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Original Article

Clinical Features of Kawasaki Disease in Children with an Atypical Age of Onset

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Abstract To evaluate the frequency of patients younger than six months and older than five years in a large cohort of patients with Kawasaki disease (KD), and to determine the clinical characteristics and outcomes of patients with an age of onset outside the typical age distribution. We performed retrospective chart review of KD patients treated at our hospital during a six-year period. Data of patients were record from discharge database. Patients were divided into three groups according to age of onset of illness. The typical age group (6 months to 5 years) was used as a reference, and the clinical features of KD patients ≤6 months old and >5 years of age were analysed. A total of 2,318 cases were enrolled in this study population consisting of 1,432 boys and 886 girls. Cases ≤6 months of age and >5 years of age accounted for 14.7% (340) and 14.0% (325) of the overall sample. Compared with the typical age group, the younger age group had longer of hospital stay, higher proportion of incomplete KD (iKD) cases, fewer illness days at admission, and fewer number of major criteria. Compared with the typical age group, the older age group had longer illness days at admission, longer total fever duration, and higher rate of delayed diagnosis. There were no significant difference between two groups in term of the rates of iKD, intravenous immunoglobin resistance, and coronary artey lesion. Patients with KD ≤6 months of age tend to manifests incomplete symptoms with more pronounced systemic inflammation, while increased awareness contributed to improvement of diagnoses and outcomes. Patients with KD >5 years of age have relatively low levels of systemic inflammation without worse treatment and outcome, but were prone to delayed diagnoses.

Key words *Age; Clinical features; Kawasaki disease*

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Introduction

Kawasaki disease (KD), also known as mucocutaneous lymph node syndrome, is a pediatric systemic vasculitis of unknown origin. Now, it becomes globally common cause of acquired heart disease in children.[1] Intravenous immunoglobin (IVIG) administration at acute onset of illness could reduce the incidence of coronary artery lesions from 15-25% of untreated patients to less than 5%.[2]

KD largely occurred in children within six months to five years of age. This may be associated with an immature immune system, because younger infants were protected by passive acquired maternal antibodies and older children were protected by acquired immunity.[3] The diagnosis and timely treatment of KD may also have improved over time, but early identification of patients at atypical age of onset

are challenge, especially for those who presenting atypical manifestations, due to no specific diagnostic markers for KD. Several study[4-9] have been reported the clinical features of younger and/or older patients with KD, but the small number of these studies weaken the power of the analysis and might resulted in instable results. More information of patients with KD at atypical age is still needed.

The goals of the present study were to evaluate the frequency of patients younger than six months and older than five years in a large cohort of patients with KD, and to determine the clinical characteristics and outcomes of patients with an age of onset outside the typical age distribution.

Methods

Study Population

We performed retrospective chart review of KD patients treated at our hospital during a six-year period (2009.1-2014.12). Data of patients were record from discharge database including three categories: (1) demographic and clinical indicators including gender, age, illness days admission, the numbers of main criteria, total fever duration, days of hospitalisation, effectiveness of the IVIG administation, echocardiographic results during hospitalisation; (2) pre- and post-IVIG complete blood count indicators including erythrocyte sedimentation rate (ESR), c-reactive protein (CRP), white blood cell (WBC), percentages and absolute counts of neutrophils (NE), lymphocytes (LY), eosionphils (EO), monocytes (MO), haemoglobin, platelet; and (3) blood biochemical indicators, including indicators of liver function (alanine aminotransferase (ALT), aspartate transaminase (AST), albumin, total bilirubin (TBil) and gamma-glutamyl transferase (GGT), and serum electrolytes (sodium, potassium, chloride and calcium), measured before IVIG therapy. This retrospective study was approved by the Institutional Review Board of our university hospital and performed in accordance with the Declaration of Helsinki. All participants were given informed consent.

Definitions

The diagnostic symptoms and signs for KD included fever, skin rash, bilateral nonexudative conjunctivitis, erythem of oral and pharyngeal mucosa, swollen extremities and/or palm and sole erythema, and acute non-suppurative cervical lymphadenopathy that is usually unilateral with a size of 1.5 cm or greater in diameter.

