Article published online: 2022-09-20

ORIGINAL ARTICLE

First report of important causal relationship between the Adamkiewicz artery vasospasm and dorsal root ganglion cell degeneration in spinal subarachnoid hemorrhage: An experimental study using a rabbit model

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ABSTRACT

Background: The blood supply of the lower spinal cord is heavily dependent on the artery of Adamkiewicz. The goal of this study was to elucidate the effects of lumbar subarachnoid hemorrhage (SAH) on the lumbar 4 dorsal root ganglion (L4DRG) cells secondary to Adamkiewicz artery (AKA) vasospasm.

Materials and Methods: This study was conducted on 20 rabbits, which were randomly divided into three groups: Spinal SAH ($n = 8$), serum saline (SS) (SS; $n = 6$) and control ($n = 6$) groups. Experimental spinal SAH was performed. After 20 days, volume values of AKA and neuron density of L4DRG were analyzed.

Results: The mean alive neuron density of the L4DRG was 15420 ± 1240/mm^3 and degenerated neuron density was 1045 ± 260/mm^3 in the control group. Whereas, the density of living and degenerated neurons density were 12930 ± 1060/mm^3 and 1365 ± 480/mm^3 in serum saline (SS), 9845 ± 1028/mm^3 and 4560 ± 1340/mm^3 in the SAH group. The mean volume of imaginary AKAs was estimated as 1,250 ± 0,310 mm^3 in the control group and 1,030 ± 0,240 mm^3 in the SF group and 0,910 ± 0,170 mm^3 in SAH group. Volume reduction of the AKAs and neuron density L4DRG were significantly different between the SAH and other two groups ($P < 0.05$).

Conclusion: Decreased volume of the lumen of the artery of Adamkiewicz was observed in animals with SAH compared with controls. Increased degeneration the L4 dorsal root ganglion in animals with SAH was also noted. Our findings will aid in the planning of future experimental studies and determining the clinical relevance on such studies.

Key words: Adamkiewicz artery vasospasm, dorsal root ganglion, spinal subarachnoid hemorrhage

Access this article online	
Quick Response Code:	Website: www.asianjns.org
	DOI: 10.4103/1793-5482.145572

Introduction

Subarachnoid hemorrhage (SAH) may arise due to trauma or spontaneously.[1,2] It is a devastating pathology.[3,4] Vasospasm

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How to cite this article: Turkmenoglu ON, Kanat A, Yolas C, Aydin MD, Ezirmik N, Gundogdu C. First report of important causal relationship between the Adamkiewicz artery vasospasm and dorsal root ganglion cell degeneration in spinal subarachnoid hemorrhage: An experimental study using a rabbit model. Asian J Neurosurg 2017;12:22-7.

following SAH is still a significant underlying cause of morbidity and death following SAH.[5,6] More than one-third of patients with SAH develop clinically significant vasospasm.[7,8] For that reason, the exact mechanisms of vasospasm remains to be an important subject. It was reported that interruption of bilateral segmental arteries at the level of Adamkiewicz artery (AKA) risks producing ischemic spinal cord (SC) dysfunction in a dog model.[8] Kato *et al*. reported that interruption of bilateral segmental arteries at >=4 consecutive levels including the level of Adamkiewicz artery risks producing ischemic spinal cord dysfunction[9]. However, Murakami *et al*. found that interruption of the artery of Adamkiewicz for total en bloc spondylectomy did not adversely affect neurologic function.[10] In this study, we investigated histopathological feature of L4 dorsal root ganglion following spinal SAH, because ganglionary neuron cell changes of this entity were investigated various authors.[1,11-13] It is well-known that spinal SAH is a rare event.[14] Unfortunately, clinical trials have mostly been disappointing, predominantly unable to prevent ischemic damage and improve patient outcome.[15] The vasospasm following spinal SAH can lead to damage of the third and the second sensory neurons of the spino-cortical sensory pathways, and result in neurodegeneration of DRG. Upper cervical ganglions innervate the anterior superior alveolar by vasodilating effects,[16] so that ischemic injuries of these structures secondary to SAH may lead to anterior spinal artery vasospasm.[17] Kanat *et al*. also reported that anterior spinal artery vasospasm after SAH may lead to degeneration in DRG neurons at C3 level.[13] The lumbosacral plexus derives its blood supply from a single artery described in 1882 by Adamkiewicz,[18] and the blood supply of the lower SC is heavily dependent on this artery, but the effects of vasospasm, as a cause of ischemia, of the artery of Adamkiewicz following spinal SAH have not been studied yet. The aforementioned artery is of enormous clinical and surgical importance. We investigated the effect of AKA vasospasm following spinal SAH on the L4DRG.

