

CLINICAL AND PARACLINICAL FEATURES OF CORONARY ARTERY ANEURYSMS IN KAWASAKI DISEASE

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ABSTRACT

Objectives: To describe clinical and subclinical features according to level of coronary artery aneurysm (CAA) in Kawasaki disease. **Patients and methods:** 545 patients with Kawasaki disease at Cardiovascular Center - Vietnam National Children's Hospital between January 2019 and June 2022. **Results:** Patients were classified as 4 groups: no involvement, small aneurysm, medium aneurysm, large or giant aneurysm (GAA). The rates of 4 groups were: 44.6%, 19.4%, 18.2%, 7%. The average age at diagnosis of 12.6 months, 49.4% under 12 months, the ratio of male: female approximates 1.5:1, 11.7% had atypical Kawasaki disease with lowest in no involvement group and highest in GAA group. Day at diagnosis, day of IVIG, total fever duration, IVIG-non-responsive, the leucocyte count pre-IVIG, CRP pre-IVIG, platelets post-IVIG increased gradually with levels of CAA, but hemoglobin pre-IVIG, albumin decreased with levels of CAA, statistically significant differences between four groups ($p < 0.05$). **Conclusion:** In the subacute phase, there is a high rate of CAA. It had higher duration of diagnosis, Resistance to IVIG, leucocyte count, CRP and lower albumin, hemoglobin, age with another groups. The inflammatory response status increases with the level of CAA. There are statistically significant differences in some clinical and laboratory variables in four groups.

Key word: Kawasaki disease, level of coronary artery aneurysm.

1. INTRODUCTION

Kawasaki disease is an acute typhus with systemic vasculitis of unknown etiology commonly seen in children under 5 years of age, gradually becoming the leading cause of acquired heart disease in children, replacing rheumatic heart disease.¹ The disease causes multi-organ lesions, systemic vasculitis is mainly inflammation at small and medium vessels, especially coronary arteries. Other lesions of the disease are self-limited, leaving no sequelae

except coronary artery aneurysms.^{1,2} Lesions to the coronary arteries may occur in 15-25% of cases if left untreated and may cause complications of acute myocardial infarction because long-term coronary thrombosis may cause myocardial ischemia due to coronary artery stenosis and stroke. Injured coronary arteries in the acute stage, especially those dilated with large size, often lead to rupture of aneurysm or stenosis in the following years.³ So what are the clinical and subclinical features in Kawasaki patients according to the level of coronary artery

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aneurysm? Therefore, we conducted this study with the aim of comparing clinical and subclinical features in Kawasaki patients according to the level of coronary artery aneurysm.

2. RESEARCH SUBJECTS AND METHODS

2.1. Subjects

Patients with Kawasaki disease at Cardiovascular Center - Vietnam National Children’s Hospital from January 2019 to June 2022. Diagnosis of Kawasaki follows American Heart Association (AHA) standards [3] in 2017. The standards for assessing the level of coronary artery aneurysm on ultrasound according to Z-score are as follows[3].

Group 1: Level 0: No lesion: < 2.5 Z-score

Group 2: Level 1: Mild dilation: ≥ 2.5 Z-score to < 5 Z-score.

Group 3: Level 2: Moderate dilation: ≥ 5 Z-score to <10 Z-score, and absolute inner diameter <8mm.

Group 4: Level 3: Large or massive dilation: ≥10 Z-score, or absolute inner diameter 8mm.

The level of coronary artery aneurysm was assessed according to the location of the largest lesion.

2.2. Research method: Descriptive study. We compared clinical and subclinical features between 4 groups with coronary artery aneurysms of different levels.

2.3. Data processing method: According to the software SPSS 20.0.

3. RESULTS

3.1. Clinical features according to the level of coronary artery aneurysm

In the period from January 2019 to June 2022, total of 545 Kawasaki patients were selected to be included in the study. Coronary artery aneurysm was taken according to the position of the largest lesion.

Table 1. Rate of coronary artery aneurysm in the acute-subacute stage

	No lesion	Lesion	Mild dilation	Moderate dilation	Large/ massive dilation
Acute stage	238 43.7%	262 56.3%	242 44.3%	51 9.4%	14 2.6%
Subacute stage	302 55.4%	243 44.6%	106 19.4%	99 18.2%	38 7%

Comment: In the acute stage, 56.3% of patients had coronary artery aneurysms, mainly with mild dilatation (44.3%). In the subacute stage, the rate of coronary artery aneurysm in 4 groups were 44.6%, 19.4%, 18.2% and 7%, respectively.

