The Important Liaison Between Onuf Nucleus–Pudendal Nerve Ganglia Complex Degeneration and Urinary Retention in Spinal Subarachnoid Hemorrhage: An Experimental Study

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OBJECTIVE: **The Adamkiewicz artery (AKA) supplies pudendal nerve roots and conus medullaris. The aim of this study was to elucidate if there is any relationship between neurodegenerative changes of the Onuf nucleus (ON)–pudendal nerve ganglia complex secondary to vasospasm of the AKA after spinal subarachnoid hemorrhage (SAH).**

METHODS: **This study was conducted on 22 rabbits, which were randomly divided into 3 groups: control ($n = 5$), sham ($n = 5$), and spinal SAH ($n = 12$). Experimental spinal SAH was induced at the L2 level. After 2 weeks, the ON–pudendal nerve ganglia complex and AKA were examined histopathologically. Bladder volume values were estimated, and results were analyzed statistically.**

RESULTS: **Two animals died within the first week of experiment. Histopathologically, severe vasospasm of the AKA and neuronal degeneration and neuronal apoptosis were observed in the ON–pudendal nerve ganglia complex in 5 animals of the SAH group. The mean volume of the imaginary AKA, mean bladder volumes, and degenerated neuron densities of ON and pudendal nerve ganglia were estimated. We found that vasospasm of the AKA led to numerous neuron degenerations in ON and pudendal ganglia and consequently urinary retention ($P < 0.005$).**

CONCLUSIONS: **ON–pudendal nerve ganglia complex degeneration secondary to vasospasm of the AKA may be a cause of urinary retention after spinal SAH.**

INTRODUCTION

Spinal subarachnoid hemorrhage (SAH) is a devastating condition,[1] and the understanding of this pathology continues to evolve. Vasospasm after spinal SAH can lead to damage of the third and the second sensory neurons of the spinocortical sensory pathways and result in neurodegeneration of dorsal root ganglion (DRG).[1,2] Turkmenoglu et al.[1] and Ozturk et al.[3] investigated the complications from Adamkiewicz artery (AKA) vasospasm. Interruption of the AKA in spinal SAH leads to spinal cord ischemia and changes in DRG because the blood supply of the lower spinal cord is heavily dependent on this artery[1]; however, there is no study to our knowledge about the occurrence of urinary retention in spinal SAH with AKA vasospasm. Parasympathetic fibers arising from Onuf nucleus (ON) located in the conus medullaris and somatosensitive fibers of pudendal nerves are responsible for urination. In this study, the relationship between ON degeneration induced by spinal SAH, terminal spinal cord ischemia, and urinary retention was examined.

Key words
- Adamkiewicz artery
- Degeneration
- Onuf nucleus
- Pudendal nerve ganglion
- Spinal
- Subarachnoid hemorrhage
- Urinary retention
- Vasospasm

Abbreviations and Acronyms
AKA: Adamkiewicz artery
CSF: Cerebrospinal fluid
CT: Computed tomography
DRG: Dorsal root ganglion
ON: Onuf nucleus
SAH: Subarachnoid hemorrhage
VSI: Vasospasm index

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MATERIALS AND METHODS

This study was conducted on 22 adult male New Zealand rabbits (3.7 ± 0.4 kg) (Ataturk University, Erzurum, Turkey) that were randomly divided into 3 groups: control ($n = 5$), sham ($n = 5$), and spinal SAH ($n = 12$). The animal protocols were approved by the Ethics Committee of Ataturk University, Medical Faculty.

