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ORIGINAL PAPER

CONCENTRATION OF MAGNESIUM IN THE SERUM AND THE ABILITY STATUS OF PATIENTS WITH RELAPSING-REMITTING MULTIPLE SCLEROSIS

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Abstract

Multiple sclerosis (MS) is the most common autoimmune disease affecting the central nervous system, characterized by the presence of scattered foci of demyelination in the brain and spinal cord. Magnesium (Mg) has a significant influence on the nervous system and the immune system. The aim of this study was to evaluate the influence of the concentration of Mg in the serum on the ability status of patients with MS. The study group consisted of 101 adults with diagnosed relapsing remitting MS. All participants were investigated on the Expanded Disability Status Scale. The control group included 41 people. The concentration of Mg in the serum was determined by the flame atomic absorption spectrometry method. The patients completed a survey and a 24-hour dietary interview. In patients with MS, the percentage of respondents with normal magnesium content was significantly lower than in the control group ($p < 0.05$). The study proved that patients with normal Mg serum concentration levels were in better clinical condition, particularly with respect to the function of the pyramidal tract ($p = 0.007$) and sphincters ($p = 0.002$), than patients with inadequate levels of Mg in the serum. External factors such as gender, smoking, immunomodulating medications or dietary supplements of Mg were found to have no effect on the concentration of Mg in the serum of MS patients. The results of

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our study suggest that an abnormal concentration of Mg in the serum of MS patients should be recognized and corrected, as this may improve the health status of people with MS.

Keywords: multiple sclerosis, magnesium, EDSS, environmental factors, diet.

INTRODUCTION

Multiple sclerosis (MS, *lat. Sclerosis multiplex*) is a central nervous system disease characterized by the presence of scattered foci of demyelination in the brain and spinal cord, with initially transient and later on often permanent neurological disability. It usually affects young Caucasian people, between 20 and 40 years of age (Lublin, Reingold 1996). It is currently believed that multiple sclerosis is an autoimmune disease where the host's immune system combats own cells in nervous tissue (Kipp et al. 2012).

Minerals supplied with a diet play important functions in the human body. Magnesium (Mg) has a significant effect on the nervous system by reducing the excitability of nerve cells. It affects autonomic ganglia by increasing their inhibitory effect and weakening their stimulant effect. Mg ions compete with calcium ions on the nerve endings, thereby preventing excessive stimulation (Kim et al. 2012). Mg deficit may induce dysfunction of nerve cells or lymphocytes directly and/or indirectly (Durlach 1991), and thus Mg depletion may be implicated in the aetiology of MS. Mg interacts with other minerals and/or metals, such as calcium, zinc and aluminium, in biological systems, affecting the immune system and influencing the content of these elements in tissues of the central nervous system (Yasui, Ota 1992). Mg activates about 320 enzymes. Several studies have shown that antioxidant therapy is beneficial *in vitro* and *in vivo* animal models for MS treatment. Since oxidative damage has been known to be involved in inflammatory and autoimmune-mediated destruction of tissue, modulation of oxygen free radical production represents a new approach to the treatment of inflammatory and autoimmune diseases (Mirshafiey, Mohsenzadegan 2009).

The aim of the study has been to find answers to the following questions: Do external factors such as gender, smoking, immunomodulatory drugs and dietary supplements affect the serum levels of Mg in patients with MS? Is the level of serum Mg reflected in the clinical status of patients with MS? Is a diet of MS patients suitably formulated in terms of the Mg content?

MATERIAL AND METHODS

Study design

The study group included 101 adults aged from 18 to 58 years, under the care of a neurologist in the health clinic NZOZ Kendron, with diagnosed re-

lapsing remitting multiple sclerosis (RR MS). Patients eligible for the study met the McDonald criteria for a diagnosis of MS and had a relapsing clinical course (McDonald et al. 2001). All participants were investigated on a 10-point EDSS scale (Extended Disability Status Scale). The EDSS quantifies disability in eight Functional Systems (FS). The FS are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual and emotional condition and evaluation of walking. FS values were assessed through an examination conducted by a neurologist physician.

Immunomodulatory drugs (*interferon beta, fingolimod, natalizumab, glatiramer acetate*) were taken by 52% of patients with MS. Blood samples were drawn from patients not treated wit corticosteroids, in remission, with a recent relapse of the disease taking place from eight months to six years ago.

