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ORIGINAL ARTICLE

Predeterminative role of Onuf's nucleus ischemia on mesenteric artery vasospasm in spinal subarachnoid hemorrhage: A preliminary experimental study

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Mesentery artery vasospasm;
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Sacral plexus;
Intestinal ischemia

Summary *Background:* Although posttraumatic mesenteric artery ischemia is attributed to various etiologies, sacral parasympathetic network/mesenteric artery relations have not been studied so far. The primary objective of this study is to elucidate whether there is a relationship between Onuf's nucleus ischemia and mesenteric artery vasospasm following subarachnoid hemorrhage (SAH).
Methods: This study was conducted on 22 rabbits. The animals were grouped as follows: 5 of animals control, 5 SHAM which saline was given, and 12 animals study group that was homologous blood injected into the spinal subarachnoid space at the L1 level. Neurodegeneration in Onuf's nucleus, axonal degeneration of S2 roots, and mesenteric arteries vasospasm indexes (VSI; Wall surface/Lumen surface), brachias of mesentery arteries in various tissues and ischemic mucosal changes of intestines of all animals were determined histopathologically. Important degenerative changes were detected in axons in S2 roots and Onuf's nucleus in

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severe mesenteric artery vasospasm observed.
Results: The mean degenerated neuron density of Onuf's nucleus (n/mm^3), degenerated axon density in S2 roots (n/mm^2), and VSI values of mesenteric arteries of control, SHAM, and study groups were estimated as 5.00 ± 1.58, 4.00 ± 1.58, 1.76 ± 0.13; 18.29 ± 4.31, 11.00 ± 2.24, 2.23 ± 0.20; and 135.21 ± 30.75, 117.33 ± 22.11, 2.81 ± 0.44, respectively. Statistical analyses between the VSI values, mucosal ischemic changes degenerated neurons in Onuf's nucleus, and axons in S2 levels were meaningful ($p < 0.005$).
Conclusion: We interestingly noticed that Onuf's nucleus—S2 roots complex degeneration plays an important role in mesenteric artery vasospasm and the development of intestinal ischemic mucosal changes following SAH which has not been extensively mentioned in the literature.

1. Introduction

The proximal gastrointestinal system is innervated by inhibitory sympathetic and excitatory parasympathetic vagal nerves. However, distal intestines and bowels are innervated by sacral parasympathetics[1] and splanchnic sympathetics.[2] Vagal nerves innervate proximal intestines and distal colon is innervated by sacral parasympathetics particularly in males.[3,4] Somato-sensitive innervation is maintained by spinal cord segments.[5] The sympathetic innervation managed by thoracal sympathetic chain.[6] Onuf 's nucleus sends their parasympathetic impulses to distal colon, pelvic organs, and urethral and anal sphincters.[7] Adamkiewicz artery (AKA) vasospasm cause distal spinal cord and Onuf's nucleus ischemia.[8] Onuf 's nucleus ischemia may be responsible for Hirschsprung's like disease[9] and causes of decreased bowel activity.[10] Mesenteric arteries are innervated by vasodilating vagal, pelvic parasympathetic, and vasoconstrictor coeliac sympathetic nerves. Very dangerous mesenteric artery ischemia cause intestinal infarcts following spinal SAH[11] but rarely reported.[12] Kamel et al published that two patients had undergone colectomy for mesenteric ischemia; however, there is no satisfying information so far.[13] The primary aim of this study is to evaluate whether there is a relationship between Onuf's nucleus-sacral parasympathetic network degeneration/mesenteric artery vasospasm and intestinal mucosal changes following SAH.

