Future CARDIOLOGY

Kawasaki Disease – Coronary artery aneurysms, from Childhood to Adulthood

Journal:	*Future Cardiology*
Manuscript ID	FCA-2017-0039
Manuscript Type:	Review
Keywords:	Kawasaki Disease, Coronary artery, Aneurysm

Kawasaki Disease- coronary artery aneurysms

Abstract

Kawasaki disease (KD) is an acute, systemic vasculitis of childhood and confers a 25% risk of developing coronary artery aneurysms (CAA). Its aetiology is unknown, but the incidence is increasing rapidly with linked gene polymorphisms having been identified. A constellation of symptoms, epidemics and seasonality all implicate an unidentified infective or environmental cause. Intravenous immunoglobulin therapy (IVIG), aspirin and steroids all form the mainstay of acute treatment and reduces the incidence of CAA if given before 7 days. However, in some, these lesions persist and require ongoing management during follow up during childhood and into adult life. Evidence for further investigations in order to minimise complications is presented in order to minimise the myofibroblast proliferation and stenosis in the long term.

Keywords

Kawasaki disease, vasculitis, coronary artery, aneurysms.

Kawasaki Disease- coronary artery aneurysms

Background

Kawasaki disease (KD) is an acute, systemic vasculitis of medium-sized, primarily muscular arteries that typically affects children and is generally self-limiting in nature(1). The incidence of KD highest in children under five years, 85% of all diagnoses are made in this demographic, but can affect any age (2). It affects boys more than girls, at a ratio of approximately 1.6:1 (3). The major complication is the development of coronary artery aneurysms CAA; a potentially life-threatening condition. Consequently, there is a higher risk of myocardial infarction, aneurysm rupture, coronary artery thrombus formation and sudden cardiac death.

The diagnostic criteria of complete KD are the presence of a fever lasting five days or more and at least four of the following five criteria:

- bilateral, painless, non-exudative conjunctivitis
- cervical lymphadenopathy; generally larger than 1.5 cm and commonly unilateral
- polymorphous exanthema
- changes in lip or oral mucosa: commonly present as red, cracked lips; 'strawberry tongue' which is seen as glossitis with hyperplastic fungiform papillae or generalised diffuse erythema or the oropharynx
- changes of the extremities, particularly erythema and oedema of the palms and soles of the feet; this can progress later to desquamation of the skin

Incomplete KD may be seen with only 3 of the criteria in addition to fever; detection of coronary artery dilatation or aneurysm on echocardiography requires only a fever and two of the criteria are to make a diagnosis of atypical Kawasaki disease.

In developed countries, Kawasaki disease has overtaken rheumatic fever as the leading cause of acquired heart disease in children (4). Rates of Kawasaki disease have steadily increased (5). In addition, while there is a prevalence of Kawasaki disease in every country, Japan has the highest incidence of this condition and it is still rising (6, 7).

The signs and symptoms of this condition develop over approximately 10 days and, in most cases, seemingly resolve spontaneously. However, this condition causes coronary artery aneurysms in up to 25% of children if left untreated: this is a statistic taken from the era of pre-intravenous immunoglobulin therapy, which is the mainstay treatment of Kawasaki disease today (8). Current data has shown a regression of coronary artery aneurysms in up to 75% of cases treated with IVIG(9), with approximately 3–6% of patients developing coronary artery aneurysms despite treatment (10, 11). 1% of patients develop giant coronary artery aneurysms, which carry the worst clinical prognosis.

There is also a subset of KD patients who fail to respond to IVIG; arguably demonstrating a more aggressive disease progression. The Kobayashi score uses laboratory findings and is routinely used in Japan to predict those with IVIG resistance, thus ensuring that second-line treatment is delivered promptly. However, this score did not predict response reliably in the US or the UK. Genetic variations between populations may lead to different laboratory results and therefore calculations may be unable to accurately predict IVIG resistance.

As a mechanism for the disease process remains unknown, no laboratory finding is pathognomonic for Kawasaki disease. Identification of KD is therefore dependent on clinical acumen alone. The constellation of symptoms is non-specific and is seen in other viral illnesses, which could delay prompt recognition and administration of treatment. Effective steps towards prevention are not feasible either and treatment options for the cardiac complications include invasive procedures such as angioplasties, stent placement and coronary-bypass surgeries (12). These reasons outline why Kawasaki disease is a paediatric research priority.