Experiment

The animals were anesthetized by subcutaneous injection of a mixture of ketamine hydrochloride (25 mg/kg), lidocaine hydrochloride (15 mg/kg), and acepromazine (1 mg/kg). X-rays obtained from a portable x-ray device were used to determine L2-3 levels. After the operative site was prepared, paravertebral muscles were dissected and L2 laminotomy was performed using a Midas Rex high-speed drill (Medtronic Midas Rex, Fort Worth, Texas, USA), and a curved needle was inserted into the subarachnoid space. After cerebrospinal fluid (CSF) aspiration, autologous auricular arterial blood (0.5 mL) was injected into the spinal subarachnoid space at the L2-3 level in the SAH group, and 0.5 mL serum saline was injected into the spinal subarachnoid space in the sham group with a 22-gauge needle. The animals in the control group were not subjected to this procedure. All animals were followed for 2 weeks and then sacrificed. Computed tomography (CT) was performed in all animals before and after the experiment, and bladder volumes were recorded. The bladder was accepted as nearly ellipsoid, and volume values were calculated using the following formula: $V = 4/3\ \pi abc$. In the 5 rabbits that had SAH, AKA vasospasms were not studied with CT scan or histopathologic methods. Volume of the AKA and vasospasm index (VSI) values were estimated by stereologic analyses.

Tissue Processing

The conus medullaris, bladder, and S2 DRG of all animals were removed for light microscopy analysis and were preserved in 10% formalin solution. Spinal cord arteries, arteriae nervorum of conus medullaris, and pudendal nerve roots and ganglia were examined histopathologically after staining by hematoxylin-eosin, neuron-specific enolase, and deoxyuride-5′-triphosphate biotin nick end labeling.

Stereologic Analyses

Histopathologic changes were investigated, and the VSI of the AKA and density of normal and degenerated neuron densities of ON and pudendal nerve ganglia were estimated. Neuronal shrinkage, perinuclear halo formation, cytoplasmic condensation, cellular angulation, and neuronal loss were assessed as neurodegeneration criteria of the ON–pudendal nerve ganglia complex. Stereologic analyses of histopathologic data were done according to the principles described previously.[4-6] Neuronal shrinkage, perinuclear halo formation, cytoplasmic condensation, cellular angulation, and neuronal loss were accepted as ganglion degeneration criteria. The stereologic method easily estimates the particle number; is readily performed and intuitively simple; is free from assumptions about the particle shape, size; and orientation; and is unaffected by overprotection and truncation. Two consecutive sections obtained from tissue samples with named references were mounted on each slide. Reference and look-up sections were reversed to double the number of dissector pairs without taking new sections. The mean numerical density of normal and degenerated neurons in the ON–pudendal nerve ganglia (Nv/GN) per cubic millimeter was estimated using the following formula:

$$Nv/GN = \Sigma Q - N/t \times A$$

Where $\Sigma Q-N$ is the total number of counted neurons appearing only in the reference sections; t is the section thickness, and A is the area of the counting frame. The Cavalieri volume estimation method was used to obtain the total number of neurons in each specimen. Total number of neurons was calculated by multiplication of the volume (mm^3) and numerical density of degenerated neurons in ON and pudendal nerve ganglia. To calculate the volumetric changes of the AKA as a result of vasospasm or vasodilation factors, we used the technique of Ozturk et al.[3] and Turkmenoglu et al.[1] All AKAs were assessed as a cylinder because of their morphologic characteristics, and simple geometric formulas were used to estimate their volumes. As a measure of the degree of vasospasm, AKA volume values were preferred to determining the degree of vasospasm.

A 3-dimensional cylindrical AKA model was created by the reconstruction of 7 consecutive histologic sections of each AKA. In the AKA model, the luminal radius is represented by "r," and the height is represented by "h." A 10-mm segment of AKA was evaluated as a standard model and was accepted as the height of the AKA. Geometric volume calculation methods were used in the reconstructed cylindrical AKA sample. The standardized AKA volume was calculated with the following formula:

