New Insights of the Fever Following Subarachnoid Hemorrhage and Introducing a new Thermoregulator Like Structure in Choroid Plexuses; Preliminary Study

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Abtract

Objective: Vagal nerves and their thermoreceptors could regulate temperature of brain. Cerebrospinal fluid (CSF) is increased in the early phases of subarachnoid hemorrhage (SAH). We hypothesised that choroid plexuses probably innervated by vagal nerves may play a role on the regulation of brain temperature and studied this subject.

Methods: This study was conducted on 32 rabbits, divided into four groups, with five rabbits in the control group (group I), five rabbits in the sham group (Group II), and 22 rabbits in the SAH group. In the SAH group, 7 of the animals were decapitated after 7 days of cisternal blood injections (Group III), and the other 15 animals were decapitated after 21 days of injections (Group IV). Brain temperature via laser thermometer 5 times a day during the experiment was measured. Normal and degenerated neuron density of nodose ganglia, water vesicles numbers of choroid plexuses were stereologicallyanalyzed. Statistical analysis was performed.

Results: At histopathologic analysis of present study, thermo regulator like structure was noted and the mean number of this structure was estimated.The mean number of water-filled vesicles, thermo regulator like structure, in SAH-induced animals,brain temperature and degenerated neuron density of nodose ganglia was statistically different between the early decapitated group (group III) and the late decapitated group (group IV) ($P<0.05$).

Conclusions: We introduce a thermo regulator like structure, describe a new syndrome. In addition, it was noted thatwater-filled vesicles of CP are increased, brain temperature in nearly normal in the early phase of SAH due to likely irritation of vagal nerves. However in the late phase, mean number of water-filled vesicles numbers decreased in accordance with increased brain temperature with degenerative changes of the nodose ganglion.

Key words: choroid plexus; nodose ganglion; vagal nerve; temperature; subarachnoid hemorrhage; fever.

Acta Neurol Taiwan 2019;28:1-11

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Received December 1, 2018.
Revised & Accepted December 18, 2018.

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INTRODUCTION

SAH (subarachnoid hemorrhage) is a devastating [(1)] neurosurgical disease. Overall, 85% of patients with nontraumatic SAH result from a saccular aneurysm rupture[(2)]. During the past 2 decades, neuroscientists have gained an improved understanding of the pathophysiological events that occur after SAH[(3)]. Despite this situation and the other technologic development of neurosurgical practice[(4),(5)], SAH still has high morbidity and mortality[(6)], which has been changed very little from what it was 40 years ago[(7)]. The management of patients with SAH remains critical[(8)]. Many studies investigated the overall critical symptoms and signs of patients with SAH. The classical view of fever production is that it is modulated in the ventromedial preoptic area in response to signaling by pyrogenic cytokines elaborated in the periphery by mononuclear phagocytes and the consequent induction of cyclooxygenase dependent prostaglandinE[(9)], in the ventromedial preoptic area[(10)]. The most meaningful way to follow a traumatic or nontraumatic brain-injured patient in the Intensive Care Unit is to perform serial bedside neurological examinations[(11)]. In these examinations, fever has been hourly checked in patients with SAH. Fever can also be seen in patients with SAH. In neurosurgical practice, fever can be attributed to infections[(12)], or surgery itself. It can increase the risk of mortality of patients with SAH, and this subject has not been well studied. Underlying mechanism of hyperthermia following SAH has definitely been unknown up to now. What occurs following SAH? We hypothesized thatCP and vagal nerves may play arole on the regulation of brain temperature, but this pathway has not been definitively investigated. This subject was studied.

MATERIAL AND METHODS

The study protocols were approved by the Ethics Committee of Erzurum Ataturk University, Medical Faculty. This study was conducted on 32 rabbits, divided into four groups, with five rabbits in the control group (group I), five rabbits in the sham group (Group II), and twenty two rabbits in the SAH group.

