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ABSTRACT

Objective: To explore the significance of cerebrospinal fluid and plasma biochemical indicator ratio in identifying the tuberculous meningitis and purulent meningitis. Methods: A total of 43 patients with tuberculous meningitis who were admitted to our hospital from August 2015 to July 2017 were included in the study and served as the tuberculous meningitis group. Moreover, 40 cases with purulent meningitis were served as the purulent meningitis group. The morning fasting peripheral venous blood was collected and centrifuged for the plasma. Lumbar puncture was used to collect cerebrospinal fluid. The fully automatic biochemical analyzer was used to detect GSH, the plasma protein, chloride, glucose, lactic acid, and ADA. GSF/plasma ratio was calculated. The immunity transmission turbidity was used to detect GSH and Cys-C. FCM was used to detect CD64. ELISA was used to detect MMP-9. Results: GSF chloride and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group, while ADA was significantly higher than that in the purulent meningitis group. The plasma protein, chloride, and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group, while ADA was significantly higher than that in the purulent meningitis group. ADA ratio in GSF in the tuberculous meningitis group was significantly higher than that in the purulent meningitis group, while chloride and lactic acid ratio was significantly lower than that in the purulent meningitis group. CD64 in GSF in the tuberculous meningitis group was significantly lower than that in the purulent meningitis group, and MMP-9 was significantly higher than that in the purulent meningitis group, while the comparison of Cys-C between the two groups was not statistically significant. Conclusions: GSF, plasma protein, chloride, lactic acid, and ADA concentration ratio in the tuberculous meningitis group and purulent meningitis group have a certain difference. Combined detection of CD64 and MMP-9 contribute to identifying the two meningitis.

1. Introduction

Meningitis is a common intracranial infectious disease in the clinic, among which the tuberculous meningitis, purulent meningitis, and viral meningitis are the most common. The clinical manifestation, peripheral hemogram, and cerebrospinal fluid (CSF) detection are easy to identify the viral meningitis. For patients with tuberculous and purulent meningitis, the clinical symptoms and laboratory examination results are similar, especially for the tuberculous meningitis, due to the limited early detection means, which results in the delay of diagnosis and treatment[1]. The discovery of Mycobacterium tuberculosis in CSF is the most objective clinical basis for the diagnosis of tuberculous meningitis, but the culture positive rate of Mycobacterium tuberculosis in CSF is only 20%-30%; moreover, 4-6 weeks and even longer time are required for the culture, which is easy to delay the best treatment time to cause the irreversible nerve injury and increase the mortality; therefore, looking for the methods with high sensitivity and strong specificity to identify the tuberculous meningitis has been the research focus[2]. Some researches demonstrate that[3] the stimulation on the meninges by the pathogenic bacteria can cause a series of inflammatory
reaction, and CSF and the biochemical indicators in the plasma will be normally changed, which is of great significance in identifying the tuberculous meningitis and purulent meningitis. The study is aimed to explore the significance of CSF and plasma biochemical indicator ratio in identifying the tuberculous meningitis and purulent meningitis.

2. Materials and methods

2.1. General materials

A total of 43 patients with tuberculous meningitis who were admitted in our hospital from August 2015 to July 2017 were selected as the tuberculous meningitis group, among which 27 were male, and 16 were female, aged from 15 to 61 years old, with an average age of (43±7) years old; their treatment course was from 13 h to 3 d, with an average course of (1.2±0.5) d. Moreover, 40 cases with purulent meningitis were selected as the purulent meningitis group, among which 24 were male, and 16 were female, aged from 16 to 60 years old, with an average age of (43±7) years old; their treatment course was from 14 h to 3 d, with an average course of (1.3±0.7) d. The comparison of age, gender, and course between the two groups was not statistically significant (P>0.05).

