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Dilcan Kotan[1, A, B, D–F], Mehmet D. Aydin[2, A, E, F], Cemal Gundogdu[3, C, F], Recep Aygul[4, B, F], Nazan Aydin[5, E, F], Hizir Ulvi[6, E, F]

Parallel Development of Choroid Plexus Degeneration and Meningeal Inflammation in Subarachnoid Hemorrhage – Experimental Study

[1] Department of Neurology, Faculty of Medicine, Sakarya University, Turkey
[2] Department of Neurosurgery, Faculty of Medicine, Ataturk University, Erzurum, Turkey
[3] Department of Pathology, Faculty of Medicine, Ataturk University, Erzurum, Turkey
[4] Department of Neurology, Ataturk University, Faculty of Medicine, Erzurum, Turkey
[5] Department of Psychiatry, Ataturk University, Faculty of Medicine, Erzurum, Turkey

A – research concept and design; **B** – collection and/or assembly of data; **C** – data analysis and interpretation; **D** – writing the article; **E** – critical revision of the article; **F** – final approval of article; **G** – other

Abstract

Background. The choroid plexuses (CPs) are brain structures located in the brain ventricles, involved in the production and reabsorption of cerebrospinal fluid (CSF) components, cerebral immune surveillance, and various endocrine-enzymatic activities and acts as a CSF-blood barrier. This study investigated to determine if there is a link between ischemic CP injury and meningo-cerebral inflammation processes.

Material and Methods. This study was conducted on 18 rabbits. Four rabbits were used as the baseline group to examine the normal structures. Fourteen of the rabbits were used as the study group by injecting 1.00cc of homologous blood into their cisterna magna. The animals were followed by daily monitoring for ten days and then slaughtered. Apoptotic degeneration of the CP cells was determined and statistical analyses were carried out using normal and apoptotic CP cell numbers. Data analyses were comprised of Mann-Whitney *U* tests. Differences were considered to be significant if $p < 0.005$.

Results. Five animals belonging to the study group died between the 5th and 8th days. Unconsciousness, neck stiffness, convulsion, fever, apnea, cardiac arrhythmia, and breathing disturbances were observed in all of the animals who subsequently died. Intraventricular blood leakage was detected in all the dead and three surviving animals. Choroidal artery spasm, choroidal ependymal cell injury, choroidal cell apoptosis, pia-arachnoid thickening, meningocortical adhesions and blood cell density in the subarachnoid spaces were more severe in the more CP degenerated animals than those of the others. There were significant differences between the apoptotic CP cell density and blood cell density in the subarachnoid spaces ($p < 0.005$).

Conclusions. Subarachnoid hemorrhage (SAH) extending to brain ventricles causes ischemic degeneration of the CP by way of triggered choroidal artery vasospasm. It should be emphasized that the prevention of CP function may be an important part of the protection of the brain in SAH (**Adv Clin Exp Med 2014, 23, 5, 699–704**).

Key words: choroid plexuses, subarachnoid hemorrhage, vasospasm.

The choroid plexuses (CPs) are brain structures located in the brain ventricles that comprise highly vascularized villi and ciliated modified ependyma [1]. CPs constitute up to 60% of the ventricular volume in the young, but the volume declines in percentage in the elderly [5]. CP epithelium consists of cuboidal epithelium with brush borders. Cubic epithelial cells have a central round nucleus, several Golgi apparatuses, lysosomes, mitochondria, free ribosomes, microtubules and rough endoplasmic reticulum. Villi of CPs contain large capillaries surrounded by a thin stroma. CPs are involved in the production, transport and reabsorption of various immune and endocrine molecules. The stromal spaces between capillaries and epithelium are very thin and contain collagen fibers, non-myelinated nerve fibers, a few macrophages or dendrite cells, certain pial cells, abundant arterioles and