Materials and Methods

This study was conducted on 20 male rabbits, which were randomly divided into three groups: Spinal SAH ($n = 8$), serum saline (SS) (SS; $n = 6$) and control ($n = 6$) groups. The animal protocols were approved by the Ethics Committee of Erzurum Ataturk University, Medical Faculty. The animals were anesthetized by subcutaneous injection of a mixture of ketamine hydrochloride (25 mg/kg), lidocaine hydrochloride (15 mg/kg), and acepromasine (1 mg/kg). After the occipito-cervical region was prepared, autologous blood (0.5 mL) was taken from the auricular artery and injected into the spinal subarachnoid space at the level L1 in the SAH group, and 0.5 mL SS injected to spinal subarachnoid space of SS groups with a 22-gauge needle. Prior to injecting 0.5 cc of saline, 0.5 cc of blood was removed from the SS group. The animals in the control group were not subjected to this procedure. All animals were followed-up for 20 days and sacrificed. For the light microscopic analysis, these materials were preserved in 10% formalin solution. Their lumbar DRGs at the L4 level were removed. AKA and lumbar 4 dorsal root ganglion (L4DRG) were examined histopathologically after stained by hematoxylin and eosin and tunel. Histopathological changes were investigated and the density of normal and degenerated neurons of L4DRG was calculated. Neuronal shrinkage, perinuclear halo formation, stoplasmic condensation, cellular angulation and neuronal loss were accepted as ganglionary degeneration criteria.

Stereological analyses of histopathological data were made by according to the principles described previously.[19-20] To obtain an estimation of the total degenerated neuron number, we used the two-dimensional dissector technique. A counting frame was placed on a monitor, and the sampled area was selected by a systematic uniform random manner via the dial indicator controlled specimen stage. Physical dissector method was used to evaluate the numbers of degenerated and live neurons of L4DRG cells. Two consecutive sections (dissector pairs) obtained from tissue samples with named reference were mounted on each slide. Reference and look-up sections were reversed in order to double the number of dissector pairs without taking new sections. The mean numerical density of neurons of L4DRG cells/mm^3 was estimated using the following formula;

$$NvGN = \Sigma \bar{Q} N / txA$$

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. 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 neurons in each L4DRG.

To calculate the volumetric changes of the AKA due to vasospasm or vasodilatation factors, a three-dimensional cylindrical AKA model was created by the reconstruction of seven consecutive histological sections of each AKA. In the AKA model, the luminal radius is represented by "r", and the height is represented by "h." 10 mm segment of AKA was evaluated as a standard model and it accepted as the height of AKA. Geometrical volume calculation methods were used in the reconstructed cylindrical AKA sample. The standardized AKA's volume was calculated with the following formula:

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

Adamkiewicz arterys vasospasm index (VSI) was preferred over the only measurement of lumen radius and volume values because the volume estimation method can be readily performed, is intuitively simple, more reliable, 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 as the following formula: S1 = πR12 - πr12. The lumen surface area was calculated as the same method. So, lumen surface value (S2) = πr12. The VSI was calculated as the proportion of S1/S2. VSI = S1/S2 = πR12-πr12/πr12 = π(R12-r12)/πr12 = R12-r12/r12: VSI = (R2 - r2)/r2.

Statistical methods

The volumetric changes of the AKA, alive and degenerated neuron number of L4DRG were compared between groups using two-tailed *t*-test. Nonparametric relationships were examined with Mann-Whitney U-tests. $P < 0.05$ was considered as significant.

