

Cerebrospinal fluid lactate and lactate dehydrogenase activity in the rapid diagnosis of bacterial meningitis

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Summary

The value of cerebrospinal fluid (CSF) lactate and lactate dehydrogenase (LD) activity in the rapid diagnosis of meningitis was investigated in three groups of patients — a 'no meningitis', an aseptic meningitis and a bacterial meningitis group. The sensitivity achieved in the detection of bacterial meningitis by CSF lactate values of 2,85 mmol/l (93,8%) and 3,9 mmol/l (89,6%) was greater than that reached by conventional chemical investigations using a CSF protein value of 1 g/l (81,5%) or a CSF glucose value of 2,2 mmol/l (68,8%) as the indicator. The sensitivity of an absolute CSF LD value of 40 U/l (86,3%) in the detection of bacterial meningitis was slightly lower than that of a CSF protein value of 1 g/l (87%) and better than the sensitivity of either a CSF/serum LD ratio of 0,1:1,0 (83,9%) or a CSF glucose level of 2,2 mmol/l (76,3%). As with conventional CSF chemistry, both investigations may give normal values in the presence of bacterial meningitis.

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The cerebrospinal fluid (CSF) lactate concentration has been known to be raised in bacterial meningitis for more than 50 years.^{1,2} After a long period of neglect the last decade has seen considerable interest in CSF lactate as an aid in rapidly differentiating viral from bacterial meningitis.³⁻⁵ While some authors doubt whether it has 'any significant role in the management of children with suspected meningitis',⁶ others have claimed it to be 'on admission . . . the most sensitive and the most efficient test to distinguish bacterial meningitis from aseptic meningitis'.⁷

Similarly, CSF lactate dehydrogenase (LD) activity is known to be increased in cases of bacterial meningitis,⁸⁻¹⁰ and it has been suggested that determination of CSF LD activity 'may be superior to that of lactate, both in the diagnosis of bacterial meningitis and in distinguishing it from aseptic meningitis'.¹¹

Experience with these two investigations as aids in the rapid diagnosis of meningitis is presented.

Patients and methods

CSF lactate and LD values were determined in three groups of patients, all of whom were children 13 years of age or younger with the exception of a small number of adults suffering from tuberculous meningitis (TBM). All CSF was collected for normal clinical indications. This investigation was approved by the Ethical Committee of the Medical Faculty of the University of Stellenbosch.

Group 1 — 'no meningitis'. These children were investigated for possible meningitis, but subsequently shown to be free from meningitis. CSF lactate levels were determined in 46 patients (median age 5,13 months) and CSF LD activity in 237 patients (median age 13,6 months). In 160 cases serum LD activity was determined simultaneously with the CSF LD activity.

Group 2 — aseptic meningitis. These patients did not receive antibiotic therapy before or after investigation. Their CSF contained more than $20 \times 10^6/l$ white cells, no organisms could be seen on microscopy after Gram staining and no bacterial organisms were cultured from the CSF or blood. CSF lactate was determined in 23 patients (median age 60,07 months) and CSF LD activity in 73 patients (median age 55,4 months). Simultaneous serum LD activity was determined in 30 of these latter cases.

Group 3 — bacterial meningitis. The diagnosis of bacterial meningitis was confirmed in these patients by culture of the relevant organism from the CSF. The CSF specimens evaluated were those drawn before starting therapy. CSF lactate was determined in 48 cases (*Neisseria meningitidis*, 33 cases; *Haemophilus influenzae*, 4 cases; *Streptococcus pneumoniae*, 4 cases; *Escherichia coli* and *Salmonella* group B, 1 case each; and *Mycobacterium tuberculosis*, 5 cases). The median age of these patients was 17,26 months (age not available in 2 patients). Eleven of these patients who presented with a CSF cell count of less than $250 \times 10^6/l$ have already been reported on in more detail.¹² CSF LD activity was determined in 95 cases (*N. meningitidis*, 55 cases; *Strept. pneumoniae*, 11 cases; *H. influenzae*, 9 cases; *E. coli*, 4 cases; group B β -haemolytic streptococcus, 3 cases; *Proteus mirabilis* and *Salmonella* group B, 1 case each; and *Myc. tuberculosis*, 11 cases). Three of the TBM patients were adults and the median age of the remaining paediatric patients was 14,20 months. In 31 cases the serum LD activity was determined simultaneously. Four of the TBM patients in whom CSF lactate was determined and 9 in whom CSF LD activity was determined have been reported on previously.¹³

CSF was collected in tubes containing Long's solution¹⁴ and lactate values were determined with an enzyme assay kit. CSF and serum LD activity were determined by an optimized standard method. CSF showing evidence of a traumatic tap and blood showing haemolysis were not analysed for LD activity.

