Cerebrospinal Fluid Lactic Acid in Diagnosis of Meningitis

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Quantitative lactate determinations were performed on cerebrospinal fluids to assess their value in the rapid diagnosis of bacterial and mycotic meningitis and to evaluate their value in assessing the prognosis in these patients. Cerebrospinal fluid lactate concentrations were elevated in all patients with untreated bacterial or fungal meningitis. Lactate concentrations proved very valuable in following patients with mycotic meningitis and in differentiating aseptic from bacterial meningitis. Elevated cerebrospinal fluid lactate is not specific for meningitis. Lactate is also elevated in situations where there is central nervous system ischemia and necrosis and in patients with brain tumors. Lactate concentration is normal in chronic degenerative brain diseases. Thus, the clinical situation must be taken into account when interpreting the lactate concentrations.

Rapid and accurate diagnosis of bacterial infections is one of the aims of clinical microbiology. This is especially true in bacterial meningitis where delay in proper treatment can be fatal. Presently used techniques have serious limitations. The Gram stain can be negative or misleading because of either the small number of organisms present or prior therapy. Cultures often require a day or so for growth, and they also may be negative in partially treated cases. A number of new, rapid methods are becoming available to aid in the rapid diagnosis of meningitis. Counterimmunoelectrophoresis (immunoelectroosmophoresis) is rapid (20). Currently, this technique is limited to testing for the common etiological organisms. Perhaps in the future antisera to a wider range of organisms will be developed. Gas-liquid chromatographic analysis of cerebrospinal fluid (CSF) sugars (2, 7) offers some promise. However, the technique is sophisticated and is unlikely to be available on a 24-h basis. Finally, the limulus assay for endotoxin (15, 19) has been reported as a simple rapid procedure for the diagnosis of meningitis caused by gram-negative bacteria in infants and children.

It has been known for over 50 years that CSF lactate is increased in bacterial meningitis (13), and it was suggested over 40 years ago that lactic acid measurement gave a more reliable index of the progression of the infection than sugar content (8). The measurement of lactate never became popular, probably because analytical methods were both technically difficult and unreliable. Over the past decade methodology has improved in both accuracy and precision. In two

recent studies (3, 6) CSF lactate proved valuable in the diagnosis of children with symptoms of meningitis who had purulent, partially treated or fully treated meningitis and aseptic meningitis. Two recent additional studies (4, 9) have shown CSF lactate concentrations to be of value in diagnosing bacterial meningitis in adults. However, neither study included patients with other neurological diseases.

Monitoring the cause and assessing the response to therapy and prognosis of patients with chronic meningitis is another difficult area. Cultures are often negative, and CSF cell counts and glucose concentrations can be misleading. We determined lactate levels in these people to see how lactate concentrations correlated with other parameters in people with mycotic meningitis.

The purpose of this study was to determine the specificity of CSF lactate elevations in acute meningitis and to assess their value in following the course of patients with chronic mycotic meningitis.

MATERIALS AND METHODS

Lactate levels were determined on all CSFs with sufficient volume submitted to the microbiology department for culture. This included fluid from most spinal taps done in the hospital. Cultures were routinely requested on most spinal fluids, if only to monitor technique in cases where infection was not suspected. For example, most people who have myelograms also have cultures requested.

Lactic acid was determined as its methyl derivative by gas chromatography on a Dohrmann 15-C3 chromatograph, using a thermal conductivity detector (12). Immediately upon receipt in the laboratory, 2.0 ml of

methanol and 0.4 ml of 50% H₂SO₄ were added to 1.0 ml of spinal fluid. This mixture was then either heated for 30 min at 55°C or saved overnight at room temperature to be run the next day. The methyl derivatives were extracted with 1.0 ml of water and 0.5 ml of chloroform. The methylated lactic acid was quantified on the gas chromatograph, using 14 μ l of the chloroform extract. A lactic acid standard, 0.3 mg/ml, was run with each CSF.

On a selected group of CSFs, lactate was determined on a DuPont Automatic Clinical Analyzer (ACA). The ACA uses a modification of the method of Marbach and Weil (16), which employs the oxidation of lactate to pyruvate and the reduction of nicotinamide adenine dinucleotide. The absorbance due to reduced nicotinamide adenine dinucleotide is directly proportional to the lactate concentration. Patients on whom a CSF lactate was determined on the ACA had a simultaneous blood lactate performed.

Over a course of 6 months 149 CSFs were studied. All had lactate determined by gas chromatography. Fifty-five also had the lactate concentration determined on the ACA. The 149 specimens were from 123 patients. All patients' charts were reviewed to determine the clinical indication for the spinal tap. Additionally, all laboratory studies were reviewed along with the clinical history and hospital course to arrive at a clinical diagnosis. In all cases of bacterial or fungal meningitis, the diagnosis was established by culture or serological studies of the CSF.

