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Research Article

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Comparison of Childhood Aseptic Meningitis with Bacterial Meningitis in a Tertiary Children's Hospital of Taiwan

Yueh-Jung Wang[1*], Nan-Chang Chiua[2,3], Che-Sheng Ho[1] and Hsin-Chia[3]

1Department of Pediatrics, MacKay Children's Hospital, Taipei. Taiwan

2MacKay Junior College of Medicine, Nursing and Management, New Taipei City, Taiwan

3MacKay Medical College, New Taipei City, Taiwan

***Corresponding author:** Nan-Chang Chiu, Department of Pediatrics, MacKay Children's Hospital, 92, Sec. 2, Zhongshan N. Road, Taipei 10449, Taiwan, Tel: +886-2-2543-3535; E-mail: ncc88@mmh.org.tw

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Abstract

Objective: The initial clinical appearances of aseptic and bacterial meningitis in children are similar, but the treatment and outcome are quite different. To clarify the clinical presentation and laboratory results, we retrospectively reviewed our patients.

Methods: The charts of hospitalized children under age 18 with discharge diagnosis of aseptic meningitis and bacterial meningitis during 2007~2014 were reviewed. Patients with aseptic meningitis were recruited as pleocytosis and negative bacterial growth in cerebrospinal fluid (CSF), while those with bacterial meningitis were recruited only who had positive CSF bacterial culture results. Traumatic tapping, contaminated cultures, or having received previous intravenous antibiotic therapy were excluded. Viral pathogens in CSF of aseptic meningitis were identified by CSF culture or polymerase chain reaction.

Results: A total of 141 patients were enrolled as aseptic meningitis and 56 patients as bacterial meningitis. Aseptic meningitis occurred more in older than one-month-old children. Fever, headache, vomiting, and neck stiffness were significantly more in aseptic meningitis children, while convulsion, consciousness change, fontanelle bulging, and desaturation were significantly more in bacterial group. Significant laboratory differences were lymphocyte dominant in CSF, lower CSF protein level, higher CSF glucose level, and lower blood CRP level in aseptic meningitis group. Aseptic patients had shorter hospital duration (5.0 ± 2.0 days vs. 20 .0 ± 8.0 days, p < 0.001). All aseptic meningitis patients survived and were discharged without significant neurologic sequel. Among bacterial meningitis patients, 54.5% recovered completely, 10.9% died, and 34.5% had sequel. The outcome of aseptic meningitis group was significantly better than bacterial group.

Conclusion: Aseptic meningitis occurred more in toddlers and older children, and had more meningeal symptoms/signs. More than half bacterial meningitis occurred in neonates and revealed more dreadful systemic presentations. Laboratory results can be helpful for differentiation of aseptic meningitis from bacterial meningitis. Careful monitoring clinical conditions and laboratory results are mandatory.

Keywords: Bacterial meningitis; Aseptic meningitis; Cerebrospinal fluid; Symptoms/signs outcome; Infants; Children

Introduction

Meningitis is a great burden for patients, families and medical staff. Even epidemiology has changed a lot after novel immunization and infection prevention strategies, bacterial meningitis continues to be associated with high mortality and morbidity especially in those still could not be vaccinated [1]. Our three decades data revealed that patient numbers of Group B *Streptococcus*, *Streptoccus pneumoniae*, and *Haemophilus influenzae* type b meningitis declined but *Escheria coli* meningitis increased in the late period [2]. The initial clinical appearances of aseptic and bacterial meningitis in children are similar, but the treatment and outcome are quite different. The classic signs and symptoms of meningitis are limited to differentiate bacterial and aseptic meningitis [3,4]. Delay in diagnosis increases mortality and early diagnosis of the etiology of meningitis provides better outcomes [5]. Not only patient history, symptoms and laboratory tests may lead to timely and accurate diagnosis, serum biomarkers such as C-reactive protein (CRP) and lactate also have some roles in differentiating bacterial meningitis from other meningitis. Gram stain, culture, glucose and cell count of cerebrospinal fluid (CSF) provide evidence to assist the clinical diagnosis. However, the pathogens and age distribution of meningitis in different areas would not be the same, so the clinical presentation of aseptic and bacterial meningitis might be variable. To clarify the clinical presentation and laboratory results of aseptic and bacterial meningitis in our place, we performed this retrospective review.

