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Abstract

Background: Kawasaki disease (KD) remains a diagnostic challenge due to its nonspecific clinical symptoms. Delayed treatment initiation increases the risk of coronary complications.

Aim: To evaluate the risk of coronary artery involvement and perform a prospective analysis of its course in children hospitalised due to KD.

Methods: KD was diagnosed in 38 children, including 25 boys and 13 girls, aged 1.5–118 months (median 37.5 months). We assessed the risk of cardiac complications in relation to the presence of a complete or incomplete form of the disease, age, gender and laboratory test results, as well as the timing of treatment initiation. Thirty-six children were followed for 1–9 years in a cardiology clinic.

Results: More than 80% of patients with KD were younger than 5 years. Eleven (29%) of them had an incomplete form of the disease. Coronary artery abnormalities were found in 10 (26%) children, insignificantly more often among those with incomplete KD. Each day of treatment delay increased the complication rate by almost 1.5 (OR 1.45, p = 0.009). Treatment initiated 10 days after the onset of the disease increased this risk almost nine times (OR 8.99, p = 0.007). No significant differences in respect to age (p = 0.431), gender (p = 0.744) and laboratory test results were found between the groups with and without coronary complications. A complete regression of coronary artery involvement was seen in 7 children, and partial regression was seen in one child. One child died and another needed coronary artery bypass grafting.

Conclusions: Coronary artery aneurysms developed at a similar rate in both complete and incomplete forms of KD and the only significant risk factor was the timing of treatment initiation. In young children with fever of unknown cause lasting longer than 5 days, echocardiography is warranted. Despite a tendency for coronary artery aneurysms to regress, late complications may occur and all children require long-term follow up in a cardiology clinic.

Key words: Kawasaki disease, coronary artery aneurysms, long-term prognosis

INTRODUCTION

Kawasaki disease (KD), an acute self-limiting systemic vasculitis involving medium- and small-size arteries, has been a challenge for paediatricians for several decades. It was described for the first time in 1967 by a Japanese paediatrician Tomisaku Kawasaki based on observations of clinical symptoms in 50 infants [1]. The highest number of cases continues to be seen in Japan [2–4] but many were also reported in the USA [5, 6], Brasil, Israel and Western European countries [7–10]. In the recent years, an increasing incidence has been also reported in Poland, which may be related to an increased detection rate [11].
The aetiology remains unknown. Taking into account patient age, the most likely causes are autoimmune or infective factors. The diagnosis is based on clinical criteria [11, 12] that include fever lasting more than 5 days with associated: (1) conjunctival injection; (2) strawberry tongue (inflammation of the oral mucosa, lips, and tongue); (3) oedema and erythema of the palms and soles with periangual desquamation; (4) polymorphic rash; (5) cervical lymphadenopathy. Although the inflammation is systemic in nature, the most dangerous complication is the development of coronary artery aneurysms which in most severe cases may be fatal.

According to the American Heart Association (AHA) guidelines, a typical form of KD may be diagnosed when fever is accompanied by 4 of 5 typical signs. However, many authors believe that these diagnostic criteria may be too strict as many atypical cases are reported in children [12].

The aim of this study was to evaluate clinical signs and symptoms, and the effect of age and gender, inflammatory parameters, and the timing of the diagnosis and treatment initiation on the occurrence of complications, and to assess the evolution of coronary artery lesions in children hospitalised in a single clinical centre.

METHODS

We analysed patients with acute or subacute KD hospitalised in the paediatric ward of the Department of Paediatrics, Endocrinology, and Diabetology, Medical University of Silesia, in 2003–2012. All children were consulted at the Department of Paediatric Cardiology, Medical University of Silesia. The diagnosis was based on the AHA diagnostic criteria. Children with incomplete KD showed less than 4 typical signs but had increased laboratory inflammation parameters, were characterised by a typical clinical course of the second phase of the disease, and responded to standard treatment.

