A REVIEW ON MIGRAINE AND OXIDATIVE STRESS

Uma revisão sobre migrânea e estresse oxidativo

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RESUMO:

A migrânea é uma doença muito prevalente na população, com importantes impactos pessoais e socioeconômicos, porém ainda pouco compreendida na sua fisiopatologia. Disfunções do sistema trigeminovascular e o fenômeno de depressão alastrante cortical são os principais mecanismos conhecidos. O desequilíbrio oxidativo a nível celular parece ser um possível mecanismo de desencadeamento dos fenômenos que levam à crise de migrânea. O presente artigo apresenta uma revisão sistemática dos estudos sobre marcadores biológicos de estresse oxidativo em 2613 pacientes migranosos, com a maior parte dos estudos demonstrando sinais de desequilíbrio oxidativo, especialmente dos sistemas do óxido nítrico e malondialdeido.

Palavras-chave: migrânea, estresse oxidativo, marcadores biológicos.

ABSTRACT:

Migraine is a highly prevalent disease, with important personal and socioeconomic impacts, but its pathophysiology is still poorly understood. Dysfunctions of the trigeminovascular system and the phenomenon of cortical spreading depression are the main known mechanisms. The oxidative imbalance at the cellular level seems to be a possible mechanism for triggering phenomena that lead to migraine crises. This article presents a systematic review of studies on oxidative stress markers in 2613 migraine patients, with most studies showing signs of oxidative imbalance, especially of the nitric oxide and malondialdehyde systems.

Keywords: migraine, oxidative stress, biological markers.

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1. INTRODUCTION

Migraine is a primary headache characterized by recurrent, moderate to severe headaches, usually unilateral, pulsatile, and lasting between 2 and 72 hours. The main associated symptoms are nausea, vomiting, and sensitivity to light, sound, and odor [1]. It is a highly prevalent health problem with significant socioeconomic and personal impacts. Its pathophysiological mechanism remains unclear despite advances in the last decade, with trigeminovascular system dysfunction and cortical spreading depression as the main mechanisms in the Migraine Without aura (MWoA) and Migraine With Aura (MWA), respectively[1].Oxidative Stress (OS) is characterized by a dysbalance between free-radical production and levels of biological antioxidant systems that can cause damage to DNA, lipids, and proteins[2]. Several studies have suggested that OS could be a part of the etiological process of many diseases, such as cerebrovascular diseases[3] and neurodegenerative disorders[4]. This article aims to review studies on markers of oxidative stress in migraine patients.

2. METHODS

The PubMed-Medline database was searched for articles published from the onset up to August 31, 2019. The following search terms were used: "migraine" AND "oxidative stress". Titles, abstracts, and full-text publications were obtained and screened for original data on clinical and laboratory features. The exclusion criteria were: 1. Non-migraine studies; 2. Non-human studies. No language restrictions were applied. Secondary references were also included if they matched all criteria.

3. RESULTS

The studies evaluated a total of 2613 migraine patients. There were two studies reported during the decade of 1990-1999 [5, 6], 11 during the 2000-2009 decade [7 – 17], 21 during the current decade [18-38] and the number of patients in each period was 62, 519, and 2032 respectively. The patients were predominantly of female gender (81%) and adult age (92%). The method of oxidative stress evaluation was not only through biochemical assays targeting markers of oxidative stress or antioxidant status (Table 1), mainly nitric oxide (NO) derivatives / nitric oxide synthase (NOS) activity and superoxide dismutase (SOD) activity (10 studies each) but also through studies of genetic polymorphisms / genotyping of antioxidant molecules such as SOD, catalase (CAT) and paraoxonase[1] (PON1).

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Table 1. Oxidative Stress in migraine patients**.**

Number of studies	Total number of migraine patients	Method of Oxidative Stress measurement (in blood components)	Studies with result higher in migraine	Studies with result lower in migraine	Studies with result neutral in migraine	References
10	532	NOx levels / NOS activity	6	2	2	8, 10-13, 16, 18, 22, 24, 38
8	525	TBARS / Thiol	3	4	1	6, 8, 11, 16, 30, 32, 35, 38
8	321	SOD activity	1	2	5	5, 9, 13-15, 20, 26, 27
7	294	MDA	5	1	1	11, 14, 15, 17, 24, 26, 27
6	538	TOS/OSI	4	-	2	21, 23, 25, 30, 34, 37
6	356	GSH/GST/GPx/GSSG-R	2	2	2	9, 15, 20, 26, 27, 37
5	228	CAT activity	1	2	2	9, 14, 20, 26, 27
3	216	Arginine/ADMA/SDMA	2	-	1	18, 22, 36
2	199	Homocysteine	-	-	2	16, 38
2	108	HOMA-IR index	2	-	-	18, 25
2	83	FRAP	1	1	-	17, 32
1	48	HNE	1	-	-	24
1	62	Arylesterase activity	-	1	-	23
1	21	15-oxo-dihydro-PGF2α and 8-iso- PGF2α	-	-	1	7

