# Kawasaki disease — a diagnostic challenge

THIRTY-TWO years ago, a seminal paper was published in Japanese entitled 'Acute febrile mucocutaneous syndrome with lymphoid involvement with specific desquamation of the fingers and toes in children'.[1] Today, we recognize the disease by its eponymous author, Tomisaku Kawasaki. While we know Kawasaki disease is important — currently the most common cause of acquired heart disease in children in the developed world — and that, with early diagnosis, complications can be prevented, the illness remains puzzling.

Most commentators acknowledge that there is an under-recognition of the disease at primary and secondary care levels leading to unnecessary childhood morbidity and mortality.[2-4] In the last United Kingdom (UK) national surveillance study only 182 cases were identified in a year.[5] The reported incidence is three times more in the United States of America (USA)[6] and 30 times more in Japan.[7] What is this elusive illness and which features enable doctors to distinguish Kawasaki disease from other, more common, self-limiting, infectious diseases?

Kawasaki disease is a systemic febrile vasculitis of uncertain aetiology. It predominantly affects the under-fives, the peak incidence being in those children aged between nine and 11 months. There is no diagnostic test. Like rheumatic fever, diagnosis is dependent on identifying a characteristic group of symptoms and signs — one 'major' and four out of five 'minor'.[8] The universal finding is a fever of five or more days' duration. Other criteria include a polymorphous exanthematous rash, oral mucosal changes (injected pharynx without exudate, dry cracked lips, strawberry tongue), cervical lymphadenopathy (greater than 15mm in diameter, painful, often unilateral), non-purulent conjunctival injection, and changes in the peripheral extremities (oedema, erythema, desquamation).

The rub is that children infected with Group A $\beta$-haemolytic streptococcus, staphylococcus, measles, adenovirus, influenza, and other viruses may all mimic Kawasaki disease.[9] So similar can the features of parvovirus B19 appear that some authors have hypothesized it is the causative agent.[10] Laboratory features, such as anaemia, raised erythrocyte sedimentation rate, and late onset thrombocytosis, are unlikely to facilitate early diagnosis. Unfortunately, with the exception of peeling palms and soles of the feet being a late sign, there is little evidence of a sequential order of appearance of symptoms and signs. Additional clues, such as extreme irritability, redness, and induration at the site of a BCG vaccination scar and desquamation in the genital area, may be useful.

Kawasaki disease is unequivocally linked with heart disease. In expert hands coronary artery aneurysms can be detected by echocardiography in about 25% of children who have the disease.[11] These lesions, predominantly affecting the left coronary artery, usually appear in the third and fourth weeks after the onset of the illness. New lesions are unusual after 28 days. Other cardiac complications include myocarditis, mitral and aortic incompetence, dysrhythmias, angina, myocardial infarction, and, regrettably, in about 1–2% of children, death.[12] While most of the aneurysms regress within two years from diagnosis, the long-term outcome is uncertain.[13] Sudden death owing to multiple coronary artery aneurysms has been reported in an adolescent with a retrospective history of Kawasaki disease in infancy.[14] The damaged coronary artery lumen may be predisposed to premature atherosclerosis and may be a significant risk factor for adult ischaemic heart disease.

Prior to 1986, the conventional treatment for Kawasaki disease had been anti-inflammatory agents, including aspirin. That year, the publication of results from a randomized control trial conducted throughout centres in the USA[15] led to significant management changes. Children treated with intravenous gamma globulin and aspirin for four days within 10 days of the onset of fever were one-third as likely to have coronary abnormalities after two weeks than those treated with aspirin alone. The results seven weeks after diagnosis were even more dramatic — children treated with gamma globulin were five times less likely to have coronary artery pathology. It has been postulated that the beneficial effect is achieved by the immunological protection of endothelial cell surfaces from antibodies induced by cytokines. The implementation of this evidence has been slow. In the UK in 1990, only 61% of children with Kawasaki disease received gamma globulin and only in 7% were the timing and dosage optimal.[16]

Three nationwide epidemics of Kawasaki disease have been recognized in Japan.[17] Other epidemics have been observed in South Korea, Hawaii, Los Angeles, Chicago, Colorado, Massachusetts, Canada, and Germany. There is no consistent seasonal pattern. Boys are more commonly affected than girls (1.4:1). Siblings are more frequently affected than the general population; despite this, secondary cases occurring in contacts of affected patients are rare. There may be a racial predisposition — American children of Japanese descent have an increased risk of developing the disease. Other interesting epidemiological associations are residence within 200 yards of a body of water and exposure to a freshly cleaned carpet.