venules. However, CPs are severely modified and calcify quickly [21]. CPs constitute a selective cerebrospinal fluid-blood barrier and participate in cerebral immune surveillance [16]. Epithelial cells of CPs secrete and/or store hormones (e.g. prolactin, growth hormone) [12], some vitamins (e.g. thiamine, vitamin C, B12 or folates) and immunoglobulins (e.g. IgA, Ig G) [20]. Recently, there are a number of studies suggesting the possibility that secretory epithelial cells of the CPs present a potential window into the central nervous system for the purposes of drug delivery [14, 25]. CPs in the lateral ventricles are mainly supplied by anterior choroidal arteries. CPs are innervated by sympathetic and parasympathetic nerves and deteriorated autonomic centers rely on CP pathologies [2, 4, 23]. CPs are highly vulnerable to damage in brain injuries [17], infections [24] and ischemic conditions [18]. CPs are involved in a variety of neurological disorders, including Alzheimer's and other neurodegenerative diseases, multiple sclerosis and other inflammatory conditions, as well as infectious, traumatic, neoplastic, and systemic diseases. An examination of molecular alterations in the brain led investigators to consider the role of CPs during systemic inflammation [7, 26]. Subarachnoid hemorrhage (SAH) cause severe vasospasm and results in ischemic brain damage [9, 11]. Focal cerebral ischemia results in apoptotic cell death in CPs [8]. Apoptosis is an active death process [13] determined by TUNNEL staining [6]. Total body hyperthermia causes CP and brain injury [10, 22]. It is imagined that a high body temperature is responsible for CP and brain injury, and CP degeneration may cause dehydrated, hypothermic, inflammatory and immuno-deficient brain injury. CP-protective treatment methods may be useful in the future.

Material and Methods

This study was conducted on 18 anesthetized adult male New Zealand rabbits (3.7 ± 0.4 kg). The animal protocols were approved by the Medical Faculty Ethics Committee of Erzurum Ataturk University. The care of the animals and the experiments themselves were conducted according to the guidelines set forth by the same ethics committee. Four of them (n = 4) were used as the control group. In control animals, the heart rate was 254 ± 26/min, the respiratory rate was 31 ± 7/min, saturation of hemoglobin with oxygen as measured by pulse oximetry was 92 ± 6% and body temperature 35.4 ± 1.2°C (Table 3).The remaining (n = 14) were left hungry for 6 h before surgical intervention. A balanced injectable anesthesia was used to reduce pain and mortality. After anesthesia was induced with isoflurane via 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 injected subcutaneously prior to surgery. During the procedure, a dose of 0.1 mL/kg of the anesthetic combination was used when required. Autologous blood (1 mL) was taken from the auricular artery and injected over the course of 1 min using a 22-Gauge needle into the cisterna magna of the animals in the SAH group (Fig. 1). The animals in the control group were not subjected to this procedure. The animals were followed for 10 days without any medical treatment and then euthanized. All the brains were rapidly removed and they were kept in 10% formalin solution for 7 days. Then, 5 μm of the tissue sections were taken and stained with H & E and TCM stain. Semithin sections were examined with an Olympus photomicroscope. The Biocomputerise system was used to measure the height of epithelial cells and villi. CPs of the fourth ventricles, meninges, subarachnoid spaces and parietal cortexes were examined. In the examination CPs, cuboid epithelial cells, choroid villi, ciliary extensions of the choroidal bodies and choroidal arteries investigated. Cellular shrinkage, angulations, cytoplasmic condensation, shortened or desquamated villi and decreased cellular height were accepted as CP epithelial cell degeneration criteria. Endothelial condensation, desquamation, inner elastic membrane convolutions and luminal narrowing were accepted as a choroidal artery vasospasm indicator of apoptotic degeneration of CP cells examined with a TUNNEL stain of the CP specimens.

Blood cell density was estimated using Cavalieri and stereological methods per mm^3 of subarachnoidal spaces (n/mm^3). Apoptotic cell density of the CPs and blood cell density in the subarachnoid spaces were compared statistically.

