Clinical research

Value of cerebrospinal fluid lactate for the diagnosis of bacterial meningitis in postoperative neurosurgical patients

Pedro Grille*, Jimena Torres, Fausto Forcires, Homero Bagnulo

Intensive Care Unit, Maciel Hospital, Montevideo, Uruguay

Abstract

Objective: To evaluate the diagnostic value of CSF lactate ($L_{CSF}$) for the diagnosis of bacterial meningitis (BM) following neurosurgery, and compare it with other CSF markers.

Methods: Prospective study of consecutive neurosurgical postoperative patients admitted to the Intensive Care Unit (ICU) at Maciel Hospital. Patients with clinical suspicion of BM were categorised, according to preset criteria, into 3 groups: (1) proven BM; (2) probable BM, and (3) excluded BM. CSF markers were plotted in a receiver operating curve (ROC) to evaluate their diagnostic accuracy.

Results: The study included 158 patients. We obtained 46 CSF samples from patients with clinical suspicion of BM by lumbar puncture (LP): 10 corresponded to proven BM, 4 to probable BM and 32 to excluded BM. Mean lactate in CSF ($L_{CSF}$) was: 10.72 ± 4.68 mM for proven BM, 6.07 ± 0.66 mM for probable BM and 3.06 ± 1.11 mM for excluded BM ($P < .001$ for proven BM and probable BM vs excluded BM; $P = N S$ for proven BM vs probable BM). $L_{CSF}$ displayed a better diagnostic accuracy for BM in the 2 scenarios studied: (1) positive bacterial CSF culture or Gram stain as positive control (gold standard) (sensitivity: 87%, specificity: 94%, cut-off value: 5.9 mM), and (2) combination of proven BM and probable BM as positive control (sensitivity: 92%, specificity: 100%, cut-off value: 5.2 mM).

Conclusions: According to our results, determination of $L_{CSF}$ is a quick, sensitive and specific test to identify the need for antimicrobial therapy in neurosurgical postoperative patients with clinical suspicion of BM.

© 2011 Sociedad Española de Neurocirugía. Published by Elsevier España, S.L. All rights reserved.

Valor del lactato en líquido cefalorraquídeo para el diagnóstico de meningitis bacteriana en el postoperatorio de neurocirugía

Resumen

Objetivo: Evaluar el valor diagnóstico del lactato en líquido cefalorraquídeo (LCR) para el diagnóstico de meningitis bacteriana (MB) después de una neurocirugía, y compararlo con otros marcadores bioquímicos del LCR.

* Corresponding author.
E-mail address: grillepm@gmail.com (P. Grille).

1130-1473/$ – see front matter © 2011 Sociedad Española de Neurocirugía. Published by Elsevier España, S.L. All rights reserved.

http://dx.doi.org/10.1016/j.neucir.2011.11.005
Infección posquirúrgica
Neurocirugía
Lactato en LCR
Diagnóstico

Métodos: Estudio prospectivo de pacientes sometidos a neurocirugía admitidos consecutivamente en la Unidad de Cuidados Intensivos (UCI) del Hospital Maciel. Los pacientes con sospecha clínica de MB, fueron categorizados por criterios predeterminados en tres grupos: (1) MB probada, y (2) MB probable, y (3) MB excluida. Los marcadores de LCR fueron analizados de acuerdo a la curva ROC (receiver operating curve) para evaluar su exactitud diagnóstica.

Resultados: Se estudiaron 158 pacientes. 46 presentaron sospecha clínica de MB, de los cuales se obtuvieron muestras de LCR mediante realización de punción lumbar: 10 fueron MB probada, 4 fueron MB probable y 32 MB excluida. La media de lactato en LCR fue: 10,72 ± 4,68 mM para MB probada, 6,07 ± 0,66 mM para MB probable y 3,06 ± 1,11 mM para MB excluida (p < 0,0001 para MB probada y MB probable vs MB excluida; p = NS para MB probada vs MB probable). El lactato en LCR demostró la mayor exactitud diagnóstica para MB en los 2 escenarios estudiados: (1) cultivo bacteriano o tinción de Gram positivo en LCR como control positivo (sensibilidad: 87%, especificidad: 94%, valor de corte: 5,9 mM); y (2) combinación de MB probada y MB probable como control positivo (sensibilidad: 92%, especificidad: 100%, valor de corte: 5,2 mM).

Conclusión: De acuerdo a nuestros resultados, la medición de lactato en LCR es un método diagnóstico rápido, sensible y específico para identificar la necesidad de iniciar antibioterapia en pacientes con sospecha clínica de MB postquirúrgica.

© 2011 Sociedad Española de Neurocirugía. Publicado por Elsevier España, S.L. Todos los derechos reservados.

