

Denervation injury of scalp hair due to trigeminal ganglion ischemia: the first experimental study

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ABSTRACT

Aim: Scalp hairs are mainly innervated by sensitive fibers of trigeminal nerves. Ischemic neurodegeneration of trigeminal ganglion can cause denervation injury of scalp hairs. We investigated if there is a relationship between the degenerated neuron densities of trigeminal ganglion neuron densities and the numbers of degenerated hair follicles numbers following subarachnoid hemorrhage (SAH).

Material and Method: Five normal (n=5), five SHAM (n=5), and ten (n=10) male rabbits were chosen from formerly experimental SAH created by cisternal homologous blood injection (0.75cc) group, which followed for three weeks. Degenerated neuron numbers of trigeminal ganglion and atrophic hair follicles numbers in the frontal areas of the scalp were examined by stereological methods. Degenerated neuron densities of trigeminal ganglions and atrophic hair follicles numbers were analyzed by the Mann-Whitney U test.

Results: The mean degenerated neuron densities trigeminal ganglions (n/mm³) and atrophic hair follicles (n/mm²) were determined as 5±2/m³ and 12±4/mm² in control; 12±3/m³ and 41±8/mm² in Sham and, 168±23/m³ and 79±14/mm² in the study group (p>0.001). In the post-hoc analysis, all groups differed significantly from each other. A linear association was observed between the degenerated neuron densities of trigeminal ganglions and atrophic hair follicles (r: 0.343, p: 0.007).

Conclusion: Trigeminal ganglion neurodegeneration may be an essential factor in hair follicles atrophy after SAH, which has not been mentioned in the literature so far.

Keywords: Denervation Injury, hair, ischemia, scalp, trigeminal ganglion

INTRODUCTION

The scalp is innervated by trigeminal, facial, glossopharyngeal, vagal and upper cervical nerves (1). The sensory nuclei of the trigeminal nerve (TN), which have somatomotor and somatosensitive fibers, are located in a wide area extending from the pons to the medulla spinalis. Motor and sensory roots pass through the subarachnoid space in separate bundles and enter the Meckel cave at the floor of the middle cranial fossa and together form the TN. Since the dermatome areas of the TN are intensely innervated, it has to get a richer network compared to other nerves. Efferent fibers extend from the motor nucleus in the pons, and afferents extend from the mesencephalon to the second cervical segment. The sensory fibers of the TN and the sensory fibers of the

facial, glossopharyngeal, vagal and upper cervical nerves innervate the craniofacial superficial and deep regions (2-4). Sensory fibers emerge from the trigeminal ganglion (TGG) located between the two leaves of the dura in Meckel's cave. After leaving the ganglion, they proceed together with the motor fibers. They leave the cranium passing through the subarachnoid and subdural distance as three separate branches as ophthalmic, maxillary and mandibular roots. While these branches carry the sense of the whole face, especially the ophthalmic nerve carries the sense of the scalp up to the vertex. The other two branches carry the sense of the scalp, especially in the temporal region. Each branch carries the afferent impulses of pain, heat, pressure, touch, and chemosensitive sensations, including the pH of all structures, including

the intracranial, intraorbital, and intranasal cavities that fall into its trace, as well as the mucosa in this area (4-7).

The temporal arteries of the scalp are innervated mainly by the TNs. A normal sensory innervation of the auriculotemporal nerve and normal vascular supply of the superficial temporal artery is required for the temporoparietal fascial flaps (8). So, we think that the TN also regulates the pH changes that occur in normal and pathological conditions in the areas it innervates. Actually, cervical dorsal root ganglia, which have vasodilator effects, have also been reported to prevent arterial vasospasm together with trigeminal-glossopharyngeal-vagal nerves (9). TN innervates ipsilateral craniofacial arteries and causes vasodilation in subarachnoid hemorrhage (SAH) (5, 9, 10).