Aetiology

The aetiology of Kawasaki disease is poorly understood and several different theories have been proposed. Current evidence suggests the interaction of an unknown infective cause(s) (13) and a genetic predisposition are

needed to develop KD. To what degree these factors influence KD, and if one is stronger than the other, has not been formally elucidated.

It is, however, possible to argue that genetic factors have an important role in KD(14). Such genome wide association studies have suggested that the polymorphism of the IgG receptor may have a part to play in the susceptibility of children to KD and to the coronary artery aneurysms(15). The rates of Kawasaki disease are significantly higher in East Asian populations: particularly Japan, which has the highest incidence of Kawasaki disease in the world, at 264 per 100,000 children under 5 years (16). This is followed by Korea and Taiwan, where rates are 134 and 66 respectively; the higher rates in these East Asian countries suggests some genetic or environmental link. It could be argued that Kawasaki disease-associated pathogens (as yet undetermined) show a degree of endemicity, or that the lifestyle followed in these three countries exposes children to the pathogens, rather than any genetic bias conferring increased susceptibility. However, population studies in the US show otherwise. The Japanese-American population that resides in Hawaii, USA has an incidence of 210 per 100,000, whereas the rate in Caucasian American children living in the same state is 13/100,000 (17). The incidence in the Japanese-American population is approximately sixteen times greater than the Caucasian population in the same environment, which could imply that the development of Kawasaki disease is dependent on genetic factors and pathogen exposure (18).

Epidemiologically, the pattern of incidence suggests an infective cause. There have been three major nationwide epidemics of Kawasaki disease in Japan, all demonstrating origination in a specific area and countrywide spread over a 3-month period; similar to an epidemic (19). The acute, self-limiting nature of KD is another hallmark of viral disease. Since the identification of Kawasaki disease, a multitude of different pathogens have been investigated; these range from the bacterial (*Staphylococcus aureus*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*), to viral (herpesvirus, adenovirus and the Epstein-Barr virus) (20). 10% of patients with complete Kawasaki disease have been shown to have low-level viral titres of human adenovirus present. The authors concluded that this presented some link between infection with human adenovirus and the onset of Kawasaki disease(21) but this has not yet been upheld as a definitive cause.

However, it is important to note that titres of human adenovirus can persist years after the onset of the initial infection (22), and that this this virus is particularly common in children: i.e. the 10% with detectable titres may have had the infection before, leading to the detectable viral load count. In addition, this study remarked that the sensitivity of their PCR quantification was high, but did not offer any way in which they could draw a discrepancy between viral load due to current infection or previous, and therefore unrelated, infection. Indeed, many papers have hypothesised different infective triggers; herpesvirus (20) is another example. The constellation of symptoms commonly seen in Kawasaki disease (fever, rash, irritability) are also seen in infection with adenoviruses and herpes viruses. Similar haematological abnormalities have also been observed, such as neutrophilia and high erythrocyte sedimentation rates (23). However, unlike the other two viruses mentioned, there is no evidence of human-to-human transmission in Kawasaki disease. Although this may appear to contradict with the earlier assertion of nationwide epidemics in Japan as these three events were comparable to viral outbreaks in their spread, epicentre, and seasonal timing, there was no evidence of human-to-human transmission found.

Peaks in occurrence appear to be dictated by the seasons, similar to what is seen in the pattern of viral infection (24). However, these peaks have a different seasonality across the world: while Japan, mainland US, Canada and the UK have all shown peaks during the winter months (25, 26) (27), in Hawaii however there was no seasonality at all, whereas China had its lowest incidence during the winter, and highest in the spring.

Peak incidence is in children between 18 and 24 months of age, with diagnoses of Kawasaki disease being made in children less than 3 months old being uncommon. This suggests that a child may have some protection from developing this disease until a certain age, implicating a role for transplacental antibodies. These antibodies play a powerful role in fighting bacterial infections, as demonstrated by children with congenital agammaglobuliunaemia (28) who commonly only begin to present with bacterial infections at 6 to 9 months (29); the onset of these bacterial infections do not generally coincide with the cessation of breast-feeding, implying that it is the antibodies transferred across the placental barrier that are responsible for this protective effect and not those found in the mother's breast milk. In addition, the effects of immunity conferred in utero tend to diminish

within the first 3 months of life; further suggesting the role of transplacental antibodies. This pattern further suggests an infective cause being a trigger in developing Kawasaki disease.