Results

CSF lactate

The CSF lactate values obtained in the three study groups are illustrated in Fig. 1. Values suggested in the literature above which a diagnosis of bacterial meningitis should be considered have been indicated at 2,75 mmol/l and 3,85 mmol/l.^{4,5} The single markedly elevated level seen in the 'no meningitis' group was obtained in a 2-month-old infant who had experienced repeated convulsions. In Table I the sensitivity and specificity achieved by

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TABLE I. SENSITIVITY AND SPECIFICITY OF CSF LACTATE, GLUCOSE AND PROTEIN LEVELS IN THE DETECTION OF BACTERIAL MENINGITIS

	CSF lactate		CSF protein	CSF glucose
	> 2,85 mmol/l	> 3,9 mmol/l	> 1 g/l	< 2,2 mmol/l
Sensitivity	93,8%	89,6%	81,5%	68,8%
Specificity	95,7%	98,6%	98,4%	97,1%

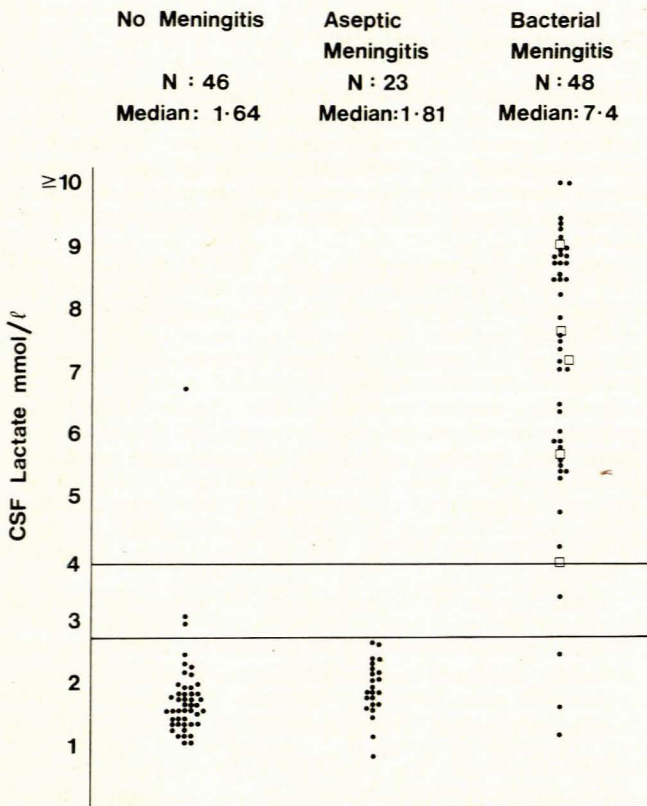


Fig. 1. CSF lactate in the rapid diagnosis of bacterial meningitis. All pairwise comparisons were significant (Mann-Whitney U-test, $P < 0,05$). □ = tuberculous meningitis.

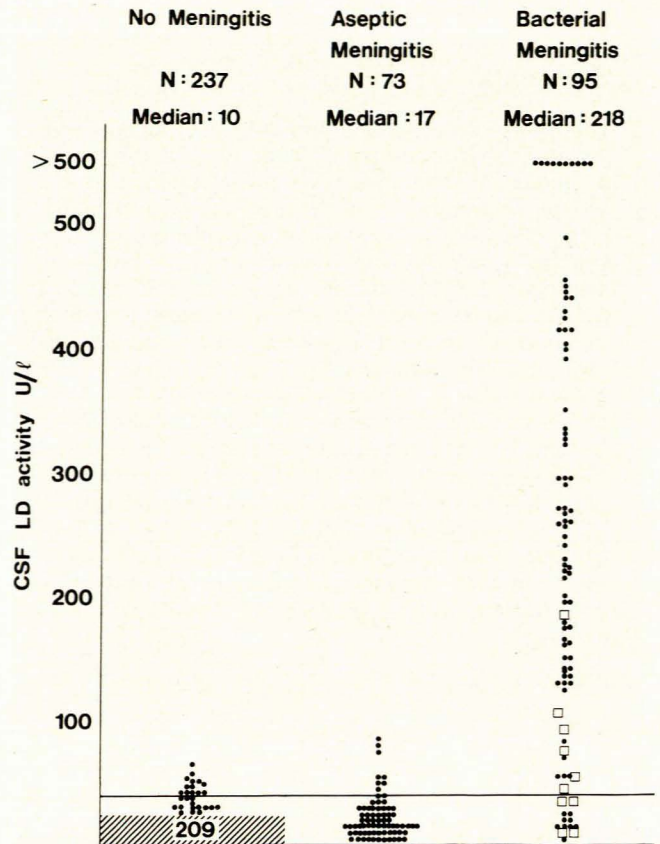


Fig. 2. CSF LD in the rapid diagnosis of meningitis. All pairwise comparisons were significant (Mann-Whitney U-test, $P < 0,001$). □ = tuberculous meningitis (median 55 U/l).

these values in detecting bacterial meningitis are compared with those associated with the conventional criteria of a CSF protein level of 1 g/l,¹⁵ and an absolute CSF glucose level of 2,2 mmol/l.¹⁶

In this series the sensitivity of CSF lactate in detecting bacterial meningitis was better than that of either CSF protein or CSF glucose, irrespective of which CSF lactate value was used. In respect of specificity the higher CSF lactate value of 3,9 mmol/l gave results only slightly better than CSF protein or CSF glucose.