Vasospasm and increased intracranial pressure are the most dangerous complications of SAH (10). Spasm of the arteries supplying the scalp threatens the prognosis of injured scalp tissue and scalp reconstruction. When SAH causes ischemia in the TN, the ischemic TN also causes a spasm in the scalp arteries, causing denervation and ischemia injuries in the entire scalp tissue together with its fibers.

Trigeminal ganglion ischemia results from vasospasm of the ipsilateral cerebral arteries supplying this nerve (11). We assumed that the temporal artery spasm of the scalp due to SAH might cause scalp ischemia. We aim to demonstrate this hypothesis.

MATERIAL AND METHOD

This study was approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 29.06.2010, Decision No: B.30.2.ATA.0.01.02/2798) and the care of the animals and the experiments were conducted according to the guidelines set forth by the same ethics committee. Because the study was designed as an animal experiment, no written informed consent form was required. All procedures were carried out in accordance with the ethical rules. We protect animal rights per the principles of the Guide for the Care and Use of Laboratory Animals (www.nap.edu/catalog/5140.html).

Study Population and Design

Five normal (n=5), five Sham (n=5) and ten male rabbits (n=10) were chosen from formerly experimental SAH. Experimentally induced SAH was created by cisternal homologous blood injection (0.75cc) in the study group. Subjects were followed for three weeks. Stereological methods examined degenerated neuron densities of trigeminal ganglions and atrophic hair follicles numbers. Electrocardiographic data and blood

pressures were recorded preoperative, intraoperative, and postoperatively.

Experimental protocol

Intracranial pressure, light reflexes, pupil diameters, electroencephalogram (EEG), and electrocardiogram (ECG) findings were recorded. Pupil diameters were measured in all animals in light and dark environments, and fundoscopic examinations were performed three times a day for two days prior to inducing SAH. Linear EEG and ECG were considered as brain and heart death. Five animals were used as the intact control group for the normal and pathoanatomical and histopathological examinations of the TN and ganglion. All animals were anesthetized by isoflurane, administered through a face mask, followed by a subcutaneous injection of 0.2 mL/kg of the anesthetic combination (ketamine HCl, 150 mg/1.5 mL; xylazine HCl, 30 mg/1.5 mL; and distilled water, 1 mL) before surgery. During the procedure, a dose of 0.1 mL/kg of the anesthetic combination was used when required; balanced, injectable anesthetics were used to reduce pain and mortality. Autologous blood (0.75 cc) was taken from the auricular artery and injected into the cisterna magna of the animals in the SAH group for 1 minute using a 22-gauge needle. In the sham-operated control group, 0.75 cc of physiological serum was injected into the cisterna magna. No injection was given to the control group. The animals were followed for three weeks to death without any medical treatment while their intracranial pressure values were recorded daily, and then the animals were sacrificed.

All animals' frontotemporoparietal scalp tissues, brain stems, TNs and trigeminal ganglions were examined for gross anatomopathological characteristics. Findings are summarized in the results section.

All deep temporal arteries with their neighbors, TNs and TGGs, including brain areas, were fixed in 10% formalin solution for five days. Then, all brain stems were horizontally sectioned at 2-mm distances from the origins of the oculomotor nerves, and oculomotor nerve roots sections were embedded in paraffin blocks. The tissues were stained with hematoxylin & eosin (H&E), van Gieson, Tunel, and Aldehyde Fuchscine methods to estimate the neuronal density of the TGG. The Stereological and Cavalieri method was used to evaluate the neuronal density of TGG.

As in our former study, the number of alive and degenerate neurons in TGG was evaluated using the physical dissector method (12). The Cavalieri volume estimation method was used to obtain the total number of neurons in each specimen, calculated by multiplying the volume (mm³) by the numerical density of neurons in each ganglion. Histologically, cellular angulation, nuclear

shrinkage, cytoplasmic condensation, and cellular darkening were accepted for neuronal and follicular degeneration criteria.

