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Kawasaki syndrome: lessons for Britain

Early diagnosis and immediate treatment should reduce mortality

Only a few conditions in medicine are serious, unexplained, and treatable—with a drug that is not a steroid. One such condition is Kawasaki syndrome—a far better name than the mucocutaneous lymph node syndrome of childhood, which describes only three of its manifestations. It was first described in 1967 by Tomisaku Kawasaki in 50 Japanese children, and there have probably been over 90 000 cases in Japan alone since then.[1]

The condition is serious because of the acute and chronic cardiac complications, which may be fatal. Treatment is almost certainly beneficial, so early recognition of Kawasaki syndrome is important, especially in countries with a low index of suspicion. It is a disease of childhood, with most patients being under the age of 5 and normally presenting abruptly with a high fever, which persists for at least five days and which is followed by bilateral conjunctival injection. Anterior uveitis has been described, and ophthalmic examination may help early diagnosis.[2]

Then follow the characteristic features of the illness: reddening of the oropharyngeal mucosa and of the lips with fissuring; strawberry tongue; and erythema, swelling, and induration of the hands and feet. These last changes are due to a vasculitis—which in one case was so severe that a prostaglandin infusion was given to save the circulation of the patient's hands.[3] The diagnosis really becomes clear when, about two weeks after the onset, the skin peels over the fingers and toes and sometimes the palms and soles as well. The rash of Kawasaki syndrome usually occurs within five days of the fever and is variable—usually a morbilliform, maculopapular rash over the trunk and limbs with an accentuation in the perineum. These signs are each observed in over 90% of patients with typical Kawasaki syndrome, whereas the final diagnostic criterion—cervical lymphadenopathy—is present in only half to three quarters of patients. Strict case definition requires the presence of at least five of the main six criteria or of four plus aneurysms of the coronary arteries. With the help of echocardiography, however, Kawasaki syndrome is being diagnosed increasingly often in patients with three or fewer of the major signs.[4] Nevertheless, the syndrome must not be confused with the acute collagen diseases, the toxic shock syndrome, or even measles. Hodgkin's disease and bacterial endocarditis have also been reported to mimic Kawasaki syndrome.[5] Hydrops of the gall bladder is an unusual presentation, usually occurring in older children.[6]

The major complication of Kawasaki syndrome is its cardiac effects. These include aortic or mitral incompetence, myocarditis, and pericarditis with effusion.[7] All patients suspected of having the syndrome should be reviewed by a paediatric cardiologist and undergo echocardiography to detect the main problem—coronary artery aneurysms, of which the incidence in untreated cases is between 15% and 20%. Two thirds of these occur in the left coronary artery, mainly proximally.[8] Stenotic lesions occur adjacent to the aneurysm, leading to myocardial infarction. Infarction is most likely to occur within the first year of the illness, though in one series a quarter of the total infarcts occurred after 12 months.[9] And there has been a report of a fit athlete dying suddenly during exercise in whom there was good retrospective evidence of Kawasaki syndrome.[10]

The results of routine investigations may suggest the diagnosis but are not specific. A mild to moderate normochromic normocytic anaemia and polymorph leucocytosis are usual. The platelet count is almost always high by the second week of the illness, as is the sedimentation rate, which may exceed 100 mm in the first hour. Most acute phase reactants will have raised concentrations—that is, interleukin 1,[11] interleukin 6,[12] C reactive protein,[12] and tumour necrosis factor alpha.[13] Immune complexes have been shown in the serum of affected patients.[14] The $T8^+$ suppressor cell count is decreased and the $T4^+$ helper cell count increased, producing an increased titre of circulating IgG and IgM. Clearly, an inflammatory process has been initiated, and the best explanation is that raised production of cytokines induces new endothelial cell antigens and that antibodies to these antigens are generated with consequential damage to the coronary arteries.[11]

The missing link is the agent that starts off this chain of events. Most probably this is infective: Kawasaki syndrome is a disease mainly of young children and has similar clinical features to other infections. Some evidence for a retroviral aetiology came from a study showing production of reverse transcriptase by mononuclear cells from affected patients,[15] but a more recent study using a different technique did not support that theory.[16] There have been no other consistent microbiological findings.

