CLINICAL AND LABORATORY FEATURES OF CORONARY ARTERY ANEURYSMS IN KAWASAKI DISEASE

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ABSTRACT

Objective: *describe clinical and laboratory features of coronary artery aneurysms (CAA) in Kawasaki disease.*

Patients and methods: *545 patiens 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 highets in GAA group. Day at diagnosis, day of IVIG, total fever duration, IVIG-non-responsive, the white blood cell 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).*

Conclusions: *In the subacute phage, there is a high rate of CAA. It had higher duration of diagnosis, IVIG resistance, white blood cell 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 labotory variables in four groups.*

Keyword: *Kawasaki disease, level of coronary artery aneurysm.*

I. INTRODUCTION

Kawasaki disease is an acute febrile illness with systemic vasculitis of unknown etiology commonly found in children under 5 years old, gradually becoming the leading cause of acquired heart disease in children, replacing rheumatic heart disease [1]. This disease causes multi-organ damage, predominantly affecting medium and small vessels, especially the coronary arteries. The other lesions from the disease are self-limiting and do not leave sequelae except for coronary artery aneurysm [1, 2]. Coronary artery aneurysm can occur in 15-25% of cases if left untreated and can lead to acute cardiac ischemia due to prolonged coronary thrombosis resulting from narrowed or dilated coronary arteries, as well as stroke. Damaged coronary arteries during the acute phase, especially dilated ones with larger dimensions, often lead to aneurysm formation or subsequent stenosis [3]. What clinical and subclinical characteristics differentiate Kawasaki patients based on the level of coronary artery aneurysm? Therefore, we conducted this study with the aim of: *Comparing the clinical and subclinical characteristics in Kawasaki patients based on the level of coronary artery aneurysm.*

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II. RESEARCH SUBJECT AND METHOD

2.1. Research subject

Patients diagnosed with Kawasaki disease at the Pediatric Cardiology Center of the Vietnam National Children's Hospital from January 2019 to

June 2022. Kawasaki diagnosis was based on the American Heart Association (AHA) criteria in 2017 [3]. Evaluation criteria for the extent of coronary artery aneurysm according to the American Heart Association (AHA) on echocardiography using Z-scores are as follows: [3]

Group 1: Grade 0: No involvement: < 2.5 Z-score

Group 2: Grade 1: Small aneurysm: ≥ 2.5 Z-score to < 5 Z-score.

Group 3: Grade 2: Medium aneurysm: ≥ 5 Z-score to < 10 Z-score, and an absolute internal diameter < 8 mm.

Group 4: Grade 3: Large or giant aneurysms: ≥ 10 Z-score, or an absolute internal diameter ≥ 8 mm.

The level of coronary artery aneurysm was assessed based on the location with the most significant damage.

2.2. Research Methodology

Descriptive study. We compared the clinical and subclinical characteristics among the 4 groups with varying levels of coronary artery aneurysm.

2.3. Data analysis method

Using SPSS 20.0 software.

III. RESULTS

3.1. Clinical Characteristics based on the level of coronary artery aneurysm

During the period from January 2019 to June 2022, a total of 545 Kawasaki disease patients were selected for the study. The coronary artery aneurysm was assessed based on the location with the most significant lesion.

Table 1. Rate of Coronary artery aneurysm in the acute-subacute phase

	No involvement	With involvement	Small aneurysm	Medium aneurysm	Large or giant aneurysm
Acute phase	238 43,7%	262 56,3%	242 44,3%	51 9,4%	14 2,6%
Subacute phase	302 55,4%	243 44,6%	106 19,4%	99 18,2%	38 7%

Comment: In the acute phase, 56.3% of patients had coronary artery aneurysm, mainly small aneurysm (44.3%).

In the subacute phase, the rates of coronary artery aneurysm for the 4 groups were 44.6%, 19.4%, 18.2% and 7%, respectively.

Table 2. Age and gender characteristics of Kawasaki patients based on the level of coronary artery aneurysm

		General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm 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%	
Covid history	Yes	14 9.9%	4 6.2%	5 11.9%	2 8%	3 33.3%	0.048 0.31
	No	127 90.1%	61 93.8%	37 88.1%	23 92%	6 66.7%	0.37 0.26 1 0.05 0.09

Table *(continued)*

		General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm n=38	p0* - p6*
Age (month)		16.4±14.1	17.3±12.8	14.9±12.6	16.6±18	12.6±11.5	0.002
Age group classification	<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: common p-value among 4 groups, p1: no involvement-small aneurysm, p2: no involvement-medium aneurysm, p3: no involvement-large aneurysm, p4: small aneurysm-medium aneurysm, p5: small aneurysm-large aneurysm, p6: medium aneurysm-large aneurysm.

Comment: The overall male-to-female ratio was 1.5:1. The average age at diagnosis was 16.4 months, with 46.1% of patients under 12 months. The proportion of patients under 12 months increased gradually based on the level of coronary artery aneurysm, with the group of large/giant aneurysms having the highest percentage (63.2%), while the no involvement group had the lowest (38.7%). The differences were statistically significant (p<0.05).