$$V = \pi r^2 h$$

Endothelial swelling, luminal narrowing, and inner elastic membrane convolutions were accepted as AKA vasospasm criteria. VSI of the AKA was preferred over the measurement of lumen radius and volume values because the volume estimation method can be readily performed, is intuitively simple, is more reliable, is free from assumptions about vessel diameter of various segments, and is unaffected by overestimation error of radius values of the AKAs. The wall ring surface values were calculated using the following formula: $S1 = \pi R^2 - \pi r^2$. The lumen surface area was calculated using the same method: lumen surface value $(S2) = \pi r^2$. The VSI was calculated as the proportion of S1/S2; $VSI = S1/S2 = \pi R^2 - \pi r^2/\pi r^2 = \pi (R^2 - r^2)/\pi r^2 = R^2 - r^2/r^2$: $VSI = (R^2 - r^2 2)/r^2$.

Statistical Methods

The volumetric changes of the bladders were compared with the number of viable and degenerated neurons of ON, and pudendal nerve ganglia among groups using the 2-tailed t test. Nonparametric relationships were examined with Mann-Whitney U tests. $P < 0.05$ was considered significant.

RESULTS

Intestinal and bladder distention, paraparesis, spastic or flask gait disturbances, and limitations of tail movements were observed in some surviving animals of the SAH group. Within the first week,

2 rabbits in the SAH group died. In the remaining rabbits of the SAH group (n = 10), the following were observed: unconsciousness (n = 1; 10%), convulsion (n = 2; 20%), meningeal irritation signs (n = 2; 20%), bowel dysfunction and urinary retention (n = 7; 70%), and paraparesis (n = 1; 10%). Bladder and bowel dilation was also detected by CT scan postoperative CT scan or by necropsy. The CT appearance of a rabbit with SAH is shown in Figure 1A, a magnified CT appearance of a bladder is shown in Figure 1B, and the gross anatomic appearance of the bladder volume estimation method is shown in Figure 1C.

The mean volume of imaginary AKAs of the anterior median sulcus of L2-3 level was estimated as 1.170 $mm^3 \pm 0.270$ in the control group, 1.140 $mm^3 \pm 0.230$ in the sham group, and 0.890 $mm^3 \pm 0.110$ in the SAH group. Volume reduction of the AKA was significantly different between the SAH and other 2 groups ($P < 0.05$).

The VSI value of the AKA was 1.092 ± 0.70 in the control group, 1.87 ± 0.26 in the sham group, and 3.02 ± 0.172 in the SAH group. The differences between the degenerated neuron density of S2 DRG and VSI values was significant in the SAH group ($P < 0.005$). Demonstrable severe neurodegeneration was detected on pudendal nerve ganglia of animals with a high VSI in the SAH group. Comparison of the sham group versus control group for degeneration of pudendal nerve ganglia, ON, imaginary AKA volumes, and VSI values did not show a statistically significant difference ($P > 0.05$). In Figure 2A, the AKA is seen between nerve roots and spinal cord, and a magnified view of the AKA is seen in Figure 2B.

Histopathologically, notable severe vasospasm of conus medullaris artery branches and arteriae nervorum, neuronal degeneration, and neuronal apoptosis was observed in ON and DRG of the pudendal nerve ganglia in 5 rabbits in the SAH group. Figure 3A shows the macroscopic appearance of the spinal cord at the level of S2 with spinal nerve roots of the pudendal nerve with DRG including degenerated neurons. Figure 3B and C show degenerated pudendal nerve axons of an animal with SAH.

The mean bladder volumes and degenerated neuron densities of ON and pudendal nerve ganglia were estimated as 49 mL ± 6, 3 ± 1/mm^3, 12 ± 4/mm^3 in the control group; 56 mL ± 8, 15 ± 5/mm^3, 278 ± 91/mm^3 in the sham group; and 69 mL ± 7, 562 ± 97/mm^3, 4678 ± 946/mm^3 in the SAH group. We found that developing vasospasm of conus medullaris and arteriae nervorum of pudendal nerve roots causes numerous neuron degenerations in ON and pudendal ganglia and consequently urinary retention ($P < 0.005$).

