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Intravenous Immunoglobulin Resistantin Complete Kawasaki Disease with Menıngoencephalitis: A Case Report

Case Report

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Abstract

Kawasaki Disease (KD) is one of the most common vasculitis of childhood. Patients with fever that last more than 5 days and fewer than four principal mucocutaneous inflammatory clinical features can be described as “atypical” or “incomplete” Kawasaki disease. The febrile phase of the disease is characterized by systemic inflammation in numerous organs, tissues, and medium-sized arteries, and aseptic meningoencephalitis may occur due to meningeal inflammation. Intravenous immunoglobulin (IVIG) -resistant KD is described as recrudescent or persistent fever at least 36 hours following completion of the first dose of IVIG.

A 5 year-5 month-old girl applied to our clinic with the symptoms of meningoencephalitis. She was diagnosed with incomplet KD, and recieved IVIG treatment. The patient had recrudescent fever and recieved a second dose of IVIG infusion. She then recieved steroid treatment in consequence of persistent clinical manifestations. As a result, significant clinical and laboratory improvement was detected.

There are many studies in the literature reporting IVIG-resistant KD. However,there are limited studies on IVIG-resistant incomplete KD patients which presents with meningoencephalitis and responds to steroid treatment.Kawasaki disease should be considered in all febrile patients lasting longer than 5 days considering the atypical cases with central nervous system involvement.

Keywords: Children; Incomplete Kawasaki disease; Aseptic meningoencephalitis

Introductıon

Kawasaki Disease (KD) is one of the most common vasculitis of childhood [1]. Patients who have fewer classical diagnostic criteria in addition to fever lasting at least 4 days and with several compatible clinical, laboratory, or echocardiographic (ECHO) findings in exclusion of other febrile illnesses are defined as incomplete or atypical KD [2]. KD is characterized by systemic inflammation in multiple organs, tissues and medium arteries during the febrile phase and aseptic meningoencephalitis may occur with inflammation of the meninges [3]. Recently many cases with central nervous system involvement have been reported. KD is typically a self-limiting condition. However, early diagnosis and treatment is important because complications such as coronary artery aneurysms may develop and cause serious mortality and morbidity. Intravenous immunoglobulin (IVIG) and acetylsalicylic

acid (ASA) are used in the treatment. IVIG-resistant KD is defined as the continuation of recurrent or persistent fever at least 36 hours after IVIG application and this is seen in 10% -20% [3]. Due to the presence of atypical cases, KD should be considered in febrile cases lasting more than 5 days.

We presented this case, because IVIG-resistant incomplete KDwith meningoencephalitis is very rare.