Table 3. Clinical characteristics among groups with coronary artery aneurysm

	General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm 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 0.0 0.002
Typical Kawasaki	481	285	92	77	27	0.0
	88.3%	94.4%	86.8%	77.8%	71.1%	0.01
Atypical Kawasaki	64 11.7%	17 5.6%	14 13.2%	22 22.2%	11 28.9%	0.0 0.0 0.0 0.0 0.1

Comment: The average fever duration was 9.2 days, peaking at 11.8 days in the large/giant aneurysm group. 11.7% of Kawasaki cases were atypical, with the lowest percentage in the no involvement group (5.6%) and the highest in the large/giant aneurysm group (28.9%). Both fever duration and atypical Kawasaki cases increased progressively with the level of coronary artery aneurysm. The differences were statistically significant (p <0.05).

Table 4. Diagnosis and treatment days among groups with coronary artery aneurysm

		General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm n=38	p0* - p6*
Diagnosis date	Average	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	
IVIG date	General	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%	
IVIG resistance		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 diagnostic day was 7.1 days, ranging from 3 to 25 days. The no involvement group had the earliest average diagnostic time (6.7 days), while the large/giant aneurysm group had the latest (8.5 days). The average intravenous immunoglobulin (IVIG) treatment day was 8.5 days, with a high proportion of patients receiving IVIG within 10 days (87.3%), with the large/giant aneurysm group having the lowest (68.4%) and the no involvement group having the highest (94%). The IVIG resistance rate was 12.5%, being lowest in the no involvement group (5.2%) and highest in the large/giant aneurysm group (34.2%), significantly higher than the other groups. The differences were statistically significant (p <0.05).

3.2. Subclinical characteristics among groups with coronary artery aneurysm

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

	General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm n=38	p0* -p6*
White blood cell count pre-IVIG 109/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

Table *(continued)*

	General n=545	No involvement n=302	Small aneurysm n=106	Medium aneurysm n=99	Large or giant aneurysm n=38	p0* -p6*
Hemoglobin pre-IVIG 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 post-IVIG 109/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 pre-IVIG 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 pre-IVIGng/ml FEU	2198±1539	2252±1521	1762±825	2374±1702	2720±2401	0.3

Comment: The average white blood cell count and CRP increased progressively with the level of coronary artery aneurysm. Conversely, hematocrit and albumin decreased progressively based on the level of coronary artery aneurysm. Differences among the groups were statistically significant ($p < 0.05$). D-dimer levels pre-IVIG increased with the level of coronary artery aneurysm, but the difference was not statistically significant ($p > 0.05$).

IV. DISCUSSION

4.1. Epidemiological, clinical and treatment characteristics among groups with coronary artery aneurysm

In our study, comprising 545 Kawasaki disease patients at the Vietnam National Children's Hospital from January 2019 to June 2022, the prevalence of coronary artery aneurysm in the subacute phase was 44.6%. Specifically, small aneurysm accounted for 19.4%, medium aneurysm for 18.2%, and large/giant aneurysm for 7%. According to studies, the incidence of large/giant coronary artery aneurysm is 0.18% in Japan [4], 0.25-2% in South Korea [5,6], 8% in Mexico [7], and 7% in the Netherlands [8]. In our research, the prevalence of large or giant aneurysm in the subacute phase was higher compared to Japan but similar to studies conducted by M. Dietz in the Netherlands [8] and Garido-Garcia in Mexico [7]. This discrepancy in findings with Japan may be due to the Japanese study defining large/giant coronary arteries with an inner diameter ≥ 8mm, whereas in our study and those of M. Dietz and Garido-Garcia, Z-scores based on body surface area were used, defining large/giant aneurysm as Z-score ≥10.

Through our study of 545 Kawasaki-affected children, we observed that the average age of Kawasaki patients was 16.4 months, with the youngest being only 1 month old. Among them, the group under 12 months old accounted for 49.4%, akin to findings in Pham Thao Nguyen's study (44.2%) [9]. The proportion of children under 12 months increased gradually with

the level of coronary artery aneurysm, with the group of large/giant aneurysm having the highest proportion of patients under 12 months (63.2%). The differences among these groups were statistically significant (p<0.05). Kawasaki disease predominantly affects children under 24 months, and various studies suggest unclear etiology, with possible triggers being infections or viral exposure. The instability of the immune system at this age likely contributes to the disease's prevalence among this age group. While Kawasaki disease tends to occur more frequently in males, with a male-to-female ratio of 1.5:1, similar to studies in Japan [4], the precise cause for this predominance in males remains unclear. The CD40 gene has been identified as a potential hidden genetic risk factor in Kawasaki disease [10], located on the X chromosome, possibly explaining the higher incidence among males.

