Aseptic Meningoencephalitis in Children with Kawasaki Disease

JG YU, Y WEI, SY ZHAO, CC ZOU, Q SHU

Abstract

Objective: To describe the clinical presentations, diagnosis and therapy of 15 Kawasaki disease (KD) patients with aseptic meningoencephalitis. Methods: Patients’ medical records were retrospectively reviewed with reference to age, gender, duration of disease, clinical presentation, laboratory findings, diagnosis and therapy. Results: There were 10 males and 5 females with an average age of 38.2 months. Headache was noted in 10 patients (66.67%), vomiting in 6 (40.0%), seizures in one (6.67%). Thirteen (86.67%) showed central nervous system (CNS) features in the acute phase while 2 patients showed headache or vomiting in the subacute phase. Elevated C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were noted in all patients, thrombocytosis in 9 (60.0%), elevated aminoleucine transferase and/or aspartate aminotransferase in 2. Also, CSF pleocytosis were noted in 9 patients. These patients had a good response to intravenous immunoglobulin (IVIG) therapy. No complications were noted in the follow-up. Conclusion: KD, like many other vasculitic diseases, can sometimes involve the CNS and present with irritability, lethargy, headache, vomiting and seizures. Aseptic meningoencephalitis should be suspected especially in KD patients with persisted elevated CRP, ESR, and CNS symptoms.

Key words: Child; Kawasaki disease; Meningoencephalitis; Vasculitis

Introduction

Kawasaki disease (KD), first described in 1967,1 is an acute febrile mucocutaneous lymph node syndrome. It is prevalent in infants and young children, and preferentially affects male infants.2-4 In Japan, an annual incidence of 112 patients per 100,000 children under age 5 years were reported.3 The basic etiology remains unknown, although immunological pathogenesis after infection has been postulated.4-6 KD is characterised by systemic small-to-medium-vessel vasculitis, mainly involving the coronary arteries.7,8 Recently, several KD patients involving the nervous system were reported, including irritability, seizures, facial palsy, cerebrospinal fluid (CSF) pleocytosis, and other central nervous system (CNS) involvements.9-12

Herein, we described the clinical presentations, diagnosis and treatment of 15 KD patients with aseptic meningoencephalitis.

Methods

A total of 548 KD patients referred to our hospital from January 2002 to December 2009 were reviewed. The diagnosis of KD is made according to the classical Japan
diagnostic criteria, which requires at least 5 of the following 6 principal symptoms: fever persisting for 5 days or more, bilateral conjunctival congestion, changes in the lips and oral cavity, polymorphous exanthema, changes in the peripheral extremities, and acute nonpurulent cervical lymphadenopathy. A total of 15 cases diagnosed to be suffering from aseptic meningoencephalitis were enrolled in this study. There were 10 males and 5 females with an average age of 38.2 months (range: 11-73 months). Their medical records were reviewed and the duration of the disease, clinical presentations, laboratory findings, diagnosis and treatment were analysed.

This study was approved by the Ethic Committee of the Children Hospital of Zhejiang University School of Medicine.

Statistics

Statistical analyses were conducted by using SPSS software (Version11.5). Pearson Chi-square was used to measure enumeration data among groups. Quantitative data with normal distribution were presented as mean ± S.D and were analyzed by independent Student t test. Data with skewed distributions were presented as median (mix-max) and analysed by Nonparametric tests (Mann-Whitney U type). Differences were considered statistically significant if P<0.05.

Results

A total of 15 KD patients with aseptic meningoencephalitis were studied (Table 1). In these patients, we noted headache in 10 patients (66.67%), vomiting in 6 (40.0%), seizures in one (6.67%). Other symptoms, including irritability or crying (6 patients, 40.0%), lethargy or drowsiness (4 patients, 26.67%), were also noted. No facial palsy, extremity dyskinesia, coma or other CNS symptoms were found.

Aseptic meningoencephalitis as a complication of KD was diagnosed at the 5th-15th day of the disease onset. In these children, 4 patients were diagnosed to have viral encephalitis at the time when periungual and perineal desquamation were noted. Thirteen patients (86.67%) showed the CNS symptoms in the acute phase with fever, 2 patients showed headache or vomiting in the subacute phase after the temperature had resolved with elevated C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), leukocytosis and thrombocytosis.