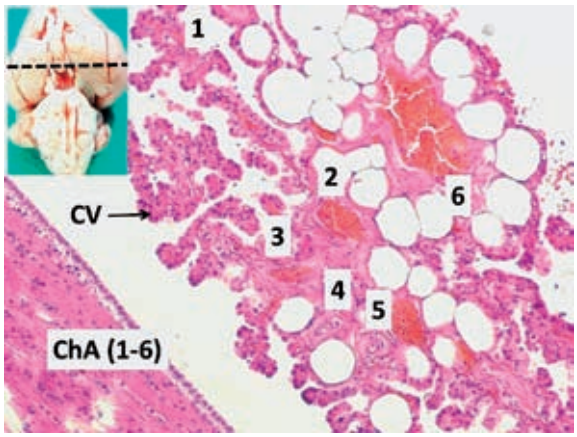

Fig. 1. Normal brain and section level to observe CPs (upper left) and histological appearance of CPs are seen (ChA1-6 – choroidal arteries, CV – choroidal villi of choroidal cells). (LM, H&E, ×100)

To evaluate the significance of the detected differences, Mann-Whitney *U* tests were used (two- - tailed, significance limit p = 0.05). All statistical calculations were performed using SPSS program 13.0 for Windows. Median and average values between the groups were used and statistical results were drawn from these results. P < 0.05 was accepted as meaningful.

Results

Five animals that belonged to the study group died between the 5th and 8th days. Clinically, ischemic attacks, convulsion, unconsciousness, cardiac arrhythmia and breathing disturbances were frequently observed in the animals that subsequently died. Massive subarachnoid and blood collection was observed in all dead and 3 surviving animals. Normal anatomical representation of the brain and histological structures of normal CPs are illustrated in Fig. 1. Abundant blood collection in the basilar regions and basal cisterns were observed in the brains of the dead animals. In the CPs of the animals, intrachoroidal hemorrhage focuses, choroidal artery vasospasm, cuboidal cell shrinkage, angulation, shortened villus and ciliary extensions were detected (Fig. 2). Blood cell density was detected as 20 ± 7 cells/mm^3 in normal animals, 480 ± 115 cells/mm^3 in the surviving animals (Fig. 3), and 1400 ± 370 cells/mm^3 (Fig. 4) in the dead animals.

After SAH, increased respiration frequency (tachypnea) and shorter inspiration and longer expiration time, apnea–tachypnea attacks, diaphragmatic breaths, and respiratory arrest were observed. The mean respiration rhythm was detected as 44 ± 8/min and pulse oximeter oxygen saturation 73 ± 5% in the dead animals. The average heart rate was 304 ± 32/min and body temperature

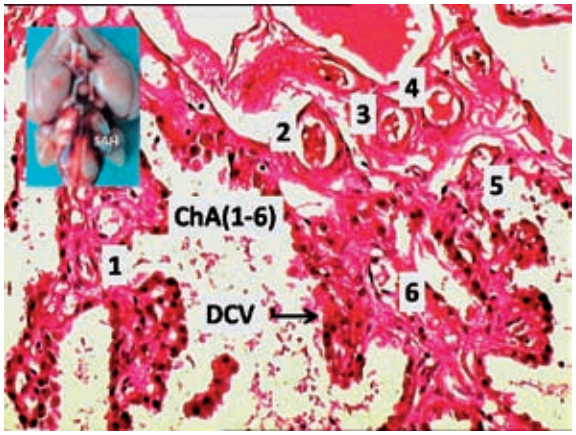

Fig. 2. A brain with subarachnoid hemorrhage (SAH – upper-left) and histological appearance of degenerated CPs is observed in a SAH created animal (ChA1-6 – choroidal arteries; DCV – degenerated choroidal villi of choroidal cells). (LM, H&E, ×100)

