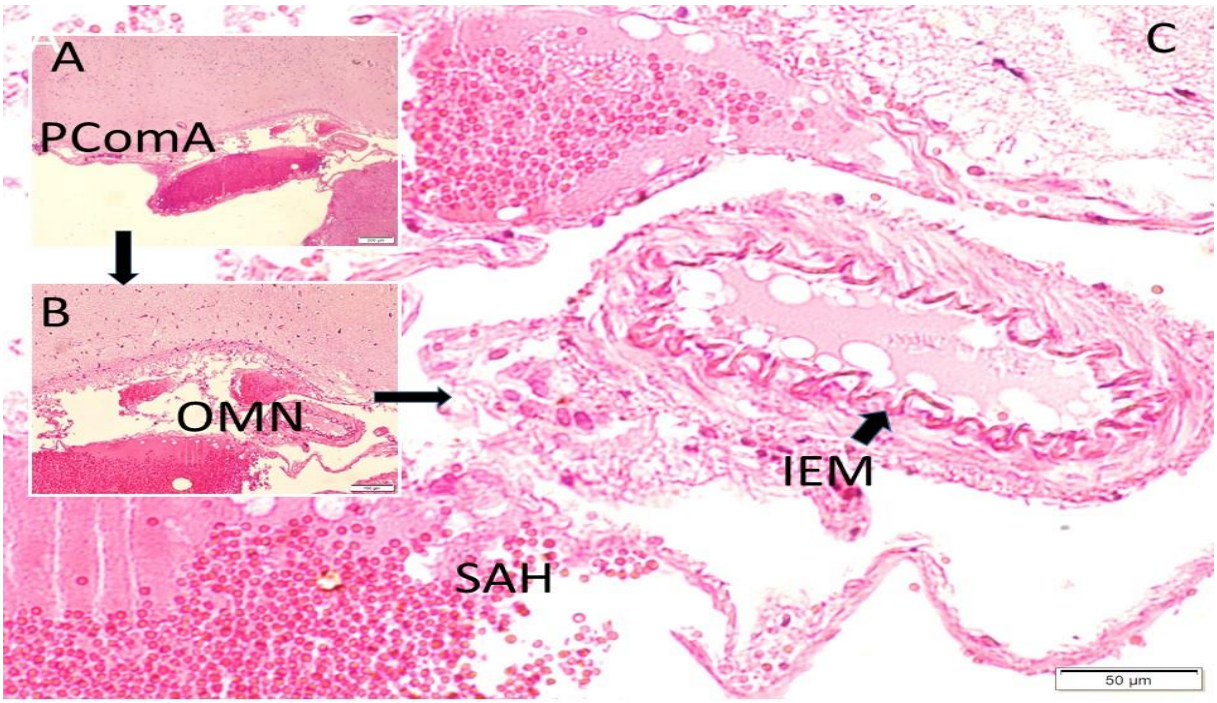

Figure 5: Posterior communicating artery (PComA), convoluted desquamated internal elastic membrane (IEM) and significantly contracted artery is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, H&E, x4/A; x10/B; x20/C).