3.1: Experimental Procedure:

A balanced, injectable anesthetics were used in order reduce pain. After anesthesia was induced with isoflurane given by a face mask, 0.2 mL/kg of the anesthetic combination (Ketamine HCL, 150 mg/1.5 mL; Xylazine HCL, 30 mg/1.5 mL; and distilled water, 1 mL) was subcutaneously injected. Five of them had been selected from the control group (n=5). Five of them were selected SHAM group (n=5) by injecting 1cc of serum saline and twenty two of them selected from which applied SAH by injecting autologous blood into their sisterna magna using a 22-gauge needle, over about one minute after 1 cc CSF aspiration. (n=22). Autologous blood (1 mL) was taken from the auricular artery. The animals in the control group were not subjected to this procedure. . In the SAH group, 7 of the animals were decapitated after 7 days of cisternal blood injections (Group III), and the other 15 animals were decapitated after 21 days of injections (Group IV). The operations were performed bilaterally. The neck was opened and both vagal nerves were exposed. The nodose ganglion its neuronal connections was extirpated, cleaned of connective tissue at low temperature (2-5°C). Histopathologic Procedures were performed as reported as other authors [(7)(13)(14),(15)]. The CP tissues were obtained through a graded alcohol series and embedded in liquid paraffin. The CPs of lateral ventricles were obtained from coronary sections of brains at the levels of temporal horns of the lateral ventricles; 5-mm sections at distances of 30 mm were created. Each 30th and 31st section was sampled to count water vesicles. Total number of water vesicles of the CP was estimated by the fractionation method. Sections were stained with hematoxylin and eosin, TUNNEL and Masson trichrome for SAH-related damage and examined stereologically to discern water-filled vesicles, which were examined under a light microscope and counted. Photographs were taken between 40X and 20X magnification. All vesicles were accepted as irregular sphere and their radius values were calculated as (a+b+c)/3. Then, volume value of each sphere were estimated as the following formula:. Then all vesicles volume values were estimated by this formula:

$$\sum_{1}^{n} \mathbf{Vf} = \sum_{f=1}^{n} n\,[[\frac{4}{3}\pi\langle\frac{a+b+c}{3}\rangle^{3}]]*$$

3.2: Stereological analyses

The analyses of histopathological data of water-filled follicles degenerated neuron density of nodose ganglion, thermoregulator- like structure of choroid plexus were performed. To obtain an estimation of the of total number of water-filled follicles, degenerated neuron density of nodose ganglion, thermoregulator-like structure of choroid plexus, 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 neuron density of nodose ganglion. 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 number of water-filled follicles, degenerated neuron density of nodose ganglion, thermoregulator- like structure of choroid plexus wereestimated using the following formula;

$$NvGN=\Sigma Q^{-}N/txA.$$

Where $\Sigma Q^{-}N$ is the total number of counted neurons, vesicles and thermoregulator- like structure 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 and vesicles in each specimen.

Brain temperatures via laser thermometer five times a day during the experiment were measured. Normal and degenerated neuron density of nodose ganglia, water vesicles numbers of choroid plexuses were stereologicallyanalyzed. Differences between groups were compared using Mann-Whitney-U test. This test is a nonparametric test that allows two groups to be compared without making the assumption that values are normally distributed. The null hypothesis asserts that the medians of the two samples are identical. The *p*-value was acceptedsignificant at the level of 0.05. (Confidence interval 95%)

RESULTS

The mean number of thermo-regulatuar-like structure was also estimated. The mean number of water-filled follicles per cubic millimeter was 8.5±2.1 the in control group (Group I), 6.5±1.2 in the sham group (Group II), 20.3±6.32 the in early decapitated group (Group III), and 5.23±1.12 in the late decapitated group (Group IV). The mean number of degenerated neuron density of nodose ganglia was 9±3, 50±9, 90±9, and 3.210±410 in the control (Group I), sham (Group II), early decapitated

