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Case Report

Reye's Syndrome Arising from the Treatment of Kawasaki Disease

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Abstract We report on a 20-month-old girl who presented with vomiting and lethargy after being discharged from the ward following treatment for Kawasaki disease. The symptoms occurred after five days of aspirin therapy. The clinical features and laboratory tests proved the presence of Reye's syndrome and she recovered after intensive treatment. In addition, we collected three similar reported cases. All the patients came from East Asia and the mortality rate reached 50%. Since salicylate is an effective and imperative treatment for Kawasaki disease, paediatricians and emergency physicians can consider using a low dose of aspirin (3-5 mg/kg) as maintenance therapy, discontinuing aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics, and having a high index of suspicion of Reye's syndrome in patients with Kawasaki disease.

Key words Aspirin; Complication; Kawasaki disease; Reye's syndrome; Salicylate

Introduction

Reye's syndrome is an acute failure of mitochondria and occurs mainly in childhood. The cause of this severe disease is still uncertain; however, the affected child usually presents with a prodrome of acute viral infection and the use of salicylate during the prodromal illness, followed by an acute encephalopathy, fatty degeneration of the liver, and metabolic decompensation.[1-4] In addition, salicylate consumption is correlated with severity of Reye's syndrome.[2] After warnings had been issued about the use of salicylates in children with those viral infections, the incidence of Reye's syndrome in the United States declined dramatically.[2]

However, some children still require long-term use of salicylate, such as those with connective tissue disorders, and these patients run a greater risk of developing Reye's syndrome.[2] We report on a 20-month-old girl who developed Reye's syndrome after treatment for Kawasaki disease and review three case reports to demonstrate the unique features of the involved children.

Case

This 20-month-old girl, who was previously well, had suffered from high fever for 5 days and was admitted to Chi-Mei Medical Center. She had a normal birth history (birth weight: 3070 gm, gestation age: full term, via normal

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spontaneous delivery), regular vaccinations, negative results of newborn screening for metabolic diseases, and normal growth and development. She was the second child in the family (G2P2A0) with no family history of sudden infant death or inborn errors of metabolism. After admission, she was diagnosed as having Kawasaki disease due to the presence of wheal-like exanthema on the palms and buttocks, erythematous fissured lips and bilateral conjunctivitis as well as leukocytosis (white cell count: 16000/μL) and elevation of C-reactive protein (62.6 mg/dL) in laboratory tests.[5] The paediatricians initiated intravenous immunoglobulin at a dose of 2 g/kg and a high dose of oral aspirin of 88/mg/kg per day. The patient's fever subsided after the initiation of treatment and her appetite and activity improved. Echocardiography showed normal coronary arterioles without dilatation. Subsequently, the aspirin dose was reduced to 55 mg/kg per day and she was discharged after 15 days of hospitalisation.

On the next day after discharge, about the fifteenth day after administering the first dose of aspirin, the patient was found with persistent vomiting, drowsiness and fever and was admitted to Chi-Mei Medical Center again. Physical examination of the patient revealed fever, tachycardia, lethargy, decreased muscle tone, and decreased urine output. A computed tomographic scan of the head demonstrated bilateral basal ganglia lesions and cortical swelling. Serum tests revealed hyperammonaemia (214 μg/dL), and elevations of aspartate aminotransferase and alanine aminotransferase (AST: 461 IU/L, ALT: 255 IU/L). Initial differential diagnosis included aspirin intoxication and Reye's syndrome, and therefore aspirin was discontinued immediately. The patient was transferred to National Cheng Kung University Hospital because of progression to coma status. A subsequent lumbar puncture found increased intracranial pressure (35 cm H_2O) and the analysis of cerebral spinal fluid showed negative results for bacterial or viral infection. A hepatic biopsy demonstrated typical manifestations of Reye's syndrome. The patient underwent tracheal intubation and mechanical ventilation for coma, supportive treatment for metabolic derangement, intravenous mannitol for cerebral oedema, and continuous veno-venous haemofiltration to eliminate aspirin. After intensive care, the patient recovered and was discharged after two weeks of hospitalisation without permanent sequelae.