Results

In the SAH group, bowel and bladder dysfunctions occurred in the majority of the animals, but this was not quantified. Figure 1 shows a normal appearance of a rabbit SC, AKA at the level of L1 vertebra. Histopathological appearance of AKA of a rabbit with and without SAH was shown in Figures 2 and 3. In histopathological examinations of L4DRG revealed degenerated and normal neurons [Figure 4a and b]. Demonstrable severe apoptosis were detected in the animals of SAH group. Normal motor neurons and degenerated motor neurons (left upper corner) at the Onufs' nucleus are seen at the L4DRG ganglion of an animal with SAH in Figure 5.

The mean alive neuron density of the L4DRG was 15420 ± 1240/mm^3 and degenerated neuron density was 1045 ± 260/mm^3 in the control group. Whereas, the density of living neurons was 12930 ± 1060/mm^3 and degenerated neuron density was in 1365 ± 480/mm^3 for the SS group. Neuron density of L4DRG was 9845 ± 1028/mm^3 and degenerated neuron density was 4560 ± 1340/mm^3 in the SAH group and hence we found that numerous neuron degenerations secondary to vasospasm of AKA at the L4DRG in the SAH group, but not in serum saline and control groups [Tables 1 and 2]. Vasospasm of AKA was also not occurred in SS and control groups. The density of living neuron was statistically significantly reduced in the SAH group compared with the control and Serum saline (SS) groups ($P < 0.05$).

The mean inner radius values of AKA was measured as 0.653 ± 0.102 mm at the entering point of the anterior median sulcus of L1 level. The mean volume of imaginary AKAs was estimated as 1.250 ± 0.310 mm^3 in the control group and 1.030 ± 0.240 mm^3 in the SF group and 0.910 ± 0.170 mm^3 in SAH group. Volume reduction of the AKAs was significantly different between the SAH and other two groups ($P < 0.05$). The VSI values of AKA was 1.042 ± 0.60 in control group, 1.75 ± 0.30 in SF and 2.98 ± 0.160 in SAH group. The differences between the degenerated neuron density of L4DRG and VSI values was meaningful in SAH group ($P < 0.005$). Demonstrable severe apoptosis was detected on DRG of animals with high VSI in SAH group. Apoptotic degeneration of AKA was also noted especially in animals with massive SAH. Comparison for the SS group versus controls for the DRG, AKA volumes, and VSI values were not showed statistically significant difference ($P > 0.05$).

Discussion

Subarachnoid hemorrhage affecting the SC is very rare, and may have disastrous consequences. The DRG is located between the dorsal root and the spinal nerve. It contains pseudounipolar neurons that convey sensory information from the periphery to the CNS.[21] These neurons are of two main types: Nonnociceptive neurons that respond to nonnoxious, low intensity, normally nonpainful stimuli; and nociceptive neurons that respond to noxious, high intensity, normally painful stimuli.[22] Ventral root afferent that causes pain in the ventral root of the spinal nerve comes from dorsal root ganglia, forms a loop, goes into the ventral root, and then goes back to the spinal cord, and this may be the reason why pain was not relieved even after posterior rhizotomy. The chronic compression of the DRG or nearby nerve roots after vertebral injuries, intervertebral disc herniation, or intervertebral foramen stenosis is an important factor causing lower back pain and sciatica,[21,23] so thorough knowledge of the ischemic neurodegenerative changes of the L4DRGs in this study may also be meaningful for understanding of pathologic anatomy in degenerative disorders.