2. Material methods

2.1. Experimental design

This study was conducted on 22 rabbits: five were used as control group (GI, n = 5), used to assess the Onuf's nucleus and spinal ganglia. Five were used as SHAM group (GII, n = 5), and twelve were used as study group (GIII, n = 12). The SHAM and study animals were anesthetized by subcutaneous injection of a mixture of 25 mg/kg ketamine hydrochloride, 15 mg/kg lidocaine hydrochloride, and 1 mg/kg acepromasine. Their thoracolumbar areas were cleaned with antiseptics and shaved. After the operation site was shaved, Th12-L1 hemilaminectomy was performed. We incised posterior mid vertebral cutaneal tissues and separate paravertebral muscles to expose posterior vertebral elements, laminectomy procedures, dural opening and blood injection to spinal subarachnoid spaces. Five of them used as SHAM and 0.7 cc physiologic serum saline; autolog blood taken from auricular artery was injected into the spinal subarachnoid space using a 7F microinjection catheter in the study group. After the operation, the fascia and skin were sutured with 3—0 absorbable wire and rabbits returned to personal cages and antibiotic/analgesic regimen was not given for seven days postoperatively. After two weeks, all animals were sacrificed under general anesthesia. Onuf's nucleus including spinal cord parts/S2 pudendal nerve roots and ganglia and all mesenteric artery complexes were extracted with all prevertebral soft tissues such as pancreas, gut, liver, and intestines. The tissues were fixated in 10% formalin solution for histological analysis. Then all specimens were embedded in paraffin blocks and taken sections were stained with hematoxylin—eosin, aldehyde fuxine and Tunel method.

The physical dissector method was used to estimate the neurons numbers in Onuf's nuclei. Data were obtained from dissector pairs consisted of parallel sections of consecutive intervals until the tissue samples were exhausted. Consecutive two reference and look-up sections were prepared of all slides. Consecutive 20 dissector pairs used to analyze the neuron densities of Onuf's nucleus. Unbiased counting consecutive sections frames were placed on a lam on a computer screen to estimate the neuron densities of all ganglions. The inferior and the left hand edges of the frames were established as exclusion lines. Other pairs of the frames were accepted as inclusion points and particles over these lines or located inside the frames were accepted as a dissector partide. The visible neurons in the reference section of the ganglions were counted as countable rational neurons. In order not to double the number of dissector pairs without taking new sections, reference and look-up sections were turned backward.

The mean degenerated numerical density of Onuf's nuclei and pudendal ganglia neurons (NvGN) per mm^3 were calculated using the following formula:

$$NvGN = \sum(Q^{-} N/t \times A)$$

Total counted numbers of neurons appearing only in the reference sections are showed as $\sum Q^{-}$ N; section thickness is presented as t, and area of the counting frame is showed as A. The Cavalieri formula was used to estimate total number of neurons in each ganglion. The total neuron numbers were estimated by multiplying the volume (mm^3) and numerical density of neurons of all Onuf's nucleus.

2.2. S2 nerve roots examinations

Their sciatic nerve roots together with spinal cords at the levels of L5-S3 and sciatic nerves at the levels of collum femoris were extracted bilaterally. For the Stereological analysis, these materials were preserved in 10% formalin solution for four days. The specimens of S2 roots were examined histopathologically after stained by H&E and Tunel method. Histopathological changes were investigated, and the density of normal and degenerated axons of sciatic nerves was calculated. Arteria nervorum spasm, axonal swelling, and axonal loss were accepted as sacral nerve degeneration criteria. Then, axon numbers of sacral nerve were counted by Cavalieri methods. All nerve root sections were divided into four segments by 900 angles and multiplied by four. The counted degenerated axons in the sacral nerve were given as mean ± SD same as our previous study.[14]

2.3. Mesenteric arteries examinations

Consecutive 20 vertical sections of all mesenteric arteries were analyzed following routinely histopathological dyes. Wall surface/lumen surface ratios were accepted as VSI values of brachial arteries. Vasospasm index calculation method was calculated as follows: 2R is the external diameter, and 2r is the internal diameter of parotid arteries. VSI values were calculated as the proportion of external surface value to lumen surface value ($\pi R2$-$\pi r2$/$\pi r2$) = (R2-r2/r2). We detected intestinal mucosal ischemic changes covering intestinal villi especially high VSI detected animals.