By contrast, the rarity of Kawasaki disease after 5 years of age (30) implies that a matured immune system may be more adept at mounting an appropriate immune response: again, suggesting an infective cause. In addition, the greater incidence in boys supports this hypothesis as many infectious disease present more commonly in males than females (31). Furthermore, recurrence rates are low (at 3-4%), once again implying that the body is able to mount an immune response which prevents future cases (3).

Genetics

There is a greater risk of developing Kawasaki disease if there is an affected sibling or parent, implying a genetic role in the development of this disease (32). However, it is also important to note potential limitations of such data. (32). In this study, the number of patients affected with Kawasaki disease increased. The number of parents that had been diagnosed with KD in their childhood also increased. This trend displayed evidence of a genetic link between developing this condition. However, it is important to note that this study was carried out over a period of ten years from 1999 to 2008 and the increased proportion of affected patients reported every year may be due to an increased awareness of the condition amongst medical professionals, and therefore a greater rate of diagnosis, rather than an actual greater rate of prevalence.

In an attempt to understand the pathophysiology of Kawasaki disease, large genome studies have been conducted in populations where prevalence is high. Certain common single nucleotide polymorphisms have been observed in specific genes in individuals affected by KD. It is possible that these confer some level of genetic susceptibility in developing this condition. A functional polymorphism was identified that exceeded the formal threshold for genome-wide significance in the IgG receptor gene (*FCGR2A*) (15). Functional polymorphisms of this IgG receptor gene influence the phenotype of the individual by stratifying their responses to IgG as 'strong' or 'weak.' The particular single nucleotide polymorphism (SNP) that was identified had been shown to confer an increased risk of developing ulcerative colitis (33) in a Japanese population. This same SNP was shown to

confer a decreased risk in developing systemic lupus erythematosus (34) in a European population. The involvement of this SNP in two autoimmune conditions suggests a dysfunctional immune response being fundamental in the development of Kawasaki disease in individuals. The role of an IgG-mediated immune response in the pathogenesis is also supported by IVIG being a mainstay of treatment, which will be discussed later in further detail.

Genomic studies showed three SNPs in a sodium-calcium transporter gene being validated for a significantly associated pathway (35). In KD patients, the carriers of homozygous 'risk' alleles of the *SLC8A1* gene have been shown to be at a greater risk of developing coronary artery aneurysms; the protein (NCX1) encoded was expressed in the inflammatory cells of the aneurysm wall. Altered calcium signalling appears to increase the risk of cardiac complications, implying a more aggressive course of disease. In addition, polymorphisms of *IPTKC*, a negative regulator of T-cell activations, have been associated with KD patients, and especially in those with coronary artery lesions (36). This is a Ca^{2+}/NFAT signalling pathway. Impaired calcium signalling suggests a more severe disease progression, as the functional polymorphism of *IPTKC* was strongly associated with patients who developed cardiac sequelae.

Calcineurin inhibitors have been shown to treat KD in IVIG-resistant patients (37): this suggests that impaired calcium signalling confers an increased risk of developing complications and its role should be further researched.

Up to 20% of KD patients fail to defervesce within 36 hours of IVIG therapy. It implies a more aggressive course of disease and longer period spent in acute inflammation, resulting in a greater likelihood of developing coronary artery aneurysm. The identification of these patients earlier could therefore improve clinical outcome, and so the Kobayashi score (38) was developed to predict patient response. It uses 7 laboratory and clinical findings to predict the unresponsiveness in KD patients to IVIG therapy. It has been used with positive results in the Japanese population; however, when used in the US and UK (39, 40), it failed to reliably predict IVIG responsiveness. Despite removal of patients with incomplete Kawasaki disease in the model, the Kobayashi

score still failed to reliably predict IVIG response in a UK population. This suggests that the pattern of disease may differ according to ethnicity.

Pathophysiology

Although a specific infectious trigger has not yet been noted, the pathophysiology of this condition has been closely studied. Vasculitis has been observed in the cardiovascular, gastrointestinal, respiratory, integumentary, dermatological, urinary and nervous system(41); however, the most clinically significant is the vasculitis of coronary arteries, leading to coronary artery aneurysms. This is because it has resulted in myocardial infarction, ischaemic heart disease and sudden cardiac death in patients (42).

The progression of acute Kawasaki disease can be split into separate stages according to the number of days from the initial onset. Stage I (0-9 days after onset) is characterised by inflammation of the adventitia (also known as perivasculitis); stage II (12-25 days) often shows vasculitis of medium-sized, muscular arteries; stage III (28-31 days) is where pan-vasculitis is most prominent, and where arterial aneurysm development is commonly observed (3).

