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Cerebrospinal fluid lactate in 78 cases of adult meningitis

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Abstract. In a retrospective study of 78 cases of adult meningitis, the CSF lactate was measured on the first spinal tap (ST); 25 had a bacterial meningitis, 28 a viral meningitis; 22 other cases had been on antibiotics prior to admission; 3 cases had meningitis of rare aetiology. The median CSF lactate level among the 25 bacterial cases amounted to 13.6 mmol/l (range: 3.5–24.5) whereas it remained low in the 28 viral cases: 2.7 mmol/l (range: 1.4–4.2). These differences are highly significant. The comparison of the CSF lactate level with the other tests routinely performed showed that the CSF lactate level had the highest sensitivity, specificity and predictive values. The CSF lactate level on the first ST had no prognostic value, but a rapid decrease of the CSF lactate during the treatment is indicative of good prognosis. Among the pretreated cases, a high lactate level could be an indication that bacteria were the causal agents. In conclusion, the measurement of the CSF lactate, quickly performed and inexpensive, is worth performing when a meningitis is suspected, as it appears to be the best way of distinguishing bacterial from non-bacterial meningitis.

Key words: CSF – Lactate – Meningitis

In a recent retrospective study of 112 consecutive cases of adult meningitis [1], it appeared that the prognosis of the 53 cases of bacterial meningitis was still severe as the mortality was 15% and the neurological sequelae 24%. In contrast, only one death and one case with neurological sequelae have been observed among the 49 cases of non-bacterial (probably viral) meningitis. This observation points out that bacterial meningitis has still a much worse prognosis than non-bacterial meningitis. In addition, if we consider that the first should be on antibiotics as quickly as possible and that the latter does not need antibiotics, it is crucial to differentiate rapidly between these two types of meningitis. As the clinical data have no reliable discriminant feature, the CSF analysis gives the best clues of the diagnosis.

The CSF Gram stain has a sensitivity of only 80% and, unfortunately, the techniques of bacterial and of viral identification are still time consuming. Their results are not available to the clinician at the time he has to make the first therapeutic decisions. Therefore he can only rely upon non-specific tests such as leucocyte count and differentiation, protein and glucose levels.

The CSF lactate level has been shown by several authors to increase in bacterial meningitis [2, 3] and seems to discriminate between bacterial and viral meningitis [4–7]. However, this measurement is not yet a routine analysis, as several publications [8–10] argue that the CSF lactate measurement has too low a specificity. Lactate increases in many situations that have nothing to do with a meningeal inflammation.

The present retrospective study was undertaken to analyse the contribution of the CSF lactate among 78 cases of adult meningitis where CSF lactate levels were measured on the first ST, after a meningitis had been suspected. This was possible in this hospital as the CSF lactate is measured routinely since previous studies [4, 5].

Patients and methods

All the cases of adult meningitis diagnosed in the hospital from January 1st 1977 to January 1st 1983 were collected: 112 cases were identified; 93 had a CSF lactate measurement performed, 78 of them on the first ST; this last group is reported here. There were 43 females (54%), median age 33 years (range 17 to 81 years) and 35 males, median age 35 years (range 16 to 76 years).

The cases have been collected in the Department of Internal Medicine (Prof. P. Burckhardt, Prof. Cl. Perret, Prof. M.P. Glauser) and in the service of Neurology (Prof. F. Regli) of the Centre Hospitalier Universitaire Vaudois (CHUV). The lactate, glucose, and protein measurements were performed by the Central Laboratory (Prof. J. Frei), the CSF leucocytes and differentiation by the CSF laboratory (Neurology Service, Prof. F. Regli) and the microbiological investigations by the Institute of Microbiology (Prof. V. Bonifas).

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Lactate measurements were performed with a lactate analyzer (Hoffmann-La Roche) for most of the cases immediately after the ST; for the other cases, the CSF was stored at 4 °C, after addition of NaF and K oxalate [7, 11]. This technique is fast, precise, and in good correlation with the enzymatic method [5].

The sensitivity of a test is defined as the ability of the test to detect a true positive. The specificity of a test is defined as the ability to detect a true negative. The positive or negative predictive values of a test are defined as the probability of disease with a positive result or the probability of exclusion of disease with a negative test.

