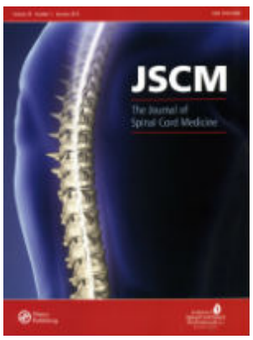

The Journal of Spinal Cord Medicine

ISSN: 1079-0268 (Print) 2045-7723 (Online) Journal homepage: https://www.tandfonline.com/loi/yscm20

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To cite this article: Selim Kayaci, Mehmet Dumlu Aydin, Baris Ozoner, Tayfun Cakir, Orhan Bas & Sare Sipal (2019): Relationship between subarachnoid and central canal hemorrhage and spasticity: A first experimental study, The Journal of Spinal Cord Medicine, DOI: 10.1080/10790268.2019.1669956

To link to this article: https://doi.org/10.1080/10790268.2019.1669956

Published online: 24 Oct 2019.

Research Article

Relationship between subarachnoid and central canal hemorrhage and spasticity: A first experimental study*

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Objective: Spastic disorders are considered as important cerebral complications of subarachnoid hemorrhage (SAH). However, there has been no research concerning the pathophysiological mechanism of its link with the spinal cord. The present study aimed to assess the relationship between the development of spasticity and neuronal degeneration after SAH and increase in spinal cord pressure after central canal hemorrhage (CCH).
Participants: Twenty-three rabbits were included.
Outcome measures: Of all rabbits, 5, 5, and 13 were allocated in the control, SHAM and study groups, respectively. Moreover, 1 cc of saline and 1 cc of autologous arterial blood were injected into the cisterna magna of the SHAM and study groups, respectively. The Muscle spasticity tension values (MSTVs) were determined according to the modified Ashworth scale. Degenerated neuron densities (DND) in the gray matter (GM) of each animal's spinal cord were stereologically calculated.
Results: The average MSTV of each group was as follows: control group (n = 5) 2; SHAM group (n = 5) 3-5; and study group (n = 13) 8–10. The DND values of the spinal cord of each group were as follows: control group, 2 ± 1/mm^3; SHAM group, 12 ± 3/mm^3; and study group, 34 ± 9/mm^3. Results showed an important linear relationship between the MSTVs and the DND of the spinal cord ($P < 0.001$).
Conclusion: Spasticity may be attributed to other causes such as ischemic neurodegenerative process that develops after spinal SAH and the de-synchronization of the flexor-extensor muscles due to the spontaneous discharge of interneuronal structures, which are crossed within the spinal cord owing to the build-up of pressure after CCH.

Keywords: Spasticity, Spinal cord injury, Subarachnoid hemorrhage, Central canal, Stereology

Abbreviations

SAH: subarachnoid hemorrhage; CCH: central canal hemorrhage; MSTV: muscle spasticity tension value; DND: degenerated neuron density; GM: gray matter; SCI: spinal cord injury; CCS: central cord syndrome; CSF: cerebrospinal fluid; LP: lumbar puncture; DRG: dorsal root ganglion.

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*This study was presented as an oral poster presentation at the Turkish Neurosurgical Society, 32th Annual Meeting in Antalya, Turkey and was accepted among the year's reports.

Color versions of one or more of the figures in the article can be found online at www.tandfonline.com/yscm.

Introduction

Spasticity is defined as muscle hypertonia that is characterized by muscle resistance, which increases in response to an externally applied movement that occurs when the muscle is tighter than its threshold level or rotation angle.[1] Such condition is a characteristic of upper motor neuron syndrome.[2] Clinically, this phenomenon refers to increased muscle tone, and widened reflex areas with increased deep tendon reflexes and clonus and is characterized by an increase in muscle resistance

DOI 10.1080/10790268.2019.1669956

in response to passive muscle tension.[3] It is an isokinetic movement disorder. Unlike that noted in hyperkinetic disorders (such as dystonia or chorea) the amount of movement does not increase.[3] This condition is distinguished from rigidity based on the speed of muscle tension and its correlation to the existence of other positive upper motor neuron symptoms.[4]

Pathologies such as ischemic or traumatic spinal cord damage, brain trauma, multiple sclerosis, cerebral palsy, and Parkinson's disease, may cause spasticity.[2] Although the etiologies are different, increased peripheral muscle tone secondary to increased alfa-motor neuron activities is commonly observed in these outcomes.[2]

The combined excitatory and inhibitory effects at the level of alpha motor neurons and spinal interneurons result in normal resting muscle tone and activity at appropriate levels.[5] Thus, pathology in all cerebral or spinal spasticity mechanisms can involve an imbalance in the excitatory and inhibitory mechanisms. Because spasticity is caused by lesions in the pyramidal and extrapyramidal pathways, the pathophysiology changes according to the location of the lesion although it generally develops in the antigravity muscles.[6]

A significant proportion of patients with spinal cord injury (SCI) develop spasticity.[7,8] Numerous mechanisms have been proposed regarding the incidence of spasticity after SCI.[2,9–15] However, studies about the relationship between neurodegenerative changes in the spinal roots after SAH and increasing spinal cord pressure after CCH with spasticity have not been conducted. In this study, we induced spinal SAH and CCH by passing blood via central canal. We assessed the relationship between ischemia in the spinal nerve roots and increased spinal cord pressure with spasticity. In relation to this, the present study first contributed important data to the literature.

