An Oxidative Stress Marker in Pediatric Migraine Patients: Dynamic Thiol-Disulfide Homeostasis

Migren Tanılı Çocukların Tiyol/Disülfit Düzeylerinin Sağlıklı Çocuklarla Karşılaştırılması

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ABSTRACT

Objective: Migraine is a common disease in childhood. Oxidative stress has been implicated in the pathogenesis of migraine. Dynamic thiol/disulfide homeostasis is proven to be a marker of oxidative stress. We aimed to investigate the correlation between migraine and dynamic thiol/disulfide homeostasis.

Material and Methods: A total of 141 children (71 migrain and 70 controls) were included. The serum total thiol, native thiol, and disulfide levels were measured and the ratios of disulfide/native thiol, disulfide/total thiol and native thiol/total thiol were compared between migraine patients and healthy children during attack-free period.

Results: Native thiol levels and native thiol/total thiol ratio were significantly lower in the migraine group than the control group (p=0.022, p=0.005, respectively); whereas disulfide levels, disulfide/native thiol and disulfide/total thiol ratios were significantly higher in the migraine group than the control group (p=0.039, p=0.022, p=0.005 respectively).

Conclusion: Our results demonstrate that there is an ongoing oxidative process in pediatric migraineurs even during attack-free period. This result may shed light on further studies analyzing dynamic changes in the oxidant-antioxidant balance during the attack and the aura phase to support the presence and importance of oxidative stress in pediatric migraine.

Key Words: Children, Migraine, Thiol/disulfide

ÖZ

Amaç: Migren çocuk ve ergen yaş grubunda değişen yaşam tarzları ve psikososyal faktörler ile birlikte görülme sıklığı giderek artan önemli bir klinik problemdir. Birincil baş ağrıları arasında yer alan migrenin biyokimyasal, genetik ve çevresel faktörlerle ilişkili nörovasküler bir hastalık olduğu bilinmektedir. Son yıllarda yapılan birçok çalışmada migren patogenezinde oksidatif stres sorumlu tutulmuştur. Oksidatif stres varlığında tiyol/disülfit homeostazisinin disülfit yönünde bozulması beklenmektedir. Tiyol/disülfit homeostazisinin çocuklarda migren ile olan ilişkisini araştıran geniş

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çaplı araştırmalar mevcut değildir. Çalışmamızda migren tanılı çocuklarda dinamik tiyol/disülfit homeostazisi ilişkisini belirlemeyi ve bu dengede disülfit yönünde bozulma görülürse migren proflaksisi ve/veya tedavisinde oksidatif stresten korunma ve/veya antioksidan tedavi kullanımı ile ilgili literatüre katkı sağlanmasını amaçladık.

Gereç ve Yöntemler: Çalışmaya Sağlık Bilimleri Üniversitesi, Ankara Keçiören Eğitim ve Araştırma Hastanesi'nde Çocuk Nöroloji Polikliniği'nde değerlendirilerek migren tanısı alan 8-18 yaş arasındaki 71 hasta ve Genel Çocuk Polikliniği'ne başvuran 70 sağlıklı çocuk dahil edilmiştir. Toplanan örneklerde serum doğal tiyol, total tiyol, disülfit, disülfit/doğal tiyol yüzdesi, disülfit/total tiyol yüzdesi ve doğal tiyol/total tiyol yüzdesi ölçümleri yapılarak migren hastaları ve sağlam çocuklar karşılaştırılmıştır.

Bulgular: Migren sıklığı yaşla birlikte artmış; 8-12 yaş %18.3, 13-15 yaş %36.6, 16-18 yaş %45.1 olarak tespit edilmiştir. Ağrı şekli %85.9 ile en sık zonklayıcı olup ağrıların %59.2'si bilateral bulunmuştur. Hastaların %11.3'ü atak ağrısının 30 dakikadan kısa sürdüğünü belirtmiştir. Gruplar karşılaştırıldığında doğal tiyol, doğal tiyol/total tiyol değerleri kontrol grubunda anlamlı olarak yüksek saptanmıştır (sırasıyla p=0.022, p=0.005). Disülfit, disülfit/doğal tiyol, disülfit/total tiyol değerleri ise hasta grubunda anlamlı olarak yüksek bulunmuştur (sırasıyla p=0.039, p=0.005, p=0.005). İstatistiksel olarak anlamlı olmasa da kontrol grubunda total tiyol değerleri hasta grubundan yüksek bulunmuştur (p=0.115).