The epidemic nature of the disease, together with the age range most commonly affected, strongly suggests an infectious aetiology. Rickettsiae, house dust mites, and the skin commensal *Propionibacterium acnes* have all been mooted, and subsequently refuted, as causative agents. More recently, research has focused on the possibility that the manifestations of Kawasaki disease are caused by a toxin.[18] Certainly there are striking clinical similarities with other toxin-induced diseases, such as staphylococcal toxic shock syndrome, scarlet fever, and scalded skin syndrome. Bacterial toxins may act as superantigens stimulating intense T-cell proliferation and consequent immune activation. However, evidence is still conflicting, and both the bacterium and the toxin remain unidentified.

What are the key messages for general practitioners? Viral exanthems are common; Kawasaki disease is relatively rare. However, Kawasaki disease is probably grossly underdiagnosed in primary care. While this may have not mattered 15 years ago, now there is a known effective treatment diagnosis has become of paramount importance. Because diagnosis is difficult and delay in treatment potentially damaging, there must be a willingness to review children with a fever and a rash within 72 hours if there are no signs of clinical improvement. Careful observation of unusual signs, such as conjunctivitis without discharge and diffuse redness of the oral mucosa, may help. General practitioners developing a heightened index of suspicion that a child may have Kawasaki disease should be prepared to refer to a paediatrician even in the absence of a 'full house' of symptoms and signs. During the evolving disease process the complete constellation of diagnostic features may not yet be present.

If children with Kawasaki disease are being missed, what diagnoses are being offered instead? These days we may well feel very pleased with ourselves in making a diagnosis of measles; however, most measles notifications turn out to be anti-

body negative[19] — could it be possible that some of these are the missing cases of Kawasaki disease?

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# Depression in pregnant and postnatal women: an evidence-based approach to treatment in primary care

NON-PSYCHOTIC depressive illness, characterized by low mood, anxiety, irritability, and insomnia.[1] is common in recently-delivered mothers and can have serious long-term consequences for maternal mood and infant development. Most studies have reported the rate of depression within the first six months after childbirth to be 10%–15%,[2] the likeliest time for onset being the first five weeks.[3] Postnatal depression occurs in women who are genetically and/or psychologically predisposed.[4] Social adversity is common;[5,6] there is little evidence of a hormonal cause, although thyroid dysfunction has been described.[7,8] The children of women with postnatal depression have higher rates of impaired cognitive development (especially boys) and disturbed behaviour.[9-11] Around one-third of cases become chronic or recurrent.[12,13]

Depression and anxiety are also common during pregnancy, particularly in the first trimester.[12,14] Some women who are depressed or anxious in pregnancy also become depressed after delivery and certain risk factors, e.g. lack of a supportive partner, are common to depression at both times.[12]

Postnatal depression is frequently undetected and therefore untreated in clinical practice, partly because women do not report their symptoms to health professionals.[15,16] However, there is an easily used screening tool, the Edinburgh Postnatal Depression Scale (EPDS),[17] which identifies probable cases. There is also satisfactory evidence on which to base treatment. Randomized controlled trials show that two simple forms of psychological intervention — non-directive counselling,[18,19] and cognitive-behavioural counselling[20] — are effective treatments. Both are brief, simple, and designed to be delivered by non-specialists in mental health, such as health visitors; but, they are distinct in their clinical approach. Non-directive counselling is supportive listening without advice or active intervention. In cognitive-behavioural counselling the patient receives advice about childcare, finding practical support, and ways of elevating mood.

Only one controlled trial has assessed the benefits of an antidepressant drug, finding the anxiolytic antidepressant fluoxetine to be an effective treatment.[20] In this trial, the benefits of cognitive-behavioural counselling and fluoxetine were equivalent and there was little additional benefit from receiving both, but women were more reluctant to take drug treatment. More severe cases of depression have been shown to benefit from oestradiol;[21] however, given that there are simple, safe, and rapidly effective alternatives, the place of oestrogen in clinical practice has not been demonstrated. There has been no satisfactory trial of progesterone compounds. No treatment trial for depression in pregnancy has been reported.

