CASE REPORT

Early combined treatment with steroid and immunoglobulin is effective for serious Kawasaki disease complicated by myocarditis and encephalopathy

Kenichi Suga, Miki Inoue, Akemi Ono, Tomomasa Terada, Masami Kawahito, and Kazuhiro Mori

Department of Pediatrics, Tokushima Prefectural Central Hospital

Abstract : Severe-type Kawasaki disease (KD) complicated by serious myocarditis and encephalopathy can be successfully treated without abnormality of the coronary arteries by steroid pulse treatment and intravenous immunoglobulin (IVIg). A 4-year-old Japanese girl was diagnosed with KD due to a 6-day history of fever, rash, flushed lips, conjunctival hyperemia, palmar edema, and cervical lymphadenopathy. The day after initiation of IVIg and aspirin, cardiac gallop rhythm was identified. Cardiac ultrasonography revealed severe left ventricular dysfunction. Disturbance of consciousness, hallucinations, and slurred speech were also observed. Magnetic resonance imaging showed no abnormalities, but electroencephalography revealed high-voltage slow waves. Despite this serious disease, cardiac function and neurological abnormalities showed complete recovery without dilatation of the coronary arteries by steroid pulse treatment and additional IVIg. Follow-up at 15 months revealed no abnormality of the coronary arteries. In conclusion, we suggest that early combined treatment with steroid and IVIg is effective for serious KD complicated by myocarditis and encephalopathy. J. Med. Invest. 63 : 140-143, February, 2016

Keywords **:** *Kawasaki disease ; myocarditis ; encephalopathy ; steroid*

INTRODUCTION

Kawasaki disease (KD) is an acute febrile illness of childhood seen worldwide, with the highest incidence in children of Asian background. The six principal clinical criteria for KD are as follows : fever persisting at least 5 days ; conjunctival hyperemia ; oral and pharyngeal erythema with strawberry tongue ; cracked lips ; edema and erythema of the hands and feet ; rashes of various forms ; and cervical lymphadenopathy. KD is a systemic vasculitis with a predilection for the coronary arteries, and approximately 20-25% of untreated patients experience coronary artery abnormalities, including aneurysms (1). The prevalence of coronary disease is reduced to only 2-4% in those treated with intravenous immunoglobulin (IVIg) and aspirin within the first 10 days of illness (1).

Subclinical asymptomatic myocarditis has been found in more than 50% of KD cases (2). On the other hand, myocarditis severe enough to require treatment is a rare complication of KD. Significant irritability is common, and is particularly prominent in infants, likely due to aseptic meningitis. However, encephalitis/encephalopathy is extremely rare in KD (3). To the best of our knowledge, only six cases of KD complicated by severe myocarditis and encephalopathy have been reported (1, 2, 4, 5). All six cases were treated by IVIg and/or aspirin and showed left dilatation or aneurysms in coronary arteries. We reported a case of KD with serious myocarditis/encephalopathy successfully treated using steroid and IVIg without showing any abnormalities in the coronary arteries.

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Address correspondence and reprint requests to Kenichi Suga, Department of Pediatrics, Tokushima University Hospital 2-50-1 Kuramotocho, Tokushima, Tokushima 770-8503, Japan and Fax : +81-88-633-7009.

CASE REPORT

A 4-year-old Japanese girl was admitted to our hospital with a 5-day history of high-grade fever and exanthema. Past and family histories were unremarkable. Physical examination showed : body weight, 19 kg ; body temperature, 39.3°C ; flushed lips ; swollen tonsils with white coat ; cardiac sounds, pure and regular ; and erythema of the palms and soles. Blood examination showed the following : white blood cell count, 5,500/μl ; aspartate aminotransferase, 35 U/l ; alanine aminotransferase, 19 U/l ; sodium, 131 mEq/l ; albumin, 4.0 g/dl ; C-reactive protein (CRP), 5.0 mg/dl ; and anti-streptolysin-O (ASO), 220 IU/ml. Culture from the pharynx yielded negative results. Initial cardiac ultrasonography showed no abnormalities, with a shortening fraction (SF) of 34%. KD was suspected, and administration of aspirin was initiated. On hospital day 2, fever continued, bulbar conjunctiva became hyperemic, and cervical lymph nodes were swollen. KD was diagnosed and IVIg was started at 2 g/kg.