They all had raised WBC (>12 × 10^6/L; range: 12.3-25.7 × 10^6/L), CRP (range: 46 - >160 mg/L; reference range, <8 mg/L) and ESR (range: 37-98 mm/hr, reference range: <20 mm/hr in male, <25 mm/hr in female). Thrombocytosis (platelets >300 × 10^9/L, range: 312-547 × 10^9/L) was found in 9 patients (60.0%), elevated aminoleucine transferase (ALT, range: 73-112 U/L; reference range, <50 U/L) and/or aspartate aminotransferase (AST, 159 U/L; reference range, <55 U/L) in 2, elevated ferritin (327 µg/L; reference range, 11.0-306.8 µg/L) in one, sterile pyuria in one, and anemia (haemoglobin ranging from 83-10.2 g/L) in 5 (33.33%). Antistreptolysin O test (ASO) was positive in one patient. Viral serologies were negative for hepatitis virus and HIV markers. Ultrasound was performed for all patients, coronary artery aneurysm was not found. Other parameters, including TORCH antibody, rapid plasma reagin, Epstein-Barr virus, tubercle bacillus antibody and DNA, antinuclear antibody, rheumatoid factor, total protein, blood culture, and CSF culture were normal or negative.

Lumbar puncture was performed for all patients. CSF pleocytosis was noted in 9 patients (60.0%, ranging from 20 to 78 cells/mL) with normal protein, glucose and other biochemical parameters. The CSF findings of the other 6 patients were normal. No tubercle bacillus or other bacteria were found in CSF. Echocardiograms were performed for all 15 patients at diagnosis, 4 weeks and 8 weeks after diagnosis, and there was no coronary aneurysm present. Electroencephalogram (EEG) showed mild abnormality in 2 of 7 patients. Computerised tomography (CT) or magnetic resonance imaging (MRI) of 8 patients showed normal results.

Seven patients had been given intravenous immunoglobulin (IVIG) therapy (1 g/kg/day for 2 days) before the diagnosis of aseptic meningoencephalitis. When compared to the other 8 cases who presented with symptoms of nervous system before IVIG therapy, no statistical difference was found (Table 2). In the 7 patients who presented with CNS symptoms after IVIG therapy, 6 were given IVIG again. Eight patients were given IVIG therapy after the diagnosis of aseptic meningoencephalitis as a complication of KD. Aspirin was administrated routinely for all 15 patients and dehydrant (mannitol and/or furosemide) was administrated for 14 patients. Dexamethasone was administrated for two patients for 3 and 5 days, respectively.
Table 1  The clinical and laboratory characteristics of 15 patients

