

# Retrospective Cohort Study of Clinical Profile and IVIg Resistance in Children with Incomplete Kawasaki Disease in a Tertiary Care Center

Bhaskar Shenoy<sup>1</sup>, Basavanhalli Chandregowda Arun<sup>2</sup>

Received on: 28 September 2020; Accepted on: 30 June 2021; Published on: 31 August 2022

## ABSTRACT

**Background:** Diagnosis of incomplete Kawasaki disease (KD) is a clinical challenge in the absence of a specific diagnostic test. Diagnosis of KD is based mainly on the typical constellation of clinical signs and symptoms. Incomplete KD is much more difficult to diagnose because they present with fewer clinical features. Hence, diagnosis and treatment are often delayed in such cases and the response to treatment with intravenous immunoglobulin (IVIg) is poor. A high index of suspicion is necessary to diagnose and manage the children presenting as incomplete KD.

**Objectives:** To study the clinical spectrum of incomplete KD and to assess the response to IVIg therapy.

**Materials and methods:** A retrospective cohort study of children with incomplete KD at a tertiary care hospital from January 2010 to April 2018. Diagnosis and treatment were based on American Heart Association (AHA) guidelines.

**Results:** Fifty-four out of 94 KD cases were incomplete KD (57.4%). Most of the incomplete KD cases were in infants (48.1%). The mean duration of fever at diagnosis was 6.3 days in complete KD and 6.9 days in incomplete KD. Clinical manifestations were oral mucosal changes (79.6%), conjunctival injection (68.5%), and polymorphous exanthema (64.8%). Less common clinical manifestations were extremity changes (14.8%), cervical lymphadenopathy (33.3%), irritability (53.7%), diarrhea (31.4%), vomiting (20.3%), and Bacillus Calmette-Guerin (BCG) scar flare-up (11.1%). Coronary artery abnormality (CAA) was detected in 27 cases (50%). Forty-nine out of 54 cases showed clinical resolution to IVIg (90.7%), 5 were resistant to the first dose of IVIg, 4 responded to the second dose of IVIg, and 1 required infliximab.

**Conclusion:** Incomplete KD is more often associated with CAA. Clinicians should have a high index of suspicion when fever persists for 5 days or more and is associated with any of the principal clinical manifestations. Few laboratory tests and echocardiography may assist in the early diagnosis and treatment. The majority of the children responded to IVIg.

**Keywords:** Coronary artery abnormality, Incomplete Kawasaki disease, Infliximab, Intravenous immunoglobulin.

*Pediatric Infectious Disease* (2022); 10.5005/jp-journals-10081-1281

## INTRODUCTION

Kawasaki disease (KD) is the most common acute, self-limited systemic vasculitis of childhood and one of the most common causes of acquired heart disease in children. In the absence of a gold standard diagnostic test, the diagnosis of KD is based mainly on the constellation of clinical findings. American Heart Association (AHA) guideline for diagnosis of KD is based on the presence of fever of at least 5 days along with four out of five principal clinical findings.<sup>1</sup> Children who have insufficient clinical findings to meet the epidemiological case definition are diagnosed as incomplete KD in the presence of compatible laboratory and echocardiographic findings and on the exclusion of other febrile illnesses. This practical difficulty in diagnosing incomplete KD makes the diagnosis often delayed compared with complete KD,<sup>2</sup> which can explain the reduced response to treatment and high risk of coronary artery abnormalities (CAA) in incomplete KD.<sup>3</sup> There is a paucity of data regarding clinical presentation, complications, and treatment outcomes of incomplete KD in Indian children. Hence, the purpose of our study is to understand the clinical profile and treatment outcomes in children with incomplete KD.

## MATERIALS AND METHODS

This retrospective cohort study of children below 18 years with KD was conducted at a tertiary care hospital. Institutional ethical

<sup>1,2</sup>Department of Pediatrics, Manipal Hospital, Bengaluru, Karnataka, India

**Corresponding Author:** Basavanhalli Chandregowda Arun, Department of Pediatrics, Manipal Hospital, Bengaluru, Karnataka, India, Phone: +91 7795417015, e-mail: arunbc04@gmail.com

**How to cite this article:** Shenoy B, Arun BC. Retrospective Cohort Study of Clinical Profile and IVIg Resistance in Children with Incomplete Kawasaki Disease in a Tertiary Care Center. *Pediatr Inf Dis* 2022;4(3):83–85.

