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Retrospective analysis of clinical characteristics and related influencing factors of Kawasaki disease

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Abstract

To compare the clinical characteristics of complete Kawasaki disease (KD) and incomplete Kawasaki disease (IKD), and analyze the possible risk factors of coronary artery lesion (CAL) in KD. The clinical data of 139 children with KD admitted to the hospital from January 2016 to June 2022 were analyzed retrospectively. The differences of clinical characteristics between children with KD and children with IKD were compared. The risk factors of CAL were analyzed using univariate and multivariate logistic regression. Comparison of clinical characteristics between KD and IKD groups, the results showed there was significant difference in terms of conjunctival congestion, rash, lymph node enlargement, hand and foot redness, intravenous immune globulin non reaction and fever time ($P < .05$). Comparison of laboratory indicators between 2 groups, the results showed that there was significantly difference in the levels of neutrophils ($P < .05$). 15 cases (15.31%) in KD group were complicated with CAL, and 17 cases (41.46%) in IKD group were complicated with CAL, and the results showed there was a significant difference between the 2 groups ($P < .05$). Univariate analysis showed that the age and Hb of children with CAL were lower than those of children with nCAL, while C-reactive protein, NT-proBNP, NEUT, and ESR were higher than those of children with nCAL ($P < .05$). Multivariate analysis showed that the increase of NT-proBNP and the decrease of Hb may be independent risk factors for the occurrence of CAL in children with KD. The clinical manifestation of children with IKD is not typical. Compared with KD children, the fever time is longer and the incidence of CAL is higher. Under-age, increased NT-proBNP and decreased Hb may be independent risk factors for CAL in KD children.

Abbreviations: CAL = coronary artery lesions, CRP = C-reactive protein, IVIG = intravenous immune globulin, IKD = incomplete Kawasaki disease, KD = Kawasaki disease.

Keywords: clinical characteristics, coronary artery disease, Kawasaki disease, risk factors

1. Introduction

Kawasaki disease (KD) is an acute febrile and eruptive disease with systemic small and medium-sized arteritis as the main pathological change.[1,2] At present, the cause of the disease is unknown, and it is mostly detected in Asian children under 5 years old.[1,3] Coronary artery lesions (CAL) are common complications of KD, which can lead to ischemic heart disease, myocardial infarction, sudden death and other serious consequences. Timely diagnosis and treatment is the key to reduce CAL. To master the risk factors of CAL and give targeted treatment to children can minimize the risk of CAL. This study aims to retrospectively investigate the clinical data of KD children in the hospital, summarized the clinical characteristics, and analyzed the risk factors of KD complicated with CAL, in order to provide evidence based medical basis for clinical diagnosis and treatment and prognosis of children.

2. Materials and Methods

2.1. General materials

Taking the KD children hospitalized from January 2016 to June 2022 as the research target, the author will analyze their clinical data retrospectively. This study was reviewed and approved by the Medical Ethics Review Committee of the First Affiliated Hospital of Anhui Medical University.

2.1.1. Inclusion criteria.

(1) In compliance with the diagnostic criteria of the American Heart Association (AHA) for KD and incomplete Kawasaki disease (IKD).[1,4]
(2) At the age of 0 to 14.
(3) Complete clinical data of our hospital.

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The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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2.1.2. Exclusion criteria.

(1) Having received intravenous immune globulin (IVIG) treatment before admission.
(2) Having a history of congenital heart disease, rheumatic disease.
(3) Recurrent cases of Kawasaki disease.
(4) Positive blood culture.
(5) Transferring to other hospital for treatment midway.
(6) Incomplete clinical data and statistical data.
(7) Coronary angiography required for CAL.
(8) Incomplete heart color Doppler ultrasound in acute stage.

2.1.3. Diagnostic criteria.

(1) Diagnostic criteria of KD: (i) more than 5 days of fever and responding to early IVIG treatment even if less than 5 days of fever; (ii) oral cavity and lip changes; (iii) conjunctival congestion in both eyes, mostly non exudative, acute iridocyclitis or anterior uveitis; (iv) a changed end of the extremities, hand and foot with edema and erythema in the acute stage, and in the recovery stage with membranous scaling; (v) polymorphic rash, mainly in the trunk, mostly in the perineum; (vi) acute non suppurative lymphadenopathy of the neck, usually unilateral, with a diameter ≥ 1.5 cm (If 5 items are met, the patient can be diagnosed; if 4 items are met, coronary angiography or 2-dimensional ultrasound can be performed to confirm coronary artery dilation or coronary aneurysm can also be diagnosed).
(2) Diagnostic criteria of IKD: on the premise of meeting KD diagnostic criteria, if it has 2 to 3 of the other 6 clinical features, and coronary artery changes are confirmed by cardiac ultrasound, it can be confirmed, excluding other febrile and eruptive diseases such as scarlet fever, measles, toxic shock syndrome, Stevens Johnson syndrome, C-reactive protein (CRP) > 30 mg/L and more than 3 laboratory auxiliary examination indicators: (a) hypoalbuminemia (<30 g/L), (b) anemia, (c) abnormal liver function (elevated alanine aminotransferase or glutamine aminotransferase), (d) abnormal peripheral white blood cell count (>15 × 109/L), (e) Urine routine examination white blood cells > 10/HP, (f) significantly increasing platelet level 1 week after onset (>450 × 109/L).
(3) Diagnostic criteria for CAL: (i) coronary artery dilation exceeding the normal range of coronary artery; (ii) enhanced echo of coronary intima in echocardiography; (iii) coronary aneurysm (coronary artery diameter at 4–7 mm); (iv) Giant coronary artery tumor (the diameter of coronary artery over 8 cm).

