

Cerebrospinal fluid changes and clinical features of aseptic meningitis in patients with Kawasaki disease

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Abstract

Objective: To assess the distinguishing features of aseptic meningitis (AM) in patients with Kawasaki disease (KD) compared with bacterial meningitis (BM) patients.

Methods: Thirty-eight patients with KD and 126 patients with BM were retrospectively investigated. The following clinical manifestations and laboratory parameters were compared between the two groups: duration of fever before lumbar puncture, conjunctival injection, oral cavity changes, rash, cervical lymphadenopathy and extremity changes, vomiting, front fontanel bulging, neck stiffness, leukocyte number, hemoglobin level, platelet number, C-reactive protein level, cerebrospinal fluid (CSF) content, liver enzyme level, and urinalysis.

Results: Vomiting and neck stiffness were more prevalent in patients with BM. KD patients with AM showed elevated blood leukocyte numbers and C-reactive protein levels in the early febrile stage. CSF glucose was significantly lower in patients with BM compared with KD patients with AM. Receiver operating characteristic curve analysis showed that the optimal cutoff value of CSF glucose for discrimination of BM and AM/KD was 2.945 mmol/L, with a sensitivity of 84.2% and a specificity of 71.4%.

Conclusions: Detailed investigations of clinical manifestation and laboratory parameters are necessary to distinguish AM and BM in patients with KD. Decreased CSF glucose is a potential indicator of BM.

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Keywords

Kawasaki disease, aseptic meningitis, bacterial meningitis, cerebrospinal fluid, glucose, diagnosis, receiver operator characteristic

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Introduction

Kawasaki disease (KD) is an acute febrile disease that primarily occurs in children younger than 5 years.¹ KD is a systemic vasculitis with various clinical manifestations, but its principal clinical features include fever, extremity changes, conjunctivitis, rash, oral changes and cervical lymphadenopathy.² Aseptic meningitis (AM) is an uncommon feature of KD. However, the presence of AM in KD patients can make accurate and timely diagnosis challenging.³ Although lumbar puncture is used to distinguish infectious diseases from KD, cerebrospinal fluid (CSF) abnormalities can complicate diagnosis, especially during the early stages of KD.⁴ Many children show atypical clinical characteristics making definitive diagnosis challenging. Clinicians sometimes administer both immunoglobulin and antibiotics simultaneously in KD patients. Typically, the CSF characteristics of KD patients are similar to those of patients with AM: CSF is culture-negative, shows pleocytosis and contains normal glucose levels. However, KD patients with elevated leukocytes, neutrophils and C-reactive protein (CRP) in the blood and pleocytosis in the CSF may easily be misdiagnosed with bacterial meningitis (BM) in the early febrile stage. Limited studies^{5,6} have focused on the characteristics of CSF in KD patients, and the available data are derived only from American and Japanese patients.

In this study, we retrospectively investigated KD patients with AM in our hospital

and compared their features with those of patients with BM. Our overall goal was to understand the characteristics of KD patients with AM and to better distinguish these patients from those with BM.

Methods

Population

KD patients with AM and BM patients admitted to our department were retrospectively investigated from January 2011 until December 2019. All patients provided informed consent including permission for use of clinical data. The study was approved by the ethics committee of the West China Second University Hospital of Sichuan University. Patients with both incomplete and complete KD were included, and patients with BM were investigated as a control group. Because most KD patients were admitted with a duration of fever of ≤ 10 days, we selectively enrolled BM patients with fever durations ≤ 10 days to study early changes in CSF. All patients enrolled in the study must have had the following data available: CSF findings, blood cell counts, CRP level, serum indicators of liver function, and urinalysis. Patients with CSF erythrocytes $> 1 \times 10^6/L$, suggestive of traumatic lumbar puncture, were excluded. Patients undergoing lumbar puncture after intravenous immunoglobulin treatment were excluded to avoid potential cases of AM induced by this intervention.^{7,8} Case records needed to

contain a complete description of symptoms and physical examinations of the oral cavity, skin, conjunctiva, lymph nodes, extremities, and nervous system.

