

## Original Article

# Diagnostic, monitoring, and prognostic value of combined detection of lactate dehydrogenase, $\beta$ 2-transferrin, and interleukin-10 for acute intracranial infections

Zhong Feng, Xuan Liu, Mengjia Lian, Li Zhang

Department of Neurology, The First People's Hospital of Wenling, Wenling 317500, Zhejiang, China

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**Abstract:** Objective: To investigate the value of the combined detection of lactate dehydrogenase (LDH),  $\beta$ 2-transferrin ( $\beta$ -2Tf), and interleukin-10 (IL-10) for identification of acute intracranial infections such as meningitis. Methods: A total of 103 patients were placed in the suppurative meningitis group (SMG), 124 patients in the viral meningitis group (VMG). Another 86 patients without any infectious diseases of the central nervous system constituted the control group (CG). The levels of LDH and  $\beta$ -2Tf in the cerebrospinal fluid were determined by enzymatic methods; IL-10 expression was measured by ELISA. The correlation between infection and the LDH,  $\beta$ -2Tf, and IL-10 levels was analyzed by linear correlation analysis, and ROC curve analysis was applied to determine the diagnostic value of combined detection of LDH,  $\beta$ -2Tf, and IL-10 levels for intracranial infections. Results: LDH,  $\beta$ -2Tf, and IL-10 levels negatively correlated with the treatment time in both the SMG ( $r = -0.52, -0.97, \text{ and } -0.24$ , respectively,  $P < 0.01$ ) and VMG ( $r = -0.70, -0.91, \text{ and } -0.25$ , respectively,  $P < 0.01$ ). Sensitivity and specificity of combined detection of LDH,  $\beta$ -2Tf, and IL-10 for the diagnosis of SM was 80.47% and 75.33%, respectively, while those for VM were 84.24% and 79.24%, respectively. Conclusion: Combined detection is an excellent indicator for the diagnosis and treatment of intracranial infections.

**Keywords:** Lactate dehydrogenase (LDH),  $\beta$ 2-transferrin ( $\beta$ -2Tf), interleukin-10 (IL-10), intracranial infection, meningitis

## Introduction

Acute intracranial infections are infectious diseases caused by pathogens invading the central nervous system [1]; some examples include meningitis, thrombophlebitis, and brain abscesses; with meningitis being the most common [2]. According to Duan et al. [3], there are  $\geq 3$  million known cases of intracranial infections in the world, and Chen et al. [4] reported that in 2015, approximately 3,80,000 people were newly diagnosed with intracranial infections worldwide, and that its incidence increases every year. The incidence of intracranial infections significantly varies from region to region, and in countries with large populations, such as China and India, patients with intracranial infections account for 40% of all patients with brain injury [5].

Intracranial infections are difficult to treat and can cause irreversible injuries because of the destruction of the central nervous system [6]. According to Akashi et al. [7],  $\geq 60\%$  patients with intracranial infections developed psychiatric disorders post treatment. In addition, the cure rate of intracranial infections is not ideal, given the current state of medical technology. The 5-year-survival rate is  $\leq 80\%$  [8]. In clinical practice, intracranial infections with extremely high incidence and morbidity (disability) are a research hotspot because of the continuous need for effective treatment. Some recent studies have shown that effective medical interventions can significantly improve the prognosis of early intracranial infections [9]; however, because of the complex pathological types of intracranial infections, the situation of patients can only be clarified by using multiple

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methods such as microbiological culture [10], which are time-consuming, expensive, less efficient, and influenced by multiple uncontrollable factors. This approach causes significant delay in the diagnosis and treatment. Thus, improving the efficiency of the identification of the etiological agents causing infection is key to timely treatment.

In cerebrospinal fluid (CSF), the level of  $\beta$ 2-transferrin ( $\beta$ -2Tf), a transferrin catalyzed by neuraminidase, significantly varies during intracranial infections [11]. The level of lactate dehydrogenase (LDH), a specific substance secreted by myocardial enzymes is also high [12]. Interleukin-10 (IL-10) is a representative factor, which is extremely sensitive to inflammatory reactions [13]. Combined detection of these three factors might be an effective method to detect intracranial infections. Therefore, the levels of LDH,  $\beta$ -2Tf, and IL-10 in the CSF of meningitis patients admitted to our hospital were retrospectively analyzed, in order to provide reference values and guiding points for the clinical diagnosis and treatment of intracranial infections.

