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Editorial

Incomplete Kawasaki disease: Lessons to be learned

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Incomplete Kawasaki disease, known to some as iKD, should be of concern all working with acutely sick children. A paper published in this issue of Journal of Pediatric Infectious Diseases contributes to the substantial body of literature on this condition. The findings reinforce two points. Firstly, this condition is relatively common in those practices where clinicians are vigilant: it may comprise more than 10% of the total Kawasaki caseload. Secondly, a proportion of the patients rapidly develop coronary artery damage. It follows that there is a clear risk of missing small numbers of children with coronary artery changes, some significant [1].

Kawasaki disease (KD), initially known as mucocutaneous lymph node syndrome [2], continues to present conundrums for clinicians. The original criteria for complete KD were based on the findings of fever of five days duration or more, as well as four out of five remaining criteria (rash, bilateral conjunctival injection, erythema and swelling of hands and feet, cervical lymphadenopathy and oral mucosal changes). Over the last 10–15 years, many children have been described that have fever, but fewer than the prerequisite number of criteria for a classical KD diagnosis [3]. This subset of patients has been termed 'iKD', and they pose particular diagnostic dilemmas for the clinician. In addition to these cases being difficult to recognize, there is evidence that these patients may be at similar, or even greater, risk of coronary artery aneurysm development compared to classic KD patients. A recent study found iKD to be an independent factor for later or delayed diagnosis [4]. The term 'incomplete' KD has now been applied where the term 'atypical KD' was previously used. 'atypical' KD is preferentially employed for cases with unusual presentations of disease such as hemophagocytic syndrome or nerve palsy [5].

One of the difficulties with the diagnosis of incomplete cases of KD is that even complete or full KD is regularly missed in primary care or average pediatric practices [6,7]. This is evident from publications and parent support groups. Further and more disturbing are the discrepancies in published mortality rates for KD, with a higher mortality cited in a British series (3.7%) than in a Japanese one (0.08%) [8]. This difference has been ascribed to a greater awareness and more prompt diagnosis of KD in Japan. Clearly, a detailed examination of how this disorder is managed is required in order to improve rates of diagnosis and levels of care.

In 2004, the American Academy of Pediatrics published an endorsed clinical report providing guidance for pediatricians on the diagnosis of KD [9]. An algorithm was proposed for incomplete KD diagnosis and its management, based on expert opinion as the evidence base for incomplete KD was limited. The algorithm employed clinical features (defined as fever plus

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2 or 3 additional criteria), as well as abnormal laboratory findings as markers for iKD (raised C-reactive protein and erythrocyte sedimentation rate, hypoalbuminaemia, anemia, elevated alanine aminotransferase, thrombocytosis, leukocytosis and greater than 10 white cells in urine). A subset of iKD patients in whom intravenous immunoglobulin treatment could be instituted prior to echocardiogram was defined, namely those with fever, 2 or 3 clinical criteria and 5 or more laboratory criteria including a raised C-reactive protein and erythrocyte sedimentation rate. The American Heart Association (AHA) recommended in the absence of a gold standard for diagnosis, infants $<$6 months old or on day $>$7 of fever without other explanation should undergo laboratory testing. If evidence of systemic inflammation is found in these infants, the AHA recommended an echocardiogram, even if no clinical criteria were identified. Current UK guidelines for iKD are based on the AHA recommendations, recommending further the involvement of specialist advice early on in the treatment process.

KD has benefited from significant innovative research input by clinical and scientific groups that have joined services around the globe. The epidemiological base for this condition is centered on patients with complete KD. Those observing T cell subsets in the acute illness in an effort to determine potential superantigen effects have revealed a complexity of responses that suggests the progress of the vasculitis is highly variable, differing from conditions such as toxic shock syndrome [10]. Genetic work so far has revealed multiple loci including cell surface molecules, signalling transduction molecules, inositol kinase and chemokines that may predispose a child to developing KD [11]. From clinical viewpoint studies of the sequelae of KD in terms of skin and behavioral changes demonstrate wide clinical variation [12]. The inflammatory landscape in vasculitis is therefore complicated and not clearly understood. The existence of incomplete Kawasaki cases may be taken to demonstrate defects in the classification system for this vasculitic condition from the perspective of individual patients, clinicians and parents. Are there practical arguments for re-classification? This subject has been debated extensively but so far no practical solution to assist the average clinician has been identified [13].

Clinicians need to be aware of KD and incomplete KD, and of the imperative of meta-analysis that early treatment is probably more effective than late treatment [14]. As iKD cases can develop coronary artery damage prior to treatment even in expert practices how can one establish best practice? Personal audit, learning from reflection and regular service reviews are likely to constitute the next most valuable strategies in designing optimal care [15]. Should we investigate and regularly measure "door to immunoglobulin" times? How can we facilitate the early application of echocardiography? With better clinical practice, we can contribute to the research critically needed in order to further our understanding of this childhood vasculitis.

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