Statistical Analysis

The differences between the degenerated neurons densities of trigeminal ganglion and degenerated hair follicles numbers were analyzed using a commercially available statistics software package (SPSS® for Windows v. 12.0, Chicago, USA). The Kruskal-Wallis and Mann-Whitney U tests were used for data analysis. Bonferroni correction was applied in post-hoc tests that determined significant differences between groups for physiological parameters, pupil diameter and density of degenerated neurons in TGG, and density of atrophic follicles. The correlation between the density of degenerated neurons in TGG and the density of atrophic follicles was analyzed by Spearman's correlation test. Differences were considered significant at a two-sided $p < 0.05$.

RESULTS

Clinical Results

Two animals in the study group died during the experiment. Cardiorespiratory disturbances, stiff neck, convulsions, urinary retention, intestinal dysmotility and gait disturbances were recorded. Weakened corneal and light reflex pupillary enlargements were recorded in the study group. Significant electrocardiographic abnormalities such as prolonged QT intervals, ST depressions, and low voltage QRS were noticed in animals with myocardial necrosis. Central tendency measurements of heart and respiratory rates of animals in control, Sham, study-live and study-death groups are as follows: 265 ± 27 /min- 19 ± 4 /min; 219 ± 22 /min- 14 ± 3 /min; 129 ± 11 /min- 10 ± 2 /min. Intracranial pressures of all animals were recorded via daily pupil examination.

Macroscobical Findings of Scalp, Brain, TN

Scalp softening, edema and hair loss were observed. Intracranial macroscopic examination with a surgical microscope revealed swollen brain with effaced sulci, thickening of the arachnoid membrane, pia-arachnoid adhesions, and edematous trigeminal ganglion in Meckel's cave.

Histopathological Results

In the microscopic analyzes of the trigeminal ganglion of the brain, thickening pia and arachnoid membranes, old or fragmented blood cells in the sulci, clot and spasm in the cortical vessels, neuronal angulation, cytoplasmic and nuclear condensation, halo formation and nuclear decentralization were observed in the trigeminal ganglion neurons.

Microscopic examination of the scalp revealed degenerative changes in glandular epithelial trigeminal ganglion cells, edema, vascular spasm, congestion, degenerative changes in hair follicles, necrosis, parafollicular destruction, loss of hair tissues and axonal pathologies in nerve fibers.

In **Figure 1**, the histological appearance of the trigeminal ganglion in the control group (**Figure 1A, B**), as well as the appearance of degenerated neurons in the Sham group and the study group with the SAH model (**Figure 1C and D**; respectively) were presented. While neuron degeneration was milder in the sham group, it was noticed that there were histopathological features, such as indicating significant degeneration in the study group. **Figure 2** represents the histological views of the normal and degenerated hair follicles. Degenerated and atrophic follicles were noted in the sham and study groups, and constructed-deformed follicular artery in the study group. In **Figure 3** and **Figure 4**, normal and variable degrees of degenerated hair follicles were demonstrated with aldehyde fuchsin and Von Gieson stains, respectively. In **Figure 5**, apoptotic hair follicles are seen in the subjects in the study group with Tunel staining.

Numerical Results

The mean degenerated neuron densities trigeminal ganglions (n/mm^3) and atrophic hair follicles (n/mm^2) were determined as $5 \pm 2/m^3$ and $12 \pm 4/mm^2$ in control; $12 \pm 3/m^3$ and $41 \pm 8/mm^2$ in Sham and, $168 \pm 23/m^3$ and $79 \pm 14/mm^2$ in the study group ($p > 0.001$). In the post-hoc analysis, all groups differed significantly from each other. A linear association was observed between the degenerated neuron densities of trigeminal ganglions and atrophic hair follicles ($r: 0.343$, $p: 0.007$).