2.4. Statistical analyses

SPSS 20.0 (SPSS Inc., Chicago, Illinois, USA) software was used for the statistical analyses. Data were presented as mean, standard deviation, median, minimum, maximum, percentage and number. The normal distribution of the continuous parameters was investigated by using the Shapiro Wilk test. ANOVA test was used when normal distribution condition was provided for comparison of more than two independent groups with continuous variables. Kruskal Wallis test was used in cases where normal distribution condition could not be achieved in comparison of more than two independent groups with continuous variables. Post-hoc tests were performed after Kruskal Wallis test. P value of <0.05 was accepted as statistically significant.

3. Results

In macroscopical analysis of spinal cord and nerve roots; meningeal thickening and adhesions in both spinal cords and nerve roots, myelomalasia, narrowed spinal arteries, adhesive nerve roots and occluded vertebral foraminas secondary to inflamed roots were detected. Gross examinations of the intestines, spastic, purple-black segments, degenerated villi and thinned mesenteric arteries were detected. In microscopical examinations, Adamkiewicz artery spasm, degenerated neurons in Onuf's nucleus, degenerated axons in sacral roots, constructed mesenteric artery branches, dilated and ischemic/degenerated/atrophic villi were detected.

3.1. Histopathological results of mesenteric arteries and intestines

Horizontal section of spinal cord and Onuf's nucleus at the level of S2 segment, sacral parasympathetic roots among paravertebral muscles and intramural arterioles and deformed neurons among normal neurons of Onuf's nucleus are seen (Fig. 1). Vertical section of mesenteric artery, with their vagal nerves just crossing the pancreas, and magnified appearances of the same tissues at this level in normal rabbit. The VSI estimation method is shown in the picture (Fig. 2). Vertical section of mesenteric artery, with their nerves just crossing the pancreas and magnified appearances of the same tissues at this level in a normal rabbit (Fig. 3). Histological appearances of colon with subserosal segmental branches of mesenteric artery and magnified form of that arteries in a normal rabbit (Fig. 4). Constructed lymphoid tissue branches of mesenteric artery and magnified appearances of the same artery in a rabbit with SAH created animal (Fig. 5). Constructed mesenteric artery branches with apoptotic/fibrotic myocytes in the colon and magnified appearances of the same artery and degenerated Auerbach neuron in a rabbit with SAH created animal (Fig. 6). Histopathological appearances of a subserosal ileal branches of mesenteric artery and magnified form is seen in a normal rabbit (Fig. 7). Histopathological appearances of ileum with ischemic and partially degenerated segments

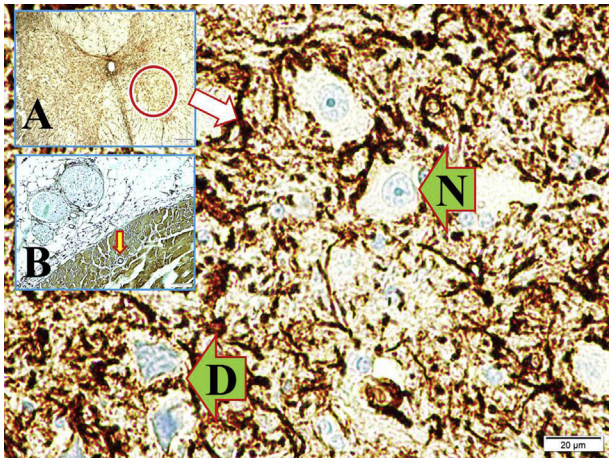

Figure 1 Horizontal section of spinal cord and Onuf's nucleus (ON) at the level of S2 segment (red circle, LM, GFAP, × 4/A), sacral parasympathetic roots (SRs) among paravertebral muscles and intramural arterioles (yellow arrow) (LM, Aldehyde fuxine, × 10/B) and deformed neurons (D) among normal neurons (N) of Onuf's nucleus are seen (LM, GFAP, x20/Base).