Introduction

Bacterial meningitis (BM) is an uncommon (0.5–4%) but serious nosocomial infection that complicates patients following intradural procedures, with a mortality of 20–40%. It increases ICU and hospital length of stay, makes further surgery necessary and increases the overall cost of hospital care. Its diagnosis is difficult due to: non-specific clinical signs, other co-infections, alterations of markers of CSF by surgical brain manipulations and bleeding. Also, these patients are prone to be under broad spectrum antibiotic therapy due to other extra neurological infections.1–5

Prompt diagnosis and combined medical and eventually surgical management, therefore, remain the cornerstone for the prevention of adverse outcome.6

In the last few years, $L_{CSF}$ levels have received increasing attention as a valid ancillary test for diagnosis of postoperative BM due to the ease, precision and rapidity with which it is measured in the clinical laboratory. However, there are still some controversies about its value such as the cut off level, the influence of neutrophils and erythrocytes on $L_{CSF}$, and with what gold standard should we compare $L_{CSF}$ with.7–9

The present study was performed to evaluate the diagnostic usefulness of $L_{CSF}$ for detection of postoperative BM, and compare it with other markers of CSF (cellularity, protein, glucose and CSF/blood glucose ratio).

Patients and methods

We conducted a prospective study of consecutive patients admitted to Maciel Hospital ICU who had intradural neurosurgical procedures from December 2008 to February 2010. All patients received prophylactic Cefazoline peri-operatively, as a single dose on induction.

Clinical parameters examined were: age, sex, simplified acute physiology score (SAPS II), diagnosis, type of surgical procedure, type of intracranial device inserted, antibiotic regimen initiated before BM appears, ICU length of stay and outcome. Patients were followed until discharge from the ICU.10

Patients with clinically suspected BM were identified. Suspected BM was defined as: fever and neurological deterioration (alteration on mental status, seizures or stiff neck), or neurological deterioration without another proven cause. A LP was performed in these patients, after a Computed Tomography (CT) cranial scan was performed to exclude significant brain midline shift or mass effect.

CSF obtained from LP was collected into sterile polystyrene tubes and immediately submitted for analysis. CSF culture and Gram stain were performed. Leukocytes, neutrophils and erythrocytes were assessed by cell counting with a calibrated Fuchs-Rosenthal chamber after staining with toluidine blue. Total CSF protein was determined using the benzethonium chloride precipitation technique standardized to the biuret method. Assessment of CSF glucose and lactate was determined using glucose/lactate oxidase enzymatic method (ABL 700 Series, Radiometer).11

Patients with clinically suspected BM were categorized according to the following preset criteria, into three groups: (1) proven BM: positive bacterial CSF culture or Gram stain; (2) presumed BM: negative CSF culture or Gram stain and CSF leucocyte count $> 1000/\mu l$ (>50% neutrophil), in patients treated with antibiotics at the time of LP; and (3) non-BM or excluded BM: negative CSF culture and Gram stain with leucocyte count $< 1000/\mu l$.

Continuous data were compared by the Student’s t-test. Fisher’s exact test was used to evaluate categorical data (p value < 0.05 was considered to be significant). The CSF markers were analyzed to determine specificity, sensitivity, positive (PPV) and negative predictive value (NPV). Receiver Operating Characteristic (ROC) curve was used to evaluate the
diagnosis accuracy of each marker. The cut-off values were based on the point of the ROC curve which presented highest sensitivity and specificity. Statistical analysis was performed with SPSS™ software, version 17.0.

Results

A hundred and fifty eight patients were studied, with a mean SAPS II score at admission of 31 ± 14 and a mortality of 25%. Clinical and bacteriological data of the patients are shown in Table 1.

In 46 patients with clinical criteria for BM, an LP was performed: 10 corresponded to proven BM, 4 to presumed MB and 32 to excluded BM. LP was performed with a mean of 11 ± 8 days after neurosurgery. Mean LCSF was significantly higher in patients with proven BM and presumed BM than in those with excluded BM (10.72 ± 4.68, 6.07 ± 0.66 and 3.06 ± 1.11 respectively; p < .001 for proven BM and presumed BM vs excluded BM). There was no significantly difference between proven BM and presumed BM LCSF mean values. CSF protein and leucocytes were also significantly higher in patients with proven BM and presumed BM than in those with excluded BM (Table 2).

The usefulness of CSF markers was studied in two scenarios, depending on which is considered the positive control or gold standard: (1) proven BM (positive bacterial CSF culture or Gram stain) as positive control; or (2) the combination of proven BM and presumed BM, as positive control.

