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Original Article (Pages: 9027-9036)

Predictors of Intravenous Immunoglobulin (IVIG) Resistance in Children with Kawasaki Disease in Calabria Region, Italy

*Valentina Talarico[1], Sara Rizzo[2], Maria Cirillo[1], Paola Chiarello[1], Roberta Bianchi[1], Roberto Miniero[2], Maria Concetta Galati[3], Giuseppe Raiola[1]

[1]Unit of Pediatrics, Pugliese-Ciaccio Hospital, Catanzaro, Italy.
[2] Department of Pediatrics, Pugliese-Ciaccio Hospital, Catanzaro, Italy.
[3] Unit of Pediatric Oncohematology, Pugliese-Ciaccio Hospital, Catanzaro, Italy.

Abstract

Background

Kawasaki disease (KD) is the second most common childhood vasculitis and one of the main causes of acquired heart disease in children. Recent work focuses on the early diagnostic importance of those risk factors that indicate resistance to intravenous immunoglobulin (IVIG) treatment. The objectives of this study were to identify clinical, laboratory and/or instrumental factors that could be correlated with the risk of resistance to IVIG and the applicability of standard score systems.

Materials and Methods

We retrospectively reviewed clinical records of 23 children with KD, diagnosed in five consecutive years. They all underwent laboratory and echocardiography investigations and initial treatment with IVIG. Based on the response to IVIG they were divided into two groups: IVIG responders (n=14), and IVIG non-responders (n=9).

Results

39% (n= 9) of patients were non-responders. Laboratory exams were overlapping between the two groups except for platelets ($p < 0.05$), and for triglycerides ($p<0.01$). Among the patients who showed cardiac involvement, 67% were IVIG-resistant ($p=0.0094$; odds ratio [OR] = 20.0). Coronary artery abnormalities (CAA) at onset were present in 8.69% of patients, all non-responders ($p=0.1423$; OR=9.66). In this group of patients there were lower values of sodium ($p<0.05$), and of albumin ($p<0.04$), and higher bilirubin ($p<0.01$).

Conclusion

In our population it has emerged that some laboratory (low platelet levels, high triglyceride levels), and instrumental factors (CAA at onset, especially if associated with hyponatremia, hypoalbuminemia and hyperbilirubinemia) should be evaluated at the time of diagnosis, as important prognostic factors with a more severe KD shape and greater resistance to IVIG.

Key Words: Children, Intravenous Immunoglobulin, Kawasaki disease, Resistance.

*Please cite this article as: Talarico V, Rizzo S, Cirillo M, Chiarello P, Bianchi R, Miniero R, et al. Predictors of Intravenous Immunoglobulin (IVIG) Resistance in Children with Kawasaki Disease in Calabria Region, Italy. Int J Pediatr 2019; 7(2): 9027-36. DOI: **10.22038/ijp.2018.34895.3074**

Corresponding Author:

Valentina Talarico (M.D), Via dei bizantini 259/b, 88046, Lamezia Terme (CZ), Italy. Fax 0961-883118.

Email: talaricovalentina@gmail.com

Received date: Aug.16, 2018; Accepted date: Sep. 22, 2018

1- INTRODUCTION

Kawasaki disease (KD) is an acute inflammatory disorder associated with vasculitis affecting medium-sized vessels (1). KD probably represents an aberrant inflammatory host response to one or more as yet unidentified pathogens occurring in genetically predisposed individuals (2-5). Coronary artery abnormalities (CAA)-aneurysm or dilatations are the most serious complication of KD, which is the most common cause of acquired heart disease in children in developed countries (1). It affects 8.1/100000 children under the age of 5 years in the UK and 123/100000 in Japan (2, 5-7). Diagnosis of KD is made on the presence of six principal symptoms, including persistent fever, bilateral conjunctival congestion, erythema of lips and oral cavity, polymorphous exanthema, changes in peripheral extremities and non-purulent cervical lymphadenopathy (8).