Case Report

Five years and eight months old girl was referred to our hospital for complaints of headache, vomiting, photophobia, leg pain, and abdominal pain for the last 2 days.On physical examination; her body temperature was 39.4°C, general status was moderate, irritable, photophobia, bilateral non-purulent conjunctivitis, left cervical painless lymphadenopathy 1cm in diameter, pain sensitivity in the legs and neck, marked meningismus were present. Laboratory results were as follows: haemoglobin 9.6 g/dL, white blood cell (WBC) count 13,300/mm^3, platelet count 333.000/mm^3, C-reaktif protein(CRP) 34 mg/L, erithrocyte sedimentation rate (ESR)88 mm/h,alanine aminotransferase 32 IU/L, aspartate aminotransferase 41 IU/L, gamma glutamil transpeptidase 110 IU/L, albumine 24 g/L urea: 7 mg/dl, creatinine 0.19 mg/dl, sodium 134 mmol/L, potasium 3.8 mmol/L.Urine analysis was normal, chest x-ray was normal. Viral serology and brucellosis serology were negative. Cerebrospinal fluid analysiswere as follows:70 WBC/mm3, glucose 54 mg/dl (serum glucose:90), protein:60 mg/dl. 88% lymphocyte was detected on giemsa stain, gram stain was negative. Vancomycin was added to the ceftriaxone treatment, which was started at previous hospital, because of partially treated meningitis. ECHO was performed for persistant fever and minimal aortic and mitral insufficiency were noted. The incomplete KD was considered because of prolonged fever, bilateral non-purulent conjunctivitis and aseptic meningoencephalitis. And high dose (2 gr/kg/12 h infusion)IVIG was given on the second day of his admission. Fever was persisted despite IVIG treatment. Asiclovir was added to treatment because of continuation of headache, letargy, photophobia, meningismus. CSF and blood culture were negative. Viral and bacterial serology of CSF were negative. Tuberculin skin test, CSFARB and tuberculosis PCR were negative.Brucella and borrelia serology of CSF and serum were negative. Cranial MR, EEG, ocular fundus examination were normal. Low dose ASA was started because of trombocytosis occurred on 4th day of admission. Repeat ECHO was performed because of persistan fever and high level of acute phase reactants (CRP 22 mg/L, sedim 112 mm/h), there was no adding result. Second high dose of IVIG was given on 5th day of admission. But fever was persisted. Abdominal and thorax tomography were normal. Lombar puncture was repeated because of persistance of fever, photophobia, iritability, letargy, meningismus. CSF analysis as follows: pressure 600mmH_2O,110 WBC/mm^3,glucose 34 mg/dl(serum glucose 120), protein:53 mg/dl. 70% lymphocyte was detected on giemsa stain. Repeat ocular fundus examination was normal. Asetozalamid was started for increased intracranial pressure. Lipid profile, ferritin, fibrinogen were normal. There was no evidence ofmalignancy or hemophagocytosis on bone marrow aspiration. 2mg/kg/day steroid in 2 doses was started on 6th day of admission. Patient became afebrile after first dose of steroid. Headache and photophobia were disappeared. Periungual peeling was started on 9 th day of admission. Repeat ECHO showed dilatation of left coronary artery. Diagnosis of IVIG-resistant incomplete KD was confirmed. Steroid treatment was tapered down and discontinued. Outpatient follow up is normal.

Discussion

KD is the most common form of acquired heart disease in childhood in developed countries [3]. Although the etiology is not known exactly, epidemiological and clinical features suggest that infections or environmental triggers are responsible in susceptible people [4]. The diagnosis is made on the basis of clinical suspicion, and the laboratory may be supportive. Incomplete KD is more prevalent in infants under six months.Prolonged fever and irritability in this age group may be the only clinical manifestation of KD, and the risk of coronary artery involvement is high [3]. The disease may be accompanied by irritability, abdominal pain, vomiting, diarrhea, sterile pyuria, anterior uveitis, moderate hepatic dysfunction, gallbladder hydrops, arthritis, arthralgia, interstitial pneumonia, pericardial effusion, congestive heart failure, myocarditis and aseptic meningitis [4]. KD should be considered in patients with prolonged fever, irritability and unexplained aseptic meningitis. In our patient, despite the fact that there was no classical diagnostic criteria other than 10 days of fever and bilateral non-purulent conjunctivitis, elevation of acute phase reactants, hypoalbunemia, GGT elevation, aseptic meningitis were thought to be related to KD, and after

periungual peeling and coronary abnormalities, diagnosis was confirmed. Although there is not a definitive diagnostic method, prolonged fever and follow-up peripheral peeling have been reported as the most common symptom of incomplete KD by some authours [5].

Central nervous system findings, especially irritability, lethargy, and aseptic meningitis, may occur in 1-30% of KD patients [6]. Facial, abducens and oculomotor nerve paralysis, convulsion, meningoencephalitis, subdural effusion, ataxia, hemiparesis, stroke and sensorineural hearing loss are other neurological manifestations [7-14] .Recently, many patients with central system involvement have been reported.A total of 15 KD patients with aseptic meningoencephalitis were studied by JG Yu et al. In this study aseptic meningoencephalitis as a complication of KD was diagnosed at the 5th-15th day of the disease onset. The complaints of patients were headache, vomiting, seizure, irritability, crying, lethargy, drowsiness [15]. In our patient, 7 days after the onset of the disease, headache, vomiting, sleepiness, tenderness in the arms and legs, irritability, and photophobia developed. The pathogenesis of aseptic meningoencephalitis is not clear in KD. It is thought to develop as a result of vascular leakage or systemic vasculitis along the blood brain barrier [16]. The findings are nonspecific and may not be differentiated from any viral meningitis and encephalitis. In CSF examination, normal/high protein, normal/low glucose and mononuclear pleocytosis can be seen. In a retrospective review lomber puncture was performed in 46 of 520 patients with KD.Of these patients 18 (39.1%) had CSF pleocytosis, 1 (2.2%) had a CSF glucose <45 mg/dl and 8 (17.4%) had an elevated CSF protein [17]. Our CSF results supported aseptic meningoencephalitis with high protein, normal/low glucose and mononuclear pleocytosis. All microbiologic test results were negative, and there were no response to antibiotics and antivirals, and this also supported the diagnosis of incomplete KD with aseptic meningoencephalitis.