Patients description

The group of the 78 patients has been divided into 4 classes according to the following criteria.

Proven bacterial meningitis: 25 cases

The culture was positive in 22 cases (associated with a positive Gram stain in 16 cases). The Gram stain alone was positive in 3 cases. Five cases received antibiotics prior to admission.

Non-bacterial meningitis (probably "viral"): 28 cases

As the diagnosis for a viral meningitis was rarely proven among the patients studied [1] (7.5% positive virus isolation and 25% positive serology), these last criteria could not be used alone. Therefore, a case was put in this class when the clinical picture showed signs of meningeal inflammation, the CSF was *clear* and showed definite inflammatory reaction, no bacteria could be seen on the Gram stain nor cultured, the evolution was favorable without antibiotics and in all the cases the final diagnosis was that of a viral meningitis.

Pretreated meningitis without identified organisms: 22 cases (received antibiotics prior to admission)

Three sub-classes were made: pretreated meningitis:
- probably bacterial (7 cases)
- probably non-bacterial (viral (8 cases)
- of unknown origin (7 cases).

A case was classified as:
- *Probably bacterial* if: CFS was *cloudy*, the leucocyte count was above 1500/mm^3, with granulocytes representing more than 50%, and/or the CSF/blood glucose ratio was less than 0.4, and/or the protein level was above 2000 mg/l, the presence of an infectious bacterial focus was detected elsewhere, and finally, the discharge diagnosis was that of a bacterial pretreated meningitis.
- *Non-bacterial meningitis*, if: the CSF was *clear*, the leucocytes amounted to less than 1500/mm^3, with granulocytes below 30%, the Gram stain was negative as were the cultures; no antibiotic was administered after ST, the outcome was favorable, the discharge diagnosis was that of a pretreated meningitis.
- Of *unknown origin*, if it did not fulfill at the above criteria.

Special types of meningitis: 3 cases

- 1 case of syphilitic meningitis
- 1 case of chemical meningitis (after myeloscintigraphy)
- 1 case of a Mollaret recurrent meningitis.

Results

The CSF lactate normal value in our laboratory is 1.8±0.06 mmol/l; the normal value in arterial blood is lower: 1.1±0.15 mmol/l.

As demonstrated by Fig. 1, the CSF lactate values in proven bacterial meningitis (class 1) are far higher than the values of non-bacterial meningitis (class 2); with a breakpoint set at 4.2 mmol/l, the exact Fischer's test shows significance ($p<0.001$).

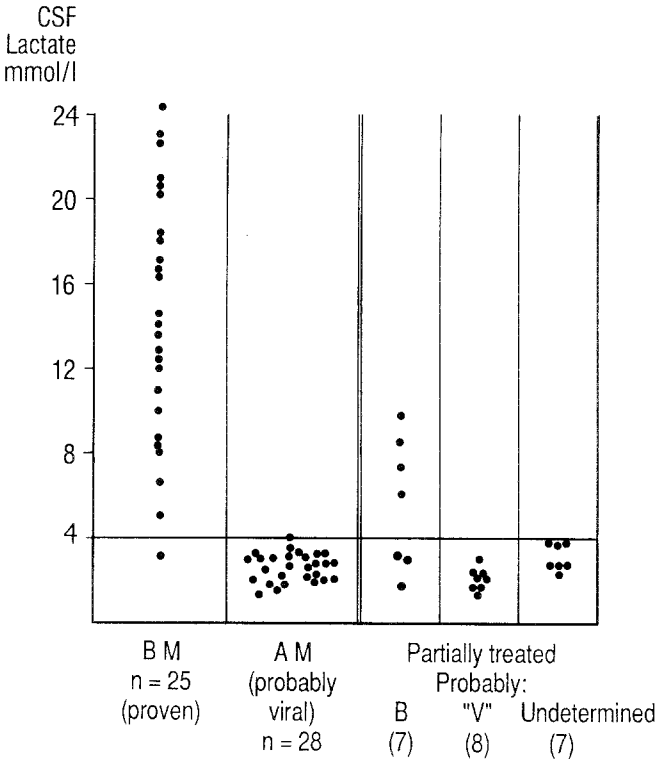

Fig. 1. CSF lactate in the first ST. The horizontal line represents the critical value of lactate and is chosen at 4.2 mmol/l. Exact Fischer's test: $p<0.001$. *B*, bacterial; *A*, aspecific; *V*, viral; *M*, meningitis

