ORIGINAL ARTICLE

The levels of trace elements and heavy metals in patients with acute migraine headache

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Abstract

Objective: To compare the levels of trace elements and heavy metal in patients with acute migraine and healthy controls.

Methods: The prospective study was conducted at Yuzuncu Yil University, Turkey, from May to July 2013, and comprised migraine patients and an equal number of healthy controls. International Headache Society classification was used for diagnosing migraine. Serum copper, zinc, lead, iron, cadmium, cobalt, manganese, and magnesium levels were measured in both groups. Metal concentrations were assessed by atomic absorption spectrophotometry. SPSS 13 was used for statistical analysis.

Results: There were 25 migraine patients with an average age of 36.4±8.9 years and 25 healthy controls with a mean age of 42.4±9.5 years. Cadmium, iron, manganese and lead levels were significantly elevated in the patients compared to the controls ($p<0.05$ each), while copper, magnesium and zinc were decreased and cobalt demonstrated no change.

Conclusions: Trace elements and heavy metals may have a role in the genesis of considerable oxidative stress in patients with acute migraine headache.

Keywords: Acute migraine attack, Trace elements, Heavy metals. (JPMA 65: 694; 2015)

Introduction

Migraine is a widespread neurovascular brain disorder. It is typically characterised by recurrent attacks of disabling headaches and associated symptoms, such as vomiting, nausea and sensitivity to light, sound and head movements.[1-3] Headaches are generally characterised by unilateral throbbing and are one of the most commonly reported complaints among the general adult population.[1,2] Headaches account for 1% to 3% of admissions to emergency department (ED) in the USA.[4] Migraines affect 12% of the general population in the USA.[5] A study conducted in Pakistan reported that migraneous headaches generate 35% of all headaches.[6]

Although the number of studies related to migraine pathophysiology have increased, especially in recent years, but the exact aetiology is not well understood. Several hypotheses have been proposed.[3,7] Additionally, the lack of specific biological markers creates a significant barrier to the treatment and diagnosis of migraines. Recently, some macrominerals and trace elements have gained recognition as important for the treatment and diagnosis of migraines.[8] Emergency medicine clinical researchers with an interest in headaches are focussed on defining efficient approaches to diagnosis, optimising acute treatment, creating improvements throughout in the ED, and reducing the need for future ED care.[8]

We hypothesised that trace elements maybe raised during migraine attacks as compared to the healthy controls.

Patients and Methods

The prospective study was conducted at Yuzuncu Yil University, Turkey, from May to July 2013, and comprised migraine patients and an equal number of healthy controls who were enrolled using a simple random sampling method. Patients with acute migraine attack (AMA) admitted to the ED represented the cases. IHS (International Headache Society) classification was used to make the diagnosis of migraine.[9] Patients were examined neurologically. All AMA patients were treated similarly in ED. Treatment was symptomatic and consisted of intravenous (IV) or intramuscular (IM) analgesic and antiemetic. Protective measures were taken, such as the low light and quiet environment. The control group comprised healthy volunteers working in a hospital. All the subjects in the control group, according to medical

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records, history and physical examination, were unremarkable. None of the subjects in either group had been taking antioxidant vitamin supplements. All the subjects were non-smokers.

The study was conducted in accordance with the Helsinki Declaration as revised in 2000 and was approved by the institutional ethics committee. All of the subjects were informed about the study and the written consent was obtained from each one of them.

According to history, previous medical records, laboratory features and physical examination, the exclusion criteria comprised alcohol abuse, habitual smoking, IV drug abuse, pregnancy, antioxidant supplements, hypertension, diabetes mellitus, liver or renal disease, pulmonary disease, history of stroke and coronary artery disease (CAD) affecting oxidative stress (OS).

Blood samples were collected from both the groups, placed into empty tubes and immediately stored at 4°C. The serum samples were then separated from the cells by centrifugation at 3000 rpm for 10min. The serum samples were stored in plastic tubes at -80°C and used to analyse iron (Fe), magnesium (Mg), manganese (Mn), Zinc (Zn), cadmium (Cd), cobalt (Co), lead (Pb) and copper (Cu) levels. Determination of serum concentrations of Fe, Mg, Mn, Zn, Pb, Co, Cd, and Cu was performed by Atomic Absorption Spectrophotometer measurements, in which a UNICAM-929 spectrophotometer (Unicam Ltd, York Street, Cambridge, UK) was used.

