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The Differential Diagnosis of Bacterial and Aseptic Meningitis Using Cerebrospinal Fluid Laboratory Tests

Summary: The lactate, lysozyme, C-reactive protein and serum amyloid-A protein concentrations in cerebrospinal fluid were measured in 11 patients with bacterial meningitis, 27 patients with aseptic meningitis and in 31 control patients. The mean concentration of each parameter was significantly higher ($p \leqq 0.0001$) in patients with bacterial meningitis than in those with aseptic meningitis or those without meningitis. The reliability of these tests in the differential diagnosis of bacterial and aseptic meningitis was compared with leucocyte counts in cerebrospinal fluid, Gram staining for bacteria, and protein and glucose levels. The cerebrospinal fluid lactate level proved to be more sensitive than lysozyme, C-reactive protein or serum amyloid-A protein and had a high degree of specificity.

Zusammenfassung: *Differentialdiagnose zwischen bakterieller und aseptischer Meningitis mit Laborparametern des Liquor cerebrospinalis.* Bei 11 Patienten mit bakterieller Meningitis, 27 Patienten mit aseptischer Meningitis und 31 Kontrollpatienten wurden die Konzentrationen von Laktat, Lysozym, C-reaktivem Protein und Serum-Amyloid-A-Protein im Liquor cerebrospinalis gemessen. Für jeden Parameter war die Konzentration bei Patienten mit bakterieller Meningitis im Mittel signifikant höher ($p \leq 0{,}001$) als bei Patienten mit aseptischer Meningitis oder Patienten ohne Meningitis. Die Verläßlichkeit dieser Tests für die Differentialdiagnose zwischen bakterieller und aseptischer Meningitis wurde mit derjenigen von Leukozytenzählung im Liquor, Bakteriennachweis durch Gramfärbung, Eiweiß- und Glukosespiegel im Liquor, verglichen. Dabei zeigte sich, daß der Laktatspiegel im Liquor empfindlicher ist als der Spiegel von Lysozym, C-reaktivem Protein oder Serum-Amyloid-A-Protein, und daß er einen hohen Grad an Spezifität besitzt.

Introduction

The differential diagnosis of bacterial and aseptic meningitis cannot always be made on the basis of total and differential cerebrospinal fluid (CSF) leucocyte counts and bacterial Gram staining. Occasionally, especially in cases of partially treated bacterial meningitis, Gram staining may be negative. Furthermore, the total CSF leucocyte count may be low during the early phase of bacterial meningitis. On the other hand, in the early stage of aseptic meningitis the CSF may show a predominance of polymorphonuclear leucocytes. Other tests have therefore been introduced for the diagnosis of bacterial meningitis, e. g. the nitroblue tetrazolium test, counter-current immunoelectrophoresis, latex agglutination and radioimmunotests for bacterial polysaccharide antigens, and the limulus lysate test (1–4). However, these tests are used and accepted to a limited extent only. We have known for more than 50 years now that the CSF lactate level is elevated in bacterial meningitis (5). The exact source of CSF lactate in this condition is not known: It could be of cerebral, bacterial or leucocytic origin. The increase in lactate may also be due to cerebral hypoxia and can thus also be seen in other conditions, e. g. cerebral trauma, infarction and haemorrhage, or subarachnoidal haemorrhage. During the last few years CSF lactate determination has been accepted as a means of differentiating between bacterial and aseptic meningitis (6–12), although it has also received a certain amount of criticism (13). Two further tests have been introduced, i. e. the CSF lysozyme analysis and the C-reactive protein (CRP) determination by using a latex agglutination test (14, 15). No comparisons between CSF lactate, lysozyme and quantitative or qualitative CRP tests have been reported so far as a means of differentiating between bacterial and aseptic meningitis. We therefore compared the reliability of these tests with each other, and with the total and differential CSF leucocyte counts, bacterial Gram staining, and protein and glucose levels.

