

# The cerebrospinal fluid changes and clinical characteristics of aseptic meningitis in Kawasaki disease

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## Research article

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# Abstract

**Background:** Aseptic meningitis is not a common feature in Kawasaki disease (KD). However, it could cause difficulty in making correct and in-time diagnosis **Methods:** We retrospectively investigated patients of KD and bacterial meningitis (BM). Totally 38 KD patients and 126 BM patients were brought into this study. Clinical symptoms, signs and laboratory examinations were compared between the two groups, which included: duration of fever before lumbar puncture, conjunctiva injection, oral cavity change, rash, cervical lymphadenopathy and extremities change, vomiting, front fontanel bulging, neck stiffness, leukocytes, hemoglobin, platelets, C-reactive protein, cerebrospinal fluid examinations, liver function and urinalysis. **Results:** In clinical signs, vomit and neck stiffness were more prevalent in BM. KD patients showed higher blood leukocyte ( $p < 0.001$ ) and C-reactive protein ( $p < 0.001$ ) in the early febrile stage. Glucose in cerebrospinal fluid of BM patients was significantly lower than KD patients ( $p = 0.003$ ). In ROC curve, the optimal cutoff value of CSF glucose was 2.945mmol/L with the sensitivity of 84.2% and specificity of 71.4%. Pyuria was more prevalent in KD patients ( $p < 0.001$ ). There was no significant difference in front fontanel bulging, hemoglobin, platelet, alanine transaminase, aspartate transaminase, albumin, cerebrospinal fluid leukocytes, cerebrospinal fluid protein and cerebrospinal fluid lactate dehydrogenase. **Conclusions** Full investigation of clinical manifestation and laboratory tests is necessary to distinguish KD with aseptic meningitis and BM. In CSF study, glucose level is more efficient than other items to distinguish these two diseases. Decreased CSF glucose is possibly an indicator of BM rather than KD.

## Background

Kawasaki disease (KD) is an acute febrile disease that happens major in children  $< 5$  years<sup>[1]</sup>. As a kind of systemic vasculitis, except for the principal clinical features including fever, extremity changes, conjunctivitis, rash, oral changes and cervical lymphadenopathy, it has various clinical manifestations<sup>[2]</sup>. Aseptic meningitis is not a common feature in KD. However, it could cause difficulty in making correct and in-time diagnosis<sup>[3]</sup>. Although lumbar puncture is suggested to distinguish infectious disease from KD, sometimes the abnormal cerebrospinal fluid (CSF) results in confused diagnosis especially at the beginning of the disease<sup>[4]</sup>. There are plenty of children with atypical clinical characteristics which make it difficult to draw to a definite diagnosis. The clinicians had to use both immunoglobulin and antibiotics simultaneously. Patient of KD with elevated leukocytes, neutrophil cells and C-reactive protein (CRP) in blood and pleocytosis in CSF may easily be misdiagnosed as bacterial meningitis (BM) in the early febrile stage. Besides, limited studies<sup>[5, 6]</sup> focused on the characteristic of cerebral fluid in KD, and the data was adopted from American and Japanese patients.

In this study, we retrospectively investigated the KD patients with aseptic meningitis in our hospital and compared it with BM in order to establish the characteristic of KD patients with aseptic meningitis and to find out how to distinguish this disease from bacterial meningitis.

## Methods

### Population

KD patients with aseptic meningitis and BM patients admitted in our department were enrolled for retrospective investigation from January 2011 to December 2019. Totally 38 patients of KD with the diagnosis of aseptic meningitis met the inclusive criteria. Besides, the patients of bacterial meningitis were also investigated as control group. Since most of the KD patients were admitted with duration of fever within 10 days, we chose the BM patients with fever  $\leq 10$  days in order to study the early change of CSF. Totally 126 patients of bacterial meningitis were brought into the control group. All the patients in this study should have the following data: CSF results, count of blood cells, C-reactive protein (CRP), liver function, urinalysis. Patients with CSF erythrocyte  $\geq 1 \times 10^6/L$ , which suggested trauma lumbar puncture, was excluded. Patients with lumbar puncture after intravenous immunoglobulin (IVIG) treatment were excluded to avoid confusion with aseptic meningitis induced by IVIG [7, 8]. Moreover, in case records, there should be complete description of the symptoms and physical examination including oral cavity, skin change, conjunctiva, lymph nodes, extremities, and nerves system change.

