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Changes in the coronary arteries during early and long-term follow-up of Kawasaki syndrome: a single centre experience

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Abstract

Background: *Kawasaki syndrome is a disease of unknown etiology manifested by fever and the so-called mucocutaneous lymph node syndrome. In some cases aneurysms of the coronary arteries may develop, which may result in myocardial infarction.*

Methods: *Four children treated for Kawasaki disease were followed up. Echocardiography was performed in the early period of the disease and during the follow-up.*

Results: *Changes in the coronary arteries were diagnosed in 3 patients in early period of the disease with one coronary aneurysm persisting in 1 patient over the entire follow-up.*

Conclusions: *Transthoracic echocardiography is usually sufficient to diagnose and monitor coronary artery changes in the course of Kawasaki disease. Despite late initiation of treatment in Kawasaki disease regression of changes in the coronaries is possible.* (Folia Cardiol. 2006; 13: 584–589)

Key words: Kawasaki disease, coronary artery aneurysms, ultrasound

Introduction

The anatomical basis for Kawasaki disease is acute systemic small-vessel vasculitis, which may also lead to changes in the coronary vessels resulting in ischaemic heart disease. The etiology of the syndrome is unknown. The increased incidence of the disease in the winter months and its cyclic recurrences, approximately every 3 years, may be suggestive of viral aetiology [1]. Genetic background cannot be ruled out either. The disease may be recurrent with a subsequent relapse occurring several years later [2].

Although its prevalence peaks usually between the age of 2 months and 5 years, Kawasaki disease may occasionally develop in patients up to 34 years of age. The typical clinical manifestations of Kawasaki disease include: fever, polymorphous rash, mucositis, conjunctivitis, lymphadenitis and the characteristic skin lesions involving distal parts of the extremities (in the order of appearance): pallor, erythema and oedema, followed by desquamation of the fingers and toes [3]. The average duration of fever is 11 days, although it may persist for up to

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3-4 weeks. The rash usually appears within 5 days of the onset of disease and the conjunctivitis develops soon after the onset of fever. Desquamation of the fingertips and toes develops later, within 2–3 weeks.

Aneurysms may develop in peripheral vessels. Cardiac complications may include pericarditis, myocarditis and endocarditis, involvement of the conduction system and coronary arteritis. The inflammation involving the coronary arteries may lead to their narrowing or the formation of aneurysms, which may result in myocardial ischaemia and myocardial infarction, which is the main cause of death. Coronary aneurysms develop within 10 days of the onset of the disease and beeing observed in 90% of cases with poor outcome [4].

The diagnosis of Kawasaki disease is established clinically with a minimum of 4 typical manifestations being required for the diagnosis [3, 5]. The differential diagnosis should include diseases with similar clinical course, such as measles, scarlet fever, roseola, allergic drug reactions and juvenile rheumatoid arthritis [6].

Laboratory tests are not characteristic (elevated WBC counts with a left shift, increased ESR, possibly mild anaemia) except for platelet count elevation above 500 000/μl which appears in the second or third week. If involvement of the coronary vessels, myocardium or the pericardium is suspected, ECG and echocardiographic monitoring is warranted. In justified cases coronary arteriography is required.

Pharmacotherapy in the initial phase of the disease involves the use of immunoglobulin at a single dose of 1–2 g/kg (administered within the first 10 days of the onset of symptoms), followed by salicylates at an anti-inflammatory dose of 80–100 mg/kg until 14 days of onset or until 2–3 days after the resolution of fever. If no improvement is seen, corticosteroids are recommended. The currently suggested treatment regimen involves intravenous pulses of methylprednisolone at a dose of 30 mg/kg once daily for 1–3 days. Such treatment may limit the formation of coronary artery aneurysms [5]. In the later phase of the disease, i.e. after 14 days of onset, salicylates at the anti-aggregation dose (3–5 mg/kg) are intended to prevent thrombotic complications in the coronary arteries. If large (more than 6 mm in diameter) or multiple aneurysms are detected, treatment with acenocoumarol (while maintaining INR within the range of 2.0–2.5) or standard-dose heparin may be indicated [5]. In spite of the treatment, the consequences of the inflammation in the coronary vessels may be very serious.

The aim of this case series report is to present the course and outcome of late follow-up of four patients managed for Kawasaki disease in whom the diagnosis was established on the basis of clinical and laboratory findings and the complications were diagnosed by echocardiography and further confirmed by coronary arteriography.