In all patients, we analysed history data, laboratory test results and echocardiographic findings, and the timing of treatment initiation and treatment effects. We also analysed data from periodic follow-up visits to the cardiology clinic at the Upper Silesian Children’s Health Centre, which is a teaching hospital of the Medical University of Silesia. In 2012, all previously hospitalised children underwent general medical check-up and a follow-up echocardiographic examination performed according to the American Society of Echocardiography recommendations [13] by 2 cardiologists who were co-authors of this paper. The analysis included evaluation of the coronary arteries and aneurysms developing in the proximal segment of the right and left coronary artery and their branches. We used a Philips 7500 machine with 5.0–7.7 MHz transducers and performed M-mode and 2-dimensional imaging with pulsed and continuous wave Doppler and colour Doppler interrogation. Images were stored on a optical disc, and 5 consecutive cardiac cycles were used for evaluation of the left ventricular (LV) function. We used substernal, apical, long- and short-axis parasternal, and suprasternal views. M-mode evaluation included LV dimensions, ejection fraction, fractional shortening, systolic thickening of the interventricular septum and LV posterior wall. Two-dimensional imaging was used for real-time evaluation of valvular function and the presence of pericardial effusion, with Doppler measurements of flow velocities. Criteria of the severity of coronary lesions were based on measurements of the aneurysm diameter in the proximal segments of the coronary arteries. Aneurysms were categorised as small when the lumen diameter was < 5 mm, moderate when the lumen diameter was 5–8 mm, and large when the lumen diameter was > 8 mm.

The study was performed according to the Helsinki Convention. Due to its non-experimental nature, a formal approval by a bioethics committee was not required.

Statistical analysis

Statistical analyses were performed using the STATISTICA PL software, version 1.0. Descriptive statistics included arithmetic mean and standard deviation for normally distributed continuous variables, and median and interquartile range for non-normally distributed variables. Normal distributions of variables were verified using the Shapiro-Wilk test. Differences between mean values were evaluated using the Student t test for normally distributed variables and the Mann-Whitney U test for non-normally distributed variables. To evaluate relation between the timing of treatment initiation and the development of coronary aneurysms, a logistic regression model was fitted and odds ratios (OR) with 95% confidence intervals (CI) were calculated. The χ² test was to evaluate relation between age categorised into three age groups (< 6 months, 6–60 months, > 60 months) and the development of coronary aneurysms. P < 0.05 was considered statistically significant.

RESULTS

Kawasaki disease was diagnosed in 38 children, including 25 (66%) boys and 13 (34%) girls. The proportion of male to female patients was 1.9:1. The number of hospitalised patients varied, with a peak incidence in 2011 (Fig. 1). No seasonal trends were identified. Patient age at the time of diagnosis ranged 1.5–118 (median 37.5) months in the overall study group, 1.5–118 (median 39) months among boys, and 4–104 (median 27) months among girls. In 31 (82%) children, KD manifested below 5 years of age, including during the first 6 months of life in 4 (10.5%) children. No significant difference in age at presentation (p = 0.612) was found between girls and boys (Fig. 2).

We performed a comparative analysis of children with complete and incomplete KD. The complete form was found in 27 (71%) children, and the incomplete form in 11 (29%) children. In the latter group, 7 children fulfilled 2 or 3 major
criteria, had fever lasting ≥ 5 days and elevated inflammation parameters, and did not respond to antibiotic therapy. Median age among children with incomplete KD was 16 (4–118) months, and median age among children with complete KD was 40 (1.5–104) months. Despite a large difference in median age between these groups, it did not achieve statistical significance (p = 0.15) (Fig. 3).

