Discrimination between incomplete and atypical Kawasaki syndrome *versus* other febrile diseases in childhood: results from an international registry-based survey

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Abstract

Objective

Kawasaki syndrome (KS) is an acute systemic vasculitis of unknown origin predominantly affecting young children. Early diagnosis is crucial to prevent cardiac complications. However, the differential diagnosis of patients with the incomplete or atypical form of the disease poses a heavy challenge for the paediatrician. Our aim was to evaluate the prevalence of incomplete and atypical cases among children with KS and to identify clinical and laboratory variables that may help differentiate incomplete and atypical KS from other febrile diseases at this age.

Methods

We established an international registry to recruit patients with KS, including those with incomplete and atypical forms. The control group included age-matched febrile children admitted to the hospital with a variety of diseases mimicking KS. The aim was to define clinical or laboratory clues to help in the discrimination of incomplete and atypical KS patients from others.

Results

Two hundred and twenty-eight patients with incomplete KS (78%) and atypical KS (22%) were compared to 71 children with other febrile diseases. Patients with incomplete and atypical KS presented a statistically significant higher frequency of mucosal changes, conjunctivitis, extremity abnormalities and perineal desquamation compared to the group of other febrile diseases. In addition, C-reactive protein and platelet counts were significantly higher in incomplete and atypical KS compared to the other group.

Conclusion

This is the largest series of incomplete and atypical KS patients of non East-Asian ancestry: we suggest that in patients with the aforementioned clinical features and laboratory evidence of systemic inflammation in terms of increased C-reactive protein and platelet counts an echocardiogram should be performed and diagnosis of KS considered.

Key words

Kawasaki syndrome, febrile disease, child

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Introduction

Kawasaki syndrome (KS) is an acute systemic vasculitis of unknown origin that mainly affects infants or young children and involves all medium-sized vessels, with morbidity and mortality deriving from a special tendency to involve the coronary arteries (1). In a national web-based surveillance among Japanese children the peak age was 5 to 11 months (2): 80% of these patients were under the age of 5 years with a male-to-female ratio of 1.8 to 1 (3). The disease is uncommon in infants younger than 3 months and very rare in neonates (4, 5). On the other hand, the diagnosis of KS needs to be established more urgently in this last group, due to the significantly increased risk of coronary artery abnormalities (CAA) and further risk of ischaemic events in adulthood (6, 7). In KS a prompt administration of high-dose intravenous immunoglobulin (IVIG) and aspirin has been proven to reduce significantly the rate of coronary artery damage to less than 4% (8) and the overall mortality rate of KS has been prominently reduced following the introduction of IVIG therapy (9). Since a specific diagnostic test is still lacking, clinical manifestations and their recognition remain the sole keys for a definite diagnosis of KS. Ozen *et al*. (10) established that high fever lasting more than five days is required as a mandatory diagnostic criterion combined with at least four of five principal criteria (listed in Table I): changes of peripheral extremities and perineum, polymorphous exanthem, bilateral nonpurulent bulbar conjunctivitis, changes in lips and oral mucosa, cervical lymph node enlargement; however, in the case of persistent fever and occurrence of CAA four criteria are not required for the diagnosis (10). Many common febrile diseases presenting with rash, lymph node enlargement or pharyngeal abnormalities can closely mimic KS (11): infections by Adenovirus (ADV), Cytomegalovirus (CMV) and Epstein-Barr virus (EBV) or scarlet fever, toxic shock syndrome and Staphylococcal Scalded Skin syndrome (SSSs) may share several symptoms and laboratory abnormalities with KS (12, 13) and even systemic onset-juvenile idiopathic arthritis (SoJIA) (14-16).

This multi-centre international collaborative survey was aimed to define the occurrence of incomplete and atypical cases of KS and compare their clinical/laboratory variables with other infantile febrile illnesses mimicking KS, in the attempt to identify features or clues that would help in the differential diagnosis with these diseases.

Methods

An international registry was established after recruitment of different paediatric hospitals in Europe, Turkey, Israel and South America in 2005. The study was conducted with the approval of the Ethics Committee of the recruiting centre in the University of Florence (Italy). The aims were: (a) to evaluate the prevalence of incomplete and atypical cases among children with KS and (b) to identify clinical and laboratory variables that may help differentiate incomplete and atypical KS from other febrile diseases at this age.

