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Diagnostic value of cerebrospinal fluid lactate as a biomarker of bacterial meningitis

Valor diagnóstico del lactato en líquido cefalorraquídeo como biomarcador de meningitis bacteriana

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Abstract

Bacterial meningitis is a serious pathology that requires an accurate and early diagnosis. Increased leukocytes, with a predominance of polymorphonuclear cells, increased proteins, and hypoglycorrhachia are indicative of a bacterial etiology, although they do not always correlate with a definitive diagnosis. The aim of this study was to evaluate the usefulness of cerebrospinal fluid lactate as a biomarker of bacterial meningitis.

This is an observational and prospective study in which 706 cerebrospinal fluids from patients treated at the Virgen de Valme University Hospital (Seville, Spain) for 20 months were analyzed. Of the fluid analyzed, in 21 cases bacterial meningitis was diagnosed, in 31 cases bacterial meningitis was compatible, and in 654 cases bacterial meningitis was ruled out. The optimal cut-off point for lactate in cerebrospinal fluid was 3.0 mmol/L, with a sensitivity of 68%, a specificity of 98%, a positive predictive value of 79%, and a negative predictive value of 97%.

Lactate concentration, protein concentration, and the number of leukocytes in cerebrospinal fluid were significantly higher in patients with confirmed bacterial meningitis. The high negative predictive value of lactate is especially useful to rule out bacterial meningitis in sick patients. Lactate is the biomarker with the best diagnostic performance of all those analyzed, so we recommend its inclusion in the cerebrospinal fluid biochemical profile.

Keywords: bacterial meningitis; cerebrospinal fluid; lactate.

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Resumen

La meningitis bacteriana es una patología grave que requiere de un diagnóstico preciso y precoz. El aumento de leucocitos, con predominio de polimorfonucleares, la proteinorraquia y la hipoglucorraquia orientan hacía una etiología bacteriana, aunque no siempre se correlacionan con el diagnóstico definitivo. El objetivo de este estudio fue evaluar la utilidad del lactato en líquido cefalorraquídeo como biomarcador de meningitis bacteriana.

Este es un estudio observacional y prospectivo en el que se analizaron 706 líquidos cefalorraquídeos de pacientes atendidos en el hospital universitario Virgen de Valme (Sevilla, España) durante 20 meses. De los líquidos analizados, en 21 casos se diagnosticó meningitis bacteriana, en 31 la meningitis bacteriana fue compatible y en 654 casos se descartó esta infección. El punto de corte óptimo del lactato en líquido cefalorraquídeo fue de 3,0 mmol/L, con una sensibilidad de 68%, una especificidad de 98%, un valor predictivo positivo de 79% y un valor predictivo negativo de 97%.

La concentración de lactato, la concentración de proteínas y el número de leucocitos en líquido cefalorraquídeo fue significativamente mayor en los pacientes con meningitis bacteriana confirmada. El alto valor predictivo negativo del lactato es especialmente útil para descartar meningitis bacteriana en pacientes enfermos. El lactato es el biomarcador con mejor rendimiento diagnóstico de todos los analizados, por lo que recomendamos su inclusión en el perfil bioquímico del líquido cefalorraquídeo.

Palabras clave: meningitis bacteriana; líquido cefalorraquídeo; lactato.

INTRODUCTION

Bacterial meningitis (BM) is a severe infectious disease. It is considered a medical emergency due to its high morbidity and mortality. Therefore, patient survival increases with a quick diagnosis and early treatment. The classic clinical presentation appears in less than half of BM cases and it is characterized by fever, altered mental status, and stiff neck. For this reason, the analysis of cerebrospinal fluid (CSF) is considered key to its diagnosis, being the typical finding an intense pleocytosis, with a predominance of polymorphonuclear cells (PMN), proteinorrachia, and hypoglycorrhachia. However, in the first hours of evolution, the results of CSF determinations may be similar in BM and viral meningitis (Huy, *et al.*, 2010; Sakushima, *et al.*, 2011).