Data was analysed using SPSS 13.The confidence interval (CI) (margin of error) was used to roughly determine the sample size. A power analysis was executed after data analysis and obtained power ranged from 0.92 to 0.99 for the traits included in this research. Descriptive statistics for studied variables (characteristics) were presented as mean, standard deviation, minimum and maximum values. Student 't' test was used to compare control and patient groups for the variables studied. The levels of statistical significance were considered as 5%.

Results

Of the 50 subjects in the study, there were 25(50%) cases and 25(50%) controls. Among the cases, 22(88%) were females and 3(12%) were males with an overall mean age of 36.4±8.9 years. Among the controls, there were 21(84%) females and 4(16%) males with an overall mean age of 42.4±9.5 years.

Serum levels of Cu (p<0.001), Mg (p<0.001) and Zn (p<0.001) were significantly lower in patients with AMA compared to the controls. Serum levels of Cd (p=0.005), Fe (p<0.001), Mn (p<0.001) and Pb (p<0.001) were higher in the cases compared to the controls. No significant difference was detected between the groups with respect to serum Co level (p=0.006) (Table).

Table: Comparison heavy of blood levels of various between cases and controls.

Parameteres	Control Group		Patient Group		p
	Mean	St.Dev.	Mean	St.Dev.	
Cd (µg/dl)	0.09	0.14	0.36	0.38	0.005*
Co (µg/dl)	0.88	0.05	0.83	0.08	0.006*
Cu(µg/dl)	8.90	0.73	4.63	0.42	<0.001**
Fe (µg/dl)	0.48	0.06	0.97	0.07	<0.001**
Mg (µg/dl)	34.51	1.99	10.58	1.09	<.0001**
Mn (µg/dl)	0.62	0.07	2.30	0.21	<.0001**
Pb (µg/dl)	0.70	0.07	1.48	0.48	<.0001**
Zn (µg/dl)	5.77	0.71	0.24	0.01	<.0001**

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*Denotes a significant difference (P < 0.05)
**Denotes a highly significant difference (P < 0.001)
Cd: Cadmium
Co:
Cu: Copper
Fe: Iron
Mg: Magnesium
Mn: Mangnese
Pb: Lead
Zn: Zinc.

Discussion

The study investigated the serum levels of essential trace elements and heavy metals in patients with migraine attack. To our knowledge, this is the first study of its kind. We found that serum levels of Cd, Pb, Fe and Mn were significantly higher but serum levels of Cu, Zn and Mg were significantly lower in patients with acute haemorrhagic stroke than in the controls. Moreover, serum Co levels were significantly lower in the patients with acute haemorrhagic stroke compared to the controls. However, this difference was not statistically significant. In the light of our results, it can be said that trace element level disturbances might predispose people to migraine attacks.

Although many studies seeking to understand the

pathophysiology of migraine have been conducted, but the exact aetiology remains unknown.[10,11] However, it is thought that migraines are a neurovascular response, and the factors causing migraine include genetics, Mg deficiency, excitatory amino acids, neurophysiological changes, monoamines, the hypothalamic-pituitary-adrenal axis, opioids and endogenous pain control systems.[10,11] Recently, some minerals and trace elements have started to gain recognition as biological parameters in the pathogenesis of migraine.[10] However, relatively little research has been performed regarding their role in various diseases, despite the vital importance of these elements. Metals may have a role in the pathogenesis of acute migraines.[10] Metals deserve attention in this field because of their diagnostic and therapeutic values in clinical trials.[10] Low levels of Mg in patients with migraine were noted, and headaches were also found to be associated with toxic metals.[10] Continuous exposure to Pb is concomitant with headaches.[1] There is a vast amount of information regarding the relationship between metal concentrations and various diseases such as malignancies and CAD.[12-14] However, there are few studies investigating the relationship between migraine and heavy metals.