### Materials and methods

#### *Selection of subjects*

The data from meningitis patients who were admitted to our hospital from July 2014 to August 2016 were used for this retrospective analysis. A total of 427 cases were selected based on the following inclusion criteria: age, 20-60 years; compliance with the clinical diagnostic criteria of meningitis [14]; presence of the clinical symptoms of meningeal or brain parenchymal injury; definite diagnosis of meningitis through a series of examinations (biochemical and microbiological examination of the CSF, electroencephalography, and computed tomography scan of the brain); use of complete medical records; and patients who were cooperative to the arrangement of medical workers in our hospital.

The exclusion criteria were as follows: patients suffering from other cerebrovascular diseases, cancer, other infectious diseases, cardiopulmonary insufficiency, physical disabilities, and mental illness; long-term bedridden patients; and patients transferred to other hospitals halfway through the study. In total, 227 cases were finally included in our study, of which 124 cases

were included in the viral meningitis group (VMG), and 103 cases were included in the suppurative meningitis group (SMG). By cerebrospinal fluid (CSF) culture, we identified 84 cases with gram-positive bacteria, 6 cases with enterococcus, 8 cases with streptococcus, 5 cases with staphylococcus aureus; 49 cases with poliovirus; 7 cases with coxsackie virus; 39 cases with mumps virus, 20 cases with herpes simplex viruses and 9 cases with adenovirus. The diagnosis required a combination of clinical, laboratory, and imaging data. The determination was confirmed by the senior director and experienced doctors of the laboratory. Furthermore, 86 patients without any infectious diseases of the nervous system during the same period were included in the control group (CG) (inclusion criteria: age, 20-60 years; manifestation of clinical symptoms similar to those of meningitis, without any intracranial infection as confirmed by serial examinations; and definite diagnosis of a non-infectious neurological disease such as neuropathic and vascular headache; exclusion criteria: same as above). There were 38 patients with cerebral hemorrhage, 29 patients with cerebral infarction, 11 patients with hypoxic encephalopathy, and 8 patients with metabolic encephalopathy. This study was approved by the ethics committee of The First People's Hospital of Wenling and informed consent was obtained from all patients.

#### *Methodology*

All patients were treated with penicillin and sulfadiazine sodium in our hospital. Viral meningitis patients receive pathogen-based antiviral therapy. About 2 mL of CSF was drawn by lumbar puncture before hospital admission (T1), and at 15 days (T2) and 30 (T3) days after hospitalization; CSF was centrifuged for 5 min at 4,000 rpm. The supernatant was used to determine the LDH level in the CSF by an enzymatic method using a kit from Shanghai Junrui Biotechnology Co., Ltd., and the levels of  $\beta$ -2Tf and IL-10 in the CSF were detected by ELISA using a kit from Thermo Fisher Scientific Co., Ltd. The testing procedures were performed strictly in accordance with the instructions of the reagent kits.

#### *Observation indicators*

Clinical information (such as gender, age, and disease duration) for the three patient groups:

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**Table 1.** Comparison of clinical data of three groups of patients [n (%)]

	VMG (n = 124)	SMG (n = 103)	CG (n = 86)	F	P
Age	41.24 ± 14.63	42.07 ± 15.04	41.56 ± 14.87	0.09	0.92
Body weight (KG)	76.20 ± 16.33	75.24 ± 15.87	77.04 ± 16.84	0.75	0.29
Disease course (d)	14.21 ± 5.81	16.04 ± 6.24	15.57 ± 6.07	2.84	0.06
White blood cell (×10 <sup>9</sup> /L)	15.12 ± 3.81	16.44 ± 4.22	15.73 ± 3.79	0.21	0.79
Red blood cell (×10 <sup>12</sup> /L)	14.86 ± 2.84	15.24 ± 3.24	15.69 ± 3.07	1.90	0.15
Gender				0.58	0.61
male	75 (60.48)	64 (62.14)	55 (63.95)		
female	49 (39.52)	39 (37.86)	31 (36.05)		
Is there a family history				0.14	0.87
yes	34 (27.42)	26 (25.24)	22 (25.58)		
no	90 (72.58)	77 (74.76)	64 (74.42)		
Smoking				0.19	0.84
yes	86 (69.35)	74 (71.84)	62 (72.09)		
no	38 (30.65)	29 (28.16)	24 (27.91)		
living environment				2.56	0.22
town	67 (54.03)	59 (57.28)	48 (55.81)		
rural	57 (45.97)	44 (42.72)	38 (44.19)		

LDH,  $\beta$ -2Tf, and IL-10 levels at T1, T2, and T3; trend of changes in the LDH,  $\beta$ -2Tf, and IL-10 levels during treatment; and the use of LDH,  $\beta$ -2Tf, and IL-10 in the diagnosis of meningitis.