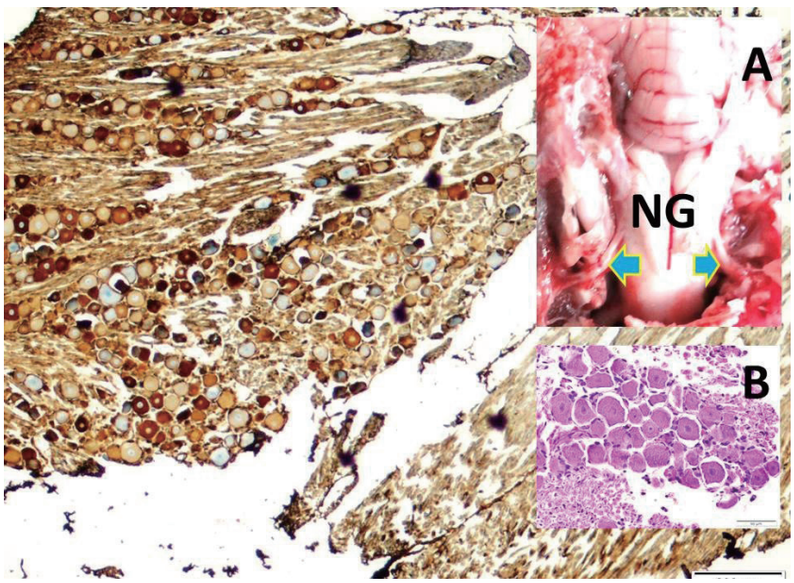

Figure 1. IX. - X. Cranial nerves and nodose ganglia (NG) of vagal nerves. A low magnified histopathological appearance of nodose ganglion (A: LM, H & E, × 10/B) and GFAP immunostaining methods of a normal rabbit (B: LM, H & E, × 40).

(Group III), and late decapitated group (Group IV), respectively. Thermoregulatuar-like structures were atrophied and degenerated with SAH. Figure 4,5,6 shows the atrophy and degeneration of this structure. Brain temperature was measured. The mean numbers of thermo regulator like structure per mm^3 and brain temperature were as 10.40±2.23 and 35.46°C in control group, 9.03±2.34 and 35.65°C in SHAM, 6.84±1.87 and 37.12°C in group III and 4.54±1.95 and 38.94°C in the group IV (see table). The mean number of water vesicles, thermoregulator like structure, brain temperature and degenerated neuron density of nodose ganglia was statistically different after SAH between the early decapitated group (group III) and the late decapitated group (group IV) ($P<0.05$) (See Table).

Cranial nerves IX and X and nodose ganglia (NG) of vagal nerves of a rabbit with SAH are seen in figure 1. In figure 2, anatomical appearance of a rabbit with SAH in (A). histopathological appearances of ischemic (B) and apoptotic neurones of nodose ganglia of vagal nerves (Base) are seen. : histopathological appearance of choroid plexus with a corpuscle like theromocorpuscle in red (Base) and magnified form (A) of a normal rabbit is seen in Figure 3. Histopathological appearance of a ischemic edematous degenerated choroid plexus (Base) and deformed corpuscle like thermoreceptor cells are seen in a rabbit with SAH (A and B) in Figure 4.

Table. shows water-filled vesicles, degenerated neuron density of nodose ganglion, thermo regulator- like structure and brain temperature of studied groups. Group I; control group, Group II; sham group, Group III; Early decapitated group, Group IV; late decapitated group.

Groups	Water-filled vesicles / mm^3	Degenerated neuron density of nodose ganglion/mm^3	thermo regulator-like structure/mm^3	Brain Temperature
Group I	8.5±2.1	9±3	10.40±2.23	35.46°C
Group II	6.5±1.2	50±9	9.03±2.34	35.65°C
Group III	20.3±6.32	90±96	6.84±1.87	37.12°C
Group IV	5.23±1.12	3210±410	4.54±1.95	38.94°C

Group I; control group, Group II; sham group, Group III; Early decapitated group, Group IV; late decapitated group.