Clinical data

The following clinical data were collected from all participants: age, gender, duration of fever before lumbar puncture, clinical features of KD (conjunctival injection, oral cavity changes, rash, cervical lymphadenopathy and extremity changes), nervous system changes including vomiting, front fontanel bulging, and neck stiffness. The following laboratory parameters were investigated: blood leukocytes, hemoglobin, platelets, and CRP; CSF parameters including leukocytes, glucose, protein, and lactate dehydrogenase (LDH); serum indicators of liver function; and urinalysis.

Statistics

Statistical analyses were conducted using SPSS 23.0 software (SPSS Inc, Chicago, IL, USA). Differences between two normally distributed variables were assessed using independent sample t tests. Differences between categorical variables were assessed using chi-square or Fisher's exact tests. To assess the diagnostic utility of CSF glucose levels in distinguishing KD/AM patients from BM patients, a receiver operating characteristic (ROC) curve was constructed. Values of $p < 0.05$ were considered statistically significant.

Results

Clinical characteristics

Thirty-eight KD patients diagnosed with AM met the inclusion criteria; 16 had incomplete KD and 22 had complete KD. A total of 126 patients with BM were enrolled as the control group. The clinical characteristics of the patients in both

groups are summarized in Table 1. The distributions of age and gender in the two groups were similar. Because BM patients with fever durations of no more than 10 days were selected to match the features of patients with acute KD, there was no significant difference in fever duration between the two groups. Very few BM patients showed the typical features of KD: one patient showed oral cavity changes, three patients had rash, and seven patients had cervical lymphadenopathy. We also investigated nervous system changes. Vomiting, which can be a symptom of intracranial hypertension, was present in 49 of 126 patients with BM but only 2 of 38 KD patients with AM ($p < 0.001$). Neck stiffness was present in only 17 of 38 KD patients with AM but in 99 of 126 BM patients ($p < 0.001$). Similar proportions of KD patients with AM (3/38) and BM patients (25/126) experienced somnolence. Front fontanel bulging was a frequent sign in both KD patients with AM and BM patients if the front fontanel was unclosed .

Laboratory examinations

The results of laboratory examinations for patients in both groups are listed in Table 2. Leukocyte counts, protein levels and LDH levels in CSF were similar in KD patients with AM and in BM patients. There was a trend toward higher percentages of neutrophils in the CSF of BM patients, but this difference was not statistically significant. Patients with BM had lower levels of CSF glucose compared with KD patients with AM ($p = 0.003$). In addition, the ratio of CSF glucose/blood glucose was dramatically decreased in BM patients compared with KD patients with AM ($p < 0.001$). Levels of leukocytes and CRP in the blood of KD patients with AM were significantly higher than those of BM patients ($p < 0.001$). Although anemia and thrombocytosis are generally prevalent in KD patients, we

Table 1. Clinical characteristics of patients with Kawasaki disease and acute meningitis and patients with bacterial meningitis.

	KD (n=38)	BM (n=126)	p-value
Age (months)	22.0 ± 23.4	26.3 ± 25.4	0.345
Gender			
Male	17	67	0.362
Female	21	59	
Duration of fever (days)	5.7 ± 1.4	5.5 ± 1.8	0.446
Conjunctival injection	35	0	<0.001*
Oral cavity changes	34	1	<0.001*
Rash	32	3	<0.001*
Cervical lymphadenopathy ^a	15	7	<0.001*
Extremity changes	19	0	<0.001*
Vomiting	2	49	<0.001*
Neck stiffness	17	99	<0.001*
Somnolence	3	25	0.065
Front fontanel bulging ^b	15 (n=19)	38 (n=45)	0.594

Data represent counts or means ± standard deviations.

a: Cervical lymphadenopathy refers to typically enlarged cervical lymph nodes ≥1.5 cm meeting the criteria for KD.

b: Front fontanel bulging could only be observed in younger children with unclosed front fontanels. There were 19 KD/AM patients and 48 BM patients with unclosed front fontanels.

*p<0.05.

KD, Kawasaki disease; BM, bacterial meningitis.

found that hemoglobin and platelet levels were similar in KD patients with AM and BM patients. Both groups had elevated alanine transaminase (ALT) and aspartate transaminase (AST) levels. However, levels of ALT, AST and albumin were similar in the two groups. Seven KD patients with AD and no BM patients had pyuria ($p < 0.001$). We constructed a ROC curve (Figure 1) to assess the diagnostic relevance of CSF glucose level for distinguishing KD patients with AM from BM patients. The area under the curve was 0.868. The optimal cutoff value of CSF glucose level to distinguish KD patients with AM from BM patients was 2.945 mmol/L, with a sensitivity of 84.2% and a specificity of 71.4%.