Methods

Experimental design

Male New Zealand rabbits (n = 23; 3.8 ± 0.4 kg) were used in this study. Five rabbits were allocated in the control group and five into SHAM group. The remaining rabbits (n = 13) were included in the SAH and CCH study groups. The ethics review board of Atatürk University approved the study. The animals were anesthetized via intramuscular injection of a mixture of ketamine hydrochloride (25 mg/kg), lidocaine hydrochloride (15 mg/kg) and acepromazine (1 mg/kg). Moreover, 1 cc of saline was injected into the cisterna magna of the SHAM group and 1 cc of autologous arterial blood collected from the auricular artery was injected into cisterna magna of the study group (see

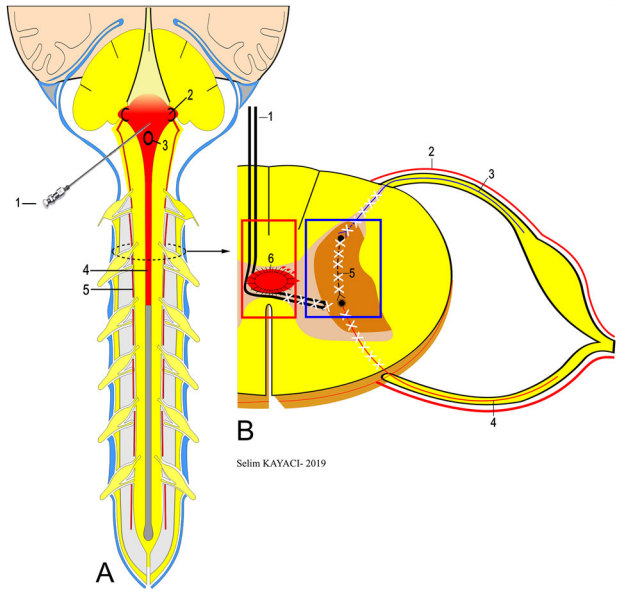

Figure 1 (A) See the schematic drawing for the experimental procedure. (1) Blood injection into the Cisterna Magna, (2) Foramen Luschka, (3) Foramen Magendi, (4) CCH (5) SAH. (B) (1) Corticospinal tract, (2) SAH (3) dorsal root (sensory neuron), (4) anterior root (motor neuron), (5) disconnection between the motor neuron, sensory neuron and interneuron (blue frame), and (6) CCH and stretch of the corticospinal tract (red frame). CCH: central canal hemorrhage; SAH: subarachnoid hemorrhage. Figure drawn by Selim Kayaci.

Fig. 1(A)). No treatment was provided to the rabbits in the control group. The rabbits were monitored for 2 weeks and were sacrificed while under general anesthesia. After cervicothoracic skin cleansing, total laminectomy + bilateral foraminotomy was performed. The Midas Rex, a high-speed drill, (Medtronic Midas Rex, Fort Worth, Texas, USA) was used in this process. The spinal cord, spinal nerve, root, ganglions and dura of all rabbits were removed.

Evaluation of spasticity

The modified Ashworth scale was used in this process.[16] The MSTVs of all animals were measured and recorded three times a week. The animals were graded on a scale of 0–10. In the application of this test, all animals were placed in supine position and measurements were performed on all four extremities. First, each front leg was brought to flexion separately. While the joint was at maximum flexion, the leg was brought to maximum extension in approximately one second. If the muscle tested was an extensor, the joint was brought to maximum extension and then to maximum flexion in 1 s. This process was repeated in the back legs. The resistance encountered was scored as follows:

No increase in tonus 0; slight increase in tone providing a catch and release, or minimal increase in resistance

at the end-range, when the limb is moved in flexion or extension, 1; slight increase in tone providing a catch, followed by minimal resistance throughout the remainder of the range of motion, 1^{+}; significant increase in tone in most range of motion, but only affected parts are easily moved, 2; considerable increase in tone, difficult passive movement and restricted joint range of motion, 3; and rigid affected parts during flexion or extension, 4.