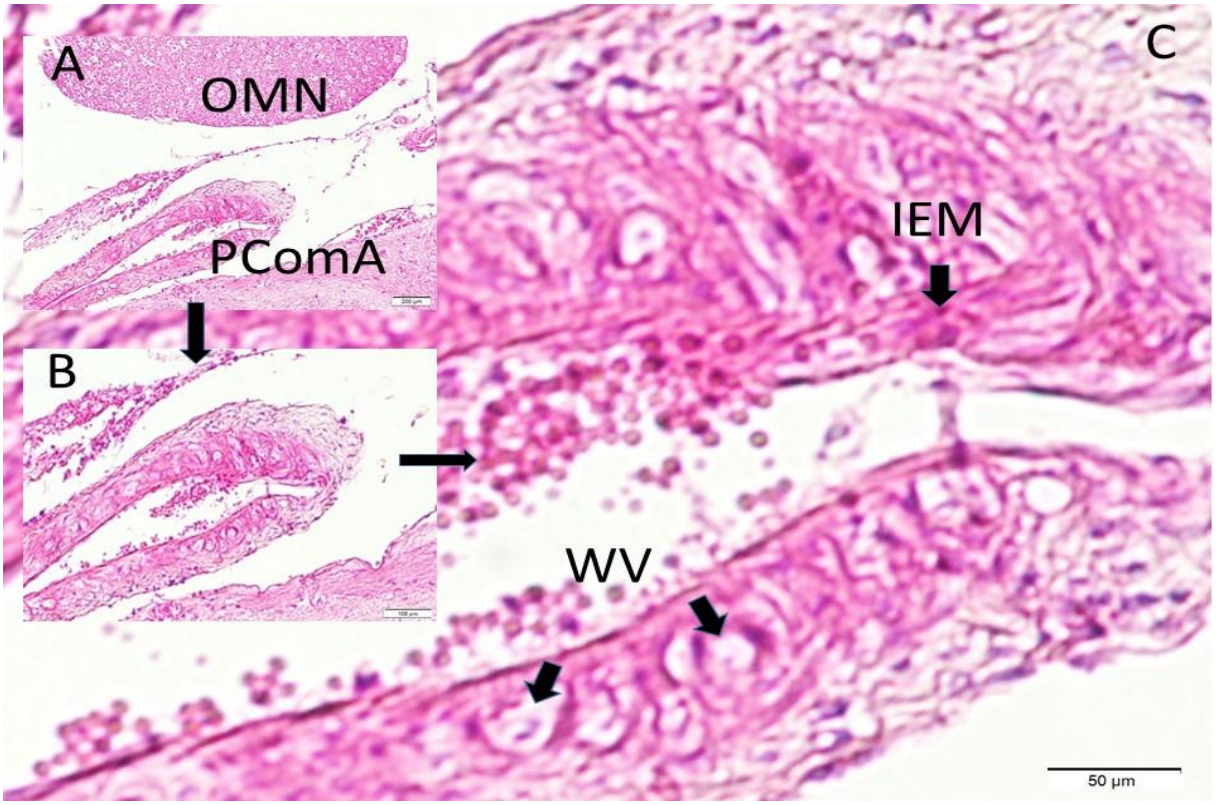

Figure 6: Posterior communicating artery (PComA), convoluted internal elastic membrane (IEM), hyperthrophied muscles and significantly edematous and water collected (WV) in nerve oculomotor nerve (OMN) is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, H&E, x4/A; x10/B; x20/C).

