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CASE REPORT

Unusual cause of cerebral vasospasm after pituitary surgery

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Abstract Cerebral vasospasm (CVS) was described in patients after trans-sphenoidal pituitary surgery due to intra-operative trauma of arteries or blood clots around the arteries of Willis' circle. We consider that in the two presented cases the main cause of CVS in early postoperative period was meningitis. Two patients with pituitary adenomas were operated with trans-sphenoidal approach. CVS developed in early postoperative period. Meningitis was revealed in both cases. CVS regressed only after successful treatment of meningitis. In the first case empiric antibiotic therapy was ineffective and CVS remained until *Klebsiella pneumonia* was detected in CSF and specific therapy was performed. In the second case empiric therapy was effective and CVS vasospasm regressed in 12 days. These cases show that meningitis can be a leading cause of CVS in early postoperative period in trans-sphenoidal pituitary surgery. Adequate treatment of meningitis shortens duration of CVS in these patients.

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Introduction

Cerebral vasospasm (CVS) was described after trans-sphenoidal pituitary adenoma removal [1–4]. Possible causes of CVS in these patients are intra-operative trauma of arteries or blood clots around the arteries of Willis' circle. CVS can worsen outcomes, lengthen postoperative treatment and it usually demands aggressive intensive care [5, 6]. Delayed treatment of CVS leads to ischemic brain damage [6, 7]. We evaluate postoperative meningitis as alternative cause of CVS in patients operated with trans-sphenoidal approach [8, 9]: intra-operative cerebral spinal fluid (CSF) leak occurs in 20–40% [10, 11]; postoperative CSF leak develops in less than 2% [11]. Surgery by trans-sphenoidal approach is relatively sterile. Intra- or postoperative external lumbar or ventricular drainage insertion is common in these patients. These factors increase the probability of postoperative meningitis. The development of CVS in patients with meningitis was described previously [12–16]. Both large and small arteries are affected in meningitis [17, 18], and cerebral blood flow autoregulation is impaired [19]. Adequate treatment of CVS developed due to meningitis combines three main targets:

1. antibiotic therapy
2. preservation adequate cerebral perfusion pressure
3. avoidance of hypovolemia [20, 21].

We present two cases with CVS and meningitis after trans-sphenoidal tumor removal.