Figure 4A shows ON which is the origin of pudendal parasympathetic fibers of a rabbit with SAH; Figure 4B and C show severe apoptosis of ON and pudendal ganglia of an animal with SAH. Finally, Table 1 summarizes our results.

DISCUSSION

SAH affecting the spinal cord is very rare, and may have disastrous consequences.[1] The AKA is the most important feeding artery of the thoracolumbar spinal cord, also known as the great anterior radiculomedullary artery.[3] Vasospasm of cerebral arteries is a

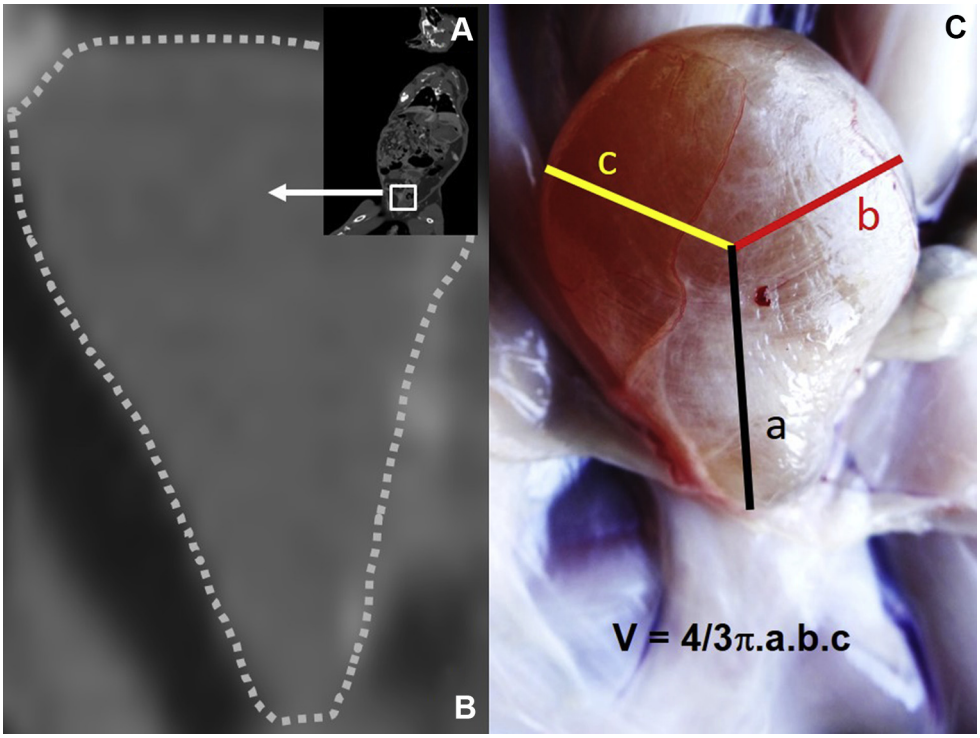

Figure 1. (**A**) Computed tomography appearance of a rabbit with subarachnoid hemorrhage. (**B**) Magnified computed tomography appearance of bladder. (**C**) Gross anatomic appearance of bladder volume estimation method.

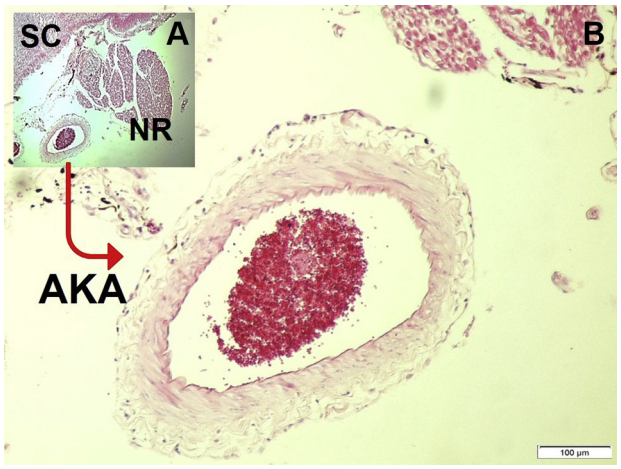

Figure 2. (**A**) Adamkiewicz artery (AKA) is seen between nerve roots (NR) and spinal cord (SC) on light microscopy (hematoxylin-eosin, ×4). (**B**) Magnified view of AKA on light microscopy (hematoxylin-eosin, ×10).