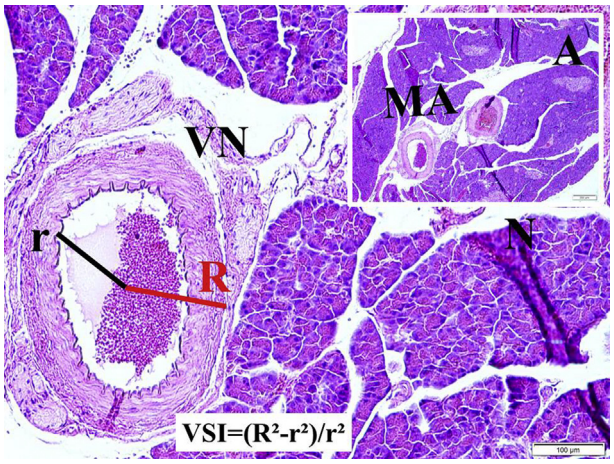

Figure 2 Vertical section of mesenteric artery (MA), with their vagal nerves (VN) just crossing the pancreas (LM, H&E, × 4/A), and magnified appearances of the same tissues at this level in normal rabbit (LM, H&E, × 10/Base). The VSI estimation method is shown in the picture.

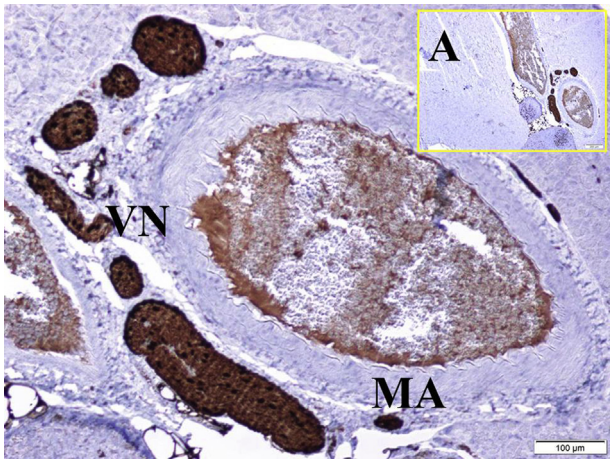

Figure 3 Vertical section of mesenteric artery (MA), with their nerves (N) just crossing the pancreas (LM, S-100, × 4/A), and magnified appearances of the same tissues at this level in a normal rabbit (LM, S-100, × 10).

and constructed mesenteric artery branch localized in ileal wall, and hemorrhagic intramural focuses and magnified form of constructed artery with swollen-desquamated endothelial and constructed muscles (Fig. 8). Normal histological appearances of ileum with normal mucosal surfaces wall, and ischemic, edematous and microhemorrhagic focuses vasospastic construction developed artery of same ileal segment, and mucosal injury, desquamations, villous degeneration and atrophy is seen in a SAH created animal (Fig. 9).

3.2. Numerical results

Numerical results are summarized in Table 1. The mean degenerated neuron density of Onuf's nucleus (n/mm^3), degenerated axon density in S2 roots (n/mm^2), and VSI

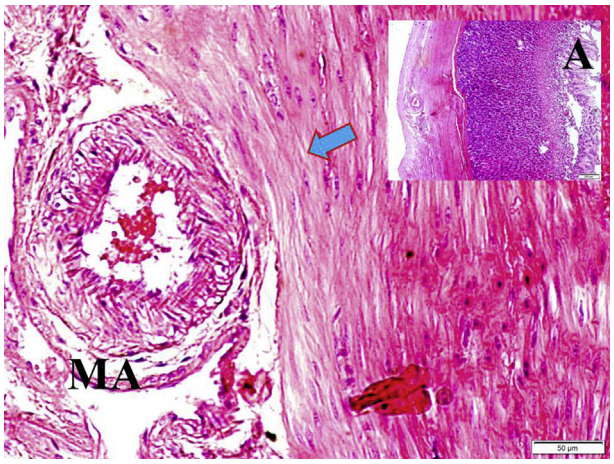

Figure 4 Histological appearances of colon with subserosal segmental branches of mesenteric artery (LM, H&E, × 4/A) and magnified form of that arteries in a normal rabbit (LM,H&E, × 20/Base).

