Medical Journal of the
Islamic Republic of Iran

Volume 17
Number 1
Spring 1382
May 2003

A STUDY COMPARING CEREBROSPINAL FLUID LACTATE LEVELS IN CHILDHOOD CULTURE POSITIVE AND CULTURE NEGATIVE MENINGITIS

M. KEYHANI, M.D., Pharm.D., Ph.D.

From the Dept. of Medical Biochemistry, Iran University of Medical Sciences, Tehran, I.R. Iran,

ABSTRACT

Despite recent innovations in the laboratory diagnosis of bacterial from non-bacterial meningitis, solid data–necessary for early determination of bacterial meningitis (BM) before organism growth in the culture medium–are missing. Therefore cerebrospinal fluid (CSF) lactate levels were evaluated as a possible means of differentiating the two clinical entities. This was a retrospective study. Patients were studied in one year. They were divided into three groups: Group one included 10 patients with culture positive meningitis; Group two included 10 patients with culture negative meningitis compatible with a viral etiology; Group three consisted of 10 febrile children without any biochemical or cytological CSF abnormality as the normal controls.

CSF lactate level determinations were made enzymatically with Boehringer Mannheim reagents in addition to the formal biochemical and cytological investigations, consisting of cell counts and differential plus glucose and protein levels and CSF/blood glucose ratio in all three groups. Group one had a mean CSF lactate level of 12.90 (±3.08) mmol/L, while in groups 2 and 3 the level was 1.89 (± 0.52) mmoL/l and 1.63 (±0.31) mmol/L respectively. Lactate levels were significantly higher in patients from group one with respect to the control group (p= 0.001) whereas there were no significant differences between group 2 and the control group. Regarding temporal profile of CSF markers and considering the rapid rise in CSF lactate levels in bacterial meningitis, its measurement seems appealing to confirm a bacterial etiology instead of awaiting the results of CSF culture.

MJIRI, Vol. 17, No. 1, 29-34, 2003.

Keywords: CSF, Lactate, Bacterial Meningitis, Non-bacterial Meningitis.

INTRODUCTION

Lactate in spinal fluid normally parallels blood levels. In case of biochemical alterations in the central nervous system, however, CSF lactate values change independently of blood values. Increased CSF levels are seen in intracranial hemorrhage, epilepsy, bacterial meningitis, tuberculous meningitis and other CNS disorders, also the presence of white blood cells in CSF may cause an increase in lactate. However, when incubated in CSF, white blood cells produce little lactate. In addition, the increase in CSF lactate observed in whom a paucity of white blood cells is the usual finding, is not explained

Correspondence: M. Keyhani, M.D., Dept .of Biochemistry, Faculty of Medical and Paramedical Sciences, Iran University of Medical Sciences, Tehran, Iran, P.O.BOX: 14155 - 6183 Phone: 021 - 8054357 - 8054353

by the hypothesis. Moreover, the presence of red blood cells in CSF, as occurs in subarachnoid hemorrhage, greatly increases lactate levels in CSF.[1]

Despite recent innovations in laboratory diagnosis of bacterial from non-bacterial meningitis, solid data necessary for early determination of bacterial meningitis (BM) before organism growth in the culture medium are missing. Therefore cerebrospinal fluid (CSF) lactate levels were evaluated as a possible means of differentiating the two clinical entities.

Physicians may not always be able to differentiate bacterial from non-bacterial meningitis (NBM) on clinical grounds. Even when the total and differential CSF leukocyte counts and bacterial Gram staining are performed it may still be impossible to differentiate between bacterial and non bacterial meningitis. For example there are cases where the patient has partially treated meningitis, resulting in negative Gram stain and culture results. Furthermore, the total CSF leukocyte count may be low during the early phase of bacterial meningitis. On the other hand, the CSF may show a predominance of polymorphonuclear leukocytes in the early stage of non-bacterial meningitis. Therefore these tests have their limitations.[2]

