

Kawasaki Disease Complicated with Cerebral Vasculitis and Severe Encephalitis

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Abstract

We report a case of a 7-year-old boy with Kawasaki disease (KD) complicated with cerebral vasculitis and encephalitis. The patient was admitted with signs of encephalopathy, seizures, and coma. The diagnosis of KD was made on the 2nd day of hospitalization based on the clinical features (fever >5 days, maculopapular rash, nonpurulent conjunctivitis, fissured lips, and cervical adenopathy). Brain magnetic resonance imaging findings suggested cerebral vasculitis. Treatment with intravenous immunoglobulin was followed by mild improvement. After a single dose of immunoglobulin, pulse methylprednisolone therapy was started resulting in gradual improvement of consciousness and eventual complete motor and cognitive function recovery with regression of brain magnetic resonance lesions. KD can present with marked neurological symptomatology. Therefore, it should be considered in the differential diagnosis of encephalitis and encephalopathy etiologies in children.

Keywords: Cerebral vasculitis, encephalitis, Kawasaki disease

INTRODUCTION

Kawasaki disease (KD) is an acute febrile systemic vasculitis of childhood. It was first described by Tomisaku Kawasaki in 1967.^[1] The disease usually occurs in children <5 years old, with greater prevalence in the Asian population.

KD is characterized by severe, predominantly medium-sized arteries vasculitis, and predilection for coronary arteries. Approximately 20%–25% of untreated patients develop coronary artery aneurysms, making KD the leading cause of acquired cardiovascular disease in children in the developed world.^[2]

The cause and pathogenesis of KD is still not completely known. It is supposed that intense inflammatory response follows infection in genetically predisposed children.^[3] Systemic vasculitis in KD can result in multisystem organ involvement including the central nervous system (CNS) with complications such as aseptic meningitis, encephalitis, seizures, ataxia, and irritability.

We report a case of a 7-year-old boy with KD complicated with cerebral vasculitis and severe encephalitis.

CASE REPORT

A 7-year-old boy was admitted with generalized convulsive status epilepticus. He had a 4-day history of high fever and diffuse skin rash. According to his medical history, he was previously healthy except for the right tibia fracture sustained after a skiing accident 2 weeks before admission. The family history was unremarkable.

On admission, seizure was treated and stopped with administration of one dose of midazolam and phenobarbital. Detailed physical examination revealed maculopapular rash on the face, trunk and extremities, nonpurulent conjunctivitis, cracked, fissured lips, and cervical lymphadenopathy. He had a fever of 39°C. Meningeal signs were negative. The Glasgow Coma Scale (GCS) score was 7. The rest of his physical examination was unremarkable.

In Table 1, the laboratory findings on admission and after the intravenous immunoglobulins (IVIGs) therapy are shown. Table 2 shows the results of immunological analysis. Cerebrospinal fluid (CSF) analysis revealed WBC of 1/mm³, protein 225 mg/dl (up to 50), glucose 4.84 mmol/l (blood glucose 5.02 mmol/l), chloride 118.0 mmol/l, and 118–132 lactate 2.5 mmol/l (1.1–2.8). Results of blood, CSF, and urine bacterial cultures were negative.

Serological tests for viruses IgG and IgM (adenovirus, Epstein–Barr virus, influenza A and B, parvovirus B19,

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anti-HCV, HBsAg, coxsackievirus, cytomegalovirus, and herpes simplex type 1 and 2) were negative except for positive IgG antibodies to cytomegalovirus and adenovirus. CSF viral screening for herpesvirus was negative. Urine analysis was normal. Computed tomographic scan of the brain was unremarkable. The results of a chest X-ray, an electrocardiogram, and a transthoracic echocardiogram were normal as well as the levels of kinase isoenzyme (creatinine kinase-muscle/brain), cardiac troponin I, and plasma N-terminal pro B-type natriuretic peptide. Neck ultrasound revealed cervical lymph nodes of 15 mm diameter bilaterally. An electroencephalogram showed cerebral dysfunction with delta frequency slowing in the parietal–temporal–occipital areas bilaterally.

The patient was admitted to the Intensive Care Unit. Initially, he was treated with phenobarbital, ceftriaxone, acyclovir, and osmotic therapy with mannitol to decrease suspected cerebral edema.