Sonuç: Migren hastalığı sık görülmesine rağmen çocuklarda bu konuda yapılmış prospektif çalışma oldukça az sayıdadır. Çalışmamızda migren tanılı çocuklarda migren hastalığı ile tiyol/disülfit homeostazisi arasındaki ilişki incelenmiş olup oksidatif strese yönelik parametreler yüksek bulunmuştur. Migren hastalarındaki yüksek oksidatif stres değerleri antioksidan etkili maddelerin hastalığın tedavisinde rol oynayabileceğini düşündürmektedir. Bu konuyla ilgili destekleyici çalışmalara ihtiyaç vardır.

Anahtar Sözcükler: Çocuk, Migren, Tiyol/Disülfit

INTRODUCTION

Migraine is one of the most common forms of primary headache in children. Two systematic reviews published in the last ten years have reported that the prevalence varies between 7.7% and 9.1% in children and adolescents (1,2). The pathophsiology of migraine remains unclear, however, increasing evidence indicates that it is related to the excitability of the cerebral cortex on the basis of genetic predisposition (3,4). In addition, oxidant/antioxidant imbalance has been shown to play an important role in the mechanism that initiates the migraine attack (5,6). Oxidative stress is defined as the disruption of the balance between reactive oxygen species (ROS) and antioxidant molecules in favor of ROS (7). Serum thiols are free radical scavengers under physiological conditions. The sulfhydryl groups they contain are mainly responsible from the antioxidant effects (8). ROS, which is formed as a result of metabolic events, transfer excess electrons to thiols to form oxides and disulfide bonds. As a result of the oxidant/antioxidant balance of the organism, these disulfide bonds can be converted back to thiols, indicating that they are reversible. This balance is called dynamic thiol/disulfide homeostasis. Thiol/disulfide homeostasis is expected to be affected in diseases caused by oxidative stress (9,10). When protein function disorders, channel disorders, transport and signal transduction disorders are considered, it may be suggested that thiol/disulfide homeostasis may be impaired in migraine.

The aim of this study is to compare the dynamic thiol/disulfide levels in pediatric migraine patients with healthy controls and to determine the possible relationship of this homeostasis with clinical features of migraine.

MATERIALS and METHODS

The study population included children diagnosed with migraine at Ankara Keçiören Training and Research Hospital, Health Sciences University, Department of Pediatric Neurology and healthy children admitted to the general pediatric outpatient clinic. Ethical approval for this study was obtained from the Ethics Committee of Keçiören Training and Research Hospital (27.12.2017-15/1571). Informed consents were obtained from all children or their parents.A total of 71 migraine patients and 70 healthy children during follow-up for routine control were included. The diagnosis of migraine was made according to International Classification of Headache Disorder - third edition (ICHD-3) (11). Both groups consisted of children aged between 8-18 years without any neurological or chronic systemic disease, history of recent infection or medication. Age, sex, height, body weight, blood pressure, detailed history of migraine (onset, frequency, duration of migraine, duration of attacks, location and type of pain, accompanying features, precipitating factors, aura, family history), physical and neurological examinations were recorded. The blood samples of the patients with migraine were collected in the attack-free period. Venous blood samples taken for thiol/disulfide measurement were centrifuged rapidly at 1500 rpm for 10 minutes, and incubated at-80°C to investigate oxidative markers. Serum thiol/disulfide levels were measured by a calorimetric and automatic method developed by Erel O et al. (9). We preferred this method because it is relatively inexpensive and easily accessible. In this method, by adding NaHB4, the dynamic disulfide bonds in the sera are reduced to form free functional thiol groups. The residues are removed by adding formaldehyde. Thus both reduced and native thiol groups are determined and the total thiol amount is reached. The amount of disulfide is obtained by substracting the native thiol from total thiol and dividing it into two. The

method automatically measures serum native thiol, disulfide and percentages of disulfide/native thiol, disulfide/total thiol and native/total thiol. All these values were compared between migraine patients and healthy children.

