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NRF2/HO-1 axis and oxidative stress in pediatric migraine with and without aura

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Abstract

Objective: Migraine is a frequent neurological disorder in childhood. Oxidative stress plays an important role in its pathophysiology. Nuclear factor erythroid 2–related factor 2 and heme oxygenase-1 regulate the antioxidant defense system. This study evaluated their serum levels and oxidative stress markers in pediatric migraine with and without aura. *Methods:* Sixty pediatric migraine patients (34 with aura, 26 without aura) and 27 healthy controls were included. Serum nuclear factor erythroid 2–related factor 2 and heme oxygenase-1 were measured by ELISA, and total antioxidant status, total oxidant status, and oxidative stress index were determined. *Results: I*n both migraine subgroups, nuclear factor erythroid 2–related factor 2, heme oxygenase-1, and total antioxidant levels were lower, while the total oxidant status and oxidative stress indexes were higher compared to controls ($p < 0.01$). Subgroup analysis showed no differences between migraine with and without aura. In all patients, nuclear factor erythroid 2–related factor 2 correlated negatively with total oxidant status and oxidative stress index, and positively with total antioxidant status ($p < 0.01$).
Conclusions: Pediatric migraine patients show reduced nuclear factor erythroid 2–related factor 2 and heme oxygenase-1 as well as altered oxidative stress markers, indicating antioxidant dysregulation. The nuclear factor erythroid 2–related factor 2/heme oxygenase-1 axis may represent a biomarker for early identification of high-risk pediatric patients, and therapies targeting this pathway could provide a novel treatment approach.

Keywords: Pediatric migraine, aura, oxidative Stress, NRF2, HO-1

INTRODUCTION

Migraine is a complex neurological disorder typically characterized by unilateral, moderate to severe headaches, often accompanied by symptoms such as nausea and sensitivity to light and sound.[1] Affecting approximately 14% of the global population, migraine ranks as the second leading cause of disability worldwide in terms of Years Lived with Disability.[2] The prevalence of migraine increases throughout childhood and adolescence, rising from approximately 5% in both boys and girls around the age of 10 to 10% in girls and 6% in boys by the age of 20.[3]

Although not yet fully elucidated, the pathophysiology of migraine is thought to involve vascular, neuroinflammatory, and neurological processes. In this context, activation of the trigeminovascular system, brainstem and/or cortical dysfunction, neurotransmitters, and ion channels play prominent roles.[4] Genetic mutations have also been identified in familial hemiplegic migraine subtypes.[5]

Disruption of the oxidant–antioxidant balance is thought to play an important role in the pathogenesis of migraine. There is strong evidence, both clinical and experimental, that oxidative stress increases in the brain and trigeminovascular system during a migraine attack. For example, clinical studies have reported that, during the attack period, serum total oxidant status (TOS) and oxidative stress index (OSI) levels increase, while total antioxidant status (TAS) and glutathione levels significantly decrease.[6] In experimental models, oxidative stress in the trigeminovascular system has been shown to increase following

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cortical spreading depression, and this process mechanistically triggers calcitonin gene-related peptide release via transient receptor potential ankyrin 1 channels.[7]

In migraine patients, increased malondialdehyde levels and decreased superoxide dismutase activity have been reported[8], along with significantly reduced antioxidant enzyme activities, such as superoxide dismutase and glutathione peroxidase, in erythrocytes and serum compared to the control group.[6]

Nuclear factor erythroid 2–related factor 2 (NRF2) is an important transcription factor that regulates the defense mechanism protecting cells against oxidative stress. During oxidative stress, NRF2 dissociates from Keap1, translocates into the nucleus, and binds to the antioxidant response element sequences in the promoter regions of the heme oxygenase-1 (HO-1) gene, thereby activating its transcription.[9] HO-1 is an inducible stress protein regulated by numerous transcription factors.[10] Under oxidative stress conditions, increased NRF2 activation enhances the synthesis of HO-1, a crucial cytoprotective enzyme that protects nerve cells from oxidative damage.[11] In animal models, significant increases in NRF2 and HO-1 levels have been detected in response to oxidative stress.[12]

This study was designed to evaluate the role of increased oxidative stress in the pathophysiology of migraine by investigating the relationship between NRF2 and HO-1 levels and oxidative stress markers such as TAS, TOS, and OSI in pediatric migraine patients with and without aura.

