Journal of Microbiology, Immunology and Infection (2015) **48**, 43—50

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ORIGINAL ARTICLE

Clinical manifestations of Kawasaki disease shock syndrome: A case—control study

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Received 6 December 2012; received in revised form 15 May 2013; accepted 24 June 2013
Available online 6 August 2013

KEYWORDS
Children;
Kawasaki disease;
Kawasaki disease shock syndrome;
Risk factors

Background: Kawasaki disease shock syndrome (KDSS) is a severe condition related to Kawasaki disease (KD), and sometimes it is difficult to diagnose. This is a case—control study to ascertain the clinical presentations, risk factors, and clinical outcomes of children who had KDSS.
Materials and methods: Children who were hospitalized during 2001—2011 with the diagnosis of KD combined with hypotension, sepsis, or shock were retrospectively reviewed and were defined as case patients. For each case patient, three season-matched patients diagnosed as having KD with normal blood pressure were identified to serve as control patients. Demographic characteristics, clinical presentations, laboratory features, therapies, and outcomes were analyzed.
Results: Nine KDSS patients and 27 control patients were identified. The average age of patients with KDSS was 3.2 ± 3.2 years. Compared with controls, KDSS patients were less likely to have a diagnosis of KD at admission (22.2% vs. 66.7%) and had a higher risk of coronary artery dilatation (77.8% vs. 11.1%). Risk factors for KDSS included higher neutrophil counts and proportions of bands, higher C-reactive protein (CRP), and lower platelet counts. All case patients received aspirin therapy; eight patients received intravenous immunoglobulin therapy, with two receiving more than one course. Seven KDSS patients required fluid resuscitation, and eight patients required vasoactive infusions.
Conclusion: Patients with KDSS may have uneven clinical course and may be misdiagnosed in the beginning. They may have more prominent inflammatory markers in the early phase and higher risk of coronary artery dilatation.

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http://dx.doi.org/10.1016/j.jmii.2013.06.005

Introduction

Kawasaki disease (KD) is a generalized systemic vasculitis predominantly involving medium-sized arteries, and the etiology is still ill defined.[1] The prevalence of KD is higher in Asian countries than in western countries. Japan has the highest annual incidence rate, followed by Korea and Taiwan, and the lowest rate is seen in Europe.[2–7] The severe complication of KD is the occurrence of coronary artery lesions and this often occurs in the subacute phase.[8] There is a 15—25% incidence of coronary artery lesions developing in KD patients without early treatment.[2] It is also the leading cause of acquired heart disease in children.[9] If the aneurysm persists and becomes occlusive, it may increase the risk of myocardial infarction or sudden death.[1,10]

However, hemodynamic instability during the acute phase of KD is uncommon. Kanegaye et al described the phenomenon and defined the term as KD shock syndrome (KDSS) in 2009.[11] The exact cause of severe hypotension in patients with KD is unknown. It is probably multifactorial, possibly including vasculitis with ongoing capillary leakage, myocardial dysfunction, and cytokine dysregulation.[12] From January 2001 to December 2011 in our hospital, we observed a number of children, admitted to the ICU, with a presumptive diagnosis of hypotension, toxic shock, or septic shock, and/or requiring hemodynamic support, later confirmed with a diagnosis of KD. They fulfilled the definition of KDSS. We performed this case—control study, comparing them with KD patients, to ascertain the clinical presentations, risk factors, and clinical outcomes of children who had KDSS.

Materials and methods

Patient selection

Hospitalized patients, ranging in age from 1 month to 18 years, diagnosed as KD were selected from discharge records [acute febrile mucocutaneous lymph node syndrome, International Classification of Diseases (ICD) Ninth Revision codes 4461] during the period from January 2001 to December 2011. Owing to the fact that the term KDSS has just been recently defined, earlier cases presenting as septic shock, toxic shock, or hypotension might have been missed. We searched the patients who were discharged from the intensive care unit (ICU) with diagnoses of KD combined with hypotension (ICD codes 4589), shock (ICD codes 78550), or sepsis (ICD codes 0389), and defined them as case patients (KDSS patients). For each case patient, we identified three season-matched patients who were diagnosed as KD with normal blood pressure, matched to each case patient by date of admission $\pm$4 weeks, and defined them as control patients (KD patients). All patients receiving a diagnosis of KD were confirmed by our pediatric infectious disease specialists during their hospitalization. We retrospectively reviewed the medical records of these children, including demographic characteristics, clinical presentations, laboratory features, cardiac sonographic findings, therapies, and outcomes.

