Changes of MMP-9 and IL-1β in serum and cerebrospinal-fluid in children with central nervous system infection

Shu-Qin Jiao*

Department of Neurology, Traditional Chinese Medicine Hospital of Muping District, Yantai, Shangdong, 264100

ARTICLE INFO

Article history:
Received 12 October 2015
Received in revised form 29 October 2015
Accepted 15 October 2015
Available online 21 October 2015

Keywords:
Purulent meningitis
Viral encephalitis
Central nervous system infection
Matrix metalloproteinases 9
Interleukin 1
Bold-brain barrier

ABSTRACT

Objective: To provide a new basis for the detection of the central nervous system infection cases, we explored and compared the role of cerebrospinal-fluid (CSF), matrix metalloproteinases 9 (MMP-9) and interleukin 1 (the level of IL-1β) in the central nervous system (CNS). Methods: Sixty cases of children acute central nervous system infection were selected, including 30 cases of viral encephalitis children (VE) and 30 cases of purulent meningitis children (PM). Forty cases of non-central nervous system infection children were control group. The serum albumin (SA1b) of each group was detected by full-automatic analysis instrument, and the CSF albumin (CA1b) was detected by immunoephelometry and the albumin index (AQ) was accounted. ELISE was used to detect the levels of MMP-9 and IL-1β in serum and cerebrospinal-fluid. Results: The level of MMP-9 in the serum of groups of VE, PM and control were (267.84 ± 91.88) μg/L, (488.98 ± 159.07) μg/L and (133.04 ± 31.68) μg/L, while in the CSF were (37.18 ± 17.78) μg/L, (117.9 ± 42.87) μg/L and (10.36 ± 5.43) μg/L; The level of IL-1β in serum of groups of PM, VE and control were (19.69 ± 11.12) ng/L, (24.37 ± 4.13) ng/L and (15.01 ± 3.89) ng/L, while in the CSF were (66.94 ± 10.65) ng/L, (106.27 ± 12.79) ng/L and (49.98 ± 12.59) ng/L; The level of CA1b were (0.53 ± 0.15) g/L, (1.05 ± 0.27) g/L and (0.17 ± 0.07) g/L and AQ were (13.75 ± 3.44), (26.99 ± 7.28) and (4.63 ± 2.04). The PM, VE were respectively compared with the control, the levels of IL-1β and MMP-9 in serum and CSF all increased, with statistically significant difference. The VE, compared to the PM, the level of IL-1β in serum and CSF all decreased, with statistically significant difference; The level of MMP-9 in serum and CSF all decreased, with statistically significant difference. The level of CA1b and AQ in the VE and PM all increased, with a statistically significant difference. The level of MMP-9 and IL-1β in serum and CSF of the PM and VE were positive correlation relationship. Conclusion: The increasing of the levels of IL-1β and MMP-9 in serum and CSF, and the increasing of AQ in children with central nervous system infection indicate that MMP-9 and IL-1β may play a role in the pathophysiologic course of blood-brain barrier impairment in the central nervous system infection.

1. Introduction

As a common infectious disease in children, central nervous system (CNS) infection has raised more and more public concerns for its relatively high morbidity, fatality and disability rates. There are several different types of central nervous system infections, including meningitis, cerebritis, encephalitis, abscessus, intervernination and so on. Even though central nervous system has a strong resistance against all kinds of pathogens, once the brain and spinal cord are infected, it can be refractory and the consequences of which are unpredictable and possibly dangerous. Central nervous system infection severely threatens the healthy grow of children, which lead to a serious social economical burden. Because of its completely complicated pathogenesis and pathophysiological
procedure, the process of central nervous system infection cannot be fully understood momentarily at present. The main measure to diagnose central nervous system infection is the detection of CSF. Because of the widely application of antibiotics, the change of CSF in purulent meningitis tends to be untypical. At the moment, there are certain limitations to distinguish viral encephalitis and purulent meningitis by the cytology, characteristics and clinical performance of CSF. Therefore, a more-reliable index needs to be found for early diagnosis and identification of central nervous system infection, which aims to achieve a precise diagnosis and timely treatment for central nervous system infection and relieve the psychological and physiological burden which is caused by the disease for human. From February 2014 to December 2014, we detected and compared the changes of the IL-1β and MMP-9 levels in CSF and serum and studied and discussed their significances, clinical diagnosis and prediction for central nervous system infection detection.

2. General material and methods

2.1. Material

Sixty cases of children central nervous system infection who had received treatment in our hospital were selected, including 30 cases of purulent meningitis children (PM) and 30 cases of viral encephalitis children (VE). In PM, 19 cases of them were male and 11 were female, with ages from 6 months to 12 months. In VE, there were 15 males and 15 females with ages from 8 months to 15 months. The symptom diagnoses of the above children patients were in the light of the diagnosed standards of purulent meningitis and viral encephalitis in Zhu Futang Practice of Pediatrics (Version 7), which required the process from onset to hospitalization was less than 6 days. Children patients were definitely diagnosed according to their medical history, sign, EEG, laboratory examination, MRI and CT and excluded tumor, immune disease, other nerve system diseases and so on. Thirty patients who were in hospital at the same time were selected to be the control group. Among them, 17 were males and 13 were females with ages from 9 months to 16 months. Those patients were all suspected diagnosed with central nervous system infection when they were in hospital, with normal EEG, normal CSF, normal biochemical test and lumbar puncture indications. After comparison, the differences of the general material of each group had no statistical significances and were comparable.

