Cerebrospinal fluid lactic acidosis in bacterial meningitis

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SUMMARY A rapid, microenzymatic method was used to measure cerebrospinal fluid lactate levels in 205 children with suspected bacterial meningitis. Fifty children with normal CSF containing fewer than $0.005 \times 10^9/l$ WBC, no segmented neutrophils, glucose 3.4 ± 0.8 mmol/l (61.2 ± 14.4 mg/100 ml), and a protein of less than 0.30 g/l had CSF lactate levels below 2.0 mmol/l (18 mg/100 ml) (mean and standard deviation 1.3 ± 0.3 mmol/l (11.8 ± 2.7 mg/100 ml)). In 31 cases of proved viral meningitis as with 58 cases of clinically diagnosed viral meningitis, levels were below 3.8 mmol/l (34.5 mg/100 ml), being 2.3 ± 0.6 mmol/l (20.9 ± 5.4 mg/100 ml), and 2.1 ± 0.7 mmol/l (19.1 ± 6.4 mg/100 ml) respectively. Sixty-six cases of bacterial meningitis had CSF lactate levels ranging from 3.9 mmol/l (35.4 mg/100 ml) to greater than 10.0 mmol/l (90.0 mg/100 ml). Longitudinal studies in 7 children with bacterial meningitis showed that cerebrospinal fluid lactate levels differentiated bacterial from viral meningitis up to 4 days after starting treatment with antibiotics. Use of CSF lactate measurement for monitoring the efficacy of treatment is illustrated in a case of bacterial meningitis due to *Pseudomonas aeruginosa*. The origin of the cerebrospinal fluid lactate acidosis and the role of lactate in the pathophysiological cycle leading to intensification of brain tissue hypoxia and cellular damage is discussed with respect to the short-term prognosis and the long-term neurological sequelae.

With the advent of antibiotics three decades ago the mortality rate in bacterial meningitis was reduced from 50-90% to about 5-10%. There has been no further comparable improvement since then.¹⁻³ However studies on children with meningitis due to *Haemophilus influenzae* indicate that as many as 30% of the survivors suffer from severe neurological and psychological sequelae.³⁻⁵

To date there is no laboratory test which is both rapid and reliable for differentiating bacterial meningitis from viral meningitis or for quantitating the effectiveness of treatment. Results from a careful inspection of the cerebrospinal fluid (CSF) with complete differential cell count, and glucose and protein levels may still leave the differential diagnosis in doubt.⁶ Gram stains may be negative in as many as 30% of cases of culture-proved bacterial meningitis.⁷ Furthermore, treatment with antibiotics before initial lumbar puncture, which occurs in about half the cases of bacterial meningitis,⁸⁻¹² increases both negative Gram stains and negative cultures.¹⁰

Several methods have been suggested for the rapid differential diagnosis of meningitis—such as CSF

lactate dehydrogenase activity,¹³ counterimmunoelectrophoresis,¹⁴ nitroblue tetrazolium test,¹⁵ the limulus lysate test,¹⁶ and CSF pH measurement. However some of these tests produced more than 10% false-negative results, others detected only some types of organisms, and the equipment needed and the expertise required were beyond the scope of most clinical laboratories. Moreover there was decreased reliability if antibiotics had been given.

In 1917 Levinson¹⁷ observed low pH values in the CSF of patients with bacterial meningitis, and believed this was due to lactic acid. In 1925 Killian¹⁸ presented supporting data on CSF lactate from 5 normal patients and 25 patients with bacterial meningitis. In 1933 De Sanctis *et al.*¹⁹ concluded that variations in lactic acid of spinal fluid offered more-reliable information about the clinical progress during treatment of bacterial meningitis than CSF sugar or total leucocyte counts.

Since Killian's report¹⁸ numerous papers have produced results in support of the measurement of CSF lactate levels in the differential diagnosis of meningitis.²⁰⁻³² Despite this, the use of CSF lactate

measurements as a rapid screening test for bacterial meningitis has not gained wide acceptance, primarily owing to the technical difficulties of its measurement.

This paper presents the results of our experience with CSF lactate measurement in normal children and children with meningitis using a rapid enzymatic micromethod suitable for a small clinical laboratory with standard laboratory equipment.

Materials and methods

CSF samples were obtained from 207 children aged between 2 days and 15 years. Each had had a lumbar puncture because of clinical features that suggested bacterial meningitis.

