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Original Article

Analysis of the changes in inflammatory cytokines, infection factors and coping strategies after intracranial tumor operation

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Abstract: Objective: This study aimed to investigate the changes in inflammatory cytokines and infection factors in patients with intracranial infection after intracranial tumor operation. Methods: Patients with meningioma admitted to our hospital from May 2015 to June 2018 were enrolled. Based on postoperative infection, the patients were divided into the infection group (n=309) and non-infection group (n=305). The levels of related inflammatory cytokines after operation were measured and the risk factors were determined by univariate analysis and multivariate logistic regression analysis. Results: Differences in the levels of serum C-reactive protein (CRP), procalcitonin (PCT), interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α) were not obvious between the two groups of patients on the 1st day after operation (P>0.05). From the 3rd d after operation, the levels were remarkably higher than those in patients of the non-infection group, and differences in the levels of serum CRP, PCT, IL-6 and TNF-α between the two groups of patients became more obvious on the 7th and 14th d after operation (P<0.05). The multivariate Logistic regression analysis revealed that age, diabetes mellitus, operation time, posterior fossa operation and postoperative cerebrospinal fluid leakage were independent risk factors for patients with intracranial infection after intracranial tumor operation (*P*<0.05). Conclusion: Infection inflammatory cytokines, CRP, PCT, IL-6 and TNF-α, along with other infection factors, function as important indicators after Intracranial Tumor Operation, which provide new leads for the countermeasures of intracranial infection in clinical practice.

Keywords: Intracranial tumor, intracranial infection, inflammatory cytokine, infection factor

Introduction

As a common brain tumor of the central nervous system, meningioma makes up about 30% of all intracranial tumors. There is a gender difference in the morbidity rate of the disease, and the ratio of the morbidity rate of males to that of females is about 1:3 [1, 2]. Meningioma is primarily derived from arachnoid trabeculae, arachnoid cap-like cells and the choroid plexus, and it commonly occurs in the tentorium cerebelli, the tuberculum sellae, the sphenoid ridge and the convex surface of the brain and beside the cerebral falx and the sagittal sinus [2]. According to the formulated tumor pathological classification by the World Health Organization in 2007, meningioma is divided into 3 grades and 15 subtypes, including about 2.8% in grade III, about 6% in grade II and about 93% in grade I [3]. Most tumor subtypes of meningioma are benign, but there are still possibilities of development of malignant tumors with the deterioration of the disease. Meningioma can possess characteristics of malignant tumors such as proneness to metastasis and recurrence, high invasiveness and rapid growth, and it has basically the same clinical manifestations as benign tumors, which are characterized in grade III in the pathological classification of meningioma [4]. The surgical resection outcome of patients with benign meningioma is relatively good, but the meningioma located in the skull base (such as the sphenoid ridge, posterior fossa and the middle part of the skull) and that with a relatively large diameter can easily damage the adjacent nerves and vessels to different degrees due to the rich blood supply. Other disadvantages of the disease exist such as difficulty in operation, large intraoperative blood loss and being prone to complications, i.e. intracranial infection after operation. According to studies, intracranial infection is primarily triggered by a purulent bacterial infection, and as such the serum inflammatory cytokines in the body will change to a certain extent. Additionally, the protective effect of the blood-brain barrier inhibits the according effects of many antibacterial agents, thus interfering with the effect of the treatment [4]. Intracranial tumors complicated with intracranial infection after an operation seriously affects the prognosis, prolongs the hospital stay, increases treatment costs and causes additional pain to patients. Particularly, in severe cases, multiple operations are needed, or the disease endangers the patient's life. Hence, in this study, the changes in inflammatory cytokines and infection factors in patients with intracranial infection after intracranial tumor operation were investigated, and the risk factors were further identified.

Patients and methods

General data

Patients with meningioma admitted to the First Affiliated Hospital of Xi'an Jiaotong University from May 2015 to June 2018 were enrolled and the clinical data were retrospectively analyzed. Inclusion criteria: 1) All patients who met the above diagnostic criteria for meningioma, and the infected patients after operation who met the diagnostic criteria for the intracranial infection, 2) patients aged at least 20 years old who met the related indications for craniotomy, 3) the study was approved by the Medical Ethics Committee of the hospital, and 4) patients who agreed and actively cooperated with the study and signed the informed consent with their family members. Exclusion criteria: 1) Patients complicated with severe heart, liver or kidney dysfunction, 2) patients complicated with brain abscess, brain empyema, meningitis or other intracranial infectious diseases before operation, 3) patients complicated with serious internal medicine diseases, 4) patients complicated with immunodeficiencies, 5) patients complicated with functional neurological diseases, cerebral hemorrhage, intracranial vascular malformations, etc., 6) pregnant or lactating patients, or 7) patients with incomplete clinical data. According to postoperative infection, the patients were divided into the infection group (n=309) and the non-infection group (n=305).

