The cerebrospinal fluid lactate is decreased in early stages of multiple sclerosis

MARÍA ASSUMPTA FONALLEDAS PERELLÓ, MD*; JOSÉ VALERO POLITI, MD†;
MARÍA ANTÓNIA LIZARRAGA DALLO, MD*; RAMÓN SEGURA CARDONA, MD*

Background: **The purpose of this study was to investigate if the concentration of lactate can provide additional information for pathologies that need examination of the cerebrospinal fluid (CSF) in their diagnostic controls or protocols.**

Methods: **A prospective study carried out in the year 2001 at the University Hospital of Bellvitge (Barcelona), on 92 samples of CSF from patients who needed this examination. The concentration of lactate, glucose, and the cell count was determined. One year later, the diagnosis revealed from the previous analyzed samples were sorted into groups according to the diagnosis.**

Results: **In the group with multiple sclerosis (MS) (n=30), there was a significant decrease in lactate concentration (1.52 ± 0.19 mmol/L) compared to the control group (1.89 ± 0.11 mmol/L) (p<0.001). The glucose concentration remained within the normal range and the cell count was < 4 cell/µL even in the relapses.**

Conclusions**: In the early stages of MS, the lactate concentration in CSF is decreased and this could be related to alterations in sensitivity observed in those patients. Further studies are needed to evaluate if this lactate concentration is a prognostic indicator of the disease.**

Key words: Cerebrospinal fluid; Lactate; Multiple Sclerosis.

In recent years, knowledge of lactic acid physiopathology has increased its usefulness as a biological indicator outside the limits of anaerobic metabolism. The ionization potential (pK) of lactic acid at 37ºC (3.87) (1), assures the dissociation to the anion lactate in the cerebrospinal fluid (CSF) within its physiological pH levels (7.35-7.40). Lactate is a more reliable indicator in CSF than in blood, owing to less variation in cerebral pH.

In some infectious processes, such as meningitis, the determination of CSF lactate has been used to establish the differential diagnosis between a viral or a bacterial aetiology (2) but, as far as we know, there is not much information about these questions, and therefore, the use of lactate as a biological indicator, is still practically unknown.

The objective of this study is to determine if the concentration of lactate can provide additional information in those pathologies that need examination of CSF in their diagnostic protocols or controls**.**

*Departament de Ciències Fisiològiques II. Facultat de Medicina. Universitat de Barcelona. L'Hospitalet de Llobregat. Barcelona, †Laboratori Clínic. Hospital Universitari de Bellvitge. L'Hospitalet de Llobregat. Barcelona.

Address correspondence to: M. Assumpta Fonalledas, MD, Departament Ciències Fisiològiques II. Facultat de Medicina.Campus de Bellvitge. Universitat de Barcelona. 08907 L'Hospitalet de Llobregat. Barcelona.Spain, Tel: 034934024517, FAX: 034934024268, E-mail: afonalledas@hotmail.com

Materials and Methods

The prospective study was carried out for 4 months in 2001. The samples of CSF were from 92 patients from the clinical laboratory at the University Hospital of Bellvitge (Barcelona).

One hour after collecting the samples obtained by lumbar puncture, the glucose values were determined using the glucose-oxidase method (Roche Diagnostics / Hitachi 911, Mannheim, Germany) and the cell count was obtained in a Fuchs-Rosenthal chamber. The samples were then centrifuged and stored at -80ºC to prevent degradation of the lactate (3).

The lactate concentration was determined in an YSI 1500 analyser (YSI Inc., EUA) by an enzymatic method that uses lactate-oxidase to transform the lactate into hydrogen peroxide, which in turn is oxidised on a platinum anode that produces electrons until it reaches equilibrium.

Two of the samples were discarded due to haematic contamination.

A year later, the clinical histories were consulted and the 90 diagnoses were checked. The cases were grouped according to generic diagnosis that included a minimum of 5 samples (Table 1).