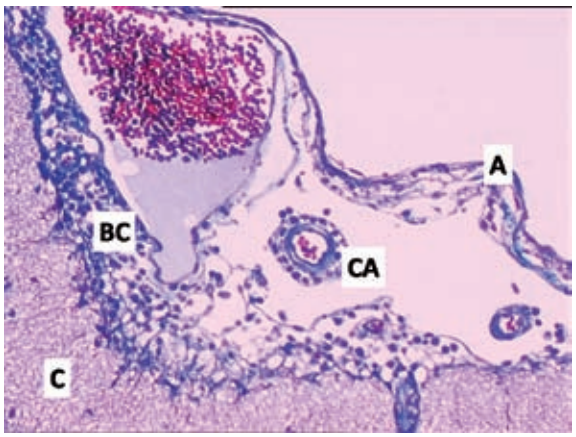

Fig. 3. Histopathological appearance of parietal region of SAH created and survived animal (CA – cortical arteries; A – arachnoid; BC – blood cells in a subarachnoid space; C – cortex). (LM, TCM, ×100)

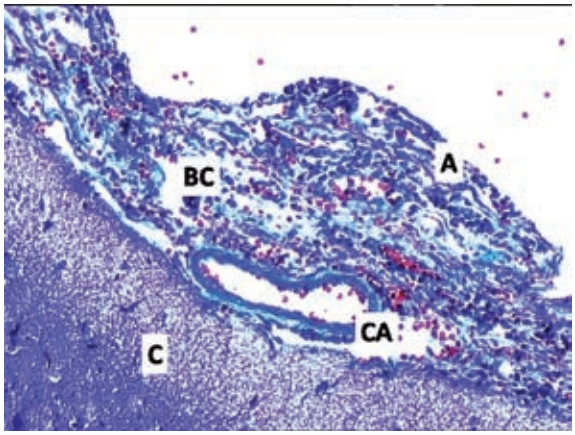

Fig. 4. Histopathological appearance of the parietal region of SAH created in a dead animal. The greater blood cell accumulation and inflammation are seen (CA – cortical arteries; A – arachnoid; BC – blood cells in a subarachnoid space; C – cortex). (LM, TCM, ×100)

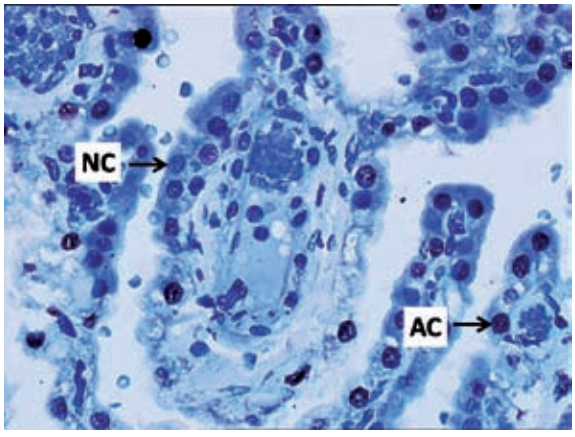

Fig. 5. Histopathological appearance of CPs of SAH created and dead animal. More apoptotic cells (dark) are observed than normal cells (clear) in the dead animals (AC – apoptotic cells). (LM, Tunnel Stain, ×100)

Table 1. The table showing the mean volume values of all CPs of all groups ± SD. Blood cell density was detected as 20 ± 7 cells/mm^3 in normal animals, 480 ± 115 cells/mm^3 in surviving animals (Fig. 3), and 1400 ± 370 cells/mm^3 in dead animals. The density of choroidal cells was estimated as 4500 ± 450/mm^3 in normal animals. The density of normal cells was estimated as 3468 ± 270/mm^3 and 1100 ± 250/mm^3 of apoptotic cells in the surviving animals. Normal cell density was 2630 ± 330/mm^3 and apoptotic cell density was 1870 ± 3100/mm^3 in the dead animals. Massive SAH may also cause apoptotic degeneration in the CP. There were a significant differences between the apoptotic CP cell density and blood cell density in the subarachnoid spaces (SAS) ($p < 0.005$)