Analysis of tissue, blood and arterial walls has provided insight into the mechanism of disease progression. Tissue infiltration of lymphocytes, macrophages, plasma cells and large mononuclear cells demonstrates that there is an acute inflammatory response (43) and despite elevated levels of neutrophils in the blood (44) the lack of neutrophil invasion shows that these cells are not the chief mediator. While physiological levels of CD4 lymphocytes outnumber CD8, there was a 4–5 fold increase reported in CD8 lymphocytes in the arterial wall as compared to CD4. This is consistent with findings that are seen in the presence of an intracellular pathogen (45), thus providing evidence for a ubiquitous agent involved in the pathogenesis of Kawasaki disease. There was no significant change reported in the number of circulating CD8 lymphocytes in the acute stage, which indicates that the disease process actively recruits these lymphocytes into the arteries.

An elevated IgA plasma cell proliferation (46) – greater than IgG and IgM – is seen in the arterial wall: this is unusual as IgA domination is seen in mucosal or lymphoid structures rather than vascular structures. This appears to suggest a stimulation of the immune system, likely at a mucosal site, which led to a systemic conversion of B lymphocytes to IgA secreting plasma cells.

A marked rise of IgA plasma cells appeared in the upper respiratory tract, pancreas, coronary arteries and kidneys of patients who had died of acute Kawasaki disease (47). This same study showed increased IgA plasma cell infiltration was also seen in children who had died of an acute respiratory tract infection; the similarity of these findings suggests the involvement of an infectious agent in Kawasaki disease. Studies have shown that the method by which IgA expansion is controlled is oligoclonal (46, 48), which suggests an infective cause. All synthetic antibodies that bound to acute KD tissues (48) detected antigen in all cytoplasmic inclusion bodies in acute KD affected ciliated bronchial epithelium. Inclusion bodies are pivotal in the pathophysiology and this finding is consistent with KD being caused by a microbial pathogen.

However, it is important to note that all of these studies used samples collected from deceased patients whose death was attributed to Kawasaki disease complications. Whilst all these data show similar results, which increases confidence in the conclusions obtained, it is unclear to what extent these conclusions can be extrapolated to patients that are a) alive, but with coronary artery lesions, b) alive, and with no coronary artery lesions and c) alive, with regressed coronary artery lesions. Due to the relatively recent history of Kawasaki disease, there has been little research into the coronary artery status of those who have died of a non-Kawasaki disease related cause, and therefore this still remains unknown. It will be interesting to study those particular patients; however, cataloguing and recruiting these patients will pose logistical challenges.

Treatment

Current guidelines outlining treatment of acute KD include intravenous immunoglobulin therapy and high-dose aspirin. Although aetiology and a definitive summary of the pathophysiology remain to be elucidated, numerous prospective, controlled trials have shown the efficacy of this regime (11, 49, 50).

Intravenous immunoglobulin therapy in the treatment of KD has reduced rates of coronary artery aneurysm formation from 25% to 3-6% in affected patients; however, around 20% of patients show IVIG-resistance, which is qualified as a fever persisting 36 hours after IVIG was administered or a recrudescent fever (51, 52). C-reactive protein levels persisting at >3 mg/L after 36 hours can also be a marker of IVIG-resistant disease.

2g/kg as a single dose is constituted as optimum therapy, and has shown greater efficacy than divided low-doses (400 mg/kg/day) administered over several days. Meta-analysis concluded that both caused defervescence, but the higher, single dose provided better protection against the formation of coronary artery lesions (49, 50). The improvement of symptoms with IVIG and the association between a functional polymorphism in an IgG receptor gene demonstrate that IgG has some role in the pathophysiology. In addition, even in IVIG-resistant patients, the rash, swelling and erythema also associated with KD often improve (53). Reduced cytokine levels, decreased number of circulating T cells, macrophages and neutrophils, and increased number of natural killer cells have all been noted after IVIG treatment; however, how these changes are induced have not been described (53).

The use of aspirin remains slightly more controversial: the use of salicylates is strongly contraindicated in most paediatric cases due to the risk of Reye's syndrome (54, 55) and KD is one of the few conditions in childhood which is treated with aspirin. Although the duration of the characteristic fever appeared to be reduced by high-dose aspirin therapy (56), there was no change noted in response to IVIG, resolution of inflammation, or incidence of coronary artery lesion (57, 58). After the febrile period, aspirin therapy is reduced from 30-50 mg/kg/day to a low dose of 5mg/kg/day for 6 weeks and reassessed, depending on the presence or absence of any coronary artery abnormalities.