2.2. Inclusion and exclusion criteria

Inclusion criteria for the tuberculous meningitis: (1) those who had acute or subacute onset; (2) those who had positive meningeal irritation sign; (3) those whose acid-fast smear and mycobacterium tuberculosis culture were positive and or were merged with extra pulmonary tuberculosis; (4) those whose bacteria, fungus, and malignant tumor cell examinations in the plasma and CSF were negative. Inclusion criteria for the purulent meningitis: (1) those who had acute onset; (2) those whose meningeal irritation sign was positive; (3) those whose CSF smear or culture bacteria was positive; (4) those whose mycobacterium tuberculosis, fungus, and malignant tumor cell examinations in the plasma and CSF were negative. The patients in the two groups were not accepted related etiology treatment, and the informed consents were obtained from all the patients or their relatives. Exclusion criteria: (1) those who had central nervous system tumor, connective tissue disease, and other diseases which can cause the abnormal biochemical indicators in CSF; (2) those who were pregnant or in the lactation period; (3) those whose medical materials were incomplete.

3. Results

3.1. Comparison of biochemical indicators in CSF

CSF chloride and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group, while ADA was significantly higher than that in the purulent meningitis group (P<0.01). The comparison of protein and glucose between the two groups was not statistically significant (P>0.05) (Table 1).

3.2. Comparison of the biochemical indicators in the plasma

The plasma protein, chloride, and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group, while ADA was significantly higher than that in the purulent meningitis group (P<0.01). The comparison of glucose between the two groups was not statistically significant (P>0.05) (Table 2).

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**Table 1.** Comparison of biochemical indicators in CSF.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein (g/L)</th>
<th>Glucose (mmol/L)</th>
<th>Chloride (mmol/L)</th>
<th>Lactic acid (mmol/L)</th>
<th>ADA (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis group</td>
<td>43</td>
<td>1.39±0.42</td>
<td>1.89±0.45</td>
<td>98.36±14.53</td>
<td>4.19±2.67</td>
<td>9.89±3.16</td>
</tr>
<tr>
<td>Purulent meningitis group</td>
<td>40</td>
<td>1.41±0.43</td>
<td>1.92±0.47</td>
<td>114.71±19.46</td>
<td>6.82±3.34</td>
<td>4.11±1.87</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>0.2143</td>
<td>0.2971</td>
<td>4.3518</td>
<td>3.9759</td>
<td>10.0449</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.8309</td>
<td>0.7672</td>
<td>0.0000</td>
<td>0.0000</td>
<td>0.0000</td>
</tr>
</tbody>
</table>

**Table 2.** Comparison of the biochemical indicators in the plasma.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein (g/L)</th>
<th>Glucose (mmol/L)</th>
<th>Chloride (mmol/L)</th>
<th>Lactic acid (mmol/L)</th>
<th>ADA (U/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis group</td>
<td>43</td>
<td>58.36±4.92</td>
<td>4.33±0.49</td>
<td>97.53±6.27</td>
<td>5.68±1.87</td>
<td>16.04±10.57</td>
</tr>
<tr>
<td>Purulent meningitis group</td>
<td>40</td>
<td>71.44±7.63</td>
<td>4.32±0.46</td>
<td>104.77±9.84</td>
<td>7.42±2.45</td>
<td>8.84±2.87</td>
</tr>
<tr>
<td>t</td>
<td></td>
<td>9.3469</td>
<td>0.0957</td>
<td>3.9874</td>
<td>3.6524</td>
<td>4.1660</td>
</tr>
<tr>
<td>P</td>
<td></td>
<td>0.0000</td>
<td>0.9240</td>
<td>0.0001</td>
<td>0.0005</td>
<td>0.0001</td>
</tr>
</tbody>
</table>
3.3. Ratio of biochemical indicators in CSF and plasma

ADA ratio in CSF in the tuberculous meningitis group was significantly higher than that in the purulent meningitis group, while chloride and lactic acid ratio was significantly lower than that in the purulent meningitis group \( (P<0.01) \). The comparison of plasma protein and glucose ratio between the two groups was not statistically significant \( (P>0.05) \) (Table 3).