Tables 3 and 4 summarize the ROC analysis of CSF markers according to highest area under ROC curve; also sensitivity, specificity and predictive values are shown. Markers were classified according to area under the curve as excellent (0.90–1.00), good (0.80–0.89), fair (0.70–0.79), poor (0.60–0.69) and failure (0.50–0.59). LCSF showed the best diagnostic accuracy for BM in both scenarios studied: (1) proven BM as positive control: sensitivity 87%, specificity 94%, cut-off value of 5.9 mM (Table 3); and (2) combined P-BM and p-BM as gold standard: sensitivity 92%, specificity 100%, cut-off value of 5.2 mM (Table 4). Figs. 1 and 2 represent the ROC curve for LCSF in these scenarios studied.

CSF leucocytes and protein showed also a good diagnostic accuracy (area under the curve of 0.821 and 0.814 respectively), and especially NPV (89% and 96% respectively). Glucose and CSF/blood glucose ratio showed poor diagnostic value.

Discussion

Neurosurgical patients are at risk of developing BM, which is a non-frequent but life-threatening infection. Its diagnosis needs to be prompt and early because of the severe complication of delayed or untreated BM. This fact, in addition with the lack of clear diagnostic criteria for postneurosurgical

![Fig. 1 – ROC curve for LCSF (proven BM as positive control).](image)

![Fig. 2 – ROC curve for LCSF (combined: proven BM plus presumed BM, as positive control).](image)
Table 2 – CSF markers values.

<table>
<thead>
<tr>
<th>CSF markers</th>
<th>Cutoff</th>
<th>Area under ROC curve</th>
<th>Std. error</th>
<th>Asy sig.</th>
<th>CI 95% bound</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LgCr (mM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven BM (n = 10)</td>
<td>10.72 ± 4.68&lt;sup&gt;a,b&lt;/sup&gt;</td>
<td>0.918</td>
<td>0.071</td>
<td>0.000</td>
<td>0.779</td>
<td>1.058</td>
<td>87%</td>
<td>94%</td>
<td>77%</td>
</tr>
<tr>
<td>Presumed BM (n = 4)</td>
<td>6.07 ± 0.66&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0.821</td>
<td>0.080</td>
<td>0.008</td>
<td>0.663</td>
<td>0.978</td>
<td>75%</td>
<td>70%</td>
<td>46%</td>
</tr>
<tr>
<td>Excluded BM (n = 32)</td>
<td>3.06 ± 1.11</td>
<td>0.814</td>
<td>0.121</td>
<td>0.018</td>
<td>0.577</td>
<td>1.051</td>
<td>83%</td>
<td>85%</td>
<td>55%</td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes (per ml)</td>
<td>0.41</td>
<td>0.201</td>
<td>0.099</td>
<td>0.010</td>
<td>0.007</td>
<td>0.394</td>
<td>37%</td>
<td>41%</td>
<td>31%</td>
</tr>
</tbody>
</table>

Results are expressed as: mean ± standard deviation.
<sup>a</sup> p = 0.05 vs excluded BM.
<sup>b</sup> p = NS vs presumed BM.

Table 3 – CSF markers diagnostic performance (proven BM as positive control).

<table>
<thead>
<tr>
<th>CSF markers</th>
<th>Cutoff</th>
<th>Area under ROC curve</th>
<th>Std. error</th>
<th>Asy sig.</th>
<th>CI 95% bound</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LgCr (mM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven BM (n = 10)</td>
<td>5.9 mM</td>
<td>0.918</td>
<td>0.071</td>
<td>0.000</td>
<td>0.779</td>
<td>1.058</td>
<td>87%</td>
<td>94%</td>
<td>77%</td>
</tr>
<tr>
<td>Presumed BM (n = 4)</td>
<td>1.80 g/l</td>
<td>0.821</td>
<td>0.080</td>
<td>0.008</td>
<td>0.663</td>
<td>0.978</td>
<td>75%</td>
<td>70%</td>
<td>46%</td>
</tr>
<tr>
<td>Excluded BM (n = 32)</td>
<td>0.40 g/l</td>
<td>0.814</td>
<td>0.121</td>
<td>0.018</td>
<td>0.577</td>
<td>1.051</td>
<td>83%</td>
<td>85%</td>
<td>55%</td>
</tr>
</tbody>
</table>

BM, explains the practice of empirical treatment of all suspected cases with high-dose broad-spectrum intravenous antibiotics.13

At present, the diagnosis of post-neurosurgical BM relies solely on the detection of bacteria on Gram stain or isolation in CSF culture. However, this method delays the diagnosis and is not sensitive enough. For example, Salord et al. performed gene amplification of CSF and concluded that many cases of culture-negative meningitis following neurosurgery are probably BM.14

