

Evaluation of Cerebrospinal Fluid Lactic Acid Levels as an Aid in Differential Diagnosis of Bacterial and Viral Meningitis in Adults

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The level of lactic acid in cerebrospinal fluid has been suggested as a useful diagnostic parameter to differentiate between bacterial and viral meningitis, especially in patients partially treated before admission to hospital. A concentration of ≥ 35 mg/dl, determined by either gas-liquid chromatography or an enzymatic method, has been considered in several studies to provide definite evidence of meningitis of bacterial origin, whereas a lower level indicates no bacterial involvement. Over the past 18 months, we have analyzed by the enzymatic method the lactate level in 493 spinal fluids submitted from 434 adult patients with various conditions involving the central nervous system. Fifty fluids had a lactate level of >35 mg/dl, of which 19 were cases of infective meningitis of varying etiology. The 435 specimens with lactate levels within the range considered normal included three cases of infective meningitis, of which two were cryptococcal and one was bacterial. In this adult study, the lactate level in the cerebrospinal fluid did not provide unequivocal evidence of bacterial infection and did not provide assistance to any greater degree than the standard parameters of leukocyte count, protein, and glucose contents in the differential diagnosis of bacterial meningitis from that of any other etiology.

The concentration of lactic acid in cerebrospinal fluid (CSF) in patients with suspected infective meningitis has recently been suggested as a useful parameter to differentiate bacterial from viral or noninfectious etiology (1, 2, 4, 7). It was hoped that this test might be especially useful in patients with bacterial meningitis partially treated before hospitalization. A lactate level of 35 mg/dl or greater has been considered by some authors (2, 7) as definitive evidence of bacterial involvement. Other investigators (5), however, have issued a caveat to the above statement and have suggested that there is no clear-cut level which separates bacterial meningitis from viral or noninfectious meningitis. The purpose of this paper is to report our findings with emphasis on lactic acid levels in cases of infective meningitis in adults and to discuss the usefulness of the test in our experience.

MATERIALS AND METHODS

Study population. All patients were adults ranging in age from 16 to 86 years. A total of 251 (57.8%) were males; 183 (42.2%) were females. These 434 patients, from whom 493 specimens of CSF were received in the laboratory, all had a greater or lesser degree of central nervous system involvement as part of their illness.

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The underlying pathology, which varied in seriousness, included intervertebral disc disease, multiple sclerosis, primary or metastatic neoplasms, intracranial hemorrhage, meningitis, and metabolic disorders. The majority of the patients admitted to the hospital with primary meningitis had received no antibiotics before admission. In several cases it was not possible to obtain a clear history because of the confused mental status of the patient, but no patient received more than one to two prehospital doses of chemotherapy, and it was felt that this did not influence the lactic acid levels.

Examination of CSF. The 493 specimens of CSF represented all such samples submitted to our laboratory over an 18-month period. The following tests were carried out on each specimen.

Cell count. Cell count was performed on a well-mixed, unspun sample of CSF unstained in a Fuchs-Rosenthal counting chamber. Corrections were made for total leukocytes present with regard to the number of erythrocytes in the specimen. When greater than nine leukocytes per mm^3 were found, a differential count was made on a Gram-stained preparation of the sediment after centrifugation of the fluid. A search for organisms was carried out on the same preparation.

Microscopic examinations. Gram-stained smears for bacteria and India ink preparations for *Cryptococcus* were routinely performed. Auramine O stains for *Mycobacterium tuberculosis* (10) were made when indicated on the basis of cell count, differential count, glucose and protein concentrations, and clinical history. Direct electron microscopic visualization for viruses was done on negatively stained preparations of

ultracentrifuged CSF when viral meningitis seemed the probable diagnosis based on the same parameters.

Cultures. Cultures were made for bacteria, fungi, viruses, and *M. tuberculosis*. If there was insufficient fluid, this routine was modified to the most appropriate cultures on the basis of cell count, glucose and protein concentrations, and clinical history, but always the specimen was cultured for bacteria.