METHODS

This prospective case–control study was conducted between January 1, 2019, and June 1, 2020, in a tertiary care medical center, with the participation of 60 pediatric migraine patients and 27 healthy controls. A power analysis was not performed; the sample size was determined based on previous similar studies and the number of patients accessible during the study period.

The study was approved by the institutional Clinical Research Ethics Committee (approval date: May 3, 2018; session no: 05; decision no: 15), and written informed consent was obtained from the parents of all participants.

The diagnosis of migraine was made according to the criteria of the International Headache Society.[1] Based on these criteria, patients were classified into two subgroups: with aura and without aura. In school-aged children capable of self-expression, the impact of migraine on quality of life was assessed using a pediatric-adapted Migraine Disability Assessment Scale.[13] Headache frequency was determined based on patient and parent diaries covering the past three months.

Children diagnosed with primary headache who had not received prophylactic treatment in the previous three months, had not used symptomatic medication in the previous three days, and were in the interictal period were included in the study. Individuals with secondary headache, obesity, a history of malignancy, or systemic chronic disease were excluded. The control group consisted of healthy children with no history of headache.

Serum samples were obtained from routine blood draws collected during clinical evaluation. The samples were centrifuged at 3500 rpm for 10 minutes to separate the serum, which was then stored at −80 °C. Measurements were performed on the day of the study using the stored samples. The storage duration of the serum samples was consistent with the study period, and all analyses were performed in a single batch. A total of four samples were excluded from analysis due to hemolysis, and data from 60 migraine patients and 27 control subjects were included in the analyses.

NRF2 and HO-1 levels were measured using a commercial ELISA kit (BT-LAB, China) according to the manufacturer's instructions. In this method, plates were pre-coated with human NRF2 or HO-1 antibodies. After the addition of serum samples, biotin-labeled secondary antibody and streptavidin-HRP were applied, followed by the substrate solution to allow color development, and absorbance was measured at 450 nm (Thermo-Go, USA). TAS and TOS levels were measured using commercial kits produced by Rel Assay Diagnostics (Gaziantep, Turkey) on a Varioskan Lux microplate reader (Thermo Scientific, USA). TAS measurement was performed using the Erel method, and the results were expressed as mmol Trolox equivalent/L. TOS measurement was based on the oxidation of ferrous ions to ferric ions, and the results were reported as μmol H_2O_2 equivalent/L.[14] The OSI was calculated as the ratio of TOS to TAS: OSI (arbitrary unit) = TOS (μmol H_2O_2 equiv./L) / TAS (mmol Trolox equiv./L).

Statistical analyses were conducted using SPSS 22.0 software (IBM Corp., Armonk, NY, USA). Differences in NRF2, HO-1, TAS, TOS, and OSI levels between the patient and control groups, as well as between subgroups (migraine with and without aura), were evaluated using the independent samples t-test. Correlations among biomarkers in the migraine group were analyzed

Table 1: Gender and age distributions of the individuals in the patient and control groups

	Patient group		Control group	
Gender	Male	Female	Male	Female
Number of patients	26	34	12	15
Mean age (months)	108.73	133.41	121.8	138.7

using the Pearson correlation analysis. A p-value < 0.05 was considered statistically significant.

RESULTS

The gender and age distributions of the patient and control groups are presented in Table 1.

When the NRF2, HO-1, TAS, TOS, and OSI levels of the patient and control groups were compared, NRF2, HO-1, and TAS levels were found to be significantly lower in the patient group, whereas TOS and OSI levels were significantly lower in the control group (Table 2) (Figure 1).