A close association between migraines and Mg has been observed.[11] In accordance with our results, a low serum concentration of Mg has been noted in patients with migraine attacks.[3,15] Mg has an important role in mitochondrial energy production.[3,10,15] Mitochondrial dysfunction leads to impaired oxygen metabolism, which has been speculated to play a role in the pathophysiology of migraine.[3] Therefore, large clinical trials have been initiated to administer Mg as a therapy for migraine.[15] As previously indicated, the positive role of Mg in the prevention of migraines may be due to a variety of mechanisms, such as its function in mitochondrial energy production, cerebral artery relaxation and substance P and other neurotransmitter production and regulation.[3] A study[16] has suggested that nitric oxide, which is a vasoactive substance, leads to migraine attacks. Nitric oxide production can be regulated by changes in Mg concentration. Low Mg might inhibit the production of nitric oxide.[12] Mg plays an important role in substance P regulation.[11] Low levels of Mg increase the release of substance P, thus causing the constriction of cerebral vessels. Serotonin, which is a potent cerebral vasoconstrictor, is released from platelets during a migraine attack. Low levels of Mg facilitate serotonin release, inducing cerebral vasoconstriction.[17] In an in vitro study, Mg was shown to have a strong vascular dilating effect. Mg is responsible for control of N-methyl-D-aspartate (NMDA) glutamate receptors, which play an important role in pain. Our findings were in agreement with the results of various studies using Mg for prophylaxis of migraines. One study observed a significant reduction in the incidence of migraine attacks in patients treated with Mg.[18] In the present study, the Mg concentration in serum was significantly reduced in patients with migraine compared to healthy controls. The results of our study show that the serum concentration of Zn was significantly reduced in patients with migraines compared to healthy controls. Zn may also be involved in migraine pathology. Zn predominantly modulates glutamatergic neurotransmission and is important in vesicles for glutamate storage. Glutamate may affect vascular tone and may cause migraine attacks.[10] Zn is stored together with glutamate in synaptic vesicles, and it acts as an antagonizing co-transmitter on NMDA receptors. Zn can inhibit the function of the NMDA receptor complex.[10] The exact role of Zn is not clear in literature.

We also found significantly higher Mn levels in patients with migraines compared to healthy controls. Mn facilitates the function of many enzymes and is essential for normal development and bodily function. Headaches were reported in patients receiving long-term parenteral Mn. After the administration of Mn was stopped, these symptoms disappeared.[10] Chronic Mn intoxication has an insidious and progressive course and typically starts with complaints of headache. Further studies are required to elucidate the exact role of Mn in migraine.

In our study, the serum levels of Pb were significantly higher in patients with migraines compared to the healthy controls. It has been reported that Pb increases OS.[19] A recent report suggested a link between occupational exposure to Pb and brain tumours.[13] The relationship between acute migraine and Pb remains largely unknown; there are several clues suggesting that Pb exposure may affect the prevalence of acute migraines. However, the epidemiological literature examining the association between Pb exposure and migraines is inconclusive. Continuous exposure to Pb causes increased blood Pb levels, leading to headaches. Blood Pb levels are influenced by smoking and wine consumption. High Pb levels may cause irreversible injury to the central nervous system. The present study also demonstrated that Fe levels were increased in patients compared to the controls. The exact reasons for this are also not clear. However, both Fe excess and Fe deficiency have been reported to lead to oxidative deoxyribonucleic acid (DNA) damage.[20] Little is known about the relationship between migraines and Fe.[2] Further research is required to clarify any role of Fe in migraine pathophysiology. Another finding in our study was lower

blood Cu levels in patients compared to controls. Serum Cu levels are known to be increased in several malignancies such as osteosarcomas, gastrointestinal tumours, and lung cancer.[14] However, detailed information regarding the relationship between migraines and Cu is lacking in literature.

In the present study, there was a minor decrease in the serum level of Co in patients with acute migraines compared to the controls. In literature, there are only five cases of severe adverse effects on the nervous system associated with Co that was released from prostheses. Moreover, Co neurotoxicity of the auditory and optic nerves has been reported after oral intake during the treatment of refractory anaemia. No relationship with headaches has as yet been reported.[21]

The study also found higher Cd levels in patients with acute migraines compared to controls. Cd is one of the most toxic environmental and industrial pollutants. Its industrial applications were developed due to its unique chemical and physical properties. Most studies have not provided information on the potential confounders of Cd toxicity. Cd is an established toxic and carcinogenic metal.[22,23]

The current study had its limitations. First, it comprised a relatively small number of AMA patients. Second, it did not obtain blood samples of stable migraine patients or the same patients before or after the attack.

Conclusions

Lower ionized Mg and Zn concentrations may be related to the frequency of migraine attacks, and administration of Mg and Zn may reduce the frequency of such attacks. Trace elements and heavy metals may have a role in the genesis of considerable OS in AMA patients. These levels may help provide a new treatment regimen. Further studies with multiple centres and large case series are required to illuminate the roles of trace elements and heavy metals in AMA patients.

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