Lactate is considered an interesting biomarker in the diagnosis of BM because its CSF concentration depends on brain production through anaerobic glycolysis, and it is independent of its serum concentration. Besides, lactate is a biomarker of tissue hypoperfusion, so in cases in which cerebral blood flow is not altered, the increase in CSF lactate is due to anaerobic bacterial metabolism (Sakushima, *et al.*, 2011).

The aim of the study was to evaluate the utility of lactate as a biomarker in CSF and to establish a cutoff point lactate that allows differentiating between BM and aseptic meningitis.

MATERIALS AND METHODS

Patients

An observational and prospective study in which 706 CSF of patients treated at Virgen de Valme University Hospital (Seville, Spain) for 20 months (between July 2018 and March 2020) were analyzed. This study met the ethical recommendations of the Declaration of Helsinki (World Medical Association, 2013) and it was approved by the Sevilla sur research ethics committee (Valme University Hospital). Patients of any age and sex with a CSF sample were included. All participants signed an informed consent form.

Selected Parameters

Cytological study: cellular and differential count was performed by microscopic techniques in the Fuchs-Rosenthal counting chamber.

Biochemical study: glucose, protein, and lactate determinations were carried out on the Cobas 8000 analyzer (Roche Diagnostics).

Microbiological study: gram stain, bacterial culture, and molecular techniques.

Statistical Analysis

The data obtained were statistically analyzed in the MedCalc v.18.9 software (MedCalcSofware, Ostend, Belgium). The groups of confirmed BM and compatible BM were considered as a single group. The samples were classified into two groups (BM and BM discarded), determining the optimal cut-off point, area under the curve (AUC), sensitivity, specificity, predictive values, and likelihood ratios using the receiver operating characteristics (ROC) curve.

RESULTS

Seven hundred and six CSF samples from patients (58% males, 42% females) aged between 1 day and 92 years (median = 46 years) were studied.

Of the CSF analyzed, 21 patients had confirmed BM (3%), 31 compatible BM (4.4%), and 654 discarded BM (92.6%). The group with confirmed BM had a mean lactate value of

11.4 mmol/L, 5,893 leukocytes/mm^3, and 479 g/L of proteins. The group with compatible BM had a mean lactate value of 3.4 mmol/L, 239 leukocytes/mm^3, and 114 g/L of proteins. The group with discarded BM had a mean lactate value of 2.1 mmol/L, 33 leukocytes/mm^3, and 54 g/L of proteins.

The optimal CSF lactate cut-off point for the diagnosis of BM obtained by analyzing the ROC curve was 3.0 mmol/L with an AUC of 0.78 (95% CI 0.75 - 0.81). Sensitivity was 68%, specificity 98%, positive predictive value 79%, negative predictive value 97%, positive likelihood ratio 34, and negative likelihood ratio 0.33.

In 46 of the 706 CSF studied, the lactate concentration was ≥ 3.0 mmol/L. Of these, 33 had more than 5 leukocytes/mm^3, with a predominance of PMN, and a protein concentration greater than 45 g/L; in 21 of these 33 patients, bacteria were isolated in CSF, so they were diagnosed with BM (Table 1). In the remaining 13 CSF, the lactate concentration was also ≥ 3.0 mmol/L, but the leukocytes count was normal, the predominance was mononuclear leukocytes, or the protein concentration was less than 45 g/L; in none of these cases bacteria were isolated in CSF, so the diagnosis of BM was ruled out.

Table 1.
Analytical results of cerebrospinal fluids with suspected bacterial meningitis.

