

Case Report

A case of Kawasaki disease refractory to initial intravenous immunoglobulin therapy linked to febrile seizures at Japanese Red Cross Maebashi Hospital, Japan

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Abstract

Febrile seizures (FS) and Kawasaki disease (KD) are both common pediatric conditions among the Asian population. However, FS rarely occur during KD, and the relationship between the two is unclear. Herein, we report the case of a 17-month-old boy of KD with FS. Despite low predictive risk scores for initial intravenous immunoglobulin (IVIG) therapy failure, none of which include seizures as a risk factor, initial IVIG failed to provide symptom relief, necessitating a second IVIG and intravenous prednisolone. In KD, FS may themselves contribute to IVIG resistance.

Keywords: Kawasaki disease; febrile seizure; intravenous immunoglobulin; prednisolone; coronary artery lesions

Introduction

Febrile seizure (FS) are convulsive events in children aged 6 months to 5 years, affecting 2–5% in Western countries and with higher incidence in Indian (5–10%), Japanese (6–9%), and Guamanian (14%) populations (1). Although FS are associated with a favorable neurological prognosis, they may increase the risk of subsequent epilepsy and Tourette syndrome (1). However, their pathogenesis remains unclear.

Kawasaki disease (KD), a common disease in Japanese and Asian children, is a systemic vasculitis syndrome of unknown etiology.

Coronary artery lesions (CALs) are its most serious complications; patients unresponsive to initial intravenous immunoglobulin (IVIG)—the gold-standard treatment—are at high risk of CALs (2). Neurological symptoms are rare in KD (3), and the association between KD and FS remains unclear.

Herein, we report a patient with KD and FS who was hospitalized at Japanese Red Cross Maebashi Hospital, Japan. Despite low predictive risk scores for initial IVIG resistance, including the Egami, Formosa, Kobayashi, Sano, and Son scores (Table 1) (2,4-8), the patient required multiple IVIG treatments

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for symptom alleviation. Notably, seizures are not included as risk factors in any of these five scores.

Table 1. Overview of the four predictive risk scores for resistance to initial intravenous immunoglobulin (IVIG) in Kawasaki disease.

	Points	Cutoff points	Sensitivity	Specificity
Egami (4)	2; ALT \geq 80 IU/L 1; age \leq 6 months 1; days of illness at initial treatment \leq 4 1; platelet count of $\leq 30 \times 10^{10}/L$ 1; CRP \geq 8 mg/dL	≥ 3	78%	76%
Formosa (5)	2; neutrophil percentage \geq 60% 1; albumin $<$ 3.5 g/dL 1; positive lymphadenopathy	≥ 3	91%	81%
Kobayashi (6)	2; days of illness at initial treatment \leq 4 2; neutrophil percentage \geq 80% 2; AST \geq 100 IU/L 2; sodium \leq 133 mmol/L 1; platelet count $\leq 30 \times 10^4/mm^3$ 1; CRP \geq 10 mg/dL 1; age \leq 12 months	≥ 4	86%	68%
Sano (7)	1; CRP \geq 7 mg/dL 1; total bilirubin \geq 0.9 mg/dL 1; AST \geq 200 IU/L	≥ 2	77%	86%

ALT, alanine transaminase; AST, aspartate aminotransferase; CRP, C-reactive protein.

Case presentation

The patient was a 17-month-old Japanese boy with no relevant medical or family history who was initially diagnosed with complex FS after experiencing two generalized tonic–clonic seizures that stopped spontaneously within 5 min on the second day of fever (day 2), without the administration of anticonvulsant medications. He was not taking any antipyretics. Because of

a cluster of convulsions, he was admitted to the hospital for observation. On day 7, he was diagnosed with KD based on the presence of five of the six principal symptoms compatible with complete KD (2). Microbial antigen tests, including adenovirus and streptococci, were negative. His symptoms, laboratory findings, and predictive risk scores for initial IVIG resistance are summarized in Table 2.

Table 2. Patient characteristics

Seizure	Two GTCs on Day 2
Main symptoms of KD	
Fever	Yes (from Day 1)
Conjunctivitis	No
Oral mucous membrane changes	Yes
Peripheral extremity changes	Yes
Polymorphous rash	Yes
Cervical lymphadenopathy	Yes
Diagnosis of KD	
Day 7	
Blood test result on Day 7 (when the diagnosis of KD was made)	
White blood cell count ($\times 10^4/\text{mm}^3$)	5,400
% neutrophils	56.5%
Platelet count ($\times 10^4/\text{mm}^3$)	20.3
Albumin (g/dL)	3.6
AST (IU/L)	41
ALT (IU/L)	17
Total Bilirubin (mg/dL)	0.3
Sodium (mmol/L)	138
CRP (mg/dL)	1.32
Egami score	1
Formosa score	1
Kobayashi score	1
Sano score	0
Initial treatment	IVIg 2 g/kg + ASA 30 mg/kg/day (started on Day 7)
Second IVIg	Yes (2 g/kg on day 9)
Additional intravenous PSL	Yes (started at 2 mg/kg/day on Day 9 and tapered off by Day 17)
Coronary artery lesion	No
Neurological sequelae of KD	No
Any other adverse events due to KD treatment	No

KD, Kawasaki disease; AST, aspartate aminotransferase; ALT, alanine transaminase; CRP, C-reactive protein; IVIG, intravenous immunoglobulin; PSL, prednisolone; GTCS, general tonic-clonic seizure; ASA, acetylsalicylic acid.