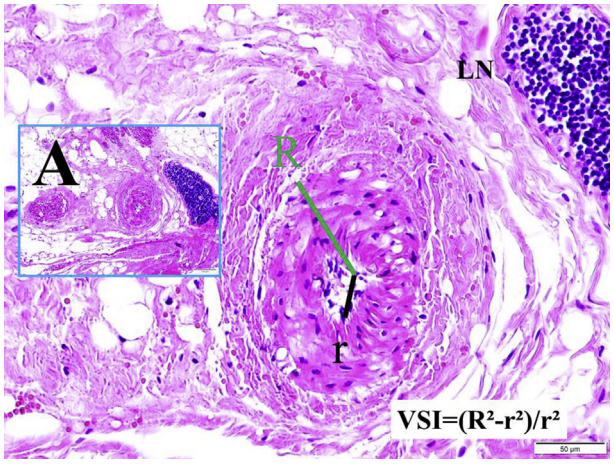

Figure 5 Constructed lymphoid tissue (LN) branches of mesenteric artery (MA) (LM, H&E, × 4/A) and magnified appearances of the same artery in a rabbit with SAH created animal (LM, H&E, × 20/Base).

values of mesenteric arteries of control, SHAM, and study groups were estimated as 5.00 ± 1.58, 4.00 ± 1.58, 1.76 ± 0.13; 18.29 ± 4.31, 11.00 ± 2.24, 2.23 ± 0.20; and 135.21 ± 30.75, 117.33 ± 22.11, 2.81 ± 0.44, respectively. Statistical analyses between the VSI values, degenerated neuron in Onuf's, and axons in S2 levels were meaningful ($p < 0.005$).

4. Discussion

4.1. Neural network of mesenteric arterial system

Intestines are innervated by the splanchnic sympathetic, vagus nerve, and the sacral parasympathetic pelvic nerves.[15] Abdominopelvic organs are innervated with vagal and sacral parasympathetics arising from Onuf's nucleus. Sacral roots contain somatic and thin parasympathetic

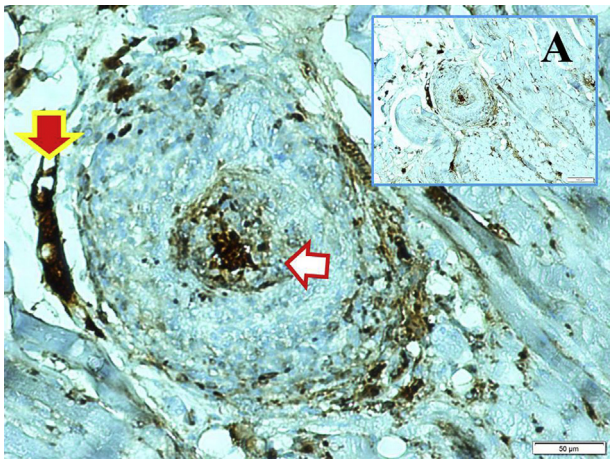

Figure 6 Constructed mesenteric artery branches with apoptotic/fibrotic myocytes in the colon (LM, Tunel, × 4/A) and magnified appearances of the same artery and degenerated Auerbach neuron (red arrow) in a rabbit with SAH created animal (LM, Tunel, × 20/Base). Red arrow show degenerated neurons and white arrow shows degenerated apoptotic endothelial cells.

