Cerebrospinal fluid $\beta_2$-microglobulin in neonates with central nervous system infections

Abstract Beta2-microglobulin ($\beta_2$m) determination in CSF of 72 neonates who underwent a spinal tap as part of a sepsis or meningo-encephalitis workup was performed to evaluate the usefulness of this test in the diagnosis of CNS infections. $\beta_2$m was measured by enzyme immunoassay. Sixty neonates had sterile culture and normal neurological status at discharge. Twelve infants had CNS infections: 8 bacterial meningitis, 3 TORCH infections (T = toxoplasmosis, O = others, R = rubella, C = cytomegalovirus and H=herpes simplex) and 1 viral meningitis. Neonates with CNS infection exhibited significantly higher CSF $\beta_2$m levels compared to neonates with sterile culture (6.24 ± 2.66 Vs 1.74 ± 0.5 mg/l; P < 0.0001). CSF $\beta_2$m levels did not correlate with the white cell count, total protein concentration or glucose level in CSF. When serum and CSF levels were measured simultaneously, the CSF $\beta_2$m level was significantly higher than the corresponding serum level in patients with CNS infection (6.98 ± 2.5 vs 3.2 ± 0.25 mg/l; P < 0.01). Sensitivity, specificity, and predictive values were estimated for different cut-off points. The best operational diagnostic cut-off value was 2.25 mg/l. Receiver operating characteristic curve analysis showed an appropriate trade-off between specificity and sensitivity and indicated that CSF $\beta_2$m was accurate in distinguishing between neonates with and without CNS infection.

Conclusion CSF $\beta_2$m may be a useful ancillary tool in neonates when CNS infection is suspected.

Key words Beta2-microglobulin · Neonatal meningitis · TORCH infections · Central nervous system infections

Abbreviations $\beta_2$m, beta2-microglobulin · ROC receiver operating characteristic
Patients and methods

The study included 77 term newborns admitted to the neonatal unit at La Paz Children’s Hospital, Madrid. A neonate was enrolled in the study if he or she underwent a spinal tap as part of a sepsis or meningitis workup and sufficient CSF was available for analysis. Concentrations in CSF and serum were measured by an investigator (T.R.) unaware of the clinical data. The determination of β₂m was performed by means of a microparticle enzyme immunoassay on an IMx analyser (Abbott Laboratories). The sensitivity of this method was 0.5 μg/l. Intra-assay and interassay variations were 9% and 10%, respectively. The method was found to give linear results up to 4 mg/l of immunoreactive β₂m. All samples were assayed in duplicate. Detailed histories were obtained within 72 h after the lumbar puncture, and all charts were reviewed at discharge by physicians who were blind to the CSF β₂m concentrations. The infants were separated according to the presence or absence of CNS infection. Infants with sterile culture and no evidence of neurological disorder at discharge were considered as the control group. Five infants with sterile culture were excluded from the study because of proven neurological disorder. The diagnosis of meningitis was based on CSF bacterial or viral culture results. The diagnosis of meningitis and TORCH infections was based on the CSF findings. All newborns had one or more cranial ultrasonographic scans performed before discharge. The study was approved by the Human Studies Committee of La Paz Children’s Hospital.

Statistics

The data are expressed as mean ± SD unless otherwise stated. The Mann-Whitney, Wilcoxon and Kruskal-Wallis tests were used as appropriate. The Spearman rank correlation coefficient was used for calculating the correlation between two variables. Sensitivity, specificity, and predictive value for a positive and negative test were estimated for different cut-off points on a continuous scale. To minimize the potential bias introduced by choosing a single cut-off for positivity, a receiver operating characteristic (ROC) curve was constructed. The area under the ROC curve was used as an index of the diagnostic accuracy of the prediction rule. The area under the ROC curve was obtained using the trapezoid method; the standard error of the area was calculated using a nonparametric method described by Hanley and McNeil [11].

Results

The studied population comprised 72 term neonates. Sixty infants had sterile culture and no evidence of a neurological disorder at discharge. Twelve neonates were diagnosed as CNS infection: 8 bacterial meningitis, 3 TORCH infections, and 1 viral meningitis. No differences were found between the two groups in birth weight, gestational age, and sex ratio (Table 1). However, in infants with CNS infections, the spinal tap was performed later than in noninfected infants (116 ± 172 vs 203 ± 176 h; P < 0.05).

<table>
<thead>
<tr>
<th>CNS infection No. of infants</th>
<th>β₂m levels (mg/l)</th>
<th>Serum to CSF ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum CSF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent 16</td>
<td>2.9 ± 0.57**</td>
<td>1.86 ± 0.6</td>
</tr>
<tr>
<td>Present 6</td>
<td>3.2 ± 0.25</td>
<td>6.98 ± 2.5**</td>
</tr>
</tbody>
</table>

* P < 0.01 versus serum level, ** P < 0.01 versus serum level, *** P < 0.005 versus the serum to CSF ratio in the group without CNS infections

β₂-microglobulin concentration in CSF of neonates without intracranial infection

The group of neonates without CNS infection had a mean CSF β₂m concentration of 1.74 mg/l (99% confidence interval, 1.55–1.94). CSF β₂m level in this group did not correlate with gender, gestational age, or the age at the time of spinal tap. Twelve infants in this group had a bloody CSF sample. These 12 infants, compared to infants without blood in the CSF (n = 48), had a higher protein level (167 ± 71 mg/dl vs 77 ± 24 mg/dl; P < 0.001) and higher nucleated blood cell count (35 ± 14 vs 6 ± 13; P < 0.001). However, no significant differences were found in CSF β₂m levels (1.9 ± 0.8 vs 1.70 ± 0.5 mg/l). In the 48 infants without bloody CSF samples correlation coefficients were calculated for CSF β₂m level with routine CSF tests. CSF β₂m levels did not correlate with the total WBC count or with the glucose level in the CSF. However, they exhibited a significant but poor correlation with the CSF protein concentration (r = 0.40, P < 0.01). In 16 of them, serum and CSF β₂m levels were measured simultaneously. No correlation was found between CSF and serum levels (r = 0.33). The CSF level of β₂m was significantly lower than the serum level (Table 2). The mean ratio of serum/CSF β₂m concentration was 1.68 ± 0.51.

| β₂-microglobulin concentration in CSF of neonates with CNS infection

Table 3 shows the main biochemical CSF findings in the 12 patients with CNS infection. All of these neonates had...