C-Reactive Protein Concentrations in Cerebral Spinal Fluid in Gram-positive and Gram-negative Bacterial Meningitis

To the Editor:
Several reports have shown an ability of C-reactive protein (CRP) to discriminate between patients with bacterial meningitis and patients with aseptic (viral) meningitis (1,2). Although a recent metaanalysis suggested that a negative CRP test in either cerebrospinal fluid (CSF) or serum can be used with a very high probability to rule out bacterial meningitis (3), a more recent report (4) suggested that serum concentrations are a better screening tool for this differential diagnosis.

To assess the ability of CSF CRP to differentiate gram-positive from gram-negative meningitis, we compared CRP concentrations in the blood and CSF, along with CSF nitric oxide (NO), protein, glucose, and leukocyte count, in 17 consecutive patients (age range, 2 months to 47 years) with suspected bacterial meningitis and in noninfected controls. The two patient groups had comparable CSF leukocyte counts and protein and glucose concentrations, and were not considerably different with respect to dispersion of gender and age. The noninfected controls had a similar age and gender distribution.

CRP was analyzed by a sensitive immunoturbidimetric assay using the Integra 400 analyzer (Hoffmann-La Roche). The concentration of nitrite, as an index for NO concentration, was analyzed by the Griess reaction. The CSF underwent microscopy of gram-stained smears, followed by microbiologic diagnosis. Organisms were seen microscopically in all cases, and CSF from all patients exhibited bacterial growth in culture. No patient had received antimicrobial therapy before CSF sampling. The gram-positive organisms were identified as Streptococcus pneumoniae (seven cases) and S. pyogenes (one case), and the gram-negative bacteria were Hemophilus influenzae group B (three cases), Neisseria meningitidis (five cases), and Escherichia coli (one case). Gram-negative and gram-positive cases could not be distinguished by CSF leukocyte counts (P = 0.55; Fisher’s exact test), CSF protein (P = 0.16), or CSF glucose (P = 0.11).

The mean CRP in CSF was significantly higher in patients with gram-negative bacterial meningitis as compared to patients with gram-positive bacterial meningitis (Fig. 1). This could not be attributed to the difference in patient age between the groups because CSF CRP was not correlated with age (not shown). An increased mean CRP in the blood was also noted (3 ± 2 mg/L in controls, 163 ± 53 mg/L in gram-positive, and 272 ± 51 mg/L in gram-negative patients), but the difference between the two patient groups was statistically insignificant (P = 0.164). In the gram-negative cases, higher mean NO was also observed (8.5 ± 2.8 μmol/L vs 2.7 ± 0.9 μmol/L), but this difference had only a borderline significance (P = 0.086). Similar conclusions on significance of the CRP and NO differences were reached with the Mann–Whitney nonparametric test.

The ratio of CRP in CSF to CRP in blood was 3.28% ± 1.11% in gram-positive bacterial meningitis vs 9.44% ± 4.08% in gram-negative meningitis (P = 0.072; Mann–Whitney U-test).

The substantial increase in CSF CRP, as well as the trend of an increased CSF/blood ratio of CRP, suggests that infection with gram-negative bacteria enhances permeability of CRP through the blood-brain barrier. It is possible that these findings reflect the ability of the endotoxin lipopolysaccharides, present in gram-negative but not in gram-positive bacteria, to affect the permeability of the blood-brain barrier (5). NO may be involved in this mechanism because its concentration in CSF is higher in gram-negative meningitis. This possibility is supported by the higher potency of gram-negative bacteria to promote macrophage NO production (6), the enhanced production of NO in the
CSF of septic meningitis (7), and the role of NO in permeability changes of the blood-brain barrier in LPS-induced experimental meningitis (8).

Another interesting potential explanation for the present observation is that lipopolysaccharide- and produced by gram-negative bacteria could induce local CRP synthesis in the central nervous system. CRP can be produced in neurons (9), and lipopolysaccharide- can induce CRP in extrahepatic sites (10). This may also explain the increase, albeit nonsignificant, in serum CRP in the gram-negative cases.

There is currently no single test to diagnose the etiology of meningitis promptly and accurately. Given its high sensitivity and easy measurability, CRP may be a useful supplement for rapid diagnosis and categorization of bacterial meningitis.

References


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Use of Sodium Measurement as a Surrogate Volume Measurement in Unmetered-Blood Collection Devices

To the Editor:

Tanaka et al. (1) describe a new blood-sampling device. Blood is applied to a membrane and travels laterally through the pores of the membrane. The red cells are trapped within the membrane and the serum can be recovered from the red-cell-free area. Some years ago we investigated this approach and encountered two problems. The first problem was hemolysis of red cells, which might interfere in the subsequent measuring process. This rendered measurement of some components (e.g., potassium and lactate dehydrogenase) impossible. Tanaka overcame this problem with the inclusion of sucrose in the membrane. The second problem we encountered was in the determination of the volume of serum extracted from the membrane to allow the use of unmetered-blood collection. Here we describe how we overcame this problem by expressing results relative to the sodium concentration.

We reasoned that because sodium is so tightly controlled and among within individuals that if the concentration of an electrolyte in blood samples was divided by the concentration of sodium in those samples, the resulting ratio would correlate closely with the original measured concentration of that analyte. If this ratio of analyte to sodium concentration was then multiplied by the mean sodium concentration of the population, the result would be little different from the original measured concentration.

We demonstrated the feasibility of this approach for several analytes in which the measured result was compared with a result calculated on the basis of the analyte/sodium ratio. For 230 consecutive results on patient samples, the mean differences, the SDs of those differences, intercepts, slopes, and correlation coefficients (r2) were the following: for albumin (mean concentration, 35.5 g/L): −0.069, 0.87, 1.00, 0.98, 0.984; for urea (mean concentration, 8.47 mmol/L): −0.01, 0.377, −0.035, 1.002, 0.997; for alkaline phosphatase (mean concentration, 114 U/L): 0.024, 4.27, −1.14, 1.013, 0.999; and for calcium (mean concentration, 2.30 mmol/L): −0.005, 0.0684, 0.007, 0.995, 0.885. The correlation coefficient was <0.98 for only calcium. This was not unexpected because the concentration of calcium in the blood is tightly controlled.

We then demonstrated the applicability of the technique for albumin (a measurement that was not affected by hemolysis of the sample). Unmetered-blood spots of ~30 μL were applied to the end of a 6 mm × 5 cm strip of Whatman GF/G6. The blood was left to diffuse up the strip for 5–10 min. After this time, the plasma within the blood sample had migrated further than the red cells. The portion of the strip containing only plasma was cut out with a scalpel and added to 1 mL of cesium chloride (1.5 mmol/L) in a 1.5-mL conical tube, left to stand for 10 min, and then centrifuged at 10 000 g in an Eppendorf 5412 microcentrifuge. The sodium concentration in the eluate was measured with an IL 943 flame photometer in the manual mode with sodium calibrators diluted in the same cesium chloride diluent. The albumin in the eluate and in plasma from the original samples