The average MSTV (M_{MSTV}) values of each rabbit were calculated according to the formula below:

$$M_{MSTV}(E_1 + E_2 + E_3 + E_4)/€,$$

where E is the MSTV of each extremity, and € represents the number of extremities (n = 4). The total M_{MSTV} value was represented by Q.

$Q = (M^{1}_{MSTV} + M^{2}_{MSTV} + M^{3}_{MSTV} + M^{4}_{MSTV} + \ldots M^{x}_{MSTV})$. If π represents the number of animals in a group, the average Q (Q_M) is stated as follows:

$$QMM^{1}_{MSTV +} M^{2}_{MSTV +} M^{3}_{MSTV +} M^{4}_{MSTV + \ldots} M^{y}_{MSTV})/\pi.$$

Histological process

After the samples were collected, they were soaked in 10% formaldehyde for 7 days. After the tissue tracking process, the samples were embedded in paraffin blocks. Then, 3 mm vertical and horizontal sections were obtained. Twenty consecutive sections separated by distance of 5 μm were obtained for stereological examinations. The spinal cord preparation was stained with hematoxylin and eosin (H&E), and the spinal cord slices were stained with TdT-dUTP nick-end-labeling (TUNEL) for the identification of apoptosis. Thus, all samples were prepared for histological examination. All preparations were examined under a light microscope.

Stereological analysis

Stereological analysis of histopathologic data was conducted according to the principles previously stated, and the physical dissector method was used to evaluate the number of neurons in the spinal cord.[17] The DNDs in the GM of spinal cord were calculated using stereological methods. Apoptosis of the neurons in the anterior horn of spinal cord confirmed the occurrence of neuronal degeneration. Data were obtained from dissector pairs consisting of parallel sections taken at known intervals. Two tagged consecutive sections obtained from the tissue samples (dissector pairs) were mounted on each slide. Twenty dissector pairs were obtained from each block for neuronal analysis. A counting frame was placed on the consecutive section photographs on the PC to conduct neuron count. Before the new sections were obtained, the reference and examination sections were reversed to double the number of dissection pairs (see Fig. 5(A and B)). The average numerical density of the spinal cord neurons per cubic millimeter (NvSC) was estimated according to the formula below.

$$NvSC = \Sigma QN/txA$$

ΣQN represents the total number of neurons found and counted in the reference sections. "t" represents the width of the section and A the area of the counting frame.[18] The Cavalieri volume estimation theorem was used to obtain the total number of neurons in each sample, which was calculated by multiplying the numerical density of the neurons with volume (mm^3).

Statistical analysis

The results were presented as mean ± standard deviation, and median (min-max) for continuous variables. The relationship between the MSTV and DND of the spinal cord was analyzed statistically. The Mann -Whitney U test was used to analyze the results. A P value < 0.05 was considered statistically significant.

Results

Two animals in the SAH group died within the first week of the experiment; hence, new rabbits were included in the study group. SAH was induced in the new animals and they were monitored for 2 weeks. The results observed in these animals were included in the scope of the statistical analysis. The heart rates of the groups were 218 ± 20/min for the control group, 197 ± 16/min for the SHAM group, and 167 ± 13/min for the SAH group. We observed SAH the spinal cord in all rabbits in the study group. Furthermore, CCH was noted along the spinal cord in eight rabbits. We observed CCH at the lower cervical level, in 5 rabbits, and at the middle thoracic level in three rabbits.

As shown in Fig. 2, one rabbit presented with SAH around the brain stem, spinal cord and nerve roots. Figure 3 shows the beginning of the central canal at the medullary level and foramen of Luchka, central canal and ependymal cells in a normal rabbit. Blood was collected from the central canal in the horizontal section, and the occluded central canal in a SAH rabbit with SAH was assessed. Figure 4 shows the basal lamina cells and desquamated ependymal cells of animals with induced SAH. Figure 5(A and B) shows degenerated/apoptotic anterior horn neurons