2.2. Methods

A total of 155 children were included in this study, and the general information (gender and age), clinical characteristics (conjunctival congestion, rash, lymph node enlargement, hand and foot redness, lip changes, perianal peeling, finger and toe peeling, days of fever), laboratory examination indicators (CRP, WBC, ESR, ALB, HCT, PLT, ALT, AST, NT-proBNP, Hb, NEUT), IVIG usage and other information obtained for retrospective analysis were collected. According to the diagnostic criteria, they were divided into KD group (n = 98) and IKD group (n = 41).

2.3. Statistical methods

The data obtained were statistically analyzed by using SPSS 25.0. The counting data were expressed in percentage (%). The mean ± standard deviation was used to express the measurement data. The independent sample *t*-test was used. Univariate logistic regression analysis was used for possible factors, and then multivariate logistic regression analysis was carried out on the factors with $P < .05$. When $P < .05$, it is considered that the difference is statistically significant.

3. Results

3.1. Comparison of basic information between KD and IKD children

There was no significant difference in gender and age composition between KD and IKD children ($P > .05$), as shown in Table 1.

3.2. Comparison of clinical characteristics between KD and IKD children

There were significant differences between KD and IKD children ($P < .05$) in conjunctival congestion, rash, lymphadenopathy, hand and foot redness, IVIG non reaction and fever time. However, there were no significant differences in labial change, perianal peeling, finger and toe peeling (P > .05) (Table 2).

3.3. Comparison of laboratory indexes between KD and IKD children

There was significant difference in NEUT between KD and IKD children ($P < .05$), but no significant difference was found in CRP, WBC, ESR, ALB, HCT, PLT, ALT, AST, NT-proBNP, Hb (P > .05) (Table 3).

3.4. Comparison of concurrent CAL between KD and IKD children

There were 15 cases of KD complicated with CAL, including 9 cases of rough coronary artery wall, 4 cases of coronary artery dilatation, and 2 cases of coronary artery aneurysm. In the IKD group, 17 cases were complicated with CAL, including 10 cases of rough coronary artery wall, 5 cases of coronary artery dilatation, and 2 cases of coronary artery aneurysm. The incidence rate in the KD group was significantly lower than those in the IKD group (15.31% vs 41.46%, P = .001) (Table 4).

3.5. Analysis of high-risk factors for CAL

Univariate analysis showed that there was no significant difference in gender, average fever time, IVIG use time, IVIG use effect, infection and PLT between CAL and nCAL children ($P > .05$). The age and Hb of children with CAL were significantly lower than those of children with nCAL, while CRP,

Table 1

Comparison of gender and age distribution of KD and IKD children.

		Gender	Age (yr)			
Groups	Cases	Male/Female	<1	1–3	3–5	>5
KD group	98	61/37	22	45	19	12
IKD group	41	24/17	10	18	9	4
χ^2		0.167		0.323		
P		.682		.956		

IKD = incomplete Kawasaki disease, KD = Kawasaki disease.

Table 2

Comparison of clinical characteristics between KD and IKD children.

Clinical characteristics	KD group (n = 98)	IKD group (n = 41)	Statistics	*P*
Fever time (d)	11.25 ± 3.68	13.56 ± 4.21	3.232	.001
Conjunctival congestion [n (%)]	95 (96.94)	34 (82.93)	8.5	.004
Labial change [n (%)]	87 (88.78)	35 (85.37)	0.313	.576
Rash [n (%)]	76 (77.55)	2 (53.66)	7.935	.005
Lymphadenopathy [n (%)]	72 (73.47)	14 (34.15)	18.947	0
Perianal exfoliation [n (%)]	45 (45.92)	16 (39.02)	0.558	.455
Redness and swelling of hands and feet [n (%)]	69 (70.41)	20 (48.78)	5.871	.015
Desquamation of fingers and toes [n (%)]	65 (66.33)	26 (63.41)	0.108	0.742
IVIG non response [n (%)]	7 (7.14)	9 (21.95)	6.223	0.013

IKD = incomplete Kawasaki disease, IVIG = intravenous immune globulin, KD = Kawasaki disease.

