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Full Length Research Paper

Diagnosis and treatment of postoperative aseptic meningitis

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To summarize the experience on diagnosis and treatment of aseptic meningitis, the clinical characteristics and corresponding treatment of postoperative aseptic meningitis were retrospectively analyzed in 108 patients. The following symptoms and findings were noticed in all patients: Fever (38 to 40°C); consciousness disturbance without progressive aggravation; increase of leukocyte count and protein in the cerebral spinal fluid (CSF); slight increase or normal glucose in the CSF; negative bacterial culture. All patients were treated with intravenous dexamethasone and lumbar puncture, and recovered completely. Among these patients, 94 recovered in the hospital and the remaining 14 requested discharge and recovered in the following one month. Within 3 to 7 days following craniocerebral operations, these patients who had the following symptoms and findings: Fever (38 to 40°C); positive meningeal irritation sign; increase of leukocyte count and protein in the CSF; normal glucose in the CSF, effectiveness following implosive therapy with large dose dexamethasone (15 or 20 mg intravenously) and 3 consecutive negative bacterial cultures of CSF, can be diagnosed as aseptic meningitis. Implosive therapy with large-dose dexamethasone and cerebrospinal fluid drainage are the main therapeutic strategies.

Key words: Craniocerebral operations, aseptic meningitis, diagnosis, treatment.

INTRODUCTION

Post-operative aseptic meningitis (PAM) is a rare complication of craniocerebral operations (Ramos-Martínez et al., 2009), and often clinically misdiagnosed as post-operative bacterial meningitis (PBM) (Carmel and Greif, 1993), which results in unnecessary or unreasonable application of antibiotics and prolongation of hospitalization. Based on our previous experience (Xu et al., 2007), the present study retrospectively reviewed the clinical characteristics of 108 patients with PAM in the last 13 years.

PATIENTS AND METHODS

General information

A total of 64 males and 44 females with a mean age of 27.68±7.28 years (7 to 65 years) who were treated in our department from Magnetic resonance imaging (MRI) and computed tomography (CT) were performed in all patients with fever to exclude the central fever caused by the damage to the brain stem or hypothalamus. In addition, patients with infection of surgical wound, respiratory system, digestive system and urinary system were excluded. The wound healing was favorable.

Etiology and patterns of craniotomy

Infratentorial surgery and supratentorial surgery were performed in 68 and 40 patients, respectively. There were Arnold-Chiari malformation (n = 33), craniopharyngioma (n = 19), medulloblastoma (n = 14), ependymoma (n = 9), glioma (n = 9), astrocytoma (n = 6), cerebral vascular malformation (n = 5), angioreticuloma (n = 4), acoustic neuroma (n = 3), meningioma (n = 2), hypertensive intracerebral hemorrhage (n = 2) and aneurysm (n = 2). Among 52 patients receiving supratentorial surgery, bone flap craniotomy and repair of dura matter were done. Of 56 patients receiving infratentorial surgery, bone window craniotomy was carried out. The dura matter was not sutured in 33 patients undergoing traditional craniotomy, and suture and repair of dura matter were done in remaining 23 patients. All surgeries were done under microscope and the duration of surgery was 2 to 6 h.

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Clinical manifestations

Fever was observed at 3 to 7 days after surgery. The body temperature was about 38 to 40℃ and a majority was 38.5℃. Concomitant headache and neck stiffness were also observed but chillness, toxicity symptoms and progressive consciousness disturbance were not noted. Meningeal irritation sign was negative and the white blood cell count and neutrophil count were normal or slightly elevated. Toxic granules were absent in these cells.

Examination of cerebral spinal fluid

The cerebral spinal fluid (CSF) was bloody and slightly turbid or clear. The CSF pressure was 210±50 mmH_2O. The number of white blood cell count in the CSF was 2500±1200 × 10^6 and neutrophilic segmented granulocytes were the main component. Perthes test was positive. The protein content of CSF was increased (1.21±0.65 g/L) and glucose level was normal or slightly low (3.0±0.76 mmol/L). The result of bacterial culture was negative in 2 to 3 consecutive cultures.