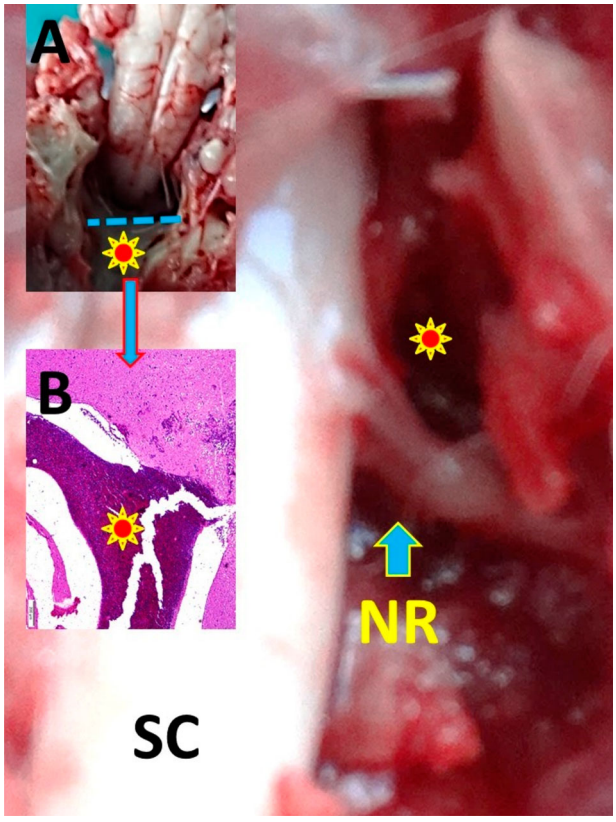

Figure 2 Anatomical view of the brainstem and section level (in A), spinal cord (SC) with a nerve root (NR) with spinal SAH (Star) at the base of the figure and histopathological appearance of the central canal orifice with blood collection (Star, LM, H&E, x10/B). SAH: subarachnoid hemorrhage; LM: light microscopy; H&E: hematoxylin and eosin.

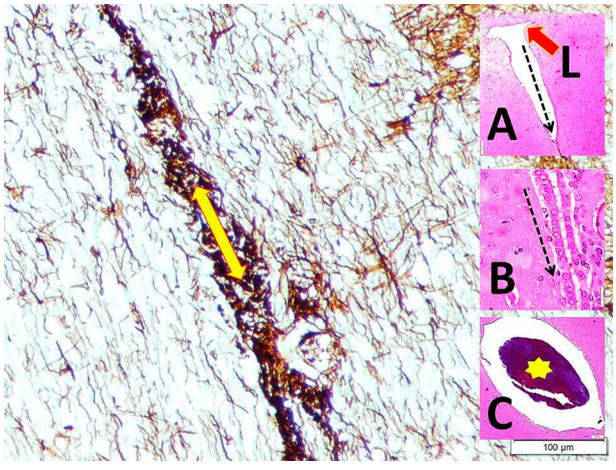

Figure 3 Beginning of the central canal at the medullary level (black dotted arrow) and the Foramen Luchka (red arrow) (LM, H&E, x4/A), central canal (black dotted arrow) and ependymal cells (LM, H&E, x4/B) in a normal animal, and blood collection in the central canal at the horizontal section (LM, H&E, x4/C) and occluded central canal (yellow arrow) were observed in a rabbit with SAH (LM, GFAP, x10/Base). SAH: subarachnoid hemorrhage; L: Foramen Lushka; LM: light microscopy; H&E: hematoxylin and eosin; GFAP: Glial fibrillary acidic protein.

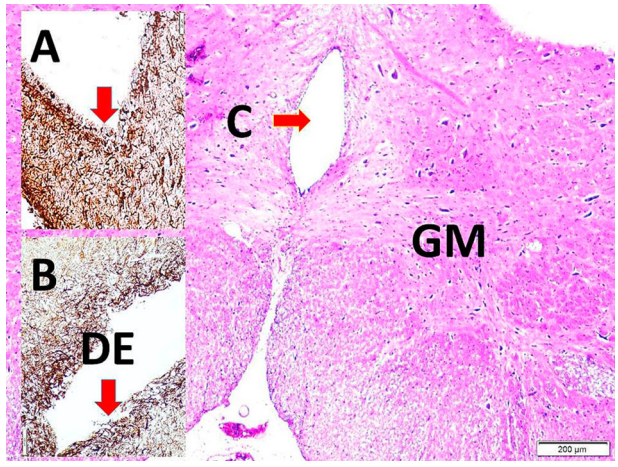

Figure 4 Central canal (C) and gray matter (GM) of the spinal cord at the mid-cervical level (LM, H&E, x20/Base), central canal (red arrow) and ependymal cells (LM, GFAP, x4/A) in a normal animal, and desquamated ependymal (DE) cells with basal lamina were observed in a rabbit with SAH (LM, GFAP, x10/B). SAH: subarachnoid hemorrhage; LM: light microscopy; GFAP: Glial fibrillary acidic protein.

and stereologic cell counting observed in a rabbit with SAH. Figure 6 shows the degenerated anterior horn neurons and adhesive central canal at the mid-thoracic level in a rabbit with SAH. Figure 7 shows the central canal and GM of the spinal cord at the thoracic level in animals with induced SAH, ruptured central canal and degenerated anterior horn neurons. Figure 8 shows the edematous and degenerated anterior horn in the GM. Moreover, the fragmented interglial/interglacial-neuronal connection in a rabbit with induced SAH is also depicted.