Patients and Methods

Patients: Sixty-nine patients (adults and children) admitted to the Aurora Hospital with a suspected infection of the central nervous system were included in this study. CSF specimens were collected immediately after admission. Twenty-seven patients had aseptic meningitis and 11 bacterial meningitis *(Neisseria meningitidis* group B, *Haemophilus influenzae* type b, *Listeria monocytogenes, Streptococcus pneumoniae),* all verified by positive bacterial cultures. The remaining 31 patients without pleocytosis served as controls. Twenty-one of these patients had infectious diseases not involving the central nervous system, eight had febrile convulsions, one hypoglycaemia and one carcinoma of the pancreas.

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Table 1: CSF analysis in 11 patients with acute bacterial meningitis, 27 patients with aseptic meningitis and 31 control patients.

	Bacterial meningitis (mean ± SE) (range)	Aseptic meningitis (mean ± SE) (range)	Controls (mean ± SE) (range)
Lactate (mmol/l)	7.3 ± 1.5* (2.2 – 20.5)	1.8 ± 0.1 (0.8 – 3.1)	1.6 ± 0.1 (0.8 – 2.5)
Lysozyme (mg/l)	4.9 ± 1.6* (0.0 – 16.3)	0.5 ± 0.1 (0.0 – 1.2)	0.3 ± 0.1 (0.0 – 1.6)
CRP (mg/l)	2.0 ± 0.7* (0.0 – 8.0)	< 0.1	0.1 ± 0.0 (0.0 – 0.8)
SAA (mg/l)	4.3 ± 1.4* (0.0 – 14.0)	< 0.2	0.2 ± 0.1 (0.0 – 3.0)

* $p \leq 0.0001$

Methods: Gram staining for bacteria, bacterial cultures, total and differential leucocyte counts as well as CSF protein and glucose determinations were performed using standard laboratory techniques.

Lactate determinations were made enzymatically with reagents obtained from Boehringer Mannheim AG, Germany. Lysozyme was determined by a turbidimetric technique (Testomar® Lysozyme, Behring Institute, Germany). CRP levels were measured both by the qualitative CRP latex test (Hyland Diagnostics, U.S.A.) and by radial immunodiffusion. Concentrations of serum amyloid-A (SAA) protein were determined by electrophoresis in gels containing antibody (16). Antiserum to human SAA protein was raised in rabbits by immunizing them with purified amyloid-A protein isolated from the liver of a patient with amyloidosis associated with rheumatoid arthritis. Purified SAA protein was used as a standard.

The lowest detectable lactate, lysozyme, CRP and SAA protein concentrations were 0.1 mmol/l, 1 mg/l, 0.1 mg/l, and 0.2 mg/l, respectively. The qualitative slide test for CRP was read as described by *Corrall* et al. (15).

The upper limits of the health-related reference intervals were taken as 3.0 mmol/l for lactate, 2.0 mg/l for lysozyme, 0.5 mg/l for CRP and 1.0 mg/l for SAA protein in the CSF.

Statistical methods: Statistical analysis was performed using the Student's t-test. When the levels of lysozyme, CRP or SAA protein were not detectable in the tests used, the concentration was regarded as zero in the statistical analysis.

Results

The mean lactate, lysozyme, CRP and SAA protein concentrations in the CSF were significantly higher in patients with bacterial meningitis than in those with aseptic meningitis or in controls (Table 1).

Of the 11 patients with bacterial meningitis, only one had a lactate concentration of less than 3.0 mmol/l, whereas four had undetectable levels of both CRP (< 0.1 mg/l) and SAA (< 0.2 mg/l). One of the last mentioned patients and two others had a lysozyme concentration of less than 2.0 mg/l. Of the 27 patients with aseptic meningitis, none had elevated lysozyme, CRP or SAA levels, whereas one patient with mumps meningitis complicated by carditis, orchitis and pancreatitis had an elevated CSF lactate concentration of 3.1 mmol/l.

Although the mean lactate and lysozyme concentrations were slightly higher in patients with aseptic meningitis than in controls, the differences were not statistically significant ($p < 0.05$). None of the 31 control patients had elevated lactate or lysozyme levels, whereas one patient with pneumonia had a slightly elevated CRP concentration (0.5 mg/l), and one with febrile convulsions and another with carcinoma of the pancreas had elevated levels of both CRP (0.5 and 0.8 mg/l) and SAA (2.0 and 3.0 mg/l). In addition, the CRP latex test was positive in the patient with carcinoma of the pancreas.