Therapeutic strategies

All patients were administrated intravenously with large dose dexamethasone (15 or 20 mg). Lumbar puncture (n = 72) or external continuous lumbar drainage (n = 36) were performed for 3 to 7 days to discharge the CSF containing pro-inflammatory cytokines. During the drainage, dexamethasone treatment was performed 2 to 3 times. For patients with severe disease condition, antibiotics were administered when bacterial infection could not be excluded (n = 5 7). The remaining 51 patients discontinued antibiotics treatment at 5 to 7 days after surgery, and the wound healing was favorable.

RESULTS

The treatment was performed for 2 to 6 weeks (mean: 25 days). Among these patients, 94 recovered completely and 14 required being discharged achieving complete recovery within 1 month following discharge. Remission was observed after treatment with dexamethasone twice and only a few patients were treated with dexamethasone for more than 3 times. Complications related to large dose dexamethasone treatment were noticed during the study. First treatment with large dose dexamethasone and concomitant lumbar puncture or external continuous lumbar drainage significantly improved the headache and symptoms related to fever. The body temperature returned to normal after treatment. Although the fever recurred, the increase of body temperature was mild. The glucose in the CSF was normal and the number of white blood cells, decreased. The disease condition did not further deteriorate.

DISCUSSION

Aseptic meningitis is a clinical syndrome in which fever, positive meningeal irritation sign and increase of white blood cells and protein in the CSF but absence of bacteria in CSF culture are the characteristics (Carmel and Greif, 1993). Aseptic meningitis frequently occurs following posterior fossa surgery and is often misdiagnosed as bacterial meningitis, resulting in unreasonable application of antibiotics and subsequent flora disequilibrium or super bacterial infection, which finally increase the hospital days and cost. Therefore, physicians should pay attention to the diagnosis of aseptic meningitis because early diagnosis of aseptic meningitis is critical for the subsequent treatment.

Early diagnosis of aseptic meningitis

Currently, there are no generally acceptable criteria for the diagnosis of aseptic meningitis. Therefore, the diagnosis of aseptic meningitis should be based on the clinical experience. Traditionally, patients with post-operative fever and increase of white blood cells following cerebral surgery are treated with the procedures in the treatment of bacterial meningitis. Some physicians even propose the treatment of meningitis with antibiotics regardless the aseptic meningitis and bacterial meningitis. Once bacterial culture was negative in 3 consecutive cultures, antibiotics should be discontinued. We speculate that it is better to confirm the diagnosis of aseptic and bacterial meningitis before treatment. Fever and progressive consciousness disturbance are the main characteristics of bacterial meningitis. The decrease of glucose level in the CSF is an important clue for bacterial meningitis diagnosis because the growth and reproduction of bacteria may consume a variety of glucose for energy supply. In the diagnosis of bacterial meningitis, bacterial culture is a gold standard (Kaufman et al., 1990). In our previous study (Xu et al., 2007), patients with aseptic meningitis developed fever at 3 days after surgery and positive meningeal irritation sign, increase of white blood cell count in the CSF and negative bacterial culture of CSF were also noted. Furthermore, the glucose level of CSF is indicative.

Cui et al. (2008) investigated 16 patients with aseptic meningitis following posterior fossa craniotomy and their results suggested the diagnostic criteria of aseptic meningitis should include: Fever at 3 days following surgery, increase of white blood cells in the CSF, negative bacterial culture and normal glucose level of CSF. Other researchers indicated, among numerous indicators (serum C reaction protein, procalcitonin, white blood cells and their sorting, protein and glucose in the CSF) for the diagnosis of aseptic meningitis; the serum procalcitonin and protein in the CSF were critical for the differentiation of aseptic meningitis and bacterial meningitis (Dubos et al., 2006; Ho et al., 2001; Gomes et al., 2005). Based on our experience, the present study analyzed the clinical characteristics and treatment of aseptic meningitis in 108 patients. Our results indicated the criteria for early diagnosis of aseptic meningitis should include: Fever at 3 to 7 days after surgery,

positive meningeal irritation, absence of progressive consciousness disturbance, increases of white blood cells and protein in the CSF and normal glucose in the CSF. Bacterial culture is a gold standard to confirm the diagnosis of aseptic meningitis.