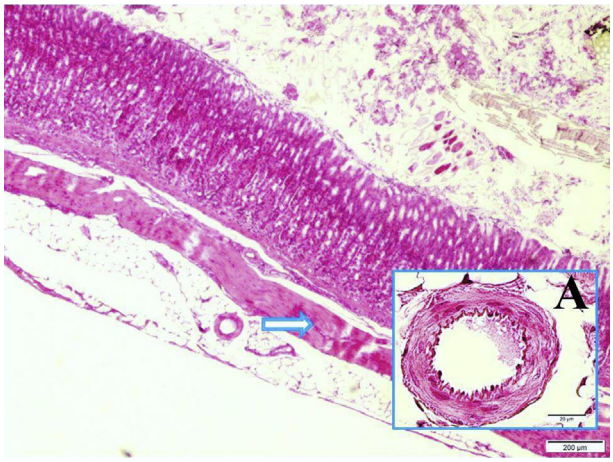

Figure 7 Histopathological appearances of a subserosal ileal branches of mesenteric artery (LM,H&E,x4/Base) and magnified form is seen in a normal rabbit (LM,H&E,x20/A).

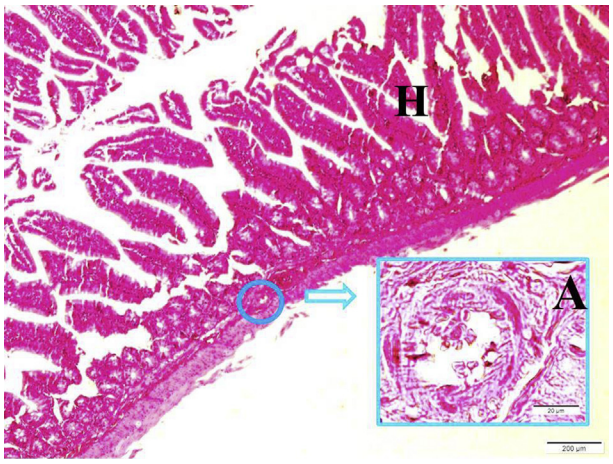

Figure 8 Histopathological appearances of ileum with ischemic and partially degenerated segments and constructed mesenteric artery branch localized in ileal wall (Blue circle) (LM, H&E, × 4/base), and hemorrhagic intramural focuses (H); and, magnified form of constructed artery with swollen-desquamated endothelial and constructed muscles (LM, H&E, x40/A).

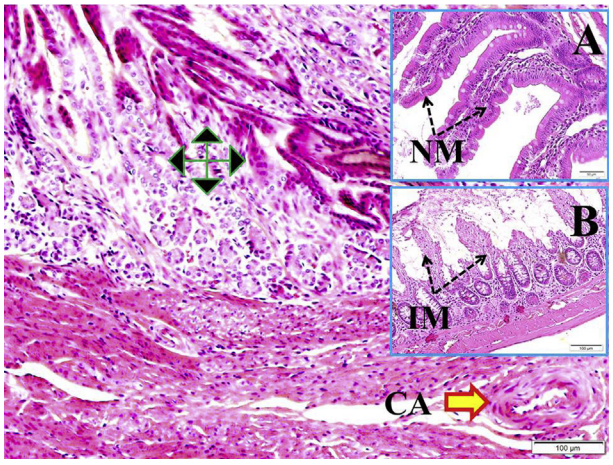

Figure 9 Normal histological appearances of ileum with normal mucosal surfaces (NM) wall (LM, H&E, × 20/A), and ischemic, edematous and microhemorrhagic focuses (Quadruplets arrows) vasospastic construction (CA) developed artery of same ileal segment (LM,H&E, x10/Base), and mucosal injury (IM), desquamations, villous degeneration and atrophy is seen in a SAH created animal (LM, H&E, x10/B).

nerve fibers that innervate the external urethral and anal sphincters. And neurons of Onuf's nucleus innervate the external urethral sphincter and distal colon.[16] Vagal nerve innervates lower abdominopelvic organs in women but not in men. The inferior mesenteric plexus send axons directly to form the pelvic plexus in four of hemipelvis.[17] Pelvic ganglia are a major source of sympathetic innervation.[18] Lower spinal segments receive afferent input from the descending colon and rectum.[19] The upper colon is innervated via vagal nerve, but lower colon is innervated by sacral spinal parasympathetic nerves, particularly in males.[3] Thoracic dorsal horn interneurons[20] and lumbar sympathetic chain[21] innervate mesenteric arteries, colon and pelvic organs. The microvasculature of intestines, pancreas, spleen, and liver is innervated by these autonomic chain extensions, myenteric plexus, and submucous plexus.[22] Any lesion of mentioned neural network can cause intestinal pancreatic, splenic, and hepatic dysfunctions.