On the basis of the present study and the work of others (3, 6), the upper limit of normal for CSF lactate was less than 0.3 mg/ml, a concentration which can be reliably determined with either the chromatograph or the ACA.

Based on a review of the charts, utilizing all available information, the patients were grouped into four major categories. Group I had patients with chronic neurological disease. It included patients with multiple sclerosis, other degenerative neurological disorders, chronic hydrocephalus, and chronic (older than 3 months) cerebrovascular accidents and people who had tertiary syphilis with either positive or negative CSF serological tests. Group II had patients with acute central nervous system trauma and acute cerebrovascular accidents and people with primary or metastatic central nervous system tumors. Group III were people with bacterial or mycotic meningitis, bacterial and fungal central nervous system (CNS) infections, brain abscesses, and CNS syphilis. Group IV (controls) were people who had fluid submitted for culture at the time of myelograms and those patients who were studied for headaches in whom all studies were eventually negative.

RESULTS

CSF lactate concentration in normal people (people undergoing myelography for lumbar disc disease) as determined on the ACA was 0.14 mg/ml, with a standard deviation of 0.02 mg/ml. With the gas chromatograph, using a 0.3-mg/ml standard, it was not possible to accurately quantitate lactate concentrations under 0.3 mg/ml because the peak height was too low. Thus, for this reason a concentration of less than 0.3

mg/ml was considered normal. When compared with the chemical method, this is well beyond two standard deviations from the mean, yet does not include patients with acute meningitis who have values over 0.3 mg/ml.

All of the patients with untreated acute bacterial meningitis had CSF lactate levels greater than 0.3 mg/ml, as did all of the patients with active mycotic meningitis. Two partially treated patients had CSF lactate levels less than 0.3 mg/ml on repeat examination. The etiology of bacterial meningitis in this series included *Neisseria meningitidis*, *Diplococcus pneumoniae*, *Staphylococcus aureus* and *S. epidermidis*, and *Escherichia coli*. On this group of patients, CSF leukocyte counts varied from 20 to 3,000; sugars varied from 43 to 75 mg/dl. Eight patients with CNS syphilis accompanied by positive CSF serological studies also had lactate levels below 0.3 mg/ml. None of the three patients with aseptic meningitis had elevated lactate.

In patients with untreated mycotic meningitis, the lactate concentration was elevated. This series included one patient each with meningitis secondary to *Cryptococcus neoformans*, *Candida albicans*, and *Coccidioides immitis*. With response to therapy, the lactate levels decreased, paralleling changes in complement fixation (CF) titers in a case of coccidioidomycosis (see case history) and the CSF cryptococcal antigen in another.

CSF lactate was elevated in patients with necrosis of the brain, whether caused by acute trauma, cerebrovascular accident, or brain abscess. Also, patients with primary and metastatic CNS tumors often had elevated lactate levels.

Lactate was not elevated in people with chronic degenerative brain disease nor was it elevated in people with disc disease, except rarely. Three patients with a severe disc disease who had sudden onset with significant neurological findings had levels of 0.3 mg/ml. The lactate levels were negative in tertiary syphilis even if serological tests for syphilis on the CSF were positive.

The results of lactate determinations of CSF in the major groups are shown in Table 1. Analysis of the data reveals that the group with CNS infection (group III) is significantly different from each of the other groups ($P < 0.001$ when tested by Yates-corrected chi-square test). This is due to the number of elevated (≥ 0.3 mg/ml) CSF lactate concentrations in this group. The sensitivity of the test to detect CNS infection (percentage of positives detected with CNS infection) is 82%. The sensitivity would have been 100% if only the untreated CNS infections had been included. However, seven partially treated cases were included, and the lactate level of five of these was below 0.3 mg/ml.

TABLE 1. Analysis of different populations with CSF lactates above or below 0.3 mg/ml^a

Group(s)	Less than 0.3 mg/ml	More than 0.3 mg/ml	Sensitivity: true +/total + (%)	Specificity: true -/total - (%)
III. CNS infections	5	23	82	
I. Neurological diseases	34	0		100
II. CNS necrosis	25	14		64
IV. Controls	45	3		94
I, II, and IV. Non-infectious controls	104	17		86

^a Chi-square (χ^2), Yates corrected; comparison with CNS infection group (df = 1): group I— $\chi^2 = 40.95$, $P < 0.001$; II— $\chi^2 = 12.29$, $P < 0.001$; IV— $\chi^2 = 41.95$, $P < 0.001$.

The specificity of the test (percentage of negatives without CNS infection) is 94% for nondisease controls; it falls to 86% when all noninfectious patients are compared. The specificity of the noninfectious total group does not differ significantly from the control group ($0.05 < P < 0.1$ when tested by the t test of binomials).

