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CORONARY ARTERY ABNORMALITIES IN KAWASAKI DISEASE

Abstract: Introduction: Kawasaki disease is the number one cause of acquired heart disease among children in developed countries.
The aim: The aim of the study was a retrospective analysis of the factors that may influence the persistence of coronary artery abnormalities in patients with Kawasaki disease.
Materials and Methods: Analyzing the medical records of patients hospitalized in the University Children's Hospital of Krakow in the years 2005–2011 we collected the data of 28 patients diagnosed with Kawasaki disease. The group was divided into two subgroups, depending on the duration of the persistence of changes in the coronary arteries — A (n = 17) for up to 6 months, B (n = 11) — for more than 6 months. Both groups were analyzed for the presence of factors that may influence the course of the disease.
Results: There were more boys in group A (11 boys (65%), 6 girls (35%)), whereas in group B the distribution was more uniform (6 boys (55%), 5 girls (45%)). The age of onset in group A was 37.9 months (SD 30.8), in group B 39.5 months (SD 16.7). 17.6% of patients in group A and 36.4% in group B were treated with glucocorticoids.
Conclusions: In the group of patients in which coronary artery abnormalities disappeared more quickly, male and slightly older children dominated. The only difference observed between the 2 groups related to the frequency of the use of glucocorticoids, they were used more often in children, in whom coronary artery abnormalities persisted longer.

Key words: Kawasaki Disease, vasculitis, aneurysm, steroids, therapy.

INTRODUCTION

Kawasaki disease is currently the number one cause of acquired coronary artery disease in young children in developed countries [1, 2].

It is an acute, self-limited, systemic vasculitis of unknown etiology that usually occurs in early childhood. In the course of Kawasaki disease the coronary arteries are most often affected. Aneurysms, or ectasia of the coronary arteries occur in 15–25% of untreated children with Kawasaki disease and may lead to the development of ischemic heart disease, including myocardial

infarction and even sudden death. Kawasaki disease is now linked with early-onset and accelerated atherosclerosis [3], a leading cause of heart disease in adults. Recent studies also suggest that early and aggressive treatment of the blood vessel inflammation caused by Kawasaki Disease may reduce the future risk of developing accelerated atherosclerosis [4].

Aneurysms most commonly form in the proximal segment of the left anterior descending artery from the left coronary artery and the proximal segment of the right coronary artery, less frequently in the left main coronary artery, the circumflex coronary artery, and the terminal segment of the right coronary artery [5]. The shape and size of aneurysms may change with time.

Aneurysms can increase their size during the first 4–6 weeks after the onset of the disease. After reaching their peak size, 50% of aneurysms disappear and the vessels return to their normal diameter in the next two years (after the onset of the illness), after this period of time, further regression usually does not occur [6]. Factors that improve the prognosis in patients who develop coronary artery aneurysms are: younger age and localization in the distal segments of the coronary arteries.

THE AIM

The aim of the study was a retrospective analysis of the factors that may influenced the persistence of coronary artery abnormalities in patients with Kawasaki disease.

MATERIALS AND METHODS

Based on the retrospective analysis of medical records of patients hospitalized at the University Children's Hospital of Krakow in the years 2005–2011 we collected the data of 28 patients who were diagnosed with Kawasaki disease. The development and regression of coronary arteries aneurysms was assessed by echocardiography. Each patient had a series of echocardiographic assesments done with a frequency that corresponded to local standards. Afterwards, the results of the subsequent control echocardiograms of each patient that were performed during the follow-up period were analyzed and the study group was divided into two subgroups.

The mean follow-up period was 612 days. Each of the patients had an average of 4.3 control echocardiographies performed.

The first group — Group A — included patients in whom no coronary artery abnormalities had been observed, or such an abnormality had been diagnosed in at least one artery and had completely withdrawn during the 6-month observation period.

The second study group — Group B — consisted of patients, in whom at least one coronary artery aneurysm had persisted for more than 6 months after the initial diagnosis.

According to criteria established by the Japanese Ministry of Health [7] coronary arteries are classified as abnormal if the internal diameter of the lumen is >3 mm in children <5 years old or >4 mm in children ≥5 years old; if the internal diameter of a segment exceeds at least 1.5 times the size of an adjacent segment or if the coronary lumen is irregular. For the purpose of this study, patients with coronary artery abnormalities were defined as having coronary artery aneurysms confirmed by echocardiography, based on measurements of the internal diameter of the lumen according to the Japanese Ministry of Health criteria. Irregularity of the coronary artery lumens was not assessed.