### Statistical analysis

SPSS 22.0 was used for data analysis. Countable data such as gender, place of residence, and diagnostic sensitivity were expressed as rate, while measured data such as LDH and  $\beta$ -2Tf levels were expressed as the mean  $\pm$  standard deviation. The data obtained for the three groups were compared using analysis of variance; the countable data for the two groups were compared by chi-square test; t-test was used to compare the measured data obtained for the two groups; linear correlation analysis was used to analyze the changes in the levels of LDH,  $\beta$ -2Tf, and IL-10 during the treatment; and the diagnostic value was analyzed by ROC curve analysis. A *P* value of < 0.05 implied a statistically significant difference.

### Results

#### Selection of subjects

No significant difference was noted in the age, gender, body weight, family residence, family disease history, smoking history, routine blood parameters, and course of disease among

patients in the three groups of patients (*P* > 0.05), indicating that the three groups were comparable (**Table 1**).

#### Levels of LDH, $\beta$ -2Tf, and IL-10

The CSF LDH level significantly differed across the three groups (*P* < 0.01): 34.17  $\pm$  8.42 U/L in VMG, 36.67  $\pm$  7.32 U/L in SMG, and 16.24  $\pm$  4.34 U/L in CG. The CSF LDH level in SMG and VMG was significantly higher than that in CG, while that in SMG was significantly higher than that in VMG (*P* < 0.05). The CSF  $\beta$ -2Tf level in VMG, SMG, and CG was 34.86  $\pm$  8.69 mg/L, 36.57  $\pm$  9.04 mg/L, and 14.33  $\pm$  4.86 mg/L, respectively, which was significantly different among the three groups (*P* < 0.01). The CSF  $\beta$ -2Tf level in the SMG and VMG was significantly higher than that in the CG. The CSF IL-10 level significantly differed across the three groups (*P* < 0.01): 8.98  $\pm$  1.12 pg/mL in the VMG, 8.74  $\pm$  1.62 pg/mL in the SMG, and 6.47  $\pm$  1.14 pg/mL in the CG. The CSF IL-10 level in the SMG and VMG was significantly higher than that in the CG (**Table 2**).

#### Changes in the LDH, $\beta$ -2Tf, and IL-10 levels over time

The CSF LDH level at T2 and T3 in the VMG was 21.62  $\pm$  6.87 U/L and 14.81  $\pm$  4.07 U/L, respectively, whereas that in the SMG was

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**Table 2.** The expression of LDH,  $\beta$ -2Tf and IL-10 in cerebrospinal fluid of three groups of patients at admission

	VMG (n = 124)	SMG (n = 103)	CG (n = 86)	F	P
LDH (U/L)	34.17 $\pm$ 8.42	36.67 $\pm$ 7.32*	16.24 $\pm$ 4.34*#	226.04	< 0.01
$\beta$ -2Tf (mg/L)	34.86 $\pm$ 8.69	36.57 $\pm$ 9.04	14.33 $\pm$ 4.86*#	224.81	< 0.01
IL-10 (pg/mL)	8.98 $\pm$ 1.12	8.74 $\pm$ 1.62	6.47 $\pm$ 1.14*#	105.6	< 0.01

Note: \*: compared with LDH expression in cerebrospinal fluid of VMG,  $P < 0.05$ ; #: compared with LDH expression in cerebrospinal fluid of SMG,  $P < 0.05$ .