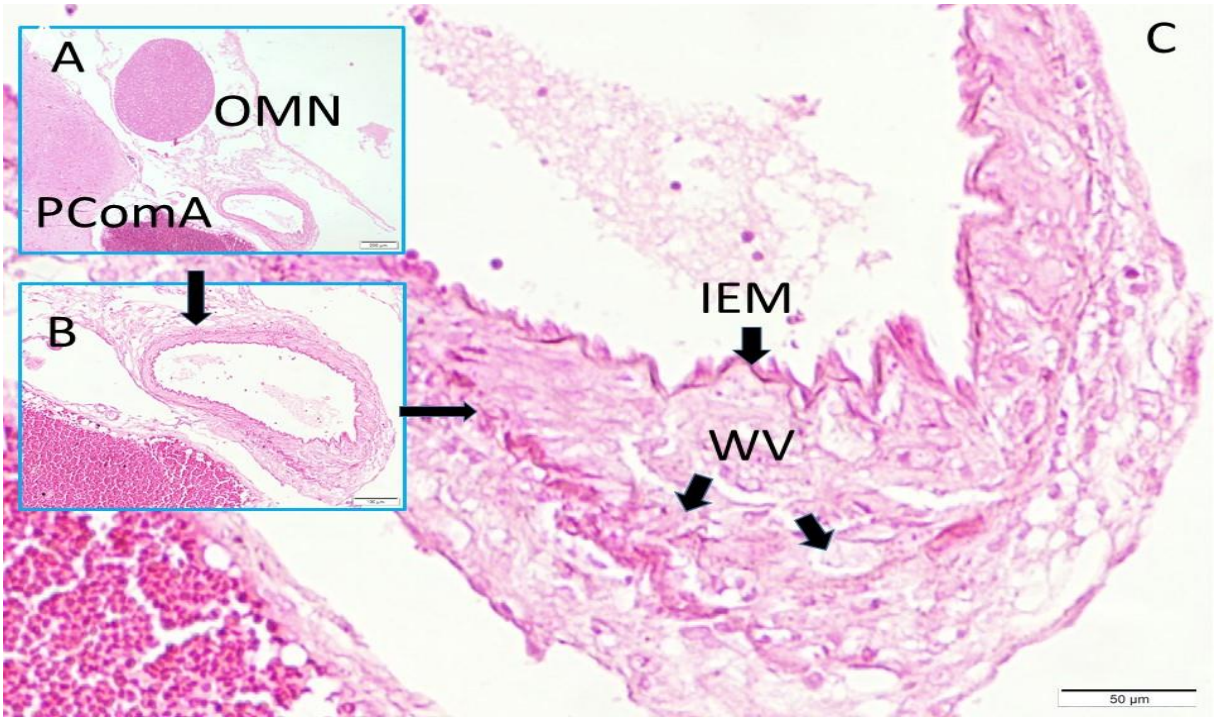

Figure 7: Hyperthrophised posterior communicating artery (PComA), convoluted internal elastic membrane (IEM) and significantly edematous and water collections among ruptured muscles in arterial wall (WV) in PComA is seen in bloody cisternal part is seen in SAH cerated animal (LM, H&E, x4/A; x10/B; x20/C).