Discussion

Apart from its typical clinical features, KD can have multiple other manifestations including arthritis, AM, and colitis.⁹⁻¹¹

Indeed, the early stages of KD often involve atypical manifestations leading to misdiagnosis. Persistent fever, nervous system symptoms and signs, and elevated leukocyte counts and CRP can be suggestive of BM.¹²

In this study, we investigated the symptoms, physical examination results and laboratory findings of KD patients with AM as well as BM patients. The typical features of KD were rare in BM patients. Neck stiffness and vomiting were both more prevalent in BM patients. Front fontanel bulging was common in both KD patients with AM and in BM patients, especially among younger age groups. In CSF, glucose levels of BM patients were lower compared with KD patients with AM. Leukocytes and protein levels in the CSF of both groups spanned a wide range, with no significant difference between groups. Neutrophils are often found at higher levels in patients with BM compared with those with AM. However, in this

Table 2. Laboratory parameters of patients with Kawasaki disease and aseptic meningitis and patients with bacterial meningitis.

Laboratory parameter	KD (n=38)	BM (n=126)	p-value
CSF			
Leukocytes ($\times 10^6/L$)	107.5 (10–340)	115 (10–2270)	0.097
Neutrophils (%)	39.2 \pm 13.6	44.2 \pm 14.2	0.057
Lymphocytes (%)	60.8 \pm 13.6	55.8 \pm 14.2	0.056
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
CSF glucose/blood glucose ratio	0.61 (0.52–0.68)	0.35 (0.23–0.45)	<0.001*
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
CRP	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*

Data represent medians (ranges), means \pm standard deviations or counts.

* $p < 0.05$.

KD, Kawasaki disease; BM, bacterial meningitis; CSF, cerebrospinal fluid; LDH, lactate dehydrogenase; CRP, C-reactive protein; ALT, alanine transaminase; AST, aspartate transaminase.

study, levels of neutrophils and lymphocytes showed no significant differences between the two groups. One potential explanation of this negative finding is the relatively small sample size in both groups. KD patients with AM showed higher blood leukocytes and CRP levels than BM patients. Serum markers of liver function and urinalysis results were similar in the two groups. None of the BM patients in this study had pyuria while seven of 38 KD patients did.

KD is a type of systemic vasculitis with multiple manifestations. By contrast, BM is a focalized disease that mainly affects the central nerves system. The typical features of KD, which reflect the presence of systemic inflammation, rarely occur in BM patients. Rash, especially hemorrhagic rash, may occur in children with BM. However, rash more frequent affects patients with

meningococcal meningitis (61%) than those with pneumococcal meningitis (9%).¹³ In this study, none of the patients with BM had meningococcal meningitis and only three patients developed skin rashes.

Vomiting is reported in 55% to 67% of children with BM.^{13–15} However, previous studies have not focused on this symptom in KD patients.^{5,6} In three case reports, vomiting affected none of the KD patients with AM.^{4,16,17} In this study, only two of 38 KD patients with AM presented with vomiting. Based on these findings, we conclude that vomiting is likely less prevalent in KD patients with AM compared with BM patients. A potential explanation of this finding is that intracranial hypertension among KD patients with AM is less prevalent than among BM patients.

