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IMPAIRED OXIDATIVE BALANCE IN MIGRAINE: THE EVIDENCE FROM D-ROMS TEST AND BAP TEST

V. Pizza§, A. Agresta, E.L. Iorio°, A. Capasso*
§Neurophysiopatology Unit, S. Luca Hospital, Vallo della Lucania (SA), International Oxidative Stress Observatory Salerno°, *Department of Pharmacy, University of Salerno, Italy

Abstract

Migraine is the most common neurological disorder, but the molecular basis is still not completely understood. An impairment of mitochondrial oxidative metabolism might play a role in the pathophysiology. Moreover there is strong evidence associating migraine with a variety of comorbid disorders, including cardiovascular disease and stroke, in which oxidative stress seems to be an important underlying mechanism. However, data are in part controversial and the possible underlying mechanism remain elusive to date and the data regarding the interictal state in migraineurs is limited.

To evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.

30 outpatients, (20 F, 10 M) mean age 35.1 years (SD 11.4), range 18-56 years, suffering from migraine without aura (ICDH-II 2004 criteria) were enrolled. The mean duration of disease was 1.1 (SD 0.3) years, range 1-2 years. Serum total oxidant capacity was determined by performing the d-ROMs test (2), which chemical principle is based on the ability of a biological sample to oxidize N,N-diethylparaphenylenediamine (normal range 250-300 CARR U, where 1 CARR U is equivalent to 0.8 mg/L H_2O_2), while serum total antioxidant capacity was assessed by means of BAP test, which measures the ability of a serum sample to reduce iron from the ferric to the ferrous ionic form (optimal value >2200 micromol/L reduced iron).

Mean values of d-ROMs tests were 387.3 CARR U (SD 134.7) while mean values of BAP test were 1703.5 micromol/L reduced iron (SD 471.4).

According to herein reported data, enrolled patients were found to be in a classical condition of oxidative stress. In fact compared to the normal range, oxidant capacity, as measured by means of d-ROMs test, was increased (>300 CARR U) and biological antioxidant potential (as measured by means of BAP test) was decreased (<2200 micromol/L reduced iron). Although preliminary our study confirm that migraine without aura is associated to oxidative stress and suggests that d-ROMs test and BAP test can be useful to identify an oxidative unbalance in clinical routine of patients suffering from this frequent disease. Our data suggest that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target. Further knowledge about this issue may contribute the cause and complications of migraine and may be essential for development of treatment approaches.

Key Words: Migraine, headache, Oxidative stress, Antioxidants

Introduction

Migraine is a common, disabling, primarily neurovascular disorder characterized by severe episodic headaches with systemic or neurological symptoms. The molecular mechanisms of migraine have not yet been clearly defined; but several hypotheses have been put forward. Inherited factors such as disturbances in the magnesium metabolism, calcium channelopathies, and abnormalities of mitochondria all increase the neuronal excitability leading to an impairment in the oxidative metabolism which can explain the threshold character of migraine attacks (1-3). Reactive oxygen species (ROS) such as superoxide radical anions, hydroxyl radicals and hydrogen peroxides are produced during metabolic and physiological processes and harmful oxidative reactions may occur in the organism. Under certain conditions, increases in oxidants and decreases in antioxidants are inevitable, and the oxidant/antioxidant balance shifts towards oxidation. Consequently, oxidative stress is implicated in over 100 disorders (4,5). Disorders of oxidant-antioxidant balance underlie a number of acute and chronic diseases of the central nervous system including epilepsy and migraine (6). The hypothesis of oxidative stress in migraine is supported by the findings in various studies (7-10). Oxygen free radicals may play a role in migraine by regulating cerebral blood flow and energy metabolism and may constitute a trigger threshold for migraine attacks (11).

The aim of the study to evaluate the oxidative balance in a sample of patients with migraine by means of routine specific serum tests, such as d-ROMs test and BAP test.

Our study showed that oxidative/antioxidative balance shifted towards the oxidative status in migraine. suggesting that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target.

Patients and Methods

The study was performed and approved by Neurophysiopatology Service, Headache Centre, S. Luca Hospital, Vallo della Lucania (SA),Italy.

The study sample consists 30 outpatients, (20 F, 10 M) mean age 35.1 years (SD 11.4), range 18-56 years, suffering from migraine without aura (ICDH-II 2004 criteria) were enrolled. The mean duration of disease was 1.1 (SD 0.3) years, range 1-2 years (See Table I).