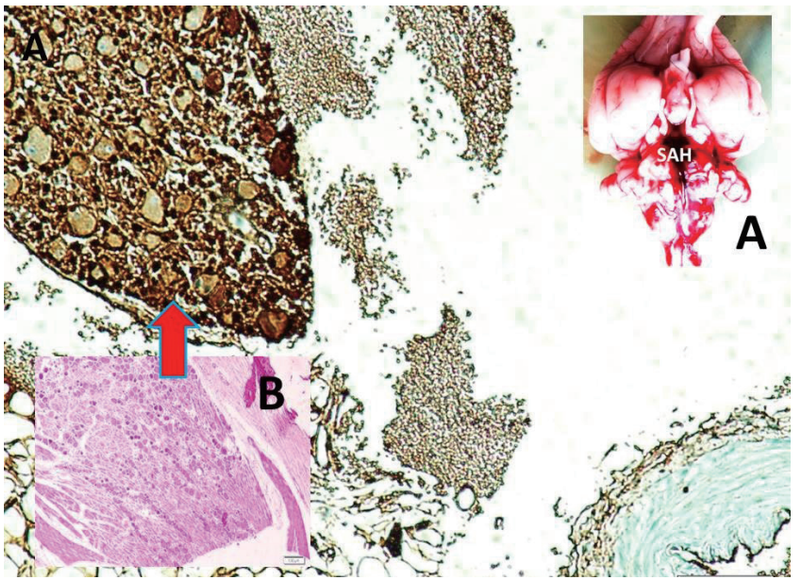

Figure 2. Anatomical appearances of a rabbit with SAH (A). Histopathological appearances of ischemic (LM, H & E, ×10/B) and apoptotic neurons of nodose ganglia of vagal nerves (LM, Tunel, ×10/Base).

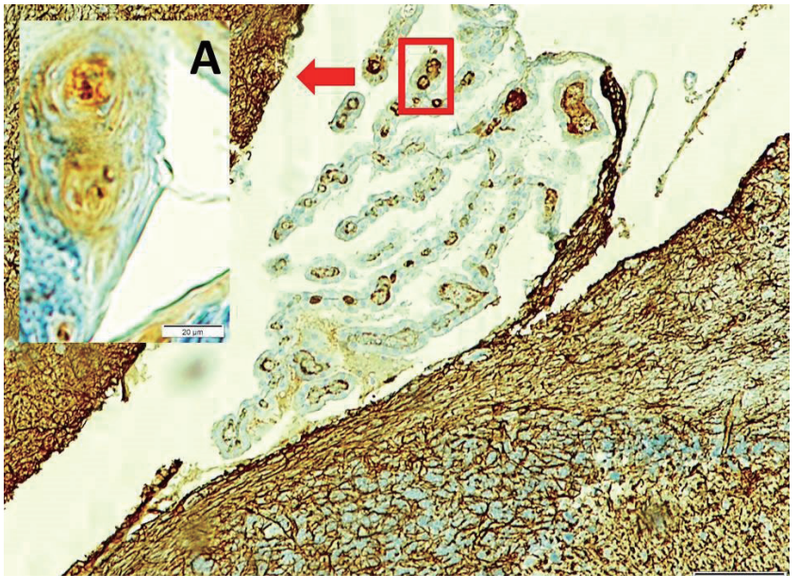

Figure 3. Histopathological appearance of choroid plexus with a corpuscle like theromocorpuscle in red (LM, NSE, ×4/Base) and magnified form (LM, NSE, ×20/A) of a normal rabbit is seen .

