Eur J Pediatr (2012) 171:609–611
DOI 10.1007/s00431-011-1629-9

EDITORIAL

Atypical Kawasaki disease—a clinical challenge

Jonathan Forsey · Luc Mertens

Received: 21 October 2011 / Accepted: 9 November 2011 / Published online: 25 November 2011

For the modern day pediatrician, the early recognition of clinical signs, a timely diagnosis and early initiation of treatment of Kawasaki Disease (KD), is a key clinical skill. It is the second most common form of systemic childhood vasculitis and the most common cause of acquired heart disease in children due to the potential for coronary artery aneurysm, myocarditis, and pericardial effusion [3, 12]. The exact etiology of KD remains elusive and hence no single diagnostic test is available to categorically confirm KD and aid in the diagnostic decision making process. There is variation in the incidence of pediatric KD dependent on race of between 9.1 and 32.5/100,000 in USA and 216.9/100,000 in Japan [2, 7]. There is a slight male preponderance of around 1.5:1 and a seasonal variation with higher numbers seen in the winter and spring. The diagnosis of KD relies on the early identification of the key clinical components of prolonged fever and presence of the following clinical signs: bilateral non-exudative conjunctivitis, erythema of the lips and oral mucosa, changes in the extremities, rash, and cervical lymphadenopathy. Additional helpful but non diagnostic clinical signs such as Bacille Calmette–Guérin inoculation site reactivation may support the diagnosis [10]. Certainly supplementary laboratory markers play an important role; elevation of acute phase reactants, C reactive protein and erythrocyte sedimentation rate along with low serum albumin levels are important correlates to the early acute phase along with thrombocytosis present later in the disease process. Noninvasive imaging with echocardiography which is not used in the diagnosis of the complete form of the disease may play a more important role in the incomplete presentation. The differential diagnosis list may be long especially in patient groups outside the typical age range with infective, rheumatologic, and hypersensitivity reactions all among the possibilities. There is a consensus that early treatment with intravenous immunoglobulin (IVIG) and anti-inflammatory doses of aspirin in the acute phase of the disease reduces the risk of coronary aneurysm development and is important for the prevention of long-term morbidity associated with the disease [8]. It is a logical assumption that early diagnosis leads to a reduced time delay before appropriate treatment with IVIG can be instigated. The difficulty and possible uncertainties in diagnosis occur when not all of the classical signs are present and the physician is faced with an incomplete or atypical presentation of the disease. Many large epidemiological studies have estimated that around 20% of all cases fall into the incomplete presentation group with four or less typical features [7]. It has been suggested that this patient group is at greater risk of developing the more serious cardiac sequelae of KD, most notably coronary artery aneurysm (CAA); this higher risk has been attributed to the delay in commencement of therapeutic treatment options in a timely fashion. Guidelines published by the American Heart Association in 2004 [8] and the Kawasaki Disease Research Committee in 2005 [1] form the framework on which diagnosis and treatment algorithms in USA and Japan have been based. These include suggestions on how to incorporate those patients who presented with an incomplete clinical picture into the KD care pathway

In this edition two large studies, one from Japan and the other from North America, study the more atypical forms of Kawasaki disease and the effect of incomplete presentation on diagnosis, treatment, and long-term outcome. Sudo et al.

J. Forsey · L. Mertens (✉)
Division of Cardiology, The Labatt Family Heart Center,
The Hospital for Sick Children,
Toronto, ON, Canada M5G 1X8
e-mail: luc.mertens@sickkids.ca

in their epidemiological paper report the findings of the 20th Japanese nationwide survey of KD taken over a 2-year period [11]. Their aim was to try and identify risk factors for the development of coronary artery aneurysm and look at variation between the complete and incomplete forms of presentation. Manlhiot and his colleagues at The Hospital for Sick Children, Toronto report their center's experience over a 17-year period [4]. In this retrospective case note review, differences in presentation, treatment options, and long-term morbidity were compared between the complete and incomplete patient groups.

Sudo et al. were able to draw data from a total of 23,263 patients presenting to 2,150 institutions across Japan between January 2007 and December 2008. Their classification is based on the Japanese criteria with a complete presentation requiring five out of six principal signs. While coronary imaging with echocardiography is used, for the purpose of their study, if only four signs were present irrespective of known coronary imaging they were classified as incomplete. What is unclear from their data set is the frequency of the different clinical criteria that were present at diagnosis and whether there was any correlation between this and the long-term outcome. From their patient group, 80% of children fulfilled the complete diagnostic criteria (five of six signs) and 20% an incomplete picture (≤four signs). The authors seek to subdivide this incomplete group further with between two and four signs only; which signs were more prevalent and what was used to confirm a diagnosis of KD in patients with only two or three signs is unclear. Due to the nature of the paper, it was not possible to standardize diagnostic criteria across all the centers and so clinician judgment and local policy may have played a significant role in those cases with few classical criteria. The criteria for diagnosis of CAA were based on the Japanese Ministry of Health criteria with echocardiography undertaken in the 'acute' and 'sequelae' phase [9]. Comparing the KD patients with typical and atypical presentation, the authors found that the incomplete patient group had a younger age at presentation (median, 17.4 vs 25.1 months) and were less likely to receive IVIG (93.2% vs 64.2%); although both groups received treatment with IVIG on day 5, there was a higher incidence of CAA (13.1% vs 8.8%). Looking specifically at patients with CAA in the acute phase, the incomplete group tended to be younger (17.6 vs 27.9 months) were proportionally less likely to receive IVIG (78.6% vs 92.8%) with a later commencement of therapy (median, day 6 vs day 5). The authors conclude that the higher incidence of CAA may be due to diagnostic bias because of the use of echocardiography; more importantly they suggest that delay in diagnosis and treatment is an important factor.

