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Research / Araştırma

Serum Lactic Acid and Pyruvic Acid Levels in Patients with Migraine and Tension Type Headache

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ABSTRACT

Serum lactic acid and pyruvic acid levels in patients with migraine and tension type headache

Objective: MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) syndrome is frequently associated with migraine like headaches. The relationship between migraine and mitochondrial diseases is interesting. Also mitochondrial disorders in tension like headache still remain to be investigated. The aim of this report is to evaluate the serum lactic acid and pyruvic acid levels in patients with migraine and tension type headache and compare them with healthy control group.

Methods: We evaluated 30 patients with migraine, 30 patients with tension like headache and 30 healthy control. Lactic and pyruvic acid levels in serum samples were measured by biochemical methods. Kruskal Wallis and Mann-Whitney tests were used for statistical analysis using SPSS 11.5 for Windows program.

Results: Serum lactic and pyruvic acid levels in patients with migraine and tension type headache were significantly higher than control group.

Conclusion: Multi-disciplinary researches are needed to determine mitochondrial diseases in patients with migraine and tension like headache.

Key words: MELAS, migraine, mitochondrial diseases, lactic acid, pyruvic acid

ÖZET

Migren tipi ve gerilim tipi baş ağrıları bulunan hastalarda pirüvik ve laktik asit seviyeleri

Amaç: Bir mitokondriyal sitopati olan MELAS (Mitokondriyal miyopati, ensefalopati, laktik asidoz ve inme benzeri epizotlar) sendromuna migren tipi baş ağrıları sıklıkla eşlik eder. Bu nedenle, migren ile mitokondriyal bozukluklar arasındaki ilişki ilgi çekicidir. Ayrıca gerilim tipi baş ağrılarında da mitokondriyal anormallikler incelenmektedir. Biz de migrenli ve gerilim tipi baş ağrılarında mitokondriyal bozukluk varlığını araştırmak amacıyla serum laktik ve pirüvik asit düzeylerini ölçmeyi ve bu değerleri sağlıklı kontrol grubuyla karşılaştırmayı amaçladık.

Yöntem: Çalışmaya, Uluslararası Baş Ağrısı Topluluğu'nun (IHS) 2004 sınıflama sistemine göre tanı almış 30 migrenli, 30 gerilim tipi baş ağrılı hasta ve 30 sağlıklı kontrol alındı. Çalışmaya katılanlardan alınan örneklerde serum laktik ve pirüvik asit düzeyleri biyokimyasal yöntemlerle çalışıldı. İstatistiksel analizler için SPSS programında Kruskal-Wallis Testi ve Mann-Whitney testleri kullanıldı.

Bulgular: Migren ve gerilim tipi baş ağrısı olan hastaların serum laktik ve pirüvik asit düzeyleri, kontrol grubuyla karşılaştırıldığında anlamlı olarak yüksek bulundu.

Sonuç: Migrenli ve gerilim tipi baş ağrılı hastalarda mitokondriyal bozuklukların araştırılması için geniş çaplı multidisipliner araştırmalar gereklidir.

Anahtar kelimeler: MELAS, migren, mitokondriyal bozukluklar, laktik asit, pirüvik asit

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INTRODUCTION

In recent years, the research on migraine pathophysiology focused on vasoactive substances with endothelial origin, cortical spreading depression, and cerebral energy metabolism, particularly in migraine with aura. In migraine patients, cerebral metabolic changes and increased oxidative stress during the process beginning with the activation of trigeminovascular system cause impairment in mitochondrial energy transport chain. Mitochondrial cytopathies are a group of disorders, presenting with different clinical pictures, which result from impaired synthesis of mitochondrial proteins which are coded by nuclear RNA or mitochondrial DNA, or due to mutation of transfer RNA and ribosomal RNA (primary) or some exogen factor such as drugs, toxins, infections (secondary). Since most of the mitochondrial proteins have a role in respiratory chain and oxidative phosphorilation, these disorders are also called respiratory chain disorders.

MELAS is a mitochondrial disorder characterized by cerebrovascular events, lactic acidosis and myopathy (1). Seizures and migraine like headaches can be seen during the course. It has been known that patients with MELAS may suffer only from migraine episodes before typical symptoms emerge (2). Particularly progress in the radiology field pave the way for scientific studies on MELAS.