major complication of SAH. Vasospasm also occurs in extracerebral arteries. For example, Ozturk et al.[3] and Turkmenoglu et al.[1] reported that vasospasm of the AKA after spinal SAH leads to changes in DRG. Acute hypoperfusion of the AKA might lead to catastrophic ischemic complications resulting in paraparesis or paraplegia with urinary bladder dysfunction.[7]

In the present study, autologous auricular arterial blood (0.5 mL) was injected into the spinal subarachnoid space at level L2-3 in the SAH group; however, AKA vasospasms occurred in only 5 of the 10 specimens with SAH. It is difficult to explain why vasospasm occurred in only half of the rabbits. AKA variations may have an effect on the occurrence of vasospasm. We did not measure blood flow of the AKA in this experiment. In addition, urinary retention did not occur to the same degree in all animals; demonstrable apoptosis of ON and pudendal ganglia secondary to vasospasm of the AKA was observed in the SAH group (Figure 4B and C) group but not the other 2 groups. Apoptosis is an important issue in neurosurgery. Retrograde neuronal death is well established in DRG after peripheral nerve injury or severe spinal cord trauma.[8] Previously, Seraslan et al.[8] reported that SAH results in bloody CSF, and this bloody or highly proteinaceous CSF may lead to neural degeneration. The DRG is

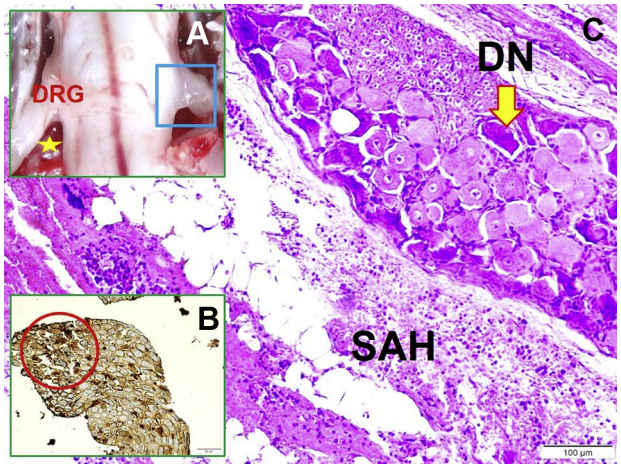

Figure 3. (**A**) Macroscopic appearance of the spinal cord at the level of S2 with spinal nerve roots of the pudendal nerve. (**B**) Degenerated pudendal nerve axons (in *red circle*) of an animal with subarachnoid hemorrhage (SAH) on light microscopy (deoxyuride-5′-triphosphate biotin nick end labeling, ×4). (**C**) Appearance of an animal with SAH including degenerated neurons (DN) on light microscopy (hematoxylin-eosin, ×10).

