Management of Kawasaki disease in the British Isles

Commentary
The report by Dhillon et al of the BPSU surveillance data obtained during 1990 provides us with important information on the prevalence, mortality, and morbidity of Kawasaki disease in the British Isles.

A total of 182 cases were reported in 1990, and with an estimated incidence of 3-4 cases per 10^5 children under 5 years, the disease is sufficiently common to be encountered not infrequently by district general hospital paediatricians. The finding that 24% of the reported cases had coronary artery abnormalities is an indication of the seriousness of the disorder. Although most patients with coronary artery abnormalities recover, there are growing concerns that damage to the coronary arteries in early childhood may predispose to coronary disease in later life. Kawasaki disease may therefore be responsible for a growing cohort of patients who may suffer long term consequences of the disorder.

The mortality rate in this study is worryingly high at 3.7%. Sixteen per cent of all the patients documented on echocardiography to have coronary artery abnormalities died. Moreover, five of the six deaths occurred in patients in whom the diagnosis was not made during life, and therefore had received neither aspirin nor IVGG. In most reported series of patients with Kawasaki disease less than 5% of patients with echocardiographically documented coronary artery abnormalities die. The apparently greatly increased mortality rate for those with aneurysms in the series of Dhillon et al probably reflects an underdiagnosis of the non-fatal cases. It is likely that Kawasaki disease would not have been diagnosed in five out of the six fatal cases had death not occurred. The implication from this is that there are probably 10 to 20 times as many children who have suffered coronary artery dilatation in 1990 as a result of an undiagnosed episode of Kawasaki disease.

The report also provides us with an indication of how patients with Kawasaki disease in the British Isles were treated in 1990. Despite the fact that controlled trials have shown that the incidence of coronary artery abnormalities can be reduced by treatment with aspirin and IVGG administered within the first 10 days of the illness,1-4 a large proportion of the 1990 patients did not receive what could be considered optimal treatment. Only 60% of patients received both aspirin and IVGG, and less than a third received the IVGG within the first 10 days of the illness. With a median time to diagnosis of nine days, most children were diagnosed and treated outside the time at which treatment with IVGG has been shown to be of benefit. Where IVGG was administered, the dose was often below that recommended or shown to be effective. Only a third of the affected children underwent echocardiography on the recommended three occasions and some did not undergo echocardiographic evaluation. We therefore do not know the full extent of the cardiac disease in this series.

For any serious and potentially fatal disease, patients and their parents should expect early diagnosis, and prompt administration of the best available form of treatment. The survey clearly shows that for children with Kawasaki disease this did not occur in the majority of cases in the British Isles in 1990.

The authors of this report have therefore provided us with data on which to base very firm recommendations. The diagnosis of Kawasaki disease must be considered in any child with a febrile erythematous illness that persists longer than four to five days. Other diagnostic possibilities including enterovirus, adenovirus, measles, parvovirus, streptococcal and staphylococcal diseases, and leptospirosis should be rapidly excluded by appropriate history and investigations, and the recommended treatment with aspirin and IVGG should be administered as soon as possible after the fifth day of the illness. All patients should undergo echocardiography on diagnosis, two to three weeks later, and two months after the onset of the disease. Because many children with febrile exanthems do not see paediatricians but are cared for by general practitioners, awareness of the disease needs to be increased among primary practitioners.

Had the authors of this report concluded their paper with these recommendations they would have conveyed a clear and important message to their paediatric colleagues in the British Isles. However, the authors have used the findings in this survey to embark on a puzzling series of speculations which could potentially undermine these recommendations. Based on the observation that the incidence of coronary artery abnormalities in this 1990's series was as high as that reported in Japan or the USA before the introduction of IVGG use, and the observation that the incidence of aneurysms was as high in those who received IVGG as those who did not receive this treatment, the authors have raised the possibility that IVGG may not be an effective treatment of Kawasaki disease in the British Isles. They speculate that the failure to observe a lower incidence of aneurysms in those receiving IVGG might be due to either Kawasaki disease in this country being caused by a different agent than that responsible in other parts of the world or, alternatively, that IVGG produced by different manufacturers may have differing effects in treating this disorder. While these would be important questions to ask had IVGG been shown to be ineffective in the British Isles, to raise this question on the basis of a retrospective survey of inadequately treated patients is an over interpretation of the available data. This speculation does, however, raise important philosophical and ethical questions.