The reason of preferring lumbar 4 dorsal root ganglion in this study

A series of detailed studies showed that the ventral portion of the rat L5-L6 intervertebral discs is innervated predominantly by the L1 and L2 DRG,[24] whereas the dorsal portion of the L5-L6

Table 1: The mean alive and degenerated neuron density of the L4DRG of three groups

Groups	Alive neuron density mean±SD	Degenerated neuron density mean±SD
SAH (*n*=8)	9845±1028	4560±1340
Control (*n*=6)	15420±1240	1045±260
Saline (*n*=6)	12930±1060	1365±480

SD – Standard deviation; SAH – Subarachnoid hemorrhage; L4DRG – Lumbar 4 dorsal root ganglion

Table 2: The mean inner radius values of AKA and VSI values of groups

Groups	Volume (mm^3) mean±SD
SAH (*n*=8)	0.910±0.170
Control (*n*=6)	1.250±0.310
Saline (*n*=6)	1.030±0.240

SAH – Subarachnoid hemorrhage; AKA – Adamkiewicz artery; VSI – Vasospasm index; SD – Standard deviatiion

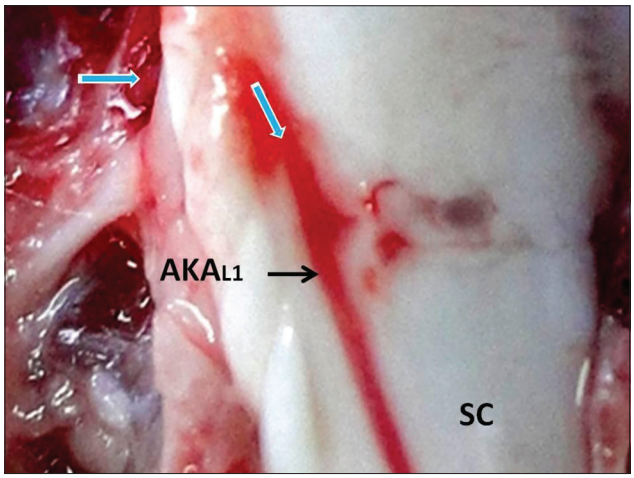

Figure 1: Adamkiewicz artery is seen in a normal rabbit at the L1 level (AKA-Adamkiewicz artery; SC-spinal cord)

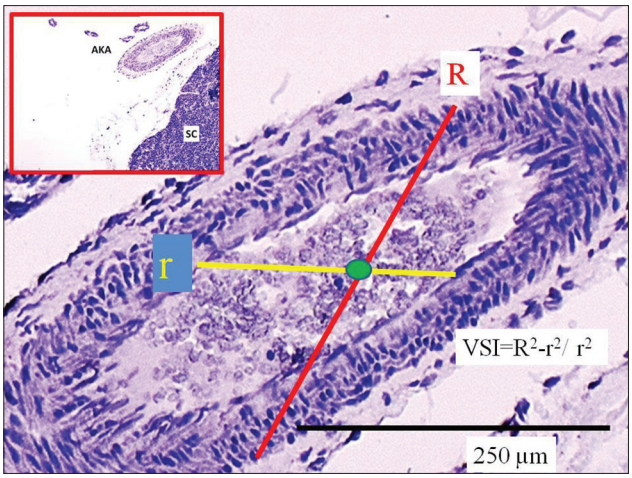

Figure 2: Histopathological appearance of an Adamkiewicz artery in a normal rabbit (light microscopic, tunnel stain, ×100)

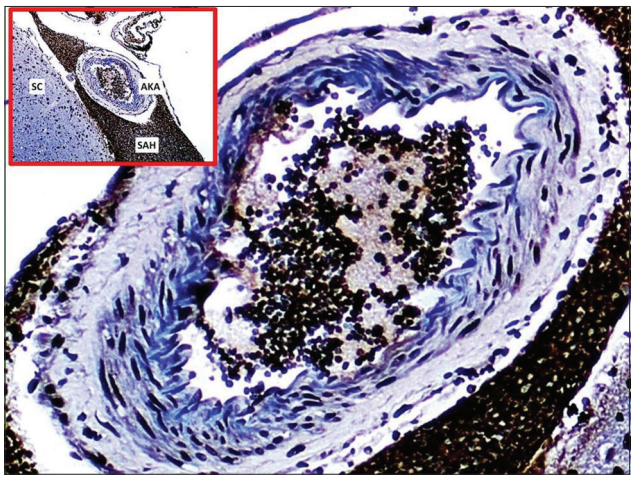

Figure 3: Histopathological appearance of an Adamkiewicz artery (AKA) in a rabbit with subarachnoid hemorrhage. Vasospastic inner elastic lamina of AKA, slight apoptotic changes at the endothelial cells and muscular cells are seen (light microscopic, tunnel stain, ×100)

