CHARACTERISTIC FINDINGS OF CORONARY ARTERY LESIONS IN INTRAVENOUS IMMUNOGLOBULIN NON-RESPONSIVE KAWASAKI DISEASE

Pham Thao Nguyen[1], Dang Thi Hai Van[1], Le Hong Quang[2], Nguyen Huong Giang[2]

1. Hanoi Medical University, 2. Vietnam National Children's Hospital (VNCH)

ABSTRACT

Objectives: *To determine characteristic findings of coronary artery lesions in acute phase of the intravenous immunoglobulin (IVIG) -non-responsive and -responsive Kawasaki children in the Vietnam National Children's Hospital (VNCH).* ***Methods:*** *Prospective, descriptive study on 251 patients who were diagnosed with Kawasaki disease at Vietnam National Children's Hospital from January 2019 to June 2020.* ***Results:*** *13.9% of patients was non-responsive with IVIG; 35.1% of patients had coronary artery lesions (CAL). Severity of CAL was mainly mild and moderate. 60% of IVIG-non-responsive patients had CAL with 28.6% mild, 28.6% moderate and 42.8% severe cases. IVIG-non-responsive patients had higher rate and more severe level of CAL than IVIG-responsive patients. White blood cells count, neutrophil count and serum C-reactive protein(CRP), albumin had statistically significant differences between two groups (p<0,05).* ***Conclusions:*** *IVIG-non-responsive patients had higher rate and more severe level of CAL than IVIG responsive patients. There were statistically significant differences in some laboratory variables between IVIG- non-responsive and -responsive group.*

Keywords: *Kawasaki disease, intravenous immunoglobulin resistant Kawasaki.*

1. INTRODUCTION

Kawasaki is an acute scarlet fever with an unexplained systemic vasculitis affecting among children < 5 years of age. The disease was first described by Tomisaku Kawasaki in Japan in 1967. Then it was declared in the world with different incidence rates between countries. The Northeast Asian countries have had a high prevalence, especially Japan and South Korea [1].

The disease causes the lesions to multiple organs, systemic vasculitis with mainly small and medium vessels, especially the coronary artery lesions. Other lesions of the disease are self-limited without leaving sequelae except for the coronary artery lesions. In developed countries, Kawasaki is the most common cause of congenital heart disease. The coronary artery lesions account for 15-25% of cases if untreated and may cause acute myocardial infarction due to coronary thrombosis and in the long term, it can cause myocardial ischemia due to coronary stenosis and stroke. This is the main cause of disability and death in Kawasaki patients [2].

Received: October 15th, 2020
Accepted: November 25th, 2020
Corresponding author: Pham Thao Nguyen
Address: Pediatrics Course- Hanoi Medical University

Many studies have shown that in the acute phase, using high doses of intravenous Immunoglobulin (IVIG) can reduce the risk of coronary artery lesions in Kawasaki patients. However, 15-20% of intravenous immunoglobulin (IVIG) -non-responsive Kawasaki patients and IVIG -non-responsive patients have a 9 times higher risk of coronary artery lesions than the IVIG-responsive patients. Therefore, if the IVIG -non-responsive patients are detected and treated early, it will reduce the rate of coronary artery lesions and the cost of treatment and length of hospital admission [3]. So, what is different characteristics of coronary lesions in the intravenous immunoglobulin (IVIG) -non-responsive and -responsive Kawasaki patients? To answer this question, we conducted the study with the objectives: To determine characteristic findings of coronary artery lesions in acute phase of the intravenous immunoglobulin (IVIG) -non-responsive and -responsive Kawasaki children in the Vietnam National Children's Hospital (VNCH).

2. SUBJECTS AND METHODS

2.1. Subjects: 251 patients were diagnosed with Kawasaki disease based on the standards of the American Heart Association and received IVIG treatment at the Vietnam National Children's Hospital (VNCH) from January 2019 to June 2020 with full medical information and records excluding Kawasaki patients who were not treated with IVIG.

2.2. Study design: Prospective, descriptive study (progressive study).

2.3. Methods

Diagnosis of Kawasaki based on the standards of the American Heart Association [2]:

* Typical Kawasaki disease: The patients had >5/6 following clinical criteria:

- High fever persisting> 5 days: compulsory.

- Bilateral conjunctival congestion.

- Changes in limbs: Red, purple palms - legs, edema of hands - feet, scalp fingertips - feet.

- Changes in the oral cavity: Dark red lips, bleeding cracks; red, prickly tongue; redness in oral cavity.