The control group consisted of 41 healthy volunteers, chosen to match the study group with regard to age and sex. The control group and study group were compared and the results are shown in Table 1.

Table 1

Characteristics of controls and patients

Variables	Controls	Patients
Sex (M/F)	12/29	37/64
Age (years) – mean (range)	40.09 ± 14.1 (19-65)	40.86 ± 10.2 (18-58)
Smoking*****/no smoking	18/23	45/56

M – male, F – female, ***** number of cigarettes: 5-20 daily

Blood sample: collection and analysis

Blood samples were drawn from patients and control group using the vacutainer system test tubes containing clot activator (Becton Dickinson, France). The samples were allowed to clot for 30 min aand were then centrifuged for 10 min at approximately 1000 × g. Serum was removed and kept frozen at −20°C.

The concentration of Mg in the serum was determined by the flame atomic absorption spectrometry method with Zeeman background correction (Z-2000 instrument, Hitachi, Japan). Certified reference material of human serum (Seronorm Trace Elements, Serum Level 1, 0903106, Sero AS, Norway) was used to test the accuracy of this method. The results of the quality control analyses corresponded with the reference values.

Questionnaires: collection and estimation

The patients filled out a survey concerning eating habits elaborated by the Committee of Human Nutrition Science, Polish Academy of Sciences (Przysławski et al. 2013) and containing questions about the age, gender, weight, height, exposure to external factors such as tobacco smoke, drugs,

supplements, affecting the health status. Additionally, food-frequency questionnaires were distributed to collect dietary data from the patients (Szponar et al. 2000).

All the data were analyzed using the computer programme Diet 5.0 recommended by the Food and Nutrition Institute in Warsaw (Poland), and compared to relevant standards (Wojtasik et al. 2012). The Food and Nutrition Institute in Warsaw (Poland) is a science research institution which elaborates nutritional recommendations for the Polish population.

Ethics approval and consent to participate

The protocol of the study was approved by the Local Ethical Committee (R-I-002/70/2011) and a written consent was taken from all patients.

Statistical analysis

Statistical analyses were performed using Statistica 10.0 Software. Descriptive statistics were used and differences between independent groups were tested with Student's *t*-test, and the Mann-Whitney *U*-test (non-parametric). The relationship between continuous categorized data was assessed with a standard ANOVA test. Normality of distribution was checked using the chi-square test.

RESULTS

Concentration of Mg in the serum

The average Mg content in the serum of people with MS equaled 0.906 ± 0.13 mmol L^{-1} and was similar to that in the control group (0.904 ± 0.11 mmol L^{-1}) – Table 2.

Table 2

Comparison of Mg (mmol L^{-1}) serum concentration in patients with MS and in control group

Specification	Mg (mmol L^{-1}) A mean ± SD (min. - max.)	Mg (mmol L^{-1}) B mean ± SD (min. - max.)	A/B *p* value
All subjects	0.903 ± 0.11 (0.736 - 1.218)	0.906 ± 0.13 (0.630 - 1.292)	0.928
Smoking	0.934 ± 0.11 (0.774 - 1.136)	0.872 ± 0.11 (0.670 - 1.086)	0.123
No-smoking	0.891 ± 0.12 (0.736 - 1.218)	0.911 ± 0.14 (0.654 - 1.292)	0.420

Reference range Mg: 0.7 - 1.0 mmol L^{-1} (Neumeister et al. 2013)
A – control group, B – MS patients

The Mg content in the serum should range from 0.700 to 1.000 mmol L^{-1} (Neumeister et al. 2013). In total, 83% determination results from the control group were within this range, while the percentage in the group with MS (65%) was significantly lower (Table 3, $p = 0.023$).

Table 3

The percentage distribution of magnesium serum concentration in MS patients and control group

Mg concentration in the serum	A (% person)	B (% person)	*p* value A/B
Below reference range	0	9	0.023
In reference range	83	63	
Above reference range	17	28	