CSF LD

The CSF LD values obtained in the three groups are illustrated in Fig. 2. A CSF LD activity of 40 U/l is indicated as the upper limit of normal.¹⁷ In Fig. 3 the CSF/serum LD ratio is indicated for those cases in which serum LD values were available. In Table II the sensitivity and specificity of an upper limit of normal for CSF LD activity of 40 U/l and a ratio of 0,1 : 1,0 in the detection of bacterial meningitis are compared with those of CSF protein and glucose values obtained in these same patients.

The CSF protein and the absolute CSF LD achieved a very similar sensitivity in the detection of bacterial meningitis — 87% and 86,3% respectively. The greatest specificity was found with CSF glucose (99%).

In group 1 48 children were aged less than 3 months. The median CSF LD value in this age group was 27,5 U/l compared with 10,0 U/l in the children older than 3 months ($P = 0,0000$).

Discussion

This experience with measurements of CSF lactate confirms its sensitivity in detecting bacterial meningitis. Whichever level was selected as a decision point, its sensitivity was better than that of conventional CSF chemical tests.

In contrast, CSF LD activity was neither more sensitive nor more specific in detecting bacterial meningitis than the conventional CSF chemical criteria. Determination of the CSF/serum LD ratio, while improving the specificity of the test, did not improve its sensitivity. The tendency for higher CSF LD values to be seen in the neonatal period has been noted before and must be borne in mind when interpreting results.

It has been previously noted that the CSF LD response in TBM is subdued in comparison with that seen in purulent

TABLE II. SENSITIVITY AND SPECIFICITY OF CSF LD ACTIVITY, CSF/SERUM LD RATIO, AND CSF PROTEIN AND GLUCOSE LEVELS IN THE DETECTION OF BACTERIAL MENINGITIS

	CSF LD > 40 U/l	CSF/serum LD ratio	CSF protein > 1 g/l	CSF glucose < 2,2 mmol/l
Sensitivity	86,3%	83,9%	87,0%	76,3%
Specificity	93,2%	97,9%	96,2%	99,0%

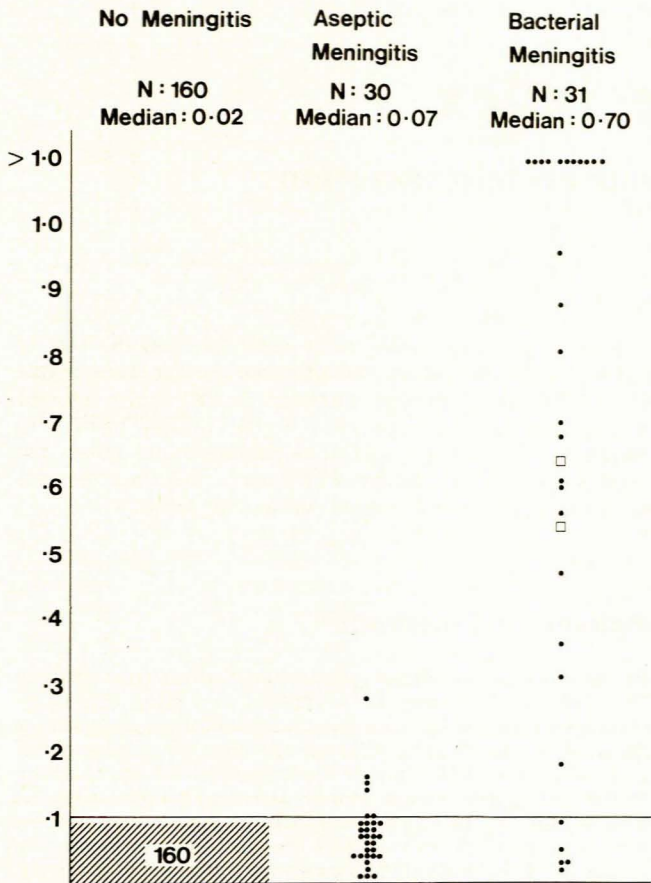


Fig. 3. CSF/serum LD ratio in the rapid diagnosis of meningitis. All pairwise comparisons were significant (Mann-Whitney U-test, $P < 0,001$). □ = tuberculous meningitis.