Until the early 1990s, only sparse information was available to guide clinicians on the safety of antidepressants during pregnancy; however, with the development of teratology information services in North America and Europe, large prospective studies have now been published. The commonly used antidepressants — the tricyclics (TCAs), e.g. amitriptyline, imipramine, dothiepin; and serotonin specific re-uptake inhibitors (SSRIs), e.g. fluoxetine, paroxetine, sertraline — have not been shown to

increase teratogenic risk.[22-25] The existing series include several hundred patients; although results at this stage are reassuring, with this number of patients a theoretical increased risk of rare malformation cannot be ruled out. The limited evidence from longer-term follow-up is also reassuring: a recent neurobehavioural study found no cognitive, language, or behavioural effects of TCAs or fluoxetine when children between pre-school and early school years, who had been exposed to these drugs *in utero*, were compared to age-matched controls.[23] Much less information exists on the use of mono-amine oxidase inhibitors (MAOIs) in pregnancy.

In depression of mild to moderate severity, it is not usually necessary to augment antidepressant treatment with lithium, carbamezapine, or valproate, though these drugs are used in more severe mood disorders. Lithium has been associated with an increased risk for the rare Ebstein anomaly of the foetal heart, but recent estimates of risk suggest that fewer than 1% of exposed babies are affected.[26] Foetal echocardiogram is warranted to rule out the more severe forms of this condition. Both carbamazepine and valproate, when taken in the first few weeks of pregnancy, have been shown to increase the risk of neural tube defects to 1% - 2%.[25]

There have been no large cohort studies of psychotropic drugs and breast-feeding. However, only small amounts of TCA and SSRI antidepressants are found in the plasma of infants breast-fed by mothers taking these drugs.[27] Adverse effects tend to be confined to individual case reports.[28] Follow-up studies of infants exposed to TCAs in breast milk have found no developmental deficits, although the number of subjects has been small.[29,30] Greater caution is required with lithium because of the risk of toxicity in the infant; lithium is compatible with breast-feeding only with monitoring of drug levels in milk and infant blood. There is less evidence on the use of MAOI drugs during breastfeeding, although no major adverse events have emerged.[31]

What do these research findings mean for the clinical management of postnatal depression? The regularity of visits and continuity of care provided by midwives, health visitors, and general practitioners (GPs) for pregnant and postnatal women offer repeated opportunities for the recognition of depression. In some parts of the country, health visitors now routinely use the EPDS to screen for postnatal depression,[32] although the cost-effectiveness of the screening has not been rigorously evaluated.

Once postnatal depression has been identified, treatment should be possible in primary care; but, the choice of treatment depends on what is available locally and on women's preferences. Both non-directive counselling and cognitive-behavioural counselling can be delivered by health visitors without referral to GPs, but the health visitors must first be trained. For women who are prepared to take antidepressant drugs, SSRIs and TCAs carry the advantage of being widely available. SSRIs are more expensive but generally cause fewer side-effects and are less sedating. Additional simple measures that may be suggested include attendance at local groups and clubs for mothers and babies, which are likely to reduce isolation. The voluntary sector also provides support organizations, such as the Association for Postnatal Illness in the United Kingdom. In the absence of specific evidence, treatment of depression during pregnancy should follow conventional lines, i.e. drugs and psychological therapies, including emotional support.

Although it is not possible to give patients full assurance, on present evidence the commonly prescribed antidepressants, both TCAs and SSRIs, do not appear to be harmful when used during pregnancy; this is also true of their use during breastfeeding, although the evidence is not as strong. There is no single drug that should be recommended before others. In women who become depressed while breastfeeding there is generally no reason to change to bottle-feeding. However, treatment decisions should be reached through discussion with the patient and should be based on the balance of risks and benefits in the individual case.

When the mother is severely depressed, suicidal, or unresponsive to treatment, or there is any concern over the safety of the baby, referral to a specialist service is needed. Ideally, this will be a dedicated mother and baby service,[33] though there are many parts of the UK, for example, where this does not exist. Perhaps Primary Care Groups, a recent innovation in the NHS that will give GPs more power to shape local services, will demand their development.

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