	Normal Animals	Surviving Animals	Dead Animals
Normal cells of CP (n/mm^3)	4500 ± 450	3468 ± 270	2630 ± 330
Apoptotic cells of CP (n/mm^3)	10 ± 3	1100 ± 250	1870 ± 3100
Blood cells in SAS (n/mm^3)	20 ± 7	480 ± 115	1400 ± 370

Table 2. The table showing the mean height values of all choroidal cells of all groups ± SD. A significant reduction in the percentage of cell density was found in the study group, especially in the dead animals, compared to the control group. There was a significant SAH-dependent decrease in the numerical density of degenerated cells within the choroid plexuses among the normal, surviving and dead animals. The mean lymphocyte density was significant in survivors compared to normals ($p < 0.005$), and more significant in dead animals compared to survivors ($p < 0.001$) and the most significant results were detected between normal and dead animals ($p < 0.0001$)

	Normal Animals	Survivors	Dead Animals	p
Mean height of epithelial cells (μm)	14.45 ± 3.20	11.35 ± 2.20	9.55 ± 1.70	0.01
Mean microvilli of choroid plexus (μm)	3.10 ± 0.85	2.20 ± 0.25	1.40 ± 0.25	0.01
Mean lymphocyte density in subarachnoid space (mm^3)	10.00 ± 2.0	1.300 ± 350	10.000 ± 2700	0.005

Table 3. The mean heart rate, respiration rate and oxygen saturation was significant in dead animals compared to normals ($p < 0.01$), and more significant in dead animals compared to survivors ($p < 0.005$) and the most significant results were detected between normal and dead animals ($p < 0.001$). Body temperature differences are significant between the dead animals and living animals ($p < 0.001$)

	Heart rate (f/min)	Respiratory rate (f/min)	Body temperature (°C)	Pulse oximeter oxygen saturation
Normal	254 ± 26	31 ± 7	35.4 ± 1.2	92 ± 6
Living animals	292 ± 39	42 ± 9	38.2 ± 0.45	79 ± 8
Dead animals	304 ± 32	44 ± 8	39.8 ± 0.6	73 ± 5

was 39.8 ± 0.6°C (Table 3). Hyperthermia was observed in all the surviving and dead animals. Under conditions of hyperthermia we observed a dramatic increase in the levels of choroid plexus degeneration in SAH.

Pia-arachnoid thickening, meningeal adhesions and blood cell density in the subarachnoid spaces were observed to be more severe in the group with more CP degeneration than in those of the group with less CP degeneration. A comparison of CP and meningocortical degeneration scores were significant ($p < 0.005$). Apoptotic degeneration was also detected in the CPs (Fig. 5). Normal and apoptotic cell density was estimated using Cavalieri and stereological methods. The density of choroidal cells was estimated as 4500 ± 450/mm^3 in normal animals. The density of normal cells was estimated as 3468 ± 270/mm^3 and 1100 ± 250/mm^3 of apoptotic cells in the less affected animals. Normal cell density was 2630 ± 330/mm^3 and apoptotic cell density was 1870 ± 3100/mm^3 in the more affected group (Table 1). Massive SAH may also cause apoptotic degeneration in the CPs. There were significant differences between apoptotic CP cell density and blood cell density in the subarachnoid spaces ($p < 0.005$) (Table 2).

Discussion

CPs are brain structures located in the lateral, third and fourth ventricles. They are comprised of highly vascularized villi and are covered by a ciliated modified ependyma. CPs constitute up to 60% of the ventricular volume in the young, but the volume declines in percentage in the elderly to 30% [5]. CP epithelium consists of cuboidal epithelium with brush borders. Cubic epithelial cells have

a central round nucleus, several Golgi apparatuses, lysosomes, mitochondria, free ribosomes, microtubules and rough endoplasmic reticulum. The villus of CPs contains large capillaries surrounded by a thin stroma. The stromal spaces between capillaries and epithelium were thin and contained collagen fibers, non-myelinated nerve fibers, a few macrophages or dendritic cells, some pial cells, abundant arterioles and venules. However, CPs are severely modified and calcify quickly [21]. CPs are innervated by sympathetic and parasympathetic nerves [2, 4]. We believe that damaged glossopharyngeal and vagal nerves at the brainstem in SAH may rely on CP innervation disorders and result in CP denervation injury. Denervated CPs cannot provide vital functions and all brain compartments must follow into irreversible degeneration.