Biochemical measurements of CSF protein and glucose as well as the CSF/blood glucose ratio can be used to distinguish bacterial from non-bacterial meningitis.[3] However, these chemical tests are not truly specific for bacterial meningitis. A reduction in CSF glucose and the CSF/blood glucose ratio or an increase in CSF protein concentration may occur in conditions other than bacterial meningitis. Biochemical measurements can not be used when bacterial meningitis has been partially treated. Although the combined findings from CSF cytology, culture, glucose and protein determination are often sufficient to establish or refute a diagnosis of bacterial meningitis, several other adjuvant biochemical markers have been investigated; the best studied of these is lactate.[4]

CSF lactate determination has been accepted as a means of differentiating between bacterial and non-bacterial meningitis. Therefore we compared the reliability of CSF lactate with the total and differential CSF leukocyte counts, bacterial Gram stain, culture, protein and glucose levels, and the CSF/blood glucose ratio in differentiating bacterial from non-bacterial meningitis.

MATERIAL AND METHODS

In a retrospective study 30 patients were chosen from the children admitted to University hospitals in Tehran, Iran from July 1999 to June 2000. The children were between 1-13 years of age. Those children that were with a suspected infection of the central nervous system (CNS) were enrolled in this study. The children were divided in to 3 groups: Group one included 10 children that had bacterial meningitis (BM) verified by positive Gram staining and positive cultures. Group two included 10 children with non-bacterial meningitis verified by negative bacterial cultures compatible with a viral etiology and group three consisted of 10 febrile children without any biochemical and cytological CSF abnormality as normal controls. CSF samples were collected immediately after admission via lumbar puncture (LP).

Gram staining for bacteria, bacterial cultures, total and differential leukocyte counts as well as CSF protein and glucose determinations were performed using standard laboratory techniques.

Glucose was measured by an enzymatic method (glucose oxidase) within 30 min of sample collection.[2]

The CSF protein was measured according to the turbidimetric method of Kingsbury.[5]

Lactate determinations were made enzymatically with reagents obtained from Boehringer Mannheim AG, Germany, according to the method of Noll.[6]

The lowest detectable lactate, glucose and protein concentrations were 1.2 mmol/L, 8mg/dL and 5mg/dL respectively. The upper limits of the health reference intervals for CSF were taken as 3 mmol/L for lactate, 40 mg/dL for glucose and 50mg/dL for protein.

Statistical methods

Statistical analysis was performed using Student's t-test. Whenever the levels of glucose or protein were not detectable the concentration was regarded as zero in statistical analysis.[4]

RESULTS

The results of the different chemical tests on CSF from the 3 study groups are illustrated in Table I. The results obtained from patients with bacterial meningitis (before antibiotic treatment) are shown, as well as the results from patients with non-bacterial meningitis (NBM) and from the control group. The discrimination limits were: glucose < 40mg/dL; CSF/blood glucose ratio < 0.3; protein > 50mg/dL; lactate >3 mmol/L.

The sensitivity, specificity and efficiency of all 8 tests were calculated. For the first lumbar puncture (LP), the values are presented in Table II.

On admission CSF lactate determination was the most sensitive and also the most efficient test, i.e. the single test, the value of the tests was hampered by their low sensitivity.

All patients with bacterial meningitis had a mean CSF lactate level over 12.90 mmol/L. Patients with non-bacterial meningitis had a mean CSF lactate level over 1.89 mmol/L. The control group had a mean CSF lactate level over 1.63 mmol/L.

Table I: The results of chemical tests on CSF in patients with bacterial (before antibiotic treatment) and non-bacterial meningitis and in controls.