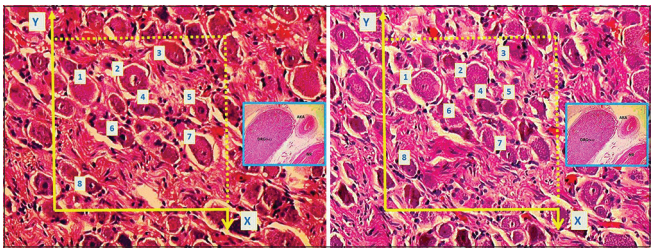

Figure 4: (a and b) L4: Spinal ganglion of a rabbit. The nucleoli marked with "2–6" are dissector particles on A section as it disappeared section B. The nucleoli marked with"1, 7, 8" not dissector particles on A section as it disappeared section B (H and E, 40, light microscopic). At the right side, L4 spinal ganglia, nerve root and Adamkiewicz artery are seen. Degenerated and normal neurons are observed at the L4 neurones. (LM, H and E, ×20)

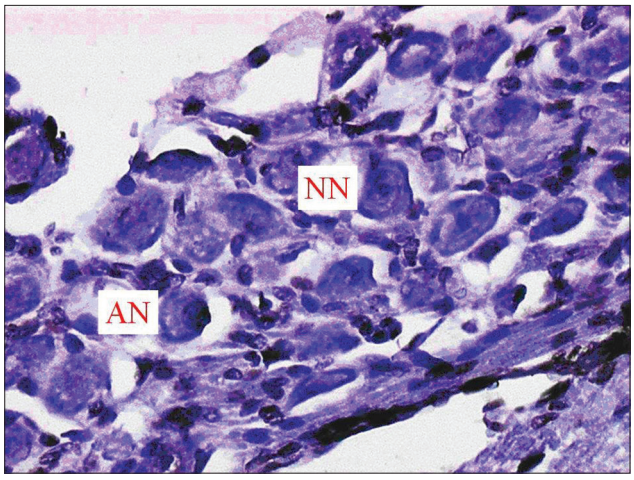

Figure 5: Apoptotic ganglion neurons are observed at the L4 nerve root ganglion (light microscopic, tunnel stain, ×40)

disc is innervated extensively by the L1-L6 DRG.[25] For that reason, we preferred to perform spinal SAH at L1 level in this study and examined histopathologic changes of L4DRG. We found that demonstrable severe apoptosis occurred in rabbits of SAH group [Figure 5], not other two groups. Retrograde neuronal death is well established in DRG after peripheral nerve injury or severe SC trauma.[14,26] Previously, it was reported that SAH results in bloody cerebrospinal fluid (CSF), and this bloody or highly proteinous CSF may lead to neural degeneration,[26] but the effect of vasospasm following SAH on DRG degeneration has not been investigated to date. Our study shows that spinal SAH with AKA vasospasm is another cause of neurodegeneration in the DRGs.

Importance of the present study

We induced SAH in eight rabbits by injecting autologous blood into the lumbar subarachnoid space, and compared findings with animals who had nothing injected as well as rabbits who were injected with saline, and found decreased volume of the lumen of the artery of Adamkiewicz in animals with SAH compared with controls, as well as increased