24.54  $\pm$  7.04 U/L and 15.55  $\pm$  5.21 U/L, respectively. In the CG, the CSF LDH level at T2 and T3 was 9.04  $\pm$  3.24 U/L and 4.21  $\pm$  2.07 U/L, respectively. Thus, the CSF LDH level at T2 was lower than that at T1 in all three groups ( $P < 0.05$ ), and the level at T3 was also lower than that at T2 ( $P < 0.05$ ). The CSF  $\beta$ -2Tf level at T2 and T3 in the VMG was 17.94  $\pm$  4.89 mg/L and 6.89  $\pm$  2.12 mg/L, respectively, whereas that in the SMG was 18.66  $\pm$  4.34 mg/L and 7.14  $\pm$  2.07 mg/L, respectively. In the CG, the CSF  $\beta$ -2Tf level at T2 and T3 was 7.52  $\pm$  1.82 mg/L and 3.57  $\pm$  1.04 mg/L, respectively. Thus, the CSF  $\beta$ -2Tf level at T2 was lower than that at T1 in all three groups ( $P < 0.05$ ), and the level at T3 was also lower than that at T2 ( $P < 0.05$ ). The CSF IL-10 level at T2 and T3 in the VMG was 4.04  $\pm$  0.90 pg/mL and 1.30  $\pm$  0.17 pg/mL, respectively, whereas that in the SMG was 4.12  $\pm$  0.84 pg/mL and 1.24  $\pm$  0.24 pg/mL, respectively. In the CG, the CSF IL-10 level at T2 and T3 was 2.75  $\pm$  0.62 pg/mL and 0.89  $\pm$  0.12 pg/mL, respectively. Thus, the CSF IL-10 level at T2 was lower than that at T1 in all three groups ( $P < 0.05$ ), and the level at T3 was also lower than that at T2 ( $P < 0.05$ ) (**Figure 1**).

### *Correlation between LDH, $\beta$ -2Tf, and IL-10 levels and treatment time*

The CSF levels of LDH,  $\beta$ -2Tf, and IL-10 in both the VMG ( $r = -0.70, -0.91, \text{ and } -0.25$ , respectively;  $P < 0.01$ ) and SMG ( $r = -0.70, -0.91, \text{ and } -0.25$ , respectively;  $P < 0.01$ ) were negatively correlated with the treatment time (**Figures 2-4**).

### *Diagnostic performance of LDH, $\beta$ -2Tf, and IL-10 detection*

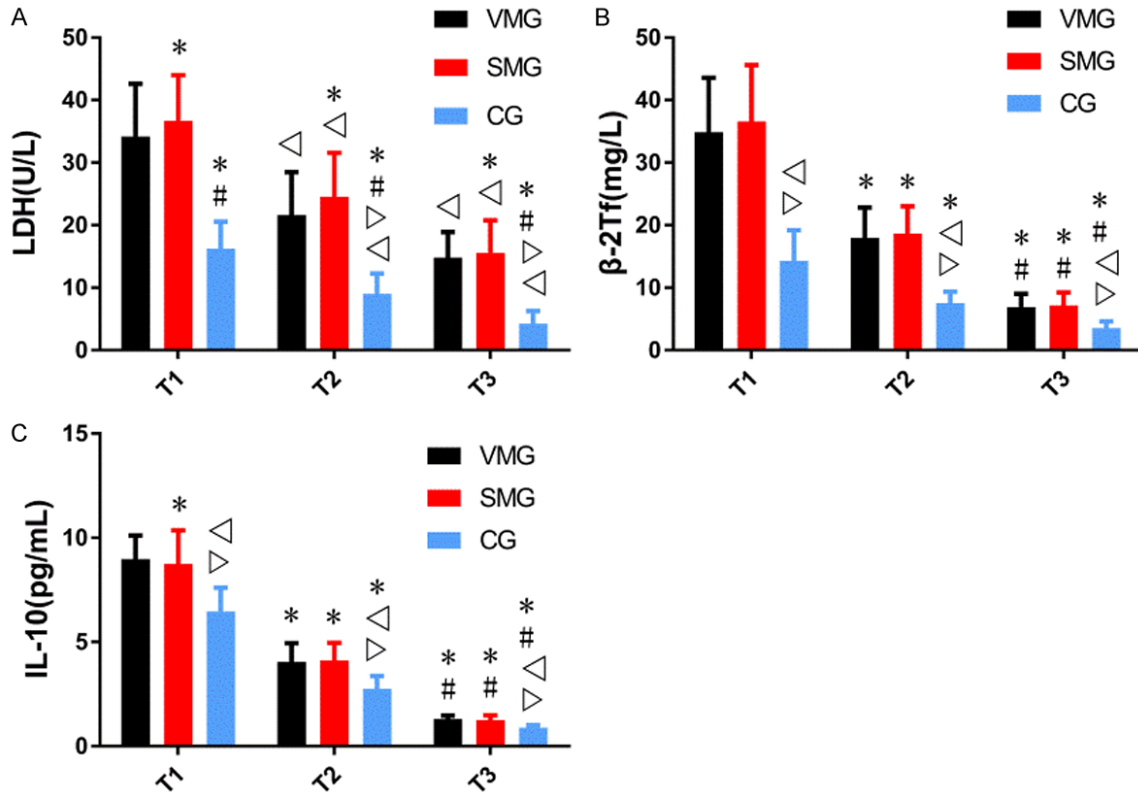
Considering a cut-off value of 23.84 U/L, 22.34 mg/L, and 7.14 pg/mL for LDH,  $\beta$ -2Tf, and IL-10, respectively, the sensitivity and specificity of the method involving the combined detec-