On the 2nd day of hospitalization, the patient remained febrile, with further impairment of consciousness and GCS score of 6.

Due to the development of respiratory failure, he was intubated with initiation of mechanical ventilation.

On the same day, urgent brain magnetic resonance imaging (MRI) [Figure 1] was performed. Axial diffusion-weighted image showed hyperintense areas scattered throughout the brain parenchyma, including the basal ganglia (A). These areas showed restricted diffusion on the apparent diffusion coefficient drop and slight hyperintensity on the axial T2-weighted (T2W) image, suggestive of cytotoxic edema (B, C). Three-dimensional time-of-flight (3D-TOF) MR angiography revealed discrete narrowings of middle cerebral artery but no aneurysms (D). Susceptibility-weighted imaging images did not reveal the presence of microhemorrhages and/or subarachnoid hemorrhage (not shown).

Based on all the above findings, the patient was diagnosed with KD complicated with cerebral vasculitis and encephalitis. Treatment with IVIG as a single infusion of 2 g/kg along with acetylsalicylic acid (50 mg/kg/

Table 1: Laboratory test before and after the immunoglobulins therapy

Laboratory tests and reference values	1 st day	2 nd day	7 th day
ESR (mm/1 h)	68	42	34
C-reactive protein (mg/l) (<5)	29.6	19.9	5.0
Procalcitonin (ng/ml) (0.51-2 - sepsis)	0.63	0.53	0.38
Leukocytes (10 ⁹ /l)	6.8	7.0	6.7
Erythrocytes (10 ¹² /l)/hemoglobin (g/l)	4.24/121	4.38/115	5.0/111
Platelets (150-400×10 ⁹ /l)	181	397	288
Blood urea nitrogen (mmol/l) (2.5-6.0)	5.3	4.7	4.8
Serum creatinine (μmol/l) (30-47)	47.1	37.0	36.1
Aspartate transaminase (μkat/l) (0.170-0.600)	2.9	1.48	0.600
Alanine transaminase (μkat/l) (0.100-0.820)	2.050	1.51	0.660
Gamma-glutamyl transferase (μkat/l) (0.050-0.370)	0.170	0.150	0.160
Lactate dehydrogenase (μkat/l) (0.00-5.53)	11.27	6.89	5.77

ESR=Erythrocyte sedimentation rate

Table 2: Immunologic tests

Laboratory tests and reference values	1 st day	2 nd month
IgA (g/l) (0.51-2.97)	1.19	NA
IgG (g/l) (6.00-13.00)	11.37	NA
IgM (g/l) (0.40-1.60)	1.08	NA
C3 (g/l) (0.80-1.50)	1.25	1.11
C4 (g/l) (0.10-0.40)	0.44	0.35
Anti-CCP antibody (AU/l) (12-18 borderline values; above 18 - positive)	15.3	9
ACL antibody - IgG/IgM (GPLU/ml) (up to 12)	12/3	8/3
Beta-2-glycoprotein IgG/iGM (AU/ml) (up to 18)	6/2	6/2
Anti-neutrophil cytoplasmic antibodies	Negative	NA
Antinuclear antibodies	Slightly positive (nucleoplasm)	Negative
Lupus anticoagulant	Negative	NA
Anti-double-stranded DNA antibody (anti-dsDNA) (IU/ml) (up to 20)	10	NA
Von Willebrand vWF antigen (%) (50-150)	287	145
Von Willebrand vWF activity (%) (49.2-125)	218	118
Rheumatoid factors	Negative	Negative

Anti-CCP=Anti-cyclic citrullinated peptide, vWF=Von Willebrand factor, ACL=Anticardiolipin, NA: Not available

day) was started. Within 24 h, the fever resolved with disappearance of skin rash and mild improvement in the level of consciousness.

On the 3rd day of hospitalization, the patient was successfully extubated. Acyclovir treatment was discontinued after laboratory investigations for herpesvirus proved to be negative. On the following days, the boy was confused, occasionally extremely irritable and delirious with persistence of GCS score in the range of 8–10, and recurrence of fever. Brain MRI on the 6th day of hospitalization showed progression of initially noted changes [Figure 2].