The average MSTV of the various groups was as follows: 2 for the control group, 3–5 for the SHAM group, and 8–10 for the study group (n = 13). The DNDs of the spinal cord were $2 \pm 1/mm^3$ for the control group, $12 \pm 3/mm^3$ for the SHAM group and $34 \pm 9/mm^3$ for the study group. According to these results, a statistically significant difference was observed in the mean MSTV of the rabbits and the DNDs of the spinal cord between the control and study groups ($P < 0.0001$). Meanwhile, a statistically significant difference was not found between the control and SHAM groups ($P > 0.05$). Similarly, no statistical difference was noted between the SHAM and study groups ($P > 0.05$) (Table 1).

Discussion

The development of SAH is attributed to various etiological factors causing the rupture of blood vessels in the subarachnoid space. Approximately 40%–70% of

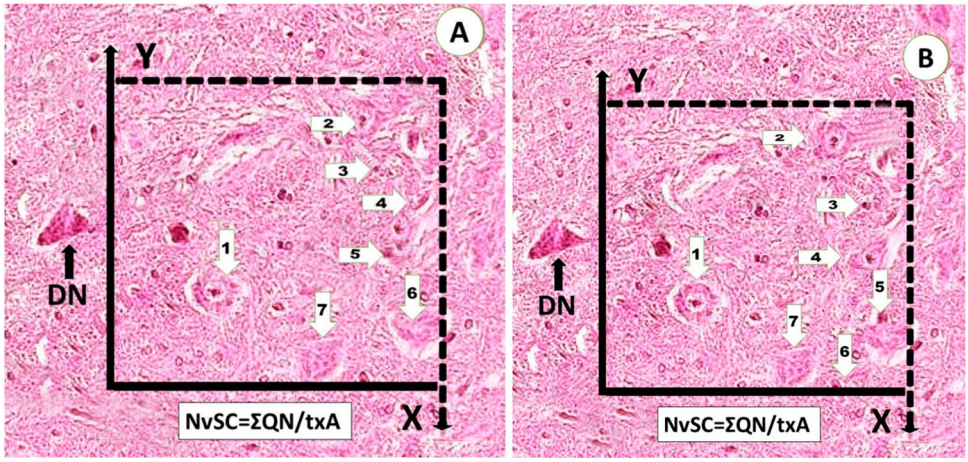

Figure 5 (A and B) Degenerated/apoptotic anterior horn neurons and stereologic cell counting were observed in a rabbit with SAH (LM, H&E, x10). Application of the physical dissector method in which micrographs in the same fields of view were obtained from two parallel, adjacent thin sections separated by a distance of 5 µm. The numerical density of the neurons is calculated as NvSC = ΣQN/txA. The bottom and left sides, along with the extension lines, were excluded for the co-counting (exclusion) lines. In this application, the nucleoli marked with 3,6,7 are dissector particles in A. However, in section B, they cannot be observed. The nucleoli marked with 1,2,4,5 are not dissector particles in A because section B shows 1,2,4,5 again. (LM, H&E, x10). SAH: subarachnoid hemorrhage; LM: light microscopy; H&E: hematoxylin and eosin; DN: degenerated neuron.

patients with SAH develop cerebral vasospasm.[19] Serious vasospasm triggered by SAH causes acute cerebral ischemia, brain edema, deterioration of the blood-brain barrier, increased intracranial pressure and decreased cerebral perfusion pressure.[19] SAH may also affect the spinal cord and related anatomical structure and can cause spinal SAH with devastating results.[20]

Decreased cerebral blood flow and cerebral perfusion pressure are the most important factors in early mortality.[21] Severe SAH causes loss of cerebral autoregulation and cardiorespiratory irregularities.[21] Hence, the rabbits in this experiment presented with clinical signs and symptoms caused by SAH. Two of the animals with induced SAH develop exitus caused by cardiovascular irregularities on day 4.

Underlying mechanisms of spasticity

The pathogenesis of spasticity after SCI remains unclear. Elbasiouny *et al.* have examined numerous mechanisms and evaluated their role and relative importance in the pathophysiology of spasticity.[2] Based on