**Source of support:** Nil

**Conflict of interest:** Dr Bhaskar Shenoy is an editorial board member & excluded from the standard peer-review process.

committee approval was obtained. Retrospectively cases were identified from the electronic database of the unit over the period of 8 years (2010–2018), those fulfilling the diagnostic criteria of KD as per AHA case definition were included. Prospectively cases that were diagnosed as KD at the same tertiary care center from 2017 to 2018 were also included in the study. Incomplete KD was defined as unexplained fever of at least 5 days duration with less than four principal clinical findings of KD and compatible laboratory and echocardiographic findings. A total of 94 children were included in the study among whom 40 cases were complete KD and 54 cases were incomplete KD. Data obtained were—(1) demographic details, (2) clinical features, (3) relevant laboratory results [hemoglobin (Hb),

total leukocyte count (TLC), platelet count, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), serum glutamic oxaloacetic transaminase (SGOT), serum glutamic pyruvic transaminase (SGPT), S. albumin, urine analysis] before and after intravenous immunoglobulin (IVIg) treatment and during follow-up, (4) echocardiogram was performed by a pediatric cardiologist. Echocardiography was done on admission, before discharge, at 6 weeks, and later depending on the echocardiographic findings at a 6-week follow-up. Coronary artery abnormalities (aneurysms or dilation) seen on echocardiogram were documented at each follow-up visit. All cases were treated with IVIg (2 gm/kg body weight over 10–12 hours) as soon as the diagnosis was made along with aspirin as per AHA guidelines. Response to IVIg treatment was based on the resolution of fever or persistence/recurrence of fever after 36 hours of completion of IVIg. Cases of resistant KD that are unresponsive to initial IVIg therapy received a second dose of IVIg. Cases unresponsive to the second dose of IVIg received steroids, infliximab.

### Statistical Analysis

The data were analyzed using the SPSS package (ver. 18.0). The results for each parameter (numbers and percentages) for discrete data and averaged (mean  $\pm$  standard deviation) for each parameter were presented in tables and figures. Proportions were compared using the Chi-square test of significance. The Student's "t" test was used to determine whether there was a statistical difference between the groups in the parameters measured. In all the above tests, a  $p$  value  $< 0.05$  was taken to be statistically significant.

## RESULTS

Ninety-four children were diagnosed with KD during the study period. Fifty-four were incomplete KD (57.4%) and 40 were complete KD (42.6%). The mean age at diagnosis of incomplete KD was 2.2 years and complete KD was 2 years. Out of 54 incomplete KD cases, 26 cases were below the age of 1 year (48.7%), 24 were between 1 and 5 years (44.4%), and 4 were above 5 years (7.4%). Out of 40 complete KD cases, 17 were below 1 year (42.5%), 22 were between 1 and 5 years (55%), and 1 was above 5 years (2.5%). Compared to complete KD cases, incomplete KD cases were more in the extremes of age that is  $< 1$  and  $> 5$  years.

### Clinical Profile of Incomplete KD

Mean duration of fever at diagnosis was 6.3 days in complete KD and 6.9 days in incomplete KD ( $p$  value 0.323). The most common principal clinical manifestations were oral mucosal changes (79.6%), conjunctival injection (63.5%), and polymorphous exanthema (64.8%). Extremity changes (14.8%) and cervical lymphadenopathy (33.3%) were less common among the principal clinical findings. Thirty-three cases (61.1%) among 54 incomplete KD had 3 out of 5 principal clinical findings, 20 cases (37%) had 2 and 1 case had only 1 principal clinical finding. Other clinical manifestations like irritability (53.7%), diarrhea (31.4%), vomiting (20.3%), and Bacillus Calmette-Guerin (BCG) scar flare-up (11.1%) were more often seen among incomplete KD cases.

In our study, the most common laboratory abnormality at the time of admission was elevated CRP (100%), elevated ESR (83%), anemia (63%), and leukocytosis (63%). Post-treatment with IVIg, most of these abnormalities reduced except for thrombocytosis (66.7% compared with 51.9% at the time of admission). Low levels of serum alanine aminotransferase, low levels of the gamma-glutamyl transferase, low frequency of hyponatremia, and low frequency of pyuria were reported in children with an incomplete presentation.

Laboratory parameters in incomplete KD took a long time to normalize compared with complete KD.

Prevalence of CAA in our study was 42.6% (40 out of 94 cases had CAA), 57.4% of cases had a normal echocardiogram (54 out of 94 cases did not have CAA). Prevalence of CAA in complete KD was 32.5%, 13 out of 40 complete KD cases had CAA. Prevalence of CAA in incomplete KD was 50%, 27 out of 54 incomplete KD cases had CAA ( $\chi^2$  value = 2.879 and  $p = 0.090$ ). Among 54 incomplete KD cases, 25 had CAA at the time of diagnosis; CAA was detected in 2 cases during follow-up. Coronary artery dilation was seen in 21 cases, a small aneurysm was seen in 5 cases, and 1 case had a giant coronary artery aneurysm.