Discussion

Nowadays, high-dose aspirin (80 to 100 mg/kg per day) and intravenous immunoglobulin are recommended as the initial treatment for Kawasaki disease, followed by a reduction of the aspirin dose after the child has been afebrile for 48 to 72 hours. The therapy effectively reduces the rate of subsequent ischaemic heart disease and sudden death[5] However, children who undergo aspirin treatment carry additional risk of Reye's syndrome. Except this presented case, we discovered another three patients with Reye's syndrome arising from the treatment of Kawasaki disease. All the reported patients were found in East Asia, three in Taiwan and one in Japan[6-8] All the affected children were under two years of age, and included three females and one male. The symptoms of Reye's syndrome appeared within 15 days after the initiation of salicylate therapy. The presented symptoms included vomiting, poor appetite, decreased activity, hepatomegaly, and lethargy. Two of the four reported cases died (50% mortality rate) (Table 1).

Takahashi and Mason indicated that the subset of children most susceptible to Kawasaki disease (Asians younger than four years of age) and the subset most susceptible to Reye's syndrome (white children older than six years of age) do not overlap.[9] The lack of overlap in the two groups of affected children might explain the low incidence of Reye's syndrome occurring in Kawasaki disease. With regard to the benefit of cardiovascular effects, children with Kawasaki disease should still undergo salicylate treatment. Though the absence of evidence concerning the correlation between incidence of Reye's syndrome and dosage of aspirin, the authors proposed that the dosage of salicylate should be kept as low as possible. In addition, the study by Saulsbury et al showed that low-dose aspirin (3-5 mg/kg) is as effective

Table 1 The clinical manifestations among three reported cases (Nejihashi 1980, Lee 1991 and Wei 2005) and our presented patient (Su 2012)

Clinical manifestations	Nejihashi 1980	Lee 1991	Wei 2005	Su 2012
Age (month)	9	7	10	20
Gender	F	F	M	F
Aspirin administration (day)*	14	4	3	15
Dose of aspirin (mg/kg/day)†	Unknown	10	3-5	55
Mortality	Expired	Expired	Alive	Alive

*symptoms of Reye's syndrome after the initiation of aspirin therapy
†maintenance dose of aspirin

as high-dose aspirin therapy.[9] Because most Reye's syndrome children have a prodrome of viral infection, those who undergo long-term salicylate treatment can discontinue aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics. In addition, those children who undergo salicylate therapy should be observing closely for symptoms of Reye's syndrome within 15 days after initiation treatment.

Though rare, Reye's syndrome arising from the treatment of Kawasaki disease does occur. Since salicylate is an effective and imperative treatment for Kawasaki disease, paediatricians and emergency physicians can consider using low doses of aspirin (3-5 mg/kg) as maintenance therapy, discontinuing aspirin for a short period or replace it with dipyridamole during influenza or varicella epidemics, and having a high index of suspicion of Reye's syndrome in patients with Kawasaki disease.

Declaration of Interest

The authors have no conflicts of interest.

References

1. Starko KM, Ray CG, Dominguez LB, Stromberg WL, Woodall DF. Reye's syndrome and salicylate use. Pediatrics 1980;66:859-64.
2. McGovern MC, Glasgow JF, Stewart MC. Reye's and aspirin: lest we forget. BMJ 2001;332:1591-2.
3. Pugliese A, Beltramo T, Torre D. Reye's and Reye's-like syndromes. Cell Biochem Funct 2008;26:741-6.
4. Newburger JW, Takhashi M, Gerbert MA, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a statement for health professionals from the Committee on Rheumatic fever, Endocarditis, and Kawasaki disease, Council on Cardiovascular Disease in the Young, American Heart Association. Pediatrics 2004;114:1708-33.
5. Nejihashi Y, Takada Y, Okazaki T, et al. An autopsied case of Reye's syndrome in progress of MCLS. Shonika Shinryo (J Pediatr Practice) 1980; 43:960-2.
6. Lee JH, Hung HY, Huang FY. Kawasaki disease with Reye's syndrome: report of one case. Zhongghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi 1992;33:67-71.
7. Wei CM, Chen HL, Lee PI, et al. Reye's syndrome developing in an infant on treatment of Kawasaki syndrome. J Paediatr Child Health 2005;41:303-4.
8. Takahashi M, Mason W. Kawasaki syndrome, Reye's syndrome, and aspirin. Pediatrics 1986;77:616-7.
9. Saulsbury FT. Comparison of high-dose and low-dose aspirin plus intravenous immunoglobulin in the treatment of Kawasaki syndrome. Clin Pediatr (Phila). 2002;41:597-601.