A questionnaire was sent to the participating centres asking them: (a) to evaluate KS patients from September 2005 to September 2007, including their sociodemographic data, clinical symptoms/signs at presentation, laboratory data and any involvement of the coronary arteries; (b) to define patients with a diagnosis of incomplete or atypical KS according to the updated definition (17) (see Table I); (c) to report clinical and laboratory data of age-matched infants and children with other non-KS febrile diseases presenting with skin rash, cervical lymph node enlargement or pharyngeal abnormalities, who had a different diagnosis than KS, including infections and SoJIA. Drug hypersensitivity reactions were excluded.

Clinical signs/symptoms at presentation inquired in the questionnaire included: duration of fever at admission, type of exanthema, features and site of lymph node involvement, conjunctivitis, lip/oral mucosa changes, abnormalities of hands or feet, erythema and desquamation in the perineum. Other different symptoms at onset had also to be specified. Laboratory data included: erythrocyte sedimentation rate (ESR),

Table I. Diagnostic definition of Kawasaki syndrome (KS).

Kawasaki syndrome (KS)	"Incomplete" KS	"Atypical" KS
Fever persisting for at least 5 days Presence of at least 4 principal features: • Changes in extremities and perineum • Polymorphous exanthaem • Bilateral bulbar conjunctival nonpurulent injection • Changes in lips and oral cavity • Cervical lymphadenopathy (>1.5 cm diameter), usually unilateral	Fever persisting for at least 5 days Presence of less than 4 principal features:	Fever persisting for at least 5 days Presence of at least 4 or less than 4 principal features:
Exclusion of other diseases with similar findings	Potential echocardiographic evidence of coronary artery abnormalities	Evidence of other organ involvement: Gastrointestinal tract (abdominal pain, hepatic dysfunction, hydrops of gallbladder, etc.) Lungs and respiratory tract (pneumonia, etc.) Central nervous system (aseptic meningitis, peripheral facial palsy, sensorineural hearing loss, etc.) Kidneys and genitourinary system (haematuria, urethritis, etc.) Musculoskeletal system (arthritides, etc.)

C-reactive protein (CRP), haemoglobin (Hb), white blood cell count, platelet (PLT) count, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (gammaGT), serum sodium level (Na^+), serum albumin and fibrinogen at the admission. Echocardiographic evaluations, performed at onset or in the first week of the disease and repeated depending on each specific case, were also included.

Statistical analysis

Comparison of the frequencies of general/clinical features and laboratory findings among patients with incomplete KS, atypical KS and the other febrile diseases was made by chi-square test, Fisher's exact test or the analysis of variance (ANOVA) as appropriate. Bonferroni's correction (*P*B) was applied as *post hoc* comparison after the ANOVA analysis. A p-value <0.005 was considered statistically significant.

Results

Twenty-eight paediatric rheumatology centres participated in the study. A total of 1466 cases of KS were inserted in the registry, all with a clinical diagnosis of KS. These patients were also evaluated for concomitant infectious diseases. Two hundred and forty-one (16%) had an incomplete or an atypical disease. Among these, 13 patients were excluded due to insufficient data, while 228 were included in the analysis. All patients deriving from the European centres were Caucasian; the ones deriving from South-America were Latin American or Caribbean. Table II shows the distribution of the 228 patients in the three study groups (incomplete KS, atypical KS and "other febrile diseases") according to the different geographical areas of the participating centres.

One hundred and seventy-eight patients out of 228 (78%, M/F: 103/75, median age at onset: 21 months) had an incomplete KS; the remainder 50 (22%, M/F: 29/21, median age at onset: 38 months) had an atypical KS. Time to diagnosis of KS occurred within day 10 for all these cases. Incomplete KS and atypical KS patients were compared to patients who ended up having "another febrile illness". Table III shows the main general and laboratory findings (expressed as mean values±standard deviations, SD) in the three groups. The classic and non-classic features of KS and rates of cardiovascular involvement were different among the groups and are listed in Table IV.