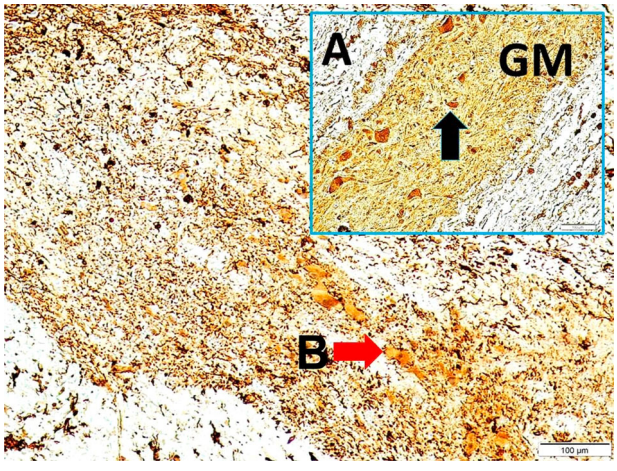

Figure 6 Central canal and GM of the spinal cord (yellow square and black arrow) at the mid-cervical level (LM, H&E, x4/Base), degenerated anterior horn neurons (LM, GFAP, x10/A) and adhesive central canal (red dotted arrow) were observed in a rabbit with SAH (LM, GFAP, x10/Base). SAH: subarachnoid hemorrhage; GM: Gray matter; LM: light microscopy; H&E: hematoxylin and eosin; GFAP: glial fibrillary acidic protein.

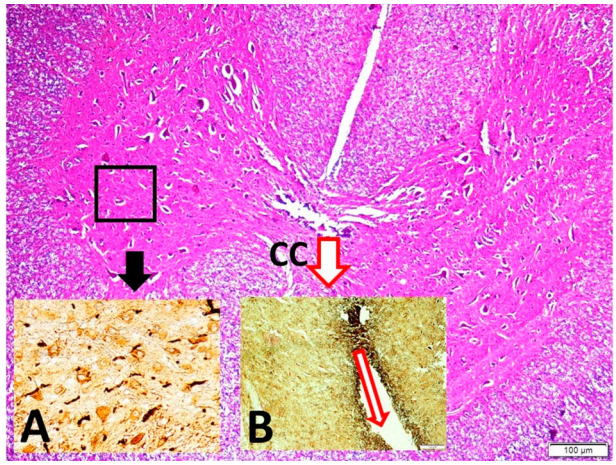

Figure 7 Degenerated anterior horn neurons (LM, GFAP, x10/A), central canal at the upper thoracic level (red dotted arrow) (LM, GFAP, x4/B) and ruptured central canal wall (CC) were observed in a rabbit with SAH (LM, GFAP, x10/Base): SAH: subarachnoid hemorrhage; LM: light microscopy; GFAP: glial fibrillary acidic protein.

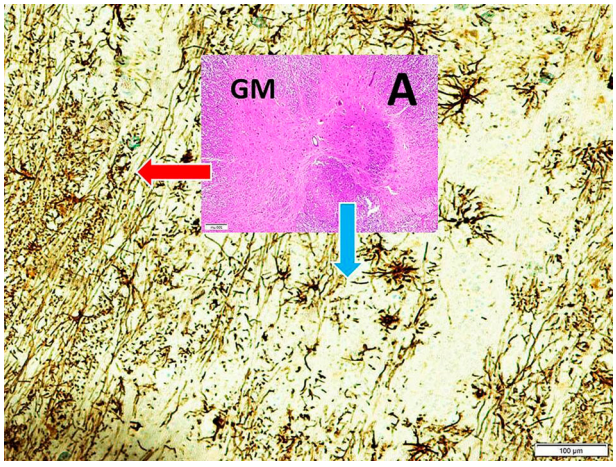

Figure 8 Edematous/degenerated anterior horn in the GM of the horizontal sections of the spinal cord (LM, H&E, x10/A). Normal structures were found (left part of the pictures; red arrow), and the fragmented interglial/interglacial-neuronal connections were observed (right; blue arrow) in a rabbit with SAH (LM, GFAP, x10/base). SAH: subarachnoid hemorrhage; GM: gray matter; LM: light microscopy; H&E: hematoxylin and eosin; GFAP: glial fibrillary acidic protein.

their study results, enhancement in the excitability of motor neurons[9] and enhancement in the excitability of interneurons[9,11] are the mechanisms consistently observed. Axonal sprouting[12] is considered another important mechanism. Other mechanisms, such as reduction in presynaptic inhibition[13], post-activation depression[14] and Ia reciprocal inhibition[15] are not logical. We believe that enhancement in the excitability of motor neurons and excitability of interneurons and axonal sprouting are the most logical mechanism of spasticity.

Renshaw inhibition

Previous experimental data have shown that harmful processes caused by spinal ischemia cause the loss of inhibitor interneurons in the spinal segments.[22] Renshaw cells are the most well-known of these inhibitor interneurons. The inhibition of these cells is most important in the pathophysiology of spasticity. Renshaw cells receive input from the collateral axions of the motor neurons and they inhibit the motor neurons once stimulated. They can effectively control the activation of all motor units of a muscle.[23] The main transmitter in the synapsis between these cells and their target neurons is glycine (with strychnine as the antagonist).[24] Neurons in the spinal cord that secrete these neurotransmitters that regulate muscle tone cannot secrete these neurotransmitters as they present with ischemic damage. As a result, the reflex arc is disrupted, and spasticity is exacerbated as inhibition will be disabled in the neurochemical pathway that regulates muscle tone via excitation mechanisms. In this study, we believe that the Renshaw cells that are a part of the neural network in the GM of the spinal cord lost their function in animals with induced spinal SAH and this plays an important role in spasticity.