Some magnetic resonance (MR) and MR spectroscopy studies suggested the possibility of mitochondrial anomalies in migraine patients (3). During mitochondrial energy transport pyruvic acid (PA) is produced from carbohydrates and fats, diffuse along mitochondrial outer membrane and turn into lactic acid (LA) through tricarboxylic acid cycle. Therefore PA and LA increase in mitochondrial energy transport anomalies. In the present study, our aim was to investigate whether there are mitochondrial functional anomalies in patients with migraine type or tension type headache, diagnosed per International Headache Society 2004 classification (4).

In order to detect mitochondrial anomalies plasma PA and LA levels of the patietns were compared with healthy controls.

METHOD

Sample included, a total of 30 patients (15 with aura+15 without aura), consistent with gender distribution, 20 women and 10 men, with migraine headache per International Headache Society (IHS) 2004 classification, and same number of patients with tension headache with same gender distribution, who applied to Bakirkoy Training and Research Hospital for Psychiatry, Neurology and Neurosurgery during October 2010-December 2010. Control group consisted of healthy volunteers with similar demographical features. Patients who are on profilactic migraine treatment in the last six months, who have a known disease which can effect plasma lactic and pyruvic acid levels, who are smoking, who use any drug regularly for any reason, and who have diabetes or other autoimmune disorder were excluded from the study.

In order to rule out the effect of physical exercise on plasma LA and PA levels, blood samples were drawn during headache free periods, between 09 and 11 am, after a rest period of 15 minutes or longer, while sitting down, from cubital vein with a 21 no injector. 0.5 ml blood sample was quickly completed to 1.5 ml. Samples were centrifuged in Eppendorf tubes (0.8 N cooled perchloric acid) and placed in ice in a few minutes. After this, the protein derived from the sample by 15 minutes of 1200 g centrifuge was stored at -20°C until measurement.

Measurement of Plasma LA Levels: Plasma LA levels were measured with Determiner LA kits. Patient samples and standard samples incubated for 3 minutes at 37°C with N-ethyl-N-(3 methyl phenyl)-N acetylethylendiamine solution. The mixture was rested for 4.5 minutes at 37°C after lactic oxydase was added. Color intensity was measured with dual-beam spectrophotometer at 660/600 nm.

Measurement of Plasma PA Levels: Plasma PA levels were measured with Determiner PA kits. Patient samples and standard samples incubated for 3 minutes at 37°C with peroxydase. The mixture obtained by

Table 1: Mean LA and PA levels of migraine, tension-type headache and control groups

	Plasma LA levels (mg/dL) Mean±SD	Plasma PA levels (mg/dL) Mean±SD
Migraine with aura	10.5±3.3	0.3±0.18
Migraine without aura	9.6±2.5	0.51±0.16
Tension-type headache	8.2±1.8	0.47±0.15
Control group	3.3±1.1	0.26±0.10

LA: Lactic acid, PA: Pyruvic acid SD: Standard Deviation

Table 2: Comparison of plasma LA and PA levels of migraine, tension-type headache and control groups

Plasma level	Group	t-value	p
Plasma LA			
Migraine with aura	Migraine without aura	1.745	>0.05
Migraine	Control group	3.523	<0.001
Migraine	Tension type headache	1.692	>0.05
Tension type headache	Control group	3.982	<0.001
Plasma PA			
Migraine with aura	Migraine without aura	1.546	>0.05
Migraine	Control group	3.471	<0.001
Migraine	Tension type headache	1.612	>0.05
Tension type headache	Control group	3.892	<0.001

LA: Lactic acid, PA: Pyruvic acid, t: Student T test

adding Bis(3-bis (4 chlorphenyl) methyl 4 dimethyl aminophenil) amine solution and ve pyruvate oxydase was rested for 4.5 minutes at 37. Color intensity was measured with dual-beam spectrophotometer at 800/750 nm.

Student t test in SPSS for Windows 11.5 software was used in the statistical analysis. $p<0.05$ was reported as significant throughout.

RESULTS

Plasma LA Levels: Mean LA level in migraine patients without aura was 9.6±2.5 mg/dL, in migraine patients with aura was 10.5±3.3 mg/dL, in tension-type headache patients was 8.2±1.8 mg/dL, and in control group was 3.3±1.1 mg/dL. When migraine patients wih control group was compared, LA levels were significantly higher in the migraine group ($p<0.001$). While LA levels were higher in paitents with migraine when compared with patients with tension-type headaches, the difference was statistically significant ($p>0.05$).