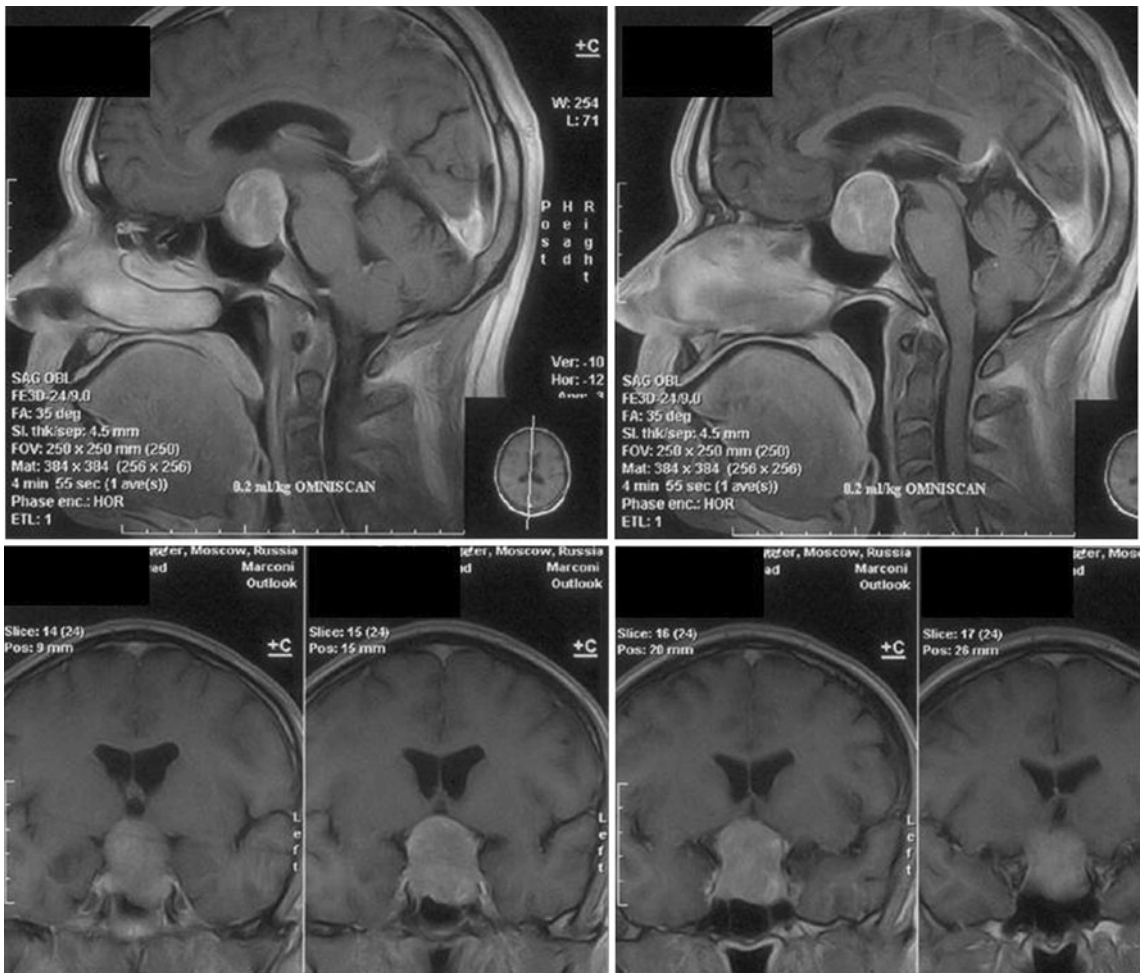

Fig. 1 MRI before operation (first case)

Case reports

First case

A 45-year-old man with endosuprasellar pituitary adenoma (Fig. 1) underwent operation of trans-sphenoidal total removal of the tumor. Intra-operative CSF leak happened. For postoperative CSF leak prophylaxis, cranial base reconstruction was performed and lumbar drainage was inserted. Patient successfully recovered after operation. Mild postoperative leukocytosis without its left shift was revealed during 3 days. Febrile temperature and only mild symptoms of meningism appeared on 4th postoperative day. CSF was hemorrhagic with elevated CSF cell count up to 336/μL with normal glucose and lactate levels (3.8 and 2.6 mmol/l, correspondingly). Transcranial Doppler (TCD) revealed accelerated blood flow velocity up to 168/91 cm/s in right MCA and 145/80 in left MCA. Lumbar drainage was removed. Count of leukocytes normalized. On 7th p/o day CSF cell count remained increased (243/μL), CSF glucose and CSF glucose/plasma glucose ratio decreased (2.7/5.4 mmol/l). Temperature remained febrile. Postoperative meningitis was diagnosed. Ceftazidime (6 g/day), vancomycin (2 g/day) were started. Blood flow velocity continued to increase simultaneously (225/101 cm/s in right MCA, 305/174 in left MCA). Fluid balance was positive.

Nasal CSF leak appeared on 19th p/o day. Revision of skull base and its reconstruction were performed trans-sphenoidally without delay. Antibiotic therapy was corrected peri-operatively: ceftazidime was replaced by sulperason (4 g/day) in accordance to microbiological situation in our department. Lumbar drainage was inserted intra-operatively again in order to decrease intracranial pressure. Delirium developed postoperatively in the ICU. Patient was sedated with propofol for synchronization with mechanical ventilation and with haloperidol for delirium treatment. Mechanical ventilation continued after operation for 3 days. After regress of delirium symptoms he was successfully extubated on the 23rd day. There was no neurologic deterioration in comparison with preoperative status, but mild meningism remained. Temperature was

febrile. Leukocytosis (18.9×10^9/l) increased. Blood flow velocity kept high (225/129 cm/s in right MCA, 180/105 in left MCA), and there was elevated CSF cell count (88/μL) with normal level of CSF glucose (3 mmol/l). SCT-angiography was performed. Two-sided spasm of supraclinoid part of internal carotid artery (ICA) was revealed. Diameter of right ICA was more narrowed then left one. Spasm M_1-segment of right middle cerebral artery (MCA) was moderate. A_1-segment of right anterior cerebral artery (ACA) was narrowed, but it might not have been spasm; it could have been hypoplasia. Right M_2- and A_2-segments were not narrowed. Spasm of both M_1-segment of MCA and A_1-segment of ACA was considerable. Left M_2- and A_2-segments were not narrowed (Fig. 2).