Definitions

Complete KD patients needed to present with fever for at least 4 days and at least four principal features (polymorphous exanthema, bilateral bulbar conjunctival injection without exudate, cervical lymphadenopathy, changes in lips and oral cavity, and changes in the extremities). Incomplete KD patients had persistent fever but fewer than four of the five characteristics and laboratory and/or echocardiographic data could assist in the diagnosis. Day 1 of illness was defined as the first day of fever. Intravenous immunoglobulin (IVIG) refractory disease was defined as persistence or recrudescence of fever $<$48 hours after completion of IVIG infusion (2 g/kg). Echocardiography was performed during the acute (0—10 days after disease onset), subacute (11—21 days), convalescent (22—90 days), and chronic (91—365 days) phases. The definition of coronary artery dilatation was according to the diagnostic criteria and reporting of coronary artery lesions in Kawasaki disease by the Japanese Ministry of Health and Welfare: if the internal diameter of a segment measures $\geq$3 mm in children aged $<$5 years or $>$4 mm in children aged $>$5 years; if the internal diameter of a segment measures $>$1.5 times that of an adjacent segment; or if the coronary lumen is clearly irregular.[13]

Statistical analysis

We performed bivariate comparisons by using the Mann—Whitney *U* test for medians and the Fisher's exact test for dichotomous or ordinal variables, as appropriate. Multivariate logistic regression analysis was also used. A p value $<$0.05 was considered statistically significant.

Results

Demographic and clinical characteristics

During the 11-year period, nine patients were identified as KDSS patients, and 27 season-matched subjects were identified as control patients (KD patients). The demographic and clinical characteristics of patients with KDSS are shown in Table 1. Most KDSS patients did not receive the diagnosis of KD on admission. Only one of these nine KDSS patients was directly admitted to the ICU from the emergency department due to gastrointestinal (GI) bleeding and suspected septic shock, and the remaining eight patients were admitted initially to the general wards and then transferred to the ICU due to deteriorating conditions. The patients with KDSS were more commonly females, with a ratio of 2:1 over males. The average age was 3.2 $\pm$ 3.3 years. The duration for diagnosis of Kawasaki disease was 3.3 $\pm$ 3.3 days after admission. The most common clinical features at time of presentation were conjunctivitis, oral—mucosal change, and skin rash. Two KDSS patients presented with incomplete KD features. Case 2 had signs of fissure lips and strawberry tongue, erythema and swelling of palms and feet, skin rash, and coronary artery dilatation. Case 5 had signs of conjunctivitis, fissure lips, skin rash, and coronary artery dilatation.

Table 1 Demographic and clinical characteristics of patients with Kawasaki disease shock syndrome (KDSS)

Case	Age (y)	Sex	ICU (d)	Hospitalization (d)	Initial diagnosis	Cause of transfer to ICU	Fever (d)	Conjunctivitis	Lip cracking, strawberry tongue	Cervical lymphadenopathy	Erythema /edema of palms, soles	Skin manifestation a. Rash b. BCG erythema c. Perianal desquamation
1	1.9	M	4	11	Generalized lymphadenitis	GI bleeding, sepsis	11	x	x	x		a
2	0.1	F	29	46	Fever	Seizure, respiratory distress	15		x		x	a, b, c
3	0.4	M	7	12	Acute gastroenterocolitis, Kawasaki disease	GI bleeding, septic shock	8	x	x		x	a, b, c
4	3.9	F	7	18	Neck lymphadenitis	Sepsis, hypotension	5	x	x	x		a, c
5	7.0	F	7	9	Fever	Septic shock	7	x	x			a
6	0.9	F	4	10	Acute gastroenterocolitis, Kawasaki disease	Sepsis, hypotension	8	x	x		x	a
7	10.0	M	7	12	Neck lymphadenitis, toxic erythema	Sepsis, hypotension	10	x		x	x	a
8	2.7	F	10	13	Retropharyngeal abscess	Respiratory distress	11	x	x	x	x	
9	2.3	F	4	11	Fever	Septic shock	6	x	x		x	a

BCG = Bacille Calmette-Guérin; F = female; GI = gastrointestinal; ICU = intensive care unit; M = male.

