Swiftly Decreasing Cerebrospinal Fluid Cathelicidin Concentration Predicts Improved Outcome in Childhood Bacterial Meningitis

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We investigated cerebrospinal fluid (CSF) cathelicidin concentrations in childhood bacterial meningitis on admission and during antimicrobial treatment. CSF cathelicidin concentrations on admission correlated with CSF white cell counts and protein levels but not with bacterial etiology. A greater decrease in the concentration in response to treatment was associated with a better outcome. Since the CSF cathelicidin concentration reflects the degree of central nervous system (CNS) inflammation, it may be used as a novel biomarker in childhood bacterial meningitis. An early decrease during treatment likely signals more rapid mitigation of the disease process and thus a better outcome.

A cute bacterial meningitis (BM) accounts globally for 2% of deaths in children younger than 5 years (1). BM triggers a strong inflammatory reaction in the central nervous system (CNS), and the extent of this reaction is associated with adverse outcomes (2, 3). Cathelicidins make up an antimicrobial peptide family, which plays an important role in innate and adaptive host defense. The only human cathelicidin, LL-37, is best known for its antimicrobial properties, although it also exerts multiple immunomodulatory effects (4). In cathelin-related antimicrobial peptide (CRAMP) knockout mice, induced pneumococcal meningitis increased the numbers of bacteria and decreased neutrophil infiltration in the CNS, which led to a mortality rate higher than that in wild-type mice (5). Moreover, intrathecally administered CRAMP reduced the meningitis-related mortality rate in wild-type mice, suggesting cathelicidin as a possible adjuvant medication (6). Elevated cerebrospinal fluid (CSF) cathelicidin levels have been reported in patients with tuberculous meningitis and BM (7, 8), but no studies so far have assessed the dynamics of CSF cathelicidin in BM in response to treatment.

The patient data were collected during a multicenter clinical trial on childhood BM in Latin America between 1996 and 2003 (9). All the patients received ceftriaxone for 7 to 10 days, and CSF samples were collected on admission (CSF1) and 12 to 24 hours later (CSF2). On admission, the pretreatment condition was graded using the Glasgow Coma Scale (GCS). At discharge, a complete neurological examination was carried out, and an audiological evaluation was performed shortly thereafter. The criteria for severe neurologic sequelae were severe psychomotor retardation, quadriaparesis or quadriplegia, hydrocephalus requiring a shunt, and/or blindness. Deafness was defined as a bilateral hearing threshold of ≥80 dB. The study protocol was approved by the ethics committees of all 10 institutions involved in Latin America. If the patient’s guardian was illiterate, oral consent was obtained after thorough information had been given. This analysis comprises patients at a university hospital in the Dominican Republic (Clinica Infantil Dr. Robert Reid Cabral, Santo Domingo) who fulfilled the criteria for BM and had at least one frozen CSF sample available for further analysis. Their outcomes were graded retrospectively with the Glasgow Outcome Scale (GOS) (10).
with a lower GCS score tended to show higher CSF cathelicidin concentrations in both samples (Table 1). CSF1 concentrations correlated with the CSF1 white cell count and protein level, whereas the CSF2 cathelicidin levels were associated with the CSF2 protein level but not with the leukocyte count of the same sample (Table 1). No differences emerged between the CSF2 cathelicidin concentrations and the specific adjuvant used in treatment (P > 0.05).

**Prognostic value.** Although no statistical significance was reached, higher CSF cathelicidin concentrations on admission were typically associated with better outcomes (higher GOS score at discharge from hospital) (Table 1). That said, lower ratios of CSF2 to CSF1 cathelicidin correlated with higher GOS scores, suggesting that a clear decrease in the CSF cathelicidin concentration during treatment predicted a better outcome (Table 1). No similar correlation between outcome and the ratio of CSF white cell counts was observed. In addition, a decrease in CSF cathelicidin concentration (44 patients), compared with either no change (3 patients) or an increase (18 patients), predicted a better recovery (GOS score 5) (odds ratio [OR], 3.75; 95% confidence interval, 1.19 to 11.81; P = 0.02).

In this retrospective analysis of 99 children with BM, we demonstrated that an early decrease in the CSF cathelicidin concentration during the first 12 to 24 hours of antimicrobial treatment was associated with a better outcome. To our knowledge, this is the first study in which CSF cathelicidin, measured twice during the course of BM, is related to the outcome in patients with this severe disease. Furthermore, the CSF cathelicidin concentration on admission reflected the degree of CNS inflammation in BM, correlating very clearly (P < 0.001) with the CSF white cell count and protein level.

There were limitations of this study. The samples were stored frozen for several years before cathelicidin was measured, and CSF samples were not available from all the patients. However, because all the samples were treated and stored similarly, a possible degradation process would presumably have had a minor effect on the ratio of CSF2 to CSF1 cathelicidin. While we acknowledge these problems, our findings are consistent with previously reported research results.

Our study’s findings indicate that CSF cathelicidin can be used as a novel biomarker of the inflammatory process in BM, since its dynamics in the early course of the disease predict the outcome.

However, further studies are needed to uncover the mechanisms behind these interesting observations.

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