Variable	Groups	No. of cases	Mean ± SD	Results of t-test BM and NBM	Range
WBC	BM	10	11155 ± 10216	$p < 0.005$	450-31000
	NBM	10	304 ± 296	t= 3.2	50-970
	Control	10	1.3 ± 1.1		0-3
%PMNs	BM	10	96.5 ± 1.35	$p < 0.005$	95-98
	NBM	10	41.5 ± 38.2	t= 4.2	2-90
	Control	10	1.3 ± 1.1		—
Concentration of glucose (mg/dL)	BM	10	30 ± 20.7	$p < 0.005$	10 - 78
	NBM	10	48.3 ± 18.5	t=2.17	8 - 77
	Control	10	59.4 ± 21		28 - 90
CSF/ blood glucose ratio	BM	10	0.27 ± 0.19	$p<0.005$	0.1 - 0.68
	NBM	10	0.54 ± 0.14	t= 3.33	0.19 - 0.77
	Control	10	0.68 ± 0.27		0.28 - 1.04
Concentration of protein (mg/dL)	BM	10	110.6 ± 71.7	$p<0.005$	31 - 225
	NBM	10	29.2 ± 22.2	t=3.02	10 - 80
	Control	10	7.7 ± 1.9		5 - 11
Concentration of lactate (mmol/L)	BM	10	12.90 ± 3.08	$p=0.001$	4.8 - 16
	NBM	10	1.89 ± 0.52	t= 10.1	1.2 - 2.9
	Control	10	1.63 ± 0.31		1.2 - 2.1

Table II: The sensitivity, specificity, predictive values, efficiency of CSF findings in differentiating 10 cases of bacterial meningitis and 10 cases of non- bacterial meningitis.

Variable	Limit	Sensitivity No. (%)	Specificity No. (%)	Predictive value Positive test No. (%)	Predictive value Negative test No. (%)	Efficiency No. (%)
WBC Count	>500 µL	9/10 (90)	8/10 (80)	9/11 (81.8)	8/9 (88.8)	17/20 (85)
PMN	>60%	10/10 (100)	6/10 (60)	10/14 (71.4)	6/6(100)	16/20 (80)
Concentration of :						
Glucose	<40 mg/dL	7/10 (70)	8/10 (80)	7/9 (77.7)	8/11 (72.7)	15/20 (75)
CSF/Blood glucose	<0.3	7/10 (70)	9/10 (90)	7/8 (87.5)	9/12 (75)	16/20 (80)
Protein	>50 mg/dL	7/10 (70)	8/10 (80)	7/9 (77.7)	8/11(72.7)	15/20 (75)
Lactate	>3 mmol/L	10/10 (100)	10/10 (100)	10/10 (100)	10/10(100)	20/20 (100)
Result of culture	+ or -	6/10 (60)	10/10 (100)	6/6 (100)	10/14(71.4)	16/20 (80)
Result of Gram stain	+ or -	7/10 (70)	10/10 (100)	7/7 (100)	10/13 (76.9)	17/20 (85)

Lactate levels were significantly higher in patients from group one with respect to the control group (p= 0.001); whereas the levels in non-bacterial meningitis did not show a significant difference from the control group. Bacterial Gram staining, culture and lactate determination all had 100% specificity and predictive value of positive tests in differentiating between bacterial and non-bacterial meningitis, although the sensitivity was rather low (Table II). On the other hand, the CSF lactate concentration proved to be both sensitive and specific in this differentiation.

Patient characteristics and the results of chemical tests on CSF in controls, NBM, and BM groups are illustrated in Tables III, IV, and V.

DISCUSSION

The lactate within cerebrospinal fluid in bacterial meningitis (BM) originates from different sources. The main source of lactate in BM is brain tissue, including

Table III: Patient characteristics and the results of chemical tests on CSF in the control group.

No.	Age (y)	Sex	WBC (µL)	PNMs %	Concentration of (glucose) and (protein) (mg/dL)		Concentration of lactate (mmol/L)	CSF/blood glucose ratio	Gram stain	Culture
1	6	M	2	-	(77)	(6)	1.7	1	-	-
2	2	M	-	-	(58)	(8)	1.6	0.63	-	-
3	10	F	1	-	(50)	(7)	1.6	0.69	-	-
4	3	F	-	-	(57)	(9)	1.6	0.55	-	-
5	9	F	-	-	(90)	(10)	1.4	0.77	-	-
6	1	M	3	-	(28)	(6)	1.7	0.28	-	-
7	1	M	2	-	(85)	(11)	1.2	1.04	-	-
8	7	F	-	-	(60)	(9)	2.1	0.74	-	-
9	2	M	-	-	(64)	(6)	2.2	0.57	-	-
10	2	M	2	-	(61)	(5)	1.2	0.82	-	-
Mean ±SD	4.3±3.2	-	2±0.63	2±0.63	63±17.8	7.7±1.9	1.63±0.31	0.71±0.21	-	-

Table IV: Patient characteristics and the results of chemical tests on CSF in non-bacterial meningitis (NBM).