Table 2 Comparison of demographic and clinical characteristics between patients with Kawasaki disease shock syndrome (KDSS) and Kawasaki disease (KD)

	KDSS ($n = 9$)	KD ($n = 27$)	p
Female sex, no. (%)	6 (66.7)	11 (40.7)	0.26
Age (y)	3.2 ± 3.3	2.0 ± 1.8	0.31
Diagnosis time after admission (d)	3.3 ± 3.3	1.0 ± 1.7	0.07
KD as initial diagnosis, no. (%)	2 (22.2)	18 (66.7)	0.05
Febrile duration (d)	9.0 ± 3.1	7.1 ± 2.3	0.12
Highest body temperature (°C)	39.6 ± 0.6	39.9 ± 0.6	0.35
Body temperature >40 °C, no. (%)	23 (33.3)	11 (42.3)	0.71
Complete KD, no. (%)	7 (77.8)	17 (63.0)	0.69
Hospitalized duration (d)	15.8 ± 11.6	6.6 ± 2.2	0.05

The comparisons of demographic characteristics and clinical characteristics between the KDSS patients and the KD patients are shown in Table 2. KDSS patients were less likely to have an initial diagnosis of KD compared with controls (22.2% vs. 66.7%, $p = 0.05$). The median length of hospital stay was 9.2 days longer for KDSS patients compared with KD patients ($p = 0.05$). There were no significant differences in age, sex, febrile days, illness duration, or percentage of complete KD between groups.

Laboratory data

The KDSS patients had significantly higher proportions of bandemia ($p = 0.001$), neutrophilia ($p = 0.03$), thrombocytopenia ($p = 0.01$), higher C-reactive protein (CRP) concentrations ($p = 0.02$), and hypoalbuminemia ($p = 0.01$) than KD patients (Table 3). There were no significant differences in white blood cell counts, erythrocyte sedimentation rate, glutamate oxaloacetate transaminase (GOT) level, glutamate pyruvate transaminase (GPT) level, or percentage of pyuria between both groups. Seven (77.8%) of the KDSS patients had hyponatremia (sodium <135 mM), four (44.4%) had metabolic acidosis (bicarbonate <18 mM), and two (22.2%) had higher creatinine concentration (creatinine >1.0 mg/dL). Four patients (44.4%) had low platelet counts ($< 100 \times 10^9$/L), three (33.3%) with positive D-dimer results, and five (55.5%) with prolonged prothrombin times/partial prothrombin times for age. Three (33.3%) of the KDSS patients and two (7.4%) of the KD patients performed a lumbar puncture, but neither group showed evidence of CSF pleocytosis.

Echocardiographic findings

All KDSS patients underwent echocardiography during the acute phase, seven patients during the subacute phase, seven during the convalescent phase, and six during the chronic phase. The KDSS patients had higher risk of coronary artery abnormality compared with KD patients (77.8 vs. 11.1 %, $p < 0.001$; Table 4). Four (44.4%) patients had persistent coronary artery dilatation until the convalescent

Table 3 Comparison of laboratory data between patients with Kawasaki disease shock syndrome (KDSS) and Kawasaki disease (KD)