Treatment of aseptic meningitis

Aseptic meningitis is usually developed at 3 to 7 days after surgery, and the clinical manifestations and changes in the CSF are similar to those in bacterial meningitis. To prevent the severe consequences of bacterial meningitis, it is generally acceptable that antibiotics should be administered at the early stage of disease. Stopping antibiotic treatment after 3 days is effective and safe for patients with postoperative meningitis whose cerebrospinal fluid culture results are negative (Zarrouk et al., 2007). We speculate aseptic meningitis and bacterial meningitis are two different diseases which should be treated differently.

Early lumbar puncture is necessary. Before bacterial culture of CSF, the application of antibiotics should be based on the glucose and white blood cells in the CSF. Evidence shows the white blood cell count of CSF is usually greater than 5000×10^6 /L in patients with bacterial pmeningitis (Ramos-Martínez et al., 2009). In the present study, the white blood cell count in the CSF of aseptic meningitis patients was less than 5000×10^6 /L and the CSF glucose level remained normal. Thus, when the white blood cell count bellows 5000×10^6/L and the glucose level is normal in the CSF, prophylactic antibiotics treatment is not recommended. Of course, at the early stage when the bacterial meningitis is not definitely excluded, antibiotics treatment can continue. In the present study, 51 discontinued antibiotics treatment when wound healing was favorable at 5 to 7 days after surgery.

Systematic treatment with steroids is a critical strategy in the treatment of aseptic meningitis (Hillier et al., 2000). In the present study, all patients were intravenously treated with large dose dexamethasone (15 or 20 mg) 2 to 3 times. After first treatment with dexamethasone, significant improvement of headache and fever was observed in a majority of patients. After 2 dexamethasone treatments, the body temperature returned normal. Although the increase of body temperature recurred, the increase was mild. In addition, the white blood cell count was also decreased. Only a few patients were treated with dexamethasone more than 3 times. No complications related to administration of large dose dexamethasone were observed. The treatment was performed for 2 to 6 weeks (mean: 25 days) achieving favorable outcome. A total of 94 patients achieved complete recovery and then discharged. The remaining 14 patients requested discharge and recovered within 1 month after discharge. According to our experience, we recommend intermittent treatment with intravenous large dose (15 or 20 mg) dexamethasone, and low dose dexamethasone is not recommended. Implosive therapy with dexamethasone is effective to improve the clinical symptoms in both aseptic meningitis and bacterial meningitis (Gomes et al., 2005).

Intermittent lumbar puncture or external continuous lumbar drainage is another strategy for the treatment of aseptic meningitis and especially the external continuous lumbar drainage is recommended. External continuous lumbar drainage has the following advantages (Peng et al., 2007): (1) A lot of pro-inflammatory cytokines (pathogenic factors) are eliminated; (2) The cerebrospinal fluid circulation is improved and the retention of shedding tumor cells or other pathogenic physical compositions in the subarachnoid is reduced which reduce the chance of tumor implantation and hydrocephalus; (3) The intracranial pressure is decreased which reduce the dose of drugs for dehydration; (4) The collection of CSF and intrathecal injection of drugs are convenient, and (5) The incidence of infection is reduced and the pain of patients and subsequent workload of physicians are decrease. In the present study, lumbar puncture was performed in 72 patients for 2 to 10 times (mean: 4 to 5 times) and external lumbar drainage in 36 patients for 3 to 7 days. When the fever and headache resolved completely and white blood cell count returned normal or nearly normal, lumbar puncture or external lumbar drainage was discontinued. All patients had favorable outcome and no patients developed complications.

Furthermore, dexamethasone therapy in combination with lumbar puncture or external lumbar drainage and no replacement or discontinuation of antibiotics could completely relieve these symptoms, which further confirm the diagnosis of aseptic meningitis.