Diagnostic criteria for meningioma

1) CT plain scan showed clear edges and a slightly higher density. The enhanced scan revealed the edema zone around the tumor, obvious enhancement and even coloration. 2) Plain image of the skull displayed a relatively compact tumor calcification, the mass shadow of the entire tumor, increased vascular markings, abnormally increased local diploic veins, changes in limited bone substance, needle-like radioactive bone hyperplasia in the external lamella, diffuse hyperplasia of bone lamellae and the thickened internal lamella. 3) Lesions showed high-signal or equisignal on magnetic resonance imaging (MRI) T1-weighted images and equisignal or slightly high-signal on MRI T2-weighted images [5].

Diagnostic criteria for intracranial infection

Intracranial infection was diagnosed according to the diagnostic criteria for the postoperative intracranial infection in the *Diagnostic Criteria for Nosocomial Infections* issued by the Ministry of Health in 2014 [5] as follows: 1) In the early postoperative stage, the disease manifested as persistent fever symptoms accompanied with varying degrees of vomiting, nausea, headache and other symptoms of increased intracranial pressure, or positive meningeal irritation sign. 2) Laboratory examinations reveal that the cerebrospinal fluid chloride does not exceed 119 mmol/L, grape vines is not more than 2.50 mmol/L, the protein quantitation is not less than 450 mg/L, and the white blood cell count is not less than 10×10^6/L. 3) The results of cerebrospinal fluid bacterial culture are positive, bacteria can be observed on the cerebrospinal fluid bacterial smear under a microscopic. Patients meeting any two of the above criteria can be definitely diagnosed with intracranial infection.

Detection of potential factors

Case data of 354 patients with intracranial tumors undergoing craniotomy in our hospital were retrospectively analyzed. The factors studied included body mass index, age, gender,

Table 1. Baseline data of the two groups of patients

Item	Infection group (n=309)	Non-infection group (n=305)	t/x^2	P
Age (years old)	20-74	21-75		
Average age (years old)	48.34±6.69	48.01±6.57	0.617	0.538
Body mass (kg)	62.83±7.37	62.35±7.54	0.797	0.426
Male/female [n (%)]	138/171	139/166	0.052	0.820

tumor site, tumor nature, tumor operation method, posterior fossa operation, drinking history, smoking history, hypertension, diabetes mellitus, intraoperative blood loss, operation time, postoperative cerebrospinal fluid leakage, postoperative application of antibacterial agents, postoperative bed rest time, postoperative catheter indwelling time and mastoid air cells or sinus opening.

Observational indexes

On the 1st, 3rd, 7th and 14th days after operation, 5 mL fasting venous blood was taken in the morning and centrifuged at a centrifugal radius of 10.5 cm and a rotational speed of 3000 r/min for 10 min using a centrifugal machine [Ortho BioVue, Johnson & Johnson Medical (Shanghai) Co., Ltd.]. Then the supernatant was taken and stored in a freezer at -75°C. The double-antibody sandwich immunoluminescence assay was adopted to determine the level of serum procalcitonin (PCT), the immunoturbidimetry was applied to detect the level of serum C-reactive protein (CRP), and the enzyme-linked immunosorbent assay was used to measure the levels of serum tumor necrosis factor-alpha (TNF-α) and interleukin-6 (IL-6). The kit was purchased from Beijing Danda Biotechnology Co., Ltd., and the operation method was carried out in strict accordance with the instructions.

Statistical analysis

The above data were sorted out and analyzed using the Statistical Product and Service Solutions 20.0 special software. Among them, count data were expressed as [n (%)] and detected via the chi-square test, while measurement data were expressed as ($\overline{x}$±s) and detected via the *t*-test. The *t*-test was used to compare the data at the same time point between the two groups. The univariate analysis was conducted for risk factors for the perioperative intracranial infection, and the multivariate Logistic regression analysis was carried out for statistically significant risk factors. P<0.05 represented that the difference was statistically significant.

Results

Comparison of general data between the two groups of patients

The patients in the infection group (n=309) with the average age of 48.34±6.69 years and in the non-infection group (n=305) of 48.01±6.57 years were enrolled and the the general data were compared. There were no significant differences in age, body mass and gender between two groups (P>0.05) (**Table 1**).

