High Sensitivity and Specificity of Serum Procalcitonin Levels in Adults with Bacterial Meningitis

Alain Viallon, Fabrice Zeni, Claude Lambert, Bruno Pozzetto, Bernard Tardy, Christophe Venet, and Jean-Claude Bertrand

It was shown in children that serum procalcitonin was the best marker to use to differentiate bacterial from viral meningitis. To evaluate procalcitonin in the diagnosis of acute bacterial and viral meningitis, we conducted a prospective study including adult patients who were suspected of having meningitis and who were admitted to an emergency department. Cerebrospinal fluid (CSF) and serum levels of procalcitonin were measured in 105 consecutive patients. The diagnosis of meningitis was based on clinical findings, gram staining, culture, and chemical analysis of CSF. Twenty-three patients had bacterial meningitis, 57 had viral meningitis, and 25 did not have meningitis. Bacteriologic and chemical analysis of CSF did not allow correct differentiation of viral from bacterial meningitis. On the other hand, a serum procalcitonin level >0.2 ng/mL had a sensitivity and specificity of up to 100% in the diagnosis of bacterial meningitis. Serum procalcitonin levels seem to be the best marker in differentiating between bacterial and viral meningitis in adults.

Bacterial meningitis requires emergency management. The key to diagnosis is CSF analysis. In case of suspected acute bacterial meningitis, antibiotic therapy should be started immediately [1]. Gram staining of CSF has a sensitivity of ~80%; moreover, CSF leukocyte count and concentrations of protein and glucose lack specificity and sensitivity for diagnosis of meningitis [1]. It was recently demonstrated that procalcitonin, a polypeptide of 116 amino acids with a 25- to 30-hour half-life in serum, was undetectable in healthy humans but increased during severe infection [2]. Previously, high procalcitonin levels have been observed in children and adults with severe bacterial infection [2, 3]. In 1996, Gendrel et al. [4] reported that serum procalcitonin was the best marker in differentiating between acute bacterial meningitis and viral meningitis in children. We do not know yet if adults, like children, have elevated serum procalcitonin levels during bacterial meningitis. The aim of this prospective study was to assess the potential role of procalcitonin levels in the diagnosis of acute bacterial meningitis and in the differentiation between viral and bacterial meningitis.

Patients and Methods

In a prospective study, we included 105 consecutive adult patients admitted to an emergency care unit for suspicion of acute meningitis. In accordance with French law, no informed consent was necessary, given that this study did not modify the existing diagnosis or the therapeutic strategy. Lumbar puncture samples of CSF and blood samples were collected immediately after admission. The diagnosis of meningitis was based on clinical findings, gram staining, culture, and chemical analysis of CSF at admission.

Meningitis was defined as proven to be bacterial by a positive result on gram staining and/or bacterial culture. Meningitis was probably bacterial if CSF was cloudy, the leukocyte count in CSF was >1,500/mm³ with granulocytes representing >50%, the ratio of glucose in CSF to glucose in blood was <0.4, and the level of protein in CSF was >2 g/L; if there was improvement in these CSF parameters after 48 hours of antibiotic treatment; and if the discharge diagnosis was a bacterial pretreated meningitis. Viral meningitis was defined as a positive result on viral culture, serological testing, or reverse transcriptase–PCR. If viral meningitis was not proven, the criteria for probable viral meningitis were clear CSF with inflammatory reaction, negative result on gram staining and sterile bacterial culture, and favorable evolution of the disease without antibiotic treatment. The control group was defined by an absence of inflammatory cells in CSF (leukocyte count, <2/mm³). According to these criteria, the patients were divided into three groups: bacterial meningitis, viral meningitis, and no meningitis (controls).

Procalcitonin was measured blindly with an immunoluminometric assay adapted from the immunoradiometric assay (Lumitest proCT; Brahms Diagnostica, Berlin). This assay has a detection limit of 0.1 ng/mL. Inter- and intra-assay variations at both low and high concentrations were <8% and 7%, respectively. This test can be realized within 2 hours, is available 24 hours, and is inexpensive. Data were expressed as mean ± SEM. Differences between groups were analyzed by nonparametric tests (Kruskal-Wallis and Newman-Keuls tests). P < .05 was considered significant.
Table 1. Values for blood and CSF parameters in patients with bacterial or viral meningitis compared with controls.