There were no significant differences regarding LA levels between migraine patients with or without aura. LA level was significantly higher in patients with tension type headache than the control group ($p<0.001$).

Plazma PA Levels: Mean PA level in migraine patients without aura was 0.51±0.16 mg/dL, in migraine patients with aura was 0.53±0.18 mg/dL, in tension-type headache patients was 0.47±0.15 mg/dL, and in control group was 0.26±0.10 mg/dL. When migraine patients wih control group was compared, PA levels were significantly higher in the migraine group ($p<0.001$). While PA levels were higher in patients with migraine when compared with patients with tension-type headaches, the difference was statistically significant ($p<0.05$).

There were no significant differences regarding PA levels between migraine patients with or without aura. PA level was significantly higher in patients with tension type headache than the control group ($p<0.001$) (Tables 1 and 2).

DISCUSSION

Currently migraine aura pathophysiology is explianed with cortical spreading depression (5). In cortical spreading depression, defined by Lao first, neuronal hyperexitability state is followed by hyperperfusion, hypoperfusion and oligemia. Anaerobic glycolysis and oxidative stress increase further during oligemia. Oligemia never reaches a threshold and generally compensated by vasodilaters like atrial natriuretic peptide. Since anaerobic glycolysis is more prominent in migraine patients with aura, cerebral pH changes and increased glycolysis products (lactate+pyruvate) are expected to be higher. This condition is consistent with our results. Measuring lactate and pyruvate levels during aura and pain episodes in migraine patients with aura and during pain episode in migraine patients without aura could be more valuable to study. However, due to technical difficulties we could not achieve that. Future studies conducted during aura and pain phases can yield more valuable data.

MELAS syndrome, which was defined in 1984 for the first time, is a mitochondrial disorder which is inherited from the mother and is seen equally common in men and women (1). Early symptoms include muscle weakness and repetitive migraine like headaches, generally emerging right after childhood.

Stroke like episodes usually begin before 40 years of age and repeated episodes can lead to vascular demantia (6). Presence of migraine like headaches, which can be one of the first symptoms and which can be seen through the course of the disorder, raised the interest of several researchers and lead to studies investigating whether migraine is a mitochondrial disorder. The accepted point of view is that the disorder is due to mitochondrial tRNA mutation. There have been several studies reporting mitochondrial tRNA mutations (7-13). Mitochondiral anomalies are characterized with heteroplasmy. Manifestation of the symptoms depend on the localization of the mitochondrial anomalies. High prevalence of migraine in mitochondrial disorders have raised the interest of several researchers and in order to investigate oxidative stress along with mitochondrial functional impairments in patients with migraine, plasma and cerebro spinal fluid (CSF) lactate and pyruvate levels have been measured. Skinhoz (14) and Uotanobe and Kuvabasa(15) showed increased CSF LA levels during migraine episode for the first time. Immediately after this, Montagno and associates (16), reported significantly higher LA level during exercise in migraine patients when compared with the control group and suggested that this was due to mitochondrial energy metabolism impairment in migraine patients and showed abnormal brain and muscle energy metabolism in patients with migraine using magnetic resonance spectroscopy technique (17). Resuls of recent SPECT studies suggested that the impaired oxidative equilibrium and increased oxydative stress and lipid peroxidation in migraine lead to mitochondrial impairment (18). Prolonged muscle contractions have been blamed for increased LA and PA levels in tension-type headaches (19). Okada and associates (20) found significantly increased plasma lactate and pyruvic acid levels in migraine patients while there was no increase in plasma levels in patients with tension-type headaches.

In this study, we found significantly higher LA and PA levels in migraine patients with or without aura and in patients with tension-type headache when compared with the control group. As expected, mitochondrial metabolism changes, and consequently increased lactic and pyruvic acid levels, were more prominent in migrain patients with aura since local blood flow changes are more pronounced in these patients. Our results suggested that mitochondrial abnormalities may accompany migraine patients. However, due to small sample size, we could not compare subgroups of migraine with aura and we could not investigate the association between pain and plasma LA-PA levels.

The pathophysiology of genetic impairment on pain is known in familial hemiplegic migraine patients which have a Mendelian inheritance. Investigating mitochondrial impairments in these type of special migraine groups may lead to more meaningful results.

In spite of limitations we believe that our study may

be reference for future studies. It would be appropriate to conduct genetics, biochemistry, neuropathology and radiology researches together. It would be helpful to conduct mitochondrial tRNA and DNA analysis along with invivo investigation of cerebral mitochondrial reagents to enlight mitochondrial abnormalities.

