Mid-term outcome of patients with Kawasaki disease, single-centre experience

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Background — More and more children, who suffered from Kawasaki disease in childhood, reach today adulthood. The future perspectives of these patients are not yet well defined, therefore, we wanted to determine mid-term outcome of our Kawasaki patients.

Methodology — All patients with the diagnosis of Kawasaki disease were selected from the database of paediatric and congenital cardiology of our hospital. The records were reviewed for disease characteristics and follow-up data. Descriptive statistics were performed.

Results — Thirty-five patients were included (18 boys, median age at diagnosis 1.9 years, range from 0.4 to 12.2 years). In 94% of the cases, the left coronary artery was affected, whereas in 58% the right coronary artery was involved in the disease process. In three patients the left ventricular ejection fraction worsened below 50%. One patient underwent a balloon dilatation and stenting of a coronary artery, and in another patient inotropic support was needed. Aspirin was given in all, sandoglobulin in thirty patients; in 10% of the cases corticosteroids were administered. The active disease process terminated after a median of 0.5 months, ranging from 0.1 to 2.0 months. The patient cohort was followed for a median of 4 years (range from 0.1 to 17.7 years). During this follow-up time, no reoccurrences, no significant arrhythmias, and no deaths occurred. In all patients, the left ventricular ejection fraction remained normal or normalized. However, at the latest follow-up, 43% was still treated with a low dose of aspirin.

Conclusions — The mid-term outcome of patients who suffered from Kawasaki disease during childhood is excellent. However, almost half of them were treated with oral aspirin during follow-up.

Keywords: *Kawasaki disease – vasculitis – coronary artery – coronaritis – outcome.*

Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is an acute, self-limiting vasculitis that occurs in children of all ages, but predominantly when younger than 5 years. The syndrome was described for the first time by Tomisaku Kawasaki in 1967[1].

Although fever, rash, conjunctivitis, adenopathy, and geographic clustering suggest an infectious cause, no aetiologic agent has been identified yet[2]. KD is markedly more prevalent in East Asia, and the incidence is reported to be highest in Japan and in children of Japanese ancestry (174 per 100,000 children < 5 years)[3,4]. The annual incidence of KD is lower in children in Western countries, ranging from 17 to 18 per 100,000 (USA) to 8.4 per 100,000 (England)[5,6]. Today, KD has become the most prevalent acquired heart disease in children in developed countries.

Because no specific diagnostic test is available, the diagnosis of KD is mainly based on clinical findings related to an epidemiological case definition (table 1)[1]. Involvement of a coronary artery is the most severe complication of KD, and occurs in 15-25% of all untreated children. This may lead to myocardial hypoperfusion, ischaemic heart disease, myocardial infarction, or even sudden death[4]. Cardiovascular sequels also tend to emerge later in life[7]. Today, KD is diagnosed earlier, treated better, and a high number of patients reach adulthood[8].

Because the future perspectives of these patients are not yet well defined, we decided to determine mid-term outcome by reviewing the medical records of our KD patients.

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Table 1. – *Diagnostic criteria for Kawasaki disease*

1. The presence of fever for at least 5 days
2. Four of the five criteria below:
– Polymorphous rash
– Bilateral conjunctival injection
– Changes of the mucous membranes of the upper respiratory tract: injected pharynx; injected, fissured lips; strawberry tongue
– Changes of the extremities: peripheral oedema, peripheral erythaema, periungual desquamation
– Cervical adenopathy

Methodology

Patients' selection

All patients, diagnosed with KD and in systematic follow-up at the department of paediatric or congenital cardiology, were selected from the corresponding hospital database to be included in the study. Our database contains the files of more than 30,000 patients with a congenital heart defect or patients who suffered from acquired heart disease in childhood. There were no exclusion criteria and the institutional ethics committee approved the study protocol.

Review process

The medical records of the selected patients were reviewed. Patients' demographics and disease characteristics were collected: gender, age at diagnosis, clinical signs at diagnosis, laboratory findings at diagnosis, affected coronary artery, echocardiographic data (left ventricular function (normal was defined as ejection fraction more than or equal to 50%), pericardial effusion, development of valvular disease or pulmonary hypertension), immediate complications, and treatment regimen. The acute disease process was considered to be terminated when the inflammatory parameters normalized. Finally, mid-term follow-up data were obtained on reoccurrence of KD, arrhythmia, death, left ventricular function, and continued treatment regimen.