Comparison of changes in the CRP and PCT levels between the two groups of patients

On the 1st d after operation, no significant differences were found in the levels of serum CRP and PCT between the two groups of patients (P>0.05). From the 3rd d after operation, the levels of serum CRP and PCT in the infection group were significantly higher than that in the non-infection group at the same time point (P<0.05), and the difference in this levels between the two groups of patients became more obvious on the 7th and 14th d after operation (**Figures 1**, **2**).

Comparison of changes in the IL-6 and TNF-α levels between the two groups of patients

On the 1st d after operation, the difference in the levels of serum IL-6 and TNF-α between the two groups was not evident (P>0.05). From the 3rd d after operation, the levels of serum IL-6 and TNF-α in the infection group was significantly higher than that in the non-infection group at the same time point, and the difference in this level between the two groups of patients became more significant on the 7th and 14th d after operation (P<0.05) (**Figures 3**, **4**).

Univariate analysis of the intracranial infection in patients after intracranial tumor operation

The univariate analysis results revealed that age, tumor site, posterior fossa operation, diabetes mellitus, operation time, postoperative application of antibacterial agents, postoperative bed rest time, postoperative catheter indwelling time, postoperative cerebrospinal fluid

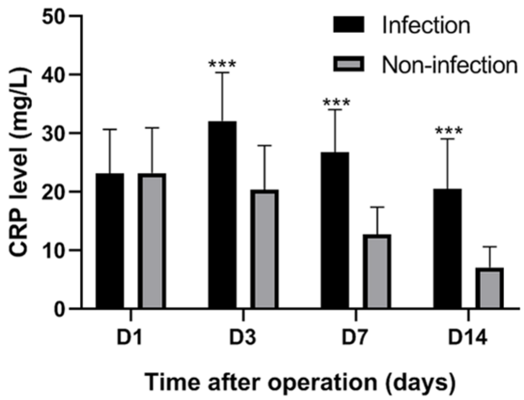

Figure 1. Comparison of changes in the CRP level between the two groups of patients ($\bar{x}$±s, mg/L). Compared with non-infection group, *** P<0.001.

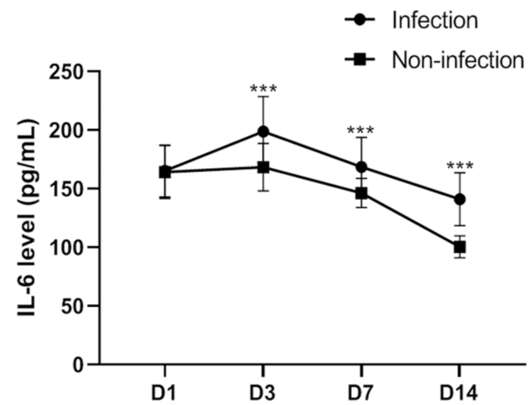

Figure 3. Comparison of changes in the IL-6 level between the two groups of patients ($\bar{x}$±s, pg/mL). Compared with non-infection group, *** P<0.001.

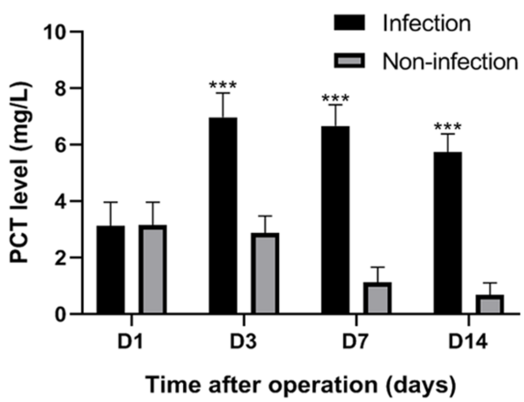

Figure 2. Comparison of changes in the PCT level between the two groups of patients ($\bar{x}$±s, mg/L). Compared with non-infection group, *** P<0.001.

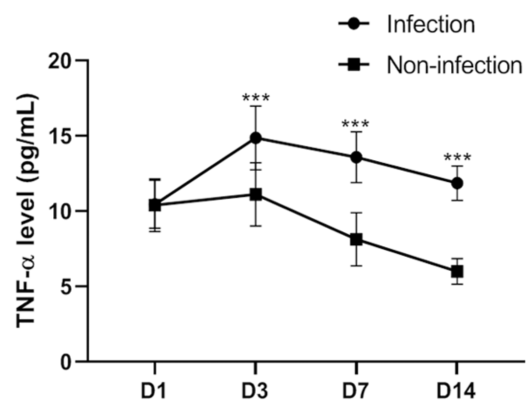

Figure 4. Comparison of changes in the TNF-α level between the two groups of patients ($\bar{x}$±s, pg/mL). Compared with non-infection group, *** P<0.001.

leakage and mastoid air cells or sinus opening were risk factors for the intracranial infection in patients after intracranial tumor operation. However factors of gender, body mass index, tumor operation method, tumor nature, drinking history, smoking history, hypertension and intraoperative blood loss were not (P<0.05) (**Table 2**).