Elevated CSF cell count and decreased glucose level in CSF remained until the next antibiotic therapy correction. Meropenem (6 g/day) was administrated when *Klebsiella pneumonia* was detected in CSF on 39th day after operation. Therapy with meropenem was continued during 21 days. Gradually, in 15 days (64th day after operation) CSF cell count decreased (13/μL), CSF glucose increased (3.5 mmol/l) and velocity of blood flow normalized (117/56 cm/s in right MCA, 107/51 in left MCA). Count of leukocytes and temperature became normal.

SCT-angiography was repeated. Diameters of both ICA and both M_1-segments of MCA increased in comparison with previous SCT (Fig. 3). However, mild narrowing of both M_1-segments remained. Thus, there was a positive trend in diameter of cerebral arteries. This concurred with decrease of blood flow velocity and with CSF normalization.

Later ventriculoperitoneal shunt was performed. When discharging from the institute patient was independent, but disabled (Glasgow Outcomes Scale: 4).

Second case

A 52-year-old woman (Fig. 4) with giant endosupracellar pituitary adenoma underwent operation of trans-sphenoidal subtotal removal of the tumor. For postoperative CSF leak prophylaxis, cranial base reconstruction was performed, lumbar drainage was inserted. Patient recovered after operation. Consciousness was clear. Mild postoperative leukocytosis without its left shift was revealed after operation during 3 days. Temperature was normal. On the 4th postoperative day delirium and respiratory insufficiency developed. Patient was intubated and mechanically ventilated. CSF cell count was 10,800/μL, glucose was 0.1 mmol/l. TCD revealed accelerated blood flow velocity in the left MCA up to 294/136 cm/s. Meningitis was diagnosed. Lumbar drainage was removed and antibiotic therapy with meropenem (6 g/day) and vancomycin (2 g/day) was started without delay. Fluid balance was positive for avoidance of hypovolemia. Blood pressure was stable. Gradually patient improved. Leukocytosis, CSF cell count and glucose level normalized in 15 days. CSF compound normalized simultaneously with blood flow velocity. Microbiological investigations of CSF were negative. Antibiotic therapy continued for 21 days. Unfortunately, we did not perform CT-angiography in this case (Fig. 5).

Patient was discharged from the clinic without neurological deterioration (Glasgow Outcomes Scale: 5).

Discussion

To our knowledge this is the first report, which deals CVS with postoperative meningitis in patients after pituitary surgery.

Today it is accepted that the cause of CVS after trans-sphenoidal pituitary adenoma is intra-operative subarachnoid hemorrhage (SAH) [1–4]. Pathophysiology of CVS is still unclarified. CVS commonly develops in patients with aneurysmal SAH. Therefore, CVS is intensively studied in this patient population. A lot of mechanisms are responsible for CVS: influence of the oxyhemoglobin, methemoglobin and other products of hemoglobin degradation to vascular wall, activation of leucocytes and platelets in subarachnoid space, decreased level of endothelial NO, increased level of endothelin, proliferation of endothelial and smooth muscle cells, impairment of cerebral vessels innervation [22–24]. Cause-and-effect pathway is very difficult in pathophysiology of CVS; however, it is evident, that aneurysmal subarachnoid hemorrhage causes inflammation. It is proved by elevated level of proinflammatory cytokines in CSF and cerebral interstitium [25–27]. Inflammation leads to oxidative stress with oxyhemoglobin and methemoglobin formation and decrease level of endothelium nitric oxide (NO) [28, 29]. Then free radicals and deficit of endothelium NO lead to narrowing of cerebral vascular diameter and endothelium and smooth muscle cell proliferation [22, 29].