### Clinical Data

The following clinical data were collected from the groups: Age; gender; duration of fever before lumbar puncture; the five clinical features of KD (conjunctiva injection, oral cavity change, Rash, cervical lymphadenopathy and extremities change); nerves system change including vomiting, front fontanel bulging and neck stiffness. In laboratory tests, we investigated blood leukocytes, hemoglobin, platelets (PLT), CRP; CSF parameters including leukocytes, glucose, protein and lactate dehydrogenase (LDH); liver function and urinalysis.

### Statistics

Data were studied by SPSS 23.0 software. The data in two groups were compared with independent samples t test. Pearson chi-square test or Fisher's exact test was used for the compare of constituent ratio in the two groups. In order to study the glucose level in CSF distinguishing KD patients from BM patients, receiver operating characteristic (ROC) curve was constructed. Statistical significance was considered p value  $< 0.05$

## Results

### Clinical characteristics

The clinical characteristics of the patients in the two groups are summarized in Table 1. The age and gender in the two groups showed no significant difference. Since the BM patients were chosen with

duration of fever no more than 10 days, which was similar with the acute stage of KD, the two groups showed no significant difference on this point ( $p = 0.867$ ). Only a very little portion of the BM patients manifested the five typical features of KD including 1 patients with oral cavity change, 3 patients with rash, 7 patients with cervical lymphadenopathy ( $p < 0.05$ ). We also investigated the nerves system changes. Vomiting, which could be a symptom of intracranial hypertension, appeared in 49 out of 126 patients in BM group. However, only 2 out of 38 KD patients with aseptic meningitis had vomiting ( $p < 0.001$ ). Neck stiffness appeared in 17 KD patients and 99 BM patients ( $p = < 0.001$ ). Besides, either in KD patients or in BM patients, front fontanel bulging seemed to be a frequent sign ( $p = 0.594$ ) if the front fontanel was unclosed.

Table 1  
Clinical characteristics of Kawasaki disease and bacterial meningitis patients

	KD (n = 38)	BM (n = 126)	P
Age (months)	22.0 ± 23.4	26.3 ± 25.4	0.345
Gender	Male	67	0.362
	Female	59	
Duration of fever (days)	5.7 ± 1.4	5.5 ± 1.8	0.446
Conjunctiva injection	35	0	< 0.001*
Oral cavity change	34	1	< 0.001*
Rash	32	3	< 0.001*
Cervical lymphadenopathy <sup>a</sup>	15	7	< 0.001*
Extremities change	19	0	< 0.001*
Vomiting	2	49	< 0.001*
Neck stiffness	17	99	< 0.001*
Front fontanel bulging <sup>b</sup>	15 (n = 19)	38 (n = 45)	0.594
a: the cervical lymphadenopathy means the typically enlarged cervical lymph nodes $\geq 1.5$ cm which meet the criteria of KD.			
b: Front fontanel bulging could only be observed in young children with unclosed front fontanel. In KD group there were 19 patients with unclosed front fontanel and in BM group 48 patients.			
* $p < 0.05$			
Abbreviations:			
KD = Kawasaki disease			
BM = bacterial meningitiss			

# Laboratory Examinations

The laboratory examinations of the two groups are listed in Table 2. The leukocyte count, protein and LDH in CSF showed no significant difference between the two groups. Notably, BM group showed a lower level of glucose compared with KD group ( $p = 0.003$ ). The leukocytes and CRP in the blood of KD group were significantly higher than BM group ( $p < 0.001$ ). Although anemia and thrombocytosis were prevalent in KD, in this study the hemoglobin and platelet level in the two groups seemed to have no significant difference. In both groups, there was elevation of alanine transaminase (ATL) and aspartate transaminase (AST) level. However, neither ALT and AST nor albumin in the two groups showed significant difference. There was 7 patient in KD group and no patient in BM group with pyuria, and the difference showed significance ( $p < 0.001$ ). We constructed ROC curve (Fig. 1) to learn the glucose level in CSF, the area under the curve was 0.868. The optimal cutoff value of glucose level in CSF to distinguish KD and BM was 2.945 mmol/L with the sensitivity of 84.2% and specificity of 71.4%.