- Multiform skin erythema

- lymph nodes in the jaw angle or below chin with a diameter> 1.5 cm.

* Atypical Kawasaki disease: According to the atypical Kawasaki diagnostic chart of the American Heart Association [2].

All patients who were diagnosed with Kawasaki in the study were treated with IVIG at a dose of 2g/kg by slow intravenous infusion within 10 to 12 hours.

Criteria of IVIG non-response based on the American Heart Association: IVIG non-response is defined as fever> 37.5°C lasting more than 36 hours after the end of IVIG or resuming fever after several days and being accompanied by one or more many major symptoms of the disease and excluding other causes of fever [2].

Variables of the study

- Age, gender, date of diagnosis, date of IVIG and clinical symptoms.

- Test of blood count, blood biochemistry before IVIG.

- All patients were performed echocardiography before and after IVIG to evaluate the CAL. Evaluating the CAL based on the standards of the American Heart Association and calculating Z-score by skin area with the level of CAL were as follows:

+ Grade 0 - No lesion: <2.5 Z-score

+ Grade 1 - Mild:> 2.5 and <5 Z-score

+ Grade 2 - Moderate:> 5 and <10 Z-score and absolute diameter <8 mm.

+ Grade 3 - Severe or very severe:> 10 Z-score or absolute diameter> 8 mm.

- Particularly for LCx, evaluating the lesion was based on the criteria of the Japan Heart Association, on the absolute diameter of the

mild of CAL. Specifically, grade 0 (no lesion): <3mm, grade 1 (mild):> 3mm and <4mm, grade 2 (moderate):> 4mm and <8mm and grade 3 (severe or very severe): > 8mm.

- Collecting the data was based on study patterns of medical records; processing the data was based on statistical methods using SPSS 20 software, appropriate statistical tests, when comparing the difference with statistical significance with p < 0.05.

3. RESULTS

3.1. General characteristics of study subjects

Among 251 Kawasaki patients from January 2019 to June 2020, there were 35 IVIG-non-responsive patients, accounting for 13.9%.

Table 1. Clinical characteristics between IVIG responders and non-responders

Clinical characteristics		Total (n =251)		IVIG responders (n=35)		IVIG non-responders (n=216)		p
		n	%	n	%	n	%	
Age (month)	<12 months	111	44,2	17	48,6	94	43,5	p>0,05
	12-24 months	78	31,1	9	25,7	69	31,9	
	>24 months	62	24,7	9	25,7	53	24,6	
	Median	13,5		12,2		13,5		
Gender	Male	146	58,2	20	57,1	126	58,2	p>0,05
	Female	105	41,8	15	42,9	90	41,8	
Kawasaki disease	Typical	211	84,1	25	71,4	186	86,1	0,028
	Atypical	40	15,9	10	28,6	30	13,9	
Median diagnosis date		6		6		6		p>0,05
IVIG	≥ ≥10 days	51	20,3	6	17,1	45	20,8	p>0,05
	<10 days	200	79,7	29	82,9	171	79,2	
	Median	7		8		7		

Comments: IVIG non-response was seen in more children under 12 months of age, but the difference was not statistically significant. The rate of atypical form in the IVIG non- responders was higher than that in the IVIG responders (p <0.05). Most patients in both groups received the IVIG 10 days before.

3.2. Characteristics of CAL in the acute phase

Table 2. Rate of CAL before and after the IVIG between IVIG responders and non-responders

Characteristics of CAL	Chung (n = 251)		IVIG non-responders (n = 35)		IVIG responders (n = 216)		p OR (95%CI)
	n	%	N	%	n	%	
Lesions before the IVIG	75	29,9	18	51,4	57	26,4	0,003 3,0 (1,4 - 6,1)
Lesions after the IVIG	13	5,2	3	8,6	10	4,6	p>0,05
Total	88	35,1	21	60,0	67	31,0	0,001 3,3 (1,6 - 7,0)

Comments: The total rate of CAL was 35.1%. Before and after the IVIG, the rate of CA in the IVIG non-responders was higher than that in the IVIG responders.