Therefore, on the 9th day of hospitalization, the patient was started on the intravenous steroid pulse therapy (methylprednisolone 30 mg/kg/day for 5 days) followed by oral prednisolone (2 mg/kg/day). The response to steroid therapy was excellent with significant improvement in neurological status. Full motor function recovery was noted on the 15th day of hospitalization. Improvement of cognitive function was slower but continuous and complete by the time of hospital discharge. Periungual desquamation of the fingers was noted in the 3rd week of illness. Repeated echocardiogram was normal. The patient was discharged after 45 days of hospitalization.

The patient did not have a functional neurological disorder symptom, and he had normal cognitive functions when he was discharged from the hospital. No antiepileptic drugs were used. The dosage of corticosteroids was gradually decreased and then stopped completely after the 3rd month. Follow-up brain MRI, 2 months after the onset of the disease, did not reveal areas with restricted water diffusion (A, B). T2W image showed parenchymal atrophy (C). 3D-TOF

MR angiography confirmed normalization of the cerebral circulation [Figure 3].

DISCUSSION

There is no specific, pathognomonic test for the diagnosis of KD. The diagnosis of classic KD is based on the diagnostic criteria, persistence of fever for at least 5 days, and four or more of the five major clinical features: (1) presence of polymorphous rash, (2) bilateral conjunctival injection without exudate, (3) changes in extremities (erythema of palms and soles, edema of hands and feet, periungual peeling of fingers, and toes in the 2nd or 3rd week of illness), (4) changes of the oral cavity and lips (erythematous and cracked lips, strawberry tongue, hyperemia of oral, and pharyngeal mucosae), and (5) cervical lymphadenopathy.^[2]

In the present case, the patient fulfilled diagnostic criteria on the 2nd day of hospitalization which lead to the diagnosis of KD. He had fever for 5 days, maculopapular rash, nonpurulent conjunctivitis, fissured lips, and cervical lymphadenopathy. The diagnosis was additionally supported by laboratory findings of elevated acute-phase reactants and erythrocyte sedimentation rate (ESR of 120 mm/h on the 8th day of hospitalization) as well as periungual desquamation of the fingers in the 3rd week of illness.

KD is a multiorgan disorder with systemic inflammation of the predominantly medium-sized arteries. Inflammation of the coronary arteries is the most frequent and the most important complication, but around 1% up to 30% of patients with KD developed some kind of CNS disorders such as meningitis, seizures, ataxia, sensorineural hearing loss, hemiplegia, and disturbed consciousness.^[4,5]

Meningoencephalitis as a complication of KD is reported with the incidence of 3.7% and can be caused by cerebral vasculitis.^[6] Histopathological findings in KD cases revealed signs of cerebral vasculitis affecting medium- and small-sized vessels, with features of endoarteritis, periarteritis, and perivascular cuffing.^[7] In the study by Ichijama *et al.*,

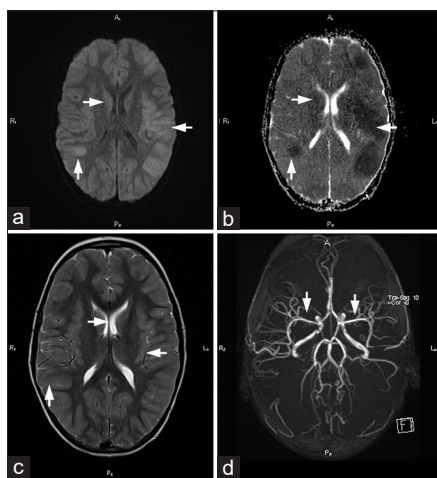


Figure 1: Axial diffusion-weighted image shows hyperintense areas scattered throughout the brain parenchyma, including the basal ganglia (a). These areas showed restricted diffusion on the apparent diffusion coefficient map and slight hyperintensity on the axial T2-weighted image, suggestive of cytotoxic edema (b and c). Three-dimensional time-of-flight magnetic resonance angiography revealed discrete narrowings of middle cerebral artery but no aneurysms (d). Susceptibility-weighted imaging images did not reveal the presence of microbleeds and/or subarachnoid hemorrhage (not shown)