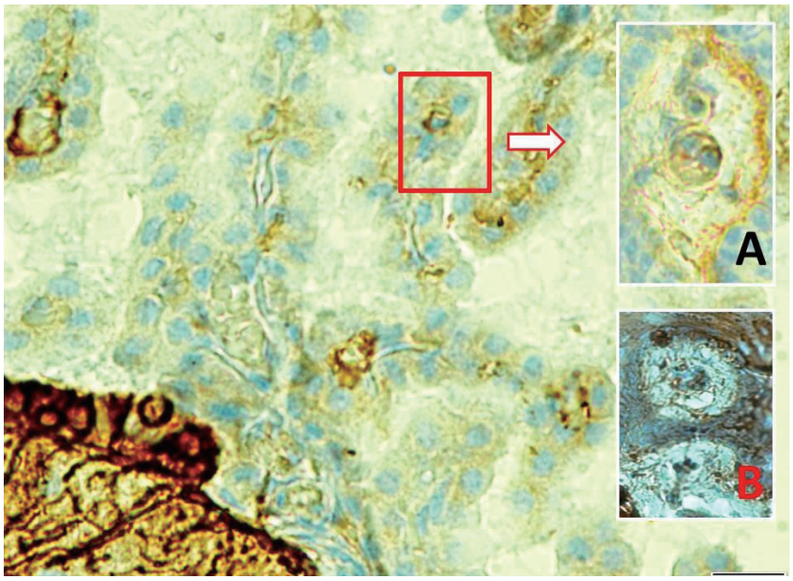

Figure 4. Histopathological appearance of a ischemic edematous degenerated choroid plexus (LM, GFAP, ×10/Base) and deformed Krause corpuscle like thermoreceptor cells are seen in a rabbit with SAH (LM, NSE, ×40/A; LM, Tunel, ×40/B).

DISCUSSION

5.1. Neurophysiology and anatomy

Having broad knowledge of anatomy is essential for practicing neurosurgery[16]. Certain anatomical structures call for detailed study due to their functional importance[14,17]. One of this structure is the nodosel ganglion. The cell bodies of vagal and spinal visceralafferents are contained within the vagal nodose and dorsal root ganglia[18]. Visceral thermoreceptors are also thought to play an important role in the regulation of body temperature[19]. Recent physiological studies have shown possible roles of the vagus nerve in thermoregulation[20]. In this study, we investigated the interaction among water-filled vesicles of CP, brain temperature and the nodose ganglion degeneration, and found an important effect of degenerated neuron density of nodose ganglion on occurring fever following SAH. The

three major findings of this investigation were (i) there is a hyperpyrexia related syndrome following SAH. We called this syndrome as subarachnoid hemorrhage-hyperpyrexia syndrome. (ii) In this syndrome, water-filled vesicles of CP are increased, brain temperature in nearly normal at the early phase of SAH, likely due to irritation of vagal nerves. (iii) at the late phase, however, mean number of water-filled vesicles numbers decreased in accordance with increased brain temperature with degenerative changes of the nodose ganglion. These two events were previously reported to occur by the role of petrous ganglion of glossopharyngeal nerve[14]. There was inverse relationship between mean number of water-filled vesicles numbers and brain temperature with degenerative changes of the nodose ganglion. (iv) In addition, these findings, we noted previously undefined a structure in choroid plexuses, named it as thermo regulator like structure (Figure 2). Virtually nothing is known about this structure and relationship of this structure with nodose ganglion of vagal nerve. There is an interaction between water-filled vesicles, degenerated neuron density of nodose ganglion, thermo regulator- like structure and brain temperature (see table). Figure 2,3,4,6 shows atrophy of thermoregulatuar-like structure, apoptosis of choroid plexus. Accepting that afferents from the vagus nerve serve to transport signals from the CP the nodose ganglion, the question then arises whether afferents from thermal regulator like structure may represent a neural route for CP and vagal nerve or not. Prevention or effective treatment of fever following SAH could considerably reduce morbidity and mortality of SAH. Our finding will add new insights into mechanism of the fever following SAH.

5.2. Perspectives; Fever following SAH: what happens within the brain? Is there a role of inflammation

Immunity is important in the brain, The brain has been considered to be an immune privileged organ[21]. After extravasated arterial blood enters subarachnoid space, SAH develops and blood mixes with cerebrospinal fluid. As a result, many pathologies develop, including blood-brain barrier (BBB) breakdown, increase in brain-blood barrier (BBB) permeability and activation of peripheral leukocytes, that in turn augments immuno-inflammatory respons, brain edema, as well as the early or delayed vasospasm. As a result of disruption of the integrity of BBB, accumulation of neutrophils and macrophages in the brain occur and initiate of the inflammatory processes[22]. Both neurogenic inflammation and the classic inflammatory cascade have been suggested to occur in SAH[23]. This inflammation is one major cause of poor outcomes of SAH, and, may play a key role in brain injury following SAH[21]. However, the exact mechanism of the development of inflammation following SAH is not well understood. Cerebrospinal fluid contacting neurons have been observed in various brain regions such as the hypothalamus, the dorsal nucleus of the raphe and around the central canal of the spinal cord but their functional role remains unclear[24]. In this study, we present new experimental data that indicate that thermo-regulator like structure of choroid plexus.