The exact effect of IVIG used in the treatment of KD is unknown. It is thought to be due to its general anti-inflammatory effect [3]. According to the Japanese Ministry of Health, 20% of children underwent dilatation of transient coronary arteries, 5% of patients underwent coronary artery aneurysm, and 1% coronary giant aneurysm despite IVIG treatment in the first 10 days of disease [3,18]. ASA, an important antiaggregant and anti-inflammatory, has been used for many years in treatment of KD, but it is not clear to lower the frequency of development of coronary abnormalities [9]. Therefore, the current recommendation is that all children diagnosed with Kawasaki disease after 10 days of onset of fever which have elevated systemic inflammatory markers, coronary arterial abnormalities or persistent fever should also receive intravenous gamma globulin treatment. It is also recommended to administer IVIG to children presenting after the 10th day of illness if they have either persistent fever orcoronary artery abnormalities withongoing systemic inflammation, as manifested by elevation of ESR or CRP [3]. Treatments such as steroids, infliximab, cyclosporine, anakinra, cyclophosphomide, plasma can be applied in patients who are unresponsive to IVIG treatment [3]. IVIG resistance is defined as the persistence or recurrent of fever at least 36 hours after IVIG application and is seen at 10%-20% [20,21]. The basic immunology of IVIG resistance is not understood. Many studies reported that patients with IVIG resistance are at risk for coronary abnormalities [22,23]. There is no definitive data on the choice of treatment of children with IVIG resistance. Many experts recommend administering second dose of IVIG [23,24]. We used IVIG treatment on 12th day of fever, because of high level of acute phase reactants and accompanyingwith meningoencephalitis.But our patient was febrile 36 hours after IVIG treatment, and we gave second dose IVIG. The effect of treatments applied in refractory cases on coronary abnormalities is not clear. The risk of coronary artery aneurysms has increased in these patients, and few studies have been conducted on the optimal management of these cases.Successful results have been reported with three days of pulse methylprednisolone or two doses of 2mg/kg/day (low dose). In a retrospective study of 359 patients with IVIG resistance, Kobayashi et al., reported that patients who received oral long-term prednisolone (2mg/kg/day) and IVIG had fewer coronary abnormalities, refractory and persistent fever than patients with IVIG monotherapy [25]. In another study, 43 of 63 IVIG-resistant patients were treated with pulse methylprednisolone, 19 patients with second dose of IVIG, and treatment failure and coronary involvement were similar between two groups. But the recurrence of fever in the group receiving pulse methylprednisolone was more frequent [26,27]. Because of unresponsiveness to second dose of IVIG treatmentwe started two doses of 2mg/kg/dayprednisolone and we got a dramatic response within the first 24 hours of treatment. However in our patient coronary abnormalities was seen despite two doses of IVIG and steroid treatment. We explained this situation with high risk of coronary abnormalities in incomplete KD.

In conclusion, KD is typically self-limiting.However, complications such as coronary artery aneurysm may cause serious mortality and morbidity.Early diagnosis and treatment are important for cardiac complications of the disease. Due to the presence of atypical cases, KD should be considered in febrile cases lasting longer than 5 days. KD should be considered in patients with prolonged fever, irritability and unexplained aseptic meningoencephalitis.

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