Lactate as an important biomarker of cerebrospinal fluid in bacterial meningitis

Majlinda Kokici[1], Elsa Kone[1], Ndok Marku[2], Piro Paparisto[1], Fahri Kokici[3], Elizana Petrela[4], Dhimitër Kraja[5]

[1]Morphology Department, Faculty of Medicine, Medical University, Tirana, Albania;
[2]Laboratory Department, Faculty of Medicine, Medical University, Tirana, Albania;
[3]University Hospital "Shefqet Ndroqi", Tirana, Albania;
[4]Statistics Department, Faculty of Medicine, Medical University, Tirana, Albania;
[5]Infectious Diseases Service, UHC "Mother Theresa", Tirana, Albania.

Corresponding author: Majlinda Kokici, MD
Address: Faculty of Medicine, Rr. "Dibres", No. 371, Tirana, Albania;
Telephone: +355672083901; E-mail: majlindakokici@yahoo.com

Abstract

Aim: Our aim was to assess the lactate level in the cerebrospinal fluid (CSF) of patients diagnosed with meningitis.
Methods: This study included 133 patients over 18 years old, who showed up at the emergency department of the Infectious Disease Clinic at the "Mother Teresa" University Hospital Center in Tirana, Albania. All patients were presented with clinical signs and symptoms of meningitis, during the period January 2007 - January 2013. CSF samples were taken within the first three hours of their arrival at the emergency. Patients were divided into four groups according to the final diagnosis: the first group consisted of 50 patients with bacterial meningitis (BM); the second group consisted of 36 patients with viral meningitis (VM); the third group consisted of 13 patients with tubercular meningitis (TM); the fourth group consists of 34 patients, which was part of the control group (CG).
Results: Lactate was found elevated in 98% of the patients with BM and in 100% of the patients with TM. Mean value of lactate in patients with BM was 110.88±38.33 mg/dl, whereas in patients with TM it was 54.71±17.07 mg/dl. Mean value of lactate in patients with BM was significantly different compared to the patients with TM and VM ($P<0.01$).
Conclusion: Measurement of lactate in CSF is of great value in the quick diagnosis of BM. Lactate in CSF helps in the differential diagnosis of BM with VM and TM.

Keywords: bacterial meningitis, cerebrospinal fluid, lactate.

Introduction

Lactate levels in the cerebrospinal fluid (CSF) of the patients with clinical signs of meningitis constitutes the first biochemical parameter measured in CSF after Gram staining in the diagnostic protocols for meningitis (1,2).

Increased levels of lactate in the CSF of the patients with tubercular or meningococcal meningitis were first mentioned by Nishimura in 1924. At the same year, Menninger found higher levels of lactate in CSF in patients with bacterial meningitis (3). Four years later, Garcia et al. came to the conclusion that the increase of lactate in CSF during bacterial meningitis was a better indicator for the progression of the disease compared to glucose changes in CSF. Posner and Plum confirmed that the values of lactate in CSF and blood are not related to each-other and that measurement of lactate in CSF is a good indicator of cerebral metabolism. Despite this fact, mostly because of the technical challenges in measuring lactates in CSF, the procedure was neglected and its potential value remained generally unknown. It was Kleine et al., who later advanced and successfully applied the enzymatic method in measuring lactates in CSF (4).

This is the first study in Albania about the use of lactate levels in CSF in patients with acute meningitis.

Methods

Our study included 133 patients over 18 years old, who showed up at the emergency department of the Infectious Disease Clinic at "Mother Teresa" University Hospital Center in Tirana, Albania. All patients presented with clinical signs and symptoms of meningitis, during the period January 2007 - January 2013. CSF samples were taken within the first three hours of their arrival at the emergency. All samples were examined under emergency conditions.

CFS samples were taken through lumbar puncture at the level of L4/L5 by the infectious disease specialist. The samples were placed into 3 tubes with 2 - 3 ml each. We used plastic, sterile tubes all of them covered with caps and marked with numbers 1, 2, 3 according to the portion of CSF taken for examination. They were also labelled with the patient's personal information.

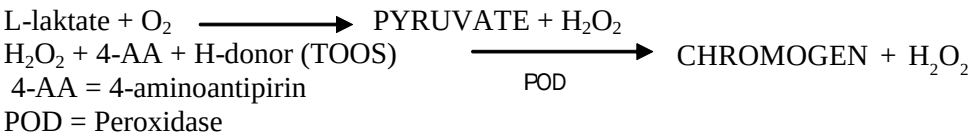
If blood was present in tube one, all the examinations and measurements were taken using tubes 2 and 3. When CSF in tube 1 was clear, standard procedure of CSF examination was followed: tube 1 was used for biochemical and serological examination, tube 2 for microbiological examination and tube 3 for cell count and determination of cell types.