The importance of choroid plexuses following SAH

The emergence of dedicated neurologic-neurosurgical intensive care units, advancements, and aggressive monitoring have contributed to overall improved outcomes for patients with aneurysmal subarachnoid hemorrhage (aSAH) over the past two decades[25], currently, neurosurgery has gone through moments of great renewal[26], but spontaneous subarachnoid hemorrhage (SAH) is still life threatening [6,15]. There is a complex autonomic innervation of the choroid plexuses by sympathetic and parasympathetic nerves[27]. The effect of SAH on the autonomic nervous system has been the focus of much investigation[7,14,16,21,28,29,30,31,32,33], however, the nerves of choroid plexuses is seldom studied. Yilmaz at al hypothesized that the choroidal artery vasospasm after SAH may be resulted in plexus injury[27]. This could be lead to atrophy of choroid plexus and diminished cerebrospinal fluid (CSF) production[27]. The diminished CSF production may be one of reasons of cerebral hypertermia[27]. In the last 5 years, several studies have shown the histopathological changes of choroid plexus following SAH. [13,14,34]. Two of these studies[14,13] demonstrated the water-filled vesicles as a cause of hypersecretion of CSF from choroid plexus. This hypersecretion may be response to hyperpyrexia following SAH. In the third study[35], it was shown that choroidal artery vasospasm–related aqueductal stenosis[34] and the caliber of the cerebral aqueduct differ in early, middle, and late phases of hydrocephalus depending on the vasospasm

of the choroidal artery. These histopathological studies have enhanced the neurologist's and neurosurgeon's view of SAH[36]. It appears that CSF secretion is tonically inhibited by the sympathetic innervation which is independent of choroidal blood flow[9], and may function to reduce CSF secretion if the drainage resistance increases. The sympathetic nerve system plays a role in the regulation of cerebral blood flow.

5.3. Clinical Messages

Message 1- Treatment of aneurysmal subarachnoid hemorrhage is important. A better understanding of the pathophysiology of fever following SAH will for sure lead to better patient outcome. Same opinion can be said for hyperthermia and hydrocephalus[13],[37].

Message2-The optimal treatment for a patient with SAH, the cause of hydrocephalus, hyperthermia, delayed cerebral ischemia should be to resolved. During the late phase of SAH, irreversible axonal injury of the vagal nerve resembles a blockade of the vagal nerves[33]. Vasospasm-induced cerebral infarct is still a significant cause of poor outcome after aneurysmal subarachnoid hemorrhage[38]). In SAH, vasospasm occurs and this alters the blood flow of the vagal nerve roots[33]. The proper functioning of brain cells relies on an abundant and continuous supply of oxygen. Continuous oxygen delivery and CO_2 clearance are paramount in the maintenance of normal brain tissue[3]. The cell death and cell proliferation have a balance and this is vital in all tissues, especially in the nervous system[39],[34], the vagal nerves, and nodose ganglia. The concept of vagal participation via nodose ganglia in conveying pyrogenic messages from the thermoregulator like structure of choroid plexus to the brain is interesting finding. We found this structure of choroid plexus under light microscopy. Our data supports the idea that the CP function similarly as sensory organs. Further ultrastructural investigations are needed to clarify the exact nature of this structure, but we suggest that this structure resemble a receptor. Decreased mean number of this structure and water-filled vesicles by degeneration of nodose ganglion may lead to hyperthermia following SAH (see table, figure 2,3,4,5,6). This is the first direct describing of the mentioned structure. In the present study, it was shown that SAH causes not only cerebral ischemic insult but also brainstem and vagal nerve injuries.

It was hypothesized that ischemic nodose ganglion injury of vagal nerve or its degeneration seem to be an important factor in the development of hyperpyrexia following SAH. It seems to be imperative to understand this process to better target treatments. For that reason, our findings in this study are functionally important. SAH clot removal which can be only made by early surgery may be effective in preventing nodose ganglion injury and fever.