Among incomplete forms of KS, 9.55% (17 patients) presented with only one principal feature of the disease, 32.58% (58 patients) had two features and the remaining 57.87% (103 patients) had three. The most relevant clinical features of atypical KS patients were neurological signs (in 21 patients), abdominal pain resembling a surgical-like disease and joint involvement (respectively in 9), cholestasis (in 5), refractory pneumonia (in 5) and renal involvement (in 4). Among the 71 children with other heterogeneous febrile diseases (M/F: 36/35) serving for the comparison with KS, 15, 21 and 13 were respectively found to have an infection by CMV, ADV and EBV, while 18 had SoJIA, 3 presented SSSs and 2 displayed an infection-related macrophage activation syndrome. The mean age of these patients was 42.7 months and this was not significantly different from patients with atypical KS

Table II. Distribution of the 228 patients in the three study groups in the different geographical areas of the participating centres.

	Incomplete KS n=178	Atypical KS n=50	Other febrile diseases n=71
Northern Europe	1	2	0
Central Europe	144	33	69
Eastern-Mediterranean countries (Israel, Turkey)	12	6	2
South America	21	9	0

Table III. Main general and laboratory data in the incomplete (group 1) and atypical KS (group 2) and in "other febrile diseases" (group 3). Values are expressed as means±SD. Differences among groups were evaluated by ANOVA one way and Bonferroni *post hoc* comparison: 1 *vs*. 2*, 1 *vs*. 3^, 2 *vs*. 3#.

	Incomplete KS (group 1) n=178	Atypical KS (group 2) n=50	Other febrile diseases (group 3) n=71	ANOVA (*p*-value)	1 *vs*. 2* (*p*-value)	1 *vs*. 3^ (*p*-value)	2 *vs*. 3# (*p*-value)
Male sex	103/178 (57.9%)	29/50 (58.0%)	36/71 (50.7%)				
Age at onset (months)	29.6 ± 29	44.6 ± 38	42.7 ± 28	<0.002	<0.008	<0.024	ns
Days of fever at admission	8.4 ± 5	7.1 ± 4	7.7 ± 5	ns	–	–	–
Fever duration (days)	9.2 ± 5	11.7 ± 7	10.9 ± 9	<0.035	=0.05	ns	ns
ESR (mm/h)	80.2 ± 31	72 ± 30	64.3 ± 27	<0.004	ns	<0.004	ns
CRP (mg/dl)	40.9 ± 57	104.4 ± 90	8.8 ± 17	<0.0001	<0.0001	<0.006	<0.0001
Haemoglobin (g/dl)	10.3 ± 2	10.4 ± 2	10.9 ± 1	ns	–	–	–
PLT count ($\times 10^3/mm^3$)	521.7 ± 241	459 ± 251	346.4 ± 167	<0.0001	ns	<0.0001	<0.038
ALT (IU/l)	58.9 ± 105	71.1 ± 90	39.9 ± 28	ns	–	–	–
AST (IU/l)	53.8 ± 78	77 ± 137	43.6 ± 53	ns	–	–	–
gammaGT (IU/l)	190 ± 665	61.7 ± 75	27 ± 54	ns	–	–	–
Na^+ (mEq/l)	134.8 ± 4	133.8 ± 4	135.1 ± 5	ns	–	–	–
Albumin (g/dl)	3.5 ± 0.6	3.4 ± 0.8	3.5 ± 0.7	ns	–	–	–
Fibrinogen (mg/dl)	509 ± 221	568 ± 236	609.5 ± 151	ns	–	–	–

ns: not significant.

Table IV. Frequencies of classic and non-classic signs of KS and rates of cardiovascular involvement in the three study groups (n, %): the comparison among groups was performed by chi-square or Fisher exact test as appropriate: 1 *vs*. 2*, 1 *vs*. 3^, 2 *vs*. 3#.

