Mortality in children with Kawasaki disease: 20 years of experience from a tertiary care centre in North India

S. Singh, S. Bhattad, A. Gupta, D. Suri, A. Rawat, M. Rohit

Paediatric Allergy Immunology Unit, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research, Chandigarh, India.

Surjit Singh, MD, FRCP, FRCPCH, FAMS
Sagar Bhattad, MD
Anju Gupta, MD
Deepti Suri, MD
Amit Rawat, MD
Manojkumar Rohit, MD, DM

Please address correspondence to:
Surjit Singh, MD,
Paediatric Allergy Immunology Unit,
Advanced Paediatrics Centre,
Post Graduate Institute of Medical Education and Research,
Chandigarh 160012, India.
E-mail: surjitsinghpgi@rediffmail.com; surjitsinghapc@gmail.com

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ABSTRACT

Kawasaki disease (KD) is a common vasculitic disorder of childhood. Reported mortality in KD in Japan is 0.014%. We report the clinical and laboratory profile of 4 children who succumbed to KD during the period January 1994 to March 2015 at the Paediatric Allergy Immunology Unit, Advanced Paediatrics Centre, Post Graduate Institute of Medical Education and Research Centre, Chandigarh, India.

A total of 460 children were diagnosed with KD based on the American Heart Association criteria. Male to female ratio was 1.96:1 and 106 children were aged 2 years or less. Children with KD received 2 g/kg of intravenous immunoglobulin (IVIg). In addition, aspirin was administered in doses of 30–50 mg/kg/day during the acute phase and 3–5 mg/kg/day thereafter. 2-D echocardiography was carried out once during the acute phase and approximately 6–8 weeks later on follow-up. Four children (2 boys, 2 girls) died during this period and their details were analysed from their clinical records. All 4 were under 2 years of age and had had significant delays in diagnosis and referral. Symptomatic myocarditis was noted in 2 children, while 2 of them had thrombocytopenia.

We report a mortality of 0.87% in children with KD. Delays in diagnosis and referral contributed significantly to this mortality. To the best of our knowledge, this is the first report on mortality in KD from any developing nation.

Introduction

Kawasaki disease (KD) is a common vasculitis affecting children and the most common cause of acquired heart disease in children in developed countries (1). KD has been reported from all continents and the incidence has been increasing worldwide. The current annual incidence rates of KD in Japan, Korea and Taiwan are 264.8, 134.4 and 69 cases /100,000 children below 5 years respectively (2-4). At Chandigarh, we diagnosed our first patient with KD in 1994. The current estimated incidence is 4.54/100,000 children below 15 years (5). Anecdotal reports suggest that KD is now being increasingly recognised in our country.

Deaths in KD can occur during the acute stage and these are usually due to coronary thrombosis, myocardial infarction or myocarditis. Long-term consequences of coronary artery lesions in KD are still not clear but these may result in significant morbidity and mortality in young adults. Mortality in KD has varied in the developed countries from 1–2% in the pre-intravenous immunoglobulin (IVIg) era to 0.014% now (2, 6). However, there are no data on mortality from KD for developing countries.

As the phenotype of KD seen at Chandigarh differs significantly from that in Japan and Northern America (5) it is important to study this aspect of KD in the context of data from developed countries.

Patients and methods

This work was carried out in the Paediatric Allergy-Immunology Unit, Advanced Paediatrics Center, Post Graduate Institute of Medical Education and Research, Chandigarh, North India. Our institute serves as a tertiary care referral centre for North-West India. During the period January 1994 to March 2015, a total of 460 children were diagnosed with KD based on standard criteria (1, 6). Male to female ratio was 1.96:1 and 106 children were aged 2 years or less. Children with KD received intravenous immunoglobulin

Table I. Studies reporting mortality in KD.

Study	Period	Country / Region	Mortality	Comments
Dhillon *et al*., 1993 (8)	Jan-Dec 1990	British Isles	**3.7%** (6/163)	Active reporting scheme based on cases reported to British Paediatric Surveillance Unit
Kato *et al*., 1996 (30)	Diagnosed: 1973-83. Follow-up: 10-21 years	Japan	**0.8%** (5/594)	Ischaemic heart disease- 4.7% MI – 1.9%
Yanagawa *et al*., 1996 (31)	Nationwide survey (1993 & 94)	Japan	**0.08%** (9/11,458)	Cardiac sequelae – 12.8%
Nakamura *et al*., 2013 (32)	Diagnosed: 1982-92 Follow-up up to 2009	Japan	**0.69%** (46/6576)	Long-term follow-up study. Mortality was high for patients with cardiac sequelae
Makino *et al*., 2015 (2)	Nationwide survey (2011-12)	Japan	**0.014%** (4/26,691)	22nd nationwide survey of KD in Japan. Coronary aneurysms and MI – 2.8%
Kim *et al*., 2014 (3)	Nationwide survey (2009-11)	South Korea	**0** (0/13,031)	MI – 2
Huang *et al*., 2009(4)	Nationwide survey (2003-2006)	Taiwan	**0** (0/3877)	Survey carried using Taiwan's national health insurance claims
Lue *et al*., 2014 (33)	5 nationwide questionnaire hospital surveys (1976-2007)	Taiwan	**0.4% (1976) 0.03% (2007)** (14/14,399)	5 nationwide questionnaire hospital surveys in 1987, 1992, 1994, 2001 and 2008 .CAL- 20.2 to 31.5%
Present study, 2015	Hospital based study (1994-2014)	India	**0.87%** (4/460)	Retrospective analysis of case records