tion of these three parameters, for the diagnosis of VM, was 84.24% and 79.24%, respectively. Similarly, for the diagnosis of SM, at a cut-off value of 25.48 U/L, 22.74 mg/L, and 7.14 pg/mL for LDH,  $\beta$ -2Tf, and IL-10, respectively, the sensitivity and specificity of the method involving the combined detection of these parameters was 80.47% and 79.24% (**Figure 5**).

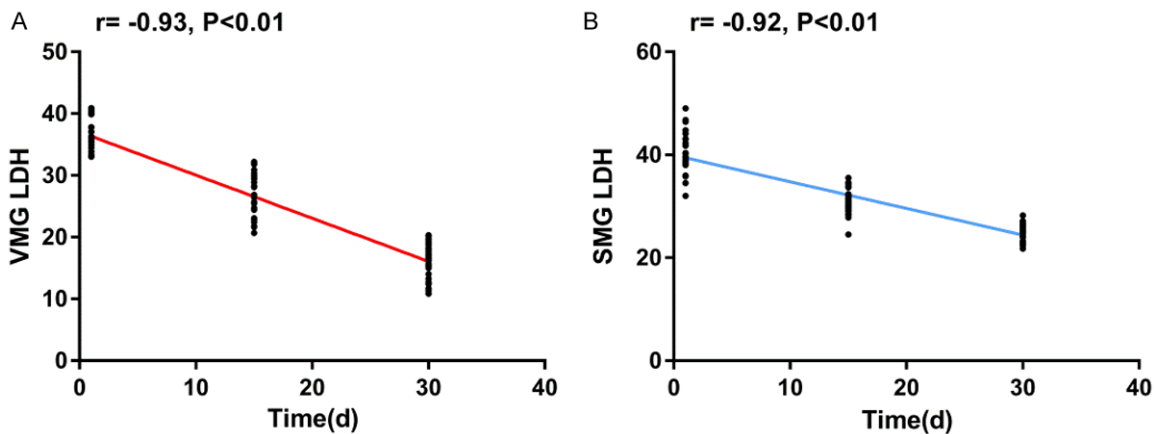
## **Discussion**

Intracranial infections are infectious diseases caused by the invasion of a pathogen into the central nervous system. The early clinical symptoms of the different types of meningitis are quite similar, and therefore, the traditional method of CSF examination fails to identify the correct etiological agent. As a result, the patient often receives inappropriate or wrong drugs or therapy, which further deteriorates the course of the disease clinically [15]. Antibiotic usage also causes changes and variations in CSF-based parameters, making diagnosis and treatment more difficult [16]. In addition, CSF is required for most detection methods, and the patient has to undergo lumbar puncture. The detection methods are expensive and time consuming, with a low detection rate; therefore, a better quick identification of the etiological agent causing intracranial infection is the key to effective diagnosis and treatment. Available findings are highly controversial, and some studies have shown that the detection of enzyme substances in cerebrospinal fluid can effectively guide the pathogen judgment [17-19]. Increased enzyme activity in the CSF causes an overflow of neuronal enzymes, damage to brain tissue, decomposition of the cells in the spinal fluid, tumors, decreased CSF clearance, high intracranial pressure, and hemodialysis-induced changes [20]. Enzyme activity in the CSF is extremely sensitive to the damage in the central nervous system and brain tissues, and therefore, it can be used

