Comparison of Cerebrospinal Fluid C-Reactive Protein and Lactate for Diagnosis of Meningitis

RICHARD A. KOMOROWSKI,* SILAS G. FARMER, AND KONSTANCE K. KNOX
Department of Pathology, Medical College of Wisconsin, Milwaukee, Wisconsin 53226
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Levels of C-reactive protein and lactate were determined on 562 consecutive cerebrospinal fluid (CSF) samples from adult patients with a variety of central nervous system diseases to compare the sensitivity and specificity of CSF lactate and C-reactive protein for the rapid diagnosis of bacterial meningitis. Neither test alone, together, or in combination with elevated CSF leukocyte count and protein had a predictive value over 60% for a positive test in this group of patients with diverse central nervous system problems. Neither test is useful as a screening test for bacterial or mycotic meningitis. Also, in patients with partially treated bacterial meningitis, the tests are often negative. CSF lactate may be useful in differentiating aseptic from septic meningitis in selected patients.

Rapid and accurate diagnosis of bacterial infections is one of the aims of clinical microbiology. This is especially true in bacterial meningitis, when delay in proper treatment can be harmful or even fatal. Because the currently used techniques such as Gram stain, culture, and counterimmunoelectrophoresis (immunoelectroosmophoresis) have serious limitations, the search for more specific, sensitive, and rapid diagnostic methods continues.

We previously evaluated cerebrospinal fluid (CSF) lactate as a rapid test to establish the diagnosis of bacterial meningitis (7). In that study we found CSF lactate to have a sensitivity of 100% in untreated bacterial meningitis. Sensitivity in partially treated meningitis was poor; only two of seven (28%) patients had positive tests. An additional problem with CSF lactate was its lack of specificity. It was elevated in any central nervous system (CNS) condition in which there was ischemia or infarction.

Recently, numerous reports have suggested that levels of C-reactive protein (CRP) in CSF and serum may be useful as a rapid test for bacterial meningitis. The majority of studies on CSF CRP in meningitis have been in infants and young children for whom the major differential diagnosis is aseptic versus bacterial meningitis (2, 4-6, 8, 10, 13). There are almost no studies in adults and only one which studies groups of patients with a variety of CNS lesions (1).

In this study, we evaluated the diagnostic utility of CSF CRP and CSF lactate on 562 consecutive CSF samples obtained in a large general hospital from patients with a variety of neurological problems. We compared the usefulness of both tests individually, paired, and in combination with other traditional tests to confirm or rule out meningitis.

MATERIALS AND METHODS

Specimens. CSF samples were obtained from 562 patients who were evaluated for a variety of neurological problems over a period of approximately 2 years. Levels of CRP and lactate in CSF were determined in addition to the usual requested procedures on those specimens for which there was an adequate sample. These included total erythrocyte and leukocyte counts, glucose, protein, Gram stain, and bacteriological cultures. Patients were grouped into five main categories based on clinical diagnosis and results of the laboratory tests.

CRP determinations. The amount of CRP in CSF was assayed by laser nephelometry by using the Hyland PDQ laser nephelometer (Hyland Diagnostics, Div. Cooper Diagnostics Inc., Round Lake, Ill.). Antiserum monospecific for human CRP was incubated at room temperature with reference sera and test specimens. A beam of collimated, monochromatic light was passed through the solutions, and the antigen-antibody complexes produced light scatter. The forward light scatter was quantitatively measured within the range of the reference sera which contained human CRP concentrations ranging from 0.8 to 8.8 mg/dl.

All CSF samples found to contain CRP, as determined by laser nephelometry, were reanalyzed for the presence of CRP by using the Rapi-tex-CRP test (Calbiochem-Behring, La Jolla, Calif.). This test is based on the principle of an immunologic reaction between CRP as the antigen and its corresponding antibody coated on the surface of biologically inert latex particles. If CRP was present in the sample at a concentration of 0.8 mg/dl or greater, agglutination of the latex particles occurred.