Table 2. Age and gender features of Kawasaki patients according to the the level of coronary artery aneurysm

		Common n=545	No lesion n=302	Mild dilation n=106	Moderate dilation n=99	Large/ massive dilation n=38	p0* - p6*
Gender	Male (%)	330 60.6%	182 60.3%	64 60.4%	59 59.6%	25 65.8%	0.92
	Female (%)	215 39.4%	120 39.7%	42 39.6%	40 40.4%	13 34.2%	

		Common n=545	No lesion n=302	Mild dilation n=106	Moderate dilation n=99	Large/ massive dilation n=38	p0* - p6*
Covid history	Yes	14 9.9%	4 6.2%	5 11.9%	2 8%	3 33.3%	0.048 0.31 0.37 0.26 1 0.05 0.09
	No	127 90.1%	61 93.8%	37 88.1%	23 92%	6 66.7%	
Age (month)		16.4±14.1	17.3±12.8	14.9±12.6	16.6±18	12.6±11.5	0.002
Classification of age groups	<12 months	251 46.1%	117 38.7%	58 54.7%	52 52.5%	24 63.2%	0.001 0.003 0.001 0.001 0.09 0.018 0.3
	12 months	294 53.9%	185 61.3%	48 45.3%	47 47.5%	14 36.8%	

* p0: p common among 4 groups, p1: no lesion - mild dilation, p2: no lesion - moderate dilation, p3: no lesion - large dilation, p4: mild dilation - moderate dilation, p5: mild dilation - large dilation, p6: moderate-large dilatation.

Comment: The overall male/female ratio is 1.5/1. The average age of diagnosis was 16.4 months, 46.1% of children under 12 months of age. The proportion of patients under 12 months gradually increased according to the level of coronary artery aneurysm, the large/massive coronary artery dilatation group had the highest rate (63.2%), the group without coronary artery aneurysm had the lowest rate (38.7%). The difference was statistically significant ($p < 0.05$).

Table 3. Clinical characteristics among coronary artery aneurysm groups

	Common n=545	No lesion n=302	Mild dilation n=106	Moderate dilation n=99	Large/ massive dilation n=38	p0*-p6*
Number of fever days	9.2±3	8.5±2.2	9.4±3.3	10.2±3.6	11.8±4.1	0.0 0.004 0.0 0.0 0.0 0.002
Typical Kawasaki	481 88.3%	285 94.4%	92 86.8%	77 77.8%	27 71.1%	0.0 0.01 0.0 0.0
Atypical Kawasaki	64 11.7%	17 5.6%	14 13.2%	22 22.2%	11 28.9%	0.0 0.0 0.0 0.1

Comment: The average number of fever days was 9.2 days, the highest in the large/massive coronary artery dilatation group (11.8 days). 11.7% had atypical Kawasaki disease, the lowest in the group without coronary artery aneurysm (5.6%), the highest in the large/massive coronary artery dilatation group (28.9%). The number of fever days and the rate of atypical Kawasaki form increased gradually with the level of coronary artery aneurysm. The difference was statistically significant ($p < 0.05$).

Table 4. Date of diagnosis and treatment among coronary artery aneurysm groups

		Common n=545	No lesion n=302	Mild dilation n=106	Moderate dilation n=99	Large/ massive dilation n=38	p0* - p6*
Date of diagnosis	Moderate	7.1±2.6	6.7 ±1.9	7.2±3.1	7.8±2.9	8.5±4.1	0.0 0.27 0.001 0.0 0.001 0.0 0.07
	Min-Max	3- 18	3- 25	3-22	3- 20	3- 25	
Day IVIG	Common	8.5±2.5	8.1±1.7	8.8±3.3	9.1±2.7	9.8±3.1	0.14
	≤10 days	475 87.3%	235 94.0%	137 87.3%	77 77.8%	26 68.4%	0.0 0.267 0.04 0.02 0.05 0.2 0.67
	>10 days	69 12.7%	15 6.0%	20 12.7%	22 22.2%	12 31.6%	
Resistance to IVIG		68 12.5%	13 5.2%	23 14.6%	19 19.2%	13 34.2%	0.0 0.001 0.0 0.0 0.003 0.0 0.02

Comment: The average date of diagnosis was 7.1 days, the earliest was 3 days, the latest was 25 days. The group without coronary artery aneurysm had the earliest mean diagnosis time (6.7 days), and the large/massive dilation group was diagnosed later than the other groups (8.5 days). The average day of IVIG treatment was 8.5 days, the proportion of patients treated with IVIG before 10 days accounted for a high rate (87.3%), in which the large/massive coronary artery dilation group was the lowest (68.4%), the group without coronary artery aneurysm was the highest (94%). The overall rate of resistance to IVIG was 12.5%, the lowest in the group without coronary artery aneurysm (5.2%), the highest in the large/massive dilatation group (34.2%), significantly higher than the other groups. The difference was statistically significant ($p < 0.05$).