We then analysed children with cardiac complications. Coronary artery lesions were found in 10 (26%) patients, including before treatment initiation in 3 patients. Vascular complications occurred in 4 (36%) children with incomplete KD and in 6 (22%) children with complete KD. In 7 children, aneurysms developed by 10 days despite immunoglobulin infusion. Treatment was initiated at mean 8.3 ± 2.8 days in children without late complications compared to mean 14.0 ± 5.2 days in those with late complications, the difference being significant (p < 0.001). Using a logistic regression model, we confirmed a significant association between the timing of treatment initiation and the development of coronary aneurysms (OR 1.48, 95% CI 1.11–1.99, p = 0.009). In the same model, we also analysed the relation between the occurrence of coronary complications and treatment initiation by 10 days, as it is recommended, versus at 11 or more days. A significant association was found between these

Figure 1. The number of children with Kawasaki disease in subsequent years and quarters

Figure 2. Comparison of age in boys and girls with Kawasaki disease; p = 0.612

Figure 3. Comparison of age in children with incomplete and complete Kawasaki disease; p = 0.15
We did not find significant associations between age and gender and the occurrence of vascular complications (p = 0.431 and p = 0.744, respectively). No significant association was also found between complete and incomplete KD and the rate of vascular complications (p = 0.37).

In 1 child admitted after 15 days of fever, coronary aneurysms were identified on the first day of hospital stay. In a 4-month-old girl diagnosed after 20 days of fever (with a history of only transient rash and subtle limb oedema), no coronary lesions were found during the hospitalisation. The patient was discharged at her parents’ request and a follow-up study 10 days after the discharge showed giant aneurysms of both coronary arteries, subsequently confirmed by computed tomography angiography. Four children did not fulfil the criterion of fever lasting for 5 days at the time when their treatment was initiated. In 1 of these children, the diagnosis was made after 16 days of the disease based on the presence of coronary aneurysms of both coronary arteries, subsequently confirmed by computed tomography angiography. Four children did not fulfil the criterion of fever lasting for 5 days at the time when their treatment was initiated. In 1 of these children, the diagnosis was made after 16 days of the disease based on the presence of coronary aneurysms. The patient was a previously reported [14] 4-year-old girl with trisomy 21. In another child, the diagnosis was made after 11 days based on persistently elevated inflammation markers, elevated platelet count, and periungual desquamation. In the remaining 2 of these 4 children, fever lasted for up to 4 days but four major criteria were present, and elevated inflammation markers persisted despite antibiotic therapy. The diagnosis was confirmed by a good response to immunoglobulin therapy and development of periungual desquamation. The duration of KD from the onset of first clinical symptoms, i.e. fever, ranged 2–21 (mean 9.8 ± 4.4) days, and the delay from the admission to the diagnosis ranged 1–15 (mean 2.5 ± 3.2) days. The diagnosis was made on the first day of hospital stay in 27 (71%) children.

In none of 38 children, echocardiography showed segmental wall motion abnormalities, coronary thrombi, or pericardial effusion.

We also compared inflammation markers in children with or without vascular complications (Table 1). No significant differences in these parameters were found between the two groups.

Follow-up evaluation in 2012 showed no early or late coronary lesions in 28 of 38 previously hospitalised children who remained completely healthy. Coronary aneurysms were found in 10 patients (Table 2), including small aneurysms in 5 patients, moderate size aneurysms in 4 patients, and giant aneurysms in 1 patient. The disease was fatal in 1 girl with giant aneurysms. Cardiac surgery was required in 1 boy in whom treatment was initiated after 21 days of the disease, on the first day of hospitalisation in our centre. Among the remaining 8 patients, follow-up echocardiographic examination showed complete lesion regression in 7 patients at 1–5 (mean 2) years of follow-up. Lesions persisted in 1 patient who continues to be treated with acetylsalicylic acid (ASA 5 mg/kg). Increased echogenicity along a previously dilated vessel was noted in another child. Increased echogenicity along non-dilated coronary arteries was also seen in 3 patients at the time of the diagnosis and it persists in 1 of these children.

All children with coronary aneurysms were treated with ASA until resolution of the observed lesions.

**DISCUSSION**

A significant improvement in the treatment of KD and its outcomes has been associated with introduction of intravenous immunoglobulin therapy which significantly reduced the rates of cardiac complications [15]. An early diagnosis remains a major challenge, as this treatment is most successful when
introduced with the first 10 days of the disease. Symptoms of KD may be very unspecific, particularly among younger children with incomplete KD.