Patients with these principal symptoms are diagnosed with typical KD (8, 9). In some cases, patients do not fulfill the classic criteria for KD and are classified as having incomplete disease. A recent Australian study estimates that this occurs in 9.6% of cases (10, 11). On the other hand, atypical KD is said to be present when there are atypical manifestations, as for instance nephritis (12), pneumonia (13), arthritis (14), myositis (15), uveitis (16), retinal vasculitis (17) and CNS involvement (18). The risk of coronary abnormalities in incomplete or atypical forms of KD is comparable with classic KD (19). Considering that KD is an inflammatory pathology, it is now confirmed that timely administration of intravenous immunoglobulin (IVIG) is fundamental to reduce inflammation of coronary artery walls and to prevent coronary damage (20). In fact, a single high dose of IVIG, combined with acetylsalicylic acid, is the gold standard therapy in the acute stage of KD (20). However, about 10-20% of KD patients have persistent fever, despite the initial IVIG therapy (2, 21). Children with IVIG resistance are at higher risk for development of CAA. Recent research has focused on identification of predictors of IVIG resistance to implement additional therapies early in the course of illness and prevent coronary lesions (23). The Randomized controlled trial to Assess Immunoglobulin plus steroid efficacy for KD (RAISE) study showed that IVIG plus prednisolone is effective as the initial treatment for CAA prevention in patients with higher risk of IVIG resistance (24).

Chen's meta-analysis provides convincing evidence that steroids combined with IVIG as initial treatment reduces overall risk of CAA in sever KD (25). Nevertheless, there is no current consensus regarding the factors for predicting patients not responsive to IVIG and several scoring systems have been developed to identify these children (2, 21). The most important are the Kobayashi et al. (26), Engami et al. (27), and Sano et al.'s scores (28). These scoring systems have identified factors such as patient age, fever duration, proportion of neutrophils, platelets count and the serum levels of sodium, p-reactive protein, total bilirubin, aspartate aminotrasnsferase (AST), and alanine aminotransferae (ALT) (21, 26-28).

Nevertheless, the score has not performed well in non-Japanese populations (20, 29). When these scores were tested in a study in the USA, they demonstrated comparably high specificity for predicting IVIG non-response, but had low sensitivity (2, 30). The clinical implication of this is that if the risk score is "negative", it does not reliably exclude IVIG resistance (2). Attempts to develop a more sensitive and specific score for patients outside of Japan have thus far been unsuccessful. Considering these data, we aimed to describe clinical characteristics and severity factors in KD patients in Calabria Region (Italy), and to analyze the risk factors of refractory form

of KD. Also, we tried to investigate the predictive value of Kobayashi et al., Engami et al., and Sano et al. (28-30), and other proposed prognostic markers for IVIG resistance and CAA.

2- MATERIALS AND METHODS

2-1. Patients

This is a retrospective study, in which we studied consecutive 23 patients who were diagnosed with KD, according to the Diagnostic guidelines for Kawasaki disease (3, 4, 8, 9), at the Unit of Pediatrics, "Pugliese-Ciaccio" Hospital of Catanzaro, Italy, between 2010 and 2015.
We retrospectively reviewed clinical records of these KD patients, and obtained their clinical information, including age at diagnosis, gender, principal symptoms, duration of fever and the results of echocardiography. Laboratory data were obtained before the initial IVIG infusions; these were: white blood cell count (WBC), neutrophils, lymphocytes, hemoglobin, platelet count, C-reactive protein (CRP), procalcitonin (PCT), serum albumin, serum total bilirubin (TB), aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum sodium, gamma-glutamyl transferase (GGT), triglycerides and alkaline fosfatase. All of the patients received a single high-dose of IVIG (2g/kg) within the first 10 days from onset of fever along with aspirin. All parents of the patients gave their informed consent.