All 94 cases were treated with IVIg on the day of diagnosis. Forty-nine out of 54 (90.7%) incomplete KD cases and 39 out of 40 (97.5%) complete KD cases showed clinical resolution to IVIg. Among six cases resistant to the first dose of IVIg, one case was complete KD and the other five were incomplete KD ( $\chi^2$  value = 1.757 and  $p$  value = 0.185). One case of incomplete KD who failed to respond even after the second dose of IVIg was successfully treated with infliximab.

Complete resolution of CAA was seen in 24 out of 27 incomplete KD cases within 1 year from the onset of illness, among which 12 cases resolved within 6 weeks (44.4%), 11 cases within 6 months (40.7%), and 1 case by 1 year. At the end of 1 year, three cases had persistent CAA (11.2%). All 13 complete KD cases with CAA had complete resolution of CAA within 1 year. No significant difference between complete and incomplete KD with respect to the duration of resolution of CAA. Eighty-four percent of cases attained complete resolution within 6 months and the rest within 1 year.

## DISCUSSION

Diagnosis of incomplete KD is a challenge because these children present with unexplained fever of  $> 5$  days with three or less compatible clinical manifestations. Diagnosis of incomplete KD should not be delayed because of the risk of coronary complications.

The reported prevalence of incomplete presentation was 15–36.2% in patients with KD.<sup>5</sup> Many studies show the incidence of complete KD to be more than incomplete KD.<sup>2,4,6</sup> In our study, incomplete KD was more common than complete KD similar to studies by Shivalingam et al., Balasubramanian et al., and Özdemir et al. which has equal incidence or incomplete KD more than complete KD.<sup>7,8,14</sup> Özdemir et al. showed that the incidence of incomplete KD is increasing year by year in different parts of the world. This can be attributed to increasing awareness in the clinicians regarding the disease.

No significant difference was found in the mean age of presentation among incomplete and complete KD cases, but incomplete KD cases were more in numbers in the extremes of age, i.e.,  $< 1$  and  $> 5$  years similar to the study by Manlhiot et al.<sup>2</sup>

The mean duration of fever at the time of diagnosis and initiation of treatment was 6.3 days in complete KD and 6.9 days in incomplete KD.<sup>7</sup> The difference is not significant ( $p$  value = 0.323) as the center is a tertiary care referral hospital and the pediatricians are well versed in the diagnosis of KD, both complete and incomplete forms. Among the principal clinical findings in all KD cases more common were—oral mucosal changes, conjunctival injection, and polymorphous exanthema, less common were—extremity changes and cervical lymphadenopathy. But the frequencies of symptoms were less in incomplete KD cases

compared with complete KD cases. This is consistent with the previous studies of Manlhiot et al. and Perrin et al.<sup>2,6</sup> There was no significant difference in the laboratory profile of complete and incomplete KD cases except that incomplete KD cases took longer time duration to normalize.

The occurrence of CAA in incomplete KD was 50% (27 out of 54 cases) and 32.5% (13 out of 40) in complete KD ( $\chi^2$  value = 2.879 and  $p = 0.090$ ). Many previous studies showed similar results where CAA was more common among incomplete KD compared with complete KD.<sup>3,6,9</sup> Manlhiot et al. showed an equal incidence of CAA in complete and incomplete KD.<sup>2</sup>

A single high dose of IVIg along with acetylsalicylic acid (ASA) is the standard treatment for both complete and incomplete KD.<sup>1,10</sup> Intravenous immunoglobulin when administered in the acute phase reduces the prevalence of CAA.<sup>10,11</sup> Persistence or recurrence of fever at least 36 hours after the end of IVIg infusion is called resistant KD. Resistance to IVIg therapy is common in incomplete KD (9.2%) compared with complete KD (2.5%), Tremoulet et al. showed resistance in 10–20% cases.<sup>12</sup> Unresponsiveness and prolonged fever have also been reported to be significant risk factors for coronary artery lesions,<sup>13</sup> 80% of the resistant incomplete KD cases in our study had CAA.

Our study clearly describes the higher association of CAA and poor response to treatment in terms of clinical resolution and complete resolution of CAA among incomplete KD compared with complete KD. However, CAA were not uniformly described in terms of Z-scores, newer laboratory tests like NT-proBNP were not routinely done and were utilized in difficult to diagnose cases only, and long-term complications of KD were not part of our study. In our study, patients were classified as complete and incomplete KD based on the history and physical examination from the day of onset of fever till the diagnosis of KD is made. Any new clinical feature appearing subsequently may not have been considered in revising the diagnosis as complete or incomplete. Another factor may be the recall bias of the parents, regarding any of the clinical features before coming to the hospital. These factors may be the reason for the higher incidence of incomplete KD. Further prospective studies of incomplete KD with an objective assessment of CAA using Z-scores and long-term follow-up for complications are needed.