Statistical Analysis

Descriptive statistics of the normal distribution data were given as mean ± standard deviation (SD). The normality of the distribution of the groups was evaluated with the Kolmogorov-Smirnov test. Descriptive statistics that do not fit to normal distribution were given as median, quartiles, maximum and minimum values. Pearson chi-square test was used to compare qualitative data. Mann Whitney U (between two groups) and Kruskal Wallis (more than two groups) tests were used for comparison of continuous variables that did not fit the normal distribution. Student t test (between two groups) and ANOVA (more than two groups) were used to compare the continuous distribution of databetween groups. SPSS 20.0 (SPSS Inc, Chicao, IL, USA) was used for statistical analysis. A p value <0.050 was considered statistically significant.

RESULTS

A total of 141 children (71 migraine patients and 70 healthy control) with a mean age of 14.7±2.32 years (range 8-17.9 years) were included. Female/male ratio was 1.51. The clinical characteristics of the patients are shown in Table I. No statistically significant difference was detected between the migraine and control groups in terms of gender, age, body weight, height or blood pressure.

In the migraine group, most of the patients had throbbing headache (85.9%) and 20.8% of the patients were diagnosed with migraine with aura. Characteristics of headache are shown in Table II.

The disulfide levels in the migraine group was statistically higher than the control group (p=0.039). Also, the disulfide/native thiol ratio and disulfide/total thiol ratio were significantly higher in the migraine group than the control group (p<0.05). Conversely, native thiol/total thiol ratio was detected significantly lower in the migraine group than the control group (p<0.05). Native thiol levels were higher in the control group than the migraine group (p=0.022). Patients in the control group were likely to have higher total thiol levels than the migraine group, but no statistical significant difference was detected (p=0.115) (Table III).

No statistically significant difference was detected between native thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native/total thiol levels and frequency of attacks (Table IV).

Table I: Clinical characteristics of the patients.

	Migraine group (n=71)	Control group (n=70)	p
Mean age ± SD (range, years)	14.82 ± 2.32 (8-17.7)	14.74 ± 2.72 (8.2-17.9)	0.629
Female/Male (ratio)	46/25 (1.84)	39/31 (1.25)	0.271
Body weight (range, kg)	56.89 ± 12.79 (27-84)	55.89 ± 13.87 (25-85)	0.650
Height (range, cm)	160.45 ± 11.64 (125-182)	158.0 ± 12.56 (126-181)	0.796

Table II: Characteristics of migraine.

	Number (n)	Percentage (%)
Generalized	12	16.9
Unilateral temporal	14	19.7
Bitemporal	15	21.1
Frontal	15	21.1
Occipital	15	21.1
Type of pain		
Throbbing	61	85.9
Pressing	4	5.6
Other	6	8.4
Duration of migraine attack		
≤ 30 min	8	11.3
31 min - 1 hr	11	15.5
1 - 2 hr	18	25.4
2 - 4 hr	10	14.1
>4 hr	24	33.8
Duration of migraine diagnosis		
≤ 2 mo	17	23.9
2- 6 mo	14	19.7
6 mo-1 year	19	26.8
1-2 y	14	19.7
>2 y	7	9.9
Frequency of attacks		
Daily	24	33.8
4-6 /pw	14	19.7
1-3 /pw	28	39.4
< 1/week	5	7
Total	71	100

min: *minutes,* ***hr:*** *hour,* ***mo:*** *months,* ***y:*** *years,* ***pw:*** *per week*

Table III: Comparison of thiol/disulfide levels in the migraine and control groups.

	Migraine Group		Control Group		p
	Mean±SD	Median (range)	Mean±SD	Median (range)	
Native thiol	344.4±63.7	340 (112.9-480.4)	368.7±52.4	368.6 (246.6-507.4)	0.022
Total Thiol	387.2±54.2	387.2 (231.3-520.0)	401.5±53.1	401.5 (305.5-572.5)	0.115
Disulfide	21.6±10.1	20.2 (0.4-61.6)	18.5±7.3	17.9 (6.7-52.3)	0.039
Disulfide/ Native thiol	7.3±7.5	5.6 (0.1-52.4)	5.1±25	4.8 (1.9-21.2)	0.005
Disulfide/ Total thiol	5.8±3.9	5.1 (0.1-25.6)	4.5±1.8	4.4 (1.8-14.9)	0.005
Native Thiol/ Total Thiol	88.2±7.8	89.8 (48.8-99.8)	90.8±3.6	91.1 (70.2-96.3)	0.005

Table IV: Data concerning the comparison of frequency of attacks and thiol/disulfide levels.