2-2. Evaluation of risk for IVIG resistance

The scoring system used for evaluation of the risk to IVIG-resistance were: Kobayashi, Egami and Sano's scores. They have identified factors such as patient age, fever duration, proportion of neutrophils, platelet count, and the serum levels of sodium, C-reactive protein (CRP), tuberculosis (TB), aspartate aminotransferase (AST), and alanine aminotransferase (ALT) (28-30). Patients were defined as IVIG-resistant when they had persistent or recrudescent fever ≥36 h after completion of initial IVIG infusion (36). Patients were divided in two groups: IVIG non responders, and IVIG responders. Baseline variables and laboratories data were analyzed on admission and in correlation with the response to IVIG. The evaluation of risk of IVIG resistance was performed by calculating each of the three risk scores in all patients and we compared the proportion of high-risk patients between IVIG-responsive group and the IVIG-resistant group. Sensitivity and specificity for each score were calculated for all three forms of KD.

2-3. Statistical analysis

Statistical analysis was performed using GraphPad Prism 7.0. Data are expressed as means ± standard deviation (SD), and percentage or medians. Fisher's exact test and Student's t-test were used to compare the data. $p<0.05$ was considered statistically significant.

3- RESULTS

Of the patients (n=23) enrolled, 47.82% (n=11) had typical, 30.43% (n=7) incomplete, and 21.73% (n=5) atypical form of KD. 12 were males and 11 were females, yielding a male-to-female ratio of 1:1. Baseline variables and the laboratory data are shown in **Table.1**. 52.17% of children with KD had cardiac complication at diagnosis: 58.3% typical KD (p=0.41), 25% incomplete KD (p=0.66), and 16.6% atypical KD (p=0.64). Cardiac involvement was represented by: pericardial effusion (83.3%), valve defects (valvular insufficiency) (33.3%), and CAA (16.6%). The correlation between the CAA, and data laboratories are represented in **Table.2**. Treatment with IVIG was given in all patients at an average of 7.60±2.18 days from the start of fever. 39% (5 males, 4 females) of patients

presented with refractory Kawasaki disease: 55.5% typical KD (p=0.68; odds ratio [OR] =1.66), 33.3% incomplete KD (p=1.00; OR=1.25), and only one IVIG resistant patient had an atypical KD (11.1%) (p=0.6106; OR=0.31).The baseline and laboratory data at the diagnosis of KD between IVIG responder and IVIG-resistant group are summarized in **Table.3**. The children with cardiological complications were about 33% (n= 4) of KD responder children and in 67% (n= 8) of IVIG-resistant (p=0.0094; OR=20), in particular CAA were present in all children with typical KD and IVIG-resistant (p=0.1423; OR=9.66). Application of the three risk scores is summarized in **Table.4** (predictive value), and **Table.5** (prevalence of high score).

Table-1: The baseline and laboratory data at diagnosis of KD.

Variables	Typical KD (Mean ± SD)	Incomplete KD (Mean ± SD)	Atypical KD (Mean ± SD)	P-value
Clinical characteristics				
Male (%)	6 (54,5)	3(42,8)	3 (60%)	1,0
Age (months)	23,90±19,9	17±5,7	45,2±41,6	0,05
Fever duration before IVIG (day)	6,72±1,4	7,8±1,28	9,2 ±3,8	0,07
Total fever duration (day)	9,27±3,0	9,14±1,9	11,6±3,6	0,5
Laboratory findings				
WBC ($x10^3/\mu L$)	14,20±6,60	18,3±4,6	15,82±6,78	0,41
Neutrophils, percent	70,35±13,70	60,70±11,41	73,70±14,29	0,20
Lymphocytes, percent	18,84±10,54	27,64±10,62	16,74±11,59	0,16
Hb (g/dL)	10,46±1,16	10,60±1,1	9,76±1,47	0,46
PLT($x10^3/\mu L$)	379,45±98,91	317,4±157,5	396,2±164,2	0,51
Na (mEq/L)	134,91 ±3,50	134,71±3,4	133±3,16	0,57
LDH (UI/L)	595,40±242,79	782,29±344,5	659,80±421,50	0,09
AST (UI/L)	77,55 ±58,45	51,43±27,06	58,60±50,05	0,52
ALT (UI/L)	103,27±92,59	25,43±10,24	53,40±73,4	*0,06*
T- bil (mg/dl)	1,64±2,25	0,18±0,07	0,76±1,14	0,10
GGT (UI/L)	114,45±76,64	15,83±6,58	54,80±42,12	<0,01
AP (UI/L)	228,73±95,64	153,50±29,57	164,60±41,99	0,10
Albumin (g/dl)	2,98±0,62	3,31±0,50	2,80±0,42	0,27
Triglycerides (mg/dl)	270,44±147,29	245,67±129,75	247,0±94,21	0,91
CR**P** (mg/dl)	11,71±10,55	7,47±3,94	18,29±14,01	0,20
PCT (ng/ml)	10,21±22,65	12,64±29,55	13,31±22,23	0,96