When the NRF2, HO-1, TAS, TOS, and OSI levels of the migraine with aura group were compared with those of the control group, NRF2, HO-1, and TAS levels were found to be significantly lower in the migraine with aura group, whereas TOS and OSI levels were significantly lower in the control group (Table 3) (Figure 2).

When the NRF2, HO-1, TAS, TOS, and OSI levels of the migraine without aura group were compared with those of the control group, NRF2, HO-1, and TAS levels were found to be significantly lower in the migraine without aura group, whereas TOS and OSI levels were significantly lower in the control group (Table 4) (Figure 2).

When the relationships between NRF2, HO-1, TAS, TOS, and OSI levels were examined in the patient group, significant positive linear correlations were found between NRF2 and HO-1, and between TOS and OSI, whereas a significant negative linear correlation was observed between TAS and OSI ($p < 0.01$) (Table 5) (Figure 3).

When the NRF2, HO-1, TAS, TOS, and OSI levels of the migraine with aura group (n= 34) and the migraine without aura group (n= 26) were compared, no significant differences were found between these parameters (Table 6).

DISCUSSION

Childhood is the period in which the central nervous system undergoes its most intense phase of plasticity and neurodevelopment. During this period, the delicate balance between oxidative stress and antioxidant mechanisms is critical for the healthy development of synaptic connections.[15] Deficiency in the NRF2/HO-1 axis can disrupt redox homeostasis in developing neurons, leading to increased oxidative damage and the establishment of a neuroinflammatory environment.[16]

Activation of the NRF2 pathway initiates the expression of antioxidant genes[17], triggering the coordinated induction of detoxifying enzymes, antioxidant proteins, and HO-1.[18] In addition, it both reduces the release of molecules involved in pain transmission within the trigeminal system[19] and modulates migraine-related neuroinflammation. Notably, microglial activation and inflammatory cytokine production have been reported to be regulated through the NRF2 pathway.[20]

Reduced NRF2 activity, accompanied by increased oxidative stress, leads to endothelial dysfunction, loss of vascular tone, and an increase in inflammatory processes[21], as well as heightened

Table 2: Comparison of NRF2, HO-1, TAS, TOS, and OSI levels between the patient and control groups

	Patient group (n= 60)	Control group (n= 27)	P-Value
NRF2	2.031	3.31	< 0.001
HO-1	3.218	6.15	< 0.001
TAS	0.981	1.530	< 0.001
TOS	13.512	10.95	< 0.001
OSI	1.381	0.725	< 0.001

NRF2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

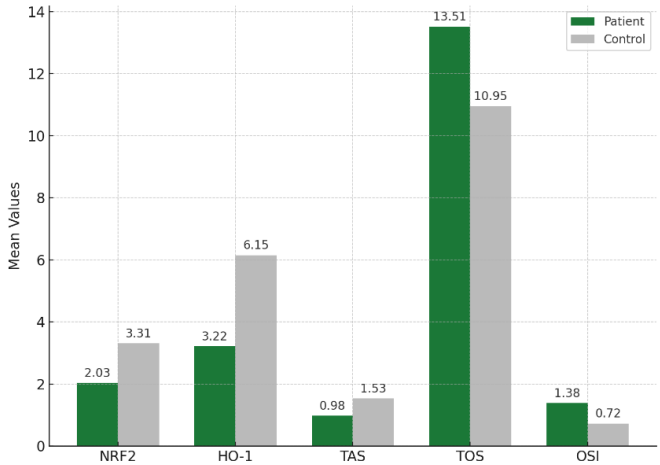

Figure 1. Oxidative stress markers in patients and controls (NRF2, HO-1, TAS, TOS, OSI).

inflammation and pain transmission in neurons.[22]