Considering a CSF lactate level above 4.2 mmol/l as a positive discriminant factor for a bacterial meningitis, the sensitivity of this test is 96%, its specificity 100%, its positive predictive value 100% and its negative predictive value 97%. Only one case of a bacterial meningitis had a lactate level below 4.2 mmol/l and one case of non-bacterial meningitis had a lactate level of 4.2 mmol/l (mumps meningitis, see discussion). Among the bacterial meningitis, one case of tuberculous meningitis had a CSF lactate of 8.6 mmol/l. No difference could be demonstrated between the different types of causal bacteria in terms of CSF lactate concentration.

In the pretreated cases (without organisms), Fig. 1 shows that in some presumably bacterial cases, CSF lactate was increased, and not in others; it remained low in the other cases. The small number of patients does not allow statistical analysis.

CSF lactate level on the first ST compared with CSF/blood glucose ratio, protein level, the leucocyte count and differentiation

The CSF/blood glucose ratio has been used as it is known to be more reliable than the CSF glucose value alone; it is generally accepted that a ratio below 0.4–0.5 favours a bacterial etiology. We have chosen 0.4 which better discriminates the bacterial meningitis from the others. In our study group, as shown by Fig. 2, the CSF/blood glu-

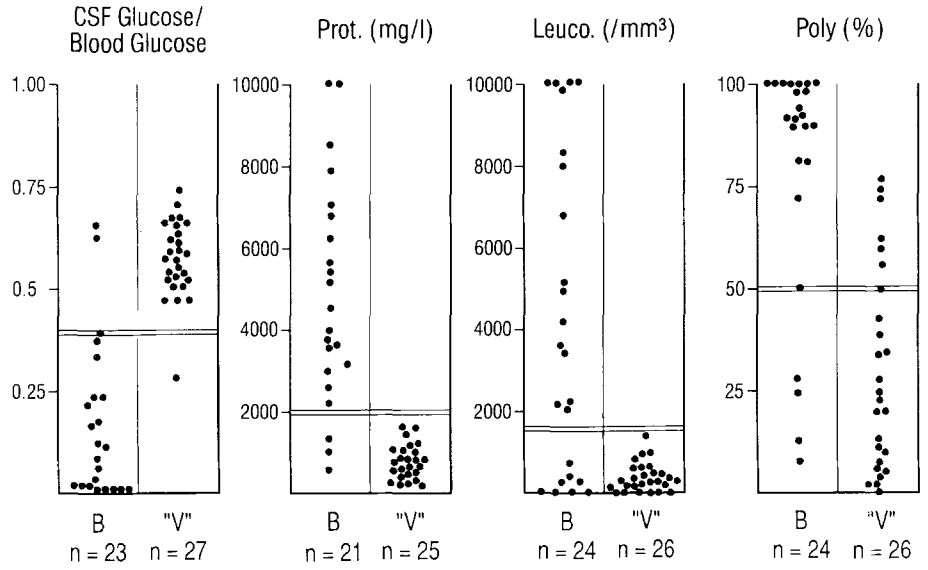

Fig. 2. CSF: blood glucose ratio, protein level and leucocyte count in the first ST. The *double horizontal line* represents the critical value of each test. *B*, bacterial; *V*, viral; *Prot*, protein level; *Leuco*, leucocyte count; *Poly*, polymorph nuclear percentage

cose ratio is lower in the bacterial meningitis cases than in the non-bacterial cases. For the proven bacterial meningitis, the median ratio is 0.11 (range 0.0 to 0.6) for the non-bacterial meningitis the median ratio is 0.57 (range 0.3–0.75).

For this test, when comparing group 1 and 2 for a discriminant level of 0.4, the sensitivity is 91%, the specificity 96%, the positive predictive value 95% and the negative predictive value 93%.