We believe that CVS happens after SAH only if associated with inflammatory response. That is why CVS very often develops in patients with aneurysmal SAH and much more rare in patients with intracranial hemorrhage due to another pathology (postoperative patients, hemorrhagic stroke, rupture of arteriovenous malformation) [30–32]. The difference in the magnitude of inflammatory response may explain why the severity of CVS varies in patients with aneurysmal SAH. We know that inflammation exists in the wall of unruptured aneurysm [33]. This process is genetically determined [33]. Therefore, aneurysmal SAH can be a trigger, which starts up genetically determined inflammation. Simultaneously such products of

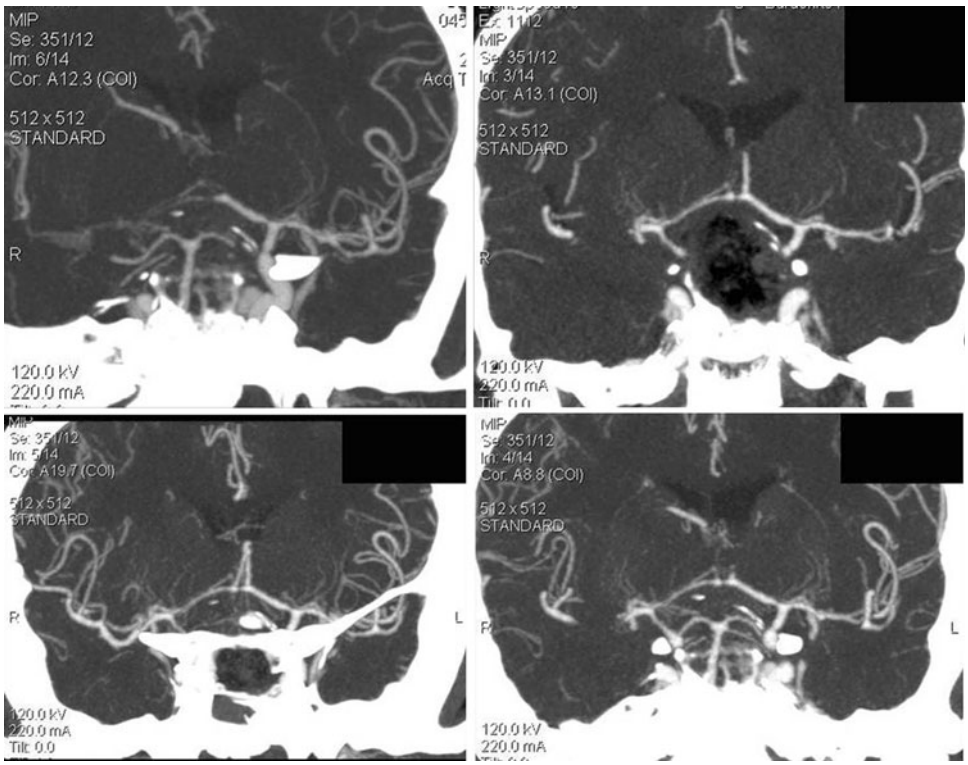

Fig. 2 SCT-angiography, demonstrated vasospasm (first case)