Table 1 Relationship between MSTV and spinal cord DND.

	Control group (n = 5)	SHAM group (n = 5)	Study group (n = 13)
MSTV	2	3–5	8–10
DND (mm^3)	2 ± 1	12 ± 3	34 ± 9

The differences in the mean MSTV of the rabbits and the DND of the spinal cord were statistically significant between the control and study groups ($P < 0.0001$). No statistically significant difference was observed between the control and SHAM groups ($P > 0.05$). Similarly, no statistically significant difference was noted between the SHAM and study groups ($P > 0.05$).
Notes: MSTV, muscle spasticity tension value; DND, degenerated neuron density.

SAH and spasticity

The injection of clean blood into the cisterna magna is one of the most commonly used methods of inducing SAH in a rabbit model.[25] In this study, the blood coming into the 4th ventricle via the cisterna magna entered the subarachnoid space via the foramen of Luschka. Thereby, leading to the development of spinal SAH. By moving in the direction of the cranium via the cerebral aqueduct, this blood also caused cerebral SAH. According to earlier studies, in SAH, cerebrospinal fluid (CSF) contains blood and high protein levels which may cause neural degeneration.[26,27] Another studies have shown that spinal SAH may also lead to neurodegeneration in the dorsal root ganglion, which results in vasospasms in arteries, such as the brachial artery, anterior spinal artery and artery of Adamkiewicz.[20,25,28,29] Thus far, the relationship between spasticity and neurodegenerative change after SAH has not been assessed. In this study, we first investigated this issue. Moreover, we believe that CSF with blood or high-amount of protein that accumulates around the spinal roots after experimental SAH caused impaired circulation and, ischemia, and ultimately led to neuronal cell degeneration. Thus, the connection between the motor neuron and interneurons in the GM and the spinal nerves was destructed, which in turn disrupted the reflex arc of spinal nerve and the affected muscles. In conclusion, the synchronized contraction process between the flexor and extensor muscles was disrupted which then caused spasticity. Hence, the MSTV of the rabbits in the study group was higher than those of the rabbits in the control

group and the difference was statistically significant (Table 1).

CCH and spasticity

Pyramidal pathway paralysis, spasticity and tonic contractions occur in the destructive lesions of the motor cortex or its appendage. Pyramidal fibers in the changing tonus have an inhibiting effect on the reflex arc. Spasticity develops when this mechanism is damaged in various illnesses.[9] For example, central cord syndrome (CCS) which is an incomplete SCI, such as intramedullary tumors or syringomyelia, can be attributed to various causes. Such condition is also observed in the degenerative ground of the cervical spine in older patients after a minor trauma.[30] CCS in the traumatic ground is similar to the model developed in this study. Traumatic CCS in turn causes spinal cord contusion, edema, and intraspinal pressure which results in a destructive lesion in the pyramidal pathway and spasticity occurs as it a significant part of these phenomena. In this study we investigated presence of traumatic incomplete SCI in the rabbit model. The central canal widened after inducing CCH. Desquamation occurred in the ependymal cells (see Fig. 4). In five rabbits, the blood in the central canal coagulated and caused adhesion which in turn disrupted the CSF circulation (see Fig. 6). The central canal widened even more and ruptured. Intraspinal pressure increased even more. We believe that such increase in pressure resulted in the stretching of the corticospinal tract (pyramidal pathway) (see Fig. 1(B)). The parenchymal circulation of the spinal cord was disrupted due to increased spinal cord pressure. In relation to such phenomenon, ischemia, edema, neuronal degeneration and interglial/interglacial-neuronal fragmentation developed in the GM (see Fig. 8). Thus, the network between motor, neurons sensory neurons and interneurons in the GM and corticospinal tract was severed. Thus, a destructive lesion developed in the pyramidal pathway and other descending pathways. Hence, the number of DND in the GM was found to be significantly higher based on the histopathologic examination of the SAH group (Table 1).

Clinical relevance

When a patient presents with cerebral SAH, the focus is generally on the localization of the blood in the subarachnoid space of the brain, cisterns, and ventricles. If it is a spontaneous SAH, the underlying aneurysm can be investigated. To identify anatomical characteristics, numerous radiological procedures, such as digital subtraction angiography, computed tomography-angiography, magnetic resonance imaging angiography are performed. However, whether the blood in the cerebral subarachnoid space passes through the spinal central canal and spinal subarachnoid space is not commonly investigated during routine procedures. Meanwhile, as described in this experimental study, cerebral SAH can pass through the spinal subarachnoid space and the central canal by passing from the cranial to caudal area.

