carbamazepine, valproic acid and phenobarbital therapy in children with epilepsy. Epilepsy Research 2000: 41: 1-7.

12. Havel RJ, Kane JP. Structure and metabolism of plasma lipoproteins. In: Secriver CR, Beaudet AL, Sly WS, Valle D (eds). The Metabolic and Molecular Basis of Inherited Disease, 7th edn, vol II. New York, McGraw-Hill, 1995; pp 1841-1851.
13. Dada G, Caksen H, Icagasioglu D. Effect of long term carbamazepine therepy on serum lipids, vitamin B12 and folic acid level in children. J Pediatr Endocrinol Metab 2003; 16: 193-196.
14. Bramswig S, Sudhop T, Luers C, Von Bergman K, Berthhold HK. Lipoprotein A concentration increases during treatment with carbamazepine. Epilepsia 2003; 44: 457-460.
15. American Academy of Pediatrics, Committee on Nutrition. Statement on cholesterol. Pediatrics 1992; 90: 469-473.
16. Tjellesen L, Christiansen C. Serum vitamin D metabolites in epileptic patients treated with two different anticonvulsants. Acta Neurol Scand 1982, 66: 335-341.

Cardiovascular Involvement in Kawasaki Disease

S. Noel Narayanan, M. Zulfikar Ahamed and M. Safia

From the Departments of Pediatrics and Cardiology, SAT Hospital, Medical College, Thiruvananthapuram 695 011, India.

Correspondence to: Dr. S. Noel Narayanan, T.C. 1/1991, Kumarapuram, Medical College P. O., Thiruvananthapuram 695 011, Kerala, India.
E-mail: noeln@asianetindia.com

Manuscript received: September 13, 2004, Initial review completed: October 19, 2004; Revision accepted: March 31, 2005.

We report 72 patients with Kawasaki disease seen at this Centre over 7 years. Cardiac involvement in the form of mild pancarditis was seen in 28% patients, but disappeared subsequently. Thirteen (18.5%) children developed coronary artery disease, out of which 4 resolved by the end of two months and another 6 after one year; 3 patients continued to show coronary artery dilatation and aneurysm formation. Children who received IV gammaglobulin in full dose within 10 days of onset of illness, showed no evidence of coronary artery disease during follow up.

Key words: *Coronary aneurysm, IV gammaglobulin, Pancarditis.*

KAWASAKI disease (KD) is considered a rare disease in the Indian subcontinent(1). During the last decade an increased incidence is being seen in Kerala(2). Since its original description by Kawasaki in Japan, KD has been reported from all parts of the world. The basic pathology is a vasculitis involving all blood vessels, predominantly the coronary arteries. The diagnosis is based on easily recognizable clinical features. Five days of fever and at least 4 of the following 5 principal clinical features should be present to make a diagnosis of KD(3). These include cervical lymphadenopathy, a polymorphous

rash, ororpharyngeal changes, bilateral non-purulent conjunctival injection, and limb changes like erythema and edema of hands and feet followed by periungual desquamation. The disease generally lasts for 6 to 8 weeks and new lesions beyond this period are unlikely.

Atypical KD in which patients have fewer than four of the five clinical features is being increasingly reported(4). Cardiac complications are the leading cause of morbidity and mortality. The etiology of KD is unclear although several compelling hypotheses point to a common infectious agent and genetic predisposition, resulting in an altered immune response(5). A single intravenous (IV) infusion of 2 g/kg immunoglobulin is recommended in addition to high dose aspirin in the first 10 days of the illness, in patients suspected to have KD(6).

Subjects and Methods

This is a retrospective study of 72 children admitted and treated with clinical diagnosis of KD at Medical College, Thiruvananthapuram from 1995 to 2001. The diagnosis of KD was based on American Heart Association criteria(3). Hemoglobin, blood count, ESR, CRP, platelet count and routine urine examination were done in all patients. Paul Bunnel test, Widal, IgM antibodies for dengue, Weil's antibodies, rheumatoid factor and other relevant investigations were done if indicated, to differentiate KD from other illnesses with similar presentation. Chest *X*-ray and ECG were done in children showing positive findings on clinical examination of the cardiovascular system. A Consultant of Pediatric Cardiology (MZA) did echo-cardiography at the time of admission during the acute phase and again at the end of convalescent phase at 8 weeks. Children showing coronary artery disease were followed up and a third echo-cardiography was done at the end of one year.