Methods

Four patients (2 boys and 2 girls) with a diagnosis of Kawasaki syndrome were followed up. The age at diagnosis ranged from 9 months to 3 years and the duration of follow-up was 1 to 10 years. The patients underwent echocardiography in the early period of the disease and in the late follow-up period (Sonos 2000, Sonos 4500 and Sonos 750 with 3.5/2.5 MHz and 7.5/5.5 MHz heads). The initial segments of the coronary vessels were imaged in the parasternal short axis view. In addition, three children underwent coronary arteriography (2 in the early and late follow-up period, and 1 in the early follow-up period only).

Results

Case 1

A 9-month-old boy (PT) developed an episode of high fever of 8 days' duration refractory to anti-inflammatory agents 6 weeks prior to presentation to our centre. The fever was accompanied by conjunctivitis, cervical lymphadenopathy and upper respiratory tract infection. The child was hospitalised at the Paediatric Intensive Care Unit, where on several occasions he developed episodes of sudden deterioration of his general condition starting with anxiety attacks. During the episodes supraventricular tachycardias accompanied by impaired consciousness were observed. The child was then transferred to our centre.

The ECG performed at our clinic revealed changes suggestive of an ischaemic episode in the past involving the anterior wall of the myocardium.

The echocardiography performed 6 weeks of the onset of the disease revealed a widening of the left coronary artery (LCA), normal myocardial contractility an no other abnormal findings (Fig. 1). Coronary arteriography was performed, which confirmed the presence of an LCA aneurysm measuring 4 mm × 15 mm. The arteriography also revealed narrowing of the iliac arteries and their branches and two hourglass-like narrowings of the aorta — one below the coeliac trunk and the other below the renal arterial ostia.

During the in-hospital observation, when the child was monitored by ECG, he developed two

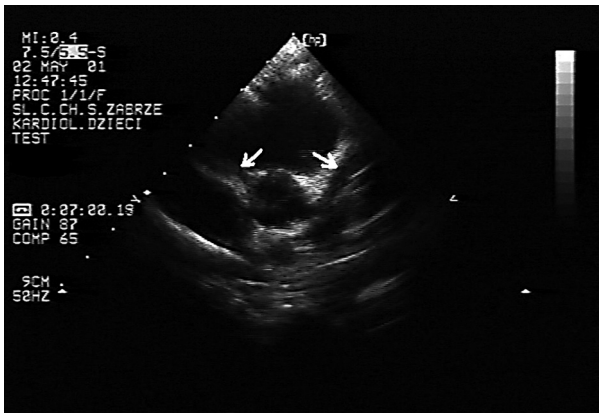

Figure 1. A 9-month-old patient with the initial diagnosis of Kawasaki syndrome, 6 weeks after the primary diagnosis. Echocardiography, parasternal view, short axis. The aortic valve and dilated initial segments of left coronary artery and right coronary artery.

episodes of flaccidity followed by generalised convulsions and impaired consciousness, which resolved several minutes later. During the episodes ECG revealed supraventricular tachycardia of up to 180 bpm. The episodes of tachycardia were managed with an infusion of Cordarone at a dose of 5 mg/kg. Taking into account the possibility of vascular changes in the central nervous system, an MRI scan of the central nervous system was performed. No such changes were, however, revealed.

Due to the considerable time interval between the first manifestations of disease and the diagnosis, immunoglobulin treatment was not initiated. Because of the presence of a coronary artery aneurysm and the elevated D-dimer levels heparin at a dose of 50 IU/kg was given for 4 days, followed by acenocoumarol (INR 2.5–3.5). In addition, salicylates at the anti-aggregation dose (5 mg/kg) were started. Arrythmia was managed with beta-blockers: propranolol at a dose of 2 mg/kg, followed by metoprolol at a dose of 1 mg/kg subsequently reduced to 0.5 mg/kg and Cordarone (at a starting dose of 10 mg/kg, followed by 5 mg/kg). After 28 days of hospitalisation the boy was discharged home in a good general condition with a recommendation to continue the anti-aggregation treatment with salicylates at a dose of 5 mg/kg, the anticoagulant treatment with acenocoumarol (with INR monitored) and the anti-arrhythmic treatment with Cordarone at a dose of 2.5 mg/kg and metoprolol at a dose of 0.5 mg/kg. Further follow-up did not reveal the previous symptoms. Six months after the onset of the disease the boy returned to our centre for follow-up examinations. Standard ECG did not reveal any signs of myocardial ischaemia or arrhythmia. The 24-hour ambulatory ECG recordings appeared normal. Echocardiography did not reveal the previously reported coronary artery aneurysm, which was subsequently confirmed by coronary arteriography. Given no abnormal findings, especially given the regression of changes in the coronary vessels, the salicylates, anticoagulants and the beta-blocker were discontinued. Six months later (i.e. a year after the start of treatment) the child returned for another follow-up visit at the outpatient clinic. ECG and echocardiography showed no abnormalities. The next visit took place 5 years after the diagnosis. The physical examination revealed no abnormal findings in the cardiovascular system and both ECG and echocardiography were unremarkable.