MI: Myocardial infarction; CAL: coronary artery lesions.

(IVIg) in the following dose: 0.4 g/kg/day for 4 days prior to 1999; and 2 g/kg thereafter. They were also administered aspirin in doses of 30–50 mg/kg/day during the acute phase and 3–5 mg/kg/day thereafter. 2-D echocardiography was done once during the acute phase and approximately 6-8 weeks later on follow-up. We have four deaths in our cohort. The work has been approved by the Departmental Publication Review Board.

Case 1

A 2-year-old boy presented to our institute in April 2008 with history of fever, cough and rapid breathing for 5 days prior to admission.

He was found to have pneumonia with empyema, for which he received intravenous antimicrobials and required intercostal tube drainage. During the hospital stay, he developed evanescent rash over the trunk, along with red cracked lips, red tongue and conjunctival injection followed by perineal and periungual peeling of the skin. At this time he was transferred to our unit (day 26 of fever) with a clinical diagnosis of KD. He had haemoglobin of 88 g/L, total leukocyte count of 8.3 x 10^9/L (N_{78}, L_{20}, M_3, E_2) and rising platelet counts (from 260 to 450 x 10^9/L). C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) (Westergren) were also elevated. Ultrasound of abdomen revealed hydrops of gall bladder (size 2.2 x 5.6 cm). Echocardiography was normal. He was administered IVIg but unfortunately developed seizures during the infusion. IVIg was discontinued and seizures were aborted with intravenous diazepam. However, he aspirated during this episode and required ventilation. His oxygen saturation progressively declined and chest radiograph revealed bilateral infiltrates. He developed acute respiratory distress syndrome and died due to refractory hypoxaemia.

Case 2

A 6-month-old baby girl presented in June 2009 with fever (up to 105°F) and rash for 3 weeks. On 2nd day of fever, she developed maculo-papular, erythematous confluent non-itchy rash, associated with redness of oral mucosa. During the second week of illness, skin peeling was noted in the perineal area and extremities. She was extremely irritable. There was no history of bleeds or altered sensorium. She was initially managed by a local physician with multiple intravenous antimicrobials to which there was no response. At admission to our hospital, she had tachycardia, strawberry tongue, peeling of skin and hepatosplenomegaly. She also developed serositis with right sided pleural effusion. Her haemoglobin was 90 g/L and total leukocyte count 20 x 10^9/L with 80% polymorphs. She had thrombocytopenia documented on multiple occasions with lowest platelet counts of 14 x 10^9/L. CRP was 133 mg/L (<6) and ESR (Westergren) 20 mm/1st hour. Transaminases were significantly elevated (ALT - 7945 and AST - 1034 U/L). She also had hypo-fibrinogenaemia, coagulopathy [(prolonged activated partial thromboplastin time (aPTT) and prothrombin time (PT)], hyper-ferritinemia (ferritin: 12,268 µg/L) but serum triglycerides were normal. Although bone marrow examination did not reveal haemophagocytosis, she satisfied criteria for macrophage activation syndrome (MAS). Serologies for Epstein Barr virus and cytomegalovirus were non-reactive. 2-D echocardiography revealed normal sized coronary arteries but poor myocardial contractility. Creatine kinase MB (CKMB) and troponin T were not assayed at that time. A diagnosis of

Table II. Profile of children who succumbed to KD in our cohort.

Sr. no	Age in months / Sex	Day of referral (from onset of fever)	Platelet counts at admission (x 10^9/L)	Echo-cardiography	Complications	Cause of death	Remarks
1	24/M	26	260	Normal	Pneumonia with right sided empyema; Developed seizures while receiving IVIg. Post seizure: aspiration and acute respiratory distress syndrome (ARDS)	Aspiration pneumonia; ARDS and refractory hypoxaemia	Atypical presentation; delayed diagnosis; adverse reaction to IVIg
2	6/F	22	14	Normal	Severe persistent coagulopathy; shock	Refractory shock; myocarditis	IVIg resistant KD (no response to 2 doses); macrophage activation; high ferritin (12,268 µg/L)
3	15/F	20	40	Normal	At 1 week of follow-up, developed fever, diarrhoea, coagulopathy, pancytopenia; probable intracranial (IC) bleed	Coagulopathy with IC bleed	Probable relapse with macrophage activation syndrome
4	3.5/M	26	190	Giant aneurysms involving RCA and LMCA	Myocarditis, congestive heart failure, cardiogenic shock	Cardiogenic shock	Intravenous dexamethasone was tried

RCA: Right coronary artery; LMCA: Left main coronary artery.