## CONCLUSION

In the present study, it was observed that incomplete KD is associated with a higher risk of CAA and poor response to treatment. Incomplete KD constitutes a significant number of KD cases; it can be diagnosed and treated only when clinicians have a high index of suspicion of KD in children with prolonged unexplained fever. So, awareness among clinicians about KD and its incomplete form is the key to timely diagnosis and early successful treatment of children with KD to prevent long-term coronary abnormalities.

Consider KD if:

Infants <6 months old with prolonged fever and irritability.

Infants with prolonged fever and unexplained aseptic meningitis.

Infants or children with prolonged fever and unexplained or culture-negative shock.

Infants or children with prolonged fever and cervical lymphadenitis unresponsive to antibiotic therapy.

Infants or children with prolonged fever and retropharyngeal, oroparapharyngeal phlegmon unresponsive to antibiotic therapy.

## REFERENCES

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: a scientific statement for health professionals from the American Heart Association. *Circulation* 2017;135(17):e927–e999. DOI: 10.1161/CIR.0000000000000484.
2. Manlhiot C, Christie E, McCrindle BW, et al. Complete and incomplete Kawasaki disease: two sides of the same coin. *Eur J Pediatr* 2012;171(4):657–662. DOI: 10.1007/s00431-011-1631-2.
3. Sudo D, Monobe Y, Yashiro M, et al. Coronary artery lesions of incomplete Kawasaki disease: a nationwide survey in Japan. *Eur J Pediatr* 2012;171(4):651–656. DOI: 10.1007/s00431-011-1630-3.
4. Gorczyca D, Postępski J, Olesińska E, et al. The clinical profile of Kawasaki disease of children from three polish centers: a retrospective study. *Rheumatol Int* 2014;34(6):875–880. DOI: 10.1007/s00296-013-2836-7.
5. Yu JJ. Diagnosis of incomplete Kawasaki disease. *Korean J Pediatr* 2012;55(3):83. DOI: 10.3345/kjp.2012.55.3.83.
6. Perrin L, Letierce A, Guitton C, et al. Comparative study of complete vs incomplete Kawasaki disease in 59 pediatric patients. *Joint Bone Spine* 2009;76(5):481–485. DOI: 10.1016/j.jbspin.2008.11.015.
7. Shivalingam G, Prashanth GP, Hebbal K, et al. Clinical presentation and cardiovascular outcome in complete vs incomplete Kawasaki disease. *Indian Pediatr* 2017;54(10):844–847. DOI: 10.1007/s13312-017-1147-6.
8. Balasubramanian S, Krishna MR, Dhanalakshmi K, et al. Factors associated with delay in diagnosis of Kawasaki disease in india. *Indian Pediatr* 2012;49(8):663–665. DOI: 10.1007/s13312-012-0130-5.
9. Baer AZ, Rubin LG, Shapiro CA, et al. Prevalence of coronary artery lesions on the initial echocardiogram in Kawasaki syndrome. *Arch Pediatr Adolesc Med* 2006;160(7):686–690. DOI: 10.1001/archpedi.160.7.686.
10. Mori M, Miyamae T, Imagawa T, et al. Meta-analysis of the results of intravenous gamma globulin treatment of coronary artery lesions in Kawasaki disease. *Mod Rheumatol* 2004;14(5):361–366. DOI: 10.3109/s10165-004-0324-3.
11. Oates-Whitehead RM, Baumer JH, Haines L, et al. Intravenous immunoglobulin for the treatment of Kawasaki disease in children. *Cochrane Database Syst Rev* 2003;2003(4):CD004000. DOI: 10.1002/14651858.CD004000.
12. Tremoulet AH, Best BM, Song S, et al. Resistance to intravenous immunoglobulin in children with Kawasaki disease. *J Pediatr* 2008;153(1):117–121. DOI: 10.1016/j.jpeds.2007.12.021.
13. Durongpisitkul K, Soongswang J, Laohaprasitiporn D, et al. Immunoglobulin failure and retreatment in Kawasaki disease. *Pediatr Cardiol* 2003;24(2):145–148. DOI: 10.1007/s00246-002-0216-2.
14. Özdemir H, Çiftçi E, Tapısız A, et al. Clinical and epidemiological characteristics of children with Kawasaki disease in turkey. *J Trop Pediatr* 2010;56(4):260–262. DOI: 10.1093/tropej/fmp110.