The control group (C) consisted of 8 samples of CSF corresponding to 8 patients that showed normality in the

analysis and a slight clinical diagnosis**.** The clinical diagnoses were: *Slight cognitive deterioration; slight traffic accident control; cortical dysfunction; subacute dementia; radiculopathy L5-S1; discopathy L4-L5; psychotic disorder and migraine*. Prior to the group distribution, 5 samples with an associated diagnosis that could mask results were excluded

Statistical analysis: The differences between groups were analysed using the Mann-Whitney U test and in all the contrasts, statistical significance was established as $p<0.05$. The data obtained was analysed using the statistical program "SPSS for Windows", version 14.0

Results

The data from the 85 CSF samples finally included in the study are shown in Tables 1 and 2.

A) All groups (Table 1)

In the multiple sclerosis (MS) group, statistically significant differences were observed with respect to group C for lactate concentration values of 19.6 % lower ($p<0.001$), and for glucose concentration values of 15.6 % lower ($p=0.003$). For cell counts, higher values were observed ($p<0.01$).

In the demyelinating diseases group other than MS (DM), statistically significant differences were observed with respect to group C for lactate concentration values of 20.6% lower ($p<0.01$).

In the subacute inflammatory diseases (SI) group, no statistically significant differences were observed with respect to group C.

In the acute infections (AI) group, statistically significant differences were observed with respect to group C for lactate concentration values of 33.3% higher ($p<0.05$), and for glucose concentration values of 48.1% lower ($p<0.01$).

In the neoformations (NEO)group, statistically significant differences were observed with respect to group C for lactate concentration values of 121% higher ($p<0.01$).

B) MS groups (Table 2)

In the relapsing remitting multiple sclerosis (RRMS) subgroup, statistically significant differences were observed with respect to the primary progressive multiple sclerosis (PPMS) subgroup for lactate concentration values of 11.1% lower ($p<0.05$).

In the clinically isolated syndrome (CIS) subgroup, statistically significant differences were observed with respect to the PPMS subgroup, for lactate concentration values of 11.6 % lower ($p<0.05$).

Discussion

In the present study, we observed that a substantial percentage of the samples had a diagnosis of demyelinating diseases, especially MS, as their diagnostic protocol included the presence of oligoclonal bands of Ig G and/or the index of Ig G in CSF (4).

In the MS group, 93% of the CSF samples collected in clinical early stages to analyse and establish the definite diagnosis show a significantly reduced lactate concentration (1.52 ± 0.19 mmol/L) as compared to group C (1.89 ± 0.11 mmol/L). The values in group C are comparable with the normal values obtained in other similar studies (2). Within the MS group, the decrease in lactate

Table 1. Clinical and CSF data in patients with various diseases.

Groups	Diagnoses	Nº. of cases	Sex (M/F)	Age years Range	Lactate mmol/L (M±SD)	Glucose mmol/L (M±SD)	Cells no/μL Range
C	Controls	8	5/3	23-75	1.89 ± 0.11	3.78 ± 0.50	0-3
MS	Multiple sclerosis	30	10/20	21-72	1.52 ± 0.19	3.19 ± 0.38	0-4
DM	Demyelinating diseases	5	4/1	31-70	1.50 ± 0.10	3.18 ± 0.59	0-4
SI	Subacute inflammations	6	4/2	31-68	1.87 ± 0.27	3.43 ± 0.54	0-20
AI	Acute infections	5	3/2	20-66	2.52 ± 0.48	1.96 ± 1.03	35-850
NEO	Neoformations	8	7/1	22-68	4.18 ± 2.06	3.17 ± 2.02	0-250
OD	Other diseases	23	11/12	21-79	1.59 ± 0.76	3.59 ± 2.01	0-7

M ± SD: Mean ± Standard Deviation

Mann-Whitney test:
Comparison C vs MS: $p<0.001$ and $p=0.003$ for lactate and glucose concentration.
Comparison C vs DM: $p<0.01$ for lactate concentration.
Comparison C vs AI: $p<0.05$, $p<0.01$ and $p<0.01$ for lactate and glucose concentration, and cell count.
Comparison C vs NEO: $p<0.01$ for lactate concentration.
The other comparisons are not significants.

Table 2. Values of parameters in the CSF of patients with multiple sclerosis.

Subgroups MS	Clinical forms	Nº. of cases	Lactate mmol/L (M ± SD)	Glucose mmol/L (M ± SD)	Cells n.º/µL Range
CIS	Clinically isolated syndrome	7	1.44 ± 0.23	3.09 ± 0.29	0-4
RRMS	Relapsing-remitting	20	1.53 ± 0.17	3.17 ± 0.38	0-4
PPMS	Primary progressive	3	1.71 ± 0.06	3.57 ± 0.46	0-1

M ± SD: Mean ± Standard Deviation.