Table 3. Locations of CAL between IVIG responders and non-responders

Locations of CAL	Total (n = 88)		IVIG non-responders (n = 21)		IVIG responders (n = 67)		p
	n	%	n	%	n	%	
RCA	77	87,5	20	95,2	57	85,1	0,023
LMCA	61	69,3	17	80,9	44	65,7	>0,05
LAD	73	82,9	20	95,2	53	79,1	>0,05
Lcx	4	4,5	2	9,5	2	3,0	>0,05
Lesions in both coronary arteries	71	80,7	20	95,2	51	76,1	>0,05
Right coronary artery extremities	6	6,8	0	0	6	9,0	>0,05
Left coronary artery extremities	11	12,5	1	4,8	10	14,9	>0,05

Comments: The most common lesion location was at RCA (87.5%), followed by LAD (82.9%) and LMCA 69.3%. LCx was least common, only 4 patients (4.5%). The same occurred in both the IVIG responders and non-responders.

Table 4. Severity of CAL in the acute phase between IVIG responders and non-responders

Severity of CAL	Total (n = 88)		IVIG non-responders (n = 21)		IVIG non-responders (n = 67)		p
	n	%	n	%	n	%	
Mild	32	36,4	6	28,6	26	38,8	0,042
Moderate	36	40,9	6	28,6	30	44,8	
Severe/giant	20	22,7	9	42,8	11	16,4	
Total	88	100	21	100	67	100	

Comments: In the IVIG non-responders, the lesions were mainly severe or giant (42.8%), which was higher than that in the IVIG responders (16.4%). The difference was statistically significant ($p < 0.05$).

Table 5. Comparison of some clinical and subclinical factors of patients with the CAL between IVIG responders and non-responders

Related factors		IVIG non-responders (n=21)	IVIG responders (n=67)	p1	p2
Age	<12 months	12 (57,1%)	40 (59,7%)	0,835	0,478
	>12 months	9 (42,9%)	27 (40,3%)		
Gender	Male	13 (61,9%)	40 (59,7%)	0,874	0,952
	Female	8 (38,1%)	27 (40,3%)		
WBC (G/L)		20,9 ± 5,7	17,7 ± 5,9	0,032	0,502
Neutrophils (ANC) (G/L)		14,0 ± 5,3	12,3 ± 13,4	0,008	0,600
CRP (mg/L)		170,6 ± 53,1	128,0 ± 58,5	0,013	0,026
Albumin (g/L)		29,2 ± 5,1	31,8 ± 4,4	0,025	0,042

p1: Univariate test

p2: Logistic multivariate regression

Comments:

- In patients with the CAL, the total WBC and ANC, CRP count of the IVIG non-responders was higher than that of the IVIG responders. In contrast, the mean blood albumin was lower in univariate analysis. The difference was statistically significant ($p < 0.05$).

- Using multivariate regression model showed that CRP and albumin were independent risk factors leading to the IVIG non-response in Kawasaki patients with the CAL.

4. DISCUSSION

4.1. General characteristics of study subjects

In our study, the mean age of Kawasaki patients was 18.3 months, and the median age was 13.5 months. Of those, 44.2% of patients was less than 12 months; 31.1% of patients was from 12-24 months and 24.7% of patients was over 24 months, similar to the study of Ya-Chiao Hu et al [4]. The disease tends to be seen in male more than female with a male/ female ratio of 1.4/1, similar to other studies [2], [4].

Although IVIG and aspirin were highly effective in treating Kawasaki and significantly reduced the CAL, there were still about 10-20% of patients who did not respond to 1st IVIG [3]. Xie et al. conducted a study on 560 Kawasaki patients and showed that the rate of IVIG non-responsive Kawasaki patients was 10%, of those more male than female [5]. According to the study by Dang Thi Hai Van, the rate of IVIG non-response was 15% [6]. Our study also noted similar results, with the IVIG non-response rate was 13.9%, of those, the male/ female ratio was 1.3/1.

According to Chbeir studies, there was no difference in age and date of IVIG between the IVIG responders and non-responders. Thus, although the age and date of IVIG was shown to be related to the CAL but not a risk factor for the IVIG non-response [7]. Our study also found similar findings.

4.2. Characteristics of CAL in the acute phase

Other lesions of the disease were self-limited without leaving sequelae except the CAL. In developed countries, Kawasaki is the most common cause of congenital heart disease. Coronary lesions occur in 15-25% of cases if untreated and can cause serious consequences

[2]. In our study, the rate of CAL in the acute phase before the first IVIG was 29.9%; this rate increased to 35.1% immediately after the IVIG, of those, 13 patients (5.2 %) with new lesions appeared after the IVIG. The studies of Xue and De La Harpe have shown that the rate of CAL in the acute phase was 46.08% and 40.9% respectively [8], [9], higher than our findings. According to the study by Dang Thi Hai Van, this rate was 29% [6]. In addition, the rate of CAL in the IVIG non- responders was higher than that in the IVIG responders (60.0% vs. 31.0%). The difference was statistically significant (p <0.05). This result was similar to the studies by Xie and Xue [5], [8].