<table>
<thead>
<tr>
<th></th>
<th>Bacterial meningitis (n = 23)</th>
<th>Viral meningitis (n = 57)</th>
<th>No meningitis (n = 25)</th>
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<tbody>
<tr>
<td>Serum findings</td>
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<tr>
<td>C-reactive protein, mg/L</td>
<td>166 ± 37* (18–662)</td>
<td>14 ± 4 (2–60)</td>
<td>17 ± 5 (2–66)</td>
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<td>Procalcitonin, ng/mL</td>
<td>13.8 ± 5.2* (0.22–101)</td>
<td>0.03 ± 0.003 (0.01–0.1)</td>
<td>0.04 ± 0.002 (0.01–0.09)</td>
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<tr>
<td>CSF findings</td>
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<td>Glucose, mmol/L</td>
<td>2.5 ± 0.5* (0.5–5)</td>
<td>3.7 ± 0.2 (2.4–6.8)</td>
<td>4.2 ± 0.4 (1.4–14)</td>
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<tr>
<td>Protein, g/L</td>
<td>5.1 ± 0.9* (0.4–22)</td>
<td>0.95 ± 0.1* (0.3–5)</td>
<td>0.5 ± 0.08 (0.3–1.7)</td>
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<td>PMNs/mm³</td>
<td>1,483 ± 427* (105–6,336)</td>
<td>83 ± 21* (19–624)</td>
<td>2 ± 0.7 (0–5)</td>
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<tr>
<td>Ratio of glucose, CSF to serum</td>
<td>0.3 ± 0.04* (0.1–0.5)</td>
<td>0.58 ± 0.02 (0.3–1.2)</td>
<td>0.68 ± 0.07 (0.5–2.4)</td>
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NOTE. Data are mean ± SEM (range). PMN = polymorphonuclear cell.
* P < .05, bacterial meningitis vs. the other two groups.
²P < .05, viral meningitis vs. controls.

Results

One hundred five consecutive patients were included in this study: 54 were women and 51 were men. The mean age ± SEM was 42 ± 21 years (range, 16–82 years). Mean Glasgow coma scores ± SEM at admission were 12 ± 2 (range, 5—15). Among 105 patients, 23 had acute bacterial meningitis, 57 had viral meningitis, and 25 had no meningitis (controls).

Cultures of CSF for bacteria yielded Streptococcus pneumoniae in 13 patients (8 positive by gram staining), Neisseria meningitidis in 3 (2 positive by gram staining), and Listeria monocytogenes in 5 (2 positive by gram staining). Two patients had negative results on bacterial culture, had had previous antibiotic therapy, and had the following findings: CSF leukocyte count, 4,200/mm³ and 5,400/mm³, with 74% and 78% polymorphonuclear cells; ratio of glucose in CSF to glucose in blood, 0.2 and 0.1; and CSF protein, 7.4 g/L and 5.3 g/L. Viral cultures, serological tests, or reverse transcriptase–PCR were positive in 19 of 57 cases: Herpesvirus was detected in 6, enterovirus and adenovirus in 9, varicella-zoster virus in 3, and measles virus in 1. In the control group, the final diagnoses were epileptic seizure (in absence of an infectious disease) related to ischemic stroke (in four patients), acute drug poisoning (two), metabolic disorder (one), chronic alcohol abuse (five), unknown cause (four), migraine (six), and temporary confusion related to electrolytic abnormalities (three).

The mean values and ranges for C-reactive protein levels and for CSF parameters (polymorphonuclear cell counts, protein levels, ratio of glucose in CSF to glucose in serum, and procalcitonin levels) in each group are shown in table 1. Individual values for procalcitonin are shown in figure 1.

There were statistically significant differences for all of these tests between bacterial and viral meningitis. However, a wide area of overlapping individual values for ratio of glucose in CSF to glucose in serum, polymorphonuclear cell counts and protein levels in CSF, and C-reactive protein levels in serum were found between patients with bacterial and viral meningitis. In the group with bacterial meningitis, 3 patients (13%) had a lymphocytic predominance in CSF at admission, and 1 had mixed cytologic count; among the 57 patients with viral meningitis, 7 had a neutrophilic predominance and 12 a mixed cytologic count. The sensitivity and specificity in the diagnosis of acute bacterial meningitis were 95.6% and 80.4%, respec-

Figure 1. Individual values for serum procalcitonin in patients with bacterial meningitis (n = 23) or viral meningitis (n = 57) and in control patients (n = 25). * 0.2 ng/mL. The inset shows values for procalcitonin <1.5 ng/mL; the horizontal line indicates 0.2 ng/mL.
tively, for CSF protein level >1 g/L and 91% and 96.3%, respectively, for CSF protein level >2 g/L. For ratio of glucose in CSF to glucose in serum <0.4, the sensitivity and specificity in the diagnosis of bacterial meningitis were 78% and 98.7%, respectively.