Patients who meet 5 of the 6 above criteria can be diagnosed with complete (cKD).[10] Patients who meet 4 criteria or fewer can be diagnosed as incomplete KD (iKD) in the presence or absence of coronary artery lesions (CAL), without other explanations for the febrile disease.[11,12] Both cKD and iKD were enrolled in our study population. Delayed-diagnosis KD was defined as initial IVIG being administrated 10 days post-onset of illness.[13] We defined IVIG resistance (IVIGR) as patients who had a continued fever or recurrence of fever >37.3°C 48 hours to two weeks after initial infusion of IVIG accompanied by at least one of the principal diagnostic criteria.[14] CAL were diagnosed based on two-dimensional echocardiography and defined as the previously reported criteria[15] either when (1) a lumen diameter of ≥2.5 mm in patients <3 years old, ≥3.0 mm in patients within 3-9 years old, and ≥3.5 mm in patients >9 years old, (2) the internal diameter of a segment measures 1.5 times that of an adjacent segment, or (3) the lumen was clearly irregular.

Statistics

Data were listed as median (P25-P75) or the number of cases (%), as appropriately. Two-group comparisons were performed using nonparametric rank sum test for the continuous data, and using chi-square test for the count data. All analyses were carried out with SPSS 16.0 for Windows. Statistical significance was set as p less than 0.05.

Results

Data Collection

A total of 2,318 cases were enrolled in this study population consisting of 1,432 boys and 886 girls. Cases ≤6 months of age and >5 years of age accounted for 14.7% (340) and 14.0% (325) of the overall sample.

Comparison Between the Younger Age (≤6-month-old) Group and the Typical Age (6-month-old to 5-year-old) Group

As shown in Table 1, longer hospital stay, higher proportion of iKD cases, fewer illness days at admission, and fewer number of major criteria were observed in the younger age group compared with the typical age group. There were no significant difference between two groups with regard to the delayed diagnosis rate, the IVIGR rate, and the CAL rate. Comparisons of pre- and post-IVIG CBC between groups were listed in Tables 2 and 3. As shown in

Table 4, higher levels of TBil, GGT, potassium, and calcium, and lower levels of albumin and serum sodium were seen in the younger age group compared with the typical age group.

Comparison Between the Older Age (>5-year-old) Group and the Typical Age Group

As shown in Table 1, longer illness days at admission, longer total fever duration, and higher rate of delayed diagnosis were observed in older age group compared with the typcial age group. There were no significant difference between two groups in term of the rates of iKD , IVIGR, and CAL. Comparisons of pre- and post-IVIG CBC between groups were listed in Tables 2 and 3. As shown in Table 4, higher levels of albumin, TBil and serum sodium, and lower levels of ALT, AST, GGT, serum chloride, serum potassium, serum calcium were in the older age group compared with the typical age group.

Table 1 Comparisons of clinical characteristics between groups

	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
Variables	**n**	**median (p25-p75)/n(%)**	**n**	**median (p25-p75)/n(%)**	**n**	**median (p25-p75)/n(%)**
Male-to-female ratio	340	1.68:1	325	1.71:1	1653	1.59:1
Illness days at admission, days	340	5 (4-7)**	325	6 (5-9)$^{\#\#}$	1653	6 (5-7)
Number of major dignostic criteria	340	3 (2-4)**	325	4 (3-5)	1653	4 (3-5)
Total fever duration, days	338	7 (6-9)	322	8 (6-10)$^{\#\#}$	1650	7 (6-9)
Length of hospitalisation, days	340	7 (5-9)**	325	6 (5-8)	1653	7 (5-8)
Incomplete KD, %	340	272 (80.0)**	325	183 (56.3)	1653	909 (55.0)
Delayed diagnosis, %	326	32 (9.8)	300	33 (11.0)$^{\#}$	1568	103 (6.6)
IVIGR, %	318	43 (13.5)	291	52 (17.9)	1517	285 (18.8)
CAL, %	338	95 (28.1)	322	70 (21.7)	1645	391 (23.8)