	Incomplete KS (group 1) n=178	Atypical KS (group 2) n=50	Other febrile diseases (group 3) n=71	1 *vs*. 2* OR (95%CI)	1 *vs*. 3^ OR (95%CI)	2 *vs*. 3# OR (95%CI)
Skin rash	119 (67%)	35 (70%)	45 (63%)	ns	ns	ns
Cervical lymphadenopathy	62 (35%)	28 (56%)	45 (63%)	0.82 (0.22–0.79)	0.71 (0.17–0.55)	ns
Mucosal changes	108 (61%)	41 (82%)	15 (21%)	0.82 (0.15–0.74)	1.58 (3.02–10.79)	5.29 (6.78–42.65)
Conjunctivitis	112 (63%)	33 (66%)	24 (34%)	ns	1.41 (0.44–0.79)	2.18 (1.77–8.16)
Extremity abnormalities	47 (26%)	15 (30%)	3 (4%)	ns	1.43 (2.44–27.09)	2.45 (2.63–35.82)
Perineal changes	18 (10%)	6 (12%)	1 (1%)	ns	1.36 (1.03–60.15)	2.12 (1.11–81.98)
Abdominal signs at onset	1 (0.6%)	9 (18%)	3 (4%)	0,12 (0,00–0.21)	0.35 (0.01–1.25)	1.99 (1.27–19.44)
Neurological signs at onset	5 (3%)	21 (42%)	2 (3%)	0,12 (0.01–0.11)	ns	3.09 (5.50–113.53)
Other symptoms at onset	39 (22%)	39 (78%)	29 (41%)	–	–	–
Cholestasis	1 (0.6%)	5 (10%)	1 (1%)	0.21 (0.01–0.45)	ns	2.13 (0.88–68.77)
Renal involvement	0 (0%)	4 (8%)	0 (0%)	–	–	–
Arthritides	1 (0.6%)	9 (18%)	4 (6%)	0.12 (0.00–0.21)	0.28 (0.01–0.86)	1.82 (1.06–12.71)
Pneumonia	9 (5%)	5 (10%)	5 (7%)	ns	ns	ns
Otitis	2 (1%)	0 (0%)	1 (1%)	ns	ns	ns
Coronary aneurysms	12 (7%)	4 (8%)	0 (0%)	ns	*p*<0.01	*p*<0.01
Coronary dilatations	43 (24%)	14 (28%)	0 (0%)	ns	*p*<0.0001	*p*<0.0001
Other cardiac involvement	39 (22%)	12 (24%)	3 (4%)	ns	1.38 (1.90–21.32)	2.23 (1.90–26.76)
Any cardiac involvement	75 (42%)	23 (46%)	3 (4%)	ns	1.60 (5.00–54.47)	3.11 (5.35–69.66)

ns: not significant.

and of borderline significance if compared with patients with incomplete KS (*p*=not significant *vs*. atypical KS and *p*<0.024 *vs*. incomplete KS).

When the clinical features were compared with patients having "other febrile diseases", patients with incomplete and atypical KS presented a statistically significant higher frequency of conjunctivitis (*p*<0.000001 and *p*<0.001, respectively), lip/oral mucosal changes with strawberry tongue (*p*<0.0001 and *p*<0.000001, respectively), extremity abnormalities (*p*<0.00001 and *p*<0.00001, respectively) and perineal peeling (*p*<0.05 and *p*<0.05, respectively) (Table IV). Only patients with incomplete or atypical KS showed cardiovascular abnormalities in the form of coronary aneurysms or dilatations. CAA (both aneurysms and dilatations) were reported in 55/178 (31.0%) of incomplete cases and in 18/50 (36.0%) of atypical cases; conversely, none of the patients with "other febrile diseases" developed any CAA.

Among the laboratory tests we observed that CRP and PLT counts were significantly higher in incomplete and atypical KS compared to the patients with infections and other causes of febrile disease (Table III). Furthermore, CRP was significantly higher in atypical KS when compared to incomplete KS (*p*<0.0001). ESR was also significantly higher in the incomplete cases of KS when compared with the group of other febrile diseases (*p*<0.004). No significant difference was observed for haemoglobin, ALT, AST, gammaGT, sodium, albumin and fibrinogen values at admission. White blood cell counts

were not statistically evaluated, as data retrieved from the registry were not equally referred to the exact onset of the disease for each patient.

Discussion

Children with KS are diagnosed when a constellation of principal clinical signs comes out in febrile children without any specific laboratory-based tests: however, a portion of these patients do not meet the well-known criteria. Discrimination of incomplete and atypical KS from infections or other febrile conditions of childhood is an arduous challenge even for an experienced general paediatrician. Despite all the awareness, KS patients might remain underdiagnosed with a substantial risk of coronary arteritis and this may cause severe morphological changes in the vascular walls, leading to aneurysms, stenosis and occlusions (18). Even if a relatively high frequency of asymptomatic heart valvular involvement has been observed in small cohorts of patients (19), KS is actually the leading cause of acquired cardiac disease in childhood with a potential risk of myocardial ischaemia and premature atherosclerosis in early adulthood (20). It is generally hypothesised that a considerable number of children with KS, mainly infants, go unrecognised and are thus denied any prevention strategy.