Results

Of 72 patients, 68 met the full diagnostic criteria for KD. Four had atypical KD with less than four principal clinical criteria. These atypical cases had strong laboratory evidence to support a diagnosis of KD and also showed the classical periungual desquamation. The youngest patient was 5 months old and the oldest 8 years; boys outnumbered girls by ratio of 2.6:1. An adolescent boy in whom the diagnosis of KD was missed at 7 years of age, later presented at 15 years with recurrent cardiac syncope, caused by severe coronary artery disease.

Distribution of clinical features is shown in *Fig. 1*. Fever of more than 5 days duration was present in 100% children. Cervical lymphadenopathy was the commonest finding and oral changes the least common. Other significant findings were arthritis or arthralgia, extreme irritability and gastrointestinal symptoms. Two children developed a second attack of KD. ESR was high in all cases and 22% had ESR above 100 mm/h. CRP, done in 66 cases, was positive in 80%. Platelet count was significantly raised above 500×10^9/L in 25% cases. Normal platelet counts were seen in 15% cases and thrombocytopenia in 2.7%.

Twenty (28%) children showed abnormal findings in the heart during the acute stage, in the form of tachycardia, gallop rhythm, soft

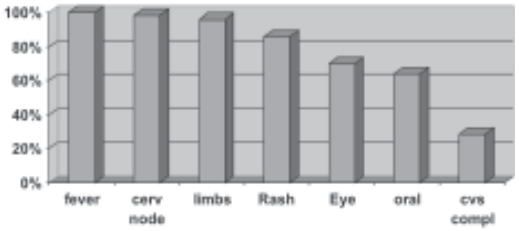

Fig. 1. Clinical features in patients with Kawasaki disease. Cerv: cervical lymph; CVS compl: cardiovascular complications.

apical systolic murmur and muffled first heart sound. Initial echocardiography showed minimal pericardial effusion in 5 patients, mild valvular leak in 3 and left ventricular dysfunction in one child. All these findings disappeared during convalescence. No patient had congestive heart failure or arrhythmia. Two of these patients subsequently developed coro-nary artery disease which later resolved by 1 year. Chest *X*-rays were normal in all cases and ECG showed minor abnormalities like tachycardia and low amplitude *T* waves.

On echocardiography, all except one child had normal left ventricular function. One patient showed decreased ejection fraction which improved during convalescence. Abnormal coronary arteries showing either ectasia or aneurysms were found in thirteen (18.5%) children. Left coronary artery (LCA) was involved in all cases. Left anterior descending (LAD) was affected in 30% and right coronary artery (RCA) in 15% cases. There were no circumflex artery lesions. An adolescent boy, who developed severe coronary artery disease, was subjected to coronary angiography after an attack of cardiac syncope. This demonstrated total occlusion of LCA with calcification, multiple aneurysms and stenosis affecting right coronary artery (RCA) and presence of prominent collaterals (*Fig. 3*).

IV gammaglobulin was administered in 75% cases only. Full dose of 2 g/kg/d was given to 55%, and the rest received a dose of 200 to 400 mg/kg/d for one to two days. Eighteen children (25%) did not receive IV immunoglobulin due to financial and other reasons like late presentation or missed diagnosis. Of these 6 showed coronary artery disease, four of which regressed by one year, while two are still persisting. Forty children received full dose of IV immunoglobulin within 10 days of onset of disease. Three of these children showed mild coronary ectasia during the acute stage. These resolved on subsequent follow up at 8 weeks. Of 14 patients who received suboptimal dose of intravenous immunoglobulin, four showed coronary artery dilatation, three of which resolved at one year and one persisted. Allergic reaction to IV gammaglobulin in the form of urticaria and hypotension was observed in four children.