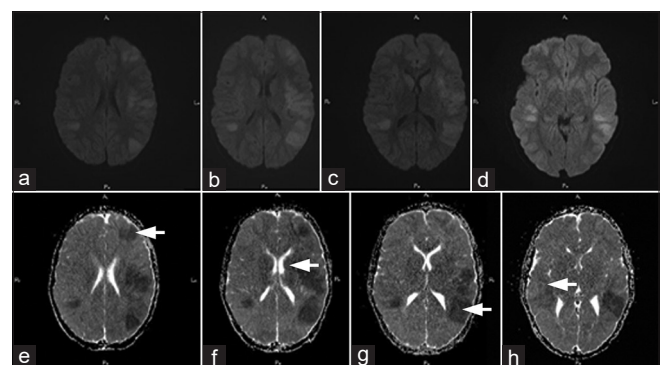


Figure 2: Axial diffusion-weighted images show hyperintense areas scattered throughout the cortex, subcortical white matter, and basal ganglia (a-d). These areas showed low ADC values on the apparent diffusion coefficient map, suggestive of cytotoxic edema in acute ischemic abnormalities (e-h)

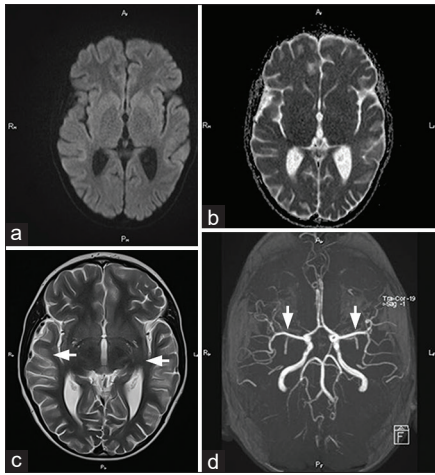


Figure 3: Follow up magnetic resonance images after the 2 months did not reveal areas with restricted water diffusion (a and b). T2 weighted image showed parenchymal atrophy (c). Three dimensional time of flight magnetic resonance angiography confirmed normalization of the cerebral circulation (d)

single-photon emission computed tomography imaging performed in children with KD showed transient localized cerebral hypoperfusion in 6 of 21 patients during the acute stage of illness,^[8] which suggests that CNS manifestations of KD occur due to cerebral vasculitis and impaired cerebral blood flow.

There are case reports describing CNS disorders such as encephalitis and meningitis as initial presentation of KD before the development of typical clinical features such as maculopapular rash, nonpurulent conjunctivitis, and desquamation.^[9,10]

In our patient, infectious encephalitis as the cause of encephalopathy was excluded by CSF analysis and negative viral and bacterial laboratory findings. Based on the clinical pictures, initial immunological analysis and their follow-up, the vasculitis (encephalitis) of the other autoimmune etiology has been ruled out. The diagnosis of noninfectious encephalitis as a part of KD spectrum was made on the grounds of clinical picture and brain MRI and MRA findings, suggesting cerebral vasculitis. Neuroradiological changes in KD with CNS involvement are not specific. They can include cerebral infarctions, atrophy, subdural effusions, reversible T2 hyperintensity in the splenium of the corpus callosum, subcortical lesions, and posterior reversible encephalopathy syndrome.^[11] IVIG and acetylsalicylic acid is the mainstay of initial KD treatment.^[12]

Approximately 10%–20% of patients do not respond to IVIG. In these cases, retreatment with additional dose of IVIG or intravenous methylprednisolone therapy should be considered.^[13] Corticosteroid treatment is associated with shorter duration of fever and lower medical costs. Our patient response to corticosteroid pulse therapy was excellent, without serious treatment side effects and good outcome.

After the IVIG therapy, there has been a significant improvement of the laboratory findings, but the clinical condition of the patient (neurological finding) has not improved, so we had a dilemma about what therapy we should continue, corticosteroids or plasma exchange. The efficiency of plasma exchange has been proven in the patients who have not had a suitable therapeutic response to IVIG. In the case, there has not been a decrease of inflammatory markers after IVIG^[14] – which our patient had, the other indication for plasma exchange has been the coronary artery dilatation^[15] which has not been detected in our patient with the successive follow-up of echocardiography. Those were the reasons why we have decided to continue treatment with the corticosteroids.

In conclusion, KD can be associated with serious CNS disorders. Therefore, KD should be considered in the differential diagnosis in all febrile children with signs of encephalopathy.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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