Mann-Whitney test:
Comparison CIS vs PPMS: $p<0.05$ for lactate concentration.
Comparison RRMS vs PPMS: $p<0.05$ for lactate concentration.

The other comparisons are not significants.

concentration is more marked in RRMS and CIS, which show values lower than those obtained in PPMS (Table 2), in agreement with other publications (5), suggesting that PPMS constitutes a separate disease entity different from RRMS.

The decrease in lactate concentration in the CSF of patients with MS, may explain the alterations in sensitivity in some of these patients. In the present study, the lowest values in the lactate concentration (mean 1.25 mmol/L) range corresponded to 3 patients from the group of other diseases (OD), with isolated symptoms of deficient sensitivity (*lower limb paraesthesias; hemibody hypoesthesia; neurosensorial hypoacusia)*, similar symptoms to those seen in some patients with early stages of MS, suggesting alterations in the ionic acid-sensitive channels, because of the increased resistance of these channels to opening and depolarisation when the effect of lactate is reduced. This facilitates the opening of the channels (pores) due to their capacity of removing Ca^{2+} cations that block them (6).

The decrease in lactate concentration in the CSF of patients with MS may be due to an increase in the consumption of lactate satisfying a double need: maintaining myelination as well as a minimum level of glucose. In fact, it has been noted that, on one hand, the oligodendrocytes prefer lactate for synthesizing myelin (7) and, on the other hand, that, experimentally, in cases of glucose depletion, the lactate is used as the energy source of first choice (8). In these conditions, thermodynamically, the step from lactate to pyruvate (when entering into the tricarboxilic acid cycle) is preferred over the conversion of glucose to pyruvate, which does not require the previous investment of adenosine triphosphate (ATP).

These observations concur with other results in the present study showing glucose concentration values in the CSF of patients with MS (3.19 ± 0.38 mmol/L) 15.6% lower with respect to group C (3.78 ± 0.50 mmol/L). Although these values remain within the normality of the method used here (interval reference: 2.8-4.2 mmol/L), they are at the lower range limit. According to our knowledge, low levels of CSF glucose in patients with MS have not been described, although reduced levels of the cerebral metabolism of glucose have been observed in the frontal cortex and the basal ganglia, using functional techniques such as positron emission tomography (PET) in patients with MS and fatigue (9).

The results of the present study are in agreement with a published article (10) whose authors have observed a decrease in lactate concentration and other gluconeogenic metabolites, such as glutamine in the CSF of patients with MS, by means of a proton magnetic resonance spectroscopy (^{1}H-RMS).

Other authors (11) are in apparent disagreement with our results. In ^{1}H-RMS, they have observed increases in lactate concentration and, correlatively, in the cell count of CSF of patients with RRMS during relapses. But, this study was done in patients who had been previously diagnosed with MS. It is known, that the diagnosis of MS always involves a certain waiting time, generally over a year. However, in our present study, the CSF samples and their subsequent analysis were done in the early clinical stages with the objective of establishing a definite diagnosis: In 65 % of the patients who were subsequently diagnosed with MS, a lumbar puncture was performed within a week of the relapse and, in not later than a month. Therefore, chronologically, the results of preceding authors are not comparable with those shown here. But, it needs to be pointed out that the low cell count levels in the CSF of patients with MS studied here, that are within the normal range (0-4 cells/ML) (12), are not in disagreement with the positive correlation between lactate and the cell count observed by these authors.

Finally, in the present study, it is important to note that, although the number of CSF samples used as controls is

small, this limitation has been corrected accepting as completely valid those results in the MS group, taking into consideration the values already known and confirmed by the parameters studied in the remaining groups that were analysed (Table 1) that contributed to verification of the results. Thus, for example, the confirmation of the high values in the lactate concentration already described from samples with a diagnosis of IA (13), or the high values in the lactate concentration from samples with a diagnosis of NEO correspond with the poly-medicated patients.