Statistical analysis

Continuous variables are reported as mean ± standard deviation (SD). Median and range (minimum and maximum) are used when the data set is not normally distributed. Proportions are reported by percentages. Descriptive statistics are applied where applicable. The cumulative freedom from disease was calculated by a Kaplan-Meier analysis. Analysis was done by SPSS (version 16.0) for Windows.

Results

Patients' characteristics

Thirty-five patients were included in the analysis, 18 boys and 17 girls. The median age at diagnosis of KD was 1.9 years, ranging from 0.4 to 12.2 years. At the latest follow-up the mean age of the patients was 10.7 ± 5.4 years (range 2.0 – 28.2 years).

Disease characteristics, treatment, and short-term outcome

The diagnostic criteria of our patient group and the corresponding laboratory findings are summarized in table 2.

In 94% and 58% of the cases, the left and right coronary artery, respectively, was affected. In 54% both coronary arteries were involved in the disease process. The diagnosis of coronaritis was made by echocardiographic evaluation (coronary artery aneurysm). In three patients, the left ventricular ejection fraction worsened below 50%. Pericardial effusion occurred in six patients, but was haemodynamically not important. No patients developed significant valvular disease, but in 9 patients there was, temporarily, mild mitral valve regurgitation. No pulmonary hypertension occurred in the acute phase.

Table 2. – *Symptoms, laboratory findings, and treatment regimens of the patients' cohort*

Clinical diagnostic criteria	Prevalence
Fever	100%
Polymorphous rash	66%
Bilateral conjunctival injection	69%
Changes of the mucous membranes of the upper respiratory tract	69%
Changes of the extremities as described in table 1	48%
Cervical adenopathy	52%
Laboratory findings	**Mean ± SD**
Sedimentation (mm/h)	88 ± 37
C-reactive protein (mg/l)	104 ± 63
Platelets (10^3/l)	785 ± 295
Treatment	
Aspirin	100%
Aspirin and sandoglobulin	83%
Corticosteroids (after failure of aspirin and sandoglobulin treatment)	10%

All patients were treated with aspirin and thirty of them received sandoglobulin. In 10% of the patients, corticosteroids were added when the inflammation process persisted under aspirin and sandoglobulin therapy (table 2). In one patient, balloon dilatation was indicated because of progressive coronary artery stenosis and regional left ventricular hypokinesis. One patient needed inotropic support because of global heart failure.

The median duration of the active disease process was 0.5 months, ranging from 0.1 to 2.0 months. Cumulative freedom from disease is plotted in figure 1.

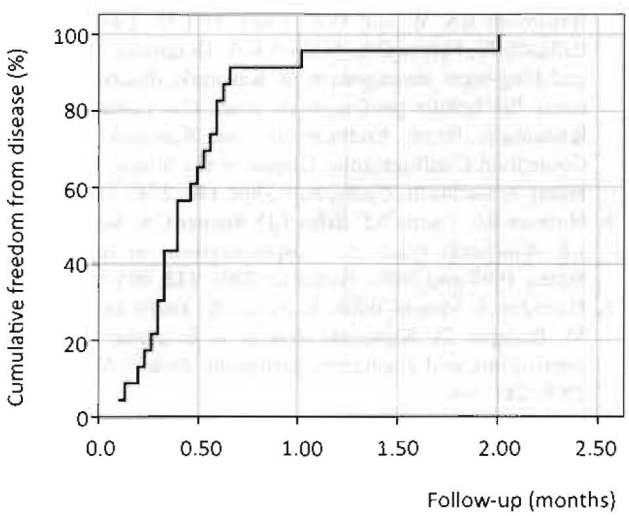

Fig. 1. – Cumulative freedom from disease.

Mid-term follow-up

The patients were followed up for a median of 4 years (range from 0.1 to 17.7 years). There was no disease recurrence, no significant arrhythmias occurred, and there were no deaths. In all patients the left ventricular function remained normal, or normalized. In one patient, 10 years after the acute event, a coronary stent implantation was needed, because of myocardial ischaemia. Forty-three percent of our patients was still treated with a low dose of aspirin, but in none of the patients symptoms related to cardiac malfunctioning were present.

Discussion

Kawasaki disease is now known for over 40 years. As a result, there are more and more adult patients who suffered in childhood from KD. Still, late outcome is not well defined yet. In this study we evaluated retrospectively the mid-term outcome of patients with a history of KD.