WBC:white blood cells; PLT:platelets; Hb:hemoglobin; Na:sodium; AST:aspartate aminotransferase; ALT:alanine aminotransferase; GGT: gamma glutamyltransferase; AP: alkaline phosphatase; CRP:C-reactive protein; PCT: procalcitonin.

Table-2: The Baseline and laboratory findings in children with CAA.

Variables	CAA (-) group (Mean ± SD)	CAA (+) group (Mean ± SD)	P-value
Clinical characteristics			
Male (%)	11 (47,8%)	1 (50%)	1,00
Age (months)	26,04±24,98	30,50±26,16	0.95
Fever duration before IVIG (day)	7,71±2,30	6,5±0,70	0,47
Total fever duration (day)	9,66±2,95	10,5±3,53	0,70
Laboratory findings			
WBC (x10^3/µL)	15,78±8,85	21,65±7,42	0,37
% Neutrophils	66,71±13,05	82,9±13,57	0,10
% lymphocytes	22,02±11,06	10,95±10,25	0,18
Hb (g/dl)	10,38±1,24	10±0,70	0,67
PLT(x103/µL)	366,38±132,74	341,5±60,10	0,79
Na (mEq/L)	134,95±2,99	129±1,41	<0,01
LDH (UI/L)	773,2±498,05	682,5±231,22	0,80
AST (UI/L)	66,61±50,73	53,5±3,53	0,72
ALT (UI/L)	69,19±82,01	64±28,28	0,93
T-Bil. (mg/dl)	0,73±1,21	3,85±4,26	<0,01
GGT (UI/L)	73,7±74,57	77±22,62	0,95
AP (UI/L)	194,55±77,97	184,5±120,92	0,86
Albumin (g/dl)	3,11±0,53	2,3±0,42	<0,04
CRP (mg/dL)	10,69±8,78	24,02±21,46	0,07
PCT (ng/ml)	12,32±24,77	4,33±1,95	0,65

WBC: white blood cells; PLT:platelets; Hb: hemoglobin; Na: sodium; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyltransferase; AP: alkaline phosphatase, CRP: C-reactive protein; PCT: procalcitonin.

Table-3: Laboratory data between the IVIG-responder and IVIG non-responder group.

Variables	IVIG- resistant group (Mean ± SD)	IVIG-responsive group (Mean ± SD)	P-value
WBC (x10^3/µL)	17,3±12,5	15,6±5,6	0,65
% Neutrophils	67,9±13,8	68,2±13,2	0,94
% lymphocytes	20,7±11,3	21,2±11,5	0,90
Hb (g/dl)	10±1,3	10,5±1,0	0,27
PLT (x103/µL)	300,3±139,1	405,2±104,4	<0,05
Na (mEq/L)	134,2±4,3	134,5±2,6	0,81
LDH (UI/L)	827±397,5	722±536,8	0,62
AST (UI/L)	53,6±22,5	73,0±59,2	0,36
ALT (UI/L)	57,5±49,9	75,9±93,4	0,59
T-Bil. (mg/dl)	1,1±2,1	0,9±1,4	0,79
GGT (UI/L)	87,6±67,8	66,2±74,2	0,51
AP (UI/L)	219,7±111,6	178,7±51,4	0,24
Albumin (g/dl)	2,8±0,6	3,1±0,4	0,11
Triglycerides (mg/dl)	360,3±125,2	212,9±98,6	<0,01
CRP (mg/dL)	12,7±10,8	11,2±10,3	0,73
PCT (ng/dl)	11,3±25,6	11,8±23,3	0,96