Multivariate Logistic regression analysis of the intracranial infection in patients after intracranial tumor operation

The multivariate Logistic regression analysis was conducted for the above-mentioned statistically significant risk factors. Age, diabetes mellitus, operation time, posterior fossa operation and postoperative cerebrospinal fluid leakage were independent risk factors for the intracranial infection in patients after intracranial tumor operation (P<0.05) (**Tables 3**, **4**).

Discussion

The incidence of intracranial infection, a common complication after intracranial tumor operation, is reported to be 2.6-19.8%, which is consistent with the results (13.84%) in this study [5]. The intracranial infection influences the prognosis of patients, increases their postoperative pain and seriously threatens the patient's life and health, and it is difficult to be treated. Hence, a screen that is sensitive and a specific diagnostic index would be conducive to the early detection of intracranial infection, which further provides reference for the subsequent treatment, reduces the hospital stay and improves the prognosis. In addition, the analysis of risk factors for intracranial infection also helps the prevention and diagnosis of intracranial infection [6, 7]. CRP is a protein reaction in the acute phase, the level of which can be rapidly increased in a short term after infection of

Table 2. Univariate analysis of the intracranial infection in patients after intracranial tumor operation

Factor		n	Infection rate [n (%)]	x^2	P
Gender	Male	160	21 (13.13)	0.126	0.723
	Female	194	28 (14.43)		
Age (years old)	≥45	230	43 (18.70)	12.971	0.000
	<45	124	6 (4.84)		
Body mass index (kg/m^2)	≥27	150	19 (12.67)	0.301	0.583
	<27	204	30 (14.71)		
Tumor operation method	Radical operation	294	37 (12.59)	2.297	0.130
	Non-radical operation	60	12 (20.00)		
Tumor site	Supratentorial area	150	6 (4.00)	21.141	<0.001
	Subtentorial area	204	43 (21.08)		
Tumor nature	Benign	179	19 (10.61)	3.162	0.075
	Malignant	175	30 (18.29)		
Posterior fossa operation	Yes	102	39 (38.24)	71.493	<0.001
	No	252	10 (3.97)		
Drinking history	Yes	189	26 (13.76)	0.002	0.960
	No	165	23 (8.68)		
Smoking history	Yes	214	32 (16.36)	0.561	0.454
	No	140	17 (12.14)		
Hypertension	Yes	39	6 (15.38)	0.087	0.767
	No	315	43 (13.65)		
Diabetes mellitus	Yes	90	39 (43.33)	88.013	<0.001
	No	264	10 (3.79)		
Intraoperative blood loss (mL)	≥500	100	16 (16.00)	0.544	0.461
	<500	254	33 (12.99)		
Operation time (h)	≥4	195	40 (20.51)	16.201	<0.001
	<4	159	9 (5.66)		
Postoperative application of antibacterial agents	Yes	270	37 (13.70)	8.379	0.004
	No	84	2 (2.38)		
Postoperative bed rest time (d)	≥7	138	36 (26.09)	28.436	<0.001
	<7	216	13 (6.02)		
Postoperative catheter indwelling time (h)	≥24	93	27 (29.03)	24.406	<0.001
	<24	261	22 (8.43)		
Postoperative cerebrospinal fluid leakage	Yes	91	28 (30.77)	29.429	<0.001
	No	263	21 (7.98)		
Mastoid air cells or sinus opening	Yes	77	23 (29.87)	21.198	<0.001
	No	277	26 (9.39)		

the body. It level can be applied for the clinical diagnosis of bacterial infection and used as a sensitive indicator for the early bacterial infection due to its relatively large individual differences and short half-life period. Basically, CRP level in patients after the intracranial infection is gradually increased [8]. Under normal circumstances, the PCT level in the human body is relatively low, but the level in serum can be increased rapidly when the body is infected. At the same time, under the state of non-specific infection, it is not obviously increased, so PCT can be regarded as a sensitive indicator for bacterial infection [9]. As an inflammatory cytokine, IL-6 is highly sensitive to the expressions of microglial cells and neuronal cells. IL-6 is widely distributed in the central nervous system and exerts crucial effects in the body's inflammatory response, immune response and stress response. Besides, IL-6 can also acti-