Methods

The charts of hospitalized children under age 18 hospitalized in MacKay Children's Hospital, a tertiary hospital in Taipei, Taiwan, with discharge diagnosis of aseptic meningitis and bacterial meningitis

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during 2007~2014 were reviewed. This study was approved by Institutional Review Board of the hospital.

Patients with aseptic meningitis were recruited as who had pleocytosis but negative bacterial growth in CSF. CSF pleocytosis of aseptic meningitis was defined as to be >10 leukocytes/mm^3 in neonates and >5 leukocytes/mm^3 for others. While those with bacterial meningitis were recruited only who had positive CSF bacterial culture results. Traumatic tapping (erythrocytes>10000/mm^3), contaminated cultures, or having received previous intravenous antibiotic therapy were excluded. Patients with sepsis (positive blood bacterial culture report) or other site bacterial infections occurred before neurological symptoms/signs appeared were excluded. Patients who had apparent inflammation of the brain in the beginning of the disease process, detected by brain sonography, computed tomography, magnetic resonance imaging, or electroencephalography, were regarded as having encephalitis and were excluded.

In patients suspected to have meningitis, their CSF was collected for examining cytology, glucose and protein content, Gram stain, and bacterial culture. In some patients who were more likely to be aseptic meningitis, identification of viral pathogens in CSF might be performed by CSF viral culture or polymerase chain reaction (PCR).

The patients' clinical presentations, laboratory data, pathogens, treatment, hospitalization days, and outcomes were reviewed and analyzed. According to the final diagnosis and the definition of this study, aseptic and bacterial meningitis patients were compared.

SPSS and adapted chi-square or Fisher's exact test were used for statistics analysis. Test of Normality by Kolmogorov-Smirnova was applied for laboratory data and hospital duration. P value less than 0.05 was regarded as statistical significance.

Results

Gender and age

A total of 141 patients were enrolled as aseptic meningitis and 56 patients as bacterial meningitis. Around two-thirds of patients were male in both aseptic and bacterial meningitis groups (66.0% and 64.3%). The average age of aseptic meningitis is 5.7 years of age and bacterial meningitis is 1.6 years. Aseptic meningitis occurred more in older than one-month-old children (p<0.001). Most patients in aseptic group were children, but in bacterial group were neonates (Table 1).

Characteristics		Aseptic group	Bacterial group	p value
Sex	female	48 (34.0%)	20(35.7%)	0.824
	male	93 (66.0%)	36 (64.3%)	
Age	<1m/o	20 (14.2%)	31 (55.4%)	<0.001
	1m/o ~ 1y/o	33 (23.4%)	14 (25.0%)	
	1y/o~7y/o	37 (26.2%)	6 (10.7%)	
	7y/o	51 (36.2%)	5 (8.9%)	
Outcome	complete recovery	136 (100.0%)	30 (54.5%)	<0.001
	death	0 (0.0%)	6 (10.9%)	
	sequelae	0 (0.0%)	19 (34.5%)	

Table 1: Comparison of characteristics between aseptic and bacterial meningitis groups.

Aseptic meningitis occurred most in June, followed by September, December and July. The patient number of bacterial meningitis patients was largest in June and zero in November. Though both groups had largest patient numbers in June, their age distribution was quite different (Figure 1).

