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Risk factors for poor prognosis in children with refractory purulent meningitis and the discharge criteria

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ABSTRACT

This study was undertaken to investigate the relationship between cerebrospinal fluid abnormalities and prognosis in pediatric refractory purulent meningitis. Ninety cases of pediatric refractory purulent meningitis were stratified into "good" (n = 33) or "poor" (n = 57) prognosis groups according to the Glasgow clinical outcome scores. The symptoms, laboratory results, and prognosis were compared by using univariate and multivariate logistic regression analyses. Univariate analysis showed that poor prognosis was associated with: unequal pupil size in both eyes; positive Babinski sign; CSF-WBC >500 × 10^6/L, CSF protein concentration >1.0 g/L, CSF glucose content <1.5 mmol/L; initial procalcitonin result >0.1 ng/dL on admission; hemoglobin <90 g/L during hospitalization; abnormal head imaging, and abnormal electroencephalogram. On multivariate analysis only unequal pupil size in both eyes and CSF glucose content <1.5 mmol/L remained significant. The CSF protein concentration was significantly different between groups at discharge. The cutoff value was 0.68 g/L. We recommend that discharged patients meet the following criteria: full antibiotic course and over 1 week of defervesce, disappearance of acute phase symptoms, CSF-WBC ≤28 × 10^6/L, CSF glucose >1.75 mmol/L, and protein <0.68 g/L. The patient may be discharged for follow-up if no relapse occurs during 3–5 days of observation after drug withdrawal.

Introduction

Purulent meningitis, also known as acute bacterial meningitis, is a common infectious disease that affects the central nervous system in children. The main clinical features of the disease include fever, increased intracranial pressure, meningeal irritation, and purulent changes to the cerebrospinal fluid (CSF) [1]. Purulent meningitis is an important cause of morbidity and mortality in neonates and children [2–9]. Mortality can reach 100% in pediatric patients without any treatment [10]. The onset of refractory purulent meningitis is acute, it develops rapidly, and mortality and morbidity are higher than those of common purulent meningitis. Some pediatric patients have poor therapeutic outcomes such as minimal effectiveness of conventional antibiotic therapy, relapse rapidly after showing signs of improvement on treatment, CSF remains abnormal, or in some cases there are serious sequelae including death. It is unclear why the disease is more refractory in some patients than others and why some patients have a better prognosis than others with a similar disease course. Therefore, early recognition of the symptoms of severe disease and understanding the risk factors resulting in poor prognosis for refractory purulent meningitis is critical to reducing the mortality and morbidity of purulent meningitis [11].

This study was undertaken with multiple objectives: (1) to understand the risk factors for poor prognosis in pediatric patients with refractory purulent meningitis; (2) characterize the relationship between CSF recovery and the prognosis of refractory purulent meningitis; and (3) provide evidence based recommendations for an appropriate antibiotic treatment course, and discharge criteria. The study is a retrospective analysis of clinical data and outcomes for 90 children with refractory purulent meningitis in the Children's

Abbreviations: CSF, cerebrospinal fluid; EEG, electroencephalography; CNS, central nervous system; GOS, Glasgow Outcome Score criteria; ROC, operating characteristic curve; WBC, white blood cell; CMA, China Medical Association; PCT, procalcitonin.

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Hospital of Chongqing Medical University from February 2011 to July 2014.

Material and methods

Subject inclusion and exclusion criteria

For inclusion in the study, subjects had to meet the following criteria: (a) age ≥1 month; (b) symptoms and findings consistent with the diagnostic criteria for purulent meningitis [2]; and (c) pediatric patients meeting one or more of the following criteria were classified as having refractory purulent meningitis [12]: (i) severe disturbance of consciousness (prolonged coma); (ii) cerebral hernia; (iii) repeated or prolonged convulsions; (iv) abnormal plate-like brain parenchymal loci on head CT or MRI; (v) complications persisting during late follow-up, such as subdural effusion, ependymitis and hydrocephalus; (vi) death, or sequelae during late follow-up such as secondary epilepsy, cranial nerve damage, and psychomotor retardation; (vii) treatment for >3 weeks according to a regular treatment program (except for a prolonged course of treatment caused by nosocomial infections or underlying disease); and (viii) unexplained recurrent suppurative intracranial infections.

This study was approved by the Ethics Committee of the Children's Hospital affiliated with Chongqing University of Medical Sciences. Informed consent was obtained from the parents or legal guardians of the subjects via signed consent forms.

Subjects were excluded from the study if they met the following criteria: (i) cases complicated with viral encephalitis, tubercular meningitis or cryptococcus meningitis and (ii) cases in which other central nervous system (CNS) disorders could not be excluded.