In 1925 Killian found an association between BM and elevated LgCr concentration.15 Since then, many studies on spontaneous BM have confirmed these initial observations.16,17 Moreover, two recent meta-analyses showed that CSF lactate is a good single indicator for discrimination of community-acquired BM from aseptic meningitis and a better marker compared to other conventional CSF markers, with a high negative likelihood ratio.18,19

However, the diagnostic value of the LgCr level for patients after neurosurgery has been tested in few studies and remains controversial.7,9,20 Leib et al. found a sensitivity of 88% and a specificity of 98%, when comparing CSF lactate with combined proven and presumed BM (they defined presumed BM as follows: negative CSF culture and Gram stain with CSF leukocytes >250/ml, if the patient was treated with antibiotics at the time of LP). In this study, the author selected a cut-off value of 4 mM on the basis of the following criteria: an extrapolation of the discriminatory level for spontaneous BM and to have a value simple enough to be remembered in clinical practice.7 In other study, Tavares et al. found a sensitivity of 86% and specificity of 90.5% when comparing LgCr with positive Gram stain or CSF culture (proven BM), with a cut-off of value of 49 mg/dl (5.4 mM), based on the ROC curve analysis.9

In our study, the diagnostic value of LgCr and other markers of CSF was evaluated in 2 scenarios: (1) P-BM as positive control, as in the study of Tavares et al.; and (2) combined P-BM and p-BM as gold standard, like Leib et al. did in their study. In both scenarios, LgCr showed the best diagnostic accuracy (with a cut-off of 5.9 mM and 5.2 mM respectively). It is important to highlight that although some authors suggest that neutrophils are responsible for the rise in LgCr level, several clinical and experimental studies argue against this.21-23 Likewise, other

Table 4 – CSF markers diagnostic performance (combined: proven BM plus presumed BM, as positive control).

<table>
<thead>
<tr>
<th>CSF markers</th>
<th>Cutoff</th>
<th>Area under ROC curve</th>
<th>Std. Error</th>
<th>Asy Sig.</th>
<th>CI 95% bound</th>
<th>Sens</th>
<th>Spec</th>
<th>PPV</th>
<th>NPV</th>
</tr>
</thead>
<tbody>
<tr>
<td>LgCr (mM)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proven BM (n = 10)</td>
<td>5.2 mM</td>
<td>0.954</td>
<td>0.045</td>
<td>0.000</td>
<td>0.867</td>
<td>1.042</td>
<td>92%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Presumed BM (n = 4)</td>
<td>1.56 g/l</td>
<td>0.934</td>
<td>0.043</td>
<td>0.000</td>
<td>0.849</td>
<td>1.019</td>
<td>75%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Excluded BM (n = 32)</td>
<td>0.40 g/l</td>
<td>0.886</td>
<td>0.077</td>
<td>0.001</td>
<td>0.736</td>
<td>1.036</td>
<td>90%</td>
<td>86%</td>
<td>75%</td>
</tr>
<tr>
<td>Protein (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose (g/l)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Leucocytes (per ml)</td>
<td>0.41</td>
<td>0.171</td>
<td>0.073</td>
<td>0.001</td>
<td>0.002</td>
<td>0.313</td>
<td>33%</td>
<td>35%</td>
<td>50%</td>
</tr>
</tbody>
</table>

CSF/blood glucose, CSF/blood glucose ratio; CI, confidence interval; Sens, sensitivity; Spec, specificity; PPV, positive predictive value; NPV, negative predictive value.
authors showed that the $L_{CSF}$ level is not affected by the presence of red blood cells in the CSF.\textsuperscript{7,24}

Our study has some limitations such as the small number of patients studied with positive bacterial CSF culture. Nevertheless, it can be argued that the prevalence of post-neurosurgical BM is low. Moreover, as with any diagnostic procedure, the value of the test is diminished when applied indiscriminately to all CSF samples from postneurosurgical patients. In this study, the test was applied only to patients with clinically suspected BM, which led to a high predictive value.

Our current results show that CSF lactate represents a good marker for BM following neurosurgical procedures, superior to other biochemical or cytological CSF markers such as CSF protein, glucose and CSF/blood glucose ratio. In conclusion, CSF lactate is a quick, sensitive and specific test to identify postneurosurgical BM. With CSF lactate values higher than 5.9 mmol/l, antibiotic therapy should be promptly started without waiting for culture results (PPV of 77%). CSF lactate values less than 5.9 mmol/l allow us to wait bacteriological confirmation before starting antibiotic therapy (NPV of 97%). Further studies are needed to confirm our findings.

Conflict of interest

The authors have no conflict of interest to declare.

REFERENCES