Case 2

A 20-month-old girl (JK) developed a protracted fever, polymorphous rash and mucositis, for which she was admitted to her local hospital. No symptoms suggestive of myocardial ischaemia were observed during this period. Two months after the onset of symptoms the child was referred to our centre with suspected Kawasaki syndrome.

Echocardiography revealed a LCA aneurysm (7 mm in diameter and 10 mm in length). These lesions were confirmed by coronary arteriography (the length of the aneurysm was 16.5 mm and its width was 8 mm to 10 mm). No clinical, electrocardiographic or echocardiographic signs of myocardial ischaemia were noted. Salicylates at an anti-aggregation dose (5 mg/kg) were added to the treatment regimen. After two weeks of observation the child was discharged home with a recommendation to continue the anti-aggregation treatment. The follow-up coronary arteriography performed 12 months after the acute phase revealed a reduction of the diameter and length of the aneurysm to approximately 5 mm and 11 mm, respectively.

The aneurysmal LCA widening of up to 4–6 mm, confirmed by repeated echocardiographies performed at the outpatient clinic (Fig. 2), and by coronary arteriography performed 9 years after the diagnosis (Fig. 3, 4), persisted over the 10-year-long follow-up. The girl denied any symptoms and there were no new changes on ECG or echocardiography. The size and systolic function of the left ventricle were normal.

Since the diagnosis of Kawasaki syndrome the child has been on long-term treatment with acetylsalicylic acid at an anti-aggregation dose (currently 5 mg/kg).

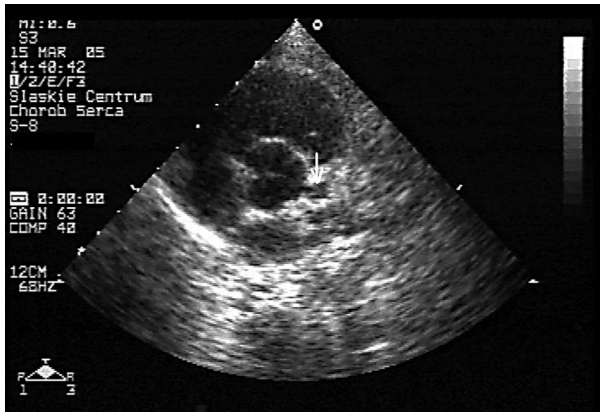

Figure 2. A 20-month-old patient with the initial diagnosis of Kawasaki syndrome, 10 years after the primary diagnosis. Echocardiography, parasternal view, short axis. The aortic valve and the initial segments of left coronary artery and right coronary artery. The arrow indicates the left main coronary artery aneurysm.

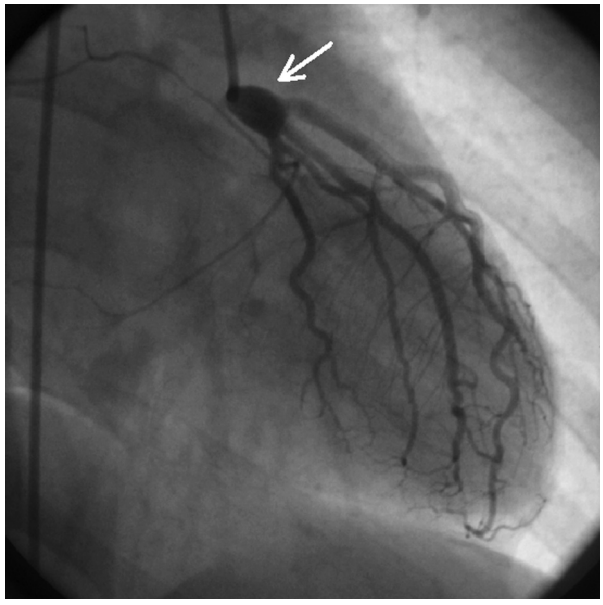

Figure 3. A 20-month-old patient with the initial diagnosis of Kawasaki syndrome, 10 years after the primary diagnosis. Coronary angiography, AP view. The arrow indicates the aneurysm of the left main coronary artery.