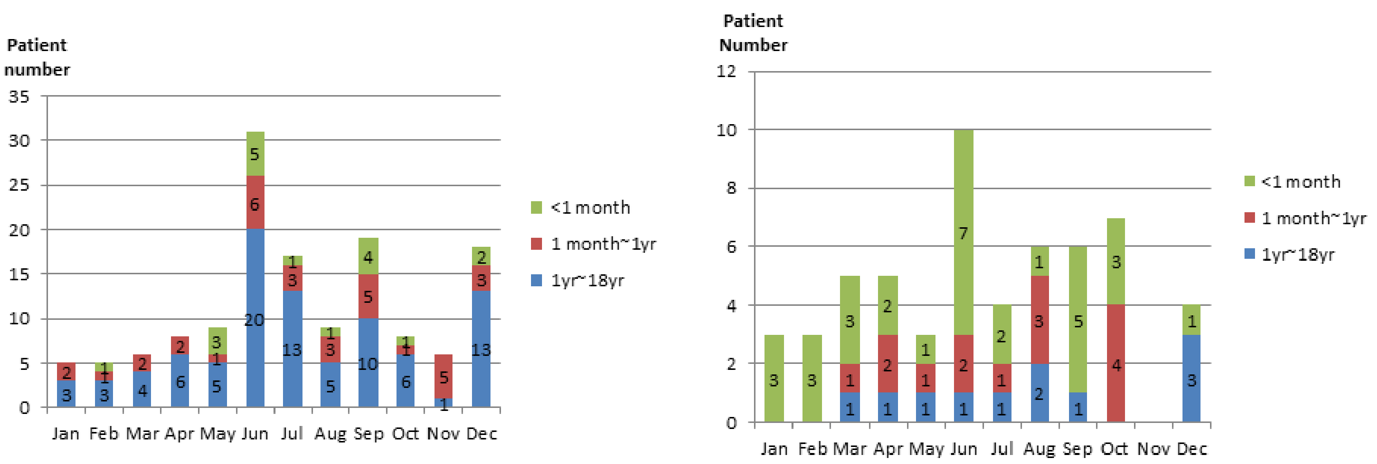

Figure 1: Month and age distribution of aseptic and bacterial meningitis patients.

Pathogens

Forty-nine (34.8%) of the aseptic meningitis patients did not perform CSF viral study, and only 36 (25.5%) patients found specific pathogens. The most common pathogen in aseptic meningitis group was echovirus (23 patients, 16.3%), followed by paneneterovirus (7 patients, 5.0%), coxakievirus (3 patients, 2.1%), and enterovirus 71 (3 patients, 2.1%). The patients diagnosed enterovirus type 71 (EV71) were done by serum EV71 rapid test, rectal and/or throat swab PCR. Except enteroviruses, there were no other confirmed viral pathogens.

The most common pathogens of bacterial meningitis was group B Streptococcus (13 patients, 23.2%), followed by Escherichia coli (10 patients, 17.9%), Streptococcus pneumoniae (7 patients, 12.5%), coagulase-negative Staphylococcus (4 patients, 7.1%), and Acinectobacter spp. (3 patients, 5.4%).

Symptoms and Signs

Fever, headache, vomiting, and neck stiffness were significantly more in aseptic meningitis children, while convulsion, consciousness change, fontanelle bulging, and desaturation were significantly more in bacterial group (Table 2).

Symptoms and signs	Aseptic group	Bacterial group	p value
	n=141	n=56	
Fever	138 (97.9%)		
Poor appetite			
Headache	83 (60.1%)	4 (7.1%)	<0.001
Convulsion	6 (4.7%)	11 (19.6%)	<0.001
Irritability	9 (7.2%)	4 (7.1%)	>0.999
Vomiting	80 (58.4%)	12 (21.4%)	<0.001
Diarrhea	14 (11.0%)	6 (10.7%)	0.951
Abdominal discomfort	11 (7.8%)	3 (5.4%)	0.761
Neck stiffness	54 (40.0%)	4 (7.1%)	<0.001
Meningeal sign	25 (17.7%)	3 (5.4%)	0.025
Consciousness change	0 (0.0%)	6 (10.7%)	<0.001
Fontanelle bulging	0 (0.0%)	4 (7.1%)	0.006
Desaturation	3 (2.1%)	15 (26.8%)	<0.001

Table 2: Comparison of symptoms and signs between aseptic and bacterial meningitis.

Laboratory data

There were significant differences between aseptic and bacterial groups on CSF lymphocyte (35.5% vs. 6.0%), CSF lymphocyte/neutrophil ratio (1.95 vs. 0.1), CSF protein (53.0 mg/dl vs. 211.0 mg/dl), CSF glucose (59.0 mg/dl vs. 38.0 mg/dl), CSF/blood sugar (0.5 vs. 0.4), and CRP (0.575 mg/dl vs. 3.92 mg/dl) (Table 3).

Laboratory data	Aseptic group	Bacterial group	p value
	Median (IQR)	Median (IQR)	
CSF-WBC (cells/mm3)	99.5 (177.3)	189.0 (1848.0)	0.707
CSF-Lym (%)	35.5 (47.5)	6.0 (16.0)	<0.001
CSF-Neu (%)	19.0 (43.8)	81 (83.0)	0.314
CSF-L/N	1.95 (7.9)	0.1 (1.1)	<0.001
CSF-Protein (mg/dL)	53.0 (52.3)	211.0 (354.0)	<0.001
CSF-Glucose (mg/dL)	59.0 (18.0)	38.0 (48.0)	<0.001
Blood-Glucose (mg/dL)	105.5 (27.3)	114.0 (50.0)	0.993
CSF/Blood-Glucose	0.5 (0.1)	0.4 (0.5)	<0.001
Blood-WBC (cells/mm3)	11900 (7300)	10600 (14910)	0.742
Blood-Neu (%)	69.0 (33.0)	52.0 (39.0)	0.237
Blood-Lym (%)	19.9 (27.3)	25.0 (36.0)	0.44
Blood-CRP (mg/dL)	0.58 (1.44)	3.92 (6.29)	<0.001

Table 3: Comparison of laboratory data between aseptic and bacterial meningitis.