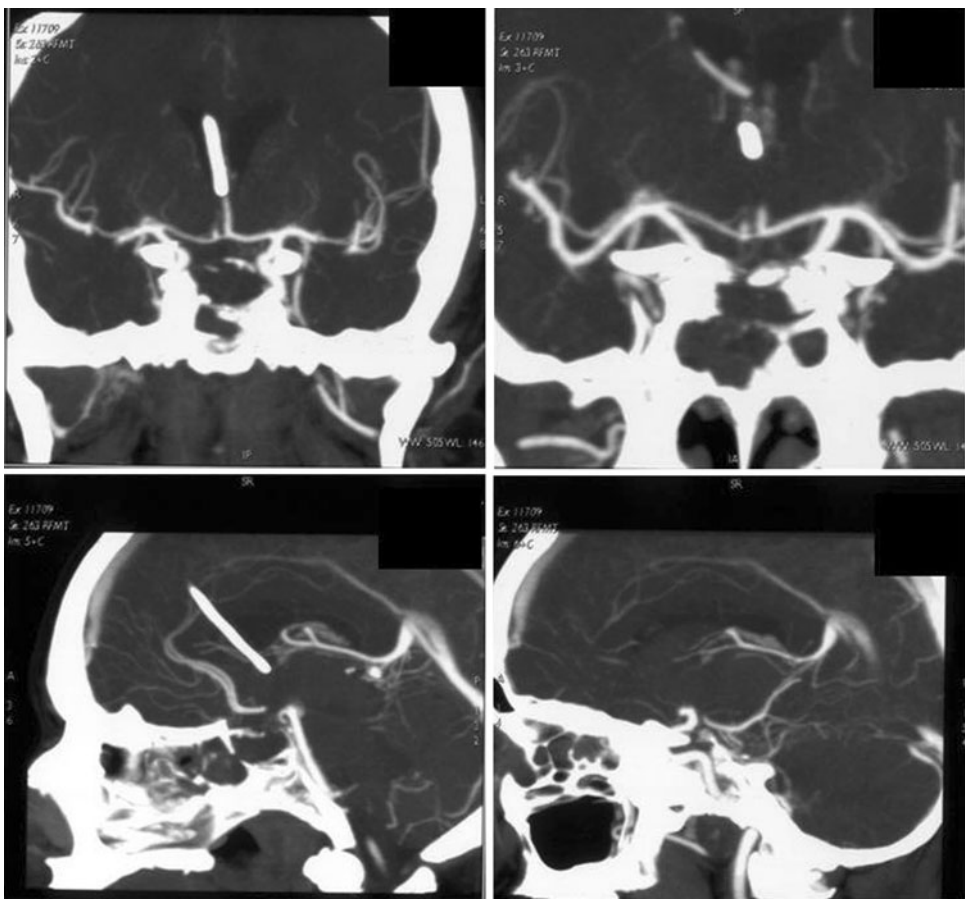

Fig. 3 SCT-angiography, demonstrated vasospasm resolution (first case)