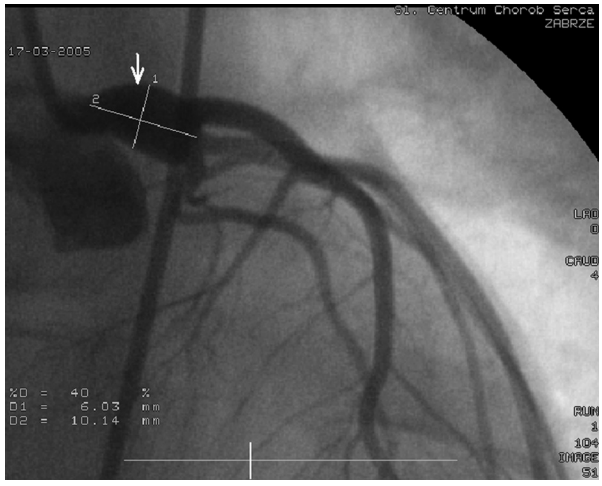

Figure 4. A 20-month-old patient with the initial diagnosis of Kawasaki syndrome, 10 years after the primary diagnosis. Coronary angiography, AP view. The arrow indicates the aneurysm of the left main coronary artery (10 mm × 4 mm).

Case 3

A 16-month-old girl (MC) presented with symptoms of pharyngitis accompanied by lymphadenopathy, a roseola-like rash, desquamation of the fingertips and toes, and protracted fever. No clinical signs of cardiac involvement were observed. After the initial outpatient treatment the child was hospitalised at a paediatric ward. Five weeks after the onset of disease the child was transferred to our centre with suspected Kawasaki disease. The echocardiography performed on admission revealed areas of cylindrical widening in the initial segments of the left and right coronary arteries (RCA) of up to 4 mm, without aneurysmal changes. No other abnormalities were found on echocardiography. ECG was unremarkable. The subsequent echocardiographies revealed a further widening of the coronary arteries of approximately 1 mm in RCA and LCA (a total diameter of 5 mm). The outlines of the vessels remained smooth.

Although 5 weeks had elapsed since the onset of the disease, a therapeutic infusion of immunoglobulin at a dose of 2 g/kg was administered. Due to the presence of elevated D-dimer levels heparin at a dose of 50 IU/kg was given for 5 days, followed by anticoagulants (INR 2.5–3.5). Salicylates at the anti-aggregation dose (5 mg/kg) were also started. Because the widening of the coronary arteries progressed, the patient was started on corticosteroids (prednisolone at a dose of 1 mg/kg for 7 days). During the hospitalisation the patient's respiratory infection exacerbated and the coronary arteriography had to be rescheduled for a later date. The girl was transferred back for further treatment. One month later she was readmitted to our centre and the haemodynamic study revealed coronary arteries of normal morphology and without postinflammatory lesions. The LCA and RCA diameters were 3.2 mm

and 3.4 mm, respectively. Similar dimensions and smooth outlines of the coronary vessels were also revealed by echocardiography. The anti-aggregation treatment with salicylates at a dose of 5 mg/kg was continued. Given an almost complete regression of the picture of the coronary artery changes, anticoagulants were discontinued after 6 weeks of use. On the 10th day of observation the girl was discharged from hospital. Over a year of outpatient follow-up since the diagnosis a normal echocardiographic picture of the coronary vessels was confirmed and the anti-aggregation treatment was discontinued.

During the follow-up outpatient visits over 3 years of observation, the child's general condition was good, no disturbing clinical manifestations were observed, the ECG tracings were normal and the echocardiographic picture did not change.

Case 4

A 3-year-old boy (KM) developed mucocutaneous lymph node syndrome and low-grade fever. He was initially managed as an outpatient with a suspected flu-like infection. Due to the lack of improvement he was admitted to the paediatric ward of his local hospital. Given the clinical picture suggestive of Kawasaki disease and considerably elevated inflammation markers, two weeks after the onset of symptoms the boy was given a single infusion of immunoglobulin at a dose of 2 g/kg and was started on acetylsalicylic acid at an anti-inflammatory dose (80 mg/kg). No signs of myocardial ischaemia were observed. The boy was transferred to our centre four weeks after the onset of symptoms.