On the other hand, serum procalcitonin level >0.2 ng/mL had a sensitivity and specificity up to 100% in the diagnosis of acute bacterial meningitis. Serum procalcitonin levels <0.5 ng/mL (0.22 and 0.24 ng/mL) were found in two patients with previous antibiotic therapy. No procalcitonin was found in CSF except in two patients (3.8 and 1.6 ng/mL) with hemorrhage following traumatic lumbar puncture. These two patients had high levels of procalcitonin in serum: 101 and 42 ng/mL.

Discussion

This prospective study demonstrated that serum procalcitonin levels at admission allow, in all cases, differentiation between acute bacterial meningitis and viral meningitis with a discriminant level of 0.2 ng/mL in adults. As previously reported, the increase in serum procalcitonin levels is low in patients with viral infection [3, 5]. In children, procalcitonin is generally not detectable in CSF [4]. In our study, two patients had procalcitonin in CSF because of hemorrhage following traumatic lumbar puncture. They had a high level of serum procalcitonin, suggesting contamination. Serum procalcitonin levels had higher sensitivity and specificity in the diagnosis of acute bacterial meningitis than did the other tests done at admission.

In this study, in accordance with the literature, gram staining of CSF was positive in only 52% of the bacterial meningitis cases, and culture was positive in 92%. For example, Marton and Gean [6] have shown that culture was positive in 60%–90% of acute bacterial meningitis cases and fell to 40%–60% in patients who had previous antibiotic therapy [7]. In bacterial meningitis, the CSF WBC count usually ranges between 1,000 and 5,000/mm³, with a neutrophilic predominance, but ~10% of the patients with bacterial meningitis had a lymphocytic predominance [7], as in our study.

The estimation of the sensitivity and specificity of CSF protein levels and ratio of glucose in CSF to glucose in serum in bacterial meningitis varies according to the study. In the diagnosis of acute bacterial meningitis, it was recently found that a CSF protein level >1 g/L gives a sensitivity and specificity of 82% and 98%, respectively [8], or a CSF protein level >2 g/L gives a sensitivity and specificity of 86% and 100%, respectively [9]. Similar results were found in this study. The ratio of glucose in CSF to glucose in serum is widely used; in diagnosis of bacterial meningitis, a value <0.4 yielded a sensitivity and specificity of 80%–91% and 96%–98%, respectively [7, 8].

Although procalcitonin seems to be the best marker in differentiating between acute bacterial and viral meningitis, two patients had low serum levels of procalcitonin. These patients had had previous antibiotic therapy, and it was demonstrated that procalcitonin decreases during treatment for acute bacterial meningitis [4].

The mechanisms and the site of synthesis of procalcitonin remain unknown so far. Intravenous injection of endotoxin to healthy volunteers induced an increase in procalcitonin, and the authors suggest that the leukocytes may be the presumed site of procalcitonin secretion [10]. Gendrel et al. [5] found high serum procalcitonin levels in patients with acute bacterial meningitis. By contrast, no procalcitonin was identified in the CSF of these patients (mean leukocyte count was 5,156/mm³). These data, as shown in our study, suggest that procalcitonin is not synthesized by leukocytes, as demonstrated in CSF. Similar conclusions were made in a study of spontaneous bacterial peritonitis [11]. This study demonstrated that a low ratio of procalcitonin in ascitic fluid to that in serum was not suggestive of any intraperitoneal synthesis of procalcitonin by leukocytes.

The role of procalcitonin is not yet understood in the systemic inflammatory response. Nylen et al. [12] demonstrated that infusion of procalcitonin exacerbates mortality in a small animal model of *Escherichia coli* peritonitis. Although procalcitonin seems to be a good marker of bacterial infection, we do not know if procalcitonin is also a mediator of the systemic inflammatory response [13]. Further study will be required to establish the source and the role of procalcitonin in infected patients.

In conclusion, in this study, serum procalcitonin levels were shown to be the best marker in differentiating between acute bacterial meningitis and viral meningitis in adults, especially in the absence of previous antibiotic therapy. Serum procalcitonin levels could become a useful marker in the management of adult patients with meningitis. These data should be confirmed in further study.

References