Echocardiographic analysis was performed using a echocardiographic system Sonos 5500, Philips Medical Systems, Amsterdam, the Netherlands, with a Philips S8 Cardiac Probe. The echocardiographic assessment was standardized and performed only by two operators in order to avoid significant interobserver variability.

Afterwards the two groups were analyzed in respect to the prevalence of factors that may influence the course of the disease, such as demographic data, laboratory results and the administered treatment.

RESULTS

The study included 28 patients, group A consisted of 17 patients and group B of 11 patients. The demographic and clinical characteristics of both groups are presented in Table 1 and the laboratory test results in Table 2. The distribution of coronary artery aneurysms and the mean time period of regression for group A is presented in Table 3, and for group B in Table 4.

Evaluating the variability of infectious parameters over time, we can see that there was a considerable, although not statistically significant, difference in CRP levels between the two groups. In the first days of the disease, higher CRP values were observed in group B (Figure 1).

Analyzing the course of the fever, it was observed that the variability was very similar in both groups, in addition absolute body temperatures also coincided (Figure 2).

Intravenous immune globulin therapy was administered to all patients enrolled in group A and to 91% of patients in group B. The total dose of immune globulins administered in group A was on average 30.4 ± 14.3 g, while in group B, 30.1 ± 11.5 g. In Group A intravenous immune globulins were administered in a single infusion to 3 patients, in 2 infusions to 10 patients, and in 3 to 4 patients. The respective values for group B were 2 patients, 6 patients and 2 patients, as visualized in Figure 3.

Table 1

Demographic and clinical characteristics of the study groups.

	Group A	Group B	p value
Number of patients	17 (61%)	11 (39%)	
Male gender	11	6	0,59[2]
Age at the onset of KD [months]	38,9 (SD 6,3)	37,9 (SD 7,8)	0,92[1]
Weight at the onset of KD [kg]	15,6 (SD 6,7)	14,7 (SD 3,6)	0,64[1]
Duration of fever until administration of treatment [days]	9,8 (SD 2,3)	8,1 (SD 3,2)	0,44[1]

[1] Student's t Test
[2] Fisher's exact test
KD — Kawasaki Disease

Table 2

Laboratory test results in study groups.

	Group A	Group B	p value
Maximum ESR [mm after 1 hour]	87,4 SD 41,4	91,6 SD 29,1	0,66[1]
Highest CRP [mg/l]	140,7 SD 65,1	169,2 SD 113,0	0,35[1]
Highest value for Leukocytosis [cell/ul]	20 500 SD 5 600	17 400 SD 6 500	0,93[1]
Highest value for Platelet count [cell/ul]	715 000 SD 160 000	793 000 SD 296 000	0,23[1]

[1] Student's t Test

Table 3

Coronary aneurysms distribution in group A.

Group A, N=17	LMCA	LAD	Cx	RCA
No of patients with aneurysm	8	4	1	5
No of patients without aneurysm	5			
Mean time to complete regression (days, SD)	22,6 SD 14,1	33,0 SD 25,6	9 (1 patient)	18,0 SD 17,8

Table 4

Coronary aneurysms distribution in group B.

Group B, N=11	LMCA	LAD	Cx	RCA
No of patients with aneurysm	10	7	5	8
No of patients without regression of aneurysm	6	2	0	1
Mean time to complete regression (days, SD)	494,5 SD 262,7	191,0 SD 315,7	191,6 SD 316,4	193,0 SD 147,3