CSF lactate. CSF lactate levels were determined on an automatic chemical analyzer (E. I. du Pont de Nemours & Co., Inc., Wilmington, Del.). The automatic chemical analyzer uses a modification of the method of Marbach and Weil (9), which uses the oxidation of lactate to pyruvate and the reduction of NAD. The absorbance to NADH is directly proportional to the concentration of lactate in CSF. The upper limit of normal was set at 3.0 mmol/liter.

Other tests performed. Routine CSF analyses were performed on all study specimens. These included total cell count and differential, glucose, protein, Gram stain, and bacteriological or fungal culture or both.

Patient grouping. Patients were grouped into five main categories, retrospectively, based on the final clinical diagnosis and review of the clinical record.

Group 1 consisted of patients with chronic neurological disease. Included were patients with multiple sclerosis, other degenerative neurological disorders, chronic hydrocephalus, chronic (older than 3 months) cerebrovascular accidents, and people who had tertiary syphilis with either positive or negative serological tests.

* Corresponding author.
TABLE 1. Analysis of CSF lactate and CRP in different patient groups

<table>
<thead>
<tr>
<th>Group (total no.)</th>
<th>Lactate&lt;sup&gt;a&lt;/sup&gt;</th>
<th>CRP&lt;sup&gt;b&lt;/sup&gt;</th>
<th>Both positive&lt;sup&gt;c&lt;/sup&gt;</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Positive (%)</td>
<td>Negative (%)</td>
<td>Positive (%)</td>
</tr>
<tr>
<td>1 (97)</td>
<td>30 (33)</td>
<td>67 (76)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>2 (128)</td>
<td>58 (45)</td>
<td>70 (55)</td>
<td>5 (4)</td>
</tr>
<tr>
<td>3 (42)</td>
<td>36 (86)</td>
<td>6 (14)</td>
<td>12 (29)</td>
</tr>
<tr>
<td>4 (5)</td>
<td>0 (0)</td>
<td>5 (100)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>5 (290)</td>
<td>67 (23)</td>
<td>223 (77)</td>
<td>7 (2)</td>
</tr>
</tbody>
</table>

<sup>a</sup> Groups are defined in Materials and Methods.
<sup>b</sup> Positive, >3.0 mmol/liter; negative, <3.0 mmol/liter.
<sup>c</sup> Positive, ≥0.8 mg/dl; negative, <0.8 mg/dl.

Group 2 included patients with acute CNS trauma, acute cerebrovascular accidents, and people with primary or metastatic CNS tumors.

Group 3 was composed of people with bacterial or mycotic meningitis or brain abscesses.

Group 4 patients had viral or aseptic meningitis.

Group 5 patients were controls. They were patients from whom CSF was submitted for culture at the time of myelograms. These specimens were from patients with headache or back problems for whom all studies were eventually negative.

RESULTS

A total of 562 CSF samples were studied. The distribution of CSF lactate and CSF CRP assays among the five clinical groups of patients is shown (Table 1). Although CSF lactate was more frequently elevated in patients with bacterial or mycotic meningitis or brain abscess (86%), it was also abnormally elevated in 39% of patients with other acute and chronic CNS disease and in 23% of the patients without documented CNS disease. Similarly, CSF CRP was more frequently present in the meningitis group. It was positive in 60% of patients with bacterial meningitis (12 of 20). It was negative in the nine patients with mycotic meningitis and the three patients with brain abscess. Both CSF lactate and CSF CRP were negative in four of the nine patients with fungal meningitis (Coccidioides immitis [2 patients], Cryptococcus neoformans [1 patient], and Candida albicans [1 patient]). Additionally, both were negative in two patients who had partially treated bacterial meningitis. CSF lactate was positive in all patients with untreated bacterial meningitis.