Protein concentration. Total protein concentration was determined by a 3% trichloroacetic acid precipitation method (8). Readings were made with a Coleman Junior II 6/20 spectrophotometer. Appropriate standards and controls were included in all determinations. Results were expressed in milligrams per deciliter.

Glucose concentration. An *ortho*-toluidine method was used to determine glucose concentration (Accu-stat, Clay-Adams, Division of Becton-Dickinson and Co., Parsippany, N.J.). Appropriate standards were used in each test. Results were expressed in milligrams per deciliter.

Lactic acid concentration. An enzymatic method was employed, using nicotinamide adenine dinucleotide and lactic dehydrogenase (Sigma technical bulletin no. 726 UV and no. 326 UV revised, June 1976, Sigma Chemical Co., St. Louis, Mo.). Readings were taken with a Coleman Junior II 6/20 spectrophotometer at 340 nm. Standard curves of known lactic acid concentrations were used to determine the unknown lactic acid concentration in the specimen. Results were expressed in milligrams per deciliter.

RESULTS

The mean lactic acid level of all samples regardless of etiology was 21 mg/dl, with a standard deviation of ±12.1. Levels ranged from 11 to 140 mg/dl. Fifty fluids from 43 patients were found to have lactic acid levels of >35 mg/dl. Of these, 19 were cases of infective meningitis of varying etiology of which three were nonbacterial, presumed viral in origin (Table 1). The remaining 24 patients with elevated lactic acid levels had a variety of intracranial or metabolic disorders (Table 2).

In the remaining 391 patients with CSF lactic acid levels of <35 mg/dl, there were 14 cases of

infective meningitis, of which one was of proven bacterial etiology and two were proven cryptococcal meningitis (Table 3). Three patients with meningococcal meningitis had repeat lumbar punctures after a 14-day course of therapy; results are shown in Table 4. The combined data of lactic acid levels in all 33 cases of infective meningitis are shown in Fig. 1. The complete CSF profile of all 33 cases is displayed in Table 5.

DISCUSSION

During the course of this study, our purpose was to ascertain whether the lactic acid level in CSF should be introduced as part of our routine for processing spinal fluids. We did not report the lactic acid levels to the attending staff unless

TABLE 2. Cases of noninfectious intracranial pathology with CSF lactate >35 mg/dl

Etiology	No. of cases
Postcraniotomy	5
Subarachnoid hemorrhage	3
Head trauma	3
Cerebral metastases	3
Pneumonia, confusion 2° hypoxia	2
Subdural hematoma	1
Postoperative hydrocephalus	1
Lymphomatous meningitis	1
SBE? ^a septic emboli (unconfirmed)	1
Postcardiac arrest	1
Coma, metabolic acidosis	1
Undiagnosed	2

^a SBE, Subacute bacterial endocarditis.

TABLE 3. Cases of infective meningitis with CSF lactic acid levels <35 mg/dl

Etiology	No. of cases
<i>Haemophilus influenzae</i>	1
<i>Cryptococcus neoformans</i>	2
Enterovirus	1
Other viral or presumed viral etiology	10

TABLE 1. Cases of infective meningitis with CSF lactate levels >35 mg/dl

Etiology	No. of cases
<i>Neisseria meningitidis</i>	6
<i>Streptococcus pneumoniae</i>	1
<i>Listeria monocytogenes</i>	1
<i>Haemophilus influenzae</i>	1
<i>Staphylococcus aureus</i>	2
Brain abscess and meningitis (anaerobic)	2
<i>Candida albicans</i>	1
<i>Streptococcus epidermidis</i> , infected ventriculo-peritoneal shunt	1
<i>Enterococcus</i> , posttraumatic	1
Viral or presumed viral	3

TABLE 4. Lactic acid levels pre- and posttreatment in meningococcal meningitis

Case	Cell count	mg/dl			
		Glucose	Protein	Lactic acid	
1	Day 1 (pre)	827 ^a	15	88	120
	Day 14 (post)	40 ^b	35	71	35
2	Day 1 (pre)	2,700 ^a	25	194	78
	Day 14 (post)	30 ^b	50	75	21
3	Day 1 (pre)	1,500 ^a	20	222	86
	Day 18 (post)	2 ^b	46	32	45

^a Polymorphonuclear leukocytes.