The HO-1 enzyme metabolizes the heme molecule, contributing to the formation of components that protect cells from the harmful effects of oxidative stress.[10] Increased HO-1 expression has been shown to suppress spinal neuroinflammation and reduce pain transmission in a neuropathic pain model.[23]

Low HO-1 activity may result in reduced production of anti-inflammatory carbon monoxide and disruption of vascular tone homeostasis.[24] Genetic studies have shown that the length of the (GT)n dinucleotide repeat (a variable number of guanine-thymine repeats) in the HO-1 (HMOX1) gene promoter affects its expression, and that individuals carrying longer repeats have increased susceptibility to oxidative stress.[25]

Similarly, chronic exposure to oxidative stress can suppress NRF2 and HO-1 gene expression through epigenetic regulators. Chronic oxidative stress has been reported to inhibit NRF2 transcription by increasing DNA methylation in the promoter region and to reduce HO-1 gene expression via histone deacetylation.[26] These mechanisms may shed light on the epigenetic foundations of migraine that begin in childhood and explain interindividual differences in response.

Under oxidative stress conditions, an increase in NRF2 and consequently HO-1 would be expected.[17] However, in our study, although oxidative stress was significantly higher in migraine patients compared with the control group, NRF2 and HO-1 levels were found to be significantly lower. This suggests that the primary problem in migraine pathophysiology may stem not from increased oxidant load per se, but from a defect in the NRF2 activation steps or in the feedback signaling of oxidative stress.

The decrease in NRF2/HO-1 levels detected in our study steers us away from implicating a defect in the NRF2–target protein relationship as the underlying pathophysiological mechanism. This is because, under physiological conditions,

Table 3: Comparison of NRF2, HO-1, TAS, TOS, and OSI levels between the migraine with aura group and the control group

	Migraine with aura group (n= 34)	Control group (n= 27)	P-Value
NRF2	2.13	3.31	< 0.001
HO-1	3.27	6.15	< 0.001
TAS	0.982	1.530	< 0.001
TOS	13.960	10.95	< 0.001
OSI	1.417	0.725	< 0.001

NRF2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

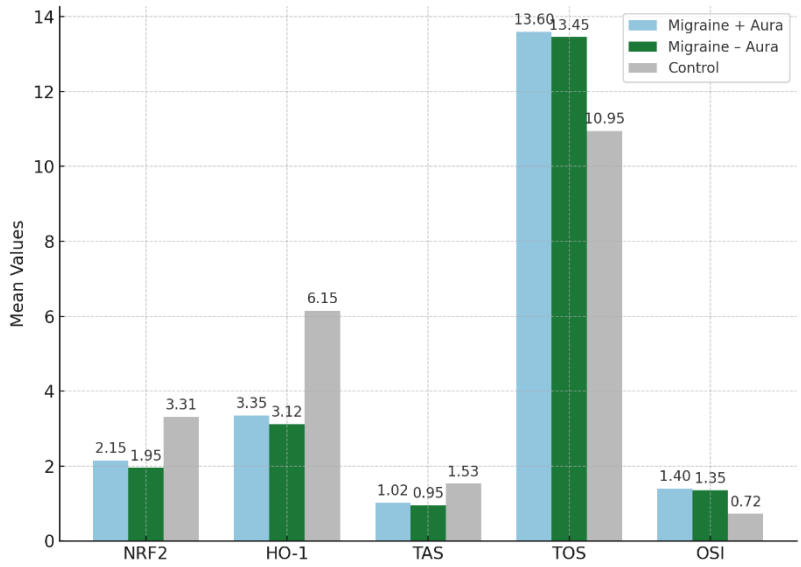

Figure 2: Oxidative stress markers across migraine with aura, without aura, and controls.

an increased oxidant load would be expected to act as a feedback signal triggering NRF2 activation.