Table 3. Variable assignment

Variable	Assignment
Age	Age ≥45 years old=0 and age <45 years old=1
Diabetes mellitus	Yes=0 and no=1
Operation time	Operation time ≥4 h=0 and operation time <4 h=1
Posterior fossa operation	Yes=0 and no=1
Postoperative cerebrospinal fluid leakage	Yes=0 and no=1

Table 4. Multivariate Logistic regression analysis of the intracranial infection in patients after intracranial tumor operation

	β	Standard error	Wald value	Odds ratio	P	95% confidence interval
Age	1.254	0.225	4.441	1.521	0.013	0.831-0.986
Diabetes mellitus	1.036	0.204	4.432	1.457	0.021	1.105-1.468
Operation time	1.035	0.115	4.425	1.358	0.005	2.147-8.364
Posterior fossa operation	1.024	0.103	4.251	1.364	0.018	0.857-1.368
Postoperative cerebrospinal fluid leakage	0.142	0.054	4.913	1.145	0.021	1.102-1.315

vate matrix metalloproteinases in the body to a certain extent, lead to neuronal damage and blood-brain barrier disorders and play a role in the prediction of the degrees of nerve injury and the intracranial infection in patients [10]. TNF-α is a polypeptide cytokine formed by the action of related inflammatory stimuli and bacterial toxins on monocytes and macrophages, which triggers a series of inflammatory responses and enhance the vascular permeability and the adhesion of monocytes to a certain extent [11]. The levels of the above indicators in patients exhibit an upward trend after infection since the intracranial infection is caused by purulent bacteria, which exert certain predictive effects on the postoperative intracranial infection.

In this study, the analysis results determined a multitude of risk factors for intracranial infection in patients after intracranial tumor operation. 1) Age: Due to significantly reduced immunity, lower anti-infection ability and the body's high stress state during operation, patients with intracranial tumor older than 45 years old have a higher risk of the intracranial infection. For the elderly patients, various tissue functions of the body are poor, so craniotomy may affect their mental state to a certain extent, reduce the resistance of pathogens and increase the intracranial infection rate. Additionally, the rate of purulent bacterial infection in some elderly patients will be also increased to a certain degree due to a large number of underlying diseases and inadequate preoperative preparation [12]. 2) Operation time: The extensive operation time of patients often increases the exposure time of brain tissues to the air and elevates the infection rate. During operation, controlled hypotension is often carried out, and a long operation time leads to a low-perfusion and traction state of brain tissues over a long term, which gives rise to the reduction of local immunity and a growing infection rate [13]. 3) Diabetes mellitus: Poor abilities of disease resistance as well as phagocytosis, wandering, chemotaxis of white blood cells result in the small number of antibodies, complements, and immunoglobulins produced in the blood and low lymphocyte conversion rate. Furthermore, a hyperglycemia environment in patients with diabetes mellitus can promote the growth of bacteria and increase the infection rate [14]. 4) Postoperative cerebrospinal fluid leakage: Postoperative cerebrospinal fluid leakage can promote the adverse current of purulent bacteria into the brain, thereby forming the intracranial infection. 5) Posterior fossa operation: During the posterior fossa operation, patients often take the supine position, and cerebrospinal fluid leakage and local sweating easily lead to the soaking of the surgical dressing and bacteria breeding. Besides, a microscope is necessary in the operation, and the long operation time increases the infection rate. In the process of surgical resection, a reservoir cavity is formed, which causes a circulation issue of cerebrospinal fluid, bacterial reproduction and infection [15].

Based on our results, targeted preventive coping measures were proposed: 1) For patients complicated with underlying disease and aged ≥45 years old, surgical indications should be well known, and related departments should be surgically coordinated. 2) Antibacterial agents, drainage tubes and incision of the trachea should be avoided to the greatest extent, and under the unavoidable condition, the monitoring of blood work, body temperature, etc. should be strengthened, so as to avoid intracranial infection. 3) Patients complicated with diabetes mellitus as the underlying disease should be given corresponding measures to control blood glucose level. 4) Surgical preparations should be conducted well as far as possible, the level of surgical operations should be improved and cooperation between doctors and nurses should be guaranteed, so as to minimize the operation time and avoid intracranial infection. 5) Preventive antibacterial agents should be reasonably given, and if necessary, pathogen monitoring can be conducted for the patient's drainage.

Conclusion

Our data demonstrate that infection inflammatory cytokines, CRP, PCT, IL-6 and TNF-α, are markedly increased due to the intracranial infection in patients after intracranial tumor operation. Age, diabetes mellitus, operation time, posterior fossa operation and postoperative cerebrospinal fluid leakage can serve as independent risk factors, which provide new leads for the prevention and control of intracranial infection in clinical practice.

Disclosure of conflict of interest

None.

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