	Median	1st and 3rd quarter	p
Native thiol			
Daily (n=24)	344.45	315.43 -375.38	
4-6/pw (n=14)	343.55	324.25 – 391.40	0.096
1-3/pw (n=28)	352.00	313.98 – 386.25	
<1/week (n=5)	285.90	127.95 – 333.40	
Disulfide			
Daily (n=24)	20.725	13.93 – 24.83	
4-6/pw (n=14)	16.925	15.00 – 23.40	0.201
1-3/pw (n=28)	19.70	16.80 – 23.58	
<1/week (n=5)	33.20	18.88 – 60.40	
Disulfide/native thiol			
Daily (n=24)	5.51	3.76 – 7.56	
4-6/pw (n=14)	4.98	3.89 – 7.01	0.136
1-3/pw (n=28)	5.96	4.59 – 7.36	
<1/week (n=5)	11.61	5.63 – 47.26	
Disulfide/total thiol			
Daily (n=24)	4.96	3.49 – 6.57	
4-6/pw (n=14)	4.525	3.60 – 6.15	0.135
1-3/pw (n=28)	5.325	4.20 – 6.42	
<1/week (n=5)	9.42	5.05 – 24.37	
Native thiol/total thiol			
Daily (n=24)	90.075	86.87 – 93.02	
4-6/pw (n=14)	90.945	87.70 – 92.79	0.136
1-3/pw (n=28)	89.35	87.17 – 91.60	
<1/week (n=5)	81.15	51.27 – 89.91	
	Mean	**Lower and Upper Bound**	
Total thiol*			
Daily (n=24)	391.24	367.41 – 415.07	
4-6/pw (n=14)	393.31	365.64 – 420.98	0.031
1-3/pw (n=28)	392.96	374.71 – 411.21	
<1/week (n=5)	318.42	235.57 – 401.26	

Pw: *per week* ****** *The mean/lower and upper bound were given for total thiol and also ANOVA was performed because total thiol levels were normally distributed.*

Table V: Comparison of frequency of attacks and total thiol levels.

	Mean Difference	Std. Error	p
Total thiol			
<1/week (n=5)			
Daily (n=24)	-72.82	25.53	0.035
4-6/pw (n=14)	-74.89	27.05	0.044
1-3/pw (n=28)	-74.54	25.21	0.026

Pw: *per week*

A statistically significant difference was found between total thiol levels of the patients and the frequency of attacks. Post-hoc analysis revealed that the group with attacks less than once a week had lower total thiol levels than the other three groups which was statistically significant (Table V).

DISCUSSION

In the recent years, mitochondrial dysfunction which tends to increase production of oxidants and downregulate antioxidant enzymes has been shown to play a role in the pathogenesis of migraine. Triggers of migraine have been also reported to increase oxidative stress. It has been suggested that oxidative stress may play a central role in the pathogenesis of migraine by deregulating brain blood flow. Therefore, the increase in free radicals has been reported to initiate a migraine attack (5,6,12,13). In this study, dynamic thiol/disulfide homeostasis developed by Erel O (9) et al. was used as an indicator of oxidative stress. This method has proven to be reliable and objective to measure dynamic thiol/disulfide balance. In diseases caused by oxidative stress thiol/disulfide homeostasis is expected to be affected and deteriorate in the disulfide direction. In the current study, we found disulfide levels, disulfide/native thiol and disulfide/total thiol ratios significantly higher in the migraine group than the control group which supported the presence of oxidative stress. There are also many tests that can measure levels of oxidant and antioxidant molecules. Endogenous antioxidant mechanisms in the body include antioxidant enzymes and various non-enzymatic molecules like catalase, superoxide dismutase, glutathione peroxidase and some peroxidation enzymes belong to the enzymatic group; uric acid, albumin, ascorbic acid, and vitamins E and C (14). However,

it is difficult to evaluate oxidative stress by measuring these molecules, since they are present in different tissues (9,15).