Treatment

A total of 107 aseptic meningitis patients (75.9%) received antibiotic treatment initially and 67.0% of the antibiotics were discontinued within 3 days. Empirical antibiotic use was not significantly related to the value of blood CRP, WBC or CSF WBC, but more young infants were more common to be applied for antibiotic prescription (p<0.001). Empirical antibiotic agents were prescribed in all the bacterial meningitis patients and were changed according to the culture results and susceptibility tests.

Outcomes

Aseptic group presented with shorter hospital duration (5.0 ± 2.0 days vs. 20 .0 ± 8.0 days, p < 0.001). All aseptic meningitis patients survived and were discharged without significant neurologic sequelae. Thirty bacterial meningitis patients (54.5%) recovered completely, 6 (10.9%) died, and 19 (34.5%) had sequelae. The outcome of aseptic meningitis group was significantly better than bacterial group (p<0 . 001).

Discussions

Early distinguishing bacterial meningitis from aseptic meningitis is necessary to improve outcome by adequate treatment. Several prognostic models have been developed for this reason. However, more information is still needed [6]. Most children with CSF pleocytosis have aseptic rather than bacterial meningitis, raising the possibility that some patients may be managed as outpatients [7]. In this study, more than half of our aseptic meningitis patients were toddlers or older children, while more than half of bacterial meningitis patients were less than one month of age. This diverse age distribution between aseptic and bacterial meningitis is related to many reasons. High immunization rate and good environmental sanitation let bacterial meningitis hardly occur in Taiwan's toddlers or children [2]. As neonatal bacterial meningitis, group B Streptococcus, the previous most common pathogen, also has become much less after application of maternal screening and intrapartum prophylaxis policy [8]. However, the situation of aseptic meningitis is quite different.

Among aseptic meningitis, enteroviruses are the most common cause [9]. Other frequently mentioned pathogens include herpesviruses, mumps, arboviruses, etc [11]. Nonetheless, we did not confirm other viral pathogens in this study. The reason may be due to the exclusion of the encephalitis cases and the high immunization rate in Taiwan, i.e. polio vaccine, measles, mumps, rubella vaccine, varicella vaccine and Japanese B vaccine. Typical manifestations of enteroviral meningitis are usually self-limited. Enteroviral encephalitis and encephalomyelitis are less common but more severe manifestations, associated with long-term debilitation and death. Endemic EV 71 outbreaks have occurred in Taiwan and other countries, associated with hand, foot and mouth disease and herpangina, and even severe brain stem encephalitis [12,13].

Seasonality of enterovirus infections has been described, which occur most common in summer and fall in temperate regions, whereas they occur throughout the year in tropical regions [14]. In Taiwan, annual spring and summer enterovirus epidemics are noted, with children under age 5 comprising the majority of cases [12,13]. Since most of our aseptic meningitis is caused by enterovirus, the monthly distribution of aseptic group follows the seasonality of enterovirus.

Fever, headache, vomiting, and neck stiffness were significantly more in aseptic meningitis children in our study. This may be related to the age distribution which possessed older age group who were able to express their clinical condition. While convulsion, consciousness change, fontanelle bulging, and desaturation were more objective and were significantly more in bacterial group. They reflect the younger age and more severe disease process of the patients. The less specific meningeal signs of bacterial group reminded us to be more alert in clinical judgment, providing timely diagnostic tests and treatment. Since neonates have higher possibility of bacterial meningitis than children, empirical antibiotic therapy may be indicated. While in children, though severity may be a clue but the clinical presentation may not be good enough to differentiate between bacterial and aseptic meningitis, laboratory data would be important.

There exists wide range of definition of CSF pleocytosis, and it changes according to different age. Some studies adopt the definition of pleocytosis to be >22 white cells/mm3 for neonates, >15 white cells/mm^3 for infants aged 1 to 2 months, and >5 white cells/mm3 for >2 months [15]. Some set the definition at >30 white cells/mm^3 for neonate and >5 white cells/mm^3 for others [16]. In our study, we define pleocytosis to be >10 white cells/mm^3 for neonate and >5 white cells/mm^3 for others. Under this criterion, significant differences between aseptic and bacterial meningitis groups include lymphocyte dominant in CSF, lower CSF protein level, higher CSF glucose level, and lower blood CRP level in aseptic meningitis group.