3.4. Comparison of Cys-C, CD64, and MMP-9 in CSF

CD64 in GSF in the tuberculous meningitis group was significantly lower than that in the purulent meningitis group, and MMP-9 was significantly higher than that in the purulent meningitis group \( (P<0.01) \), while the comparison of Cys-C between the two groups was not statistically significant \( (P>0.05) \) (Table 4).

4. Discussion

The discovery of Mycobacterium tuberculosis in CSF is the golden criteria for the diagnosis of tuberculosis meningitis, but it is proved by the clinic that the detection rate of Mycobacterium tuberculosis in CSF is not high. The Mycobacterium tuberculosis culture can enhance the positive rate, but it requires longer time, which is not beneficial for the early diagnosis and treatment. Detection of DNA fragment of Mycobacterium tuberculosis has a relatively high sensitivity and rapid speed, but due to the higher requirement for the personnel technology and detection equipment, it is unable to be popularized\[4\]. The purulent meningitis can be caused by various bacteria, with a more acute onset compared with the tuberculous meningitis. The extensive application or abuse of antibiotics, the diversity of clinical manifestations, and the atypical CSF detection results have caused a certain difficulty in diagnosis of purulent meningitis\[5\].

Table 3
Ratio of biochemical indicators in CSF and plasma.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Protein ratio</th>
<th>Glucose ratio</th>
<th>Chloride ratio</th>
<th>Lactic acid ratio</th>
<th>ADA ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis group</td>
<td>43</td>
<td>0.023±0.010</td>
<td>0.44±0.03</td>
<td>1.01±0.12</td>
<td>0.72±0.08</td>
<td>0.78±0.32</td>
</tr>
<tr>
<td>Purulent meningitis group</td>
<td>40</td>
<td>0.019±0.010</td>
<td>0.45±0.04</td>
<td>1.11±0.14</td>
<td>0.93±0.13</td>
<td>0.49±0.24</td>
</tr>
<tr>
<td>( t )</td>
<td>0.1436</td>
<td>1.2943</td>
<td>3.5013</td>
<td>8.9317</td>
<td>4.6434</td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td>0.8862</td>
<td>0.1992</td>
<td>0.0008</td>
<td>0.0000</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

Table 4
Comparison of Cys-C, CD64, and MMP-9 in CSF.

<table>
<thead>
<tr>
<th>Groups</th>
<th>n</th>
<th>Cys-C (mg/L)</th>
<th>CD64 (%)</th>
<th>MMP-9 (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculous meningitis group</td>
<td>43</td>
<td>3.18±1.12</td>
<td>0.40±0.17</td>
<td>89.46±14.75</td>
</tr>
<tr>
<td>Purulent meningitis group</td>
<td>40</td>
<td>3.15±1.19</td>
<td>0.56±0.19</td>
<td>53.63±15.28</td>
</tr>
<tr>
<td>( t )</td>
<td>0.1183</td>
<td>4.0485</td>
<td>10.8683</td>
<td></td>
</tr>
<tr>
<td>( P )</td>
<td>0.9061</td>
<td>0.0001</td>
<td>0.0000</td>
<td></td>
</tr>
</tbody>
</table>