The increase in both native and total thiol values in the control group in our study was higher than the migraine group and the difference was statistically significant in terms of native thiol. Kurt ANC et al.(16) also found total and native thiol levels to be higher in the control patients than the migraine group, whereas the difference was not statistically significant. However, in a previous report in adults, total and native thiol levels were higher in the migraine group than the control group (17). Thiols are known to be physiological free antioxidants. However, it has been reported in the literature that they are biochemically very active and generally antioxidant but may be pro-oxidant due to the fact that they are sometimes affected by the oxidative stress level of the organism (8,18). The concentration of sulphur compounds can alter the antioxidant structure of enzymes and proteins and become pro-oxidative and participate in the structures. This equilibrium is dynamic and represents an assessment of the oxidative stress level of the organism for a given period of time (8,9). As the oxidative stress level is reported to increase with age, high level of thiols may be explained by acting of thiols as prooxidant molecules in the situation of adult migraineurs (19).

In our study, we found lower thiol and higher disulfide levels in children with migraine which demonstrate that there is an ongoing oxidative process in these patients. One of the reasons for low thiol level in pediatric migraine patients may be greater extent thiol consumption to remove excess free radicals generated. Also, dynamic changes in the oxidant-antioxidant balance may play a different role in pediatric patients than adults. We found high levels of disulfide in children with migraine during the attack-free period and according to the hypotesis that migraine is a response to increased levels of oxidative stress in the brain, further increase may be expected at the time of attack. However, some components of the migraine attack like substance P, platelet activation, serotonin are suggested to be neuroprotective by reducing oxidant production and delivering antioxidants to the brain (12). The choice of time is a limitation of our study. In which way the oxidant-antioxidant balance will shift during an attack can be demonstrated with future prospective studies.

The vascular theory of headache proposes that aura is represented as a consequence of vasoconstriction and cortical hypoxia. In animal models, intermittent hypoxia is reported to cause oxidative stress via mitochondrial dysfunction. Moreover, oxidative stress may help account for the relationship between cortical spreading depression and the subsequent attack in migraine with aura (20). Studies on the relationship between aura and oxidative stress are controversial. Tuncel et al. and Tripathi et al. reported that patients with aura were more prone to oxidative stress, however, Eren Y et al. (23) and Gümüşyayla et al. (17) did not find statistically significant relationship between migraine groups with and without aura (21,22). We did not find any correlation between presence of aura and thiol/disulfide parameters. If our study could be performed during the aura phase, more definite results could be reported on this issue.

Alp et al. (24) detected significant negative correlation between total thiol levels and the duration of headache in adult migraineurs. They suggested that oxidative stress may not only play a role in migraine pathogenesis but also is a triggering factor for attack severity and duration. In another study, there was no significant correlation between oxidative stress markers and duration of migraine attack (25). We also did not find any correlation between duration of attacks and thiol/disulfide parameters. Many studies about migraine and oxidative stress include adult patients. As defined in theInternational Headache Society (IHS) criteria and studies in the literature, the minimum duration of headache in adults is 4 hours, however in young children migraine attacks frequently last less than 4 hours (11,25). In our study, only 34% of the patients reported that the pain lasted more than 4 hours. The absence of a relationship between oxidative stress parameters and the duration of the attack in our study may be due to the fact that the duration of the attacks in children is not as long as in adults.

Erol et al. (26) reported that neither duration of disease nor frequency of attacks affected antioxidants in children with migraine. Similarly, there was no significant difference between the frequency of attacks and native thiol, disulfide, disulfide/native thiol, disulfide/total thiol, native/total thiol levels in our study. However, the group with attacks less than once a week had lower total thiol levels than the other groups.

Female adults appear to have lower levels of oxidative stress compared to male adults. One reason for this apparent gender difference could be due to the anti-oxidant properties of estrogen (27). No statistically significant correlation was found between gender and thiol/disulfide values in our study. Approximately 65% of our patients were female and about 90% of them were pubertal and postpubertal. However, there was no difference between gender or puberty and thiol/disulfide parameters which might support that not only estrogen but also some other mechanisms are responsible for the lower levels of oxidative stress in adult females compared to male adults.

CONCLUSIONS

High oxidative stress values are determined in children with migraine which could play a role in migraine pathogenesis. Despite the limitations mentioned above, our data constitutes one of the largest studies investigating the relationship between pediatric migraine and oxidative stress in the literature. Prospective studies analyzing the dynamic changes in the oxidant-antioxidant balance during the attack and the aura phase are needed to support the presence and importance of oxidative stress in pediatric migraine.

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