Our study suggested more prominent CSF lymphocytes (35.5% vs. 6.0%) and L/N ratio (1.95 vs. 0.1) in aseptic meningitis over bacterial group, compatible with previous studies [17-19]. The ratio of CSF neutrophils was higher but not significantly different in our bacterial group. Although it was usually considered to be bacterial meningitis when the CSF data presented with PMN predominance, there was noteworthy overlap of neutrophils for bacterial and aseptic cases [20]. Neutrophil predominance has been reported in aseptic meningitis during enteroviral season but was incapable of discriminating between aseptic and bacterial meningitis [21], like our study.

Though some studies reported protein not to be a good predictor for central nervous enteroviral infection for low sensitivity and specificity, some study found it was significant [21,22]. CSF white blood cell count and plasma C-reactive protein at all ages, and CSF protein in infants <3 months of age have been reported to be distinguished between bacterial meningitis and viral meningitis [22]. CSF/blood glucose ratio has been suggested to be the most precise predictor bacterial meningitis in CSF [23]. The differences of CSF protein (53.0 mg/dl vs. 211.0 mg/dl), CSF glucose (59.0 mg/dl vs. 38.0 mg/dl), CSF/blood glucose ratio (0.5 v.s. 0.4) between aseptic and bacterial meningitis groups are significant in our study. Blood-CRP (0.58 mg/dlvs.3.92 mg/dl) was also significant in our study suggesting to be an efficient diagnostic tool as previously reported [23]. Although CSF lactate and serum procalcitonin have been reported to be useful to distinguish bacterial meningitis from aseptic ones [24,25], they were not routinely checked in our department due to low cost effectiveness.

Virus identification by virus culture is difficult, and only one-fourth of our aseptic meningitis patients had pathogen confirmed, all were enteroviruses. In our review, many patients were clinically diagnosed to be aseptic meningitis but their parents refused lumbar puncture, so were not recruited into this study. A more detailed and acceptable explanation for this procedure is needed to avoid delayed diagnosis. Some patients did not perform viral studies, because the clinicians considered no such necessity. Although most aseptic meningitis has quite good outcomes, to have a definite diagnosis still would be better especially during a viral endemic condition. In our aseptic meningitis group, 92 patients performed CSF viral study but only 36 patients (39.1%) confirmed viral pathogens. Many viruses are hard to be proved by culture, more advanced technique such as PCR or viral serologic studies would be helpful.

For most patients considered to have the possibility of meningitis, empirical antibiotic treatment will be applied unless there is strong evidence suggesting viral origin, e.g. herpangina and hand, foot and mouth disease for enterovirus, gingivostomatitis for herpes simplex virus, vesicles for varicella, etc. Three-fourth of our aseptic meningitis patients received empirical antibiotic therapy initially is acceptable. However, if quick and reliable diagnosis can be made, the unnecessary antibiotic agents can be stopped and sometimes crucial antiviral agents can be prescribed earlier. Basic CSF laboratory results, therefore, would be useful.

In conclusion, the main pathogens of aseptic meningitis in Taiwan's children were enteroviruses. Aseptic meningitis occurred more in toddlers and older children and had more meningeal symptoms/signs. While more than half bacterial meningitis occurred in neonates and revealed more dreadful systemic presentations. There were some parameters in our study may provide as a reference for discrimination aseptic and bacterial meningitis, including lymphocyte dominant in CSF, lower CSF protein level, higher CSF glucose level, and lower blood CRP level in aseptic meningitis group. Careful monitoring clinical conditions and laboratory results are mandatory.

Conflicts of Interest

All authors declare that they have no conflicts of interest associated with the materials discussed in the article.

References

1. Agrawal S, Nadel S (2011) Acute bacterial meningitis in infants and children: epidemiology and management. Paediatr Drugs 13: 385-400.