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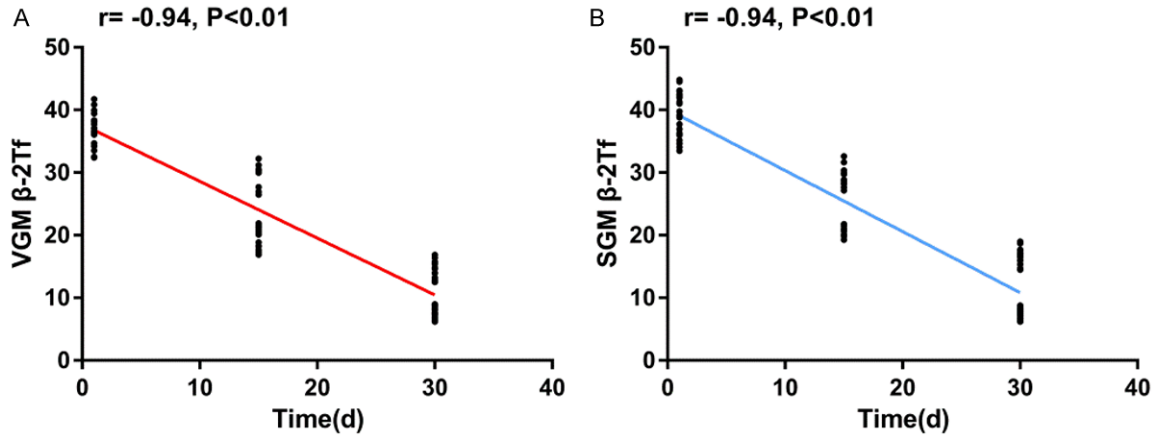
**Figure 1.** LDH,  $\beta$ -2Tf and IL-10 level in the three groups during treatment. A: At T2 and T3, the LDH level was significantly lower than that at T1 ( $P < 0.05$ ). The level of LDH in the CG was lower than that in the other two groups ( $P < 0.05$ ). \* represents  $P < 0.05$ , compared to the LDH level in VMG. # represents  $P < 0.05$ , compared to the LDH level in SMG.  $\Delta$  represents  $P < 0.05$ , compared to the LDH level in the same group at T1.  $\nabla$  represents  $P < 0.05$ , compared to the LDH level in the same group at T2. B: At T2 and T3, the  $\beta$ -2Tf level was significantly lower than that at T1 ( $P < 0.05$ ). The level of  $\beta$ -2Tf in the CG was lower than in the other two groups ( $P < 0.05$ ). \*  $P < 0.05$ . # represents  $P < 0.05$ , compared to the  $\beta$ -2Tf level at T2.  $\Delta$  represents  $P < 0.05$ , compared to the  $\beta$ -2Tf level in VMG.  $\nabla$  represents  $P < 0.05$ , compared to the  $\beta$ -2Tf level in SMG. C: At T2 and T3, the IL-10 level was significantly lower than that at T1 ( $P < 0.05$ ). The level of IL-10 in the CG was lower than in the other two groups ( $P < 0.05$ ). \* represents  $P < 0.05$ , compared to the IL-10 level at T1 in the same group. # represents  $P < 0.05$ , compared to the level of IL-10 at T2 in the same group.  $\Delta$  represents  $P < 0.05$ , compared to the level of IL-10 in VMG.  $\nabla$  represents  $P < 0.05$ , compared to the level of IL-10 in SMG.