WBC: white blood cells; PLT: platelets; Hb: hemoglobin; Na:sodium; AST: aspartate aminotransferase; ALT: alanine aminotransferase; GGT: gamma glutamyltransferase; AP: alkaline phosphatase, CRP: C-reactive protein; PCT: procalcitonin.

Table-4: Predictive value for prediction of IVIG resistance in subtype of KD.

Variables	Number (%)	Odds ratio	P-value	Sensitivity	Specificity	PPV	NPV
Kobayashi risk score							
Typical KD	36,3	1,74	0,66	36,3%	75,0%	57,1%	56,2%
Incomplete KD	14,2	0,27	0,36	14,2%	62,5%	14,2%	62,5%
Atypical KD	40,0	1,73	0,62	40,0%	72,2%	28,5%	81,2%
Engami risk score							
Typical KD	54,5	6,0	0,08	54,5%	83,3%	75,0%	66,6%
Incomplete KD	–	–	_	–	–	–	–
Atypical KD	40,0	1,33	1,00	40,0%	66,6%	25,0%	80,0%
Sano risk score							
Typical KD	27,2	4,12	0,31	27,2%	91,6%	75,0%	57,8%
Incomplete KD	–	–	_	–	–	–	–
Atypical KD	20,0	1,25	1,00	20,0%	83,3%	25,0%	78,9%

PPV: Positive predictive value; NPV: Negative predictive value; IVIG: intravenous immunoglobulin.

Table-5: Prevalence of high risk scores for IVIG resistance.

Variables	IVIG – responsive group	IVIG-resistant group	Odds ratio	P-value	Sensitivity	Specificity	PPV	NPV
High risk by KOBAYASHI	21,4%	44,4%	2,93	0,36	44,4%	78,5%	57,1%	68,7%
High risk by EGAMI	28,5%	44,4%	2,00	0,65	44,4%	71,4%	50,0%	66,6%
High risk by SANO	21,4%	11,1%	0,45	1,00	11,1%	78,5%	25.0%	57,8%

PPV: Positive predictive value; NPV: Negative predictive value; IVIG: intravenous immunoglobulin.

4- DISCUSSION

The aims of our study, the first one on Kawasaki disease conducted in Calabria, were to analyze the relationship between demographic data, laboratory and cardiological parameters in patients with KD in relation with IVIG-resistance and the utility of the current scoring system for predicting patients not responsive to IVIG. We showed that these scoring systems, when applied to our population, were low predictors of resistance to IVIG. Moreover, we found that some laboratory (low platelet levels, high triglyceride levels), and instrumental factors (CAA at onset, especially if associated with hyponatremia, hypoalbuminemia and hyperbilirubinemia) should be evaluated at the time of diagnosis, as important prognostic factor for resistance to IVIG. Analyzing demographic data we showed a greater percentage of patients with incomplete form (21.73%) than reported in the past studies (36). There was no statistical significance between sex and the age of onset of KD, except for a later delay of the atypical forms ($p<0.05$). All patients presented elevated inflammatory indices and neutrophilic leukocytosis and median hemoglobin value lower than normal, a sign of anemia probably due to the

inflammatory state. In our study the median value of total bilirubinemia, alkaline phosphates and GGT was higher in patients with typical MK, with statistically significant values for GGT ($p < 0.01$), demonstrating frequent hepatic involvement at the onset of classical pathology (37). The two-dimensional echocardiography showed a cardiovascular involvement in 52.17% of our patients during the acute phase. A recent case report described patients with precocious pericardial effusion and later development of CAA (20). Pericardial effusion in our patients was associated with CAA in 10% of cases and was documented prior to coronary involvement, confirming previous results. Among the different subtypes of KD the incomplete and atypical forms would appear to be associated with a higher risk of developing CAA (38); however, in our study no statistically significant differences in the incidence of CAA between the different subtypes of KD were found, concordant with the findings of the Polish study of Gorczyca (39).