	KDSS ($n = 9$)	KD ($n = 27$)	p
WBC count ($\times 10^9$/L)	14.5 ± 7.0	13.5 ± 4.9	0.70
WBC >15 × 10^9/L, no. (%)	3 (33.3)	7 (25.9)	0.69
WBC >17 × 10^9/L, no. (%)	3 (33.3)	5 (18.5)	0.38
Bands (%)	17.1 ± 14.7	3.1 ± 9.0	0.02
Bands >6%, no. (%)	6 (66.7)	2 (7.4)	0.001
Bands >10%, no. (%)	5 (55.6)	2 (7.4)	0.01
PMNs (%)	69.7 ± 18.1	60.5 ± 19. 5	0.22
PMNs >75%, no. (%)	5 (55.6)	4 (14.8)	0.03
Platelet count ($\times 10^9$/L)	171.1 ± 97.8	361.0 ± 126.8	<0.001
Platelet <100 × 10^9/L, no. (%)	3 (33.3)	0 (0.0)	0.01
ESR (mm/h)	50.6 ± 29.9	51.4 ± 25.3	0.96
ESR >40 mm/h (%)	40.0	69.2	0.33
CRP (mg/dL)	21.3 ± 13.4	6.2 ± 4.9	0.06
CRP >10 mg/dL (%)	80.0	17.6	0.02
Albumin (g/dL)	2.2 ± 0.3	3.4 ± 0.9	0.02
Albumin <3 g/dL (%)	100.0	33.3	0.01
GOT (IU/L)	66.7 ± 77.2	88.2 ± 140.2	0.63
GOT >50 IU/L (%)	33.3	33.3	>0.99
GPT (IU/L)	59.2 ± 43.7	131.7 ± 187.6	0.17
GPT >50 IU/L (%)	44.4	40.0	>0.99
Pyuria (> 5 WBCs/HPF), %	33.3	44.4	0.71
Blood culture negative (%)	100.0	100.0	>0.99

CRP = C-reactive protein; ESR = erythrocyte sedimentation rate; GOT = glutamate oxaloacetate transaminase; GPT = glutamate oyruvate transaminase; HPF = high-power field; KD = Kawasaki disease; KDSS = Kawasaki disease shock syndrome; PMNs = polymorphonuclear neutrophils; WBC = white blood cell.

Table 4 Comparison of cardiac sonographic findings between patients with Kawasaki disease shock syndrome (KDSS) and Kawasaki disease (KD)

	Echocardiographic findings	KDSS ($n = 9$) no. (%)	KD ($n = 27$) no. (%)	p
Overall	Coronary artery dilatation	7 (77.8)	3 (11.1)	<0.001
Acute phase	Coronary artery dilatation	5 (55.5)	2 (7.4)	0.01
	RCA	4 (44.4)	1 (3.7)	0.01
	LCA	4 (44.4)	1 (3.7)	0.01
Convalescent phase	Coronary artery dilatation	4 (44.4)	0 (0.0)	0.002
	Coronary artery dilatation	4 (55.5)	1 (3.7)	0.01
	RCA ectasia	1 (11.1)	0 (0.0)	0.25
Chronic phase	Coronary artery dilatation	2 (22.2)	0 (0.0)	0.06
	MR/TR	2 (22.2)	0 (0.0)	0.06

LCA = left coronary artery; MR = mitral regurgitation; RCA = right coronary artery; TR = tricuspid regurgitation.

phase. Case 2 had mitral regurgitation during the subsequent period of 4.5 years, Case 4 had right coronary artery ectasia after 3.5 months of illness, which then became persistent right coronary artery dilatation during the subsequent period of 6 years, and Case 7 had dilated right ventricle, mitral regurgitation, and tricuspid regurgitation during the subsequent period of 2 years and then recovered to a normal state after 2.2 years.

Clinical outcomes and management

All KDSS patients received aspirin therapy. Four KDSS patients used high dose aspirin initially, and the others started with low dose aspirin because thrombocytopenia, GI hemorrhage, or fever had subsided when KD was diagnosed. Eight KDSS patients received IVIG, and the time of first IVIG therapy was 2.3 ± 2.1 days after admission and 5.0 ± 2.0 days after onset of symptoms. Two of the KDSS patients had IVIG-refractory disease and required further IVIG treatments, but there was no IVIG-refractory case in the KD patients ($p = 0.06$). Seven of the KDSS patients received fluid resuscitation, eight required vasoactive agents, three required blood transfusion, and all nine patients received albumin infusion (Table 5). The vasoactive agents, dobutamine, dopamine, and epinephrine, were prescribed individually or in combination. The average duration of vasoactive agent use was 6.0 ± 4.5 days.