CPs are involved in the production of cerebrospinal fluid (CSF), various immune and endocrine molecules and numerous CSF components such as CSF electrolytes, carbohydrates and immunoglobulins. CPs are involved in the secretion and reabsorption of these materials according to blood and CSF pH levels [21]. CPs constitute a selective CSF-blood barrier and participate in cerebral immune surveillance [16] and various enzymatic activities [15]. The epithelial cells of CPs provide concentrative transport towards certain CSF hormones such as a prolactin-growth hormone [12], some vitamins such as thiamine, vitamin C, B12 and folates, and such immunoglobulins as IgA, G and M [20].

CPs are highly vulnerable to damage in brain injuries [17], infections [24] and ischemic conditions [18]. Focal cerebral ischemia in rats subjected to 6 h of occlusion of the middle cerebral artery resulted in apoptotic cell death in the CPs [8]. Apoptosis is an active death process requiring adequate energy supply to the beginning and ending of the apoptotic death process. The intracellular energy level plays a pivotal role in determining whether a cell degenerates by apoptosis or necrosis [13]. Apoptotic degeneration of the CPs can be determined by TUNNEL staining [6]. SAH causes severe vasospasm and results in ischemic CPs and brain damage [9, 11]. Deteriorated autonomic centers rely on CP pathologies in SAH. It is imagined that CPs may play an important role in the regulation of brain temperatures [23]. It is well known that hyperthermia can cause irreversible injury in the CPs and whole brain structures [22]. If total body hyperthermia causes CP injury [10], CP injuries can result in low CSF production, low CP auto regulation, less endocrine-immunologic function and high brain temperature. All of these conditions result in untreatable cerebral insults. The anatomical evidence of plexus injury after SAH demonstrates that CSF production by plexuses is affected [27].

In SAH, high morbidity and mortality is believed to be the result of a combination of reasons such as increasing blood pressure volume, decreased cerebral and spinal cord blood flow, increased intracranial pressure, neurogenic pulmonary edema, respiratory disorders and pulmonary diffusion defects [19]. Because of the large capacity of brain arteries, narrowing of the arteries as the result of delayed cerebral vasospasm following SAH is one of the leading causes of death and morbidity [1]. Brain-stem herniation is known to be one of the most significant factors in both the etiology of respiratory disturbances and sudden death in neurosurgical practices [3]. Clinically, unconsciousness, meningeal irritation signs, convulsion, hyperthermia, apnea, cardiac arrhythmia, and breathing disturbances were frequently observed in the periods before death of all the dead animals and in 5 of the living animals.

The present study also shows the role of CP degeneration on meningeal inflammation in SAH. During meningeal inflammation, we detected decreased CP degeneration at an early stage. The observations reported here suggest that further study may be warranted of the degeneration of the CPs and meningeal inflammation that are brought forth by SAH.

In summary, CPs are important constitutions for brain functions. Due to their secretion of CSF, these structures play important roles in cerebral nutrition, detoxification and cooling, enhance cerebral immunity due to immunoglobulin production, maintain endocrine secretion, function as a repository, and regulate blood-CSF pH, and we theorize that their impairment could be crucially significant in a worsening prognosis in SAH [10, 25, 26]. Therefore, CP injuries may deteriorate the thermoregulatory, immunoregulatory, metabolic and detoxifying mechanisms of the brain. CP protective approaches will be extremely useful treatment modalities in the future.

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Address for correspondence:

Dilcan Kotan
Department of Neurology
Medical Faculty of Sakarya University
Sakarya
Turkey
E-mail: dilc ankotan@yahoo.com
Tel: +90 533 387 08 10

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