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ORIGINAL ARTICLE

Analysis of clinical outcomes in pediatric bacterial meningitis focusing on patients without cerebrospinal fluid pleocytosis

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Background: Cerebrospinal fluid (CSF) cell count and biochemical examinations and cultures form the basis for the diagnosis of bacterial meningitis. However, some patients do not have typical findings and are at a higher risk of being missed or having delayed treatment. To better understand the correlation between CSF results and outcomes, we evaluated CSF data focusing on the patients with atypical findings.
Methods: This study enrolled CSF culture-proven bacterial meningitis patients aged from 1 month to 18 years in a medical center. The patients were divided into "normal" and "abnormal" groups for each laboratory result and in combination. The correlations between the laboratory results and the outcomes were analyzed.
Results: A total of 175 children with confirmed bacterial meningitis were enrolled. In CSF examinations, 16.2% of patients had normal white blood cell counts, 29.5% had normal glucose levels, 24.5% had normal protein levels, 10.2% had normal results in two items, and 8.6% had normal results in all three items. In logistic regression analysis, a normal CSF leukocyte count and increased CSF protein level were related to poor outcomes. Patients with meningitis caused by *Streptococcus pneumoniae* and hyponatremia were at a higher risk of mortality and the development of sequelae.
Conclusions: In children with bacterial meningitis, nontypical CSF findings and, in particular, normal CSF leukocyte count and increased protein level may indicate a worse prognosis.

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Introduction

Bacterial meningitis continues to be a leading cause of mortality and morbidity in children despite the development of new medications.[1–3] Patients suspected of having bacterial meningitis remain a clinical emergency requiring an immediate diagnosis and early treatment. Cerebrospinal fluid (CSF) cell count and biochemical examinations and cultures are fundamental laboratory examinations for making a diagnosis. Typical CSF findings among adult patients are elevated white blood cell (WBC) count ($>1000 \times 10^6$/L and >50% polymorphonuclear leukocytes), decreased glucose level (<2.2 mmol/L), and increased protein concentration (>1 g/L).[4] Nigrovic et al[5–7] proposed the Bacterial Meningitis Score which classifies children at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF protein level greater than 0.8 g/L, CSF absolute neutrophil count greater than 1000×10^6/L, peripheral absolute neutrophil count greater than 10×10^9/L, and a history of seizures before or at the time of presentation. The score has good sensitivity and specificity to identify bacterial meningitis in children with CSF pleocytosis. However, some patients do not have typical laboratory findings or CSF pleocytosis. The patients with atypical laboratory findings are at a higher risk of being missed or of experiencing a delay in receiving appropriate treatment, which increases the risk of a poor prognosis.[8–10] In order to understand the correlation between CSF results and outcomes, we evaluated CSF data and outcomes of patients with culture-proven bacterial meningitis. We focused on children with bacterial meningitis without abnormal CSF laboratory findings. Our main purpose was to identify the risk factors for poor outcomes, so that clinicians are alert while treating patients who may be easily missed but are actually at a high risk of mortality and morbidity.

Methods

This study was conducted in a tertiary medical center in northern Taiwan. A database was created to record the children with meningitis. We selected patients from a registry database, and enrolled all patients with the diagnosis of culture-proven bacterial meningitis aged from 1 month to 18 years, from January 1984 to December 2012. We collected demographic information and laboratory findings by retrospective chart review. Laboratory findings included WBC count, glucose levels, sodium levels, total protein levels, and CSF and blood culture results. Age, sex, treatment, complications, and outcomes were also recorded for analysis.

In patients suspected of having meningitis, lumbar punctures and blood tests were performed on admission before initiating antibiotic treatment. Routine laboratory examinations included CSF cell count, biochemical examinations and cultures, and blood cell count and cultures. Serum sodium and glucose levels were reviewed in most patients but were not part of routine examinations. The CSF-to-serum glucose ratio was calculated in patients with available data. We excluded children diagnosed with bacterial meningitis without bacteria isolated from the CSF or whose CSF cultures yielded normal skin flora (e.g., coagulase-negative staphylococci) and clinical presentation suggested contamination. We also excluded patients with congenital infections. Some patients had traumatic lumbar punctures or poor sample collection, and their CSF WBC count, glucose, or protein data were excluded. If a patient had multiple laboratory results, we registered only the first in each episode. For those with recurrent meningitis, the laboratory findings in each episode were separately calculated.

The patients were divided into infants (age: 1 month to <1 year) and children (age $\geq$ 1 year). We defined a normal CSF WBC count as 20×10^6/L or less in all patients; a normal CSF protein level was defined as 1 g/L or less in infants and 0.5 g/L or less in the children. A normal CSF glucose level was defined as 2.2 mmol/L or greater, a normal CSF-to-serum glucose ratio as 0.6 or greater, a normal serum sodium level as 130 mmol/L or greater, and a normal serum WBC count as between 4.5×10^9/L and 11×10^9/L in all patients.

The outcomes were divided into "death or sequelae", "recovery", and "lost to follow up". Sequelae were defined as physical or psychological morbidities lasting longer than 6 months after the meningitis episode, including mental retardation, cerebral palsy, ataxia, hearing impairment, and epilepsy. Lost to follow up was defined as an inability to reach the patient at 6 months after the meningitis episode. We excluded those patients who were lost to follow up from outcome analysis. The patients who died or had sequelae were classified into the poor outcome group, and those who were followed up and recovered without sequelae into the good outcome group.

Statistical analysis

In each single laboratory item or combined items, patient outcomes were compared using the Chi-square test, Fisher's exact test, or one-way analysis of variance. We further analyzed the outcomes of patients with different CSF WBC count results and those with normal CSF WBC count results. For identifying the relationships between different items, we used logistic regression to define the strongest outcome predictors. The threshold of statistical significance was set at $p < 0.05$. Statistical analyses were performed using SPSS version 12.0 (SPSS, Inc., Chicago, IL, USA).

Results

This study enrolled 175 patients between 1 month and 18 years of age with culture-proven meningitis, including 64 girls (36.6%) and 111 boys (63.4%). The age distribution of the patients is shown in Fig. 1. A total of 107 patients (61.1%) were aged 1 month to less than 1 year and were classified as infants. Twenty-one patients (12.0%) were lost to follow up, 81 (46.3%) recovered without sequelae (good outcome group), and 73 (41.7%) died or had sequelae (poor outcome group).