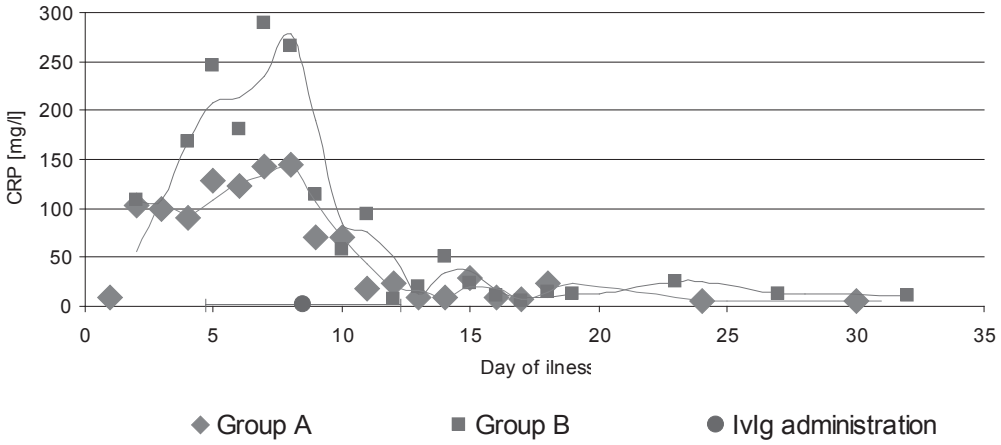

Fig. 1. Variability of CRP depending of the day of illness.

The first dose of immune globulins was administered on average in both groups on the 8.5 day of illness (SD 3.8 day). Glucocorticoids (GCS) were included in the therapy of 17.6% of patients in group A and in 36.4% of patients in group B.

Glucocorticoids were included in the therapy of patients in the following clinical situations: presence of joint involvement, the desire to minimize the risk of an allergic reaction to immune globulins, visibility of pericardial effusion or myocardial contractility disorders in echocardiographic studies, and finally resistant forms of Kawasaki disease.

All patients were treated with high-dose aspirin (80–100 mg/kg/day) which was introduced in both groups on average on the 9 ± 4.5 day of illness.

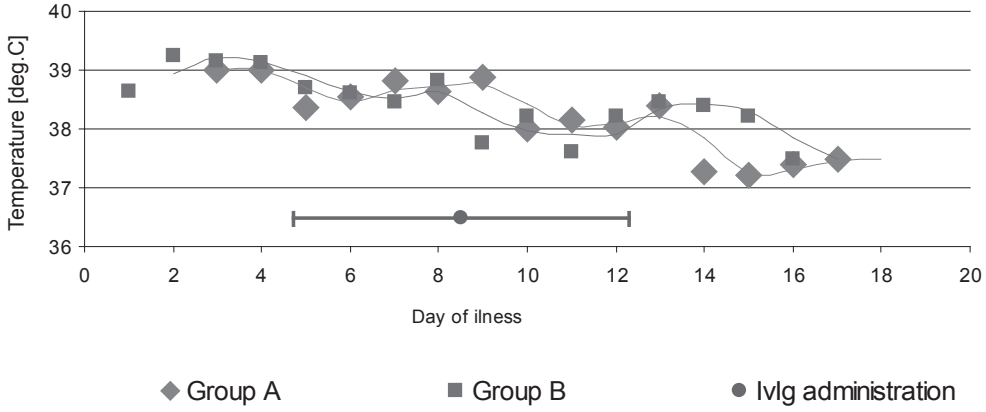

Fig. 2. Variability of the body temperature depending of the day of illness.

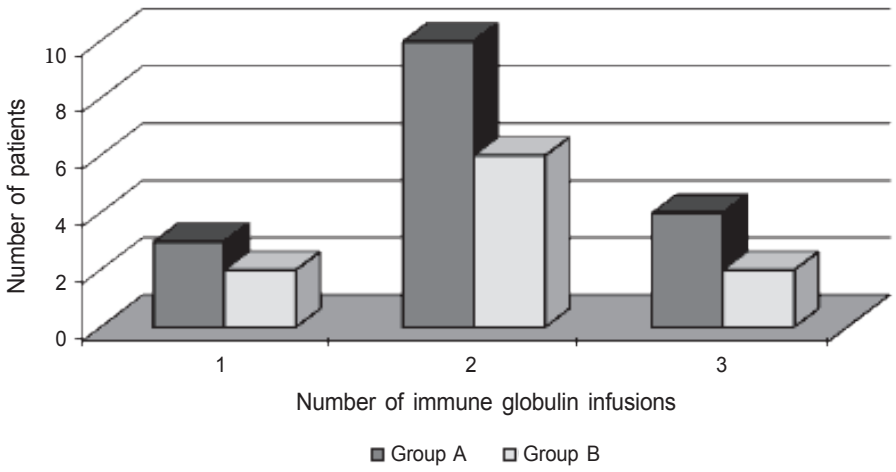

Fig. 3. Number of immune globulin infusions in both groups.