On hospital day 3, fever continued and the general condition of the patient showed rapid deterioration. Physical examination revealed the following : cardiac gallop rhythm on auscultation ; blood pressure, 111/69 mmHg ; heart rate, 162 beats/min (tachycardia) ; liver, not palpable ; and edema of the face and extremities. Disturbance of consciousness was also identified, with a Glasgow Coma Scale score of 12 (E 4, V 3, M 5). The patient made statements that did not make sense, had slurred speech, and complained of visual hallucinations. Chest X-ray showed cardiomegaly (cardiothoracic ratio, 61%). Cardiac ultrasonography revealed that SF decreased to 19%, mitral and tricuspid regurgitation were present, and pericardial fluid was identified. Mild ST-elevation was found in leads II, III, and aVf on electrocardiography. Blood examination showed that CRP level had increased to 8.1 mg/dl, and that sodium and albumin levels had decreased to 123 mEq/l and 2.6 g/dl, respectively. Brain natriuretic peptide (BNP) levels had increased markedly to 1200 pg/ml (normal, 0-18.4 pg/ml). Levels of troponin

T and creatine kinase were normal. Cerebrospinal fluid (CSF) showed : cells, 1/μl ; protein, 26.3 mg/dl ; and glucose, 65 mg/dl. Interleukin (IL)-6 level in CSF did not show a significant increase, 12.9 pg/ml (normal, < 12 pg/ml), whereas plasma IL-6 level increased to 137 pg/ml (normal, < 4.0 pg/ml). Severe myocarditis with complicating encephalopathy was diagnosed. We started steroid pulse treatment, milrinone, restriction of water intake, diuretics, and correction of serum sodium level (Figure 1). On hospital day 4, fever subsided and left ventricular motion was slightly improved. Level of consciousness did not improve despite correction of sodium level, and electroencephalography (EEG) showed diffuse high-voltage slow waves (Figure 2). Magnetic resonance imaging (MRI) and magnetic resonance angiography showed no abnormalities. Additional IVIg at 1 g/kg and edaravone were added to the management of encephalopathy on the assumption of vasculitis. After steroid pulse treatment, oral prednisolone was started and gradually tapered. Level of consciousness gradually improved, normalizing on hospital day 8. No abnormal findings were evident on a second MRI and 99m Tc-ethyl cysteinate dimer single-photon emission computed tomography on hospital day 8. Cardiac ultrasonography showed improvement of SF to 41.6% and no abnormality of the coronary arteries on hospital day 12. Blood examinations showed normalization of BNP to 18.6 pg/ml and ASO was further elevated to 401 IU/ml on hospital day 16. The patient was discharged on hospital day 22. At follow-up after 15 months, she was healthy, and cardiac ultrasonography showed normal findings.

DISCUSSION

To the best of our knowledge, only 16 cases of KD complicated by severe myocarditis have been reported (4). Clinical symptoms with myocarditis are severe, but respond well to treatment. However, coronary artery aneurysm (CAA) is often seen in KD with severe myocarditis despite IVIg and aspirin treatment, with giant aneurysm in 30%, small to moderate aneurysms in 30%, dilatation in 10%, and normal findings in 20% (2). Patients with KD complicated by encephalopathy also show CAA at a high rate (about 30%) (5) with IVIg and aspirin alone. Only 6 patients with KD complicated by both severe myocarditis and encephalopathy have been described (Table 1). Such severe-type KD appears associated with a high rate of coronary artery abnormalities, and 5 of these 6 patients (83%) developed CAA despite IVIg treatment, while the remaining patient exhibited mild dilatation of a coronary artery. Steroid was not used in any of these 6 patients. On the other hand, the present case recovered completely without any abnormal findings for the coronary arteries during the course. We started steroid pulse treatment as soon as we diagnosed cardiomyopathy, because we were afraid of volume overload resulting from additional IVIg. One possibility is that steroid pulse helped to suppress systemic vasculitis early, including in the coronary arteries. Although steroid use for KD has been controversial, Kobayashi *et al.* (6) recently reported that combined treatment with steroid and IVIg significantly reduced the risk of CAA in a high-risk group showing a lack of responsiveness to IVIg. According to the procedure described by Kobayashi *et al.*, the predictive score for the present case would be 5 points, suggesting a high risk of IVIg resistance, and steroid therapy would thus have been started 1 day earlier. We suggest that steroid treatment should be started as early as possible when myocardial damage is identified.