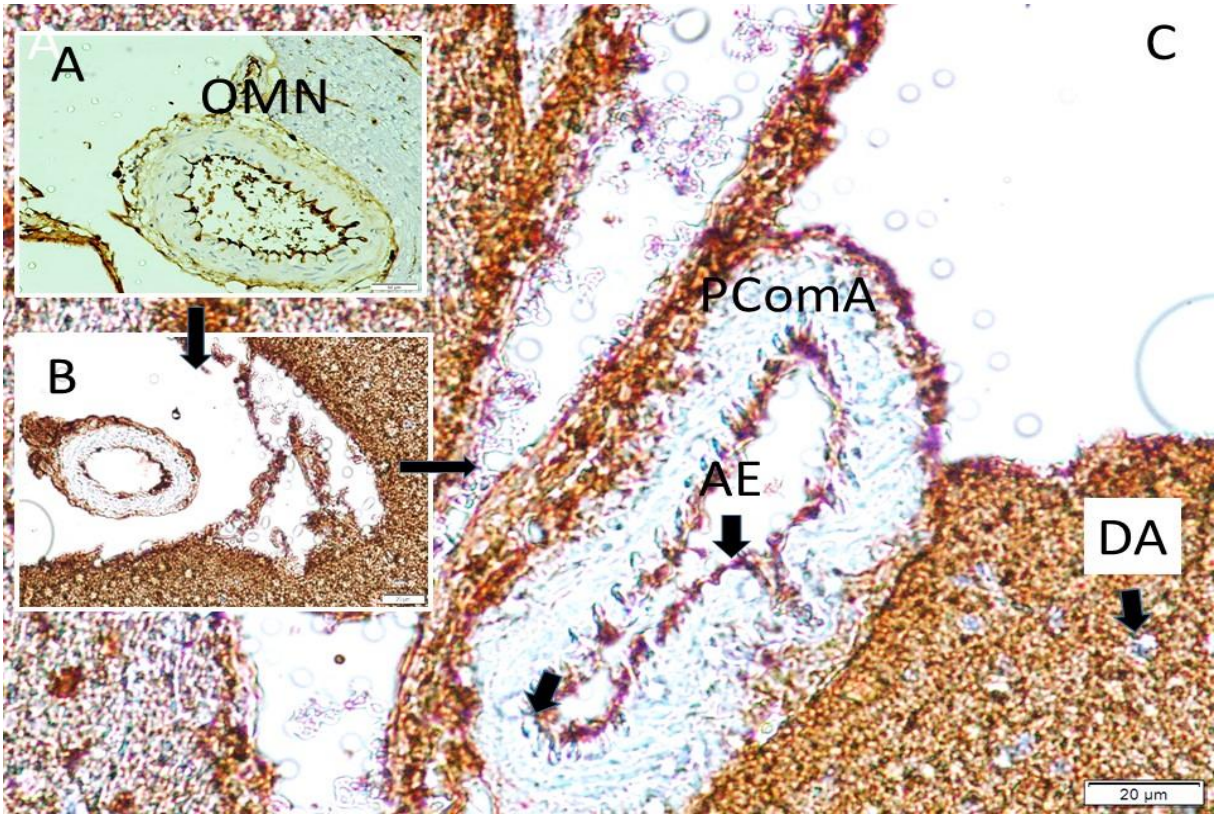

Figure 8: Posterior communicating artery (PComA), convoluted internal elastic membrane (IEM) and significantly edematous and water collected PComA and OMN, degenerated OMN axons (DA) is seen in bloody cisternal part of OMN is seen in SAH cerated animal (LM, Tunel, x20).