The bacterial cases show a higher CSF protein level than the non-bacterial: median level 4530 (range 520–15000) versus: median level 740 (range: 280–1560 mg/l). If we put the discriminant level between the bacterial and the non-bacterial meningitis at 2000 mg/l, this dosage has a sensitivity of 86%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 89%.

The median leucocyte count is 3600/mm^3 (range 10–21330) for the bacterial meningitis and 160 (range 10–1320) for the non-bacterial. Figure 2 shows that 8 bacterial meningitis have a low leucocyte count, similar to that of the non bacterial. Those cases had a poor evolution: 4 deaths, 3 neurological sequelae and only one complete recovery! With a discriminant level located at 1600 cells/mm^3, the leucocyte count has a sensitivity of 67%, a specificity of 100%, a positive predictive value of 100% and a negative predictive value of 76%. It is apparent that the CSF leucocyte differentiation did not discriminate between the bacterial and the non-bacterial cases: in ten cases of the 2 classes, the percentages of granulocytes are similar. For a discriminant percentage of 50%, the sensitivity is 83%, the specificity 73%, the positive predictive value 72% and the negative predictive value 83%.

A correlation could not be demonstrated between the CSF lactate level and the CSF/blood glucose ratio (R: bact. 0.5, non bact. 0.32), the CSF protein level (R: bact 0.5, non bact. 0.53), the leucocyte count (R: bact 0.14, non bact. 0.13), the granulocyte percentage (R. bact. 0.13, non bact. 0.09).

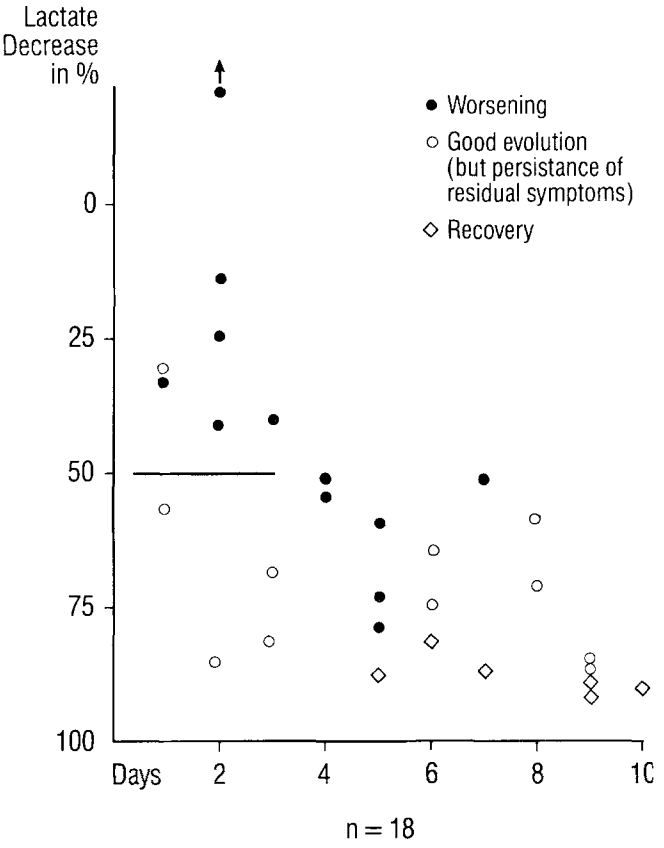

Fig. 3. CSF lactate evolution during treatment in correlation with clinical evolution. Numbers *above* the horizontal line represent a lactate decrease <50%, numbers *under* the line a lactate decrease >50%. Exact Fischer's test: $p < 0.02$

In terms of evolution in the first 3 days:

	W	OK
<50	6	1
>50	0	4

W = worsening; OK = good evolution

CSF lactate during treatment

The evolution of the CSF lactate level in 25 patients with bacterial meningitis in whom successive CSF lactate measurements were performed is presented in Fig. 3. A drop of more than 50% during the first 3 days parallels a good evolution, while a drop of less than 50% is encountered among cases with clinical worsening, and that independantly of the value in the first ST.

Among the non-bacterial cases the CSF lactate level always remained below 4.2 with only one exception: a case with a lactate level of 4.5 on day 3 who developed a concomitant encephalitis (the only non-bacterial case with neurological sequelae).