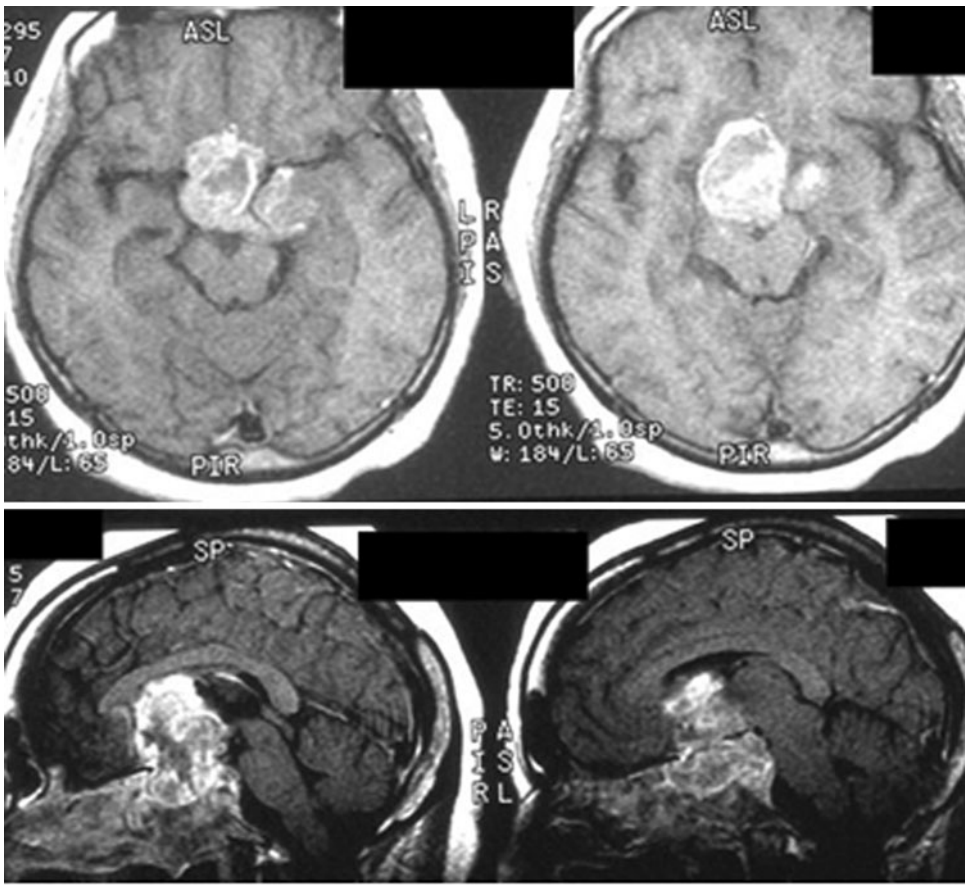

Fig. 4 MRI before operation (second case)

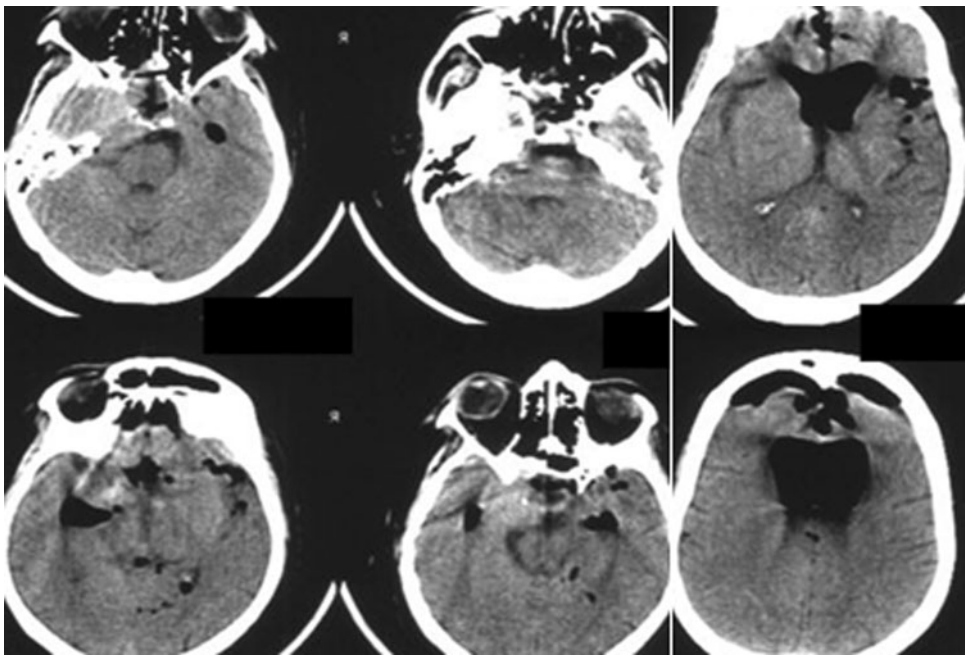

Fig. 5 Postoperative CT-scans (second case)

hemoglobin degradation, as iron and bilirubin do not lead to vasospasm [34]. Moreover, bilirubin acts against CVS as a free radical scavenger and chain-breaking antioxidant [34–36]. Oxy- and methemoglobin, products of oxidative stress, lead to CVS [22, 28]. These facts show that the presence of hemoglobin per se in subarachnoid space is not sufficient for the development of CVS. Leucocytes and platelets are, when not stimulated, relatively inert cells

[22]. Inflammation is needed for the activation of these cells [37, 38]. All these facts confirm the hypothesis that CVS is the result of coexistence of SAH and inflammation. The difference in the magnitude of inflammatory response may be determined genetically; genetic polymorphism has considerable importance[39]. Endothelial NO synthase (eNOS) polymorphism can be impressive example [40]. NO produced by eNOS is a potent vasodilator, inhibitor of inflammation, smooth muscle proliferation, and platelet aggregation [41]. Endothelial NO synthesis is genetically determined, and eNOS polymorphism contribute to individual variability in angiographic vasospasm [40]. Biological evidence from animals and humans suggests that differential expression of eNOS leads to decreased NO levels after SAH [42]. Specifically, the promoter -786T->C polymorphism has been associated with decreased eNOS promoter activity [40, 43–45]. Thereby indispensable condition of CVS development is combination of blood in subarachnoid space, inflammation and specific types of genetic polymorphisms.