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender/ Age (month)</th>
<th>Symptoms of nervous system</th>
<th>Onset (day)</th>
<th>WBC (x10^9/L)</th>
<th>CRP (mg/L)</th>
<th>ESR (mm/hr)</th>
<th>CSF WBC (cells/mL)</th>
<th>Other laboratory parameters</th>
<th>Therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Male/11</td>
<td>Vomiting, crying</td>
<td>7*</td>
<td>21.5</td>
<td>63</td>
<td>43</td>
<td>31</td>
<td>Elevated ALT and AST</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>2</td>
<td>Female/13</td>
<td>Seizures, irritability, crying</td>
<td>5</td>
<td>25.7</td>
<td>&gt;160</td>
<td>77</td>
<td>12</td>
<td>EEG abnormality, normal brain CT</td>
<td>Mannitol, furosemide, IVIG and aspirin, dexamethasone</td>
</tr>
<tr>
<td>3</td>
<td>Male/16</td>
<td>Crying</td>
<td>9*</td>
<td>17.4</td>
<td>46</td>
<td>32</td>
<td>46</td>
<td>Normal EEG</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>4</td>
<td>Female/17</td>
<td>Crying, lethargy, drowsiness</td>
<td>5</td>
<td>12.3</td>
<td>75</td>
<td>37</td>
<td>9</td>
<td>Normal brain CT, sterile pyuria</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>5</td>
<td>Male/20</td>
<td>Crying</td>
<td>8</td>
<td>15.3</td>
<td>116</td>
<td>55</td>
<td>78</td>
<td>Normal EEG</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>6</td>
<td>Male/26</td>
<td>Headache, crying, vomiting</td>
<td>12*</td>
<td>17.3</td>
<td>62</td>
<td>68</td>
<td>20</td>
<td>Normal EEG</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>7</td>
<td>Male/31</td>
<td>Headache, crying, lethargy</td>
<td>5</td>
<td>22.1</td>
<td>&gt;160</td>
<td>83</td>
<td>53</td>
<td>Elevated ALT, normal brain MRI</td>
<td>Mannitol, IVIG and aspirin, dexamethasone</td>
</tr>
<tr>
<td>8</td>
<td>Female/37</td>
<td>Headache, vomiting</td>
<td>6*</td>
<td>15.7</td>
<td>&gt;160</td>
<td>98</td>
<td>8</td>
<td>Normal brain CT</td>
<td>Mannitol, and aspirin</td>
</tr>
<tr>
<td>9</td>
<td>Male/47</td>
<td>Headache, lethargy</td>
<td>6</td>
<td>16.5</td>
<td>49</td>
<td>53</td>
<td>24</td>
<td>Normal brain CT</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>10</td>
<td>Female/49</td>
<td>Headache, vomiting, lethargy</td>
<td>11*</td>
<td>19.3</td>
<td>126</td>
<td>51</td>
<td>11</td>
<td>Normal EEG</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>11</td>
<td>Male/53</td>
<td>Headache</td>
<td>8</td>
<td>24.6</td>
<td>56</td>
<td>74</td>
<td>36</td>
<td>Normal brain MRI</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>12</td>
<td>Male/55</td>
<td>Headache, vomiting</td>
<td>6*</td>
<td>13.2</td>
<td>99</td>
<td>47</td>
<td>17</td>
<td>Normal EEG</td>
<td>IVIG and aspirin</td>
</tr>
<tr>
<td>13</td>
<td>Female/57</td>
<td>Headache, vomiting</td>
<td>7</td>
<td>15.3</td>
<td>76</td>
<td>63</td>
<td>11</td>
<td>EEG abnormality</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>14</td>
<td>Male/68</td>
<td>Headache</td>
<td>15</td>
<td>20.6</td>
<td>78</td>
<td>33</td>
<td>24</td>
<td>Positive for ASO</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
<tr>
<td>15</td>
<td>Male/73</td>
<td>Headache</td>
<td>8*</td>
<td>17.7</td>
<td>&gt;160</td>
<td>46</td>
<td>37</td>
<td>Normal brain MRI</td>
<td>Mannitol, IVIG and aspirin</td>
</tr>
</tbody>
</table>

*Presentation the symptoms of nervous system after IVIG.

ALT, aminoleucine transferase; ASO, antistreptolysin O test; AST, aspartate aminotransferase; CRP, C-reactive protein; CSF WBC, white blood cell of cerebrospinal fluid; CT, computerized tomography; EEG, electroencephalogram; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging.
All patients with CNS symptoms responded well to IVIG therapy. CNS symptoms disappeared within 2-5 days in all patients, and the median CRP after 5 days declined from 78 to 21 mg/dl. The hospital stay ranged from 10 to 21 days. No sequela was noted in the 6 months follow up.

Discussion

Recently, some patients with CNS involvements were reported. In this cohort, encephalopathy was noted in about 2.73% (15/548) KD patients. As investigations performed had excluded the common causes with CNS involvements, including metabolic diseases, bacterial meningitis, tuberculosis, and viral infections, encephalopathy in these patients could be considered as specifically related to Kawasaki disease.

Our patients had a male to female ratio of 2:1 which is similar to other reports, in contrary to KD patients with facial nerve paralysis (female to male, 1.4:1). The average age was 38.2 months, which was older than reported previously. The older age in these children might be explained as follows: firstly, CNS involvement might be more common in older children with KD, as some reports showed that the clinical features might be associated with age, although reports from adults KD showed less incidence of meningitis. Second, most infants and younger children are unable to readily communicate their CNS symptoms, such as headache. Moreover, mild vomiting, irritation, crying, being dispirited might considered as the results of fever in some circumstances. Hence, some younger patients with aseptic meningoencephalitis without obvious CNS features might be missed.

The course of KD can be divided into acute, subacute, and chronic or convalescent phases. Similar to the development of coronary artery aneurysms, we noted in our study that most aseptic meningoencephalitis (83.33%) developed in acute phase, even with prior IVIG treatment. However, it is notable that 2 patients showed headache, or vomiting in the subacute phases after the temperature recovered. All aseptic meningoencephalitis patients had elevated CRP and ESR. We should consider the possibility of aseptic meningoencephalitis in KD patients with persisted elevated CRP and/or ESR.