Complete differential cell count, a Gram stain, glucose and protein determinations were performed on each CSF sample.

No special preparation of the CSF was required for lactate determination except immediate centrifugation, using the supernatant if grossly blood-stained. If a sample could not immediately be assayed it was stored at a temperature of -20°C .

For this method³³ lactate was converted to pyruvate by the enzyme lactic dehydrogenase (LDH EC 1.1.1.27) in a stoichiometric reaction with nicotinamide adenine dinucleotide (NAD⁺). Pyruvate inhibition of LDH was removed by reaction of the pyruvate with either glutamate pyruvate transaminase (GPT EC 2.6.1.2) to form alanine at pH 8.9, or alternatively, with hydrazine to form the hydrazone at pH 9.5. The increase in reduced nicotinamide adenine dinucleotide was measured fluorometrically or spectrophotometrically.

The assay protocol consisted of adding 2–10 μl of the CSF sample to 1.0 ml of reaction mixture containing 25 ml glutamate buffer (Sigma) to a concentration of 0.120 mol/l, 60 ml fresh glass distilled H_2O , 5 ml of NAD (Sigma grade III) to a concentration of 0.80 mmol/l, and either 2 units/ml of GPT (Boehringer Mannheim from pig heart) or 5 ml of hydrazine (BDH AR grade) to a concentration of 0.103 mol/l, made up to 100 ml with distilled H_2O .

Samples were measured in duplicate in 10×75 mm Pyrex disposable tubes (Corning). Stock standard of lithium l-lactate (10 mmol/l) was diluted with the reaction mixture to 1 mmol/l, and 0–50 μl per tube containing 0–50 nmol/l was used to construct a standard curve.

Fourteen units of LDH from rabbit muscle (Boehringer Mannheim) stored in tris buffer 20 mmol/l, pH 8.0, and 0.02% bovine serum albumin were added to each tube.

The tubes were vortexed and incubated for 30 minutes at 37°C , allowed to cool, and then read in either a Perkin Elmer fluorimeter 650 10S (on sensitivity 3 and slits 3 nm, excitation wavelength 360 nm, analytical wavelength 465 nm) or a Unicam SP 500 spectrophotometer at 365 nm.

Each patient was placed in one of four groups.

Group 1 ($n = 50$). Normal, $\text{WBC} < 0.005 \times 10^9/\text{l}$ with no segmented neutrophils, normal glucose and protein, and a clear Gram stain. No cultures were set up on these samples.

Group 2 ($n = 31$). Viral meningitis, identified virus isolated from CSF.

Group 3 ($n = 66$). Bacterial meningitis, positive culture with identification of the organism.

Group 4 ($n = 58$). Miscellaneous, leucocytosis of unknown aetiology. These were presumed to be patients with viral meningitis from whose CSF no bacteria or virus could be isolated.

Results

CSF results for the four groups are given in Table 1.

The normal children all had CSF lactate levels less than 2.0 mmol/l (18.0 mg/100 ml) (mean and standard deviation 1.3 ± 0.3 mmol/l (11.8 ± 2.7 mg/100 ml)). Children with proved or suspected viral meningitis had CSF lactate levels less than 3.8 mmol/l (34.5 mg/100 ml)— 2.3 ± 0.6 and 2.1 ± 0.7 mmol/l (20.9 ± 5.4 and 19.1 ± 6.4 mg/100 ml) respectively. Children with bacterial meningitis had CSF lactate levels from 3.9 mmol/l (35.4 mg/100 ml) to greater than 10.0 mmol/l

Table 1 CSF measurements (means and SD) made in 205 children

Group	Median age (years)	WBC ($\times 10^6/\text{l}$)	% segmented neutrophils	Glucose (mmol/l)	Protein (g/l)	Lactate (mmol/l)
Normal ($n = 50$)	3.8	<5	0	3.4 ± 0.8	<0.30	1.3 ± 0.3
Viral ($n = 31$)	5.0	335 (23 – 1250)	37 (0 – 100)	3.3 ± 0.8	0.10 – 5.50	2.3 ± 0.6
Bacterial ($n = 66$)	1.1	8227 (125 – 50000)	81 (2 – 100)	<1.0 – 3.8	0.15 – >10.0	3.9 – >10.0
Others ($n = 58$)	3.7	572 (100 – 3600)	31 (0 – 100)	3.2 ± 0.7	0.10 – >10.0	2.1 ± 0.7

Conversion: SI to traditional units: Lactate 1 mmol/l $\approx$ 9.0 mg/100 ml, glucose: 1 mmol/l $\approx$ 18 mg/100 ml. Figures in brackets are ranges.