**p<0.01 vs group C, $^{\#}$p<0.05 vs group C, $^{\#\#}$p<0.01 vs group C.

IVIGR: intravenous immunoglobin resistance; CAL: coronary artery lesions

Table 2 Comparisons of pre-IVIG CBC between groups

	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
Variables	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**
ESR, mm/h	299	59 (42-84)**	301	58 (34-86)$^{\#\#}$	1511	69 (45-92)
CRP, mg/L	313	90 (49-141)**	299	55 (17-113)$^{\#\#}$	1508	71 (32-123)
WBC, x 10^9/L	314	14.1 (10.5-18.8)**	301	11.0 (7.2-15.3)$^{\#\#}$	1522	12.4 (9.0-16.4)
NE, %	314	55.0 (40.9-67.0)**	301	73.1 (58.4-83.4)$^{\#\#}$	1522	61.2 (46.6-73.8)
Absolute NE, x 10^9/L	314	7.9 (4.7-11.1)	301	7.7 (4.2-12.2)	1522	7.4 (4.4-11.2)
LY, %	314	33.8 (24.6-44.8)**	301	17.4 (10.4-30.6)$^{\#\#}$	1522	28.5 (18.3-41.1)
Absolute LY, x 10^9/L	314	4.7 (3.3-6.2)**	301	1.9 (1.1-2.5)$^{\#\#}$	1522	3.3 (2.3-4.7)
EO, %	313	3.1 (1.3-5.4)**	301	1.5 (0.8-3.1)$^{\#\#}$	1518	2.1 (0.9-4.2)
Absolute EO, x 10^9/L	313	0.42 (0.19-0.73)**	301	0.17 (0.07-0.32)$^{\#\#}$	1518	0.26 (0.11-0.49)
MO, %	313	6.2 (3.8-8.9)*	301	5.9 (3.4-8.3)	1518	5.6 (3.3-8.1)
Absolute MO, x 10^9/L	313	0.8 (0.46-1.36)**	301	0.57 (0.35-0.92)$^{\#\#}$	1518	0.66 (0.40-1.00)
Haemoglobin, g/L	314	97 (90-102)**	301	115 (109-121)$^{\#\#}$	1520	108 (101-114)
Platelet, x 10^9/L	314	450 (352-567)**	301	317 (236-406)$^{\#\#}$	1520	364 (291-459)

*p<0.05 vs group C, **p<0.01 vs group C, $^{\#\#}$p<0.01 vs group C.

CBC: complete blood cell count; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; NE: neutrophils; LY: lymphocytes; EO: eosionphils; MO: monocytes

Discussions

Several investigations about age-related KD have been conducted in the past decades. Chuang et al[4] reported 25 cases of KD in patients ≤3 months of age from 1994-2004; the incidences of changes in the lips and tongue, conjunctivitis, rash, swollen lymph nodes, changes in the extremities and CAL were 84%, 80%, 68%, 28%, 24% and 80%, respectively. Liu et al[5] reported 30 cases of KD in patients <6 months old and also found that swollen cervical lymph nodes were rare and more frequent CAL were seen in these patients, with lower haemoglobin and albumin and higher platelet. Moreno et al[6] reported 25 infants with typical KD in Spain from 1992-2006 and showed

Table 3 Comparisons of post-IVIG CBC between groups

	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
Variables	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**
ESR, mm/h	207	67 (43-88)**	220	75 (53-92)	1139	77 (52-96)
CRP, mg/L	315	6 (3-13)	288	7 (3-16)	1522	6 (2-14)
WBC, x 10^9/L	321	9.4 (7.3-12.1)**	292	6.9 (5.5-8.9)$^{\#\#}$	1540	7.9 (6.2-10.4)
NE, %	321	25.2 (17.4-34.0)**	292	50.1 (41.9-60.9)$^{\#\#}$	1540	35.4 (26.0-47.5)
Absolute NE, x 10^9/L	321	2.3 (1.4-3.7)**	292	3.6 (2.3-5.2)$^{\#\#}$	1540	2.6 (1.8-4.3)
LY, %	321	61.3 (53.7-70.2)**	292	39.7 (30.1-48.6)$^{\#\#}$	1539	52.9 (41.8-62.3)
Absolute LY, x 10^9/L	321	5.5 (4.5-7.1)**	292	2.6 (2.1-3.2)$^{\#\#}$	1539	3.9 (2.9-5.2)
EO, %	321	3.4 (1.9-5.7)**	291	2.1 (1.1-3.6)$^{\#\#}$	1538	2.7 (1.4-4.5)
Absolute EO, x 10^9/L	321	0.33 (0.18-0.50)**	291	0.15 (0.08-0.25)$^{\#\#}$	1538	0.20 (0.11-0.35)
MO, %	321	7.5 (4.7-10.2)**	291	6.1 (4.3-8.1)$^{\#}$	1538	6.6 (4.3-9.4)
Absolute MO, x 10^9/L	321	0.65 (0.42-0.98)**	291	0.45 (0.28-0.6)$^{\#\#}$	1538	0.52 (0.33-0.77)
Haemoglobin, g/L	321	96 (89-103)**	292	115 (108-121)$^{\#\#}$	1540	108 (101-114)
Platelet, x 10^9/L	321	708 (573-830)**	291	439 (349-533)$^{\#\#}$	1540	532 (426-648)