The echocardiography performed on admission revealed coronary vessels of normal morphology and the ECG tracing was unremarkable. After 10 days of observation, the child was discharged home in good general condition. Treatment with salicylates at a dose of 50 mg/kg was continued for 1 month, when the dose was reduced to an anti-aggregation dose of 5 mg/kg. No clinical, electrocardiographic or echocardiographic abnormalities were observed during the outpatient follow-up examination performed 3 months after the diagnosis or over the subsequent 1.5 years of observation. Given the normal picture of the coronary vessels, the anti-aggregation treatment was discontinued at 3 months after the diagnosis.

Discussion

Coronary artery aneurysms in the course of Kawasaki disease are found in 15–25% of children who have not received appropriate treatment [5]. In the literature, the need for early (i.e. within the first 10 days of onset) administration of immunoglobulin and anti-inflammatory treatment to prevent the involvement of coronary vessels is emphasised [5]. In some cases this is obviously difficult due to delayed diagnosis (unclear clinical picture). Kawasaki disease may be misdiagnosed as another exanthaematous disease. Although not all patients with Kawasaki disease may present with all the four characteristic symptoms and in some cases the disease mayby oligo- or asymptomatic, the coronary vessels may still become affected (the so-called atypical Kawasaki syndrome) [5]. Even patients who have been treated with immunoglobulin at the early phase of the disease may still develop structural and functional intimal changes in the coronary vessels. Until they develop into a serious coronary artery narrowing, such changes are clinically silent and echocardiographically undetectable at the early stage of the disease [7]. In some patients, coronary artery aneurysms spontaneously regress [5]. This regression, however, occurs at the expense of abnormal remodelling and dysfunction of the coronary vessel endothelium [5, 8]. According to the current recommendations, anti-aggregation treatment with salicylates (5–10 mg/kg) is continued for 6–8 weeks in patients who, despite other manifestations of the disease, have not developed coronary artery changes or in patients who have developed a transient widening of a coronary artery (i.e. a widening which regressed within 1.5–2 months). Patients with a single coronary vessel aneurysm with a diameter of 3–6 mm require anti-aggregation treatment for as long as the aneurysm is present. Patients with giant aneurysms (exceeding 10 mm in diameter) or with complex aneurysms usually require permanent anti-aggregation treatment due to the low probability of regression of such large aneurysms. Anticoagulants are also indicated in these patients.

In none of the cases of Kawasaki syndrome presented above was it possible to establish the diagnosis within the first ten days of onset of the disease, which caused delay of initiation of appropriate treatment. In two cases, however, a decision to administer immunoglobulin infusion was made. While one of the patients showed no changes in the coronary arteries, the coronary changes observed in the other one regressed within a month. In one case, the lesions regressed spontaneously within 6 months of observation despite the lack of treatment with immunoglobulin and anti-inflammatory agents. Only in one case the coronary artery aneurysm has persisted over the 10 years of follow-up. This

patient was diagnosed relatively late, which was why only prophylactic antithrombotic treatment was initiated. Only one patient developed clinical manifestations of myocardial ischaemia, which subsequently resolved. No cases of myocardial infarction were observed (this includes the child with the coronary aneurysm persisting over the 10 years of follow-up).

In the diagnosis of coronary artery involvement, apart from cardiac ultrasound, coronary angiography is useful. It is particularly helpful in visualisation of the distal coronary segments at early stages of the disease as well as at later stages in patients in which cardiac ultrasound revealed regression of proximal coronary aneurysms. In the cases described above, the diagnosis was mainly based on echocardiography and the results of coronary arteriography were consistent with the echocardiography findings. Other coronary vessel imaging techniques are also available, such as MRI or ultrafast CT [5].

Due to its non-invasiveness, wide availability and the possibility of being frequently repeated, echocardiography still remains the mainstay of diagnosis of cardiac complications in Kawasaki disease [5, 9, 10].

Conclusions

1. Transthoracic echocardiography is usually sufficient to diagnose and monitor coronary artery changes in the course of Kawasaki disease.
2. Despite late initiation of treatment in Kawasaki disease regression of changes in the coronary vessels is possible.

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