Fig. 1 CSF lactate levels in 205 children. Each dot represents level found in one child.

(90.0 mg/100 ml). Individual levels from the 205 children are shown in Fig. 1.

Two false-negative results were obtained. One was from a child who had meningococcal septicaemia when an initial lumbar puncture showed WBC $0.002 \times 10^9/l$, 1 being a polymorph, RBC $0.014 \times 10^9/l$, and a protein concentration of less than 0.10 g/l; glucose was 4.1 mmol/l (73.8 mg/100 ml), lactate 2.4 mmol/l (21.8 mg/100 ml), and the Gram stain was clear. However a culture grew *Neisseria meningitidis*. Because the child's condition rapidly deteriorated a second lumbar puncture was performed 8 hours later; this showed WBC $8.85 \times 10^9/l$, 98% polymorphs, protein 2.5 g/l, glucose 1.5 mmol/l (27 mg/100 ml), and lactate 10.0 mmol/l (90 mg/100 ml).

The other false-negative result was also from a child with septicaemia, the lactate changing from 2.2 mmol/l (20 mg/100 ml) to 15.4 mmol/l (140 mg/100 ml) in 12 hours.

Thirty-nine per cent of patients in the bacterial group had had treatment with antibiotics.

A breakdown of the various agents responsible for meningitis in the viral and bacterial groups is given in Table 2.

Table 2 Causative agents in groups 2 and 3

	No
Group 2	
Viral meningitis	
Mumps virus	15
Echo 30	6
Coxsackie B4	4
Coxsackie B3	3
Echo 11	2
Coxsackie B2	1
Group 3	
Bacterial meningitis	
<i>Haemophilus influenzae</i>	30
<i>Streptococcus pneumoniae</i>	14
<i>Neisseria meningitidis</i>	13
<i>Escherichia coli</i>	4
Group B streptococci	2
<i>Pseudomonas aeruginosa</i>	1
<i>Klebsiella aerogenes</i>	1
<i>Citrobacter diversus</i>	1

Fig. 2 shows the effect of antibiotics on lactate levels in 7 children with bacterial meningitis. Three had infections due to *Escherichia* sp., one with *H. influenzae*, one with *Pseudomonas aeruginosa*, one with *Citrobacter diversus*, and one with *N. meningitidis* group A. In each case the organism was sensitive to the antibiotic that was given parenterally in appropriate doses.

Fig. 2 Effect of treatment with antibiotics on CSF lactate in 7 children with bacterial meningitis. Levels measured in any one child on different days are shown by same symbol.

Fig. 3 CSF lactate profile in a patient with meningitis due to *Pseudomonas aeruginosa*. Figures in brackets are WBC $\times 10^6$. Dotted line represents upper limit to the normal range.

An individual response of lactate to antibiotic treatment of bacterial meningitis is illustrated in Fig. 3. This patient, a 1-month-old boy (Case 1), was admitted with a history of persistent central nervous system infection due to *P. aeruginosa* that did not respond well to 21 days of parenteral gentamicin treatment. An initial CSF sample on admission showed WBC $4.3 \times 10^9/l$ of which 85% were polymorphs, protein greater than 10 g/l, glucose 2.0 mmol/l (18.0 mg/100 ml), and lactate 7.0 mmol/l (63.6 mg/100 ml). A culture of the CSF subsequently grew *P. aeruginosa*. Treatment with intravenous gentamicin (4 mg twice daily) and carbenicillin (250 mg four times daily) was started on day 1, followed by intraventricular gentamicin (2 mg daily) on day 3 after insertion of a Rickham reservoir.

His clinical condition improved with a rapid fall in leucocytes in his CSF, and the lactate level was 2.0 mmol/l (18.0 mg/100 ml) on day 5 when carbenicillin was stopped because the organism was shown to be resistant to it. Intraventricular gentamicin was also stopped and on day 8 the dose of intravenous gentamicin dose was halved. Later that day he became febrile, a CSF sample on day 10 showed WBC $1.54 \times 10^9/l$ of which 75% were polymorphs, protein greater than 10 g/l, glucose

1.9 mmol/l (34.2 mg/100 ml), and a lactate level of 5.1 mmol/l (46.3 mg/100 ml). A culture of this sample again showed growth of *P. aeruginosa*.