No.	Age (y)	Sex	WBC (µL)	PNMs %	Concentration of (glucose) and (protein) (mg/dL)		Concentration of lactate (mmol/L)	CSF/blood glucose ratio	Gram stain	Culture
1	6	M	370	90	(50)	(10)	1.6	0.65	N	N
2	11	M	120	20	(8)	(40)	1.9	0.19	N	N
3	3	F	50	80	(38)	(21)	2.6	0.5	N	N
4	11	F	270	80	(40)	(15)	2.2	0.59	N	N
5	4	F	140	90	(77)	(16)	1.2	0.77	N	N
6	7	M	280	10	(50)	(14)	1.8	0.47	N	N
7	6	M	650	2	(56)	(20)	1.6	0.57	N	N
8	7	F	970	25	(68)	(60)	1.9	0.66	N	N
9	5	M	110	3	(46)	(80)	1.2	0.48	N	N
10	9	M	170	15	(50)	(16)	2.9	0.54	N	N
Mean ±SD	6.9±2.6	-	304±296	41.5±38.2	48.3±18.51	29.1±22.24	1.89±0.52	0.54±0.14	N	N

neurons and glial cells, which produce lactate by distinct mechanisms.[7] Bacterial pathogens also produce varying amounts of lactate, accounting for approximately 10% of the total CSF lactate in patients with BM.[3]

Acute meningitis is a medical emergency that requires the utmost in diagnostic and therapeutic skills.[8] The death rate is about 30 percent. To lower the mortality rate further will require earlier recognition of meningitis, more rapid determination of the most likely etiologic agent and initiation of appropriate anti-microbial therapy.[9] Culture remains the gold standard of diagnosis for specific causes of acute meningitis;[10] however it has potential drawbacks.

These include:

1- A latent period of 1-2 days for the growth of bacterial colonies.[2]

Table V: Characteristics of patients and the results of chemical tests on CSF in bacterial meningitis (BM).

No.	Age (y)	Sex	WBC (µL)	PNMs %	Concentration of (glucose) and (protein) (mg/dL)		Concentration of lactate (mmol\L)	CSF/blood glucose ratio	Gram stain	Culture
1	2	F	4600	97	(22)	(137)	15.2	0.2	Dip(-)*	N.M.**
2	1	F	11000	97	(10)	(31)	11.2	0.1	Dip(-)*	N.M.
3	6	M	6500	95	(16)	(225)	14.4	0.13	Dip(+)***	N°
4	6	M	450	98	(78)	(35)	4.8	0.68	N°	N°
5	13	M	31000	95	(15)	(64)	12.3	0.1	N°	N°
6	10	M	28000	98	(49)	(208)	14	0.4	Dip(-)*	Pne ⊤
7	3	M	5000	98	(25)	(147)	12.1	0.3	N°	N°
8	5	F	6000	95	(18)	(145)	15.6	0.14	Dip(-)*	N.M.
9	4	F	12000	97	(50)	(74)	13.4	0.15	St	Stβ ⊤
10	7	M	7000	95	(17)	(40)	16	0.58	B(-)Δ	Ent ◊
Mean ±SD	5.65±3.46	-	11155±10216	96.5±1.35	30±20.7	110.6±71.7	12.90±3.08	0.27±0.19	-	-

*= Gram-negative diplococci
**= *Neisseria meningitides*
***= Gram-positive diplococci
° = Negative
⊤ = Pneumonia
⊤ = β-hemolytic streptococci
◊ = *Enterobacteriacae*
Δ = Gram-negative bacilli

2- Partially treated meningitis patients usually yield negative culture results.[8]

3- Iatrogenic contamination could yield false positive results.