The test results for infections caused by different organisms are shown (Table 2). In each instance, CSF lactate was more frequently positive than CSF CRP. In fact, there was no case of meningitis in which CRP was positive and lactate was negative. All three patients with meningococcal meningitis and three patients with brain abscesses were characterized by an elevated CSF lactate and a negative CSF CRP. Neither CSF lactate nor CRP was positive in patients with partially treated bacterial meningitis. Both lactate and CRP were negative in all five patients with aspergic meningitis.

Utility of tests. The utility of these and other tests to predict or rule out meningitis is presented. The sensitivity, specificity, predictive value (PV) of a positive or negative result(s), and false positivity of CSF lactate and CSF CRP singularly, paired, and in combination with traditional tests are found in Table 3. The calculations in Table 3 compared group 3 patients, those with bacterial or mycotic meningitis or bacterial brain abscess, with the total population studied.

Comparison of laser nephelometry and latex tests for CSF CRP. The 50 CSF samples which had CRP determined by both the nephelometric and latex methodologies gave identical results.

DISCUSSION

The levels of lactate and CRP in CSF were determined for 562 specimens from patients with a variety of diagnoses to assess the sensitivity and specificity of these tests alone or in combination with CSF leukocyte and protein concentration for the diagnosis of bacterial and mycotic meningitis. We have previously determined that CSF lactate is a sensitive diagnostic test for patients with untreated bacterial or mycotic meningitis (7). Unfortunately, CSF lactate levels above 3.0 mmol/liter are found in a large variety of other conditions with cerebral anoxia or infarction. More recently, CRP has been reported to be a useful test for diagnosing children with bacterial meningitis (4). Since the great majority of these studies were limited to infants less than 2 years old and control groups included only infants with the diagnosis of aseptic meningitis, we felt it worthwhile to extend these studies to a more general adult hospital population.

In this study, CSF lactate again was shown to be a sensitive indicator of untreated bacterial meningitis. All patients with untreated bacterial meningitis had elevated levels of lactate in CSF. Lactate was elevated in patients with meningitis caused by both gram-positive and gram-negative cocci and bacilli. However, two patients with partially treated meningitis had negative CSF lactate levels. Patients with mycotic meningitis were not universally positive in this series. Of nine patients, five had positive lactate levels; four were negative. Also as expected, patients with brain abscesses were lactate positive. While CSF lactate distinguished bacterial from aseptic meningitis in all cases, CSF lactate was positive in patients who had CNS ischemic processes and tumors. Lactate was also positive in a significant number of patients with chronic CNS diseases. Thus, lactate must be interpreted in the light of clinical findings and other parameters and cannot be used as the sole determinant in assessing whether a patient has meningitis. Although the sensitivity of the lactate determination varied from 86 to 90%, because of a high number of false-positives, an elevated result had a PV of only 19%. Even in the patient population preselected with an elevated CSF leukocyte count and protein, a positive lactate result had a PV of only 23%. However, the PV of a negative determination was greater than 97% in meningitis patients.

CRP is a protein synthesized by hepatocytes, which is one of the acute-phase reactants. CRP is normally present in
TABLE 3. Utility of tests, singly and in combination, for predicting meningitis in patients with CNS symptoms

<table>
<thead>
<tr>
<th>Subgroup of study population</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive PV (%)</th>
<th>False-positive PV (%)</th>
<th>Negative PV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Without regard to other tests</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CSF lactate positive</td>
<td>86</td>
<td>70</td>
<td>19</td>
<td>81</td>
<td>98</td>
</tr>
<tr>
<td>CSF CRP positive</td>
<td>29</td>
<td>97</td>
<td>48</td>
<td>52</td>
<td>94</td>
</tr>
<tr>
<td>Protein (&gt;45 mg/dl)/leukocyte count (&gt;10/μl)</td>
<td>48</td>
<td>74</td>
<td>22</td>
<td>78</td>
<td>90</td>
</tr>
<tr>
<td>With CSF leukocyte count &gt;10/μl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate positive</td>
<td>90</td>
<td>55</td>
<td>23</td>
<td>77</td>
<td>97</td>
</tr>
<tr>
<td>CRP positive</td>
<td>35</td>
<td>93</td>
<td>44</td>
<td>56</td>
<td>90</td>
</tr>
<tr>
<td>Both positive</td>
<td>30</td>
<td>96</td>
<td>48</td>
<td>52</td>
<td>91</td>
</tr>
<tr>
<td>With elevated CSF leukocyte count and protein &gt;45 mg/dl</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactate positive</td>
<td>90</td>
<td>58</td>
<td>23</td>
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<td>35</td>
<td>96</td>
<td>58</td>
<td>42</td>
<td>91</td>
</tr>
</tbody>
</table>