Table 2  
Laboratory examinations of Kawasaki disease and bacterial meningitis patients

Laboratory examination (median, range)		KD (n = 38)	BM (n = 126)	P
CSF	Leukocytes ( $\times 10^6/L$ )	107.5(10–340)	115 (10-2270)	0.097
	Glucose (mmol/L)	3.37(2.50–5.30)	2.71(1.18-4.00)	0.003*
	Protein (mg/L)	632.4(270.8-1054.6)	610(196.2-2722.1)	0.276
	LDH (U/L)	37.5(16–56)	34.5(14–98)	0.253
Blood	Leukocytes ( $\times 10^9/L$ )	17.2(9.7–27.5)	13.65(7.7–23.8)	< 0.001*
	Hemoglobin (g/L)	110.5(78–126)	114(79–142)	0.241
	Platelets ( $\times 10^9/L$ )	368(123–604)	397.5(109–744)	0.137
C-reactive protein		64.5(28–180)	26(8–81)	< 0.001*
Liver function	ALT	35.5(7-173)	37(9-460)	0.541
	AST	31(16–213)	39.5(15–432)	0.356
	Albumin	37.35(27.3–46.0)	38.25(30.8–47.4)	0.059
Pyuria		7	0	< 0.001*
* p < 0.05				
Abbreviations:				
KD = Kawasaki disease				
BM = bacterial meningitis				
CSF = cerebrospinal fluid				
LDH = lactate dehydrogenase				
ALT = alanine transaminase				
AST = aspartate transaminase				

## Discussion

Except for the typical five clinical features, KD could have multiple other manifestations including arthritis, aseptic meningitis, colitis, etc [9–11]. Indeed, KD in early stage with atypical manifestations often leads to misdiagnosis. The persistent fever, nervous system symptom and signs, elevated leukocyte count and CRP could sometimes result in confusion with bacterial meningitis [12].

In this study, we investigated the symptoms, physical examinations and laboratory tests of KD and BM patients. The typical five features of KD seemed to be rare in BM patients. Neck stiffness and vomit were more prevalent in BM patients. Front fontanel bulging in younger patients was common in both KD patients and BM patients. In CSF examination, the glucose in BM patients showed a lower level compared with KD patients. The leukocytes and protein in CSF of both groups were in a wide range, however, the difference showed no significance. KD patients showed higher blood leukocytes and CRP than BM patients. The examination of liver function and urine test in the two groups remained no significant difference. None of the BM patients in this study had pyuria which was not rare in KD patients.

KD is a kind of systemic vasculitis with multiple manifestations. On the other hand, BM is sort of a focalized disease mainly affects central nerves system. The typical five features, which suggest a systemic inflammation, rarely appear in BM patients. Rash especially haemorrhagic rash may be found in BM patients of children. However, it is more frequent in meningococcal meningitis (61%) rather than in pneumococcal meningitis (9%) [13]. In this study, none of the patients in BM group was documented meningococcal meningitis and only 3 patient had skin rash.

Vomiting is reported in 55–67% children with BM [13–15]. However, previous studies did not focus on this symptom in KD [5, 6]. Besides, in 3 case reports, vomiting appeared in none of the patients of KD with aseptic meningitis [4, 16, 17]. In this study, only two of the KD patients presented with vomiting. Based on the findings above, we consider maybe vomiting is less frequent in KD compared with BM patients. The possible reason is that the intracranial hypertension of aseptic meningitis in KD is less prominent than that in BM.

Lumbar puncture is often considered to exclude infectious disease from KD [18]. However, in this study, the CSF results suggested that leukocytes, protein, LDH in the two groups showed no significant difference. However, glucose in BM patients was at a lower level than KD group. ROC curve indicates 2.945 mmol/L as the optimal cutoff value. Other studies also suggested that decrease in CSF glucose was not prevalent in KD patients [5, 6]. Although we can't easily exclude BM only with normal glucose in CSF because CSF glucose in either KD patients or BM patients could be normal, it seems that obvious decreased CSF glucose level strongly suggests the diagnosis of BM.

Both KD and bacterial infection could result in elevation of blood leukocytes and CRP. Previous study suggested that CRP was not specific in diagnosis of KD compared with bacterial infections [18]. However, we observed in our study a higher leukocyte and CRP level in KD patients compared with BM patients. The possible reasons may be as follows. First, the sample size is quite limited. Second, in order to be comparable with KD, we chose BM patients with fever no more than 10 days. At this period, the inflammatory reaction of KD possibly reached the highest level, but in BM, it was still in an early stage. Anyhow, relative higher CRP level might be helpful in excluding BM in a relative early stage of fever.

The change in liver function including ALT and albumin is considered as auxiliary laboratory findings in the diagnosis of KD [1]. Meanwhile, bacterial infections including BM could also result in elevated ALT and

AST level and decreased albumin level [20–21]. In this study, the change of ALT, AST and albumin manifested no significant difference in the two groups and the result suggested that ALT, AST and albumin were not indicators in distinguishing between KD and BM patients.