3.2. Subclinical features among coronary artery aneurysm groups

Table 5. Some hematological and biochemical characteristics among coronary artery aneurysm groups

	Common n=545	No lesion n=302	Mild dilation n=106	Moderate dilation n=99	Large/ massive dilation n=38	p0*-p6*
Leucocyte count before transfusion 10 ⁹ /L	17.0±6	16.3±5.9	17.0±5.2	18.1±6.4	19.0±6.8	0.01 0.28 0.02 0.0 0.02 0.01 0.16
Hemoglobin before transfusion g/L	100.2±12.4	103.1±13.8	95.9±9.6	97.1±11.6	96.9±13.3	0.0 0.0 0.0 0.0 0.0 0.04 0.81
Platelet count after transfusion 10 ⁹ /L	736.2±245.9	717.1±227.4	826.7±243.2	707.6±261.3	684.8±281.2	0.0 0.0 0.0 0.3 0.2 0.2 0.1
CRP before transfusion mg/L	121.4±71.2	112.4±69.2	130.1±69.7	133.6±76.4	137.6±69.4	0.0 0.0 0.0 0.0 0.0 0.1 0.7
D-dimer before transfusion ng/ml FEU	2198±1539	2252±1521	1762±825	2374±1702	2720±2401	0.3

Comment: The average leucocyte count, CRP gradually increased according to the level of coronary artery aneurysm, in contrast, the hemoglobin and albumin decreased gradually according to the level of coronary artery aneurysm. The difference among the groups was statistically significant ($p < 0.05$). D-dimer before IVIG transfusion gradually increased according to the level of coronary artery aneurysm, the difference was not statistically significant ($p > 0.05$).

4. DISCUSSION

4.1. Epidemiological, clinical and therapeutic features among coronary artery aneurysm groups

In our study, there were 545 patients with Kawasaki disease at the Vietnam National Children's Hospital from January 2019 to June 2022 with the rate of coronary artery aneurysm in the subacute stage was 44.6%, in which the rate of

mild dilation was 19.4%, moderate dilatation was 18.2%, large/massive coronary artery dilatation was 7%. According to studies, the rate of large/massive coronary artery aneurysm was 0.18% in Japan, [4] 0.25-2% in Korea is, [5,6] 8% in Mexico, [7] 7% in the Netherlands. [8] In our study, the rate of large or massive coronary artery dilation in the subacute stage was higher than that in Japan, but similar to studies by M. Dietz in the Netherlands[8] and Garido-Garcia in Mexico.[7] This result was different from the study in Japan, because the study in Japan identified large/massive coronary vasodilation when the inner diameter ≥ 8 mm, in our study and the study of M.Dietz, Garido - Garcia used Z-score according to skin area, large/massive rim dilation when Z-score was ≥ 10 .

Through the study of 545 children with Kawasaki disease, we found that the average age of patients with Kawasaki disease was 16.4 months, the lowest was 1 month old, in which the group less than 12 months of age accounted for 49.4%, similar to the study of author Pham Thao Nguyen (44.2%).[9] The rate of children under 12 months of age gradually increased according to the level of coronary artery aneurysm, the large/massive coronary artery dilation group had the highest rate under 12 months of age (63.2%). The difference among the groups was statistically significant ($p < 0.05$). Kawasaki disease occurred mainly in children under 24 months of age, through studies, the cause of the disease was not clear, the onset of the disease could be caused by infection or viral infection, at this age the immune system was not stable, That was the reason that children get sick most often in this age group. The disease tended to be more common in men than women with a male/female ratio of 1.5/1, similar to a study in Japan.[4] Although the male prevailed, the cause was unknown. CD40 was shown to be an allele with potential genetic risk in Kawasaki disease, [10] in the X-linked gene and was therefore more infected in male than female.

The clinical symptom of Kawasaki was very rich and varied, the prevalence of atypical Kawasaki disease was 11.7%, the lowest in the group without coronary artery aneurysm (5.6%), the highest in the large/massive coronary artery dilation group (28.9%). It was similar to the study of author M.Dietz.[8]

IVIG was thought to be a specific therapy, indicated for early treatment within the first 10 days of the disease. In our study, the mean number of diagnosis days was 7.1 days. The time of diagnosis gradually increased according to the level of coronary artery aneurysm, the lowest in the non-lesion group (6.7 days), the highest in the large/massive coronary artery dilation group (8.5 days). The rate of IVIG transfusion before 10 days was 87.3%, the majority of patients without coronary artery aneurysm received IVIG before 10 days (94%), the large coronary artery aneurysm group had the lowest rate of IVIG transfusion before 10 days with the lowest of (68.4%). Due to the late diagnosis, the large/massive coronary artery dilation group had a later IVIG treatment time and a longer duration of fever than other groups. This result was similar to the study of M. Dietz. The difference between the groups was statistically significant with $p < 0.05$.