Discussion

The present retrospective study confirms that the CSF lactate level on the first ST allows differentiation between bacterial and non-bacterial meningitis. With a discriminant level of 4.2 mmol/l, all the bacterial cases had values far above that except one, and all the non-bacterial cases below that value, except one mumps meningitis with a value of 4.2 mmol/l and a case who got worse with concomitant encephalitis (4.5 mmol/l) on day 3. The only exception among the bacterial cases is interesting because it points to the time needed for the lactate to increase in the CSF. This patient had a ST done in the context of ongoing septic shock, when only minimal meningeal signs were present. The CSF examination showed a lactate level of 3.5 mmol/l, a protein level of 520 mg/l, a normal CSF glucose level and 10 leucocytes/mm^3! On the same CSF sample, *E. coli* were cultured; the blood cultures were also positive for this bacteria. A second ST was performed 36 h later, when the patient was on antibiotics: the CSF lactate level had risen to 7.1 mmol/l! Previous observations allow us to estimate that 3 h at least are needed for the lactate to significantly increase in the CSF after the first meningeal symptoms [5, 12].

As a discriminant between the bacterial and the non-bacterial meningitis, the CSF lactate of the first ST proved to be the best in terms of sensitivity, specificity and predictive value when compared with the other non-specific tests performed: CSF/blood glucose ratio, protein level, leucocyte count and differentiation. On the other hand a low leucocyte count in 8 cases of bacterial meningitis was accompanied with a poor prognosis in 7! It is unclear why a low initial leukocyte count is indicative of a fatal or complicated outcome. It is conceivable, that in these cases there is an inadequate inflammatory response intrathecally, resulting in a decreased or delayed granulocyte influx. This would allow a rapid bacterial growth in the CSF.

Interestingly enough, the percentage of granulocytes, although thought by many to be a good discriminant, proved to be the worst, as many of the cases of viral meningitis showed a granulocytic reaction early in the course of the disease.

Looking at the evolution now, the retrospective aspect of the present study led us to disregard several cases where all the measurements were either not concomitantly performed nor found in the records. So only the CSF lactate levels could be followed among those patients. The results show that, in the first 3 days, a decrease of an initially elevated lactate of more than 50% indicates a good prognosis and a decrease lower than 50% parallels a clinical worsening. However, the magnitude of the initial lactate level has definitely no prognostic value; this is in agreement with previous publications [6].

In pretreated cases, if a high CSF lactate value would favour a bacterial origin, a low value would not exclude it, as some values are low among cases which were apparently bacterial (Fig. 1).

When considering the origin of the CSF lactate, one has to bear in mind that all types of cells with glycolytic capability can be a source of lactate: neurones and glial cells, erythrocytes, leucocytes, alone or in their interaction with bacteria [13, 14] or parasites [15], tumour cells, mycotic cells etc. In addition, a passive diffusion from the blood or from the extracellular space of the brain can also enrich the CSF. This explains why, beside meningitis, an elevated CSF lactate level has been reported in many different clinical situations: perinatal asphyxia [16], epileptic seizures [17], cerebral infarction and brain death [5, 8], cerebral and subarachnoidal hemorrhage [5], brain trauma [8]. It is elevated in cerebral malaria and here it seems to have a prognostic value [15].

Therefore, before interpreting a CSF lactate value, one should first delineate, as precisely as possible, the clinical context and exclude possible causes of error by careful case history, physical examination, CSF examination, and when indicated, by comparison with arterial blood values. Omitting to distinguish a priori between these different conditions has led to the wrong conclusion that CSF lactate is useless because it is non-specific [8–10]. In the present study, the CSF lactate level proved to be the best discriminant between bacterial and non-bacterial meningitis.

The technique is easy, rapid, and inexpensive. In cases where the Gram stain does not show any bacteria (in 20% of untreated bacterial cases and in some pretreated cases), a CSF lactate higher than 4.2 mmol/l gives positive clues for a bacterial process; it helps the clinician to decide if the meningeal inflammation is caused by a bacteria or not, and thus, if antibiotics are indicated or not.