Specificity (group IV) of the controls versus the other groups is seen in Table 2. It is apparent that the group with CNS necrosis (group II) is also significantly different from the controls.

The predictive value of a positive result (predictive value = true positives/total positives $\times$ 100) is 58% in the total group versus the group with CNS infection. Excluding group II, the predictive value of a positive result for infection is 88% (23 of 26). The difference is due to the number of positives with elevated lactate levels in CNS necrosis. This predictive value underscores the necessity of considering all parameters such as history, physical, sugar, cell count, protein, etc., when evaluating the patients with CNS symptomatology.

Fifty-five CSFs were run on both the ACA and the gas chromatograph. There were no significant differences in results with either of these methods ($P > 0.05$).

CASE HISTORY

A 46-year-old Chinese woman who lived in the United States for the past 15 years developed respiratory symptoms and a left lower lobe infiltrate. After considerable work-up the diagnosis of coccidioidomycosis was established. There was no evidence of dissemination except for persistent headaches. CSF examination revealed 400 cells/mm³, with: lymphocytes, 98%; protein, 119 mg/dl; glucose, 38 mg/dl, with blood glucose, 155 mg/dl. Therapy was begun with amphotericin B.

TABLE 2. t test for probability of specificity (group IV) of controls versus group(s) I; I, II, and IV; and II

Group(s)	t	df	P
I	1.75	80	$0.05 < P < 0.1$ (NS) ^a
I, II, and IV	1.72	167	$0.05 < P < 0.1$ (NS)
II	3.56	85	< 0.001

^a NS, Not significant.

icin B. A total of 5 g was eventually given. Symptoms promptly abated, but serum CF titers remained persistently elevated, 1:128. The spinal fluid coccidioidin CF titer was 1:32. Intrathecal amphotericin B was administered. CSF glucose promptly returned to normal levels. CSF leukocytes dropped to a range between 15 and 40, with greater than 80% lymphocytes. Lactate levels paralleled coccidioidin CF titers. CF titers of 1:16 or greater were associated with lactate concentration greater than 0.3 mg/ml. Titers of 1:8 had lactate levels approximately equal to 0.3 mg/ml, and when the CF titers dropped below 1:8 the CSF lactate was below 0.3 mg/ml in this patient.

DISCUSSION

CSF lactate was elevated in all cases of untreated bacterial and mycotic meningitis studied. Values returned to normal as the patients responded to therapy. Although we did not have many patients with aseptic meningitis, in other studies (3, 14, 22) children with aseptic meningitis had normal lactate levels. It was felt that one of the most useful applications of CSF lactate determinations was differentiating aseptic viral from bacterial meningitis. Lactic acid determinations may be of particular value in following the course of patients with fungal meningitis. In the patient illustrated in the case history with coccidioidomycotic meningitis, lactic acid levels paralleled changes in CSF CF titers; in another patient with cryptococcal meningitis the lactic acid changed, as did cryptococcal antigen, as determined by counterimmunoelectrophoretic methods. Although further study is needed, lactic acid may prove very useful in following patients with mycotic meningitis, since in this group of patients CSF leukocyte counts and glucose often rapidly return to normal after the initiation of therapy.

No patients in our series had tuberculosis meningitis, but CSF lactate concentrations may prove valuable in this group of patients in whom there are no good serological tests available for assessing prognosis and response to therapy (8).

Whereas CSF lactic acid is elevated in untreated meningitis, it returns to normal with response to therapy. The decrease in lactate concentrations is slow, often occurring over a

few days. Therefore, even if antibiotic therapy has been initiated and masks the detection of the etiological agent, this would not immediately influence the level of the CSF lactate. There is good evidence that lactic acid is cleared from the CSF by diffusion into the brain (21), which probably accounts for the slow clearance.

Elevated CSF lactic acid is not specific for bacterial and mycotic infections. It is elevated under conditions in which there is CNS hypoxia (17) and infarction (23). It has also been reported to be elevated after motor seizures (5). Our series supports these findings. The elevated lactate in patients with tumors is also possibly related to relative ischemia and necrosis.

A number of factors may contribute to the elevated concentrations of CSF lactic acid (11). The increase may be due to any of the following: the presence of leukocytes, organisms, or increased production by cerebral tissue secondary to hypoxia. Hyperventilation, if present, may also contribute to the total lactate concentration.

Finally, an important consideration is the relationship of blood to CSF lactic acid concentration. Blood and CSF lactate generally vary independently of each other (18). Lactic acid at physiological pH levels is fully ionized and thus for theoretical reasons would be expected to diffuse across the blood-brain barrier very slowly. Such is the case both in animal experiments (1, 10) and in human studies (18).

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