In a physiological condition, due to the existence of blood-brain barrier, the protein, chloride, and glucose in the blood can only selectively penetrate the blood-brain barrier to enter CSF; the protein, chloride, and glucose levels in CSF are closely associated with the content of plasma. In a pathological condition, the blood-brain barrier is damaged, the permeability is increased, and the carbohydrate metabolism and transportation are in disorder, resulting in the protein entering CSF, which can alter the component and nature of CSF; therefore, the calculation of the ratio of biochemical indicators in CSF and plasma can be used to identify the tuberculous and purulent meningitis\[6\]. The chloride ion enters into CSF mainly in a way of active transport. Due to the influence by different pathogenic bacteria infection, the chloride ion consumption in CSF and the chloride concentration in a way of active transport are affected\[7\]. Some researches demonstrate that\[8\] the reduction of chloride concentration in CSF can reflect the transition function of positive ion and chloride ion, showing that the blood-brain barrier in patients with tuberculous meningitis is severely destroyed. Due to the basicranial inflammation in patients with tuberculous meningitis, ADH secretion is insufficient, resulting in the reduction of plasma chloride content. Excluding the factor of plasma, the reduction of CSF/plasma chloride is of great significance for the differential diagnosis. The protein in CSF is increased both in the tuberculosis and purulent meningitis patients. Due to the long course and chronic consumption in patients with tuberculous meningitis, the plasma protein concentration is lower than that in patients with purulent meningitis; therefore, the protein ratio of CSF/plasma in patients with tuberculous meningitis is higher than that in patients with purulent meningitis\[9\]. The lactic acid is the end product of glucose anaerobic reaction, whose elevation in CSF can be caused by the cerebral anoxia. When there is a meningitis, the brain tissues are destroyed by the pathogenic bacteria, resulting in the release of glucose decomposing enzyme, which can promote the transformation of glucose in CSF into the lactic acid\[3\]. ADA is the key enzyme of purine nucleotide metabolism. When the meningeal tissues are destroyed, the neuronal endoenzye is released, and the permeability of blood-brain barrier is changed, which can cause the change of enzyme in CSF\[10\]. Some researches demonstrate that\[11\] Mycobacterium tuberculosis infection can cause the elevation of ADA concentration. Detection of ADA activity in CSF can contribute to the diagnosis of tuberculous meningitis. It is reported by some scholars\[12\] the plasma ADA concentration in patients with tuberculous meningitis is higher than that in patients with purulent meningitis. Due to the most invasion of meninges by...
Mycobacterium tuberculosis, the difference of ADA concentration in CSF is more obvious; therefore, ADA ratio in CSF/plasma in patients with tuberculous meningitis is higher than that in patients with purulent meningitis. The results in the study showed that CSF chloride and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group, while ADA was significantly higher than that in the purulent meningitis group. The plasma protein, chloride, and lactic acid in the tuberculous meningitis group were significantly lower than those in the purulent meningitis group (P<0.01); ADA ratio in CSF in the tuberculous meningitis group was significantly higher than that in the purulent meningitis group, while chloride and lactic acid ratio was significantly lower than that in the purulent meningitis group (P<0.01). ADA ratio in CSF and plasma can be served as the indicators for the differential diagnosis of tuberculosis meningitis and purulent meningitis.

Cys-C can inhibit the damage of malignant tumor endoenzyme and cell death on other tissues, and protect the endogenous cells, whose reduction can increase the destruction of cathepsin, resulting in nervous system disease, inflammation, and Cys-C imbalance. It is reported that the brain cell degeneration in patients with tuberculous and purulent meningitis can release the cysteine protease, and stimulate the secretion of Cys-C to inhibit the activity of cysteine protease, thus playing a role in protecting the body; therefore, it is argued that Cys-C is of great significance in the diagnosis of central nervous system disease. CD64 plays a key role in the humoral immunity and cellular immunity, whose expression is associated with the regulation of cytokines and the level is obviously elevated when there is a bacterial infection, and is involved in the neutrophil sterilization and phagocytosis. MMP-9 can destroy the cell basement membrane through the degradation of ECM, which can increase the permeability of blood-brain barrier, resulting in the invasion of immune cells into the brain tissues. MMP-9 can also cause the remodeling of abnormal tissues, and is involved in the fibrosis of tuberculous meningitis, while the proliferation and fibrosis of a large amount of granulation tissues are the key factors to enter the chronic stage for the tuberculous meningitis. The results in the study showed that CD64 in GSF in the tuberculous meningitis group was significantly lower than that in the purulent meningitis group, and MMP-9 was significantly higher than that in the purulent meningitis group (P<0.01), while the comparison of Cys-C between the two groups was not statistically significant (P>0.05), indicating that CD64 and MMP-9 levels in CSF can contribute to identifying the tuberculous and purulent meningitis.

In conclusion, GSF, plasma protein, chloride, lactic acid, and ADA concentration ratio in the tuberculous meningitis group and purulent meningitis group have a certain difference. Combined detection of CD64 and MMP-9 contribute to identifying the two meningitis.

References