IVIG-resistant therapy encompasses a second dose of IVIG at 2 g/kg, corticosteroids or both administered. Early analyses showed a positive association between corticosteroid therapy and increased coronary artery abnormalities. However, this finding has now been contributed to confounding, as in these retrospective studies the sicker patients were more likely to be given corticosteroids, and therefore more likely to develop lesions (59). The main indications for using adjunct corticosteroid therapy are:

1. Patients who are IVIG resistant, with a persisting or recrudescent fever after 36 hours from IVIG treatment onset
2. Patients with features of very severe disease. In Japan, the Kobayashi score is used; however it has proven to be less accurate in other countries. Therefore, persistently high markers of cell injury and inflammation, such as raised CRP levels, liver dysfunction and anaemia are used
3. Patients with pre-existing coronary artery and/or peripheral aneurysms

Serum tumour necrosis factor-α (TNF-α) is elevated in KD patients, and in particular those who develop coronary artery aneurysms. Thus, anti TNF-α therapies such as infliximab are being investigated as alternative therapies; especially in patients unresponsive to IVIG. A 3-year-old patient, unresponsive to IVIG and methylprednisolone, defervesced in response to one dose of anti TNF-α (60). A retrospective study compared defervescence and length of hospital stay in IVIG-resistant patients treated with a second dose of IVIG and those treated with one dose of infliximab (61). Infliximab resulted in faster fever resolution and a shorter hospital stay. A recent randomised controlled trial (62) showed the same two results, with a greater response to infliximab (90.9%) than second-dose IVIG (65.6%). The size and power of these studies is limited, but demonstrates anti TNF-α as a potential therapeutic option.

Calcineurin inhibitors (such as cyclosporin A) have been used in the treatment of refractory KD (63, 64); however, they should be used with caution as they can be toxic to the endothelium (65). The decision to prescribe these medications must therefore be made on a case-by-case basis.

Coronary Artery Aneurysms

Current studies suggest that 20- 24% of children, even if treated, will suffer from coronary artery aneurysms(27). The definition of an aneurysm can now be recorded as an indexed (z score) size of the coronary artery, based on the body surface area of the child (66). Coronary artery dilation is defined as z score +2 to 2.5, small aneurysms are with z score ≥ 2.5 but less than 5, moderate size CAA is seen in those with z score ≥ 5 but less than 10 and those who have giant CAA have a z score ≥10. We now know that it takes several years for many of these to

resolve, with reducing likelihood of complete resolution correlating with increasing size and complexity of coronary artery involvement (67). Recent AHA guidance details the long term outcome based on a severity scoring system, which may be opinion for the USA, but which has little evidence base there and uncertain relevance to the European or Asian population (68). We know that those children with giant CAA are those most likely to suffer from Major Adverse Coronary Events in the longer term, necessitating antiplatelet and anti-coagulant medication and multiple and regular repeat imaging.

For those children with just coronary dilation, or with no involvement at all, at the current time there is no evidence from the western world that these children are at risk. There is evidence from a variety of studies that the coronary arteries in this group may be abnormal in the long term in terms of coronary flow reserve (69) and endothelial-dependent brachial artery reactivity (70) but there is dispute about the presence or absence of coronary artery dysfunction (71) (72). No child, as far as we are aware, has been seen in the UK population, without having had CAA, who has then grown up to demonstrate premature coronary artery disease. Hence the recommendation is that these children can stop their aspirin and can be discharged from follow-up. The recent AHA guidelines concur with this, but it is clear that until we have five decades of follow-up in the UK population, we cannot be certain about the long-term outcome in this group. Since this group is 76% of the current UK incident population of children with KD (27), it will be important to revisit this in future years when we have longer term follow up.

There is some evidence that those children who had small or medium CAA, in whom these resolved, should be followed up in the longer term (68, 73, 74). Our group have shown that they have circulating endothelial cells (75). This is in line with the American Heart Association Guidelines (76) (68) that suggest that there may be ongoing risk in these patients and advise ongoing imaging and dynamic myocardial and coronary flow studies. Long term outcome after even moderate aneurysms suggests that there may be coronary artery stenosis, only recognised by thallium scanning and not by stress testing (77). Hence there is recommendation that these children can either stop or continue their aspirin and could have long-term follow-up. In the UK, there is no evidence, yet, that these children are at risk of coronary events

The evidence that those children with persistent CAA may develop complications is now overwhelming. The risk of Major Adverse Coronary Event (MACE) increases with size, complexity and location of CAA (9) (68). In those with persisting CAA >4mm, there is a high risk of coronary artery endothelial thickening which might lead to complications of ischaemia, especially on exercise (78). In those with giant CAA (>8mm) or z>10, long-term outcome is poor, with 40% having MACE with myocardial infarction often leading to death.