The etiology of encephalopathy associated with KD has yet to be elucidated. Hyponatremia, aseptic meningitis due to IVIg, cytokine

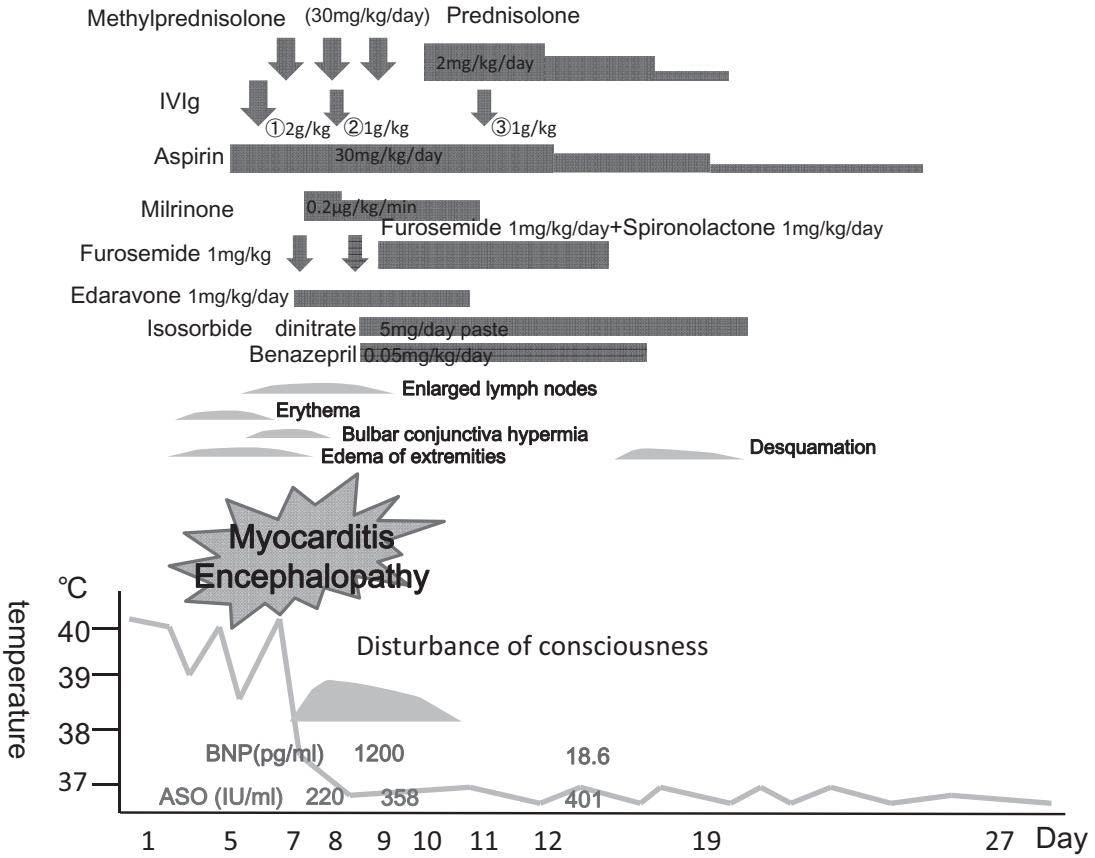

Figure 1. Clinical course

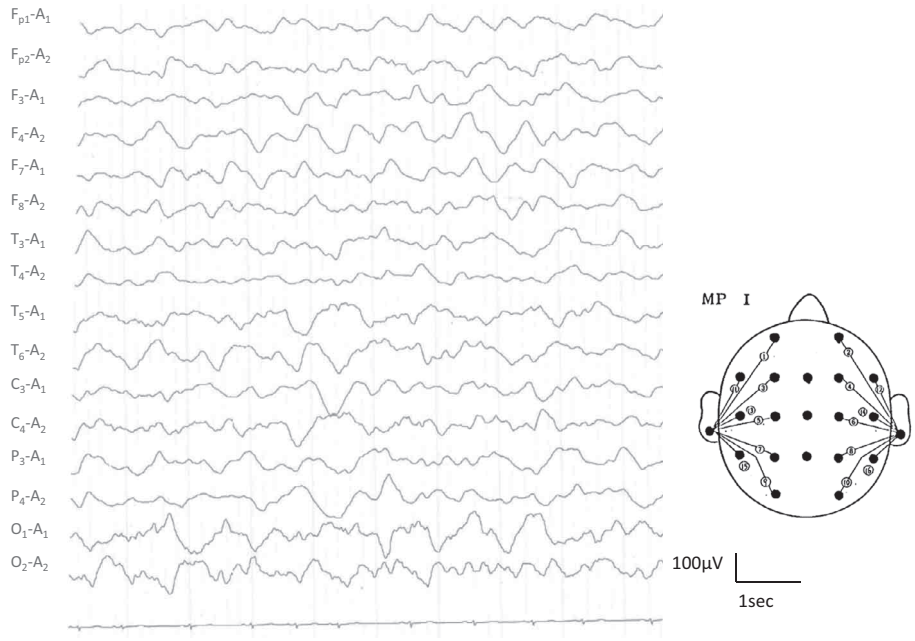

Figure 2. Electroencephalography on hospital day 4
While resting with eyes closed, alpha waves were not clear, and high-voltage slow waves were observed in bilateral parietal and occipital lobes.

Table 1. Kawasaki disease complicated by severe myocarditis and encephalopathy

	Age (years)	Sex	SF (%)	Neurological findings	MRI	Treatment	Coronary findings
2006[2]	6	F	18	altered consciousness	N.D.	IVIg+aspirin	dilataion
2006[2]	7	M	16	altered consciousness	N.D.	IVIg+aspirin	CAA
2011[1]	14	F	25	visual hallucination	MERS	IVIg	CAA
2012[s]	4	M	20	GCS 10	normal	IVIg	CAA
2012[4]	3	M	23	GCS 14	normal	IVIg	CAA
2012[4]	9	F	20	GCS 12	normal	IVIg	CAA
2014	**4**	**F**	**19**	**GCS 12**	**normal**	**Steroid+IVIg**	**Normal**

(SF, shortening fraction ; MRI, magnetic resonance imaging ; CAA, coronary artery aneurysm ; IVIg, intravenous immunoglobulin ; GCS, Glasgow Coma Scale).
The last case is the present case.

storm, and vasculitis have been considered responsible in previous reports (4, 5). In the present case, we considered systemic vasculitis as the likely cause of encephalopathy. First, we identified severe hyponatremia and hypoalbuminemia, which are suggested to reflect increased vascular permeability associated with vasculitis. Severe hyponatremia and hypoalbuminemia are common features in previous reports of myocarditis/encephalopathy complicating KD (2). Second, no other alternatives besides systemic vasculitis appeared plausible. After correcting serum sodium levels, disturbance of consciousness continued. Aseptic meningitis was ruled out as a complication after normal results were obtained from CSF examination. The normal level of IL-6 in CSF indicated that levels of this cytokine were unrelated to encephalopathy in this case. Accordingly, we considered systemic vasculitis as most likely associated with progressive encephalopathy in this case.

In conclusion, we have reported a case of KD complicated by severe myocarditis and encephalopathy. We suggest that early steroid pulse treatment combined with IVIg for such severe-type KD may inhibit formation of aneurysms in coronary arteries. Further investigation is required to confirm the effectiveness of this treatment strategy.

CONFLICTS OF INTEREST

None

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