KD is a self-limiting vasculitis and the most severe complication of the disease process is coronaritis. In our population, almost all patients had echocardiographic signs of coronaritis. In 94% and 58% of the cases, the left and right coronary artery, respectively, was affected. In 54% both coronary arteries were involved. This high prevalence might be related to a referral bias. Coronaritis usually leads to dilated coronary arteries and aneurysms, that determine the echocardiographic diagnosis. The common sites of coronary aneurysms include, in order of highest to lowest risk, the proximal left anterior descendens and proximal right coronary artery, followed by the left main coronary artery, then the left circumflex artery, and finally the distal right coronary artery and the junction between the right coronary artery and the posterior descending coronary artery[4]. Although most of the coronary aneurysms will regress, the arterial vessel structure and function remain abnormal[9]. Some parts of the affected vessels remain unchanged, but might also become stenotic (with or without re-canalization). In some very rare occasions, rupture of an aneurysm has occurred[10-12].

Not only the coronary arteries might be involved in the disease process. Pericardial effusion was found in 6 (17%) of our patients, and mitral valve regurgitation occurred in 9 patients; the noticed valve dysfunctions regressed completely. Valvular insufficiencies are mostly diagnosed in the acute disease process, and involve the mitral and in a lesser extent the aortic valve. The incidence of valvular KD disease reported in literature (1-5%) is lower than the incidence we found in our group. Valve dysfunction is caused by valvulitis/pancarditis and tends to resolve spontaneously. Persistent valve regurgitation is thought to be the result of myocardial ischaemic damage[4,13,14] and late-onset valve regurgitation has been related to progressive valve thickening and formation of fibrotic leaflets[13,15]. Fukunaga et al. reported 2 cases in which aortic valve replacement was needed[16].

The treatment of KD in the acute phase focuses on controlling inflammation and preventing thrombosis in the affected coronary arteries. The long-term treatment is to avoid myocardial ischaemia or infarction due to persistent coronary artery lesions[14,17,18]. Aspirin is used for its anti-inflammatory and antiplatelet activity, but seems to have no effect on the development of coronary abnormalities[19]. In the acute phase it is administered in a high dose (80-100 mg/kg daily), the dose is lowered afterwards, and, if no coronary arteries are damaged, stopped after normalization of inflammation markers[1]. The efficacy of gamma globulin infusion to reduce coronary artery abnormalities was proven during the late 1980s, and, therefore, accepted as the mainstay therapy for KD, the latter in combination with aspirin. A single dose of 2 g/kg gamma globulin infused over 10-12 hours is now the

standard therapy in the USA, UK, Europe, Australia and several parts of Asia[1,20]. All of our patients were treated with aspirin and intravenous gamma globulin, except one. Four of them (10%) were additionally treated with corticosteroids. The use of corticosteroids has been limited in children with KD[21]. Studies performed in the past showed no potential benefit, so the usefulness of steroids in the initial treatment of KD is not yet clear[4,14,22].

However, when the coronary artery lesions lead to myocardial ischaemia, intervention is needed. Different interventions have been performed on patients with complicated KD, including catheter interventions, coronary artery bypass grafting (CABG), and even heart transplantation[23]. In 1976, Kitamura was the first to perform CABG in a patient with a coronary artery lesion due to KD[24]. He recently showed an excellent long-term survival after CABG (95% after 25 years), which was performed in patients as young as 1 year of age. But, on the other hand, in some series, the coronary artery-related event-free rate seems to decline progressively (60% after 25 years), which mandated continued follow-up[25]. In our series, the proximal right coronary artery was stented in one patient 10 years after the acute phase of KD. Stent implantation is preferable to balloon dilatation, especially in adults, because it may prevent new aneurysm formation and re-stenosis. In patients with severe calcified coronary artery stenosis, percutaneous transluminal coronary rotational ablation may be the only effective treatment. One study with 23 patients showed a good short-term outcome, but long-term outcome of catheter intervention in KD is still unclear[20,26-28]. In 2001, the research committee of the Japanese Ministry of Health, Labour, and Welfare, published guidelines for KD catheter interventions[27].

Finally, we found that at the latest follow-up almost half of our patients were still treated with a low dose of aspirin, because there were still echocardiographical signs of coronary lesions. However, long-term prospective data with aspirin are lacking.

This study has some limitations. First, there might be a selection/referral bias; KD children suspected with involvement of the heart were probably preferentially referred to the paediatric cardiologist. Second, it is a single-centre study, therefore extrapolation of our data needs careful interpretation. Third, this is a retrospective study, hence data could only be obtained by reviewing the patients' files.

Summary

The mid-term outcome of patients who suffered in childhood from Kawasaki disease is excellent. However, almost half of them were treated with oral aspirin during follow-up.

Conflict of interest: none declared.

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