In the study, the CAL was mainly mild and moderate (36.4% and 40.9%) and severe or giant rate was smaller (22.7%). The rate of severe or giant CAL in the IVIG non-responders was much higher than that in the IVIG responders (42.8% vs. 16.4%). The difference was statistically significant (p <0.05). In which, the most common lesions were in the right coronary artery system than the left coronary artery, most commonly found in RCA (87.5%), followed by LAD (82.9%) and LMCA (69.3%). LCx was least common, only 4 patients (4.5%). The rate of CAL at different positions in 2 different groups was not statistically significant (p> 0.05). These results were similar to other studies in the world [7], [8], [10].

The table 5 showed the difference in some clinical and subclinical values of patients with the CAL between the IVIG responders and non-responders. Specifically, according to the study, the average number of leukocytes, the total WBC and ANC, CRP count of the IVIG non-responders was higher than that of the IVIG responders. In contrast, the mean blood albumin was lower in univariate analysis. The difference was statistically significant (p <0.05). This difference was likely due to a stronger inflammatory response in the IVIG non-responders than that in the IVIG responders. However, there was no statistically significant difference in age and gender between the two groups (p> 0.05). Using the logistic multivariate regression model for age, gender, WBC and ANC, CRP count and albumin showed that CRP and albumin were independent risk factors leading to the IVIG non-response in patients with the CAL. These results were similar to the studies by Sano, Xie [3], [5].

5. CONCLUSIONS

Kawasaki occurred mainly in children < 5 years of age with median age of 13.5 months; the female rate was more than male with the male/ female of ratio of 1.4 / 1. There are 15.9% of atypical Kawasaki cases. The rate of IVIG non-response of the study was 13.9%. The patients with the CAL in the acute phase accounted for 35.1%, of which mainly mild and moderate lesions. The IVIG non-responsive patients had higher rate of CAL and severity than those of IVIG responsive patients (p <0.05). Some subclinical values showed statistically significant differences between two IVIG responders and non-responders (p <0.05).

REFERENCES

1. Kawasaki T. (2006). Kawasaki disease. Proc Jpn Acad Ser B Phys Biol Sci, 82(2), 59-71.

2. McCrindle B.W., Rowley A.H., Newburger J.W., et al. (2017). Diagnosis, Treatment, and Long-Term Management of Kawasaki Disease: A Scientific Statement for Health Professionals From the American Heart Association. Circulation, 135(17).

3. Sano T., Kurotobi S., Matsuzaki K., et al. (2006). Prediction of non-responsiveness to standard high-dose gamma-globulin therapy in patients with acute Kawasaki disease before starting initial treatment. European Journal of Pediatrics, 166(2), 131-137.

4. Hu Y.-C., Liu H.-M., Lin M.-T., et al. (2019). Outcomes of Kawasaki Disease Children With Spontaneous Defervescence Within 10 Days. Front Pediatr, 7.

5. Xie T., Wang Y., Fu S., et al. (2017). Predictors for intravenous immunoglobulin resistance and coronary artery lesions in Kawasaki disease. Pediatr Rheumatol Online J, 15.

6. Dang Thi Hai Van, Le Nam Tra, Ho Sy Ha. (2007). Clinical and subclinical characteristics of Kawasaki disease in children. Journal of Medical Research, 55 (6), 26-33.

7. Chbeir D., Gaschignard J., Bonnefoy R., et al. (2018). Kawasaki disease: abnormal initial echocardiogram is associated with resistance to IV Ig and development of coronary artery lesions. Pediatric Rheumatology, 16(1), 48.

8. Xue M. and Wang J. (2020). Utility of color Doppler echocardiography combined with clinical markers in diagnosis and prediction of prognosis of coronary artery lesions in Kawasaki disease. Experimental and Therapeutic Medicine, 19(4), 2597-2603.

9. De La Harpe M., di Bernardo S., Hofer M.,et al. (2019). Thirty Years of Kawasaki Disease: A Single-Center Study at the University Hospital of Lausanne. Front Pediatr, 7.

10. AM Schroh. (2015). Coronary lesions in Kawasaki Disease. Argentine journal of cardiology, 83(1).