Aspirin was given at a dose of 80-100 mg/kg/d in four divided doses during the acute phase to all children. Subsequently a dose of

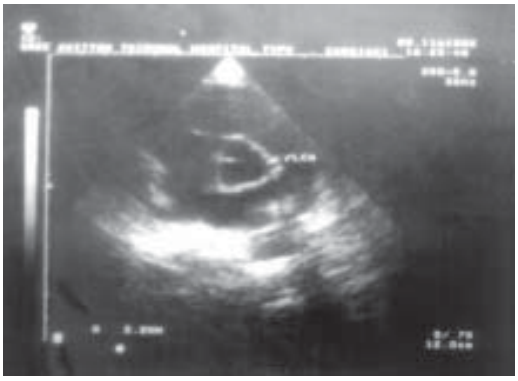

Fig. 2. Echocardiography showing dilated left coronary artery.

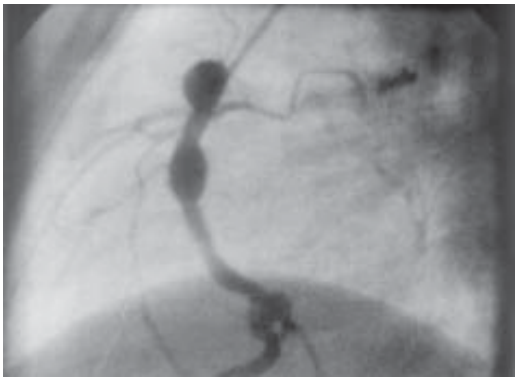

Fig. 3. Aneurysm and stenosis affecting right coronary artery and obliterated left anterior descending.

3-5 mg/kg/d was continued till the end of convalescent period. In children showing coronary artery disease, low dose aspirin was continued for more than one year. An antistaphylococcal antibiotic was given in the acute phase to all children, in view of the reports of a possible association of toxic shock syndrome producing staphylococcal infection and KD(7).

Patients with cardiac involvement were followed up with echocardiography at one year, for vascular and other abnormalities including valvar leak, pericardial effusion and left ventricular dysfunction. Thirteen (18.5%) children developed significant dilatation of coronary arteries. These subsided in 4 children by the end of two months and in another 6 by one year. Three children, including the adolescent with missed KD, continued to show coronary aneurysms. There were no deaths. However, the condition of the adolescent boy with severe coronary artery disease is unstable, and may require cardiac revascularization in the future.

Discussion

Increased incidence of KD is being seen in Kerala since 1995. Increased awareness and possibly some unidentified infectious agent or a genetic susceptibility could explain this phenomenon. In the present study of 72 children with KD, 28.5% showed mild pancarditis during the acute stage. These findings disappeared by the end of convalescent phase without any sequel. Two of these children subsequently developed coronary artery lesions, which later resolved. Coronary artery abnormalities in the form of ectasia or aneurysm were detected in 18.5% patients on echocardiography. Rowley, *et al.* reported coronary artery abnormalities in 20 to 25 % of children with KD(8). In the present series 40 subjects received IV gamma-globulin in full dose within 10 days and none of them showed any coronary artery disease at the end of eight weeks. Coronary artery dilatation disappeared in four (30%) children by eight weeks and in another six (46%) by one year. Only 3 (23%) children showed persistent coronary artery aneurysms beyond one year. Long term follow up of children with coronary artery aneurysm showed that at least 50% resolved within 5 to 18 months(9,10). Burns, *et al.* have reported 74 adult patients with coronary artery disease, which were attributed to childhood KD(11). As per the guidelines of the American Heart Association Committee on Rheumatic fever, Endocarditis and Kawasaki diseases, the adolescent with multiple coronary aneurysms is likely to require surgery for coronary revascularisation(12). At least 13 cardiac transplantations have been done so far in patients with KD and chronic deteriorating left ventricular function(13). A nationwide survey on KD in Japan showed that the mortality from coronary artery disease decreased from 1% in 1974 to 0.04% in 1992(14). There were no deaths in our series.

KD is an emerging disease and increased awareness among doctors regarding early recognition is important. Clinical diagnosis is not difficult and timely treatment can prevent potentially life threatening cardiac complications. A collaborative study on mortality rate in KD revealed that only boys with cardiac involvement showed an increase in mortality rate(15). Recent reports of early and accelerated atherogenesis occurring in arteries affected by KD as measured by elevated levels of inflammatory markers is of great concern, since this could accelerate ischemic heart disease in young adults(16).