4.2. Special considerations about Onuf's nucleus

The sacral parasympathetic autonomic preganglionic nucleus named as Onuf's nucleus is localized chiefly in the S1–S4 segments[23] and control the lower urogenital/digestive tract[24] sphincters.[25] Parasympathetic pelvic, hypogastric, pudendal, and vagal nerves[26] regulate recto-colonic reflexes. Onuf's nucleus and inferior spinal nerves supplied heavily by AKA.[27] Although bowel problems has not been attributed to following SAH, AKA spasm based spinal

Table 1 Numerical results of study.

	Group Control (n = 5)	Group SHAM (n = 5)	Group Study (n = 12)
Degenerated neuron density of Onuf's nucleus (n/mm^3)	5.00 ± 1.58	18.29 ± 4.31	135.21 ± 30.75 $^{\alpha,\beta}$
Degenerated axon density in S2 roots (n/mm^2)	4.00 ± 1.58	11.00 ± 2.24	117.33 ± 22.11 $^{\alpha,\beta}$
VSI values of mesenteric arteries	1.76 ± 0.13	2.23 ± 0.20	2.81 ± 0.44 $^{\beta}$

The values represent the mean ± standard deviation, VSI: vasospasm index.
$^{\alpha}$ $p < 0.0001$ Group study vs. SHAM, One way ANOVA post-hoc Kruskal wallis test.
$^{\beta}$ $p < 0.001$ Group study vs. control, One way ANOVA post-hoc Kruskal wallis test.

cord/onuf's nucleus ischemia should has been elucidated as a cause of mesenteric artery spasm related intestina ischemic disorders.

Although it is well known that vagal and sacral parasympathetic stimulations can be required for gastrointestinal functions; there is no satisfied knowledge how spinal cord lesions induce gastrointestinal dysfunctions. Yolas et al shown that spinal subarachnoid hemorrhage induced Adamkievicz artery vasospasm triggering Onuf's nucleus degeneration could cause parasympathetic deficiency based urinary dysfunctions.[28] In the same manner, it is possible that described neuropathological mechanisms may be responsible for mesenteric artery vasospasm due to Onuf's nucleus centralised parasympathetic network insufficiency. Because we detected that spinal subarachnoid hemorrhage cause a numbered degenerated neurons in Onuf's nucleus which that neurons are the Origining of sacral parasympathetic nerves.

4.3. Spinal cord centralized neural network injury

Consequently, in most of the spinal cord injuries; the foregut and midgut functions could remain normal, whereas the hindgut functions lose due to disruption of Onuf's nucleus connections. Thus, retention and/or incontinence occur following Onuf's nucleus ischemia.[29] Distal spinal cord transection blocks micturition and defecation reflex.[30] AKA sparing operations[8] minimize the risk of mesenteric artery vasospasm. Low neuron density of dorsal root ganglion (DRG) or degeneration[31] may cause severe AKA vasospasm in SAH.[32]

4.4. How innervation pathologies of mesenteric arteries cause intestinal syndromes

The pathophysiological roles of the Onuf's nucleus ischemia in bowel dysfunction are related to mesenteric artery innervation.[33] Chronic abdominal pain appears during spinal ischemia.[34] The absence of myenteric ganglia results in intestinal dysfunctions.[35] Sacral agenesis is associated with changes in anorectal functions.[36] Our studies reveal that ischemic neuronal degeneration of ON could rely on Hirschprung and Ogilvie syndrome presenting neurohistopathological findings.