The literature on KD in Poland is scarce and mostly consists of single case reports. Two studies reported long-term follow-up of 30 and 11 children, respectively, diagnosed and followed up in a single centre [16, 17]. The largest group of 112 patients was analysed by Kowalczyk et al. [11] based on data obtained from 8 centres including our own, in an attempt to establish a Polish database on children with KD.

Our patients with KD were mostly below 5 years of age, and 4 of them were younger than 6 months. Similar age profile was reported in studies from Japan, Korea, France, Israel, and the USA [2–10, 18]. However, median age of our patients was higher (37.5 months) compared to 24–26 months in the mentioned studies, with peak incidence ranging from 5–11 months in Japan to 1–2 years in the USA and France. In contrast, the gender proportion was similar, with male preponderance.

We did not observe seasonal incidence peaks reported in winter and spring in the USA, Israel, and France [5, 8, 9]. However, the number of admissions in 2011 was significantly higher compared to the other years, which may suggest cluster occurrence of the disease, related by some authors to an increased rate of viral infections in a given period [2].

Reported complications of KD develop in a widely varying proportion of patients and are related to the quality and duration of treatment, and also depend whether only aneurysms or also milder dilatations are included. The complication rate reported in Israel [9] was very low, ranging 4–6%, compared to 25–44% in the USA [5, 6]. In contrast, Perrin et al. [10] reported coronary artery dilatations in as many as 48.7% of French children with complete KD and 90% of those with incomplete KD. After introduction of immunoglobulin infusion as a standard therapy, complication rates reduced significantly over the years. In Japan, where most epidemiological data come from, the proportion of chil-

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
<th>Therapy delay [days]</th>
<th>Initial ECHO</th>
<th>Follow-up</th>
<th>Follow-up ECHO</th>
</tr>
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<tbody>
<tr>
<td>4 years</td>
<td>15</td>
<td>LCA: 5 mm aneurysm; RCA: 6 mm aneurysm</td>
<td>9 years</td>
<td>Normal coronary arteries</td>
</tr>
<tr>
<td>10 years</td>
<td>15</td>
<td>LCA: 6 mm aneurysm; RCA: 4.5 mm aneurysm</td>
<td>7 years</td>
<td>Normal coronary arteries</td>
</tr>
<tr>
<td>1.5 years</td>
<td>21</td>
<td>LCA: 5 mm aneurysm; RCA: 4 mm dilatation</td>
<td>After 3 years CABG in another centre; did not show up for a follow-up visit in 2012</td>
<td>After 2 years: LCA: 3–3.5 mm dilatation; RCA: normal</td>
</tr>
<tr>
<td>4 months</td>
<td>20</td>
<td>At 10 days (after discharge at mother’s request): LCA: 8.2 mm aneurysm; RCA: 8–10 mm aneurysm (large aneurysms)</td>
<td>Patient transferred to another centre and died there</td>
<td></td>
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<tr>
<td>16 months</td>
<td>21</td>
<td>LCA: increased echogenicity along the vessel, 3.2 mm dilatation; RCA: normal</td>
<td>3.5 years</td>
<td>Normal coronary arteries</td>
</tr>
<tr>
<td>14 months</td>
<td>10</td>
<td>LCA: 4 mm aneurysm; RCA: normal</td>
<td>1 years 9 months</td>
<td>LCA: increased echogenicity along the vessel; RCA: normal</td>
</tr>
<tr>
<td>5 months</td>
<td>8</td>
<td>LCA: 4 mm aneurysm; RCA: 3 mm aneurysm, increased echogenicity around coronary arteries</td>
<td>14 months</td>
<td>Normal coronary arteries</td>
</tr>
<tr>
<td>2 years 2 months</td>
<td>13</td>
<td>Increased echogenicity around RCA and LCA: LCA: 3.5 mm aneurysm</td>
<td>1.5 years</td>
<td>Normal coronary arteries</td>
</tr>
<tr>
<td>3 years 9 months</td>
<td>8</td>
<td>LCA: 7 mm aneurysm; RCA: 6 mm aneurysm</td>
<td>1 year</td>
<td>RCA, LCA: 3–4 mm dilatation, no aneurysms</td>
</tr>
<tr>
<td>3 years 9 months</td>
<td>9</td>
<td>LCA: 3.5 mm aneurysm; RCA: 2–2.5 mm</td>
<td>1 year</td>
<td>Normal coronary arteries</td>
</tr>
</tbody>
</table>