Treatment with gentamicin was continued systemically, intraventricularly, and, finally, intrathecally (after removal of the Rickham reservoir on day 17). There was a progressive clinical improvement with a concomitant fall in the level of CSF lactate.

Discussion

The fact that CSF lactate levels overlap between the normal and viral groups has been observed by others (Table 3). In the present series CSF lactate levels were higher than in viral meningitis in all cases of bacterial meningitis with the exception of two. These 2 false-negatives show that the CSF lactate level is a measure of hypoxic brain damage rather than an indicator of organisms. Theoretically there must be some point at which an organism responsible for the septicaemia crosses the blood brain barrier. While it is present in the CSF of the child with meningitis there would be a time lag before any appreciable central nervous system damage takes place and the lactate level becomes increased. These results show

Table 3 CSF lactate levels taken from other reports

Reference	Date	Controls (mmol/l)	Meningitis		Method
			Viral (mmol/l)	Bacterial (mmol/l)	
18	1925	0.9–1.7 (n=5)	—	1.2–8.5 (n=17)	Colorimetric
19	1933	1.3–1.8	—	3.0–19.6 (n=27)	Colorimetric
20	1964	1.6±0.4 (n=23)	2.0±0.2 (n=5)	6.6–21.5 (n=10)	Enzymatic
21	1970	1.6±0.2 (n=20)	2.3±0.8 (n=17)	6.7±41.8 (n=19)	Colorimetric
22	1972	1.7±0.6 (n=46)	2.1±0.7 (n=35)	7.2±2.1 (n=21)	Enzymatic
23	1974	1.6±0.1 (n=25)	2.2±1 (n=25)	8.3±0.7 (n=15)	Enzymatic
24	1977	1.5±0.7 (n=20)	1.5±0.7 (n=36)	6.0±1.9 (n=16)	Enzymatic
26	1977	0.5–8.4 (n=106)	1.1–5.0 (n=15)	8.0±28.5 (n=8)	GLC
28	1977	1.3±0.6 (n=10)	2.1±0.7 (n=10)	6.4±3.6 (n=22)	Colorimetric
30	1978	1.6±0.8 (n=25)	2.3±1.0 (n=26)	6.5±1.0 (n=4)	GLC
This report		1.3±0.3 (n=50)	2.3±0.6 (n=31)	3.9–>10.0 (n=66)	Enzymatic

that this time lag is less than 8 hours and may in fact only be a matter of minutes.

Thus CSF lactate levels could be used to differentiate bacterial from viral meningitis in most of our cases. Some studies have described such an overlap especially in cases of tuberculous meningitis.^{24 28 32} We had only one child who was clinically diagnosed as having tuberculous meningitis but in whom no organism could be cultured; the CSF lactate was 3.5 mmol/l (31.8 mg/100 ml). Brook *et al.*³⁰ have shown that there is no age or sex difference in CSF lactate levels regardless of the aetiological group.

All CSF measurements (Table 1) were similar for the viral and miscellaneous groups, as would be expected.

The CSF lactate levels in the 7 treated patients with bacterial meningitis (Fig. 2) showed that such children could still be distinguished from children with viral meningitis up to 4 days after starting antibiotics.

The decrease in lactate levels after initiation of antibiotic treatment in the 7 patients agrees with other studies.^{18 19 21 22 24 28} The time for the lactate concentration to reach viral levels in these reports varied from 1 to 5 days. It is evident from our results as well as those from other reports that each child responds in a different manner. Brook *et al.*³⁰ showed that the rate of decrease was dependent on the type of organism, tuberculous meningitis requiring more than 6 weeks before lactate levels reached normal levels. Since lactate is cleared only slowly from the CSF by diffusion into the brain

tissue,^{34 35} the lactate level before starting treatment and the 'aggressiveness' of treatment would be two additional factors.