A sample of CSF was kept in the fridge for 12-24 hours in all the cases suspected for tubercular meningitis and it was observed for clot formation after 24 hours. The samples were then immediately sent to the laboratory to evaluate the leukocyte count using manual method in Burker camera and to determine leukocyte cell types using Giemsa staining. After the leukocyte count and their identification the CSF sample went through biochemical examination to measure lactate.

Hemorrhagic CSF samples, patients with intracranial hemorrhage, primary malignant or metastatic tumors were excluded from the examination. Examination of cerebrospinal fluid samples was performed in the first 30 minutes after they were taken.

Method for measuring lactate in CSF: to measure lactate in CSF, we used a colorimetric assay designed to measure blood and CSF levels of lactate (Olympus AU-400).

Assay principle: Lactate is oxidated in pyruvate and H_2O_2 by lactate oxidase (LOD). H_2O_2 interacts with 4-aminoantipirine in the presence of peroxidase and an oxygene donor giving colour according to the reactions as follows:



Refering to the definitive diagnosis the patients were ddivided into four groups:

1. 50 patients with bacterial meningitis (BM);
2. 36 patients with viral meningitis (VM);
3. 13 patients with tubercular meningitis (TM);
4. 34 patients included in the control group (CG).

Control group: taking CSF in normal conditions for studies in a control group represents a real challenge for many research laboratories. The low number of cases with meningitis makes it almost impossible to find a considerable control group. For this reason we have considered as a control group 34 patients who presented at the hospital with signs of acute encephalopathy with a normal CSF result. These patients have been discharged from the hospital diagnosed with meningismus.

Statistical analysis: statistical package SPSS, version 17.0 was used for the data analysis. Continuous variables were presented as mean values and standard deviations (SD). Discrete variables were presented in absolute values and respective percentages. One-way ANOVA was used in order to analyze the differences among numerical variables. Linear associations between two numerical variables were assessed by use of Kendal's tau correlation coefficient. In all cases, values of $P \leq 0.05$ were considered as statistically significant.

Results

Table 1 presents the lactate values according to definitive diagnosis among all patients included in this study. On the whole, there were 13 cases with lactate values of >35 mg/dl who were diagnosed with TM, as opposed to no such cases with lactate values of ≤35mg/dl. On the other hand, there were 49 cases with lactate values of >35 mg/dl who were diagnosed with BM, compared to only one such case with lactate value of ≤35mg/dl.

Table 1. Lactate in CSF according to definitive diagnosis

Lactate value	Definitive diagnosis			
	BM	VM	CG	TM
≤35 mg/dl	1 (2.0%)	36 (100%)	34 (100%)	0 (0%)
>35 mg/dl	49 (98.0%)	0 (0%)	0 (0%)	13 (100%)

Table 2 presents the summary statistics of lactate for each definitive diagnosis of the patients included in the study.

Table 2. Number of cases, average value, maximimum value and standard deviation of lactate in CSF for each definitive diagnosis

Definitive diagnosis	No.	Average value	Standard deviation	Minimum	Maximum
Bacterial meningitis	50	110.88	38.33	28.80	193.90
Viral meningitis	36	16.03	5.65	6.00	29.40
Control group	34	14.06	6.40	4.00	34.00
Tubercular meningitis	13	54.71	17.07	39.00	102.90

From Table 2, there is evidence that patients with BM have the highest average value of lactate in CSF.

Discussion

Lactate is a product of carbohydrate anerobe metabolism formed by conversion of pyruvate to lactate through the lactate dehydrogenase (LDH) enzyme and reduced nicotinamide adenine dinucleotide (NAD) in a reversible reaction (5). In the presence of oxygen, lactate is reconverted to Pyruvate and this is converted to Acetyl Coenzyme A which ends up in the Krebs cycle (6,7). During inflammation, under the influence of proinflammatory cytokines like TNF-α and IL-1 β, the endothelial cells of the capillary increase their permeability and the number of pinocytic vacuoles (8,9). This is followed by a disruption of the tight junction among the endothelial cells leading to inflammation of the small blood vessels known as vasculitis, followed by the inflammation of the larger vessels. The inflammation of the blood vessels reduces the volume of the blood supplying the nervous tissue, thus promoting the anaerobic glycolysis. This process is also enhanced by the cranial hypertension following the cerebral edema. As a result of the inflammation of the blood vessels leading to vasoconstriction and an increased risk for thrombosis as well as the presence of cranial hypertension, the blood supply to the nervous tissue is reduced considerably leading to hypoxia and anaerobe glycolysis. On the other hand, the leukocytosis of the CSF during this process increases glucose consumption, thus promoting glycorhakia and anaerobe glycolysis (10,11).

In our study we found increased levels of lactate in 98% of the patients with BM. Average value of lactate for the BM group was 110.88 mg/dl. In all the patients with VM the lactate was within the normal range (lower than 35 mg/dl). In the patients with VM, the average value of lactate was 6.03 mg/dl.