^b Mononuclear leukocytes.

it was specifically requested. As can be seen from Fig. 1, there were major false positives and false

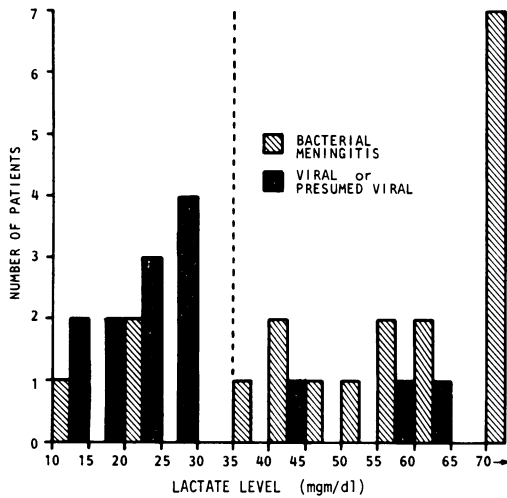


FIG. 1. Histogram illustrating CSF lactic acid levels in 33 cases of infective meningitis.

negatives among the cases of infective meningitis. The false negatives were the most worrisome in that one case of *Haemophilus influenzae* meningitis and two cases of cryptococcal meningitis had lactate levels below 35 mg/dl (cases 20, 21, and 22, Table 5). Case 21 with *H. influenzae* meningitis was culture positive, but the other parameters, including lactic acid level, were of little help. Clinically, this patient was severely ill and, despite the immediate CSF findings, was treated, as having bacterial meningitis, with both penicillin and chloramphenicol pending culture results. Case 22 was a renal transplant patient who presented with fever, nuchal rigidity, and confusion. Despite the benign CSF parameters, the India ink preparation was positive, as was culture. Case 20 was apparently a "classical" viral meningitis from CSF analysis. However, the culture was positive for *Cryptococcus neoformans*, as was a sample of aspirate from an upper lobe lesion in the right lung. This patient had no underlying disease and was perfectly healthy before presenting with symptoms. The three cases of presumptive viral meningitis

TABLE 5. Complete CSF profile of 33 cases of infective meningitis

Case	Cell count	mg/dl			Gram stain	Culture	Diagnosis
		Glucose	Protein	Lactic acid			
1	16,200 ^a	0	290	140	+	+	<i>Neisseria meningitidis</i>
2	827 ^a	15	88	120	+	+	<i>Neisseria meningitidis</i>
3	42 ^a	180	133	40.5	-	+	<i>Neisseria meningitidis</i>
4	14,000 ^a	ND ^b	ND	100	+	+	<i>Neisseria meningitidis</i>
5	2,700 ^a	25	194	78	-	+	<i>Neisseria meningitidis</i>
6	1,500 ^a	20	222	86	+	+	<i>Neisseria meningitidis</i>
7	13,800 ^a	62	130	42	+	+	<i>Streptococcus pneumoniae</i>
8	300 ^a	20	290	64.5	+	+	<i>Listeria monocytogenes</i>
9	5,200 ^a	55	162	56	-	+	<i>Haemophilus influenzae</i>
10	1,600 ^a	50	106	48	-	+	<i>Staphylococcus aureus</i>
11	98 ^a	40	140	60	+	+	<i>Staphylococcus aureus</i>
12	3,200 ^a	25	210	130	-	+	Mixed anaerobic
13	2,700 ^a	40	123	37	-	+	Mixed anaerobic
14	209 ^a	80	252	57	+	+	<i>Candida albicans</i>
15	53 ^c	120	48	42	-	-	Viral meningitis
16	1,700 ^c	70	32	60	-	-	Viral meningitis
17	13 ^c	65	40	59	-	-	Viral meningitis
18	1,120 ^a	57	88	50	-	+	<i>Staphylococcus epidermidis</i>
19	800 ^a	20	142	96	+ ^d	+	<i>Enterococcus</i>
20	192 ^c	45	86	24	-	+	<i>Cryptococcus neoformans</i>
21	161 ^a	40	75	13.5	-	+	<i>Haemophilus influenzae</i>
22	2	85	18	24.5	+ ^d	+	<i>Cryptococcus neoformans</i>
23	197 ^c	70	37	24	-	-	Viral meningitis
24	126 ^c	55	50	29	-	+	Viral meningitis
25	60 ^c	60	35	21	-	-	Viral meningitis
26	194 ^c	40	60	29	-	-	Viral meningitis
27	3	55	22	20	-	-	Viral meningitis
28	4	65	48	15.5	-	-	Viral meningitis
29	1	65	37	13.5	-	-	Viral meningitis
30	60 ^c	45	55	27	-	-	Viral meningitis
31	1	60	23	11	-	-	Viral meningitis
32	3	75	32	27	-	-	Viral meningitis
33	1	65	28	16	-	-	Viral meningitis