Recent research has shown that the NRF2 signaling pathway is directly associated not only with oxidative stress but also with the suppression of glial cell–derived neuroinflammation and the balance of neurotransmitters.[27] Therefore, reduced NRF2 levels in children with migraine may also indicate an impairment in the regulation of excitatory neurotransmitters such as glutamate.

Experimental models[28] and human serum studies have reported that increases in NRF2 and HO-1 levels raise TAS while significantly reducing TOS and OSI.[29] In chronic inflammation models, studies with HO-1-inducing compounds have demonstrated that increased HO-1 levels decrease oxidative stress, improve antioxidant status, and reduce parameters such as OSI.[30]

In our study, consistent with the literature[31], pediatric migraine patients exhibited decreased TAS levels and significantly increased TOS and OSI levels. This increased oxidative load may trigger the activation of immune cells, particularly microglia, initiating a pro-inflammatory response.[32] The release of pro-inflammatory cytokines by microglia and peripheral macrophages under oxidative stress plays a key role in the activation of hypersensitivity and pain pathways.[33]

The elevated OSI and reduced TAS levels observed in our study align with biomarker patterns indicative of mitochondrial dysfunction and disruption of energy metabolism. In migraine pathogenesis, impairments in mitochondrial biogenesis and functional deficiencies may lead to oxidative stress-induced energy deficits, constituting a critical molecular component of the disease.[34] NRF2 has been shown to regulate the expression of transcriptional co-activators

Table 4: Comparison of NRF2, HO-1, TAS, TOS, and OSI levels between the migraine without aura group and the control group

	Migraine without aura group (n= 26)	Control group (n= 27)	P-Value
NRF2	1.90	3.31	< 0.001
HO-1	3.15	6.15	< 0.001
TAS	0.980	1.530	< 0.001
TOS	12.93	10.95	< 0.001
OSI	1.335	0.725	< 0.001

NRF2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

Table 5: Correlations between NRF2, HO-1, TAS, TOS, and OSI levels in the patient group

	HO-1	TAS	TOS	OSI
NRF2	0.000	0.238	0.225	0.226
HO-1		0.071	0.977	0629
TAS			0.922	0.000
TOS				0.000

NRF2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

such as PGC-1α, which control mitochondrial biogenesis.[35] In this context, NRF2 deficiency may contribute to migraine pathophysiology not only by impairing antioxidant defenses but also by disrupting cellular energy production.

In our study, the strong positive correlation observed between NRF2 and HO-1 in the patient group indicates that these two antioxidant factors function in a coordinated manner, whereas the positive correlation between TOS and OSI suggests that OSI is a robust pro-oxidant marker. The negative correlation between TAS and OSI further supports the notion that increased oxidative stress suppresses antioxidant capacity. These findings indicate that the defense systems are insufficient against the increase in oxidative load and that the antioxidant response is suppressed. In addition, HO-1 did not show significant correlations with TOS or OSI, indicating that, unlike NRF2, HO-1 is not directly associated with oxidative load indices in pediatric migraine.

In the subgroup analysis, no significant difference in biomarker levels was found between patients with and without aura. This suggests that despite the clinical differences between migraine phenotypes, the underlying oxidative stress, epigenetic mechanisms, and molecular pathology are shared, and that oxidative stress and antioxidant defense mechanisms may represent a general feature of migraine. This further implies that similar molecular therapeutic targets could be valid across subgroups, even in the presence of clinical differences. Considering that the aura phenomenon may be based on different mechanistic processes such as cortical spreading depression, it is likely that future studies with larger sample sizes will reveal distinct molecular patterns.[36]

Strategies aimed at modulating the NRF2/HO-1 axis may offer innovative targets for both the prevention and treatment of migraine. Experimental models have demonstrated that certain NRF2 inducers, particularly sulforaphane and similar phytochemicals, reduce pain[12], and that natural compounds such as curcumin can alleviate migraine symptoms through antioxidant and anti-inflammatory mechanisms. In a nitroglycerin-induced rat model of migraine, curcumin administration reduced TOS and malondialdehyde levels and significantly improved pain behaviors.[37]