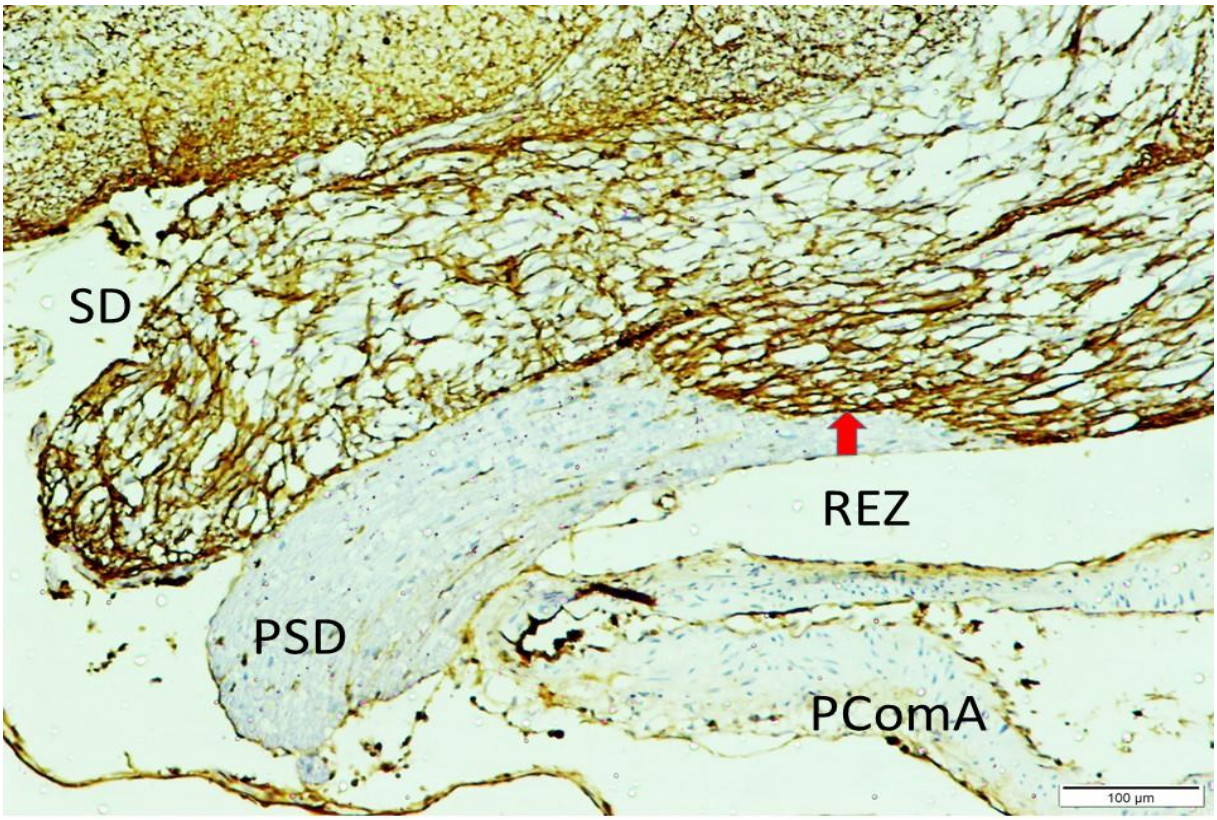

Figure 9: Oculomotor nerve (OMN) with their parasympathetic division (PSD), somatomotor division (SD), root entry zone (REZ) and PComA is seen in cisternal part of OMN is seen in a normal animal (LM, NSE, x4/A; x10/B; x20/C).

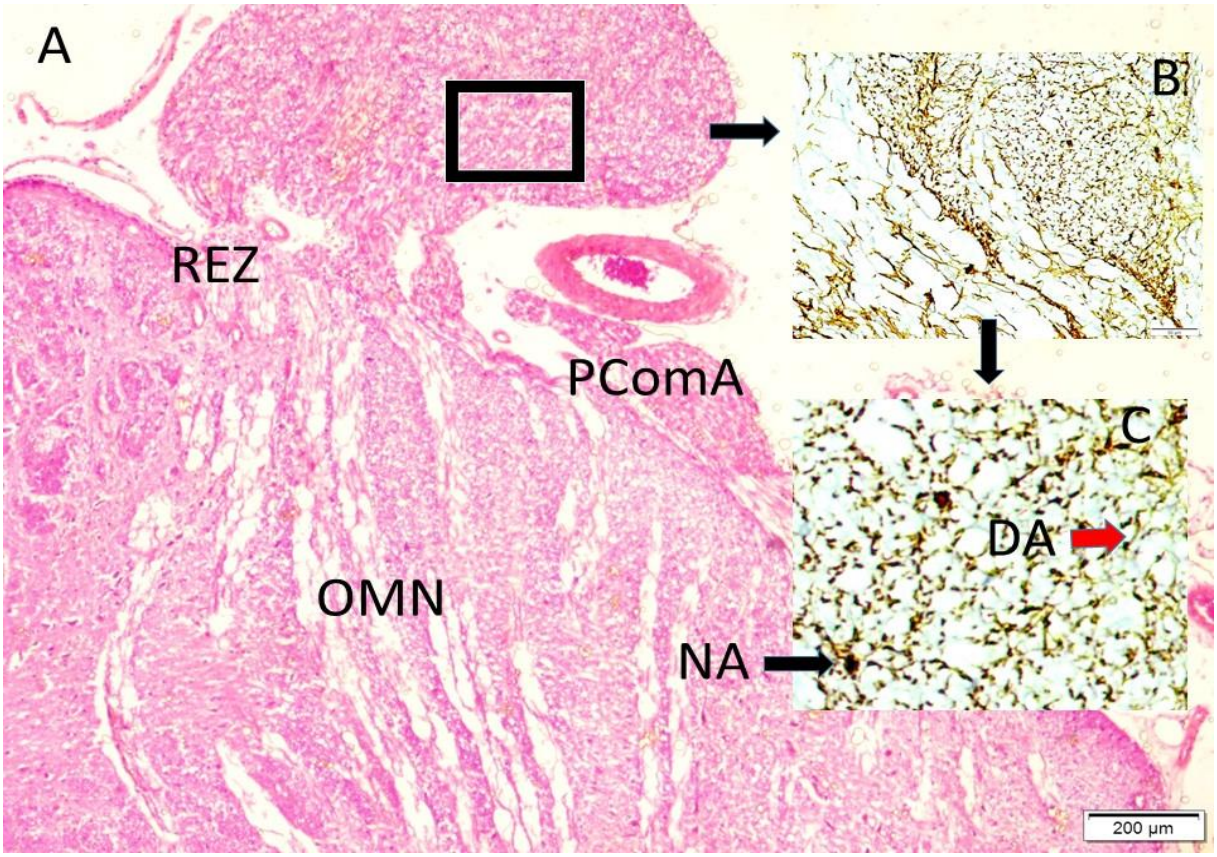

Figure 10: Oculomotor nerve (OMN) with their root entry zone (REZ) and PComA is seen in cisternal part of OMN is seen in a normal animal (LM, H&E, x4/A). Please note that autonom and somatic parts are different each other. Also, REZ zone is seen in (LM, NSE, x20, B) and axon numbers estimation method is seen in c (LM, NSE, x20/C).