Lumbar puncture is often used to exclude infectious diseases in patients with

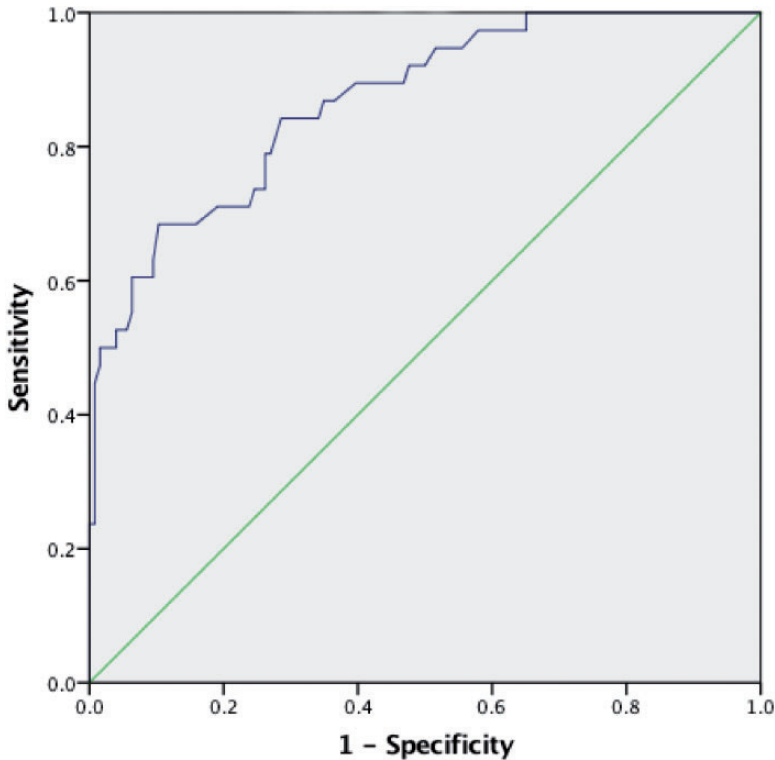


Figure 1. Receiver operating characteristic curve of cerebrospinal fluid (CSF) glucose level in patients with Kawasaki disease and acute meningitis vs. patients with bacterial meningitis. The area under the curve was 0.868. The optimal cutoff value for CSF glucose level was 2.945 mmol/L, with a sensitivity of 84.2% and a specificity of 71.4%.

suspected KD.¹⁸ However, in this study, CSF results suggested that levels of leukocytes, protein, and LDH in KD patients with AM and in BM patients were similar. By contrast, BM patients showed significantly lower CSF glucose levels and CSF glucose/blood glucose ratios compared with KD patients with AM. Because CSF glucose is affected by blood glucose, the CSF glucose/blood glucose ratio is important to exclude the possibility that low CSF glucose is caused by hypoglycemia. ROC curve analysis indicated that 2.945 mmol/L was the optimal cutoff value for discrimination of KD patients with AM and BM patients. Other studies also suggested that decreased CSF glucose was uncommon in KD

patients.^{5,6} This criterion would inefficiently discriminate between BM patients with normal CSF glucose and KD patients with AM. However, decreased CSF glucose levels are strongly suggestive of BM.

Both KD and bacterial infection could result in elevated blood leukocytes and CRP. A previous study suggested that CRP was not specific in discriminating KD and bacterial infections.¹⁸ However, in our study we observed higher levels of leukocytes and CRP in KD patients with AM compared with BM patients. There are several explanations of these findings. First, the sample size of our study was quite limited. Second, we selected BM patients whose fever had lasted for no more than 10 days to

enable comparison with KD patients with AM. At this time, the inflammatory reaction in KD patients may have reached its maximum, but in BM patients it was still in an early stage. Thus, relatively higher CRP levels might be helpful in excluding BM during the early stages of fever.

Changes in liver function, including ALT and albumin, are considered auxiliary laboratory findings for diagnosis of KD.¹⁹ Bacterial infections including BM can also result in elevated ALT and AST levels and decreased albumin levels.^{20,21} In this study, levels of ALT, AST and albumin were not significantly different in the two groups suggesting that indicators of liver function are not useful in distinguishing KD patients with AM and BM patients.

Pyuria is another clinical manifestation of KD and has an incidence of 38%.²² In this study, seven of 38 KD patients had pyuria while none of the BM patients did. As a systemic vasculitis, KD is more likely than BM to produce both pyuria and CSF pleocytosis.

In summary, full investigation of clinical manifestations and laboratory parameters is necessary to distinguish KD patients with AM and BM patients. In CSF, glucose level is more efficient than other biomarkers in distinguishing these two diseases. Decreased CSF glucose is potentially an indicator of BM rather than KD and AM.