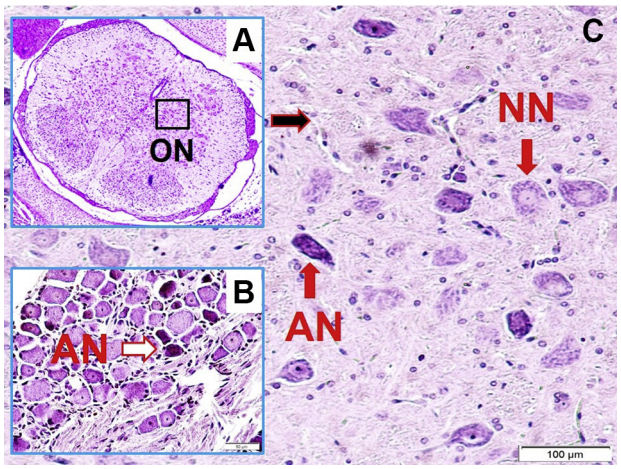

Figure 4. (**A**) Onuf nucleus (ON) which is the origin of pudendal parasympathetic fibers of a rabbit with subarachnoid hemorrhage, on light microscopy (S-100, ×4). (**B** and **C**) Severe apoptosis of ON and pudendal ganglia of an animal with subarachnoid hemorrhage on light microscopy (deoxyuride-5′-triphosphate biotin nick end labeling, ×10). NN, normal neurons; AN, apoptotic neurons.

Table 1. Summary of AKA and Bladdes Volumes, Normal and Degenerated Neuron Densities of ONs and PGs

	Control (Normal) Group	Sham Group	SAH Group
AKA volume, mm^3	1.170 ± 0.270	1.140 ± 0.230	0.890 ± 0.110
Bladder volume, mL	49 ± 6	56 ± 8	69 ± 7
NN/mm^3 in ON	6430 ± 320	6230 ± 295	5248 ± 196
DN/mm^3 in ON	3 ± 1	15 ± 5	562 ± 97
NN/mm^3 in PG	13,248 ± 1267	10,248 ± 1267	8248 ± 1267
DN/mm^3 PG	12 ± 4	278 ± 91	4678 ± 946
Dead animals	—	—	2

SAH, subarachnoid hemorrhage; AKA, Adamkiewicz artery; NN, normal neuron density; ON, Onuf nucleus; DN, degenerated neuron; PG, pudendal ganglion.

located between the dorsal root and the spinal nerve.[1] We induced SAH in 5 rabbits by injecting autologous blood into the L2-3 subarachnoid space and compared findings with animals that had nothing injected and animals that were injected with saline and found decreased volume of the lumen of the AKA in animals with SAH compared with the control animals as well as increased degeneration of ON and pudendal nerve ganglia in these animals. The finding of degeneration of ON and pudendal nerve ganglia may be a cause of urinary retention after spinal SAH with AKA vasospasm.

What Is the Mechanism?