He was treated with IVIG (2 g/kg) and oral acetylsalicylic acid (ASA) (30 mg/kg/day); however, fever and other symptoms persisted. A second IVIG dose and intravenous prednisolone (PSL) (2 mg/kg/day) were administered on day 9. Subsequently, fever resolved

by day 10, and all the other symptoms disappeared by day 12. He had no recurrent seizures

or CALs. Despite receiving PSL therapy until day 17, he experienced no steroid-related adverse effects, such as hypoadrenocorticism, hyperglycemia, or obesity. The patient did not receive any antibiotic therapy, nor did he undergo head computed tomography, magnetic resonance imaging, or cerebrospinal fluid testing during the clinical course. As part of long-term follow-up for KD, he underwent regular medical examinations, electrocardiography, and echocardiography. Neither CALs nor recurrence of KD was observed at 2 years after disease onset. The patient's clinical course is chronologically summarized in Table 3.

Table 3. Chronological clinical course of the patient.

Day	BT (°C)	Symptom	Therapy	CA Z-score
1	38.2			
2	38.0	Two GTCSs Peripheral extremity changes (until day 11)	Admission	
7	39.7	Oral mucous membrane changes (until day 9) Polymorphous rash (until day 10) Cervical lymphadenopathy (until day 11)	First IVIG 2 g/kg ASA 30 mg/kg/day (until day 11)	RCA -0.56 LAD 0.36
9	38.1		Second IVIG 2 g/kg PSL 2 mg/kg/day (until day 11)	RCA -0.18 LAD 0.37
10	36.6			
12	36.5		ASA 5 mg/kg/day (until day 50) PSL 1 mg/kg/day (until day 14)	RCA -0.18 LAD -0.69
15	36.2		PSL 0.5 mg/kg/day (until day 17)	
17	35.9		Discharge	RCA 0.17 LAD 0.04

BT, body temperature; GTCS, generalized tonic-clonic seizure; IVIG, intravenous immunoglobulin; ASA, acetylsalicylic acid; PSL, prednisolone; CA, coronary artery; RCA, right coronary artery; LAD, left anterior descending artery.

No symptoms were observed after day 11.

Discussion

Neurological symptoms are relatively rare manifestations of KD. Liu et al. reported complication rates of 5.1% for neurological symptoms and 0.9% for seizures, noting no association between neurological symptoms and IVIG resistance (3). However, the relation between seizures and IVIG resistance remains unclear. Elevated levels of inflammatory cytokines can enhance neuronal excitability and trigger FS (9). Therefore, the risk of FS may also increase in KD, which is characterized by elevated blood levels of inflammatory cytokines; however, this hypothesis has not yet been validated. Our patient was classified as low risk by all five IVIG resistance scores (Egami, Formosa, Kobayashi, Sano, and Son) (4-8) and had no CAL risk factors based on the American Heart Association statement (2). Nevertheless, the patient was IVIG-resistant, requiring re-administration of IVIG. The addition of PSL to IVIG resulted in a favorable treatment course. IVIG is extremely costly, with a growing shortage of globulin products worldwide (10). If seizures are an independent predictor of IVIG resistance, concomitant steroid therapy during initial therapy for patients

with KD and seizures may be considered to avoid the increased medical costs and resource pressures associated with repeated IVIG administration. Importantly, although seizures may be risk factors for IVIG resistance, based on this report, they do not appear to predict worse long-term prognosis, as this patient recovered without developing sequelae.

This case has one major limitation. We could not rule out the possibility that the seizures developed as a manifestation of mild meningitis or encephalitis/encephalopathy complicated KD, as central nervous system imaging and cerebrospinal fluid testing were not performed. However, the absence of recurrent or prolonged neurological symptoms supported this decision, which is consistent with guidance from a previous review on FS management (9). Further studies of patients with KD and seizures are needed to clarify the pathogenesis of KD with seizures.

Declarations

Ethical consideration: The patient's parents provided informed consent for the publication of this study and the accompanying data.

Author contributions: TI, RS, and MS designed the study and prepared the manuscript for publication. KT and AM revised the manuscript. All the authors have read and approved the final version of the manuscript.

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