**p<0.01 vs group C, $^{\#}$p<0.05 vs group C, $^{\#\#}$p<0.01 vs group C.

CBC: complete blood cell count; ESR:erythrocyte sedimentation rate; CRP: C-reactive protein; WBC: white blood cell count; NE: neutrophils; LY: lymphocytes; EO: eosionphils; MO: monocytes

Table 4 Comparisons of blood biochemical indicators between groups

	≤6 months (A)		>5 years (B)		6 months - 5 years (C)	
Variables	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**	**n**	**median (p25-p75)**
ALT, U/L	331	24 (15-42)	313	15 (11-37)$^{\#\#}$	1609	22 (13-53)
AST, U/L	331	33 (24-46)	313	26 (20-37)$^{\#\#}$	1609	31 (24-46)
Albumin, g/L	331	35.0 (32.0-37.4)**	313	36.9 (34.0-39.8)$^{\#}$	1609	36.4 (33.4-39.1)
TBil, μgmol/L	331	5.2 (3.4-8.5)**	312	4.6 (3.1-6.9)$^{\#}$	1609	4.2 (2.8-6.6)
GGT, U/L	331	46 (23-109)**	312	12 (9-36)$^{\#\#}$	1609	21 (10-71)
Sodium, mmol/L	311	136 (134-138)*	283	137 (134-140)$^{\#}$	1508	137 (134-139)
Chloride, mmol/L	311	105 (103-108)	283	104 (101-107)$^{\#\#}$	1506	105 (103-108)
Potassium, mmol/L	311	3.9 (3.7-4.3)**	283	3.5 (3.2-3.7)$^{\#\#}$	1508	3.7 (3.4-4.1)
Calcium, mmol/L	311	1.16 (1.10-1.22)**	283	1.09 (1.03-1.15)$^{\#\#}$	1504	1.13 (1.07-1.19)

*p<0.05 group A vs group C, **p<0.01 group A vs group C, $^{\#}$p<0.05 group B vs group C, $^{\#\#}$p<0.01 group B vs group C

ALT: alanine aminotransferase; AST: aspartate transaminase; TBil: total bilirubin; GGT: gamma-glutamyl transferase

of the cases were nonresponsive to IVIG infusion and 24% of the cases were complicated with CAL. Tseng et al[7] analysed 48 infants with KD over a 10-year span and showed that patients were more likely to be atypical forms and that echocardiography was helpful for early diagnosis. One hospital in northern India reported[8] 97 cases with KD between Jan. 1994 and Apr. 2006, of which 38 patients were >5 years of age; they found that the peeling of extremities and arthritis were more common in the older age group, whereas swelling of hands and feet was infrequent. Stockheim et al[9] reported 28 KD cases ≥8 years of age and showed that the clinical features were mostly male, Caucasian, and difficult to timely diagnosis, accompanied by other atypical signs and symptoms and with a CAL incidence of 21%. These studies indicated that KD at extreme age of onset had their own unique features, facing the challenge of early recognitions and having poor treatment and outcomes. However, most of these studies including small sample led to instable and inconsistent findings. In this study, the clinical features of KD patients ≤6 months old and >5 years of age were reviewed.

After comparing the younger age and the typical age groups, it was found that the number of main criteria of the younger age group was lower but that the proportion of iKD was higher, indicating that younger patients often exhibited atypical symptoms. It was also found that illness days at admission were shorter in younger age group, and that fever duration and the incidences of delayed diagnosis, IVIGR and CAL were not significantly different between the two groups, suggesting increased awareness in younger infants with KD for their parents or guardians reduced the delaying visit, and for healthcare providers reduced the delaying of diagnosis, both of which resulted in improvement of the treatment and outcomes and were consistent with previous report by Lee et al.[16] Comparisons of complete blood count indicators showed that before and after treatment, WBC, LY, absolute LY, EO, absolute EO, MO, absolute MO, and platelet were all elevated in the younger age group, whereas ESR and NE were decreased. The difference in inflammatory cell components in the younger age group, coupled with the physiological characteristics of varying proportions of blood cells (i.e., the percentages of NE and LY from 4-6 days of age to 4-6 years of age were inverted and approached the normal levels found in adults by 4-6 years), indicated that systemic inflammation was more pronounced in the younger age group. Comparisons of blood biochemical indicators revealed that TBil and GGT in the younger age group were elevated, whereas albumin and serum sodium were lowered; these indicators can be used as auxiliary inflammation indicators in younger patients with KD. In addition, pre- and post-IVIG decreased levels of haemoglobin in the younger age group were likely related to age.