In all the patients with definitive diagnosis of tubercular meningitis the lactate level was found increased with an average value of 54.71 mg/dl. We found that the average value of lactate in the BM group, compared with the TM group, had a significant statistical difference ($P<0.001$).

In our study, the average value of lactate measured in the CSF of the BM group was different from the lactate average value in the VM group. The difference was statistically significant ($P<0.001$). This difference makes Lactate levels in the CSF of the patients with meningitis the best reliable marker in the diferential diagnosis between BM and VM. Lactate sensitivity for BM (for values higher than 35 mg/dl) was 98%, whereas specificity was 87%.

Theoreticaly, it is considered that the increase of Lactate in CSF during BM and TM is in line with the drop in glucose levels (1,2). There is also another opinion suggesting that Lactate in these patients increases before the drop in glucose levels (12). There are many studies about the level of Lactate in the SCF of the patients suspected for neuroinfection.

For example, Donald et al., measured Lactate in the CSF of the patients with BM, VM and a control group where they found that Lactate levels in BM was considerably higher than in the group of patients with VM. Considering Lactate levels above normal at 25 mg/dl, they found that sensitivity of Lactate measurement for BM was 93.8%. When the Lactate level was considered above normal at 35 mg/dl, the sensitivity was 89.6% for BM (13).

Viallon et al. in their work on Lactate level in CSF of the patients with BM compared with direct negative microbiological examination, found a sensitivity of 94% and a specificity of 92% (the Lactate level was considered above normal at 35 mg/dl). Negative predictive value was 99%, whereas positive predictive value was 82%. They

concluded that measuring Lactate in CSF is highly discriminating in the differential diagnosis between BM and VM (14).

Komorovski et al. measured Lactate in the CSF of the patients with definitive diagnosis of BM (patients with TM were also included) and VM. They found that in 86% of the patients with BM lactate was increased (higher than 35 mg/dl), while 14% of them had normal Lactate level in their CSF. On the other hand, none of the VM patients had increased Lactate levels. Sensitivity of Lactate level in the diagnosis of BM was 86%, whereas specificity was 70% (15).

Nikolic et al. measured Lactate in the CSF of the patients with definitive diagnosis of BM, TM, VM and CG. They found that patients with BM had Lactate level over 60 mg/dl and the maximum value was 140 mg/dl. They found that Lactate in BM was significally higher compared with patients with TM, VM and CG ($P<0.001$). They also found a correlation between Lactate and the leukocyte level in the CSF ($r=0.78$, $P<0.01$) and between Lactate and PMN ($r=0.80$, $P<0.01$) (16).

In all patients with TM, Lactate was increased and the difference was statistically significant between the Lactate values in the CSF of the TM patients and the VM patients and the CG ($P<0.01$). There was no statistically significant difference between Lactate levels in the patients of the CG and VM groups ($P>0.05$).

In their work on Lactate, Cameron et al. measured Lactate levels in 12 patients with definite diagnosis of BM, in 14 patients with definite diagnosis of VM and in 40 patients with clinical signs of meningitis with a normal CSF examination. They found that in the patients with BM the average value of Lactate was 65 mg/dl, minimal value was 45 mg/dl and maximum value was 97 mg/dl. While in the patients with VM the average value of Lactate was 26 mg/dl, minimum value was 7 mg/dl and maximum value was 36 mg/dl. They found that between the values of Lactate in BM and VM there was a statistically significant difference ($P<0.01$) (17).

Controni et al. studied 396 patients for the early diagnosis of bacterial meningitis. They found that the value of Lactate in CSF was increased in 62 patients with proven bacterial meningitis or meningitis from mycoplasmae (60 bacterial, 2 mycoplasmae). All the 334 patients who did not have bacterial meningitis and 15 patients with aseptic meningitis had normal Lactate levels.

Beside tubercular meningitis, a high level of Lactate in CSF has been found also in fungal meningitis. For example Body et al. recently have reported 10 cases of fungal meningitis where Lactate was the only non specific indicator in all the cases (18).

Even though Lactate in the CSF of the patients with TM is increased less than in the patients with BM, we found that in all patients with TM, Lactate was higher than 35 mg/dl. There was a statistically significant difference between Lactate levels in BM and VM ($P<0.001$). By this we conclude that the normal level of Lactate in CSF of the patients clinically suspected for meningitis sugest a viral nature of the infection.

In our study we found that the sensitivity of Lactate measurement in CSF of the patients with TM was 100% and the specificity was 67%.

In conclusion, our study confirms that evaluation of Lactate in CSF is of great value in the quick diagnosis of BM, and helps in differential diagnosis of BM with MT and MV.

Conflicts of interest: None declared.

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