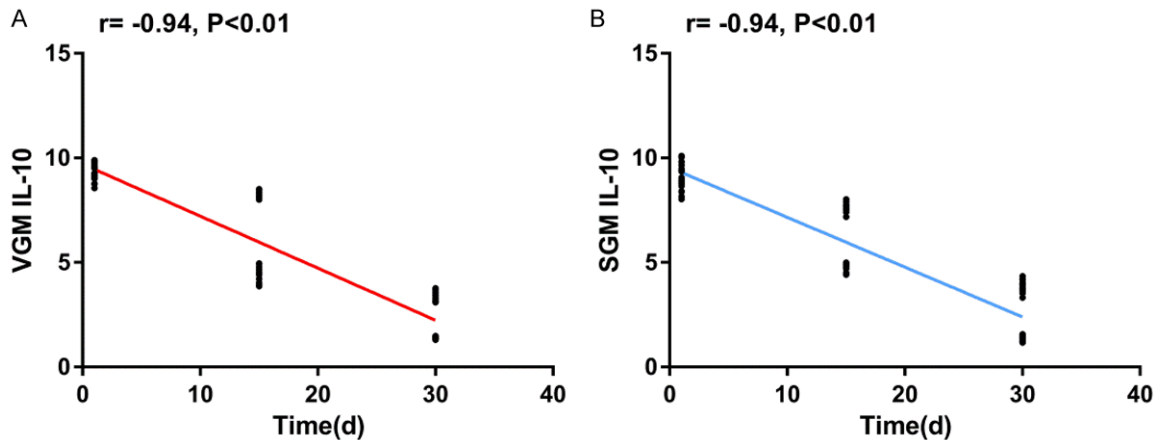
**Figure 2.** Correlation analysis of LDH level and treatment time in VMG and SMG. A: Linear correlation analysis showed that the LDH level in VMG negatively correlated with the treatment time ( $r = -0.25$ ,  $P < 0.01$ ). B: Linear correlation analysis showed that the LDH level in SMG negatively correlated with treatment time ( $r = -0.52$ ,  $P < 0.01$ ).



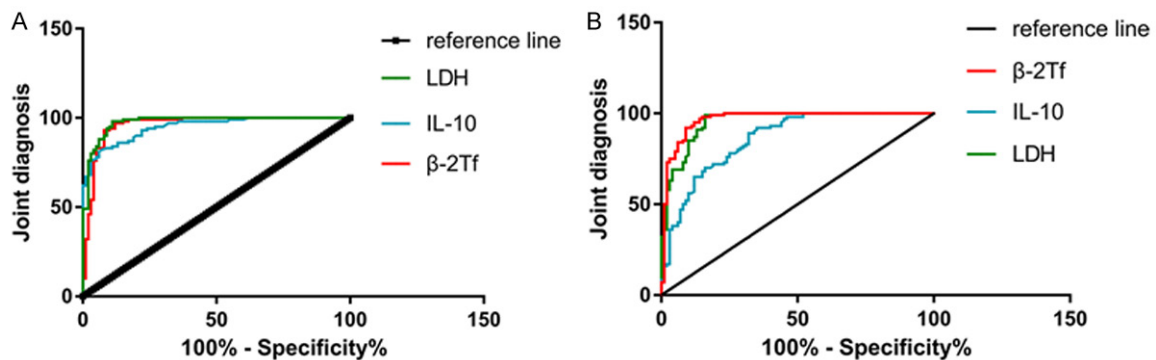
## Significance of the combined detection for LDH



**Figure 3.** Correlation analysis of  $\beta$ -2Tf level and treatment time in VMG and SMG. A: Linear correlation analysis showed that the  $\beta$ -2Tf level in VMG negatively correlated with the treatment time ( $r = -0.91$ ,  $P < 0.01$ ). B: Linear correlation analysis showed that the  $\beta$ -2Tf level in SMG negatively correlated with treatment time ( $r = -0.97$ ,  $P < 0.01$ ).



**Figure 4.** Correlation analysis of IL-10 level and treatment time in VMG and SMG. A: Linear correlation analysis showed that the IL-10 level in VMG negatively correlated with treatment time ( $r = -0.25$ ,  $P < 0.01$ ). B: Linear correlation analysis showed that the IL-10 level in SMG negatively correlated with treatment time ( $r = -0.24$ ,  $P < 0.01$ ).



**Figure 5.** ROC curve analysis of the role of LDH,  $\beta$ -2Tf, and IL-10 levels in the diagnosis of viral meningitis and purulent meningitis. A: The cut-off value for LDH was 23.84; for  $\beta$ -2Tf, 22.34; and for IL-10, 7.14. The sensitivity and specificity of the combined diagnosis of viral meningitis was 84.24% and 79.24%, respectively. B: The cut-off value for LDH was 25.48; for  $\beta$ -2Tf, 22.74; and for IL-10, 6.92. The sensitivity and specificity of the combined diagnosis of purulent meningitis was 80.47% and 75.33%.