Although IVIG and aspirin were highly effective in treating Kawasaki disease and significantly reduced coronary artery aneurysm, about 10-20% of patients failed to respond to IVIG for the first time. According to Pham Thao Nguyen's study, the rate of resistance to IVIG was 13.9%. [9] Our study recorded similar results (12.5%). The rate of resistance to IVIG was lowest in the group without coronary artery aneurysm (5.2%), the highest in the large/massive dilatation group (34.2%), significantly higher than other groups. The difference was statistically significant ($p < 0.05$). The high rate of IVIG non-response in the large/massive dilatation group required improvement of primary therapy for severe cases of Kawasaki disease. A recent meta-analysis suggested that corticosteroid supplement may

be helpful. However, favorable results were found only in the Japan's study and not in the two US's studies.[11]

4.2. Some subclinical features among coronary artery aneurysm groups

From the study result in Table 5, the average leucocyte count before IVIG transfusion of Kawasaki patients was 17 G/L, the group without coronary artery aneurysm had the lowest leucocyte count (16.3 G/L), The massive dilation group had a much higher leucocyte count than the other groups (19G/L), the difference was statistically significant ($p < 0.05$). CRP was a test that reflected the body's inflammatory condition, CRP was usually elevated in the acute stage, decreased in the subacute stage and returned to normal after 6-8 weeks, the average CRP before IVIG transfusion in our study was 121.4 mg/L, the highest was 373.8 mg/L. The group without coronary artery aneurysm had the lowest mean CRP (112.4 mg/L), the highest in the large aneurysm/massive coronary artery dilation group (137.6 mg/L). This result was also similar to that of Pham Thao Nguyen.[9] The leucocyte count, CRP increased gradually according to the level of coronary artery aneurysm, showing a very strong inflammatory response in the moderate dilation – large/massive coronary artery aneurysm dilation groups compared with the groups without lesion - mild coronary artery dilation.

Most of the patients in the study group had mild anemia manifestation, the average hemoglobin before IVIG transfusion was 100.2 G/L, the group without coronary artery aneurysm had the highest hemoglobin (103.1 G/L), the mild dilation group had the lowest hemoglobin (95.9 G/L). This result was consistent with McCrindle's study.[12]

The mean platelet count after IVIG transfusion of the study group was 736.2 G/L, the highest in the group with mild coronary artery dilation (826.7 G/L), the lowest in the with large/massive coronary artery dilatation group (684.8 G/L). From

the results of Table 5, there was the lowest decrease in serum albumin in the large/massive coronary artery dilation group (31.2 g/l), the highest in the group without coronary artery aneurysm (34 g/l). This result was similar to McCrindle's study.[12] The decrease in albumin was higher in the large/massive coronary artery dilation group due to the strong inflammatory response, many various types of cytokines causing capillary leakage: IL-1 β , TNF- α , IL-4, IL-6, IL-8.

Masuzawa found that leukocytosis, low albumin, and elevated D-dimer were risk factors for coronary artery aneurysm.[13] The mean D-dimer value before transfusion was 2199 ng/ml, the highest in the large/massive coronary aneurysm dilation group (2720 ng/ml), the lowest in the mild dilation group (1762 ng/ml). There was no difference in D-dimer among the groups because the number of patients tested for D-dimer was small (80 patients), D-dimer was elevated after the acute stage. Hypercoagulability and vascular inflammation were closely related. Elevated D-dimer level may be caused by vascular infection and were therefore associated with coronary artery aneurysm in patients with Kawasaki disease. D-dimer was an important factor in Kawasaki disease with complex coronary artery aneurysm.

5. CONCLUSION

Kawasaki was seen mainly in children younger than 5 years old, with an average of 16.4 months, more seen in male than female, the male/female ratio was 1.5/1. Patients with coronary artery aneurysm in the subacute stage accounted for 44.6%, mainly the mild-moderate dilatation group, the large/massive coronary artery dilation group had the lowest rate (7%). Large/massive coronary artery aneurysm dilation had a longer diagnostic time, higher resistance to IVIG, elevated CRP, reduced blood albumin, reduced Hb and statistically significant younger age compared with other groups.

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