Pyuria is another clinical manifestation of KD with an incidence of 38% [22]. In this study, 7 out of the 38 KD patients had pyuria while none of the BM patients had. As a kind of systemic vasculitis, KD is more likely than BM to manifest both pyuria and CSF pleocytosis.

In summary, full investigation of clinical manifestation and laboratory tests is necessary to distinguish KD with aseptic meningitis and BM. In CSF study, glucose level is more efficient than other items to distinguish these two diseases. Decreased CSF glucose is possibly an indicator of BM rather than KD.

## Abbreviations

ALT= alanine transaminase

AST= aspartate transaminase

BM= bacterial meningitis

CRP=C-reactive protein

CSF=cerebrospinal fluid

IVIG=intravenous immunoglobulin

KD= Kawasaki disease

LDH=lactate dehydrogenase

PLT=platelet

ROC=receiver operating characteristic

## Declarations

### Ethics approval and consent to participate

All the patients in this study have given informed consent including permission of using clinical data. The study was approved by the ethic committee of West China Second University Hospital of Sichuan University.

### Consent for publication

Not applicable

## Availability of data and materials

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

## Competing interests

The authors declare that they have no competing interests.

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## Authors' contributions

FH contributed to the design of the work, interpretation of data and has drafted the work. XQS was a major contributor to acquisition of data. YF contributed to acquisition and analysis of data. HML contributed the conception of the work and substantively revised it. KYZ was a major contributor to design of the work and substantively revised it.

## Acknowledgements

Not applicable

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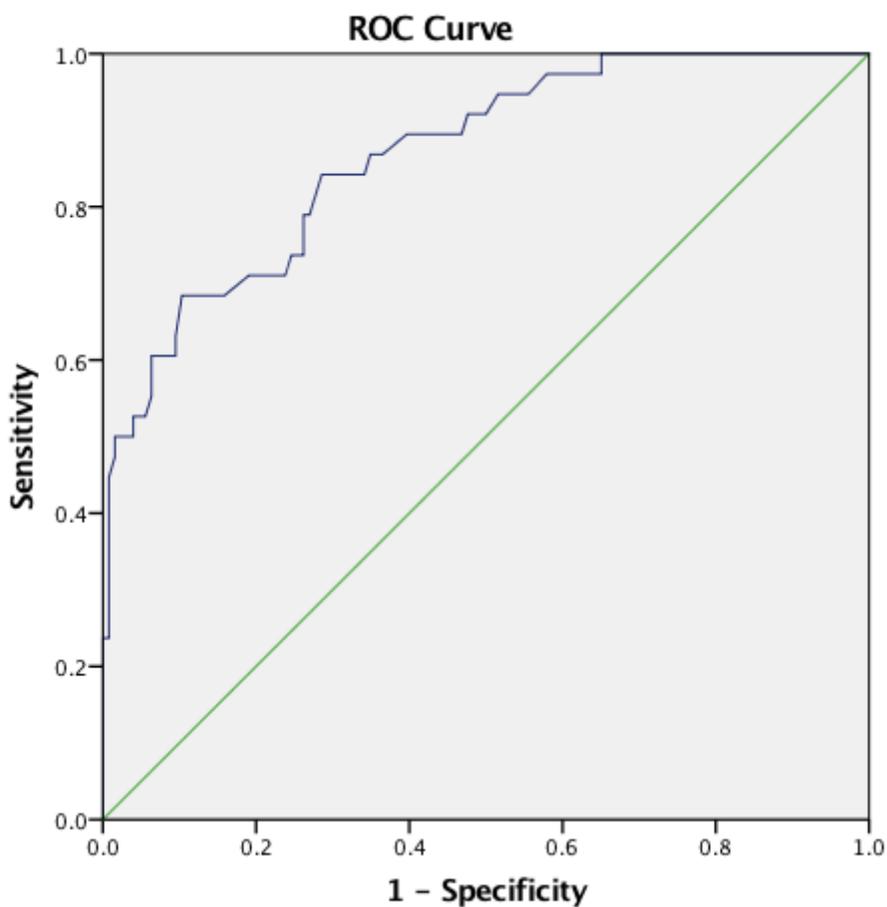
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## Figures



**Figure 1**

ROC curve of CSF glucose level in KD group and BM group. The area under the curve was 0.868. The optimal cutoff value of CSF glucose level was 2.945mmol/L with the sensitivity of 84.2% and specificity of 71.4%.