degeneration of the DRG in these animals. We also noted apoptosis in animals of SAH group. Results of this study may be due to ischemia or vasospasm in AKA. Edema of the cord and raised intramedullary pressure may be other responsible causes. We assumed that vasospasm of the AKA leads to these changes in rabbits. The model used by us would have value in cases of spinal SAH that is very rare. The spinal SAH may occur by trauma or vascular lesions. We know that minimal invasive surgery and anterior surgery, which do not usually produce spinal SAH, but AKA vasospasm following spinal SAH noted in this study, may be a model for AKA injury during thoraco-lumbar spinal surgical procedures. Lumbar nerve root blocks and epidural steroid injections are frequently studied in the management of degenerative conditions of the lumbar spine.[27] In evaluating the significance of our observations, paraplegia and paraparesia complicating lumbar nerve root blocks and epidural steroid injections must be borne in mind. The factors responsible for this disaster should be clarified. Houten and Errico proposed that the mechanism for this rare but devastating complication is the concurrence of two uncommon circumstances, the presence of an unusually low origin of the artery of Adamkiewicz and an undetected intraarterial penetration of the procedure needle.[27] Acute hypoperfusion of AKA might lead to catastrophic ischemic complications resulting in paraparesis or paraplegia.[28] Such a complication, particularly, during anterior or minimally invasive approaches, after otherwise successful spinal surgery is a devastating complication for both patient and physician. We think that the pathogenesis of such complications requires an understanding of the vascular supply of the DRG and spinal cord. AKA occlusion may result in severe neurological deficit.[10] Our study shows that AKA has clinical and surgical importance. It is hoped that our observations will not discourage clinicians from using lumbar nerve root blocks and epidural steroid injections for the relief of pain in properly selected patients. However, until morphological detail concerning the damage done to AKA in human patients is available, it would seem prudent not to apply lumbar nerve root blocks and epidural steroid injections at the upper lumbar level, especially on the left side. Because AKA originates between T9 and L2 on the left side in 85% of people.[29] At present, neurosurgical practice is confronted by an explosion of technology,[30,31] but SAH is still a devastating condition,[16,4] so it is possible that recent advances in magnetic resonance angiography and computed tomography angiography may lead to changes in the detectability of this artery before surgical approaches in this area. Casual association of the AKA vasospasm and L4 dorsal root ganglion cell degeneration in spinal SAH was first-time studied in an experimental rabbit model. Our results mean that the arterial supply of L4DRG by AKA crucial.

Limitation of the study

Several limitations of this study deserve mention. Stereologic methods were used for the determination of degenerative changes of the L4DRG cells. We know that spinal SAH is a rare entity. An estimate of the number of live or degenerated neurons in each specimen was the basis of our results. It was noted that there is a direct link between degeneration of L4DRG and AKA vasospasm. We strictly emphasize that this is an experimental, observational study, and the relationship between AKA vasospasm and degeneration L4DRG has first-time been reported in rabbits by us, and they can be inhuman too. Perhaps the most important limitation of study, it is not possible to see these changes *in vivo* or autopsy, particularly in man with spinal SAH. Another limitation is that our experimental rabbit model of SAH may not accurately mimic the human disease process. For that reason, our experimental rabbit model cannot be represent a human SAH model. In addition, blood was injected at the same lumbar level (L1) in each rabbit, but the AKA is often variable. Lumbar spine SAH in the human is a rare happenstance and does not often cause paraplegia when it does occur. We stated that SAH-animals had bowel and bladder dysfunction, but this was not quantified. No motor functional testing was done because the aim of this study is not to show the bowel and bladder dysfunction and motor deficit following spinal lumbar SAH in rabbits.

Conclusion

In this study, neurodegeneration of animals with AKA vasospasm was occurred which were not observed in animals in SS and control groups. The balance between cell proliferation and cell death is crucial in all tissues, particularly in the nervous system and DRG. Several studies have examined the occurrence of medical complication after spine surgery. Identification of risk factors can be beneficial to spinal surgeons. Our results show that AKA vasospasm with spinal SAH leads neurodegeneration of L4DRG, which was first-time reported. Knowledge of this neurodegeneration of L4DRG cells by the AKA vasospasm may be important in reducing the risk of paraplegia or paraparesis, disturbances of urination and defecation, and impairment of pain and temperature sensations following lumbar spinal surgery. In addition, documenting such an irreversible ischemic neuron degeneration of the L4DRG with AKA vasospasm will aid in the planning of future experimental studies and determining the clinical importance of this artery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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