In Manlhiot's retrospective paper, a single center's experience (The Hospital for Sick Children, Toronto) over a 17-year period was reviewed. A total of 955 patients were included with classification based on the American Heart Association recommendations [8]. In their group 77% had met the full criteria with 23% presenting with fever and less than four clinical signs. Again echocardiography results were not included when classifying the patients' presentation. Being a single center study, there is a standardized approach to diagnosis, treatment, and follow-up. The authors were able to report not only patient demographics but also the patterns of presentation. Assessment of coronary artery abnormalities are reported as indexed to body surface area (*z* scores) [5, 6]. Their population presented at a slightly later age (2.8 years incomplete vs 3 years complete) but with the incomplete patient group more likely to be at the extremes of the age range (less than 1 year and older than 9 years). Interestingly they were able to report frequency of clinical signs. The incomplete group were more likely to present with conjunctival injection (71%), mucosal changes (67%), and polymorphous rash (69%) and far less likely to display cervical lymphadenopathy (29%) and changes in extremities (40%). While patients in incomplete presentation group had a longer delay to diagnosis (7 vs 6 days) and less likely to receive IVIG (86% vs 96%), there was no differences in the rates of CAA between the two groups (13% incomplete vs 11% complete).

Both sets of authors report a delay in the diagnosis and subsequent treatment for patients presenting with the incomplete form. The equal rate of coronary involvement reported by Manlhiot et al. is in contrast to both the findings of Sudo et al. and previous reports. It is worth noting that the incomplete population in the Japanese study was younger (17.4 vs 33.6 months) and less likely to receive IVIG (64.2% vs 86%); both of which have been shown to place the child at higher risk of CAA.

So what messages can be drawn from these studies? Both report large patient groups adding weight to their findings. It is agreed that an incomplete presentation often delays diagnosis and appropriate treatment; however, the rate of coronary artery involvement is varied. A single center has the advantage of a structured and consistent protocol-driven approach coupled with a high index of suspicion. This may explain the higher rates of initial treatment with IVIG and possibly the subsequent lower rates of coronary involvement overall. Manlhiot et al. conclude that the two forms of presentation should not be thought of as separate entities but more of a spectrum of the same disease. Both authors agree that over reliance on restrictive diagnostic criteria may delay diagnosis and treatment. The clinician should continue to have a high suspicion of KD in the febrile child, especially those under a year of age and low threshold to instigate treatment. Only if this approach is taken then we may see an overall fall in the rates of cardiac complication and mortality associated with the disease.

References

1. Ayusawa M, Sonobe T, Uemura S, Ogawa S, Nakamura Y, Kiyosawa N, Ishii M, Harada K, Kawasaki Disease Research C (2005) Revision of diagnostic guidelines for Kawasaki disease (the 5th revised edition). Pediatr Int 47(2):232–234
2. Holman RC, Curns AT, Belay ED, Steiner CA, Schonberger LB (2003) Kawasaki syndrome hospitalizations in the United States, 1997 and 2000. Pediatrics 112(3 Pt 1):495–501
3. Kato H, Sugimura T, Akagi T, Sato N, Hashino K, Maeno Y, Kazue T, Eto G, Yamakawa R (1996) Long-term consequences of Kawasaki disease. A 10- to 21-year follow-up study of 594 patients. Circulation 94(6):1379–1385
4. Manlhiot C, Christie E, McCrindle BM, Rosenberg H, Chahal N, Yeung RSM (2011) Complete and incomplete Kawasaki disease: different ends of the same spectrum. Eur J Pediatr (in press)
5. Manlhiot C, Millar K, Golding F, McCrindle BW (2009) Improved classification of coronary artery abnormalities based only on coronary artery *z*-scores after Kawasaki disease. Pediatr Cardiol 31(2):242–249
6. McCrindle BW, Li JS, Minich LL, Colan SD, Atz AM, Takahashi M, Vetter VL, Gersony WM, Mitchell PD, Newburger JW, Pediatric Heart Network I (2007) Coronary artery involvement in children with Kawasaki disease: risk factors from analysis of serial normalized measurements. Circulation 116(2):174–179
7. Nakamura Y, Yashiro M, Uehara R, Sadakane A, Chihara I, Aoyama Y, Kotani K, Yanagawa H (2010) Epidemiologic features of Kawasaki disease in Japan: results of the 2007–2008 nationwide survey. J Epidemiol 20(4):302–307
8. Newburger JW, Takahashi M, Gerber MA, Gewitz MH, Tani LY, Burns JC, Shulman ST, Bolger AF, Ferrieri P, Baltimore RS, Wilson WR, Baddour LM, Levison ME, Pallasch TJ, Falace DA, Taubert KA (2004) 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. Circulation 110(17):2747–2771
9. Research Committee on Kawasaki Disease (1984) Report of subcommittee on standardization of diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease. Ministry of Health and Welfare, Tokyo
10. Sinha R, Balakumar T (2005) BCG reactivation: a useful diagnostic tool even for incomplete Kawasaki disease. Arch Dis Child 90(9):891
11. Sudo D, Monobe Y, Yashiro M, Naka Mieno M, Uehara R, Tsuchiya K, Sonobe T, Nakamura Y (2011) Coronary artery lesions of incomplete Kawasaki disease: the nationwide survey of 2007–2008 in Japan. Eur J Pediatr (in press)
12. Taubert KA, Rowley AH, Shulman ST (1991) Nationwide survey of Kawasaki disease and acute rheumatic fever. J Pediatr 119 (2):279–282