2.2. Detection methods

Within 24 h after hospitalization, the PM and VE’s serum specimen and CSF specimen of lumbar puncture (with aseptic manipulation) were selected, while the same quantities of serum specimen and CSF specimen of lumbar puncture of the control group were selected as soon as they were hospitalized. One milliliter of CSF and two milliliters of venous blood specimen of the two groups were selected and centrifuged for 15 min (at room temperature 3000 r/min), and then, the supernatant was selected and placed in fridge at -20 °C temperature, waiting for detection. ABCELISA was used to test the levels of IL-1β and MMP-9 in CSF and serum. Full-automatic analysis instrument (made by Axis-Shield Company, Norway) and the matched reagent were applied to test CA1B, and immunoephelometry was used to detect CA1b and calculate CA1b index (AQ).

2.3. Statistical methods

SPSS16.0 was used. Mean ± SD was used to represent measurement data. After the homogeneity variance and analysis of variance, F-test was used to multigroup mean comparison and q-test was used to make comparison among groups. P<0.05 showed that differences had statistical significant.

3. Results

3.1. Comparison of the levels of IL-1β and MMP-9 in CSF and serum of each group

Compared with the control, the levels of IL-1β of the PM and VE in serum and CSF all increased, with statistically significant difference (P<0.001, P<0.001, P<0.001, P=0.034); the level of MMP-9 in serum and CSF all increased, with statistically significant difference (P<0.001); The VE, compared to the PM, the level of IL-1β in serum and CSF all increased, with statistically significant difference (P<0.001, P=0.035); the level of MMP-9 in serum and CSF all increased, with statistically significant difference (P<0.001) (Table 1).

<table>
<thead>
<tr>
<th>Group</th>
<th>IL-1β (ng/L)</th>
<th>MMP-9 (μg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CSF</td>
<td>Serum</td>
</tr>
<tr>
<td>PM</td>
<td>105.39±13.12</td>
<td>24.37±4.13</td>
</tr>
<tr>
<td>Control</td>
<td>48.98±13.22</td>
<td>15.01±3.89</td>
</tr>
<tr>
<td>F</td>
<td>157.661</td>
<td>12.649</td>
</tr>
<tr>
<td>P</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Compared with the control, *P<0.001; compared with the VE, †P<0.001.
3.2. Comparison of CA1b, SA1b and AQ of each group

Compared with the control, the levels of CA1b and AQ of groups PM and VE all increased, with statistically significant difference \((P<0.001)\); compared with the VE, the levels of CA1b and AQ of the PM all deceased, with statistically significant difference \((P<0.001)\) (Table 2).

<table>
<thead>
<tr>
<th>Group</th>
<th>CA1b (g/L)</th>
<th>SA1b (g/L)</th>
<th>AQ</th>
</tr>
</thead>
<tbody>
<tr>
<td>VE</td>
<td>0.53 ± 0.21</td>
<td>39.58 ± 3.89</td>
<td>13.67 ± 3.54</td>
</tr>
<tr>
<td>PM</td>
<td>1.05 ± 0.32</td>
<td>38.76 ± 2.81</td>
<td>25.98 ± 7.19</td>
</tr>
<tr>
<td>Control</td>
<td>0.19 ± 0.11</td>
<td>39.36 ± 4.13</td>
<td>4.65 ± 2.03</td>
</tr>
<tr>
<td>(F)</td>
<td>106.457</td>
<td>0.404</td>
<td>150.961</td>
</tr>
<tr>
<td>(P)</td>
<td>&lt;0.001</td>
<td>0.670</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Compared with the control, \(P<0.001\); compared with the VE, \(P<0.001\).

3.3. The correlation analysis of MMP-9 and IL-1 \(\beta\) in CSF and Serum of the VE and PM

The level of MMP-9 and IL-1 \(\beta\) in serum and CSF of the PM and VE were positive correlation relationship \((r=0.306, all \ P=0.017)\); the levels of MMP-9 and IL-1 \(\beta\) in CSF were positive correlation relationship \((r=0.836, P<0.001)\).

4. Discussion

In recent years, with improvements of healthcare, we have got a certain understanding about body fluids and cellular immunity in the pathological process of CNS infection and the pathogenesis mechanism and pathological and physiological changing principle of CNS infection. Because different people have different immune responses, their responses to a same pathogenic factor are different. Some lead to mild illness; some lead to severe illness; and some happened repeatedly. So, those situations should be taken into consideration when source of infection was treated and controlled. Although with improvements of healthcare, the morbidity and mortality of CNS infection have been well controlled and decreased, there are few satisfactory improvements of its clinical treatment. Severe patients usually accompany with sequelae which mostly represents as repeated epilepsies and certain neurological function damages, such as weakening memory, brain atrophy, brain damage or craniocerebral disease, which has a strong impact on patients’ physical and psychological health and causes heavy social burdens. Clinical researches show that BBB plays an important role in CNS infection. It can maintain stability of the internal environment of the CNS.