4.5. Focusing information about mesenteric system

Widespread ischemic necrosis in the anterior gray matter of the spinal cord cause intestinal pathologies.[37] Physician should be more careful while blocking lumbar roots to spare AKA.[38] Because AKA vasospasm based Onuf's nucleus ischemia[39] may rely on intestinal injury[40]

4.6. Pathophysiological results of neuro mesenteric complex insults

The blood flow of colon increase following parasympathetic stimulation and decreases sympathetic activation.[9] Mesenteric artery ischemia relies on pancreatic dysfunctions,[41] Meissner's, Golgi-Mazzoni and Pacinian corpuscles dysfunctions based intestinal mechanical problems.[42] Perivascular arteries of mesenteric nerves are dilated by parasympathetic and constructed by sympathetic impulses.[43] The AKA vasospasm following SAH causes neural degeneration in Onuf's nucleus[44] might lead to catastrophic paraplegia[45] and abdominopelvic organ dysmotility.[10] This study implied that Onuf's nucleus complex degeneration plays an important role in mesenteric artery vasospasm and the development of intestinal ischemic changes following SAH.

If there are many numbers of arteries which supply of distal spinal cord at the level of location of Onuf's nucleus, vasospasm could be transient because degenerated neurons in Onuf's nucleus could not be undergone apoptosis in that circumstances. Or else, vasospasm could be permanent. On the other hand, vasospasm may be transient in female animals because vagal nerve innervates all abdominopelvic organs in female but not males. This complicated status may be understand by mesentera artery angiography. As expected, important ischemic mucosal desquamations, intestinal bleeding focuses in various numbers and volumes and villous atrophy were detected in severe vasospasm detected animals.

4.7. Rational of preferring rabbits in this study

The effects of AKA vasospasm-induced Onuf's nucleus degeneration, as a cause of intestinal ischemia, following SAH have not yet been studied in any experimental rabbit model. Rabbits are laboratory animals frequently used in studies of the spinal cord ischemia damage.[46] Mazensky et al reported that http://www.ajnr.org/cgi/ijlink?linkType=ABST&journalCode=jtcs&resid=117/5/898 AKA was present in all the rabbits they studied. Using rabbits in the study of AKA ischemic injury has technically some advantages than using other animals, such as mouse or rat, because of the bodily proportions of these two species. Moreover, there are some studies that

make the presence of the artery of Adamkiewicz in rats questionable.[47]

4.8. Clinical perspectives of the presented study

The most of parasympathetic/sympathetic neurons projecting to the pelvic and pudendal nerves are located primarily in the L6—S2 ganglia.[48] Mesenteric artery vasoconstriction-related mesenteric artery infarcts are not rare following stroke or SAH.[11] Nonocclusive mesenteric ischemia have extremely high mortality because of intestinal gangrene.[12] Mesenteric ischemia could cause intestinal necrosis.[13] Mesenteric artery vasospasm related ischemic degenerative enteric complications should be considered as a forgotten etiological factors on the worsened prognosis of SAH.

4.9. Limitations

This study shows the histopathological results following AKA vasospasm-induced Onuf's nucleus degeneration and mesenteric artery vasospasm-related intestinal macro/micro structural changes following SAH. To obtain better results, mesenteric artery angiography, abdominal USG, and some neurophysiological research should be conducted.

5. Conclusions

Sacral parasympathetic network injury may be considered a possible cause of undiagnosed acute intestinal problems. Finally, All intensive care units physicians should remember that mesenteric artery vasospasm and related complications could be most forgotten etiological factors on the development of mesenteric artery circulation disorders. Unfortunately, the effects of spinal cord ischemia-related intestino-pelvic disorders generally have been ignored in past—current medical applications.

Conflict of interest statement

The Authors declare that they have no conflict of interest to disclose concerning the topic of the present paper.

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Ethical approval

Ethics Committee for Animal Experiments approval was obtained. All procedures performed in studies involving animals were in accordance with the ethical standards of the institution or practice at which the studies were conducted.

Disclosure statement

Nothing to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.asjsur.2018.12.004.

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