CABG — coronary artery bypass grafting; ECG — electrocardiogram; ECHO — echocardiography; LCA — left coronary artery; RCA — right coronary artery
Children with complications was reduced from 18% in 1997 to 12% in 2006 [4].

In our study group, coronary lesions developed in the subacute phase in 26% of children, although all of them received typical treatment consisting of a single immunoglobulin infusion at a dose of 2 g/kg of body mass. During this therapy, we observed resolution of fever within 24–48 h in most patients, associated with an improvement of the overall clinical condition of the patients and gradual normalisation of laboratory parameters. Only 1 boy aged 14 months required repeated immunoglobulin infusion due to recurrent fever.

In all children, ASA was started on the first or second day of treatment at 50–100 mg/kg of body mass per day, with later gradual tapering of the dose. In 3 patients, coronary lesions developed before treatment initiation (in 2 of them, the disease was diagnosed after 15 days due to incomplete symptoms, and in 1 patient after 21 days of the disease, on the first day of hospital stay). Delay to diagnosis and treatment increased in atypical cases, mostly with short duration of fever, and in 2 children the disease was diagnosed only when coronary aneurysms were identified. Each day of treatment delay increased the risk of aneurysm development by almost 1.5, and treatment initiation 10 days after the onset of the disease increased the risk of vascular complications almost 9 times.

Although the proportion of patients with complications in our study group was higher compared to reports from Japan and Israel, Szymanowska and Pośnık-Urbańska [19] reported much more severe course of KD in 10 Polish patients, including 2 who died. In a single centre study, Kowalczyk et al. [16] reported cardiac complications in as many as 57% of children, and in a multicentre study they were identified in 57–67% of children depending on the presence of complete or incomplete disease [11]. This was most likely related to a delayed diagnosis, as the treatment was initiated more than 10 days after the symptom onset in more than 60% of those patients, compared to only 10 (26%) of children in our study. Patients in our study who developed coronary complications despite early treatment initiation were at risk due to gender and age, as these were boys aged 5–38 months. Initial laboratory test results showed much elevated inflammatory markers, platelet count above 1000 × 10³/µL, and low albumin level. In the overall study population, however, we did not identify significant associations between any of the evaluated parameters and the risk of complications, although some reports suggested such associations [2, 15, 18]. We also did not find such complications reported by other authors as arthritis, ocular complications, or late hearing loss [8]. Transient sterile leukocyturia was found in several children, as also reported in other studies [8, 12]. Coronary lesions regressed in most patients, which is also consistent with other reports. Follow-up examination showed coronary artery dilatation without a definite aneurysm persisting at one year in 1 child. In addition, increased echogenicity along coronary arteries was noted in 2 children. This finding is not unanimously considered pathological but requires further follow-up, particularly if present in a child known to have no coronary lesions previously [18].

Relatively good outcomes observed in our patients are likely related to close cooperation between our paediatricians and paediatric cardiologists. Echocardiography was performed on the first day of hospital stay in as many as 24 children, and 25 patients underwent echocardiographic examination by 10 days since the onset of symptoms, which allowed earlier treatment initiation in some patients with incomplete KD. Such timing of echocardiographic evaluation is similar to that reported in a study published by French authors who recommended as early echocardiography as possible, particularly in children with incomplete KD, which is usually most challenging diagnostically [12].