^a Polymorphonuclear leukocytes.
^b ND, Not done.
^c Mononuclear leukocytes.
^d India ink preparation.

(cases 15, 16, and 17, Table 5) with lactic acid levels of >35 mg/dl all had cell counts, protein and glucose levels, and a clinical picture suggestive of viral etiology. Cultures for bacteria, viruses, and *M. tuberculosis* were all negative. Case 17 was restudied at 24 and 48 h to ensure that no bacteria were present, and the patient was not treated with antibiotics at any time. By 48 h the lactate level had returned to <35 mg/dl, and the patient made an uncomplicated recovery without specific therapy. She had no other disorder that might have accounted for the elevation of lactic acid. One further case deserves mention (case 3); in this case it appeared that the elevated lactate could have helped to make the diagnosis of bacterial as opposed to nonbacterial meningitis. However, clinically this patient was severely obtunded with fever and nuchal rigidity. Despite the low cell count, the fluid was turbid, and this plus the clinical presentation was highly suggestive of bacterial infection and was treated as such pending culture results, which were positive within 24 h. Some of the cases of viral meningitis (cases 27, 28, 29, 31, 32, and 33, Table 5) were not seen by the infectious diseases consultation team. The diagnosis is taken from the discharge diagnosis in the medical records. The low cell count, i.e., <5 , makes the diagnosis of viral meningitis questionable; however, all these patients had lactic acid levels (and all other measured parameters) within the normal ranges.

Perhaps the most interesting data obtained from this study relate to the elevated lactic acid levels after craniotomy. These studies were usually performed to rule out postoperative complications such as hemorrhage or meningitis. We found the lactate levels of no help in this situation as they were always elevated postcraniotomy for several days. In this instance, cell count, protein, glucose, and Gram stain had to be relied upon to provide the clue to a possible infectious etiology.

In another study (2), it was suggested that the lactic acid could be used to evaluate adequacy of treatment and that after therapy the lactic acid should return to levels below 35 mg/dl. Failure of the lactate to fall was thought to indicate that complications, such as relapse, were likely. In three of our cases of meningococcal meningitis, lumbar puncture was performed at completion of therapy (Table 4). All patients were clinically symptomless, none had any complications, and in only one case did the lactate fall below 35 mg/dl.

In general, we found that in adult cases of bacterial meningitis the lactic acid was indeed elevated, but other parameters of high cell

count, differential leukocyte count, low glucose, and increased protein had already supplied the necessary information, with additional confirmation when the stained smear was positive for bacteria. In cases where doubt existed as to etiology, we felt unable to rely on the lactic acid level as a major aid in differential diagnosis, and in patients after neurosurgery, in whom infection was suspected, the lactate was of no help. If lactic acid levels are to be used at all in the differential diagnosis of bacterial versus viral or noninfectious meningeal involvement, great care must be used in interpretation of the results. Other intracranial or metabolic abnormalities that may cause elevation of lactic acid in the CSF, such as hypocapnia, hydrocephalus, cerebral ischemia (4), seizures (2, 9), or any other clinical condition associated with reduced oxygenation of the brain or raised intracranial pressure, must be considered. As a result of our findings, it was decided that the routine measurement of lactic acid levels in CSF even in cases of suspected bacterial meningitis offered little advantage over the standard parameters and has not been introduced into our laboratory routine.

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