4-Different species require different culture media and incubators, otherwise yielding false negative results. Lactate levels in CSF cannot differentiate the organisms; however, it can ascertain a bacterial etiology rapidly and equally for various bacteria even if the patient has received antibacterial treatment.[11]

5- CSF pleocytosis is another useful indicator for pyogenic meningitis, but it may show an aseptic pattern in the early stage[12] and vice versa, this can lead to an erroneous assumption of the etiology and consequently a delay in empirical therapy in up to 30% of patients, while CSF lactate levels rise very rapidly, because of early employment of the glycolytic pathway by the offending organism's non-oxidative metabolic route.

CSF glucose and protein levels have been described as an adjunct to diagnosis.[11] Although CSF glucose levels decline rapidly in bacterial meningitis, however the net level is a function of blood sugar which may play a role as a confounding factor and at least 4 hours is required for an equilibrium to be achieved. On top of that in some viral meningitides such as mumps and herpes simplex, the CSF glucose levels may be lower than expected.

In summary, this study showed that if the CSF lactate level is low, the meningitis has a non-bacterial origin; however, if the CSF lactate level is elevated, the meningitis is bacterial in origin. It can also be used in the detection of partially treated bacterial meningitis.

REFERENCES

1. Sacks DB: Carbohydrates. In: Burits CA, Ashwood ER, (eds), Tietz Textbook of Clinical Chemistry. 3rd ed, Philadelphia: W.B. Saunders Company, pp. 787-8, 1999.
2- Bailey EM, Domenico P, Cunha BA: Bacterial or viral meningitis? Measuring lactate in CSF can help you know quickly. Postgrad Med 88: 217-9, 223, 1990.
3- Salord F, Boussaid O, Eynard N, Perret C, Grando J, Chacornac R: Value of D(-) lactate determination for the fast diagnosis of meningitis after craniotomy: an initial study. Ann Fr Anesth Reanim 13: 647-53, 1994.
4- Smith CP, Kyeldsberg CR: Cerebrospinal, synovial and serous body fluids. In: Henry JB,(ed), Clinical Diagnosis and Management by Laboratory Methods. 19th ed., Phila-

delphia: W.B. Saunders Company, pp. 457-67, 1996..

5- Vanprapar N, Chavalittamrong B, Limsathayurat N: Cerebrospinal fluid lactate level in childhood purulent meningitis. Southeast Asian J Trop Med Pub Hlth 14(2): 186-90, 1983.

6- Noll F: Determination with LDH, GPT and NAD. In: Bergmeyer HU, (ed.), Methods of Enzymatic Analysis. 2nd ed., NewYork: Academic Press Inc, pp. 1474-7, 1974.

7- Tureen J: Effect of recombinant human tumour necrosis factor-a on cerebral oxygen uptake, cerebrospinal fluid lactate, and cerebral blood flow in the rabbit: role of nitric oxide. J Clin Invest 95: 1086-91, 1995.

8- Viallon A, Zeni F, Lambert C, Pozzetto B, Tardy B, Venet C, Bertrand JC: High sensitivity and specificity of serum procalcitonin levels in adults with bacterial meningitis. Clin Infec Dis 28(6): 1313-6, 1999.

9- Leib SL, Boscacci R, Gratzl O, Zimmerli W: Predictive value of cerebrospinal fluid (CSF) lactate level versus CSF/blood glucose ratio for the diagnosis of bacterial meningitis following neurosurgery. Clin Infec Dis 29: 69-74, 1999.

10- Carrol ED, Thomson AP, Shears P, Gray SJ, Kaczmarski EB, Hart CA: Performance characteristics of the polymerase chain reaction assay to confirm clinical meningococcal disease. Arch Dis Child Sep; 83(3): 271-3, 2000.

11- Watson MA, Scott MG: Clinical utility of biochemical analysis of cerebrospinal fluid. Clin Chem 41(3): 343-60, 1995.

12- Negrini B, Kelleher KJ, Wald ER: Cerebrospinal fluid findings in aseptic versus bacterial meningitis. Pediatrics 105(2): 316-9, 2000.