2. Lin MC, Chiu NC, Chi H, Ho CS, Huang FY (2015) Evolving trends of neonatal and childhood bacterial meningitis in northern Taiwan. J Microbiol Immunol Infect 48: 296-301.
3. Dubos F, Martinot A, Gendrel D, Bréart G, Chalumeau M (2009) Clinical decision rules for evaluating meningitis in children. Curr Opin Neurol 22: 288-293.
4. Nigrovic LE, Malley R, Kuppermann N (2009) Cerebrospinal fluid pleocytosis in children in the era of bacterial conjugate vaccines: distinguishing the child with bacterial and aseptic meningitis. Pediatr Emerg Care 25: 112-117.
5. Bamberger DM (2010) Diagnosis, initial management, and prevention of meningitis. Am Fam Physician 82: 1491-1498.
6. Jonge RC, Van Furth AM, Wassenaar M, Gemke RJ, Terwee CB (2010) Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. BMC Infect Dis 5; 10:232.
7. Nigrovic LE, Malley R, Kuppermann N (2009) Cerebrospinal fluid pleocytosis in children in the era of bacterial and aseptic meningitis. Pediatr Emerg Care 25: 112-7. conjugate vaccines: distinguishing the child with bacterial
8. Lin CY, Hsu CH, Huang FY, Chang JH, Hung HY, et al . (2011) The changing face of early-onset neonatal sepsis after the implementation of a maternal group B Streptococcus screening and intrapartum prophylaxis policy--a study in one medical center. Pediatr Neonatol 52: 78-84.
9. Berlin LE, Rorabaugh ML, Heldrich F, Roberts K. Doran T, et al. (1993) Aseptic meningitis in infants <2 years of age: diagnosis and etiology. J Infect Dis 168: 888-892.
10. Nigrovic LE (2013) Aseptic meningitis. Handb Clin Neurol 112: 1153-1156.
11. Tan le V, Thai le H, Phu NH, Nghia HD, Chuong LV, et al. (2014) Viral aetiology of central nervous system infections in adults admitted to a tertiary referral hospital in southern Vietnam over 12 years. PLoS Negl Trop Dis 8: e3127.
12. Chia MY, Chiang PS, Chung WY, Luo ST, Lee MS (2014) Epidemiology of enterovirus 71 infections in Taiwan. Pediatr Neonatol 55: 243-249.
13. Lo SH, Huang YC, Huang CG, Tsao KC, Li WC, et al. (2011) Clinical and epidemiologic features of Coxsackievirus A6 infection in children in northern Taiwan between 2004 and 2009. J Microbiol Immunol Infect 44:252-257.
14. Sathish N, Scott JX, Shaji RV, Sridharan G, Theophilus VS, et al. (2004) An outbreak of echovirus meningitis in children. Indian Pediatr; 41:384-388.
15. Mulford W S, Buller RS, Arens MQ, Storch G A (2004) Correlation of cerebrospinal fluid (CSF) cell counts and elevated CSF protein levels with enterovirus reverse transcription-PCR results in pediatric and adult patients. J Clin Microbiol 42: 4199–4203.
16. Graham AK, Murdoch DR (2005) Association between cerebrospinal fluid pleocytosis and enteroviral meningitis. J Clin Microbiol 43: 1491.
17. Greenlee JE (1990) Approach to diagnosis of meningitis. Infect Dis Clin North Am 4: 583–598.
18. Nye F (1983) The value of initial laboratory investigations in the management of meningitis. J Infect 7: 31–38.
19. Singer JI, Maur PR, Riley JP, Smith PB (1980) Management of central nervous system infections during an epidemic of enteroviral aseptic meningitis. J Pediatr 96: 559–563.
20. Spanos A, Harrell FE, Durack DT (1989) Differential diagnosis of acute meningitis. JAMA262: 2700–2707.
21. Negrini B, Kelleher KJ, Wald ER (2000) Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics ;105: 316-319.
22. Tamune H, Takeya H, Suzuki W, Tagashira Y, Kuki T, et al. (2014) Cerebrospinal fluid/blood glucose ratio as an indicator for bacterial meningitis. Am J Emerg Med 32: 263-266.
23. Sadarangani M, Willis L, Kadambari S, Gormley S, Upimg Z, et al. (2015) Childhood meningitis in the conjugate vaccine era: a prospective cohort study. Arch Dis Child 100:292-294.
24. Schwarz S, Bertram M, Schwab S, Andrassy K, Hacke W (2000) Serum procalcitonin levels in bacterial and abacterial meningitis. Crit Care Med 28: 1828-1832.
25. Viallon A, Zeni F, Lambert C, Pozzetto B, Tardy B, et al. (1999) High sensitivity and specificity of serum procalcitonin levels in adults with bacterial meningitis. Clin Infect Dis 28:1313-1316.