bacterial meningitis,¹⁸ while Verrey¹⁹ reported normal CSF LD values in TBM. Fig. 2 again illustrates the tendency for a lower CSF LD activity in TBM than in bacterial meningitis, and CSF LD estimation is not in our experience a reliable test to distinguish TBM from aseptic meningitis.¹³ CSF LD values greater than 200 U/l are very unusual in TBM. It is therefore of interest to note that studies of the iso-enzyme distribution of LD in purulent meningitis have indicated that much of the CSF LD activity is derived from granulocytes.^{20,21} This may provide a partial explanation for the lower CSF LD values obtained in TBM in which relatively small numbers of cells are found in the CSF.

While determination of CSF lactate and CSF LD activity provides the clinician with extra information, cases of bacterial meningitis will be encountered in which both these investigations and conventional CSF chemical tests will give results falling within 'normal' or 'aseptic' limits. By contrast, conditions other than bacterial meningitis may be responsible for elevated levels of CSF lactate²²⁻²⁴ and CSF LD activity.^{8,25}

Recognition of these facts places the emphasis in doubtful cases upon careful repeated clinical evaluation of the patients, followed by repeat lumbar puncture when indicated. The final decision whether or not to treat these patients for bacterial meningitis will then be clinical, assisted by chemical evaluation of the CSF but not blindly dependent upon it.

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The protein/creatinine index

A semiquantitative assessment of 24-hour protein excretion

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Summary

The 24-hour protein excretion is important in estimating the severity of a renal lesion and is used extensively for diagnostic and prognostic purposes and also to follow the response of patients to treatment. The disadvantages of timed 24-hour collections are that they are cumbersome, inconvenient, expensive, and unreliable in up to one-third of cases. The aim of this study was to correlate the protein/creatinine (P/cr) index in a random spot urine sample and protein excretion in a 24-hour urine sample from the same patient. The P/cr index was derived as follows:

$$\frac{\text{Spot urinary protein (mg/l)}}{\text{Spot urinary creatinine } (\mu\text{mol/l} \times 10^{-4})}$$

In the 34 patients investigated there was a highly significant correlation ($r = 0,9017$) between the P/cr index and 24-hour protein excretion. The P/cr index is a useful and quick method of assessing proteinuria in most patients with renal disease.

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Abnormal proteinuria in the patient with a renal lesion has important connotations for diagnosis and prognosis, and the level of protein excretion is routinely used to monitor progress.¹ Great reliance has been placed on the amount of protein excreted in a 24-hour urine sample, even though it is known that protein excretion can fluctuate from day to day and that errors in timing 24-hour samples are common. In addition, all physicians know how cumbersome and time-consuming these collections are.

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In a given patient with stable renal function the rate of urinary creatinine excretion is fairly constant.² It is reasonable to assume that if protein excretion is also fairly constant during one day then the ratio of the urinary protein to creatinine (P/cr) in a single urine sample would reflect the total excretion of protein over a 24-hour period, since the ratio of two stable rates would cancel out the time factor.³

Patients and methods

Fifty-seven patients with proteinuria were investigated between May 1983 and December 1983. Patients were given written instructions regarding the collection of a 24-hour urine specimen. At the time of delivery of the 24-hour specimen the following day, each patient was asked to supply a spot specimen for determination of the P/cr index. Eleven patients were excluded because the laboratory did not receive all the specimens, and 12 other patients when questioned directly claimed they had brought incomplete specimens. The remaining 34 patients were included in the study. There were 20 males and 14 females, aged from 13 to 70 years (mean 39 years). Serum creatinine values ranged from 65 to 480 $\mu\text{mol/l}$. The causes of renal disease were hypertension (9 cases), nephritis or nephrotic syndrome (23) and diabetes mellitus (2).

All analyses were done in a routine manner. Protein was estimated by the biuret method and the creatinine levels were determined by the Jaffe reaction using a Technicon auto-analyser. The P/cr index in the spot specimen was derived as follows:

$$\frac{\text{Spot urinary protein (mg/l)}}{\text{Spot urinary creatinine } (\mu\text{mol/l} \times 10^{-4})}$$

The degrees of proteinuria were as follows: < 1 g (3 patients), 1-3 g (6 patients), 3-10 g (14 patients), and > 10 g (11 patients). In 7 patients the P/cr index for both an early-morning spot urine specimen and a random daytime spot urine specimen were assessed to look for an orthostatic component in the early morning specimen.

Results

Using the least-squares method, the correlation coefficient was found to be significant ($r = 0,9016$; $P < 0,000001$) (Fig. 1). Of the 7 patients tested for the orthostatic component in the early morning specimen, 5 had a lower P/cr index for the early morning specimen than for the daytime one (Fig. 2).