DISCUSSION

Several years have passed since the first clinical description of a patient with Kawasaki disease (Kawasaki Tomisaku, 1962) and linkage of the disease with abnormalities in the coronary arteries (Noboru Tanaka, 1965) [8]. Since that time, there is no doubt that the most serious complications in the course of the systemic vasculitis, which is Kawasaki disease are associated with the development of abnormalities in the coronary circulation, which can then lead

to myocardial ischemia, myocardial infarction, arrhythmia or even sudden death. Therefore researchers have often tried to select a group of patients diagnosed with Kawasaki disease, that are particularly at risk of developing complications in the form of pathological changes in the coronary arteries and their subsequent consequences.

Based on numerous publications we know that boys are affected more often by Kawasaki disease than girls (60 vs 40%) [9–13], similar findings were also noted in the analyzed population. Elevated inflammatory markers such as CRP [14] or ESR [15], predispose to the development of aneurysms and increase the risk of complications which was also observed in our study group. An additional adverse prognostic factor is an elevated platelet count in the initial phases of the disease [16], we also found this to be true.

Other factors affecting the prognosis are atypical age of onset of Kawasaki disease (less than 1 year of age[34] or over 6 years of age [17]), hypoalbuminemia [18], low hematocrite [19] or hyponatremia [20]. Most probably due to the limited size of the study group, we failed to observe such patterns in the above analyzed population.

Analysing the factors that contributed to a poorer prognosis in patients with Kawasaki disease based on the analysis of our data, we found that if a correlation between age and body weight was taken into account — it seemed that patients who were slightly younger and with a lower body weight had worse prognosis. Patients with a poorer prognosis also had a slightly lower leukocytosis, coupled with increased inflammatory markers such as ESR or CRP. It should be noted, that the authors did not find any confirmation of these observations in the latest publications.

The majority of patients received intravenous immune globulins at a dose of 2 gm/kg of in two consecutive infusions. Ever since there have been reports of improved disease outcome after immune globulin administration in a single infusion, the treatment strategy at our hospital has changed and patients have started receiving one instead of two. There was a small group of patients who received 3 doses of immune globulins. These patients had been referred from a district hospital and most of them had received a very low dose of immune globulins therefore the decision was made to launch a full treatment regimen after the admission of these patient to the University Children's Hospital.

Results of the latest published trial [21] suggest that the addition of prednisolone to the standard regimen of intravenous immune globulins and aspirin improves coronary artery outcomes in patients with severe Kawasaki Disease. In patients from this study 2 types of steroids were used; hydrocortisone and prednisolone, furthermore they were not part of the standard treatment but added to immune globulins and aspirin in certain clinical situations such as presence of joint involvement, minimizing the risk of an allergic reaction to immune

globulins, visibility of pericardial effusion or myocardial contractility disorders in echocardiographic studies, and finally resistant forms of Kawasaki disease.

Based on the analysis of data concerning patients diagnosed with Kawasaki disease, we can conclude that in the group of patients in whom abnormalities in the coronary arteries disappeared more quickly, male and slightly older children with a higher body weight dominated. Lower levels of inflammatory markers such as ESR, CRP, lower platelet counts but a higher leukocytosis were also observed. Analyzing the treatment regimen administered to both groups of patients, we can conclude that it was quite similar. The only difference observed between the 2 groups related to the frequency of the use of glucocorticoids, they were used more often in children, in whom coronary artery abnormalities persisted longer than 6 months. It must be taken into account though that the patients from that group had higher inflammatory markers such as CRP, ESR, a higher platelet count and a slightly earlier time of introduction of immune globulins so that the increased incidence of complications could not necessarily have resulted from the use of the steroids but a more severe disease course.

The aim of this paper was a retrospective analysis of pre-defined groups of patients and should not be used as a basis for defining risk factors that influence the prognosis of patients diagnosed with Kawasaki disease in the future. Notwithstanding we hope that our results could be taken into account in planning further studies aimed at a detailed analysis of the above mentioned factors in the future.

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