Etiology and prevention of aseptic meningitis

Marion (2000) speculated that the aseptic meningitis following cerebral surgery belonged to chemical meningitis, caused by bloody CSF, necrotic tumor cells or contents of cystic lesions. The fever was developed in the presence of antibiotics treatment following absorption fever at about 3 to 7 days after surgery. In selected patients, hyperpyrexia may be noted in the absence of skin eruption. Headache and meningeal irritation sign can be present. These manifestations together with increase of white blood cell count and protein in the CSF may lead to misdiagnosis as bacterial meningitis. Other researchers also propose the causes of aseptic meningitis as follows: Long-term traction, mechanical injury, response of astrocytes, subcutaneous effusion following infratentorial craniotomy, gelatin sponge and denatured protein caused by electric coagulation (Wang and Zhang, 2005). Patients receiving infratentorial craniotomy are more susceptible to aseptic meningitis which can be explained by the deep surgical field, the thick soft tissue, the large exposed wound, release of

numerous inflammatory cytokines, increase of blood loss, accumulation of denatured protein caused by electric coagulation, untight suture of dura mater, long term supine position and accumulation of CSF in the wound (even formation of occipital pseudocyst (Yin and Wei, 2007).

In traditional infratentorial craniotomy, the dura mater is not sutured for decompression which results in direct contact between cerebellum and muscles and disorderliness of normal structure. Thus, post-operative effusion and aseptic meningitis are frequently observed. Reconstruction of dura mater can significantly reduce the incidence of the complications aforementioned in traditional infratentorial craniotomy (Yin and Wei, 2007; Guo et al., 2004). In the present study, infratentorial craniotomy was performed in 56 patients and a majority of patients (n = 33) had no suture and repair of dura mater. In the past 5 years, suture and repair of dura mater was also carried out in the infratentorial craniotomy in our department. The wound was irrigated with isotonic saline during surgery and drainage tube was placed in the epidural space, which significant reduce the incidence of post-operative aseptic meningitis. Thereafter, we postulate that post-operative tight suture of dura mater and complete irrigation of the wound in the surgery and placement of drainage tube in the epidural space but not the subdural space are important strategies to prevent occurrence of post-operative aseptic meningitis because these procedures prevent the epidural accumulation of CSF and reduce the stimulation of dura mater by pro-inflammatory actors including the tissue debris in the wound. Posterior fossa bone flap craniectomy is another method to reduce the incidence of aseptic meningitis (Lin et al., 2005).

Some cystic lesions can lead to aseptic meningitis including craniopharyngioma which was found in 19 patients in the present study. In addition, in the cholesteatoma, dermoid cysts and epidermoid cyst, the protein containing contents, keratin and cholesterol esters in the cyst may enter the subarachnoid resulting in aseptic inflammation. The prevention of aseptic inflammation should focus on the intra-operative procedures. Before opening the cyst, the surrounding tissues should be protected with brain cotton pad and the contents should be thoroughly removed aiming to avoid the entry of contents into subarachnoid. In addition, the wound should be completely irrigated and the suture or repair of dura mater should be assured. In spite of this, there were 19 patients developing aseptic meningitis following the surgical removal of craniopharyngioma, which may be related to incomplete removal of tumors resulting in occurrence of chemical meningitis (Hillier et al., 2000; Peng et al., 2007).

Taken together, we speculate the early diagnosis of aseptic meningitis should be based on the following clinical manifestations and laboratory parameters: Development of fever at 3 to 7 days after surgery, positive meningeal irritation sign, absence of progressive consciousness disturbance, increase of white blood cell count and glucose in the CSF, normal glucose in the CSF and active response to large dose dexamethasone treatment. Further bacterial culture as a gold standard can confirm the diagnosis. Treatment with large dose intravenous dexamethasone (15 or 20 mg) and lumbar puncture or external continuous lumbar drainage are important strategies for prevention of aseptic meningitis. Of note, the negative bacterial culture also has the possibility of misdiagnosis. Once treatment has been given based on the diagnosis of aseptic meningitis achieving poor response, re-evaluation should be done.

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