To summarise, the results of the present study show a decrease in CSF lactate concentration in the early stages of MS that may explain some alterations in the sensitivity of these patients, and also suggest a greater consumption of lactate as an alternative energy source, in order to preserve a minimum level of glucose. However, further studies are necessary to confirm these results and evaluate if the lactate concentration is a prognostic indicator of the disease.

Resumen

La propuesta de este estudio era investigar si la concentración de lactato puede aportar información adicional en aquellas patologías que precisan el examen del liquido cefalorraquídeo (LCR) en sus protocolos de diagnóstico o control. Estudio prospectivo realizado en el año 2001 en el Hospital Universitario de Bellvitge (Barcelona), sobre 92 muestras de LCR de pacientes que precisaban este examen, determinándose la concentración de lactato, de glucosa y el recuento de células. Un año después se develaron los diagnósticos de las muestras previamente analizadas, y se clasificaron en grupos según los diagnósticos. En el grupo con esclerosis múltiple (EM) (n=30), se halló una concentración de lactato (1.52 ± 0.19 mmol/L) significativamente disminuida en comparación con el grupo control (1.89 ± 0.11 mmol/L) ($p<0.001$). La concentración de glucosa permaneció dentro de los límites de la normalidad y el recuento de células fue < 4 cel/μL, incluso en los brotes. En las fases tempranas de la EM, la concentración de lactato en el LCR se haya disminuida, pudiendo estar relacionada con alteraciones de la sensibilidad observadas en estos pacientes. Serán necesarios más estudios para valorar si esta concentración de lactato es un indicador pronóstico de la enfermedad.

Acknowledgements

To Prof. Dr.Txomin Arbizu, Unidad de Esclerosis Múltiple, Hospital Universitari de Bellvitge, Barcelona, Spain, for reviewing the manuscript and the Fonalledas Foundation of Puerto Rico for the financial support.

References

1. Nims LF, Smith PK. The ionization of lactic acid from zero to fifty degrees. J Biol Chem 1936;113:145-152.
2. Genton B, Berger JP. Cerebrospinal fluid lactate in 78 cases of adult meningitis. Intensive Care Med 1990;16:196-220.
3. Brook I. Stability of lactic acid in Cerebrospinal Fluid Specimens. Am J Clin Pathol 1982;77:213-216.
4. Poser CM, Paty DW, Scheinberg L, et al. New Diagnostic Criteria for Multiple Sclerosis: Guidelines for Research Protocol. Ann Neurol 1983;13:227-231.
5. Peltola J, Ukkonen M, Moilanen E, Elovaara I. Increased nitric oxide products in CSF in primary progressive MS may reflect brain atrophy. Neurology 2001;57:895-896.
6. Immke DC, Mc Cleskey EW. Protons Open Acid-Sensing Ion Channels by Catalyzing Relief of Ca^{2+} Blockade. Neuron 2003;37:75-84.
7. Sanchez-Abarca LI, Tabernero A, Medina JM. Oligodendrocytes use lactate as a source of energy and as a precursor of lipids. Glia 2001;36:321-329.
8. Schurr A, West CA, Rigor BM. Lactate-Supported Synaptic Function in the Rat Hippocampal Slice Preparation. Science 1988;240:1326-1328.
9. Roelcke U, Kappos L, Lechner-Scott J, et al. Reduced glucose metabolism in the frontal cortex and basal ganglia of multiple sclerosis patients with fatigue. $A^{18}F$-fluorodeoxyglucose positron emission tomography study. Neurology 1997;48: 566-571.
10. Aasly J, Garseth M, Sonnewald U, et al. Cerebrospinal fluid lactate and glutamine are reduced in multiple sclerosis. Acta Neurol Scand 1997;95:9-12. .
11. Simone IL, Federico F, Trojano M, et al. High resolution proton MR spectroscopy of cerebrospinal fluid in MS patients. Comparison with biochemical changes in demyelinating plaques. J Neurol Sci 1996;144:182-190.
12. Andersson M, Alvarez-Cermeño J, Bernardi G et al. Cerebrospinal fluid in the diagnosis of multiple sclerosis: a consensus report. J Neurol Neurosurg Psychiatry 1994;57:897-902.
13. Cunha BA. The Diagnostic Usefulness Cerebrospinal Fluid Lactic Acid Levels in Central Nervous System Infections. Clin Infect Dis 2004;39:1260-1261.