The clinical symptoms of Kawasaki disease are diverse and extensive, with an atypical occurrence rate of 11.7%. This rate is lowest in the no involvement group (5.6%) and highest in the large/giant aneurysm group (28.9%). Similarly, M. Dietz's study showed parallel findings [8]. Intravenous immunoglobulin (IVIG) is considered a specific treatment method, recommended for administration within the first 10 days of the disease. In our study, the average diagnostic time was 7.1 days. The diagnostic time increased progressively with the level of coronary artery aneurysm, being lowest in the no involvement group (6.7 days) and highest in the large/giant aneurysm group (8.5 days). The proportion of IVIG administered within 10 days was 87.3%, with the majority of patients in the no involvement group receiving IVIG within this timeframe (94%). However, the large/giant aneurysm group had the lowest proportion of IVIG administered within 10 days (68.4%). Due to delayed diagnosis, the large/giant aneurysm group received IVIG treatment later and had a longer duration of fever compared to other groups. These results align with M. Dietz's study, showing statistically significant differences among the groups (p<0.05).

Even though intravenous immunoglobulin (IVIG) and aspirin are highly effective in treating Kawasaki disease and significantly reducing coronary artery aneurysm, approximately 10-20% of patients do not respond to the initial IVIG treatment. According to Pham Thao Nguyen's study, the IVIG resistance rate is 13.9% [9]. Our study yielded similar results (12.5%). The lowest IVIG resistance rate was in the no involvement group (5.2%), while the highest was in the large/giant aneurysm group (34.2%), significantly higher than other groups with a statistically significant difference (p<0.05). The high rate of non-response to IVIG in the large/giant aneurysm group necessitates improved primary therapies for severe Kawasaki cases. Recent meta-analyses have suggested that adjunctive corticosteroid therapy might be beneficial. However, favorable outcomes have been found only in Japanese studies and not replicated in two studies conducted in the United States [11].

4.2. Some subclinical characteristics among groups with coronary artery aneurysm

The results from Table 5 indicate that the average white blood cell count pre-IVIG in Kawasaki disease patients is 17 G/L. The no involvement group had the lowest white blood cell count (16.3 G/L), while the large/giant aneurysm group had significantly higher white blood cell counts compared to other groups (19 G/L), with a statistically significant difference (p < 0.05). CRP, a marker of body inflammation, typically rises during the acute phase, decreases in the subacute phase, and returns to normal after 6-8 weeks. In our study, the average CRP pre-IVIG was 121.4 mg/L, peaking at 373.8 mg/L. The no involvement group had the lowest average CRP (112.4 mg/L), while the large/giant aneurysm group had the highest (137.6 mg/L). These results align with findings from Pham Thao Nguyen's study [9]. The white blood cell count and CRP increased progressively with the level of coronary artery aneurysm, reflecting a robust inflammatory response in the moderate to large/giant aneurysm groups compared to the no involvement to small aneurysm groups.

Most patients in the study cohort exhibited mild anemia, with the average hematocrit pre-IVIG being 100.2 G/L. The no involvement group had the highest hematocrit level (103.1 G/L), while the small aneurysm group had the lowest (95.9 G/L). These findings are consistent with McCrindle's study [12].

The average platelet count after IVIG administration in our study cohort was 736.2 G/L. It was highest in the small aneurysm group (826.7 G/L) and lowest in the large/giant aneurysm group (684.8 G/L). Results from Table 5 show a decrease in serum albumin, with the lowest levels observed in the large/giant aneurysm group (31.2 g/L) and the highest in the no involvement group (34 g/L). These findings mirror McCrindle's study [12]. The greater decrease in albumin levels in the large/giant aneurysm group is due to a strong inflammatory response and the leakage of various cytokines, including IL-1β, TNF-α, IL-4, IL-6, and IL-8, through capillary vessels.

Masuzawa noted that increased white blood cells, low albumin, and elevated D-dimer are risk factors for coronary artery aneurysm [13]. The average D-dimer value pre-IVIG was 2199 ng/mL, peaking in the large/giant aneurysm group (2720 ng/mL) and lowest in the small aneurysm group (1762 ng/mL). There was no significant difference in D-dimer among the groups due to fewer patients undergoing D-dimer testing (80 patients). Elevated D-dimer levels post-acute phase suggest potential blood vessel infections, closely linked to Kawasaki disease-associated coronary artery aneurysm. Increased D-dimer is an important factor in complex coronary involvement in Kawasaki disease.

V. CONCLUSION

Kawasaki disease predominantly affects children under 5 years old, with an average age of 16.4 months. It occurs more frequently in boys than girls, with a male-to-female ratio of 1.5:1. Among the patients, 44.6% exhibited coronary artery aneurysm during the subacute phase, primarily in the mild to medium aneurysm groups, while the large/giant aneurysm group had the lowest occurrence (7%). Large/giant aneurysm coronary involvement was associated with prolonged diagnostic periods, higher IVIG resistance, increased CRP levels, decreased serum albumin, reduced hemoglobin, and significantly younger ages compared to other groups.

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