The highest incidence of KS among children of East-Asian ancestry supports the assumption that a genetic predisposition plays a pathogenetic role in combination with environmental factors (21,22). Large cohorts of Japanese patients have shown that the prevalence of CAA is particularly high in males, infants younger than 1 year and children older than 5 years (23). The risk of CAA is significantly higher in children with incomplete forms of KS. Among over 15.000 patients with KS, reported by Sonobet *et al*. in 2007 (24), 83.9% satisfied all principal clinical criteria (defining a complete KS) and 16.1% an incomplete form of the disease: the prevalence of CAA in the complete forms was 14.2% and in the incomplete 18.4%, reaching a percentage of 19.3% in those patients with one to three signs (24).

In our group of patients from different geographic backgrounds, 16% had the incomplete or the atypical form of KS. This reminds us that this population constitutes a significant portion of the patients. With 241 patients, our study presents the largest series of KS patients with incomplete and atypical form of the disease of non East-Asian ancestry, though the control group with other febrile diseases includes small numbers of heterogeneous and mostly benign conditions, which might have hampered the statistical analysis.

We have tried to define features that may urge the paediatrician to consider KS instead of other causes of febrile diseases in a child who fails to present the principal criteria of KS. In our evaluation, the duration of fever was not different among groups and thus would not be helpful in the differential diagnosis, but mucosal changes, non-purulent conjunctivitis, distal extremity changes and perineal desquamation were significantly associated with the incomplete and atypical cases of KS: therefore, even if nonspecific, they should be checked and sought in all febrile children. Among the laboratory parameters, a high CRP and elevated PLT counts were significantly more frequent among incomplete and atypical KS patients. Although viral infections may share some mucocutaneous features with KS, their CRP and PLT counts will tend to be normal. Clinical and laboratory features of KS children were retrospectively compared with those related to acute ADV infection by Barone *et al*., finding that conjunctivitis with purulent features and pharyngitis with exudative features are more specifically observed in ADV infections (25). In addition, inflammatory markers can be increased in SoJIA as well as in KS and hence will not be helpful in the differential diagnosis.

However, in any patient with the above features an echocardiogram appears mostly indicated, since pre-aneurysmatic abnormalities (as perivascular brightness, ectasia or lack of tapering) as expression of arteritis in the coronary arteries might be more frequently displayed in the acute stage of KS than in SoJIA or at no time in common viral diseases. Newburger *et al*. have attempted to develop supplementary criteria to diagnose patients with incomplete KS (26): they suggested a diagnostic algorithm for KS, including anaemia, white blood cell count, serum albumin, ALT levels as further criteria in the work-up of a patient with a suspected KS. However, in our study these laboratory parameters were not different among patients with incomplete or atypical KS patients *versus* those with other febrile illnesses, suggesting that the supplementary criteria could not be validated. Ling *et al*. have identified three different biomarker panels (7 clinical parameters routinely obtained during the evaluation of fever, 32 blood lymphocyte-specific genes, 13 urine peptides) and have developed a diagnostic algorithm to accurately diagnose KS: for febrile patients with the confident diagnosis of KS a timely administration of IVIG could be feasible to prevent the development of CAA, while in those febrile patients for whom the confident diagnosis is not feasible a sequential algorithm, integrating clinical and molecular findings should be used to improve the accuracy of KS diagnosis, though prospective testing is necessary to confirm the diagnostic feasibility (27).

In conclusion, 16% of patients with KS display incomplete features or atypical findings and, therefore, they constitute a major concern in the diagnostic process of a child with fever of >5-day duration. The paediatrician should be able to do a conscientious analysis of both clinical and laboratory features listed above, which should prompt her/him to follow accordingly a child with no other explanation for the febrile illness and to perform an echocardiogram, which might give useful hints in heightening or reducing the suspicion of KS. Whether increased CRP and/or PLT counts should be included in the classification criteria for KS needs to be established on future collaborative studies.

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