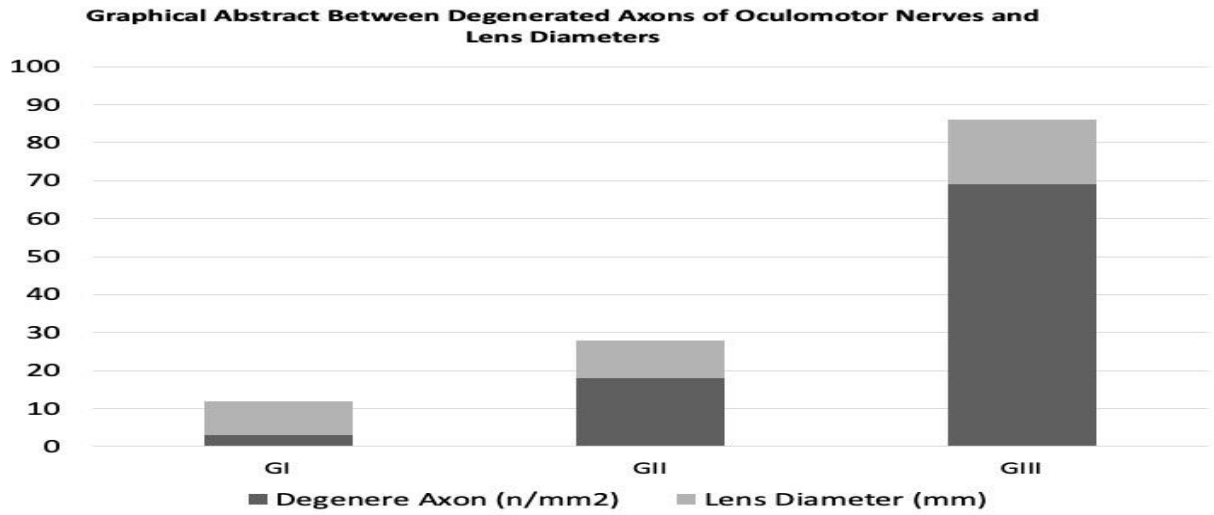

Figure 11: Lens diameter measurement graphical abstract is seen.

4. Discussion

The OcN network receives blood supply from the basilar, posterior cerebral, SCA, and PCom [1]. Primarily, the PCom supply the nerve roots. The OcN's are closely connected with various arteries, such as the SCA, posterolateral pontine artery, basilar artery, mesencephalic perforating arteries, the P1 segment, and the accessory collicular artery (3.7%) [2]. The nerve's dorsal surface has close connections with several arteries and their branches 3. Vascular penetration is observed in the third nerve, with the collicular artery and its branches being the most common penetrating vessels. The cisternal segment of the OcN is frequently supplied by mesencephalic perforators (88.9%) [2]. Clipping the PCom can result in third nerve palsy due to insufficient blood supply to the third cranial nerve root and mechanical nerve damage 3. Aneurysms of the PCom are the most common cause of third nerve palsy [4].

Mesencephalic infarcts can cause intra-axial involvement of the OcN with a fascicular lesion, leading to various eye dysfunctions [14]. Closed head traumas may result in diffuse axonal injury and OcN avulsion [5]. Ischemic OcN palsy can develop after non-aneurysmal subarachnoid hemorrhage, presenting symptoms such as mild headache, acute onset of blurry vision, and eye ptosis [15]. Recovery from OcN palsy caused by PCom aneurysm is possible [1]. Perimesencephalic subarachnoid hemorrhage can lead to third cranial nerve palsy, and focal subarachnoid hemorrhage may cause delayed oculomotor palsy [6, 16]. Aneurysmal subarachnoid hemorrhage localized to the interpeduncular cistern can result in permanent OcN palsy due to ischemic damage of the OcN web [17]. Facial ischemia can worsen PCom spasm and increase the risk of OcN ischemia [7].