KD was made and she was treated with 2 gm/kg of IVIg but she remained febrile and the inflammatory parameters continued to be elevated. A 2nd dose of IVIg was administered but her clinical condition worsened and she developed shock that was refractory to multiple inotropes and succumbed to her illness.

Case 3

A 15-month-old girl presented in June 2010 with fever for 20 days documented up to 102°F associated with watery non-bloody diarrhoea 8–10 episodes/day. She also had history of excessive irritability. On examination, she had no signs of dehydration but was noted to have conjunctival injection, strawberry tongue with periungual desquamation and non-pitting oedema of the extremities. Her haemoglobin was 118 g/L, TLC 11.5 x 10^9/L (N_{71}). She had thrombocytopenia at admission (platelet counts 40 x 10^9/L) and hypo-albuminaemia (serum albumin 12 g/L). Electrocardiogram and echocardiography were normal. A diagnosis of incomplete KD was made and she received IVIg 2g/kg to which she showed a brisk response. She was discharged on aspirin (5 mg/kg/day). After 1 week, she was again admitted with recurrence of fever and loose motions. She was severely dehydrated, had hepatomegaly and oedema of limbs. Her haemoglobin was 40 g/L, total counts of 3.4 x 10^9/L (N_{22}, L_{74}, M_2, E_2) and platelet counts of 120 x 10^9/L: these subsequently dropped to 15 x 10^9/L. There was coagulopathy (prolonged aPTT and PT). Blood cultures were sterile. Bone marrow examination revealed maturation arrest in granulocytic series. She developed skin and mucosal bleeds and later developed shock that was refractory to medical measures. At day 4, she developed alteration of sensorium probably secondary to intracranial bleed. Computed tomography of the head was planned but she deteriorated rapidly and succumbed before imaging could be carried out.

Case 4

A 3.5-month-old male baby presented in November 2012 with history of fever (up to 102.4°F) for 15 days and cough for 12 days. He had been treated with oral and intravenous antimicrobials elsewhere but had showed no response. Blood, urine and cerebrospinal fluid (CSF) cultures were sterile. He was referred on 26th day of illness to our institute. At admission, he had red lips and tongue and was in congestive cardiac failure. He had haemoglobin of 79 g/L, TLC of 16.7 x 10^9/L (N_{77}) and platelet counts of 190 x 10^9/L that rose to 541 x 10^9/L during hospital stay. Initial echocardiography was reportedly normal and child was managed as a case of viral myocarditis. A repeat echocardiography performed 2 days later showed severe mitral regurgitation, moderate aortic regurgitation and giant aneurysms in left main and right coronary arteries and a markedly decreased ejection fraction. CKMB was high (0.54 g/L, normal <0.2). A diagnosis of KD was made and he was treated with IVIg 2g/kg, aspirin and low molecular weight heparin. However he showed progressive worsening of cardiac failure. Intravenous dexamethasone was added as he had severe myocarditis. He developed cardiogenic shock; was treated with inotropes but succumbed rapidly.

Discussion

Kawasaki disease is an acute necrotising vasculitis affecting medium-sized vessels, principally the coronaries. Coronary artery abnormalities (CAA) develop in approximately 20–25% of untreated children and can manifest as dilatation and aneurysms (1, 6). Thrombosis in these CAA is a real risk

and these can present with acute myocardial infarction (MI). Myocarditis secondary to KD is a common problem. Long-term complications of KD can result in myocardial ischaemia in young adults.

The first case of KD was diagnosed by Dr Tomisaku Kawasaki in 1961 and he reported the first 50 cases in 1967 (7). Since then incidence of KD has been constantly increasing in Japan, Korea and Taiwan. KD has now been increasingly recognised in India too and the incidence has been increasing over the past two decades (5). While the developed world has made significant advances in the management of these children, there is paucity of information on this aspect of KD from any developing country. In the pre-IVIg era, the mortality reported from US and Japan was 1–2% and in UK it was upt o 3.7% (8). However with improved access to IVIg, early diagnosis and timely therapy, this has substantially reduced to 0.014% (2). Previous studies that report mortality in KD have been tabulated (Table I).