Oxidative status measurements

Serum total oxidant capacity was determined by performing the d-ROMs test (derived Reactive Oxygen Metabolites) (18), whose chemical principle is based on the ability of a biological sample to oxidize N,N-diethylparaphenylenediamine (DPPD) and serum total antioxidant capacity was assessed by means the BAP tests (Biological Antioxidant Potential) which measures the ability of a serum sample to reduce iron from (optimal value >2200 micromol/L reduced iron). These test were determined using the Free Radical Electing Evaluator (FREE, Diacron, Grosseto, Italy) photometric system.

Results

Mean values of d-ROMs tests were 387.3 CARR U (SD 134.7) while mean values of BAP test were 1703.5 micromol/L reduced iron (SD 471.4) (See Table I).

The results of our study indicates that the mean values of d-ROMs tests is 387,3 (SD 134.7) (range normal values is 250-300 U.CARR (Carratelli Unit; 1 U. CARR = 0.8 mg/L H_2O_2.) The mean value of BAP test is 1703,5 (SD 471.4) (range normal values is 2200-4000 microMol/L) (See Table I). Values □'3f□'3fin the normal range were measured for 7 patients for the values □'3f□'3fof Droms and for 3 patients for the values □'3f□'3fof BAP.

Discussion

The pathophysiology of migraine and other headaches is still unknown; and research is mostly conducted on neurotransmitters, biochemical and

vascular mechanisms. The neuro-vascular theory of migraine seizure pathogenesis is the most widely accepted one. Stimulation of the trigeminal nerve occurs via neuronal and chemical pathways, through serotonin, histamine and prostaglandins. Migraine inducing factors can act directly on these chemical mediators or via the nervous system mediators. One of the hypotheses of the origin of headache in migraine is that of neurogenic inflammation of dura mater presented by Moskowitz et al. (15). According to that model, central stimulation in the trigeminal nerve endings causes an antidromic release of substance P, calcitonin gene-related peptide (CGRP) and neurokin A, which increase the permeability of vascular walls, dilates them with a likely involvement of nitric oxide (NO) and enhances the action of blood-derived factors, such as histamine and serotonin. This leads to inflammatory reactions and blood vessel oedema, i.e. aseptic inflammation of arteries (6,16.17). Oxidative stress is a term used to describe situations during which the organism's production of oxidants exceeds its capacity to neutralize them.

The result can be damage to cell membranes, lipids, nucleic acids, proteins, and constituents of the extracellular matrix such as proteoglycans and collagens (18). It has been suggested that oxidative stress caused by free radicals may play a role in migraine pathogenesis (10,19). The enhanced ROS attack might be explained by the existence of cytokines and increased neutrophils activation in the blood of patients with migraine. Various studies demonstrated the inappropriate release of ROS such as nitric oxide (NO) and superoxide anion from activated polymorphonuclear leucocytes, both in the bloodstream of patients with migraine (6,8,20-23).

Oxidative stress can be defined either as an increase in the level of oxidants and/or a decrease in the antioxidant capacity. Although determination of either oxidant or antioxidant components alone may give information about oxidative stress; determination of oxidants along with antioxidants is more useful in this context. Thus, oxidants and antioxidant capacities should be measured simultaneously to assess oxidative stress more exactly.

Our study showed that oxidative/antioxidative balance shifted towards the oxidative status in migraine suggesting that oxidative stress may represent a key event in the pathophysiology of migraine and a suitable therapeutic target.

Further knowledge about this issue may contribute the cause and complications of migraine and may be essential for development of treatment approaches.

Our findings suggest that oxidative stress may not only play a role in migraine pathogenesis but also is a triggering factor for attack severity and duration. Supplementation of regular treatment regimes with powered antioxidants may be considered in these patients.

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Patients	Sex	Age	Age disease	BAP	dROMs
1	f	29	1	1227	658
2	f	38	1	1073	422
3	m	18	1	2144	233
4	f	18	1	2579	270
5	f	49	1	1662	469
6	m	31	2	1660	178
7	f	39	1	1780	510
8	m	45	1	1034	425
9	f	33	1	2075	181
10	f	56	1	1392	439
11	m	30	1	2112	509
12	f	55	2	2333	400
13	f	34	1	1456	534
14	f	33	2	1987	245
15	f	29	2	1876	211
16	m	48	1	1655	332
17	f	52	1	2459	321
18	m	35	1	1687	156
19	f	44	1	1945	567
20	f	41	1	1995	425
21	f	38	1	1502	234
22	f	46	2	1583	578
23	f	30	2	1539	352
24	f	31	2	1058	393
25	f	22	1	1028	298
26	m	20	2	1746	368
27	m	19	1	1850	468
28	m	23	2	1683	475
29	f	26	1	1535	455
30	m	40	1	1450	546

Table I: Data sample and value BAP and dROMs test