In any rare but serious disease, there is always a great tendency to administer unproved treatments on an empiric basis. The authors and their institutions must now consider and respond by demanding carefully conducted placebo controlled trials in order to determine which forms of treatment should become standard practice. Placebo controlled, randomised trials, in sufficiently large numbers of patients to achieve statistically significant results are...
extremely difficult to do, are enormously costly and time consuming. Once they have been done another series of questions are usually raised: Are the conclusions of the trial valid? Was the trial of sufficient size and adequately carried out? Were the entry criteria and end points clear? Are the conclusions referable to patients in other countries? How many control trials do we require before accepting a modality of treatment as being proved benefit? For a country with a relatively small paediatric and scientific community an increasingly common question is how often we should simply accept the results of trials that have been undertaken in countries with more patients and more resources than we have available, and when instead should we insist on UK based trials before accepting conclusions from trials in other countries.

In the case of Kawasaki disease there are now at least four published randomised controlled trials documenting that IVGG is beneficial in reducing the incidence of coronary artery abnormalities.1-4 The two Japanese studies1 2 and the 1986 multicentre US study3 all concluded that IVGG given in a dose of 400 mg/kg/day for 4–5 days resulted in a significantly lower incidence of coronary artery abnormalities than the use of aspirin alone. The second multicentre US study confirmed that a single large dose of IVGG (2 g/kg) was more effective than the four day low dose regimen in reducing the incidence of aneurysms. In addition the use of IVGG decreased the duration of fever and caused more rapid resolution of symptoms, and a more rapid reduction of acute phase markers than was seen with aspirin alone. All four studies have been conducted by centres with extensive experience in Kawasaki disease, the entry criteria, end points and cardiacological assessments were all clear and uniform, and the findings in all four studies have been similar. Most clinicians and many ethical committees would probably feel that further placebo controlled trials of IVGG would be unethical in view of the marked beneficial effect documented in these trials.5 What then should we make of the speculation in this report that IVGG may be ineffectual in the British Isles?

The clearest explanation for the high incidence of coronary artery abnormalities in the IVGG treated patients is that selection bias has occurred in determining who received IVGG and who did not. A large number of publications have established that risk factors for the development of coronary artery abnormalities include young age, a prolonged and more severe illness, and an intense inflammatory response with higher concentrations of acute phase proteins, platelets, and white cell counts.6 7 Those receiving IVGG in 1990 in this series were significantly younger and had significantly higher platelet counts than those who did not receive IVGG. Clearly, the sickest patients were those most likely to receive IVGG, and this selection bias is the most likely explanation for the high rate of coronary artery abnormalities. Further support for this comes from comparing the platelet count, white cell counts, and duration of fever in the British Isles patients treated within the first 10 days of the illness, with those in the multicentre US study.8 The British Isles patients had higher platelet counts, white cell counts, more prolonged fever, and were started on treatment later than those in the US. The higher rate of coronary artery abnormalities in the studies in the British Isles is almost certainly due to our current recognition of only the most severely affected patients with Kawasaki disease, and a selection of the worst patients for treatment.

The results of a retrospective study of inadequately assessed and suboptimally treated patients cannot be used to question the results of four multicentre controlled trials. We should use the information in this report to press for increased awareness of Kawasaki disease, earlier diagnosis, and prompt treatment with the best available modality of treatment. While better treatments should continue to be sought this must be done in the form of controlled trials comparing any new modality of treatment against the best available treatment; this is currently IVGG and aspirin.

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