Having broad knowledge of anatomy is essential for practicing neurosurgery. Certain anatomic structures call for detailed study because their functional importance.[1,9] One of these structures is the DRG.[1,9] The pudendal nerve ganglion is a DRG. Various authors have investigated the ganglion and neuronal cell changes after SAH.[9-16] DRG neurons convey somatosensory information from the urinary bladder to the central nervous system. The bladder is innervated by sympathetic autonomic motoneurons. These motoneurons are located in the upper lumbar spinal cord and innervate the bladder through ganglion cells in the sympathetic chain and the hypogastric nerve. It has been reported that a major function of the sympathetic bladder innervation is to decrease bladder pressure during the filling phase to limit the number of micturition episodes.[17] In contrast to the bladder itself, the external sphincter of the bladder consists of striated musculature. The parasympathetic bladder motoneurons innervating the sphincter are also located in the sacral spinal cord. This cell group was first described in 1899 by Onufrowicz and became as known as Onuf's nucleus.[18] ON motoneurons act continuously contract the pelvic floor muscles to close both the bladder and the anal sphincters.[19] Only when there is strong reason for the pelvic floor muscles not to contract (i.e., during micturition or defecation, and, at least in males, during sexual activity), the pelvic floor sphincters relax (i.e., only during these activities ON motoneurons have to be inhibited). Motoneurons in the ventrolateral ON innervate the bladder sphincter muscles, and dorsomedial ON motoneurons innervate the anal sphincter.[7,20,21] ON also contains motoneurons innervating other pelvic floor muscles, such as ischiocavernosus and bulbospongiosus. ON motoneurons represent a distinct class of motoneurons because, on one hand, they are somatic motoneurons innervating striated muscles and are under voluntary control, but on the other hand, they behave as autonomic motoneurons. Other autonomic motoneurons, including the parasympathetic bladder motoneurons, receive direct afferents from the paraventricular nucleus of the hypothalamus in some animals[22] as well as in humans.[23,24] In this study, we observed the neuronal degeneration and severe apoptosis of ON in some rabbits with SAH ($n = 5$) (**Figure 4**) Spinal SAH was induced at the L2-3 level in the present study, and bladder retention occurred by pudendal nerve ganglia and ON degeneration. DRG are sensitive to ischemia.[25] Can our results be explained by disturbance of the sacral micturition reflex? To our knowledge, there is no documentation of urinary retention or disturbance of the sacral micturition reflex caused by pudendal nerve ganglia and ON degeneration secondary to AKA vasospasm induced by spinal SAH. The first evidence for the existence of sacral micturition reflexes was provided by De Groat in 1975,[26] and De Groat et al.[27] observed in 1981 that micturition and defecation were elicited in kittens. This perineal-to-bladder reflex is quite prominent during the first 4 postnatal weeks, after which it becomes less effective and usually disappears at 7–8 weeks postnatally, the approximate age of weaning of kittens. Although there is a weak supraspinal bladder reflex present during this early postnatal period,[28] the perineal-to-bladder reflex is so prominent that thoracic cord transections of the spinal cord did not abolish it. Thus, the perineal-to-bladder reflex is a sacral cord reflex. After 7–8 weeks, the supraspinal bladder reflexes have replaced the perineal-to-bladder reflex. Transection of the spinal cord in older kittens or adult cats causes re-emergence of perineal-induced micturition within 1–2 weeks. In humans, this spinal cord reflex system is functionally nonexistent except in patients with spinal cord transection rostral to the sacral cord. Although pathways exist within the sacral cord in adult animals and humans that can produce bladder and sphincter contractions, they are usually not well coordinated and often dyssynergic. In bladder dyssynergia, when the bladder contracts, the sphincter contracts also, preventing micturition. In this study, we think that this dyssynergia and urinary retention probably occurred as a result of pudendal nerve ganglia and ON degeneration secondary to AKA vasospasm induced by spinal SAH.

Importance of the Present Study

Occlusion or acute hypoperfusion of the AKA might lead to catastrophic ischemic complications resulting in paraparesis or paraplegia.[29] Such a complication, particularly during anterior or minimally invasive approaches, after otherwise successful spinal surgery is devastating for both the patient and the physician.[1] An understanding of the vascular supply of the pudendal nerve ganglia and ON and spinal cord is required to an understanding of the pathogenesis of such complications. It is well known that the AKA supplies the terminal spinal cord and that this part of the spinal cord includes the sacral parasympathetic ON and somatosensitive motor innervation network of the urinary bladder.

Our study shows that the AKA has clinical and surgical importance for urinary retention. Vasospasm is a major source of morbidity and mortality after SAH,[30] and this subject has been of substantial research interest.[14,16,31] It was previously reported that vasospasm after SAH affecting upper sensory pathways may lead to degeneration in DRG neurons at the C3 level.[16] It is well known that the lumbosacral plexus derives its blood supply from a single artery described in 1882 by Adamkiewicz.[2] It is a single artery, and it is unique to investigate the ischemic changes in sacral area.

Previously, it was reported that SAH results in bloody CSF, and this bloody or highly proteinaceous CSF may lead to neural degeneration.[8] Edema of the spinal cord and increased intramedullary pressure may be other causes. Entrapment, tumors, trauma, and various surgical procedures may be potential causes of lower spinal cord, ON, and pudendal nerve ganglia degeneration. In the present study, AKA vasospasm led to damage of the third and the second sensory neurons of the spinocortical sensory pathways, and resulted in ON and pudendal nerve ganglia neurodegeneration. Our observation of severe apoptosis in the rabbits of the SAH group, but not in the sham and control groups, adds another mechanism for

neurodegenerative changes in DRG. AKA vasospasm is responsible for these changes.