Hydrocephaly is an important complication of SAH. The most important factor in the development of acute hydrocephaly after SAH is the amount of blood in the subarachnoid and intraventricular space.[31] The cause of this is obstruction of circulation in the intraventricular or subarachnoid space of the brain spinal cord fluid and such condition develops after SAH at a rate of 20%.[31,32] The aim of external ventricular drainage implemented for curative purposes is to clean the blood from the subarachnoid and intraventricular space. To date, an evacuative lumbar puncture (LP) is also used instead of external ventricular drainage in some centers.[31] During cerebral aneurysm surgery, the cisterns are opened to facilitate CSF drainage. The aim of such procedure is to evacuate blood from the subarachnoid and intraventricular space to prevent the development of hydrocephaly. In light of this information repetitive LPs may be helpful for the treatment of complications that may occur after spinal SAH and CCH. Cleaning out blood in the subarachnoid space via LP may prevent it from disrupting the circulation around the nerve roots. Decreasing/cleaning the blood in the central canal may also decrease/prevent increased pressure in the spinal cord. In conclusion, evacuative LPs may be beneficial in preventing spasticity that may develop after spinal SAH and CCH.

Independent variables associated with the outcome of the experimental study

Numerous variables were independent of the result of the experimental study, which were as follows: (1) Although we induced spinal SAH, such condition may progress to the brain and cause cerebral SAH. The spinal cord may affect different pathways and clusters of neurons in the brain stem and brain by affecting the ascending and descending pathways in the spinal cord. (2) The anesthetic agents used in this study included ketamine hydrochloride, lidocaine hydrochloride and acepromazine, and such drugs may have some side effect. For example, ketamine causes sympathomimetic activity because it inhibits catecholamine reuptake. Thus, blood pressure, heart rate, pulse volume and myocardial oxygen consumption may increase at a mild to

moderate rate.[33] Moreover, lidocaine hydrochloride may have side effects, such as hemolytic anemia and convulsions. Acepromazine, which causes hypotension, can cause reflex sinus tachycardia. (3) The rabbits used in experimental studies may have a neurodegenerative or metabolic disease. However, the rabbits used in the current experiment were healthy. (4) In this study, we developed intraspinal parenchymal pressure after inducing CCH and spinal SAH. The increase in pressure may progress toward the cranium and cause an increase in intracranial pressure, which may accelerate the formation of spasticity. Elevated intracranial pressure also increases intraspinal pressure, thus, damage in the intraspinal network can be more severe due to the pressure increase. (5) Neuronal degeneration also occurred in the dorsal root ganglion (DRG) after inducing spinal SAH.[25] This may also be a progenitor factor for spasticity.

The limitations of this study

This study had some limitations. This is an experimental and observational study conducted on rabbits. The most important limitation of this study is that the changes (neuronal degeneration and increased intra-spinal cord pressure) could not be observed *in vivo* or during autopsy, particularly in individuals with SAH or CCH. We observed spinal SAH along the spinal cord in all the rabbits in the study group. However, CCH was not found in the spinal cord in five rabbits in the study group. We identified CCH at the lower cervical level in five rabbits and at the middle thoracic level in three rabbits due to the coagulated blood from the cranial to caudal area, and this is another limitation of this study. In this case, the fact that spasticity developed in all animals that could be viewed cautiously. However, this can be explained by the pathophysiology of SCI. After inducing SCI, the microcirculation disorder in the capillaries and venules affected in the early phase was not restricted to the injured area but continues to the cranial and caudal areas. The resulting ischemia becomes more widespread.[34] In later phases, the membrane stabilization is compromised due to ion metabolism disorder, and intracellular hypercalcemia develops. Cytotoxic edema occurs due to the build-up of Na in the cell.[35]

Conclusion

Spasticity causes soreness and contractures, and it is a secondary complication of SCI. Multiple spinal mechanisms play a role in the pathogenesis of spasticity after SCI. Identifying possible mechanisms and their role in the pathophysiology of spasticity is important for the development of treatment modalities. According to the findings of this study, the ischemic neurodegenerative process develops in the spinal roots after SAH, and increased pressure in the spinal cord after CCH causes functional or anatomical tears in the neural network between the motor neurons, Renshaw interneurons and DRGs, which in turn results in spasticity.

Acknowledgements

We would like to thank Atatürk University experimental research laboratory staff for their contribution.

Disclaimer statements

Disclosure Selim Kayaci, Mehmet Dumlu Aydin, Baris Ozoner, Tayfun Cakir, Orhan Bas, Sare Sipal have nothing to disclose in relation to this article.

Funding This research did not receive any specific grants from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest The authors declare no potential conflicts of interest with respect to the research, authorship and/or publication of this article.

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