Table 5 Comparison of therapy between patients with Kawasaki disease shock syndrome (KDSS) and Kawasaki disease (KD)

	KDSS ($n = 9$)	KD ($n = 27$)	p
Duration from admission to IVIG therapy (d)	2.3 ± 2.1	1.4 ± 1.1	0.22
Duration from symptom onset to IVIG therapy (d)	5.0 ± 2.0	4.8 ± 1.5	0.75
Received aspirin, no. (%)	9 (100.0)	27 (100.0)	>0.99
Received IVIG, no. (%)	8 (88.9)	20 (74.1)	0.65
Second dose of IVIG, no. (%)	2 (22.2)	0 (0.0)	0.06
Received antibiotics, no. (%)	9 (100.0)	17 (63.0)	0.04
Requiring vasoactive infusions, no. (%)	8 (88.9)	0 (0.0)	<0.001
Requiring albumin, no. (%)	9 (100.0)	0 (0.0)	<0.001

IVIG = intravenous immunoglobulin.

Multivariate logistic regression analysis for risk factors

The KDSS patients had a greater chance of coronary artery dilatation, might need more than one dose of IVIG therapy, and had risk factors, i.e., bandemia, neutrophilia, thrombocytopenia, and elevated CRP (Table 6).

Discussion

The etiology of KD is still unclear and there is no single pathognomonic clinical or laboratory finding for the diagnosis. We know that it is a systemic inflammatory reaction, resulting in vasculitis and even coronary artery lesions. Some researchers think that an infectious agent triggers an inflammatory response, resulting in host immune dysregulation in genetically predisposed individuals.[14,15] Several studies support the hypothesis through the study of the genome-wide associated with KD in individuals of Japanese, Korean, Taiwanese, and European descent.[3,16–19]

In our 11-year study period, there were nine patients (1.9% of total KD patients) admitted to our ICU due to hypotension, shock, or sepsis. Kanegaye et al reported that 7% of KD patients had shock syndrome, and 31% of KDSS patients had ejection fraction <54%.[11] Dominguez et al found that 3.3% of KD patients were admitted to the ICU during the acute phase.[12] The above cases presented with atypical features, prominent inflammatory markers and severe clinical conditions, so it was difficult to diagnose KD early. Our prevalence of KDSS was lower than the above studies, and numbers might be underdiagnosed because of their atypical manifestations.

Recently, several studies have described case reports of KD patients combined with initial presentations of shock syndrome.[20–24] The cause of severe hypotension in patients with KD is unknown. Some authors propose the hypothesis of proinflammatory cytokine overexpression in KD, which

Table 6 Multivariate logistic regression analysis for risk factors of Kawasaki disease shock syndrome (KDSS)

	Odds ratio	*p*
Female sex	0.403	0.53
WBC $>15 \times 10^9$/L	0.131	0.72
Band >6%	7.138	0.01
PMN >75%	4.738	0.03
Platelets $<100 \times 10^9$/L	15.812	<0.001
CRP >10 mg/dL	6.431	0.01
Coronary artery dilatation	13.125	<0.001
BT >40 °C	0.022	0.88
Second IVIG	7.047	0.02

BT = body temperature; CRP = C-reactive protein; IVIG = intravenous immunoglobulin; PMN = polymorphonuclear neutrophil; WBC = white blood cells.

leads to myocyte contractile dysfunction.[22] Park et al reported one case of a KD patient with suspected development of a systemic capillary leak syndrome (SCLS).[25] SCLS is reversible plasma extravasation and vascular collapse accompanied by hypoalbuminemia due to increased vascular leakage.[25,26] These patients could experience shock and noncardiogenic edema and be treated with vasopressor therapy and colloid solutions for osmotic effects. SCLS could also occur in patients with KD because elevated interleukin-2 increased endothelial permeability, and IVIG might have a beneficial effect by post-transcriptional interleukin-2 suppression.[27] Two recent studies suggest that KD patients with shock have more severe systemic inflammation associated with myocardial involvement.[11,12]

Myocardial destruction linked to acute myocarditis is suggested by the elevated troponin I level in another study.[25] Kim et al found a significant elevation in the troponin I level in the acute phase of KD. [28] However, Checchia et al reported no significant increase in the troponin I level in KD patients.[29] In our study, the troponin I level was only examined in four KDSS patients when they were initially admitted to the ICU, and only one had an elevated troponin I level.