Table 3

Comparison of laboratory indexes between KD and IKD children.

Clinical characteristics	KD group (n = 98)	IKD group (n = 41)	Statistics	*P*
CPR (mg/L)	75.36 ± 24.35	70.48 ± 25.31	1.065	.289
WBC ($\times 10^9$/L)	17.02 ± 4.58	16.52 ± 5.14	0.566	.572
ESR (mm/h)	45.32 ± 5.62	43.38 ± 5.61	1.857	.065
ALB (g/L)	35.42 ± 6.72	36.43 ± 7.02	0.797	.427
HCT (%)	30.32 ± 3.89	28.96 ± 4.12	1.847	.067
PLT ($\times 10^{12}$/L)	440.65 ± 120.57	465.12 ± 128.59	1.072	.287
ALT (U/L)	65.86 ± 10.36	64.83 ± 11.72	0.514	.608
AST (U/L)	58.75 ± 11.05	55.35 ± 15.37	1.466	.145
NT-proBNP (ng/L)	500.25 ± 87.56	512.37 ± 95.64	0.724	.47
Hb (g/L)	102.35 ± 18.71	104.37 ± 15.46	0.609	.543
NEUT (%)	67.24 ± 12.58	61.73 ± 10.75	2.453	.015

IKD = incomplete Kawasaki disease, KD = Kawasaki disease.

NT-proBNP, NEUT, ESR were significantly higher than those of children with nCAL (Table 5). Multivariate analysis showed that the increase of NT-proBNP and the decrease of Hb may be independent risk factors for the occurrence of CAL in children with KD (Table 6).

4. Discussion

KD, also known as mucocutaneous lymphoid syndrome, is an acute systemic vasculitis disease of infants under 5 years old.[1,3] The pathogenesis of the disease has not been clarified yet. It is difficult and controversial to diagnose and treat the disease because of its recurrence, diversity, atypical, degree of illness and many other characteristics.[5] In clinical practice, quite a few KD children do not have typical characteristics, and some of them get late or even do not, but judging from the clinical characteristics, they cannot meet the diagnostic criteria of KD.[6]

The current research results show that infants under 3 years old are the high-risk group for KD. Since then, with the increase of age, the incidence of KD has become lower and lower.[1,6,7] Although the reason for the obvious age difference in children with KD cannot be fully explained, recent studies believe that the immature immune system in infants and young children and the inability to defend against many microbial infections are important reasons for KD.[8–10] In this study, 68.34% of children are under 3 years old, which is consistent with the research results of most scholars.[2,11] It can be seen from the comparison of age distribution of KD and IKD that there is no significant statistical difference between the 2, indicating that the age distribution of IKD and KD is consistent. Relevant studies showed that KD has a special male susceptibility. Among 139 children included in the study, 85 were male infants, accounting for 61.15%, which is consistent with previous studies.[12,13] There was no difference in gender between KD and IKD children.

Fever is the first and main clinical manifestation of KD.[14] In this study, all children had persistent fever, the fever time was basically more than 5 days, and the fever temperature was up to 41°C. Compared with KD, the average fever time of children with IKD was longer ($P < .05$). At present, some research results have shown that the fever time of IKD patients is longer than that of KD patients.[15,16] Some scholars have shown that the clinical symptoms of IKD are incomplete, difficulties in diagnosis, treatment delays, and increased complications are fairly common, resulting in long-term fever.[17]

The incidence of conjunctival congestion, rash, lymph node enlargement, and hand and foot redness in the IKD group was significantly lower than that in the KD group. The rate of IVIG non reaction in the IKD group was significantly higher than that in the KD group, suggesting that the sensitivity of children with IKD to IVIG was lower than that of children with KD, which may result in missing the best treatment time for children with IKD and IVIG, because it is harder or takes longer to diagnose.

As an immune mediated systemic vascular inflammation, abnormal activation of the immune system and vasculitis are the main features.[1] Laboratory examination plays a role in assisting KD diagnosis. Children with KD often show elevated WBC, PLT, accelerated ESR, elevated CRP level, abnormal

Table 4

Comparison of concurrent CAL between children with KD and IKD.

Groups	Cases	CAL	nCAL	χ^2	*P*
KD group	98	15 (15.31)	83 (84.69)	11.16	.001
IKD group	41	17 (41.46)	24 (58.54)		

CAL = coronary artery lesions, IKD = incomplete Kawasaki disease, KD = Kawasaki disease.