The phenomenon of CVS after trans-sphenoidal pituitary adenoma resection was firstly described in 1980 [1]. The authors suggested that the cause of CVS, developed within 7 days after first operation and on the next day after second, was SAH with direct flow to the basilar cisterns or direct influence of fat and synthetic material for skull base plastics to the region of basilar cisterns. In spite of three operations, CSF leak, and two insertions of ventricular drainages the authors ruled out meningitis. This case is very similar to ours. In our first case CVS was verified with SCT-angiography, in the second, with TCD. CVS developed in early postoperative period—at 4th day after operation. Hypothetically CVS could be linked with postoperative blood in subarachnoid space. However, CVS continued longer than 60 days in the first case. Such long vasospasm is uncommon for CVS due to blood in subarachnoid space. Besides CVS is relatively rare complication in postoperative period after brain tumor surgery compared with aneurismatic subarachnoid hemorrhage (SAH). Thus, blood per se in subarachnoid space is probably not the cause of CVS in our patient.

Different types of cerebral blood flow (CBF) alterations were previously described in literature: stenosis of middle and anterior cerebral arteries, impairment of autoregulation of CBF, cerebral vasculitis, and both global and regional CVS [12–19, 46, 47]. Meningitis determined vascular events usually appear during a week and continue for 3 weeks, or longer [17]. Inflammation during meningitis causes oxidative stress and decreased level of NO, produced by eNOS [48–52], like in aneurysmal SAH. Interestingly, in meningitis levels of NO, produced by neuronal and inducible NO synthase (nNOS, iNOS), are increased [53, 54]. As opposed to NO produced by eNOS, NO produced by nNOS and iNOS, lead to additional brain damage in meningitis [55]. Thereby there are pathophysiological conditions for CVS development in meningitis. Severe CVS can cause ischemic stroke. Some authors consider ischemic brain injury as an early manifestation of meningitis [56].

We revealed meningitis in both cases, which was a leading cause of CVS. However, presence of blood and its clots in the subarachnoid space in patients with meningitis can be an additional cause of CVS. In the second case diagnosis of meningitis was undoubted. Adequate therapy of meningitis allowed us to achieve regression of CVS relatively quickly. An outcome was good. In the first case adequate therapy of meningitis was procrastinated, because the meningitis was unobvious and the microorganism was more problematic. This lead to extension of CVS duration and the outcome was worse. Careful maintenance of positive fluid balance and avoidance of arterial hypotension made it possible to prevent severe ischemic brain damage in our patients.

These cases emphasize extreme difficulty of meningitis diagnostics in postoperative neurocritical care patients. Obviously clinical examination, CSF analysis and blood inflammation markers test have low validity for diagnostics of postoperative meningitis [21]. Consciousness can be depressed due to surgery complications, such as postoperative hematoma, brain ischemia, hydrocephaly, etc. [11, 57]. CSF is usually hemorrhagic, when CSF cell count is increased and sometimes lactate can be increased too. After neurosurgical operations levels of systemic markers of inflammation increase in majority cases, because it is a normal physiological response. Some authors even suggest using cerebral microdialysis for meningitis diagnostics in neurocritical care patient with CVS [57]. On the other hand CVS is a rare phenomenon after pituitary surgery [4]. Thus, we believe that if patient has CVS, signs of inflammatory process in CSF and increased level of systemic markers of inflammation in the blood, meningitis can be suspected. Timely adequate therapy of meningitis is absolutely necessary in these clinical situations. In the setting of inadequate antibiotic therapy CVS will continue, and in spite of aggressive intensive care ischemic brain injury will be inevitable due to cell proliferation.

Conclusion

Meningitis can be a leading cause of vasospasm in early postoperative period in trans-sphenoidal pituitary surgery. If patient has vasospasm and signs of inflammation in CSF, the therapy of meningitis should be start up without any

delay. It can shorten duration of CVS in postoperative meningitis after pituitary surgery.

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