A high proportion of KDSS patients in our study (7/9) had coronary artery abnormalities, which was in keeping with the reported increased risk of coronary artery abnormality in KD with shock from other studies.[11,12,21,30] Mitral regurgitation and left ventricle dysfunction have been widely discussed in the past.[11,31,32] Lin et al reported that approximately one-third of KD patients in the ICU group developed moderate tricuspid regurgitation on initial echocardiography.[33] They proposed that the cause of valvular regurgitation was possibly attributable to myocarditis or papillary muscle dysfunction. Shinohala et al also reported one KD patient with severe tricuspid regurgitation and left ventricle dysfunction after an endomyocardial biopsy, and suggested the involvement of myocarditis in the development of tricuspid regurgitation.[34] Although our study dose not show the evidence of valvular regurgitation nor myocarditis from KDSS patients in the acute phase, we still need to keep in mind that KDSS resulted in a severe inflammatory reaction and even transient valvular regurgitation, myocarditis, and heart failure.

Kanegaye et al revealed that KDSS patients had lower age-adjusted hemoglobin *z* scores,[11] and Dominguez et al found that KDSS patients had lower serum albumin levels.[12] Both studies showed female sex predominance and had greater proportions of bands, lower platelet counts, and higher CRP concentrations. There were no differences in age between shock and hemodynamic normal groups. By contrast, we found that the KDSS patients had risk factors such as bandemia, neutrophilia, thrombocytopenia, and elevated CRP, but there were no significant differences in age and sex between the KDSS and KD groups. Younger age does not imply a higher risk of developing KDSS. Female sex is strongly associated with shock,[11,12] but KD is more common in males. The reason for this finding is unclear and merits additional investigation.

In our study, we found that three KDSS patients had prolonged cardiac complications: one had mitral regurgitation, another had right coronary artery, and the other had dilated right ventricle, mitral regurgitation, and tricuspid regurgitation. A national database study showed that coronary complications occurred in 5.37% of KD cases. An acute myocardial infarction occurred in 0.08%, of whom one-third were aged 10—15 years.[35] Therefore, we need to follow-up these KDSS patients as long as possible because they have a higher prevalence of developing cardiac complications and may have sequelae of coronary artery disease accompanied with a higher risk of mortality.

Compared with KD patients, our KDSS patients had a higher failure rate after first IVIG treatment. IVIG has a generalized anti-inflammatory effect with reduction of fever and acute markers of inflammation, included modulating cytokine levels and production, downregulating antibody synthesis.[36] KDSS patients may be misdiagnosed initially, so delay in treatment with IVIG may occur. More prominent inflammatory markers are found in these patients. We suppose that delayed treatment and more severe inflammation may make them more likely to be IVIG resistant.

The limitations in our study are that its retrospective nature might misclassify patients with KDSS, and our case number is too small to analyze the full spectra of this phenomenon and to identify all the independent risk factors. Our control group had a high proportion of incomplete KD.[37,38] This is a case—control study, and the control patients were selected by season matching to each case patient by date of admission ±4 weeks. We supposed that KD has seasonal variation, so we randomized selected control patients during the same period. The KDSS patients had atypical clinical presentation especially at admission, but they might develop other KD signs later. Patients in the control group also had a high proportion of atypical features in this study, which may reveal a trend of incomplete KD disease at the same period, but they were diagnosed and received treatment earlier. Because KDSS patients were not diagnosed and treated early enough, their course persisted and became more severe. Five of our control incomplete KD patients had BCG erythema. This presentation has been regarded as an important sign for diagnosis of KD,[39,40] but it is not regarded as a KD diagnostic criterion for calculation in this study.

In conclusion, patients with KDSS may have an uneven clinical course and may be misdiagnosed when they are first examined. They may have more prominent inflammatory markers and result in shock and hypotension, which requires critical care support at an early stage. They have a greater risk of coronary artery abnormalities, which may become coronary artery disease. These patients frequently fail to fulfill the full spectra of KD in the early phase, so delay in IVIG treatment may occur. They are also likely to be IVIG resistant because of more severe inflammation. Early recognition of KDSS and provision of adequate therapy are most important.

Conflicts of interest

The authors have no conflicts of interest to declare.

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