ADMA: asymmetric dimethylarginine, CAT: catalase, FRAP: Ferric reducing activity of plasma, GPx: glutathione peroxidase, GSH: glutathione, GST: glutathione-S-transferase, GSSG-R: glutathione reductase, HNE: 4-hydroxy-2-nonenal, HOMA: Homeostasis Model Assessment, MDA: malondialdehyde, NOS: nitric oxide synthase, NOx: nitric oxide stable metabolites, OSI: oxidative stress index, SDMA: symmetric dimethylarginine, SOD: superoxide dismutase, TBARS: thiobarbituric acid reactive substances, TOS: total oxidant status

4. DISCUSSION

The crescent number of publications on the subject of oxidative stress concerning migraine probably reflects a growing interest of researchers on its pathophysiology mechanisms. Still, in the 1990 decade, migraineurs` lower platelet concentration and activity of superoxide dismutase (SOD) and lower plasma thiobarbituric acid reactive substances (TBARS) were the initial clues on the importance of oxidative status on the pathophysiological mechanism of migraine [5, 6]. In the early 2000s, it was demonstrated that during the headache-free period urinary nitric oxide stable metabolites and TBARS levels were higher in migraine sufferers than in controls[8]. Also, the role of platelets was reinforced with the finding of lower Na+/K+ ATPase activity, higher peroxynitrite production, higher anisotropy of TMA-DPH in platelet membranes, and higher iNOS

protein levels in the platelets of migraine patients compared to controls [10]. Erythrocytes also seemed to have a role in oxidative stress dysregulation in migraine[14, 15,] but not leucocytes[9]. The global analysis of the studies has shown evidence of oxidative stress dysbalance in migraineurs through different methods as nitric oxide system, malondialdehyde (MDA), TBARS, Thiol, Catalase, SOD, Glutathione, Arginine, among others. A previous meta-analysis demonstrated that migraine patients had higher plasma levels of TBARS, lower SOD activity, and higher nitrate/nitrite levels, considering oxidative and nitrosative stress as key events in the pathophysiology of migraine[39].

More recently, genetic studies brought more light into the knowledge of the OS-Migraine relationship. Although some studies failed to demonstrate differences in a panel of 10 polymorphisms in 8 OS-related genes in women with chronic migraine 29, others have shown that SOD2 16 C/T genotype was more frequent in migraineurs than in controls[31], frequencies of the genotype PON1 192QQ and the allelic variant PON1 192Q were significantly higher in patients with earlier onset of migraine[19], and the rs4880 TT (Val/Val) genotype was associated with the presence of unilateral cranial autonomic symptoms in MWA patients[28].

The endogenous reactive oxygen species-produced damage disrupts functions of cytoprotective proteins such as metabolic enzymes and cell membrane transporters[40]. The finding in migraine patients of a higher level of 8-hydroxy-2′-deoxyguanosine (8-OHG), which is an indicator of oxidative DNA damage, suggested evidence of oxidative stress-related DNA damage in migraine[34]. Also, there is evidence of OS induction in the trigeminal nociceptive system by cortical spreading depression [2]. These two studies raise the question if OS could be a consequence of migraine rather than a cause. Nevertheless, there is experimental evidence that reactive oxygen species accumulation might be a trigger of cortical spreading depression[41], an important mechanism in the pathogenesis of migraine with aura. There is also evidence that oxidative stress plays a role in central sensitization[42, 43,] a possible mechanism in the chronification of migraine. There is a critical role of the nuclear factor E2-related factor 2/antioxidant response element (Nrf2/ARE) signaling pathway in nitroglycerin-induced hyperalgesia in rats, and the Nrf2 activator, sulforaphane, inhibited the trigeminovascular system activation and prevented the induction of hyperalgesia, suggesting the potential application of antioxidants in drug development for migraine[44].

5. CONCLUSION

Migraine is a complex multifactorial disease that involves oxidative stress in its pathophysiological process. Knowledge of this process by health professionals is important to better understand and treat migraine patients. More studies are still needed to evaluate the precise mechanisms of OS in migraine pathophysiology.

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