very low quantities in the blood. An elevation in serum CRP is a sensitive indicator of inflammation and necrosis (12). Within a few hours after the onset of illness, CRP synthesis increases (14). It is increased in an extremely broad range of disorders, including trauma, infections, infarctions, neoplasms, and collagen-vascular disorders (15). Additionally, in meningitis, CSF CRP has been reported to be elevated (4, 6). Since many of the patients in our hospital have complex medical problems which would elevate serum CRP, we chose to evaluate CSF CRP.

The sensitivity of CSF CRP was only 29% in this series of patients. This gave a PV of only 48%. Even in patients preselected with elevated CSF leukocyte counts and elevated CSF protein, the sensitivity of a positive CSF CRP was only 35%, with a positive test having a PV of only 44%. The PV of a negative test was 94%.

In our study, high sensitivity was found when the CSF lactate test was positive (86%). On the other hand, CSF protein and leukocyte levels were increased in only 48% of meningitis patients. As diagnostic test panels for bacterial or mycotic meningitis, the addition of an elevated CSF lactate to elevated CSF leukocyte counts increased the sensitivity of the panel from 48% to 90%. Conversely, the CRP determination did nothing to enhance the sensitivity in detecting meningitis (Table 3).

In our study, the specificity of lactate and CRP levels in series was 96% (Table 3). This might appear at first glance to suggest a reliable pair of tests to confirm meningitis in the study group. However, inasmuch as the prevalence of meningitis in our group was only 7%, the positive PV was not as good as the flip of a coin in confirming this disease state (48 versus 50%). It is apparent that the more definitive one can make a study group, from clinical observation and examination, the greater the utility of laboratory procedures to distinguish among patients with and without the disease. In only one instance was the use of CRP, lactate, or both levels of greater benefit than chance alone in predicting the diseased state. The positive PV with the lactate and CRP procedures, in series, in the patient population that was clinically suspect of meningitis and who had an elevated leukocyte and protein concentration, was 58% (Table 3). That was the highest positive PV obtained in this study. However, because of the low prevalence of meningitis in the suspect group and the nonspecificity of the tests, a false-positive interpretation was obtained almost 42% of the time.

The utility of CSF CRP for the rapid diagnosis of bacterial meningitis is controversial. In some studies, CSF CRP has been reported to have high sensitivity and specificity (1, 8), whereas in other series, as in our study, the sensitivity of the test has been questioned (2). The reason for these different results is not entirely clear. Test methodologies were either comparable or identical in the various studies. There are, however, significant differences in the study populations. Also the prevalence of meningitis in the study group and the composition of the control group have a great effect on the apparent sensitivity, specificity, and PV of a test. In addition, previous studies have largely been limited to pediatric or neonatal populations (1). However, even in these young patients there is not complete agreement that the test has good sensitivity and specificity (2, 11; J. N. Walterspiel, Letter, Pediatr. Infect. Dis. 2:174, 1983). On the other hand, CSF lactate has shown to be an excellent test to separate septic from aseptic meningitis (3, 7).

In conclusion, neither CSF CRP nor lactate alone, together, or grouped with other laboratory tests is useful in the rapid diagnosis of bacterial or mycotic meningitis. CSF lactate is reliable in differentiating septic from aseptic meningitis, especially in the neonate if there are no other causes of cerebral ischemia or necrosis.

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LITERATURE CITED