REFERENCES

1. Wong LJ. Mitochondrial syndromes with leukoencephalopathies. Semin Neurol 2012; 32:55-61.
2. Pavlakis SG, Phillips PC, DiMauro S, De Vivo DC, Rowland LP. Mitochondrial myopathy, encephalopathy, lactic acidosis, and strokelike episodes: a distinctive clinical syndrome. Ann Neurol 1984; 16:481-488.
3. Tsujikawa T, Yamamoto T, Ikawa M, Yoneda M, Kimura H. Crossed cerebellar hyperperfusion after MELAS attack followed up by whole brain continuous arterial spin labeling perfusion imaging. Acta Radiology 2012; 53:220-224.
4. Headache Classification Subcommittee of the International Headache Society. The International Classification of Headache Disorders Second ed. Cephalalgia 2004; 24 (Suppl.1):9-160.
5. Buzzi MG, Moskowitz MA. The pathophysiology of migraine. J Headache Pain 2005; 6:105-111.
6. Hirano M, Pavlakis SG. Mitochondrial myopathy, encephalopathy, lactic acidosis, and stroke like episodes (MELAS): current concepts. J Child Neurol 1994; 9:4-13.
7. Desquiret-Dumas V, Gueguen N, Barth M, Chevrollier A, Hancock S, Wallace DC, Amati- Bonneau P, Henrion D, Bonneau D, Reynier P, Procaccio V. Metabolically induced heteroplasmy shifting and l-arginine treatment reduce the energetic defect in a neuronal-like model of MELAS. Biochim Biophysic Acta 2012; 24:12-15.
8. Emmanuele V, Silvers DS, Sotiriou E, Tanji K, DiMauro S, Hirano M. MELAS, MERRF and Kearns-Sayre overlap syndrome due to the mitochondrial DNA m.3291T>C mutation. Muscle Nerve 2011; 44:448-451.
9. Suzuki T, Nagao A, Suzuki T. Human mitochondrial diseases caused by lack of taurine modification in mitochondrial tRNAs. Wiley Interdiscip Rev RNA 2011; 2:376-386.
10. Wojewoda M, Zabłocki K, Szczepanowska J. Diseases caused by mutations in mitochondrial DNA. Postepy Biochem 2011; 57:222-229.
11. Mende S, Royer L, Herr A, Schmiedel J, Deschauer M, Klopstock T, Kostic VS, Schroeder M, Reichmann H, Storch A. Whole blood genome wide expression profiling and network analysis suggest MELAS master regulators. Neurol Res 2011; 33:638-655.
12. Glatz C, D'Aco K, Smith S, Sondheimer N. Mutation in the mitochondrial tRNA(Val) causes mitochondrial encephalopathy, lactic acidosis and stroke-like episodes. Mitochondrion 2011; 11:615-619.
13. Pilch J, Asman M, Jamroz E, Kajor M, Kotrys-Puchalska E, Goss M, Krzak M, Witecka J, Gmiński J, Sieroń AL. Surveyor nuclease detection of mutations and polymorphisms of mtDNA in children. Pediatr Neurol 2010; 43:325-330.
14. Skinhoz E. Hemodynamic changes in migraine aura. Arch Neurology 1973; 29:95-98.
15. Uotanobe H, Kuvabasa T. A Migraine study on MRI findings cerebral lactat levels. Acta Radiology 1986; 30:21:123-126.
16. Montagno P. Mitocondrial abnormality in migraine. Headache 1998; 28:477-480.
17. Montagno P. MR spektroskopy in migraine sufferres. Cephalalgia 1994; 14:184-193.
18. Aoyagi J, Ikeda K, Kiyozuka T, Hirayama T, Ishikawa Y, Sato R, Yoshii Y, Kawabe K, Iwasaki Y. Alleviation of brain hypoperfusion after preventative treatment with lomerizine in an elderly migraineur with aura. Int J Mol Imaging 2011; 2011:782758.
19. Ashina M, Stallknecht B, Bendtsen L, Pedersen JF, Galbo H, Dalgaard P, Olesen J. In vivo evidence of altered skeletal muscle blood flow in chronic tension-type headache. Brain 2002; 125:320-326.
20. Okada H, Araga S, Takeshima T, Nakashima K. Plasma lactic acid and pyruvic acid levels in migraine and tension-type headache. Headache 1998; 38:39-42.