The more severe the symptoms at initial presentation the more likely are coronary artery abnormalities—for example, a high sedimentation rate, a persistent fever, a high white cell count, and the presence of anaemia.[17] Children under the age of 1 year and boys may also be at more risk.

To date, steroids alone or in combination with other anti-inflammatory drugs are of no proved benefit in either the

acute or the chronic stages of Kawasaki syndrome. After early Japanese studies had suggested benefit from gammaglobulin[18] a multicentre study in the United States compared treatment of a group of children with intravenous gammaglobulin plus aspirin with treatment with aspirin alone.[19] Two weeks after enrolment 23% of the children treated with aspirin alone had evidence of coronary artery abnormalities on ultrasonography compared with 8% in the group receiving gammaglobulin. This and other studies confirmed that gammaglobulin has a definite protective effect on the coronary arteries. The consensus view is that a daily infusion of gammaglobulin should be given in a dose of 400 mg/kg a day.[20] The presumption is that its beneficial effect is achieved by an immunological blockade on endothelial cell surfaces against antibodies induced by cytokine. The optimum dosage and duration of treatment with aspirin have not been definitively evaluated, but the usual practice is to use an anti-inflammatory regimen until the fever has settled and then to convert to an antithrombotic regimen. Aspirin is stopped when the sedimentation rate has returned to normal, but it should be continued indefinitely in patients with persistent coronary artery aneurysms. The prognosis for resolution of aneurysms is good unless the aneurysm is "giant"—that is the size is more than four times that of the vessel wall.[21] Patients with giant aneurysms are at greatest risk of myocardial infarction leading to late death.

Although Kawasaki syndrome is an important public health problem in Japan, it is uncommon in those Western countries where regular or ad hoc surveys have been undertaken. In the British Isles surveillance of the syndrome has been conducted jointly by the British Paediatric Association and the Public Health Laboratory Service Communicable Disease Surveillance Centre since 1983. The transfer to reporting through the British Paediatric Surveillance Unit in mid-1986[22] caused a threefold increase in case ascertainment,[23] but the annual total for 1987 was still only 82 cases. In 1988 this increased to 112 (1·5 per 100 000 children under 5 years), and the provisional total for 1989 was 106 cases. The incidence in Britain in 1988 was very similar to the annual average in the United States in 1976-85 of 1·1 per 100 000 children under 5 years,[24] but the figure in Japan in 1984 (a non-epidemic year) was 85 per 100 000.[4] In other respects, the clinical and epidemiological features of Kawasaki syndrome in Britain are similar to those in Japan, including an excess incidence in oriental compared with white children. Mortality in Britain, however, at 2% is similar to that in Japan in the 1960s—whereas it was 0·1% in that country in 1986.[4]

Improved outcome is related to early diagnosis, prompt referral for expert cardiac assessment, and immediate treatment. The message for paediatricians in Britain is clear.

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Adolescent sexuality

Better, more accessible sex education is needed

When Johann Sebastian Bach was alive the voices of young boys dropped at a mean age of 17·5; they now drop at 13·5.[1] Secondary characteristics in boys, including voice drop, occur late in puberty so fertility develops even earlier—at a mean age of 12·5.[2] Likewise, girls now experience their first menses at 12·5 with ovulation occurring two years later. They thus have a potential for fertility two years earlier than girls in 1900,[3] but in neither girls nor boys is the capacity for reasoning, anticipation, and planning fully developed until the age of about 14 or 15.[4] Thus sexual maturity is occurring earlier than in past generations while the capacity for predicting the consequences of sexual activity is not.

The results of adolescent sexual activity are seen in the figures for births and abortions in teenage girls and increased rates of positive cervical smear tests, pelvic inflammatory disease, and other sexually transmitted diseases. In 1969 there were 6·8 births per 1000 among 16 year olds in Britain, but in 1986 the rate had risen to 8·7, a total of 9194 live births.[5] In 1988 some 3568 legal abortions were performed among under 16 year olds and 37 928 among 16-19 year olds resident in England and Wales.[6] In 1985, 3908 positive cervical smear tests were recorded among women aged under 25, compared with 1149 in 1975.[7,8]

Undoubtedly, the environment in which the young grow up has also had an influence. The media portray the romantic, exciting aspects of sex, while cohabitation and the high rate of divorce among adults are doubtful models of sexual behaviour for the young. A Gallup poll published in September 1989