Patient	Lactate (mmol/L)	Leukocytes (/mm^3)	PMN (%)	MN (%)	Proteins (g/L)	GLU_{CSF}/GLU_{Serum}	Microbial isolation
1	26.4	4,689	93	7	1,015	ND	*S. pneumoniae*
2	21.0	1,086	94	6	1,167	ND	*S. aureus*
3	19.6	5,781	99	1	827	ND	*S. pneumoniae*
4	13.7	12,363	98	2	671	ND	*N. meningitidis*
5	13.1	159	72	28	398	0.01	*N. meningitidis*
6	12.7	1,575	94	6	347	ND	*S. pneumoniae*
7	12.3	6,847	94	6	516	0.16	*S. agalactiae*
8	12.2	14,358	99	1	660	ND	*S. pneumoniae*
9	12.1	39,550	77	23	207	ND	*N. meningitidis*
10	12.1	2,967	99	1	1,175	0.08	*S. pneumoniae*
11	11.4	2,513	83	17	176	0.1	*S. pneumoniae*
12	11.2	6,125	98	2	153	0.28	*S. agalactiae*
13	9.1	501	79	21	366	0.09	*L. monocytogenes*
14	8.9	102	60	40	171	0.12	*S. pneumoniae*
15	8.8	3,234	75	25	273	0.34	*S. pneumoniae*
16	7.3	11,886	95	5	266	0.05	*E. coli*
17	6.8	1,267	78	22	255	0.33	*S. pneumoniae*
18	6.1	433	68	32	389	0.18	*S. aureus*

Patient	Lactate (mmol/L)	Leukocytes (/mm³)	PMN (%)	MN (%)	Proteins (g/L)	GLU_{CSF}/GLU_{Serum}	Microbial isolation
19	5.7	209	51	49	158	0.4	*N. meningitidis*
20	3.7	299	95	5	73	0.35	*N. meningitidis*
21	3.4	6,660	97	3	250	ND	*S. pneumoniae*
22	7.9	155	70	30	348	0.85	-
23	6.7	2,579	85	15	436	0.21	-
24	6.4	44	60	40	87	0.51	-
25	6.0	1,513	93	7	103	0.60	Enterovirus
26	5.3	6	51	49	62	0.78	-
27	5.2	1,037	82	18	61	0.45	-
28	5.0	188	86	14	179	0.58	-
29	4.9	8	75	25	83	0.50	-
30	4.1	464	60	40	69	0.43	-
31	3.9	26	77	23	77	0.62	-
32	3.3	250	92	8	399	0.34	Enterovirus
33	3.1	37	89	11	47	0.55	-

PM: polymorphonuclear cells; MN: mononuclear cells; GLU: glucose; ND: not detected.

DISCUSSION

The results obtained confirm the diagnostic value of lactate in CSF as a biomarker of BM. These findings agree with previous studies that found CSF lactate levels higher in patients with BM than in patients with viral meningitis (Buch, *et al*. 2018; Huy, *et al.*, 2010; Sakushima, *et al.*, 2011). Unlike other studies (Buch, *et al*. 2018), our study includes cases of bacterial meningitis, viral meningitis, and non-infectious meningitis, both in adults and in the pediatric population.

However, lactate is a biomarker of tissue hypoperfusion that also increases in patients with hypoxia and cerebral ischemia. This explains that ten of the patients included in this study had elevated CSF lactate concentrations, but they did not present meningeal symptoms, and they were finally diagnosed with ischemic stroke or seizure status (Sanei, *et al.*, 2017; Buch, *et al.*, 2018). Due to this, the positive predictive value of lactate is 79%. The high negative predictive value (97%) is especially useful for ruling out BM in sick patients.

Treatment of patients with antibiotics before performing the lumbar puncture may explain why the sensitivity is only 68%; in these cases, a normal CSF lactate concentration does not rule out BM (Sanei, *et al.*, 2017). Based on the positive likelihood ratio, a CSF

lactate concentration greater than 3.0 mmol/L is 34 times more likely to be found in a patient with BM than in one without such pathology.

The predominance of PMN leukocytes rises as a result of inflammatory cytokines released during meningitis and it is, therefore, a good diagnostic indicator of BM; although it can occur in the early stages of viral meningitis caused by Enterovirus (Hussein, *et al*., 2017). Glycorrhachia has a lower sensitivity than lactate since its concentration in CSF is influenced by the concentration of plasma glucose. Finally, proteinorrachy is the most nonspecific parameter, since it can be modified by a traumatic puncture (Jiménez, *et al*., 2011).

In conclusion, CSF lactate determination can be considered a highly useful biomarker in the diagnosis of BM, complementing classic laboratory measurements. CSF lactate can be determined easily and quickly on automated analyzers. The results of this study indicate that lactate is the biomarker with the best diagnostic performance of all those analyzed, and, for this reason, its inclusion in the biochemical profile of the CSF is recommended.

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