Oculomotor nerves and ciliary ganglion relationships:

The ciliary ganglion is a type of parasympathetic ganglion associated with the OcN's. Postganglionic fibers are responsible for inducing miosis, which controls the light and accommodation reflex. Although the degenerated neuron density of the ciliary ganglion cannot be solely attributed to pupil dilation caused by parasympathetic pupilloconstrictor palsy, it is essential to consider the high neuron density present in the pupillodilatory superior cervical sympathetic ganglia as a significant contributing factor to pupil dilation, according to [8]. Photophobia results from denervation injury of the ciliary ganglion due to PCom spasm-induced OcN root insult [18]. Subarachnoid hemorrhage can cause denervation injury in the ciliary ganglion [10]. A study conducted by Aydin et al. revealed that meningitis often leads to the development of arachnoiditis and axonal degeneration at the cisternal segments of both oculomotor and optic nerves. These conditions subsequently result in neurodegenerative changes in the ciliary ganglion [9]. Aneurysmal compression of PCom causes axonal degeneration in OcN's and denervation degeneration in ciliary ganglia [11].

The ciliary muscles, which control the diameter and thickness of the lens, are largely controlled by the parasympathetic fibers of the oculomotor nerves and the cervical sympathetic fibers. These parasympathetic signals are transmitted to the pupillary and ciliary muscles of the eye by axons originating from the Edinger-Westphal nuclei in the brain stem. These fibers, which cause miosis as a result of contraction in the pupil, also contract the ciliary muscles, causing the lens to thicken and thus reduce its diameter. Thus, the suspension bonds are loosened, and the lens thickens and adjusts the accommodation for near-far vision. Thus, the lens with increased refractive power can focus better on nearby objects [19]. On the other hand, semaptics do the opposite of these functions [20]. Damage to the oculomotor nerve and the ciliary muscle formation it modulates leads to disruption of the accommodation reflex and visual defects [21]. In subarachnoid hemorrhages, axonal degeneration of the oculomotor nerve causes paresis or paralysis in the ciliary muscles, preventing their contraction. As a result, since the ciliary muscles cannot contract, the

lens cannot expand towards the periphery and becomes thicker, that is, its equatorial diameter decreases. This leads to near vision defects

5. Conclusion

In summary, the OcN network and its relationship with the ciliary ganglion are critical for understanding various neurological pathologies affecting the light reflex and other eye functions. The interactions between blood supply, nerve damage, and denervation injury in the ciliary ganglion can provide valuable insights into the development of mydriatic pupils in both normal and pathological conditions. In the eyes, there is often a condition called PCOM spasm, which can result in paresis or paralysis of the ciliary muscles that control the thickness of the lens, as they are fed by the radix of the oculomotor nerve. As a result of paresis or paralysis of the ciliary body, the muscles are unable to contract, causing an increase in the diameter of the lens, which results in myopia. A comprehensive understanding of these factors can help guide the development of targeted treatments and preventive strategies for oculomotor nerve-related disorders.

Limitations of the Study

This study does not include electrophysiological data.

Future Insight

Trigeminal nerve stimulation may be used to dilate PCom spasm.

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Conflict of Interests

Author declares no conflict of interest with this study and manuscript.

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There is no financial support in this study.

Author Contributions

The entire text of the work is attributed to the responsible author and the second author.

Ethical Approval

This experimental investigation was approved by the Health Research Ethics Committee of the Medical Faculty at Ataturk University (E-42190979-000-2200225459).

Data sharing statement

Authors declares; All data generated by this work are publicly available as long as reference rights are not violated if any part of the work is used.

Consent to participate

All authors participated equally to this study.

Informed Consent

Scientific works undertaken with this study did not require any informed consent.

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