Contributors: MS collected and analyzed the data. MZA did cardiac evaluation and echocardiography and revised the manuscript critically. SNN supervised the data collection and analysis, wrote the manuscript and will act as guarantor for the same.

Key Messages

- Critical coronary artery involvement occurs in about 18% cases of Kawasaki disease (KD) and may be prevented by timely administration of IV gammaglobulin and aspirin.
- Evidence of acute carditis resolves completely by the end of the convalescent phase.
- Increased awareness of this condition is essential for early diagnosis and prompt treatment.

Funding: None.

Competing interests: None stated.

REFERENCES

1. Pendse RN, Bhandari H, Vats AK, Bhabdari B. Kawasaki disease-Indian perspective. Indian J Pediatr 2001; 68: 775-777.
2. Narayanan SN, Krishna V, Sabarinathan K. Kawasaki disease. Indian Pediatr 1997; 34: 139-143.
3. Dajani AS, Bisno AL, Chung KJ, Durack DT, Gerber MA, Kaplan EL, *et al* . American Heart Association Committee on rheumatic fever, endocarditis and Kawasaki diseases. Diagnostic guidelines for Kawasaki disease. Am J Dis Child 1990; 144: 1218-1219.
4. Genozo J, Miron D, Spiegel R, Fink D, Horowitz Y. Kawasaki disease in very young infants: high prevalence of atypical presentation and coronary arteritis. Clin Pediatr 2003; 42: 263-267
5. Mason WH, Takahashi M. Kawasaki syndrome. Clin Infect Dis 1999; 28: 169-187
6. Shulman ST, de Inocencio J, Hirsch R. Kawasaki disease. Pediatr Clin N Am 1995; 42: 1205-1222.
7. Curtis N, Chan B, Levin M. Toxic shock syndrome toxin secreting Staphylococcus aureus in Kawasaki syndrome. Lancet 1994; 343: 299.
8. Rowley AH, Duffy CE, Shulman ST. Prevention of giant aneurysms in Kawasaki disease by intravenous gammaglobulin therapy. J Pediatr 1988; 113: 290-294.
9. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, *et al.* Long term consequences of Kawasaki disease. Circulation 1996; 94: 1379-1385.
10. Fukushge J, Takashashi N, Ueda K, Hiju T, Igarashi H, Ohshima A. Longterm outcome of coronary abnormalities in patients after Kawasaki disease. Pediatr Cardiol 1996; 17: 71-76.
11. Burns JC, Shike H, Gordon JB, Malhotra A, Schoenwetter M, Kawasaki T. Sequelae of Kawasaki disease in adolescents and young adults. J Am Coll Cardiol 1996; 28: 253-257.
12. Adnans, Dajani A, Kathryn A, Taubert K, Masato T, Fred ZB, *et al.* Guidelines on long term management of patients with Kawasaki disease. Report from the Committee on Rheumatic fever, endocarditis and Kawasaki disease Council on Cardiovascular disease in the young. American Heart Association. Circulation 1994; 89: 916-922.
13. Chechia PA, Pahl E, Shaddy RE, Shulman ST. Cardiac transplantation for Kawasaki Disease. Pediatr 1997; 100: 695-699
14. Yanagawa H, Yashiro M, Nakamura Y, Kawasaki T, Kato H. Results of 12 nationwide epidemiological surveys on Kawasaki disease in Japan. Arch Pediatr Adolesc Med 1995; 149: 779-783.
15. Nakamura Y, Yanagawa H, Harada K, Kato H, Kawasaki T. The fifth look. Arch Pediatr Adolesc Med 2002; 156: 162-165.
16. Mitani Y, Sawada H, Hayakawa H, Aoki K, Ohashi H, Matsumura M, *et al.* Elevated levels of high-sensitivity C-reactive protein and serum amyloid-A late after Kawasaki disease: Association between inflammation and late coronary sequelae in Kawasaki disease. Circulation 2005; 111: 38-43.