The NRF2/HO-1 axis is also known to be influenced by various external factors such as diet, stress, and environmental toxins. Accordingly, lifestyle interventions such as exercise are suggested to improve redox balance and strengthen

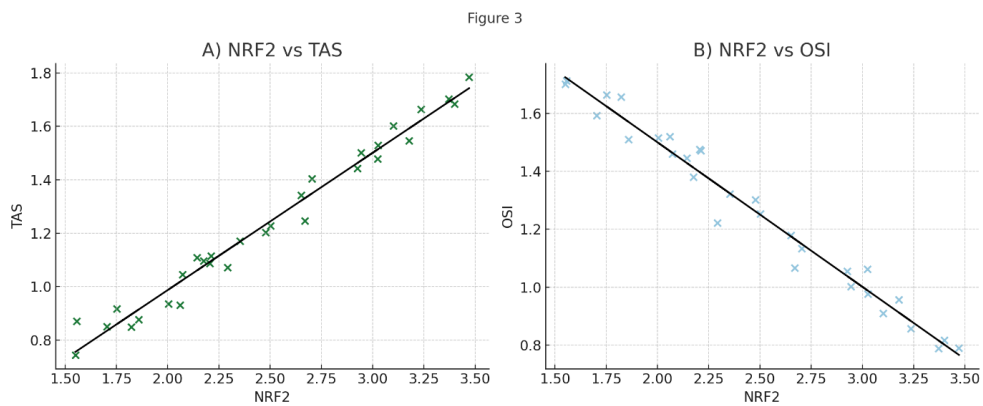

Figure 3: Correlations between NRF2 and oxidative stress indices (TAS, OSI).

Table 6: Comparison of NRF2, HO-1, TAS, TOS, and OSI levels between migraine with aura and without aura

	With aura (n=34)	Without aura (n=26)	P-value
NRF2	2.13	1.91	0.374
HO-1	3.27	3.15	0.697
TAS	0.982	0.980	0.962
TOS	13.96	12.93	0.353
OSI	1.417	1.335	0.525

NRF2: Nuclear factor erythroid 2–related factor 2; HO-1: Heme oxygenase-1; TAS: Total antioxidant status; TOS: Total oxidant status; OSI: Oxidative stress index.

antioxidant defenses.[38] Moreover, diet, stress management, and environmental toxins have been reported to exert a protective potential by modulating the NRF2/HO-1 signaling system and thereby affecting cellular redox balance.[39]

Our study has certain limitations. First, the relatively small sample size and the cross-sectional design may partially limit the generalizability of the findings to larger populations. Although no power analysis was performed to determine the sample size—an aspect that may limit statistical power—all eligible cases reached during the study period were included, which likely reduced the magnitude of this limitation. In addition, the study was conducted in a single center; conducting similar studies in populations with different geographic and demographic characteristics could enhance the generalizability of the results. Future research involving larger, multicenter cohorts combined with genetic and epigenetic analyses is expected to clarify the biological basis of the observed findings more precisely.

To the best of our knowledge, this is one of the first studies to comprehensively evaluate the relationship between oxidative stress and antioxidant defense mechanisms through the NRF2/HO-1 axis in pediatric migraine. In our study, NRF2, HO-1, and TAS levels were markedly lower, while TOS and OSI levels were higher in pediatric migraine patients, indicating both an increased oxidant load and a deficiency in antioxidant defense. The reduction in NRF2 levels suggests a possible impairment in the activation of this transcription factor or in the feedback mechanisms involved in oxidative stress regulation. The absence of significant differences between migraine with and without aura indicates that these molecular axes contribute to the shared pathophysiology of both subtypes. Overall, our findings highlight that the NRF2/HO-1 pathway may serve not only as a biomarker but also as a potential therapeutic target in pediatric migraine.

DISCLOSURE

Conflict of interest: None.

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