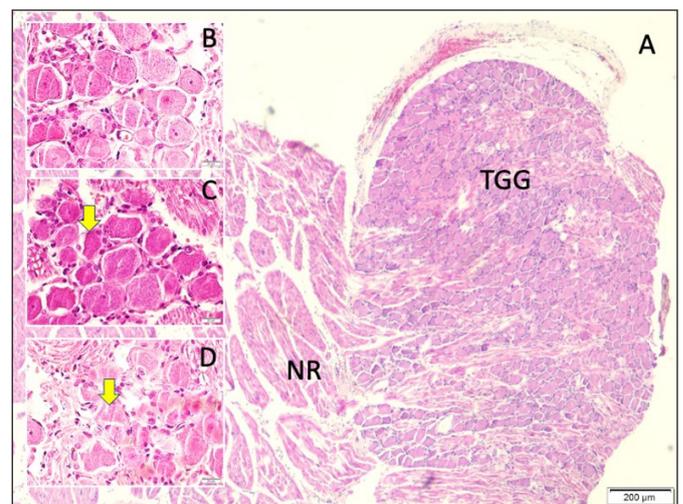


Figure 1. Histological appearances of trigeminal ganglion (TGG/A) (LM, H&E, x4/A; x10/B); histopathological appearances in with slightly degenerated neurons in Sham (Yellow arrow) (LM, H&E, x20/C), and significant degenerated neurons in study group (Yellow arrow) (LM, H&E, x10/D)
TGG: trigeminal ganglion, LM: Light microscope, H&E: Hematoxylin-eosin

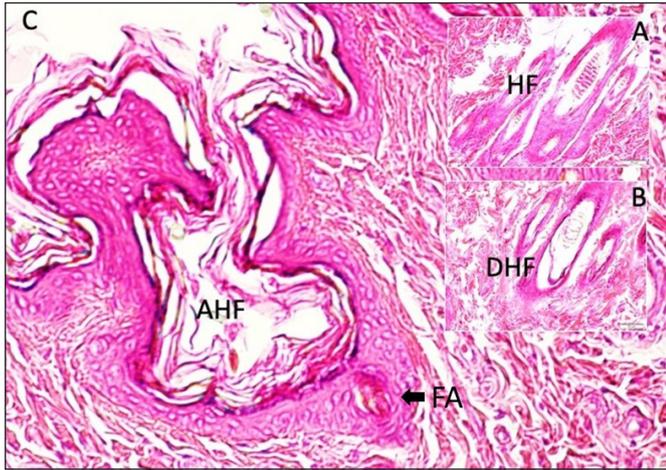


Figure 2. Histopathological appearances of normal hair follicle (HF) (LM, H&E, x20/A); slightly degenerated hair follicle (DHF) in SHAM (LM, H&E, x20/B), and significant degenerated, atrophic hair follicle (AHF) and constructed-deformed follicular artery (FA) (LM, H&E, x20/C) in study animal. LM: Light microscope, H&E: Hematoxylin-eosin

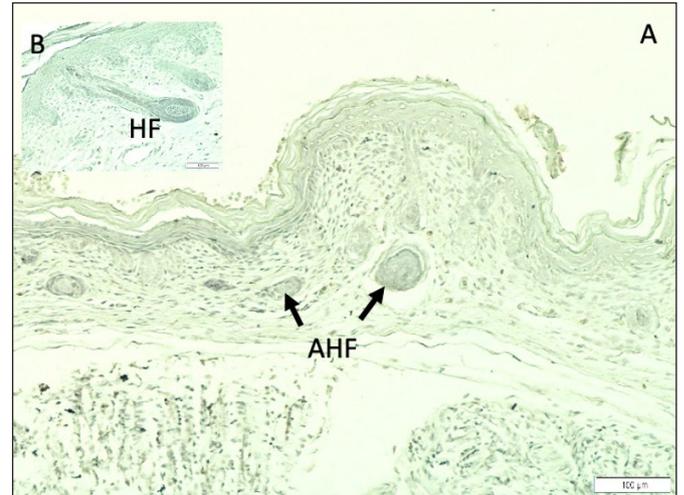


Figure 5. Histopathological appearances of the apoptotic hair follicles (AHF, Black arrow) (LM, Tunel, x10/A) in study animal and normal hair follicle in control group (LM, Tunel, x10/B). LM: Light microscope