Fever and SAH

Fever is commonly seen in patients with SAH, and this fever or hyperthermic state is not always associated to the presence of an infection. We suggest that nodose ganglion is injured due to SAH and aggravates the mortal effect of hyperpyrexia in SAH Neuroprotection with prevention of hyperpyrexia might be accepted as an ultimate target following SAH. We copiously stress the fact that we are the first ones to report on hyperpyrexia associated with nodose ganglion injury following SAH and that the recognition of this fact is of importance. If indeed one is the first to report something, that something is ofvalue[40),(41),(42),(43)]. The opening of new horizons of this kind of knowledge will helpunderstand the complex challenge of SAH.

5.4. Limitation of the study

In the present study, it was concluded that "the cause of hyperpyrexia in SAH may be due to secondary injury to nodose ganglion of vagal nerve due to cerebral herniation", but we have not proven herniationin this experiment; however the cause and effect relationship was recognized at the end of the experiment. This is a great disadvantage of the study. Although our hypothesis about thermoreceptors like structure in choroid plexuses and the role nodose ganglia of vagal nerves underlying temperature regulation seems to be attractive, it will be difficult to accept this finding on the basis of a single experimental study. There can be concern about why the structure identified in the choroid plexus has been considered to be a receptor/thermoreceptor. The link between hyperpyrexia and the histological findings is questionable, i.e. cause or effect of a different process altogether. In this study, the mean numbers of thermo regulator like structure per mm^3 was 10.40 ± 2.23 in control group, 9.03 ± 2.34 in SHAM group. In this study, the

saline injection for itself led to a slight decrease the mean numbers of thermo regulator like structure per mm^3. Those changes were prominent in Group III and IV animals with SAH. Saline injection in SHAM group can be harmful, and lead to some changes in subarachnoid space[44]. SAH produces bloody cerebrospinal fluid, and neural degeneration can occur as a result of this bloody or highly proteinous cerebrospinal fluid[45,46]. The fever following SAH may be response to this bloody or highly proteinous cerebrospinal fluid.. In a study, where saline was injected in the sciatic nerve,swelling surrounding the axons of some nerve fibers, formation of degenerated regions in the myelin sheaths, separation of the lamellae of myelin from each other, and mild degeneration of axons in some nerve fibers were detected[44]. There are several animal models of experimental SAH techniques (endovascular puncture, cisterna magna blood injection, and blood clot placement) that have been used by neuroscientest. However, we and other some investigators[17,37,34] suggest that experimental model of SAH may not accurately mimic the human disease process, however our finding may have some relevance to the human SAH model.

CONCLUSION

The management of SAH requires a comprehensive understanding the pathophysiology, which is paramount to defining treatment strategies and algorithms In this study, thermo regulator like structure of choroid plexuses, and a distinct pathway of fever induction in response to SAH were introduced. We found that water-filled vesicles of CP are increased, brain temperature in nearly normal in the early phase of SAH due to likely irritation of vagal nerves. However in the late phase, mean number of water-filled vesicles numbers decreased in accordance with increased brain temperature with degenerative changes of the nodose ganglion.The present study also provides evidence about a temperature-sensitive structure of CP which has in vagal afferent neurons in the nodose ganglion of CN X. These structures may play a role in the sensory innervation of the CP and are likely to confer temperature sensitivity on some vagal afferent neurons following SAH. Induction and regulation of fever following SAH result from complex bilateral communication among thermo regulator like structure of choroid plexuses, the nodose gangliaof vagal nerves and central nervous system. Our study also adds new insights into mechanism of the fever following SAH. More detailed studies are needed.

Conflict of interest: None

ABBREVIATIONS

BBB: blood–brain barrier

CP: choroid plexus

CSF: Cerebrospinal fluid

ICP: intracranial pressure

JG: jugular ganglia

NG nodose ganglia

PG: petrosalganglia,

SAH: subarachnoid hemorrhage.

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