Gram staining and glucose, lysozyme, CRP and SAA concentrations all had 100% specificity and the predictive value of a positive test in differentiating between bacterial and aseptic meningitis, although the sensitivity was rather low (Table 2). On the other hand, the lactate concentra-

Table 2: The sensitivity, specificity and predictive values of CSF findings for differentiating 11 cases of acute bacterial meningitis from 27 cases of acute aseptic meningitis.

Variable	Limit	Sensitivity no.	(%)	Specificity no.	(%)	Predictive value Positive test no.	(%)	Negative test no.	(%)
Leucocyte count	> 500 cells × 10^6/l	7/11	(64)	25/27	(93)	7/9	(78)	25/29	(86)
PMN count[1])	> 200 cells × 10^6/l	7/11	(64)	21/27	(78)	7/13	(54)	21/25	(84)
Glucose	< 2.2 mmol/l	5/10[2])	(50)	27/27	(100)	5/5	(100)	27/32	(84)
Protein	> 500 mg/l	10/11	(91)	16/27	(59)	10/21	(48)	16/17	(94)
Gram stain	positive	7/11	(64)	27/27	(100)	7/7	(100)	27/31	(87)
Lactate	> 3.0 mmol/l	10/11	(91)	26/27	(96)	10/11	(91)	26/27	(96)
Lysozyme	> 2.0 mg/l	8/11	(73)	27/27	(100)	8/8	(100)	27/30	(90)
CRP	> 0.5 mg/l	7/11	(64)	27/27	(100)	7/7	(100)	27/31	(87)
CRP latex test	+ + +	8/11	(73)	27/27	(100)	8/8	(100)	27/30	(90)
SAA	> 1.0 mg/l	7/11	(64)	27/27	(100)	7/7	(100)	27/31	(87)

[1]) PMN = polymorphonuclear leucocytes

[2]) One patient who had received an intravenous glucose infusion before specimens were collected was excluded

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tion proved to be both sensitive and specific in this differentiation. The predictive value exceeded 90% for both positive and negative tests. Only one of the 11 patients (9%) with bacterial meningitis had a lactate concentration of less than 3.0 mmol/l, and one of the 27 patients (4%) with aseptic meningitis had a lactate concentration of greater than 3.0 mmol/l.

Discussion

In accordance with earlier studies (6–12), our results suggest that the CSF lactate concentration is frequently elevated in bacterial meningitis but not in aseptic meningitis. For this reason, it can be used together with the traditional tests, i. e. total and differential CSF leucocyte counts, bacterial Gram staining, and protein and glucose determinations, when trying to differentiate between these two forms of meningitis. However, lactate values in bacterial and aseptic meningitis overlap to a certain extent and thus a definite limit cannot be set. We found that by taking 3.0 mmol/l as the limit, CSF lactate determinations had a sensitivity, specificity, and predictive value of over 90% for both negative and positive tests.
High lysozyme, CRP and SAA concentrations were more specific, and the positive tests had a higher predictive value than lactate when differentiating between bacterial and aseptic meningitis. However, these tests were insensitive and the predictive value of negative tests was lower. In addition, elevated CRP and SAA concentrations were also found among controls. This finding is in accordance with that of *Gorevic* et al. (17) who also observed elevated SAA concentrations in septic patients with no evidence of meningeal infection. *Corrall* et al. (15) concluded that the detection of CRP in the CSF may prove to be a practical and reliable method for differentiating between bacterial and aseptic meningitis. In their series, all 24 patients with bacterial meningitis had positive CRP latex tests; only two of the 32 patients with aseptic meningitis were positive. We found a positive CRP latex test in eight of the 11 patients with bacterial meningitis, but in none of the 27 patients with aseptic meningitis.
We suggest using CSF lactate determination as a routine test in patients with meningitis during the acute phase of the illness. We also regard CRP determination as a useful supplementary test in differentiating between bacterial and aseptic meningitis, even if the sensitivity of the test is not as good as that of lactate.

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