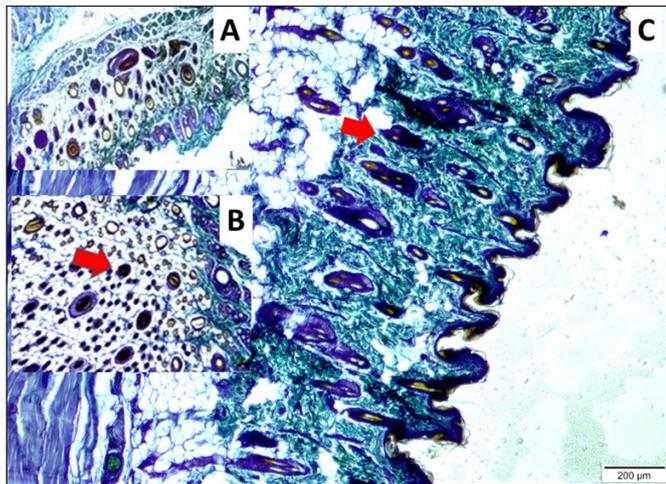


Figure 3. Histopathological appearances of the normal hair follicle (LM, Aldehyde fuchsin, x4/A); slightly degenerated hair follicle (Red arrow) in SHAM (LM, Aldehyde fuchsin, x4/B), and significant degenerated hair follicle (Red arrow) (LM, Aldehyde fuchsin, x4/C) in study animal. LM: Light microscope

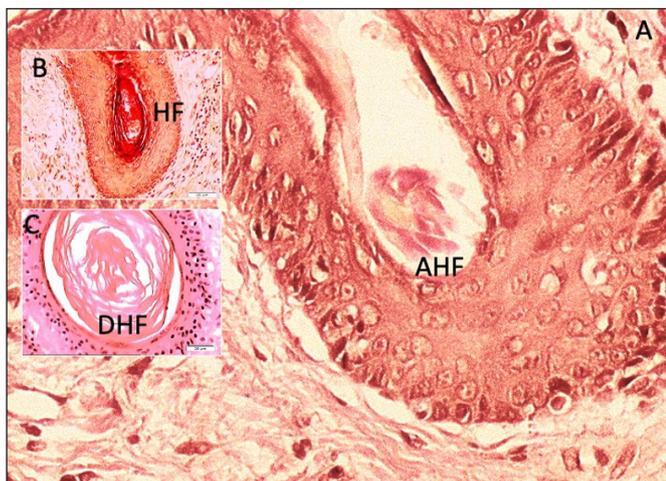


Figure 4. Histopathological appearances of normal hair follicle (LM, Van Gieson, x40/A); slightly degenerated hair follicle in SHAM (LM, Van Gieson, x40/B), and significant degenerated hair follicle (LM, Van Gieson, x40/C) in study animal. LM: Light microscope

DISCUSSION

The craniofacial region's circulation is provided by supraorbital, supratrochlear, facial, maxillary artery, temporal and occipital arteries and their plexuses intracranial artery branches (13, 14). Cerebral vasospasm is the main cause of focal cerebral ischemia after SAH. Vasospasm is characterized by various degrees of narrowing of the vessel lumen, which develops early or late following arterial rupture. Cisternal blood injections mimicking SAH in animal models produce angiographically demonstrable vasospasm (9). In contrast to cerebral vasospasm, external carotid artery vasospasm has not been described much in the literature (10). In the case of cerebral vasospasm, the collateral system helps maintain the blood supply in the brain and allows for its self-treating process. Özdemir et al. (15) reported that this mechanism would be impaired in the case of external carotid spasm concurrent with cerebral vasospasm and, therefore, severe neurodegeneration developed in the temporal lobe fed by both the internal and external carotid systems. Özdemir et al. (9) theorized that decreased vasodilator functions of cervical dorsal root ganglia increased vasospastic effects of trigeminal-glossopharyngeal-vagal nerves and cervical sympathetic ganglia may be responsible for this phenomenon. Indeed, cerebral vessels also have a neural and humoral arrangement similar to the peripheral vascular system (15). Cerebrovascular sensory nerves are also mainly innervated from the trigeminocerebrovascular system. Trigeminal sensory nerves are distributed to the ipsilateral internal carotid artery (ICA), middle cerebral artery (MCA), anterior cerebral artery (ACA), rostral part of the basilar artery, posterior cerebral artery (PCA) and posterior communicating artery (5, 9, 10). Cranial arteries and