Figure 3 shows the macroscopic appearance of the spinal cord at the level of S2 with spinal nerve roots of the pudendal nerve with DRG including degenerated neurons, specifically degenerated pudendal nerve axons, in an animal with SAH. Figure 4A and Figure 4B shows severe apoptosis of ON and pudendal ganglia of an animal with SAH. We know that the AKA has clinical and surgical importance and that surgical procedures are associated with the risk of serious neurologic damage of the AKA. The blood supply to the roots of lumbar and sacral DRG are predominantly from the AKA. The AKA also supplies a considerable part of the spinal cord and is of great functional importance. Our results indicate that the arterial supply of ON and pudendal nerve ganglia and spinal cord by the AKA is crucial.

The balance between cell proliferation and cell death is crucial in all tissues, particularly in the nervous system. In this study, neurodegeneration of animals with AKA vasospasm developed that were not observed in the animals in the sham and control groups. Using the rabbit in study of AKA ischemic injury has technically some advantages over the use of other animals, such as the mouse or rat, because of the bodily proportions of these 2 species; some studies question the presence of the AKA in rats.[32] The medullary cone of the rabbit is made up of 9 segments with a total length of approximately 30.0 mm. It begins with a transverse diameter of 5.0 mm and tapers caudally to 1.0 mm at its terminal end. In the lumbar region, L2 has the greatest size (11.0 mm) among both the spinal cord as a whole and the lumbar region, then the sizes gradually decrease.[33] The surgical procedures are associated with the risk of serious damage of AKA. Knowledge of neurodegeneration of ON and pudendal nerve ganglia and urinary retention as a result of AKA vasospasm is important. Our experimental rabbit model represents the first study of this causal association of AKA vasospasm and ON and pudendal nerve ganglia degeneration and urinary retention in spinal SAH. Our results show that the arterial supply of ON and pudendal nerve ganglia by the AKA is crucial for bladder function. Therefore, it is important to identify the AKA to minimize the risk of urinary complications during surgical approaches in the lumbar area.

Limitations

The present study has several limitations. This is an experimental, observational study in rabbits, and the relationship between AKA vasospasm and ON and pudendal nerve ganglia degeneration could occur in humans as well. Perhaps the most important limitation of this study is that these changes are not seen in vivo or at autopsy, particularly in humans with spinal SAH. No motor functional testing was done because the aim of this study was not to show the motor dysfunction following spinal SAH in rabbits. Another important limitation is that our experimental rabbit model of SAH may not accurately mimic the human disease process.[1,3,34] However, our study may be a model for AKA injury during thoracolumbar spinal surgery. Lumbar nerve root blocks and epidural steroid injections are frequently studied in the management of degenerative conditions of the lumbar spine.[35] In evaluating the importance of our findings, urinary and sexual dysfunction, paraplegia, and paraparesis complicating lumbar nerve root blocks and epidural steroid injections must be borne in mind. Another important aspect of our study is that it brings attention to the occurrence of urinary retention secondary to AKA vasospasm by ON and pudendal nerve ganglia degeneration. The recognition of this fact may be important if one is the first to report new finding and that new finding is of value.[36-38]

CONCLUSIONS

The present study shows that the interruption of the AKA by vasospasm may lead to ON and pudendal nerve ganglia degeneration. Urinary retention can occur as a result. Our results are important for understanding the neuropathophysiologic mechanism of bladder distention after spinal SAH. Documenting AKA vasospasm in this situation can aid in the planning of future experimental and clinical studies and determining the clinical importance of this artery.

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