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as an excellent indicator for the diagnosis of intracranial infections. Of these enzymes, LDH exerts the most significant inflammatory response, and many studies have shown that LDH expression increases in diseases [21, 22].  $\beta$ -2Tf is an asialotransferrin isoform, highly specific to the CSF [23], and the combination of IL-10,  $\beta$ -2Tf, and LDH is an effective diagnostic indicator of intracranial infection, which was also confirmed in this study.

It is speculated that the cause of LDH elevation in such patients could be that as an isoenzyme, LDH catalyzes the conversion of lactic acid and acetone. Once the tissues are damaged, the transformation barrier causes rapid activation of LDH [24]. In patients with intracranial infections, a large number of pathogens invade the central nervous system, and anti-inflammatory cytokines secreted in response to systemic tissue damage leads to the secretion of massive amounts of LDH in the tissue. The hypoxic and ischemic conditions of the brain caused by acute infections also increase the permeability of the blood-brain barrier and lead to the mixing of LDH with CSF under the stimulation of inflammatory factors. It cannot be ruled out that possible disturbance to the functioning of the hypothalamus is caused by the destruction of the central nervous system, which could further lead to dysfunction, resulting in a cycle of hypoxia and necrosis, and thus increasing LDH activity.  $\beta$ -2Tf is generated by transferrin under the action of specific enzymes involving negatively charged tiny molecular structures, and therefore, it can easily cross the blood-brain barrier. Jeswani et al. [25] stated that  $\beta$ -2Tf is produced by a neuraminidase-catalyzed reaction involving transferrin, and that all pathogens causing intracranial infections can produce massive neuraminidase, which presumably causes an increase in  $\beta$ -2Tf expression. Increase in the IL-10 level exerts an anti-inflammatory effect, and at the same time, inhibits the immune function of the body, which further elevates the risk of infection in patients and makes IL-10 an effective indicator to monitor the prognosis of various types of diseases. The significantly high expression of IL-10 in patients with intracranial infections makes it easier to monitor infected patients. The levels of the three parameters gradually reduced during the course of the treatment, which indicated that the clinical condition has been effectively con-

trolled, the inflammatory response of the central nervous system is inhibited, and the immune function of the body has recovered by automatic regulation after treatment. The detection combination can be used as an evaluation criterion for the future rehabilitation of patients with intracranial infections. The LDH level of SM patients was found to be higher than that of VM patients. We found that the reproduction and growth of pathogenic bacteria caused tissue necrosis, enhanced local tissue glycolysis, and increased the activity of catalytic enzymes. When pathogens invaded the CSF, inflammatory factors such as sialic acid and endotoxins stimulated enzyme secretion by macrophages and glial cells and caused an increase in the expression of LDH, which was consistent with the results obtained by Zhou et al. [26]. The use of the combination of the three indicators for the detection of the etiological agent responsible for the intracranial infection showed high sensitivity and specificity, indicating that it can be used as one of the diagnostic criteria for diagnosis of early acute intracranial infections, but the underlying mechanism needs to be explored further.

The indicators such as glucose, lymphocyte and neutrophil levels have significant sensitivity and low specificity, which cannot effectively determine the pathological type of intracranial infection. Moreover, it is sensitive to the response of nerve injury, and it is easy to misjudge damaged neurological brain tissue as infectious encephalitis. In this study, the combined detection of LDH,  $\beta$ -2Tf and IL-10 has excellent sensitivity and specificity, and shows good clinical application value.

Because of the experimental conditions, this study has some limitations. The number of cases in the CG is small. In addition, the patient population is confined to a small base of subjects. Furthermore, the mechanism of action of LDH and  $\beta$ -2Tf in acute intracranial infections is not yet fully clarified. Therefore, we will continue to conduct in-depth studies and then undertake long-term follow-up investigations to obtain the best results.

In summary, LDH,  $\beta$ -2Tf, and IL-10 levels are closely related to the occurrence and development of acute intracranial infections. Combined detection using the three parameters can

help identify the cause of acute intracranial infections and can be used an excellent indicator for the diagnosis and treatment of intracranial infections in the near future.

### Disclosure of conflict of interest

None.

**Address correspondence to:** Li Zhang, Department of Neurology, The First People's Hospital of Wenling, No. 333, Chuan'an South Road, Chengxi Street, Wenling 317500, Zhejiang, China. Tel: +86-15957650658; E-mail: zhangli58@163.com

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