The lactate profile in Case 1 (Fig. 3) illustrates the potential use of CSF lactate for monitoring the effectiveness of treatment in bacterial meningitis. The initial rapid fall in CSF lactate levels from 7.0 mmol/l (63.6 mg/100 ml) on day 1 to 2.0 mmol/l (18.0 mg/100 ml) on day 5 took place when the leucocyte count was falling, cultures were negative, and there were signs of clinical improvement. Synergism between carbenicillin and gentamicin³⁶ together with combined intravenous and intraventricular gentamicin might have been responsible for this rapid improvement. The fact that carbenicillin was stopped on this day, and the intravenous dose of gentamicin halved on day 8 (at a time when the penetration of gentamicin through the blood brain barrier might have been decreasing³⁷) and the fact that intraventricular gentamicin was given only sporadically would explain the re-isolation of the organism on day 10. The lactate rose to 5.1 mmol/l (46.3 mg/100 ml) during this period demonstrating that the biochemical deterioration was parallel to the clinical condition. Intravenous, intraventricular, and intrathecal treatment with gentamicin was continued and this produced aseptis associated with virtually normal lactate levels.

Despite many suggestions, the cause of the lactic acidosis in bacterial meningitis is still not clear.³⁸ Montani and Perret²⁰ claimed that the CSF lactate level was dependent on two factors—the number of organisms and the number of leucocytes present. The relationship to the number of leucocytes is debatable for a number of reasons. Firstly only a small amount of lactate is produced by endotoxin-stimulated leucocytes,^{38–40} increased CSF lactate occurs in tuberculous meningitis in patients with few bacteria and a mononuclear cellular response,⁴¹ and CSF lactic acidosis can be found in severe cases of acute encephalitis in the presence of a low leucocyte count. Hansen *et al.*⁴² suggested the increase in lactate was due partly to inflamed brain tissue and partly to decerebrate rigidity and convulsions. Simpson *et al.*⁴³ demonstrated moderate increases in CSF lactate in 7 of 22 patients with prolonged seizures (longer than 30 minutes) or recurrent short convulsions.

Kopetzky and Fishberg⁴⁴ suggested that the lactic acidosis in purulent meningitis might be due to a decrease in cerebral blood supply caused by increased intracranial pressure. In fact a moderate increase in intracranial pressure will appreciably reduce cerebral perfusion pressure thereby reducing cerebral blood flow, shifting brain metabolism from aerobic to anaerobic glycolysis, with increased lactate levels in

brain tissue and CSF.⁴⁵⁻⁴⁶ Raisis *et al.*⁴⁷ have demonstrated the dependence of cellular oxidative metabolism on the maintenance of adequate perfusion pressure in hydrocephalus, and Paulson *et al.*⁴⁸ found that cerebral blood flow was decreased by as much as 40% in pyogenic meningitis, while CSF lactate was increased, CSF bicarbonate reduced, and autoregulation often impaired.

CSF hydrogen ion concentration and lactate are concerned in a cycle of pathophysiological mechanisms (Fig. 4) involving vasoparalysis with the loss of vasomotor autoregulation, CO₂ regulation of vasomotor tone, resulting in the spreading of initially localised oedema.⁴⁹ Thus CSF lactic acidosis is dangerous because of its intensification of tissue hypoxia.

It is worth noting that several studies⁵⁰⁻⁵⁴ on conditions other than infection indicate that CSF lactate levels below 3.0 mmol/l (27 mg/100 ml) are neurologically 'safe' while values above 4.0 mmol/l (36 mg/100 ml) are found in life-threatening states in which survival could lead to permanent neurological damage. This suggests the prognostic value of CSF lactate in determining cellular damage, and may prove to correlate with the long-term neurological and psychological deficits observed in children surviving bacterial meningitis.

Seitz and Ocker,⁵⁴ in an attempt to break the vicious circle (Fig. 4) that leads to non-reversible hypoxia in the brain tissue of severely brain-injured patients with CSF lactic acidosis, used a solution of 8.4% sodium bicarbonate administered intrathecally. This treatment resulted in an increase in overall cerebral blood flow of 33%, with 60% of the patients showing an improvement in clinical condition.

Fig. 4 Pathophysiology of CSF lactic acidosis.

The rehabilitation of such patients improved and the mortality rate was reduced.

This study confirms the value of the estimation of CSF lactate as a diagnostic aid in meningitis. It also indicates the potential of lactate as a biochemical measurement for monitoring the efficacy of treatment in bacterial meningitis. With respect to short-term prognosis and the long-term neurological sequelae, the possible use of intrathecal sodium bicarbonate in the treatment of severe brain injury with life-threatening CSF lactic acidosis would seem worthy of investigation in bacterial meningitis.

We thank Dr H Kilham and Dr H Kitson for constructive criticism and Lina Pipitone for secretarial expertise.

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Received 9 June 1980