In the context of meningitis, excluding alternative causes of high CSF-lactate, this parameter can be interpreted as follows:

- A value below 3.5 mmol/l favours a non-bacterial process.
- A value above 4.2 mmol/l implies a bacterial (including tuberculosis) meningitis, especially if above 6 mmol/l.
- A CSF value between 3.5 and 4.2 mmol/l is in the "grey zone", where one can find early cases of bacterial meningitis, mumps meningitis, complicated viral meningitis (i.e. encephalitis), and some partially treated meningitis.
- The CSF lactate level in the first ST has no prognostic value. In the course of treatment, however, a rapid CSF lactate decrease is indicative of good prognosis.

In conclusion, it is still worthwhile to perform this measurement, until new techniques, hopefully in a near future, will permit a bedside identification of the causal agent itself.

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References

1. Genton B, Berger JP (1988) Les méningites de l'adulte au Centre Hospitalier Universitaire Vaudois: Diagnostic, prise en charge et évolution de 112 cas. Rév Méd Suisse Rom 108:795–803
2. Killian JA (1925) Lactic acid for normal and pathological spinal fluids. Proc Soc Exp Biol Med 23:255–257
3. Mdaghri El N, Benbachir M, Tazi Lakhasassi L, Himmich H (1985) Intérêt du dosage d'acide lactique dans le liquide céphalo-rachidien pour le diagnostic différentiel des méningites. Pathol Biol 33:227–231
4. Montani S, Perret Cl (1964) Acidose lactique du liquide céphalo-rachidien dans les méningites bactériennes. Schweiz Med Wochenschr 94:1551–1557
5. Berger JP, Fawer R (1979) Cerebrospinal fluid lactate and pyruvate in acute neurological situations. In: Bossart H, Perret C (eds) Lactate in acute conditions. Karger, Basel München Paris London New York Sydney, pp 115–133
6. Controni G, Rodriguez WJ, Deane CA, Hicks JM, Ross S (1976) Cerebrospinal fluid lactate determination: a new parameter for the diagnosis of acute and partially treated meningitis. Chemotherapy 1:175–182
7. Lauwers S (1978) Lactic acid concentration in cerebrospinal fluid and differential diagnosis of meningitis. Lancet II:163
8. Jordan GW, Statland B, Halsted C (1983) CSF lactate in diseases of the CNS. Arch Intern Med 143:85–87
9. Lannigan R, McDonald MA, Marrie TJ, Haldane EV (1980) Evaluation of cerebrospinal fluid lactic acid levels as an aid in differential diagnosis of bacterial and viral meningitis in adults. J Clin Microbiol 11:324–327
10. Lester A, Stilba I, Bartels P, Bruun B (1985) Value of CSF lactate in the differential diagnosis between bacterial meningitis and other diseases with meningeal involvement. Acta Pathol Scand (Sect B) 93:21–25
11. Prockop LD (1968) Cerebrospinal fluid lactic acid. Neurology 18:189–196
12. Ruuskanen O, Stahlberg ML, Korvenranta H, Nikoskelainen J, Irjala K (1985) CSF lactate in bacterial meningitis with minimal CSF abnormalities. Acta Paediatr Scand 74:292–293
13. Petersdorf RG, Garcia M, Swarner DR (1959) Mechanism of hypoglycorrhachia in experimental pneumococcal meningitis. Proc Soc Exp Biol Med 102:669–672
14. Cohn ZA, Morse SI (1960) Functional and metabolic properties of polymorphonuclear leucocytes. II. The influence of a lipopolysaccharide endotoxin. J Exp Med 111:689–704
15. White NJ, Warrel DA, Looareesuwan S, Chanthavanich P, Phillips RE, Pongpaew P (1985) Pathophysiological and prognostic significance of CSF lactate in cerebral malaria. Lancet 776–778
16. Svenningsen NW, Siesjo BK (1972) Cerebrospinal fluid lactate/pyruvate ratio in normal and asphyxiated neonates. Acta Paediatr Scand 61:117–124
17. Brooks BR, Adams RD (1975) Cerebrospinal fluid acid base and lactate changes after seizures in unanesthetized man. Neurology 25:935–948
18. Bland RD, Lister RC, Ries JP (1974) Cerebrospinal fluid lactic acid level and pH in meningitis. Am J Dis Child 128:151–156

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