Kawasaki disease in Adulthood

There has been no formal collection of data regarding the number of adult patients with a previous history of Kawasaki disease in the US or the UK. Estimations are that approximately 24,000 young adults (≥18 years) in the US (42), with 8,400 of these patients classified at an AHA Risk level II or higher. Estimates for the UK have not yet been published but it appears that about 4% of young adults presenting with myocardial infarction have coronary angiograms indicative of previous KD (79). It is accepted that those patients who presented with giant aneurysms should undergo regular and routine follow up through adulthood. However, it is unclear what level of follow up treatment should be given to those with regressed aneurysms and those who presented with no coronary artery abnormalities. Prompt treatment with IVIG means that the majority of patients (76%) do not have these coronary artery lesions in the acute stage of KD.

Due to the growing rate of diagnosis, cardiologists will be dealing with adult patients who have long-term sequelae from this condition. Although coronary artery aneurysms are the main complication, other cardiovascular abnormalities should also be investigated: myocarditis and valvulitis (80) has also been observed in KD patients. Myocardial fibrosis and aortic and mitral regurgitation can follow and lead to death.

Studies in Japan showed that the standard mortality ratio (SMR) for young males with previous KD and cardiac sequelae was significantly higher than females with KD and age-matched population (81). This is one of few studies conducted that has investigated mortality rates in people with KD with no cardiac sequelae, and may indicate that patients with KD and no sequelae do not need routine follow-up. It suggests that paediatricians can

stop seeing these patients during childhood, as this demographic does not have a significantly greater risk of mortality.

Childhood diagnosis of KD has been cited as a risk factor for accelerated coronary artery disease in adulthood (82) irrespective of lipid profile, suggesting that these patients should be followed up by cardiologists routinely. The only patients included in the test group for this study were patients with a historical KD diagnosis and cardiac sequelae: whether a KD diagnosis alone is a risk factor for accelerated atherosclerosis cannot be concluded. KD being a risk factor can be cited as a reason to follow up all patients in later life. However, as only those with coronary artery lesions were included in this study, it is not entirely possible to state that KD with no cardiac sequelae is also a risk factor.

Autopsy results of those with KD who died after the acute stage (all individuals were ≥15 years old at the time of death) showed different histological results in non-aneurysm coronary arteries(83). There was increased 'new' intimal thickening of the non-affected arteries, along with previous thickening during the arteritis phase in acute KD. Although these arteries were declared non-affected, there were still histological changes that remained during the patient's life, and can therefore not be excluded as a risk factor for atherosclerosis. The coronary arteries of a KD patient with no coronary artery lesion were compared to KD patients with the cardiac sequelae, and both showed platelet-derived growth factor (A) and inducible nitrate synthase in intimal smooth muscle cells (84). This was not seen in patients with no KD. Inflammatory markers were still present in this patient at 13 months post diagnosis, with an apparently normal coronary artery, and therefore KD with no coronary artery lesions can still pose as a risk factor for atherosclerosis. Although these are the histological findings of only one patient, and the results cannot be extrapolated to all, autopsy reports of children with no cardiac sequelae are incredibly rare. Obtaining tissue from patients to investigate this poses a challenge in itself, and in light of the data available, it is better practice to regularly follow up KD patients: even those with no history of coronary artery aneurysms.

Future perspective

There are a variety of issues yet to be solved. First of all we need a certain marker for diagnosis and a known aetiology. Then we need to have better recognition and diagnosis with more effective acute treatment to reduce the incidence of coronary artery aneurysms. This would reduce long term complications and would be best accompanied by effective therapy at reducing myofibroblastic proliferation and hence the risk of major adverse coronary events.

Executive summary

In summary, therefore, we have described the presentation, treatment and long term management strategy for children and young adults with this increasingly common disease.

Financial Disclosure

Neither author has any financial disclosures relevant to this manuscript. No commercial involvement was connected to this study at any stage. Both authors contributed to the writing.

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