When the older age and typical age groups were compared, it was found that the former had a longer illness day at admission and a higher proportion delayed diagnosis in the older age group suggesting that the understanding of older patients with KD needs improvement for both their parents and clinicians. The longer duration in older age group were related to delayed visit and treatment. It was also found that the gender ratio, the number of the main criteria, the proportion of iKD cases, the rate of IVIGR and the incidence of CAL were not significantly different between two groups. Comparison of complete blood count indicators indicated that before and after treatment, NE of the older age group were elevated, whereas WBC, LY, absolute LY, EO, absolute EO, MO, absolute MO, and platelet were decreased; before treatment, CRP and ESR were decreased. Coupled with the aforementioned physiological characteristics of varying proportions of blood cells, the extent of inflammation in the older age group was relatively low. The comparison of blood biochemical indicators showed that albumin, TBil and serum sodium were elevated in the older age group, whereas ALT, AST and GGT were decreased, which were also responses to low severity of systemic inflammation. Additionally, pre- and post-IVIG elevated haemoglobin in the older age group might be related to age.

A number of studies about age-related KD showed similarity with and discrepancies from our findings. A group from Taiwan[17] reported 120 KD cases (20 cases in patients <6 months old) from 1994-2003 and showed that in the younger age group, WBC and platelet were elevated, haemoglobin was decreased and iKD was common, which were similar to our findings, although more frequent CAL and delayed KD diagnosis showed differences from ours. Lee et al[16] analysed the characteristics of three age groups in 136 KD cases from 1999-2003 and showed that the rate of CALs in the older age group, the younger age group and the typical age group were 42%, 20% and 17%, respectively, indicating that coronary artery damage was frequent in the older age group but that there was no difference between the levels in the younger age group and the typical age group, which is partly different from the findings in this study. Kim et al[18] reported the characteristics of three age groups in 185 KD cases from

2006-2007 and found that the overall incidence of CAL was 9% and that the incidence of CAL was not different among the groups, which is similar to the findings in this study but different from our findings on similar iKD proportions among the groups. Manlhiot et al[19] reported a large sample study with 1,374 cases of KD and divided the cases into different groups based on age; they showed that the <1-year-old and >9-year-old groups had elevated incidences of CAL and that the >9-year-old group had frequent delayed diagnoses, indicating that the age of onset was associated with coronary artery outcomes, which is different from our findings. However, the frequent delayed diagnoses in the older age group were consistent with our findings. A group from Wuhan in China reported[20] 113 cases of KD (20 patients >5 years old) from 2004-2010 and found that the older age group had longer fever durations and a long duration of fever process before and after IVIG treatment, which is consistent with our findings; however, the ESR, IVIGR and CAL incidences were high, which is inconsistent with our findings. The characteristics of different age groups reported in different regions may be related to differences such as knowledge about KD, sample size and inclusion criteria of KD patients.

Our retrospective study has some limitations. Some items of the data were missing, which could have led to biases in statistical analyses; therefore, we have listed the number of cases for each group and each item. A minority of cases (22 cases in younger group, 34 case in older group and 136 cases, because these patients were all diagnosed after 10 day of onset of KD and the temperature and inflammation marker came back to normal) did not receive IVIG therapy, having an influence on accurate evaluation of IVIG resistance. Because the data were collected over 6 consecutive years, the cases with large sample sizes were able to enhance the stability of the data, which compensates for these weaknesses to a certain extent.

Conclusions

Patients with KD ≤6 month of age tend to manifests incomplete symptoms with more pronounced systemic inflammation, while increased awareness contributed to improvement of diagnoses and outcomes. Patients with KD >5 years of age have relatively low levels of systemic inflammation without worse treatment and outcome, but were prone to delayed diagnoses.

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Conflict of Interest

No authors' financial ties to products in the study or potential/perceived conflicts of interest

Ethical Standards

Not applicable

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