Methods

Ninety (n = 90) cases met the inclusion criteria in the neurology ward in the Children's Hospital of Chongqing Medical University between February 2011 and July 2014. The cases were divided into the "good prognosis" group and "poor prognosis" group based on the clinical Glasgow Outcome Score criteria (GOS; Table 1) [13]. The cases scoring a 5 on the GOS were stratified to the "good prognosis" group and those scoring 1–4 points were stratified to the "poor prognosis" group.

Statistical analysis

Statistical analysis was performed using SPSS22.0 statistical software package. Measurement data were analyzed with the t test and rank sum test; and count data were analyzed with the chi-square test. If measurement data were not normally distributed, then they were converted to count data to be analyzed by chi-square test. Multivariate logistic regression analysis was used for the indicators with statistical significance in the univariate statistical analysis. A receiver operating characteristic (ROC) curve was used to determine the best cut-off value for diagnosis. Statistical significance was established at $P < 0.05$.

Table 1
Glasgow outcome score criteria.

Score	Criteria
5	Cure: purulent meningitis symptoms and the signs have disappeared completely, two consecutive CSF values are normal, peripheral blood is normal, no complications or sequelae are present. Significant improvement: purulent meningitis symptoms and signs are relieved significantly, CSF results are basically normal, various complications are improved, no sequelae.
4	Frequent seizures or movement disorders occur due to central nervous system dysfunction, CSF values show no improvement, no complications mitigation is available
3	Severe central nervous system disorders
2	Vegetative state
1	Death

Results

For the ninety cases, the onset age range was from 1-month-old to 14-years-old. The average duration of antibiotic usage in this study was 37 days, and the range was 6–76 days. Subjects were followed for a minimum of 8 months and a maximum of 4 years. Of the 90 enrolled subjects, 33 (33/90; 36.67%) were included in the "good prognosis" group. Of these, 9 cases were cured and 24 cases showed improvement. The "poor prognosis" group included the remaining 57 subjects (57/90; 63.33%). Of these, 12 cases died (12/90; 13.33%), and none of the subjects underwent an autopsy. The incidences of sequelae in the "poor prognosis" group were: 35 cases of mental retardation (35/90; 38.89%), 9 cases of secondary epilepsy (9/90; 10%), 6 cases of hydrocephalus (6/90; 6.67%), 4 cases of hearing impairment (4/90; 4.44%), and 3 cases of movement disorders (3/90; 3.33%). Eleven (11) cases (11/90; 12.22%) were complicated with two or more sequelae, including 4 cases of mental retardation complicated with secondary epilepsy, 3 cases of mental retardation complicated with hydrocephalus, 2 cases of mental retardation complicated with hearing impairment, 1 case of mental retardation complicated with movement disorders, and 1 case of mental retardation complicated with hydrocephalus and movement disorders.

Etiology and treatment

CSF culture was performed in 90 patients. CSF smears were positive in 4 patients (Gram-positive cocci), while CSF cultures were positive in 19 patients (total: 19/90, 21.11%). Blood cultures were performed in 90 patients. Blood smear was positive in only 1 patient (Gram-positive cocci), while blood cultures were positive in 35 patients (total: 35/90, 38.89%) (Table 2). The isolates from CSF and blood matched.

After admission, antibiotics were administered to all 90 patients (100%). The empirical antimicrobial therapy for purulent meningitis was based on patient age and specific predisposing condition. Targeted antimicrobial therapy was based on positive pathogen identification by CSF or blood cultivation. Surgery was performed in 25 patients (25/90, 27.78%) (Table 3).

Table 2
The etiology of CSF and blood cultures.

Item	Etiology	N
CSF cultures	*Streptococcus pneumoniae*	9
	Escherichia coli	6
	Enterobacter cloacae	1
	Staphylococcus aureus + *Streptococcus pneumoniae*	1
	Klebsiella pneumoniae subsp. *pneumoniae* + *Acinetobacter baumannii*	1
	Klebsiella pneumoniae subsp. *pneumonia* + *Staphylococcus aureus*	1
Blood cultures	*Streptococcus*	15
	Staphylococcus	9
	Escherichia coli	4
	Klebsiella pneumoniae	2
	Listeria monocytogenes	1
	Pasteurella pneumotropica,	1
	Staphylococcus aureus + *Streptococcus pneumoniae*	1
	Staphylococcus hominis subspecies + *Staphylococcus epidermidis*	1
	Staphylococcus haemolyticus + *Staphylococcus capitis*	1

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