Studies have showed that the effects of BBB was extremely important in CNS[1,2]. MMPs are a proteolytic enzyme which can promote the degradation of ECM. MMPs is a promoting factor for destructive inflammation and it can destroy BBB and blood-nerve barrier[3]. When inflammation occurs, inflammatory cells produce MMPs and release various cytokines, such as IL-1, IL-6, TNF-\(\alpha\), VEGF, etc., these cytokines can promote the growth of inflammatory cells. Especially IL-1, it can adjust the expression of MMPs by using multiple signals transduction. Proinflammatory factors’ activity improves because of the feedback effect of MMPs[4,5]. The two can play an interaction effect and lead to inflammation, which can destroy BBB and injured tissues[6].

MMPs are a kind of calcium-zinc-dependent proteolytic enzyme. It is the most important protease when disintegrating BBB. MMPs can promote the occurrence of destructive inflammation, including destroy BBB and blood-nerve barrier and form edema, causing disintegration of neurovascular unit[3,7]. Vascular basement membrane of brain nerve is composed of IV- collagen, fibronectin, laminin, heparin sulfate proteoglycan and so on[8,9]. When inflammation occurs, nervous tissue is intruded by pripherial immune cells. Inflammatory cells not only produce MMPs, but also release multiple cytokines, such as IL-1, IL-6, TNF-\(\alpha\), VEGF, etc. These proinflammatory cytokines could activate transcription factor NF-\(\kappa\)B and adjust the expression of MMPs by these the signal transcription factor PKN, p38MAPK and JNK[10]. At the same time, the activation of MMP-9 can serve as a mediate to promote the inducement of IL-1 for neurotoxicity and neuronal cell death. MMPs has a positive feedback effect on proinflammatory cytokines and increases its activity[11]. Some studies showed that MMP-9 and MMP-2 could destroy EMC and prompt the opening of BBB. Numerous researches indicated that the increase of serum MMP-9 has closely associated to BBB dysfunction of infectious encephalitis[12]. When the inflammatory of the encephalitis reacts, the levels of MMP-8 of patients’ CSF and MMP-9 are higher than those of the control group. MMPs can open BBB and blood-nerve barrier. As a result, nervous tissue is intruded by immune cells of the blood vessel effusion. What is more important is that high-lever MMP-9 in CSF is an extremely dangerous factor of sequelae for patients with bacterial meningitis.

IL-1 \(\beta\) is also a kind of proinflammatory cytokines, since it can widely participate various pathological damage processes, such as edema formation and tissue destruction. Under the circumstances of brain damages by intracranial infection and epilepsy, the lever and activity of IL-1 \(\beta\) would significantly improve[13]. It mechanism can up-regulate the expression of MMPs, and MMPs could damage BBB and enhance its permeability by degrading EMC of mesenchyme and basilar membrane, which lead to water exosmose of serum protein and capillary, moisture improvement and then form vascular prototype brain edema[14]. These study results are similar to the foreign reports, which all showed that the levels of IL-1 \(\beta\) and
MMP-9 in the VE, PM serum and CSF are higher than those of the control group[12]. However, the statistical difference of the lever of IL-1β in children patients’ serum of the VE and PM could not be compared. It was concerned that IL-1β may have difficulty with passing blood-cerebrospinal fluid barrier. What’s more, the research also showed that MMP-9 and IL-1β in the CSF and serum of the VE and PM showed positive correlation, which indicated that the two might have interactions. They might promote inflammation reaction of the host together and destroy BBB and cause tissue damage.

There are few proteins in normal CSF, and albumin is the main one. It can invade CSF through BBB in serum. When CNS infection happens, albumin with relatively small molecular weight can easily invade CSF by injured BBB. Since the processes of compound and metabolic of albumin are not carried out in the CNS, it could be an index to judge whether BBB is intact. When BBB is damaged, albumins (in serum) which get into the CSF increase and AQ also increase. If AQ >8, it indicate BBB is damaged. Generally speaking, normal AQ <8.8-10 is regarded as mild damage, 10-30 as moderate damage and >30 as severe damage[11]. At present, AQ and CA1b are widely used as qualitative indexes to evaluate BBB damage and plasma protein exosmosis. The study showed the levers of AQ and CA1b of the control group were lower than those of the PM and VE. Besides, the levers of AQ and CA1b of the VE were lower than those of the PM, which indicated that the BBB function of CNS infection patients was damaged in different degree and it could be worse when cells were infected. Therefore, detection of the levers of CA1b and AQ has important reference value for diagnosing and identifying viral encephalitis, purulent meningitis and extent of damage of BBB.

In conclusion, we draw the following conclusions: the MMP-9 and IL-1β in children patients with CNS infection participate in physiological and pathological processes of CNS infected brain function; the detection of MMP-9 and IL-1β possesses important implications for evaluation and prediction of CNS infection. So clinically we should pay attention to detect the levers of MMP-9 and IL-1β so as to evaluate and predict patients’ condition precisely.

References