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Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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References

1. McCrindle BW, Rowley AH, Newburger JW, et al. Diagnosis, treatment, and long-term management of Kawasaki disease: A scientific statement for health professionals from the American Heart Association. *Circulation* 2017; 135: e927–e999.
2. Singh S, Jindal AK and Paliania RK. Diagnosis of Kawasaki disease. *Int J Rheum Dis* 2018; 21: 36–44.
3. Rossi M, Siani P, Grossi A, et al. Aseptic meningitis as onset of Kawasaki disease. *Minerva Pediatr* 2020; 72: 135–137.
4. Türel O, Güzeltaş A, Aydoğmuş C, et al. Kawasaki disease presenting as meningitis in a two months old infant. *Anadolu Kardiyol Derg* 2011; 11: 369–370.
5. Dengler LD, Capparelli EV, Bastian JF, et al. Cerebrospinal fluid profile in patients with acute Kawasaki disease. *Pediatr Infect Dis J* 1998; 17: 478–481.
6. Yeom JS, Park JS, Seo JH, et al. Initial characteristics of Kawasaki disease with cerebrospinal fluid pleocytosis in febrile infants. *Pediatr Neurol* 2012; 47: 259–262.
7. Kemmotsu Y, Nakayama T, Matsuura H, et al. Clinical characteristics of aseptic meningitis induced by intravenous immunoglobulin in patients with Kawasaki disease. *Pediatr Rheumatol Online J* 2011; 9: 28.
8. Bharath V, Eckert K, Kang M, et al. Incidence and natural history of intravenous immunoglobulin-induced aseptic meningitis: A retrospective review at a single tertiary care center. *Transfusion* 2015; 55: 2597–2605.
9. Peng Y, Liu X, Duan Z, et al. Prevalence and characteristics of arthritis in Kawasaki disease: A Chinese cohort study. *Clin Exp Med* 2019; 19: 167–172.

10. Zhang Y, Wan H, Du M, et al. Capillary leak syndrome and aseptic meningitis in a patient with Kawasaki disease: A case report. *Medicine (Baltimore)* 2018; 97: e10716.
11. Ohnishi Y, Mori K, Inoue M, et al. A case of Kawasaki disease presenting as sigmoid colitis. *J Med Ultrason (2001)* 2017; 45: 1–4.
12. Eleftheriou D, Levin M, Shingadia D, et al. Management of Kawasaki disease. *Arch Dis Child* 2014; 99: 74–83.
13. Vasilopoulou VA, Karanika M, Theodoridou K, et al. Prognostic factors related to sequelae in childhood bacterial meningitis: Data from a Greek meningitis registry. *BMC Infect Dis* 2011; 11: 214.
14. Snaebjarnardottir K, Erlendsdottir H, Reynisson IK, et al. Bacterial meningitis in children in Iceland, 1975–2010: A nationwide epidemiological study. *Scand J Infect Dis* 2013; 45: 819–824.
15. Franco-Paredes C, Lammoglia L, Hernandez I, et al. Epidemiology and outcomes of bacterial meningitis in Mexican children: 10-year experience (1993–2003). *Int J Infect Dis* 2008; 12: 380–386.
16. Cabral M, Correia P, Brito MJ, et al. Kawasaki disease in a young infant: Diagnostic challenges. *Acta Reumatol Port* 2011; 36: 304–308.
17. Husain E and Hoque E. Meningoencephalitis as a presentation of Kawasaki disease. *J Child Neurol* 2006; 21: 1080–1081.
18. De Graeff N, Groot N, Ozen S, et al. European consensus-based recommendations for the diagnosis and treatment of Kawasaki disease – the SHARE initiative. *Rheumatology (Oxford)* 2019; 58: 672–682.
19. Huang MY, Gupta-Malhotra M, Huang JJ, et al. Acute-phase reactants and a supplemental diagnostic aid for Kawasaki disease. *Pediatr Cardiol* 2010; 31: 1209–1213.
20. Van Ettehoven CN, Van De Beek D and Brouwer MC. Update on community-acquired bacterial meningitis: Guidance and challenges. *Clin Microbiol Infect* 2017; 23: 601–606.
21. Ljungström L, Pernestig AK, Jacobsson G, et al. Diagnostic accuracy of procalcitonin, neutrophil-lymphocyte count ratio, C-reactive protein, and lactate in patients with suspected bacterial sepsis. *PLoS One* 2017; 12: e0181704.
22. Shike H, Kanegaye JT, Best BM, et al. Pyuria associated with acute Kawasaki disease and fever from other causes. *Pediatr Infect Dis J* 2009; 28: 440e3.