cephalic blood vessels, such as pial and dural vessels innervated by sensory fibers of trigeminal, facial and vagal ganglia (16, 17). Autonomic nerves reinnervated the grafts can contribute to the functional recovery of the transplanted tissues by their vessel diameters and blood flow (18). Adrenergic nerves cause vasospasm in cerebral and pia mater vessels, so desymmetrization prevents vasospasm (19). There is evidence that vasodilation of cranial vessels results from facial nerve stimulation (20). TNs have significant roles in the blood flow regulation of cerebral, dural, skull bone and scalp arteries (16). SAH is associated with craniocervical vessels vasospasm secondary to TN ischemia (21). Decreased trigeminal impulses cause facial artery spasms (22). If the vagal and facial nerve networks have a weak parasympathetic effect, adequate vasodilation will not occur in the arteries supplying TGG, and this will increase TGG ischemia.

Conversely, in those with weak external carotid artery spasms, the increased relative strength of the cervical sympathetic chain will also lead to vasoconstriction (1). While Gasser ganglion injury increases intracranial pressure with cerebral vasospasm, it can increase ischemic damage to scalp arteries and TN fibers distributed on the scalp surface (23). TN insufficiency may be responsible for weak scalp tissue and sunburns, infections, malignancies, and immune diseases usually involving the local lymph network or peripheral sensory nerves (24,25). Sensory neuropathies of the trigeminal, glossopharyngeal and vagal nerves may cause scalp and facial skin injuries (26). Trigeminal and upper cervical branches innervate the hair cells (27). Alopecia on the frontal area of the scalp may be originated from TN lesions (28,29). The mechanoreceptive innervation of the scalp has a major role in scalp life (30). Gasserian ganglion ablation may cause hair loss and craniofacial sensory-motor disabilities (31). In our study, the relationship between TGG ischemia secondary to SAH and significantly degenerated hair follicles points to denervation injury of the scalp.

The facial-scalp flap must be transferred as a single unit with a unilateral common carotid artery and external jugular vein (32). Trigemino-facial communicating fibers have important indicators for wound and flap healings (33). Supraorbital and supratrochlear nerve injuries may cause hair loss of the superciliary crescent (28). Facial allotransplantation in patients with facial injuries may be failed because of neurovascular injuries (33). We think that TN ischemia may be the crucial threatening factor in terms of scalp survival and surgery. Trigeminal ganglion stimulation has a vasodilatory effect in the acute phase of SAH (34). With this method, both denervation and hydropic degeneration of hair

follicles can be prevented by vasodilation in the arteries involved. Therefore, electrophysiological recordings for the TN may help determine the prognosis of craniofacial surgery in patients with SAH. TN stimulation can be tried as a new treatment method.

CONCLUSION

This study showed that; ischemic damage of the TN, which has the richest network in the innervation of the head and neck region, may be the remarkable factor not mentioned in the prognosis of craniofacial trauma or surgery. Trigeminal stimulation may be a promising treatment method in such cases. We hope this study will inspire further studies.

ETHICAL DECLARATIONS

Ethics Committee Approval: This study was approved by the Atatürk University Animal Experiments Local Ethics Committee (Date: 29.06.2010, Decision No: B.30.2.ATA.0.01.02/2798) and the care of the animals and the experiments were conducted according to the guidelines set forth by the same ethics committee.

Informed Consent: Because the study was designed as an animal experiment, no written informed consent form was required.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All of the authors declare that they have all participated in the design, execution, and analysis of the paper and that they have approved the final version

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