All our patients remain under care in an outpatient paediatric cardiology clinic, although regression of arterial lesions was noted in most of them. However, subclinical atherosclerotic lesions were reported even several years after an episode of KD [15, 20].

**Limitations of the study**

A limitation of our study was a relatively low number of patients compared to some Japanese and American studies. Also, some patients were followed up for a too short period to definitely exclude late complications. However, all children were treated by the same team of paediatricians and cardiologists, which might have had a significant effect on relatively good outcomes in most patients as compared to other reports.

**CONCLUSIONS**

Coronary artery aneurysms developed at a similar rate in both complete and incomplete forms of KD and the only significant risk factor was the timing of treatment initiation. In young children with fever of unknown cause lasting longer than 5 days, echocardiography with evaluation of the coronary arteries is warranted. Despite a tendency for coronary artery aneurysms to regress, late complications may occur and all children require long-term follow up in a cardiology clinic.

**Conflict of interests:** none declared

**References**

Analiza czynników ryzyka i prospektywna ocena powikłań kardiologicznych choroby Kawasaki u dzieci: badanie jednoośrodkowe

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Streszczenie
Wstęp: Choroba Kawasaki (KD) ze względu na często nietypowe objawy kliniczne sprawia trudności diagnostyczne, a późne wdrożenie leczenia wiąże się z ryzykiem wystąpienia zmian w tętnicach wieńcowych.
Cel: Celem pracy była analiza czynników ryzyka wystąpienia powikłań kardiologicznych i prospektywna ocena ewolucji zmian w tętnicach wieńcowych u dzieci hospitalizowanych z powodu KD.
Metody: Chorobę rozpoznano u 38 dzieci (25 chłopców i 13 dziewcząt) w wieku 1,5–118 miesięcy (mediana 37,5 miesiąca). Analizowano zależność wystąpienia powikłań kardiologicznych od postaci choroby, wieku i płci pacjenta, wyników badań laboratoryjnych oraz czasu rozpoczęcia leczenia. U 36 dzieci przeprowadzono badania kontrolne po upływie 1–9 lat od zachorowania.
Wyniki: U ponad 80% dzieci choroba wystąpiła przed ukończeniem 5. r. U 11 (29%) dzieci występowała postać niepełnoobjawowa. Powikłania ze strony naczyń wieńcowych rozpoznano u 10 (26%) dzieci, niezmiennie częściej u pacjentów z postacją niepełnoobjawową. Opóźnienie leczenia o każdy dzień zwiększało ryzyko powikłań ok. 1,5-krotnie (OR = 1,45; p = 0,009). Wdrożenie leczenia po 10. dobie trwania choroby zwiększało ryzyko powikłań prawie 9-krotnie (OR = 8,99; p = 0,007). Nie stwierdzono zależności wystąpienia zmian w tętnicach wieńcowych od wieku i płci (odpowiednio p = 0,431; p = 0,744) oraz od wartości parametrów stanu zapalnego, transaminaz, albumin, stężenia sodu i profilu lipidowego. W badaniach kontrolnych całkowitą regresję zmian w naczyniach wieńcowych stwierdzono u 7 pacjentów, u 1 — częściową, 1 dziecko zmarło, a 1 pacjenta poddano zabiegowi pomostowania tętnic wieńcowych.
Wnioski. Tętniaki naczyń wieńcowych występują z podobną częstością w postaci niepełnoobjawowej i w pełnoobjawowej KD, a jedynym czynnikiem ryzyka ich powstania jest czas wdrożenia leczenia. U małych dzieci gorączkujących bez uchwytnej przyczyny dłużej niż 5 dni istnieją uzasadnione wskazania do wykonania badania echokardiograficznego tętnic wieńcowych. Mimo istotnej tendencji do cofania się zmian w tętnicach wieńcowych możliwość wystąpienia poważnych powikłań, również w późniejszym okresie choroby, wskazuje na konieczność stałej kontroli kardiologicznej.
Słowa kluczowe: choroba Kawasaki, zmiany w tętnicach wieńcowych, obserwacja odległa

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