The clinical manifestations of aseptic meningoencephalitis included headache, vomiting, seizures, irritability, irritation, crying, lethargy, drowsiness, presenting between 5 and 15 days of the disease onset. In this study, pleocytosis was observed in the CSF in 60.0% patients. Although previous reports showed other CNS involvements in KD, we did not find these features in our study. Hence, aseptic meningoencephalitis should be considered in KD patients with CNS symptoms, including headache, vomiting, seizures, irritation, crying, dispirited, and drowsiness.

The pathogenesis of aseptic meningoencephalitis in KD is unclear. Although IVIG treatment may be associated with aseptic meningitis, in this series, we did not find any difference between patients presented with the symptom of aseptic meningitis before and after IVIG administration. Moreover, all patients had a good response to IVIG. These suggested that meningoencephalitis was most likely to be associated with KD itself, but not IVIG. KD is characterised by systemic vasculitis, mainly involving the coronary arteries. Such a pathologic mechanism may also affect the CNS and be responsible for the neurologic symptoms. This

Table 2  The clinical and laboratory characteristics between patients presented with nervous system symptoms before and after IVIG

<table>
<thead>
<tr>
<th></th>
<th>Before IVIG</th>
<th>After IVIG</th>
<th>χ2/t/Z</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (male/female)</td>
<td>3/5</td>
<td>2/5</td>
<td>0.134</td>
<td>0.714</td>
</tr>
<tr>
<td>Age (months)</td>
<td>39.0 (13.0-68.0)</td>
<td>37.0 (11.0-73.0)</td>
<td>0.116</td>
<td>0.908</td>
</tr>
<tr>
<td>Onset (day)</td>
<td>7.38 ±3.34</td>
<td>8.43±2.37</td>
<td>0.695</td>
<td>0.499</td>
</tr>
<tr>
<td>Blood WBC (x 10⁹/l)</td>
<td>19.05±4.88</td>
<td>17.44±2.62</td>
<td>0.776</td>
<td>0.451</td>
</tr>
<tr>
<td>CRP (mg/l)</td>
<td>77.0 (49.0-&gt;160.0)</td>
<td>99.0 (46.0-&gt;160.0)</td>
<td>0.117</td>
<td>0.907</td>
</tr>
<tr>
<td>ESR (mm/hr)</td>
<td>59.38 ± 18.33</td>
<td>55.00 ± 21.80</td>
<td>0.423</td>
<td>0.680</td>
</tr>
<tr>
<td>CSF WBC (cells/ml)</td>
<td>24.0 (9.0-78.0)</td>
<td>20.0 (8.0-46.0)</td>
<td>0.406</td>
<td>0.685</td>
</tr>
</tbody>
</table>

* Presented with nervous system symptoms after IVIG.

CRP, C-reactive protein; CSF WBC, white blood cell of cerebrospinal fluid; ESR, erythrocyte sedimentation rate; IVIG, intravenous immunoglobulin.
was speculated to be the result of systemic vasculitis or the result of vascular leakage through the blood-brain barrier. A previous study with single-photon emission computed tomography imaging demonstrated localised cerebral hypoperfusion without neurologic findings. In another autopsied study, varying degrees of inflammatory changes in brain vasculature (leptomeningeal thickening, mild endarteritis, and periarteritis) was noted. In another autopsied study, varying degrees of inflammatory changes in brain vasculature (leptomeningeal thickening, mild endarteritis, and periarteritis) was noted.

The treatment for meningoencephalitis in KD included dehydrant, IVIG and aspirin. We noted that patients had a good response to IVIG, although repeated dose of IVIG was needed in several patients and potential risks of IVIG therapy (e.g. infusion reactions, volume overload, and osmotic nephropathy) had been reported. Aspirin is usually administered for 1 to 3 months in patients without aneurysms while it was suggested to be continued until 2 years after the aneurysms resolve in patients with coronary artery aneurysms. Aspirin in these patients were discontinued for 2 months and recurrence was not found in this study. We are still not sure if aspirin should be given for a longer period in aseptic meningoencephalitis patients. Moreover, if corticosteroid therapy can reduce the rate and/or duration of the aseptic meningoencephalitis is not known, although corticosteroid therapy is not recommended for initial management of KD. In several reports, some sequelae, including myoclonic seizures and mild hemiparesis, had been reported in KD patients. However, the prognosis of the neurologic complications in this study is good. Large sample and longer time follow up studies are required to give further insight this rare event.

In summary, our data showed that KD, like many other vasculitic diseases, can sometimes involve the CNS. We should pay more attention to this event, especially in KD patients with persisted elevated CRP, ESR, with CNS symptoms.

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**References**