The efficacy of IVIG treatment for KD has been confirmed in several studies (21). However, despite the timely IVIG infusion, approximately 10-20% of patients do not respond to treatment, and show persistent fever (19, 21, 22). These patients, defined as IVIG-resistant, are at higher risk of developing CAA (23). In our study the percentage of IVIG-resistant patients was 39%, with a higher prevalence in male sex (55%), and in patients with typical KD (55.5%). As expected, the group of resistant IVIG patients showed significantly longer mean fever duration than responders ($p<0.01$). Among patients who showed cardiac involvement, the highest incidence occurred in IVIG-resistant subjects (67%), with strongly significant p-value ($p < 0.0094$, OR 20); indicating a clear association between IVIG resistance, and the development of cardiovascular alterations. Evaluating laboratory data in correlation with IVIG-resistance, statistical significance was found only for high triglyceride levels and low platelet values; while none of the other laboratory data correlated with IVIG resistance. By reporting the same laboratory parameters with CAA, statistically significant values were observed for hyponatremia ($p<0.01$), hypoalbuminemia ($p<0.04$), and hyperbilirubinemia ($p<0.01$), all of which are clear predictors of CAA in previous studies, including a large-scale study performed in Japan (40). An important fact is that the patients with CAA are all IVIG-resistant, so these laboratory data in correlation with cardiac alteration, at the diagnosis, represent high risk factors for resistance to IVIG. About the scoring systems, useful for predicting the IVIG resistance, in our study we assessed the ability of Kobayashi (28), Egami (29), and Sano (30), because they are the more established scores.

We showed that the proportion of patients identified as high risk of resistance to IVIG using these scores was not significant between the two groups of responders and IVIG resistant patients, in line with other studies (31-33); however, the evaluation of the OR for the scores of Kobayashi and Egami values >1, indicates that these scores, when high, are strongly associated with the IVIG resistance and can be considered as good indicators. In contrast with moderate/high specificity, their sensitivity never exceeds 50%, so the risk of false negatives is quite high. In our study we observed that the highest percentage of patients at risk of typical KD was with the score of Egami (54.5%), despite the non-significant p-value and the sensitivity and specificity values of 54.5% and 83.3%, respectively. For the incomplete KD the only positive result score was Kobayashi's, but with the absence of positive p-value and low OR.

Among the three risk scores that we investigated for atypical KD, the Kobayashi and the Egami scores showed overlapping results in terms of percentage of patients with indicative values of high risk (40%), but the Kobayashi score has shown higher values of OR, with similar sensitivity and specificity. In accordance with CAA, the Kobayashi score reported indicative values of high risk in 100% of patients with coronary involvement, with the lowest value of p-value and odds ratio of 15, representing the best indicator of coronary involvement risk with respect to other risk scores.

4-1. Limitations of the study

The limits of our study were first of all the small size of the sample under examination; so this means that there was not enough statistical power to identify the certainty of the risk factors of the IVIG resistance; also, it was a retrospective analysis of a series of medical records with the limit of the absence of a follow-up study.

5- CONCLUSION

In conclusion, we have described clinical and laboratory data, assessed their correlation with treatment resistance and the development of cardiac anomalies, especially coronary dilatations. We have shown that in our group of patients with KD the Japanese scoring systems were low predictors of resistance to IVIG, with non-significant values of association of scores with IVIG resistance, sensitivity and variable specificity and therefore do not provide reliable support to determine which patients need corticosteroid treatment. This study is useful to recognize the most frequent clinical and laboratory characteristics at the onset of KD, so as to be able to provide an accurate early diagnosis, implementing the appropriate therapeutic approach as soon as possible, in order to assure a favorable prognosis.

6- CONFLICT OF INTEREST: None.

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