In our cohort of 460 patients, four children succumbed to acute KD (Table II). All of them had presented late (mean duration of referral being 23.5 days). In our set up, there are many factors that result in such undue delay. Many physicians involved in managing these children may not be familiar with diagnosis of KD. The condition is often mistaken for a viral exanthem. As many features of KD are transient, parents may not report them and physicians may fail to note these. Age below 6 months, incomplete KD and geographic distance from the treating centre have been reported to be independent risk factors that result in delayed diagnosis (>10 days) in the American cohort (9). Lack of awareness amongst paediatricians and socioeconomic factors are other important problems noted in our set up. Children with delayed diagnosis are associated with increased risk of coronary arterial lesions (10, 11). There was substantial delay in diagnosis and referral in our cohort (20–26 days). This was probably the most important factor that led to complications and mortality in these children.

KD occurs more frequently in children above 5 years of age in our cohort as compared to the West. 39.2% of children were above 5 years in one of our previous studies (12). However all the 4 children who succumbed to KD were below 2 and 50% of them were below 6 months. It is well recognised that KD in infants and very young children is a more serious disorder (13). KD is more often atypical and incomplete in children below 1 (13). Thus, more often than not, either the diagnosis is missed or there is a significant delay in young children. Case 1 had complete KD but in addition had several other clinical features which may have led to delays in diagnosis. Cases 2 and 3 had incomplete KD but it is possible that some features may have disappeared by the time these children were hospitalised. Case 4, the youngest of the 4 patients being reported here, had giant aneurysms involving left main and right coronary arteries.

Not only coronary arteritis but myocarditis is an integral and important component of Kawasaki syndrome (14, 15). Myocarditis is noted in 1/3rd to ½ of the patients in the acute phase (in the first week) and its occurrence is independent of the occurrence of coronary lesions. Severe myocarditis causing cardiogenic shock was noted in two of our children. Managing such children is a clinical challenge, as administering IVIg is very difficult as it adds to the volume overload in the failing heart. Glucocorticoids have been tried in such setting with some success (16). One of our children with myocarditis was administered intravenous dexamethasone along with IVIg; but the cardiac status failed to improve.

While thrombocytosis is a well-known entity in second week of KD, thrombocytopenia points towards severe KD with poor outcome (17). Thrombocytopenia may be secondary to MAS and one needs to consider this possibility when children with KD present with cytopenias. Case 2 presented with severe thrombocytopenia (platelet counts - 14 x 10^9/L) and features of macrophage activation with very high ferritin levels (12,268 μg/L). He showed no response to 2 doses of IVIg and also had severe myocardial dysfunction. Case 3 had resurfacing of thrombocytopenia after being afebrile for 6 days and probably died of an intracranial bleed.

KD is the third most common rheumatic disease that can get complicated with MAS, following systemic onset juvenile idiopathic arthritis and systemic lupus erythematosus (18). MAS is much more common in children with KD than is usually thought of and it can be a presenting feature of KD (19, 20). While Case 2 satisfied criteria for MAS, Case 3 with pancytopenia also had probable MAS. MAS is associated with high mortality (21). Children who present with MAS are likely to represent the most severe form of KD and have an increased risk of IVIg resistance (22). Case 2 probably had IVIg resistant KD with MAS.

Giant aneurysms involving left main coronary artery (LMCA) and right coronary artery (RCA) were noted in Case 4. This baby was only 3.5 months old. He also had severe myocarditis and succumbed to refractory cardiogenic shock. An experienced paediatric cardiologist with training in performing coronary-echocardiography is required to diagnose CAA. In the developing world, there is dearth of paediatric cardiologists. Most of the echocardiographs are performed by cardiologists catering to adult population who may lack adequate experience in performing echocardiographs in children with KD. Initial echocardiograph was reportedly normal in case 4; however, repeat echocardiography revealed giant aneurysms.

The most important cause of death in acute KD is myocardial infarction (MI). While majority of children develop MI during the first year following KD, around 1/4th develop this complication later. In a series reported by Kato *et al*., 37% had silent MI (23). This possibility cannot be completely excluded in our children, as CKMB and troponin T tests were not carried out at that time.

IVIg is the drug of choice for treatment of KD (24, 25). Although well tolerated by majority, severe anaphylactic reactions have been reported previously (26, 27). Acute encephalopathy following IVIg infusion has been reported by Soto *et al*. (28). Case 1 developed

generalised seizures during administration of IVIg. Dyselectrolytaemia was ruled out and the aetiology of seizure remained unclear.

In conclusion, we report a mortality of 0.87% in our cohort of 460 patients with KD over the past 2 decades. Mortality in our cohort equals to that of pre-IVIg era in the developed world. Delays in diagnosis contributed significantly to this mortality. However, in this study we have not explored the role of serum lipid abnormalities in the context of mortality in KD (29). Our work emphasises the fact that KD in infants and young children is a serious disorder and early diagnosis is of utmost importance. To the best of our knowledge, this is the first study documenting mortality from KD in developing countries.

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