Table 5

Univariate logistic regression analysis of 32 children with CAL.

Factors	CAL (n = 32)	nCAL (n = 107)	Statistics	*P*
Gender			0.032	.858
Male	20 (23.53)	65 (76.47)		
Female	12 (22.22)	42 (77.78)		
Age (yr)			36.842	< .001
<1	20 (62.50)	12 (37.50)		
1–3	8 (12.70)	55 (87.30)		
3–5	3 (10.71)	25 (89.29)		
>5	1 (6.25)	15 (93.75)		
Average fever time (d)			2.003	.157
≤14	14 (18.42)	62 (81.58)		
>14	18 (28.57)	45 (71.43)		
IVIG use time (d)			0.16	.69
≤4	7 (25.93)	20 (74.07)		
>4	25 (22.32)	87 (77.68)		
IVIG use effect			1.203	.273
Sensitive	10 (18.18)	45 (81.82)		
Unresponsive	22 (26.19)	62 (73.81)		
Infection			0.691	.406
Yes	5 (31.25)	11 (68.75)		
No	27 (21.95)	96 (78.05)		
CPR (mg/L)	82.65 ± 5.61	70.52 ± 8.31	7.737	< .001
NT-proBNP (ng/L)	562.73 ± 104.31	496.75 ± 95.23	3.364	.001
NEUT (%)	69.23 ± 15.31	62.75 ± 12.26	2.472	.015
ESR (mm/h)	45.32 ± 4.87	41.75 ± 5.41	3.348	.001
PLT ($\times 10^{12}$/L)	450.18 ± 108.56	446.35 ± 120.74	0.161	.872
Hb (g/L)	98.31 ± 14.05	105.62 ± 16.30	-2.294	.023

CAL = coronary artery lesions, IVIG = intravenous immune globulin.

Table 6

Multivariate logistic regression analysis of 32 children with CAL.

Factors	β	S.E.	Wald	OR (95% CI)	*P*
Age	0.035	0.246	4.853	2.212 (1.524–2.729)	.037
CPR	0.542	0.647	2.263	1.420 (0.953–1.758)	.462
NEUT	1.224	0.892	2.156	2.02 (0.785–2.594)	.096
NT-proBNP	1.231	0.558	4.239	2.562 (1.452–4.276)	.031
Hb	-0.012	0.035	4.621	0.973 (0.956–0.993)	.023
ESR	0.024	0.295	0.015	1.218 (0.905–1.976)	.893

CAL = coronary artery lesions.

liver function, and abnormal urine test.[1,18] Although they cannot be used as diagnostic indicators alone, their changes are helpful for the early diagnosis of IKD. The results of this study showed that the laboratory indexes of KD children, such as CRP, WBC, ESR, ALB, HCT, PLT, ALT, AST, NT-proBNP, Hb, NEUT, had some changed when compared with the normal range. In the comparison between KD group and IKD group, it was found that only NEUT showed significant statistical difference, suggesting that NEUT has a certain role in helping to distinguish KD and IKD.[19,20] However, there is no significant difference in other indicators, which is somewhat different from the research results of other scholars. This may be that the indicator data used in this study are all indicators after treatment in the acute phase, and cannot reflect the situation in the acute phase.

CAL is the most serious complication of KD, which directly affects the prognosis and even threaten the life safety of children. In this study, the incidence of CAL in children with IKD was significantly higher than that in children with KD, which may result from the late diagnosis and treatment. The analysis of the risk factors of KD children complicated with CAL will help to carry out targeted prevention and improve the prognosis. Li et al showed that long heat duration before IVIG treatment was an independent risk factor for CAL in KD children under 6 months old.[21] Wang et al have also showed that IVIG treatment more than 10 days and hypersensitive CRP more than 100 mg/L were independent risk factors.[22] The analysis of many possible risk factors in this study found that age younger than 1 year, NT-proBNP increase and Hb decrease may be independent risk factors leading to CAL in children with KD, and there is a certain discrepancy with the research results of other scholars, which may be caused by the differences in sample selection and regional differences included in the study.

Our study had several limitations. First, this was a retrospective study and therefore subjected to the inherent limitations of any retrospective study, that is, the current physical and mental state of the subject will affect the authenticity and accuracy of past data reports. Second, there were a limited number of patients enrolled in the present study and therefore more research with lager samples are required to verify these findings. Third, detection of symptoms before hospitalization was partly based on interviews with the parents, who may have failed to recognize some symptoms. Therefore, further study including a greater number of samples is needed to overcome these limitations.

To sum up, the clinical manifestations of children with IKD are not typical. Compared with children with KD, they have a longer fever time and a higher incidence of CAL. The low age, increased NT-proBNP and decreased Hb may be independent risk factors for CAL in KD children.

Author contributions

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