A, B – see Table 1

Concentration of Mg in the serum and EDSS

The average value achieved on the FS EDSS scale was 3.34±1.5. The minimum and maximum points on the EDSS scale scored by MS patients received were 1 and 6.5, respectively. 14% of MS patients scored 1-1.5 points. Most patients (29%) had an overall EDSS score of 2 to 2.5, while the fewest patients (10%) obtained 6-6.5 points, no-one received 7 or more points. The duration of the disease averaged 5.44 ± 5.3 years. The one-way ANOVA analysis performed demonstrated that FS scores were significantly better in patients with MS whose serum Mg levels were within the reference values, particularly regarding the function of the pyramidal tract (FS = 2.00 ± 0.9) and sphincters (FS = 0.33 ± 0.6), compared to MS patients with inadequate Mg levels (too low: pyramidal FS = 3.00 ± 0.6; sphincters FS = 1.33 ± 0.8) (too high: pyramidal FS = 2.30 ± 0.7; sphincters FS = 0.84 ± 0.9) – Table 4. Patients with normal Mg serum concentration levels were in better clinical condition than people with inadequate levels of Mg in the serum.

Concentration of Mg in the serum and another factors

Factors such as gender, smoking, immunomodulatory medications or supplements did not have any significant influence on the concentration of Mg in the serum of MS patients (Table 5).

Concentration of Mg in diet

Analysis of a 24-hour dietary recall study by MS patients, including only food products but excluding supplements, showed that an average content of Mg in a diet was 300.56±127.9 mg/day (min. 73.61, max. 764.54), whereas an estimated average requirement for adults is about 300 mg d^{-1} (Wojtasik et al. 2012). More than half of the people with MS (58%) did not cover the demand for Mg from their diet. The intake for each person was determined individually, taking into account the age and gender.

Table 4

Disability status of patients with MS depending on the concentration of Mg in the serum

Disability status	Group			*p* value	F
	I (n = 9)	II (n = 64)	III (n = 28)		
EDSS overall	4.333 ± 1.43	2.989 ± 1.46	3.864 ± 1.49	0.019	4.16
Pyramidal	3.000 ± 0.63	2.000 ± 0.91	2.526 ± 0.70	0.007	5.32
Cerebellar	2.000 ± 0.63	1.119 ± 1.06	1.684 ± 1.25	0.063	2.88
Brainstem	1.167 ± 0.75	0.833 ± 0.91	1.368 ± 1.16	0.138	2.04
Sensory	2.000 ± 0.89	1.643 ± 0.82	1.895 ± 1.05	0.462	0.78
Bowel and bladder	1.333 ± 0.81	0.326 ± 0.64	0.842 ± 0.96	0.002	6.50
Visual	0.833 ± 0.98	0.738 ± 0.89	0.842 ± 1.01	0.910	0.09
Emotional condition	0.333 ± 0.82	0.186 ± 0.55	0.211 ± 0.42	0.822	0.19

Group I – patients with MS who have a concentration of Mg in serum below norm < 0.7 mmol L^{-1}
Group II – patients with MS who have a concentration of Mg in serum in norm 0.7- 1.0 mmol L^{-1}
Group III – patients with MS who have a concentration of Mg in serum above in norm > 1.0 mmol L^{-1}

Table 5

Mg (mmol L^{-1}) serum concentration in patients with multiple sclerosis (MS)

Variable	Mg (mmol L^{-1}) mean ± SD (min. - max.)	Mg (mmol L^{-1}) mean ± SD (min. - max.)	*p* value
Gender	male (n = 37) 0.903 ± 0.15 (0.667 - 1.294)	female (n = 64) 0.909 ± 0.12 (0.631 – 1.142)	0.840
Immunosuppressive drugs	taking (n = 52) 0.897 ± 0.13 (0.655 - 1.142)	no taking (n = 49) 0.916 ± 0.14 (0.639 – 1.294)	0.444
Smoking/No smoking	yes (n = 45) 0.872 ± 0.11 (0.667 - 1.087)	no (n = 56) 0.911 ± 0.14 (0.655 - 1.293)	0.233
Mg supplementation	yes (n = 23) 0.894 ± 0.12 (0.654 - 1.054)	no (n = 77) 0.910 ± 0.15 (0.631 - 1.294)	0.598

n – number of patients

A total of 23% of MS patients supplemented Mg in the diet, while only 17% did so in the control. No correlation was established between the Mg concentration in the serum and Mg in a diet.

DISCUSSION

There have been few studies on the concentration of Mg in the blood of people with MS. However, our research showed that although the average

serum Mg concentration was normal, there were certain abnormalities, because a high number of patients with MS had an inappropriate concentration of Mg in the serum (too low or too high).

Other authors revealed a decrease in the concentration of Mg in patients with MS in the central nervous system tissues and in visceral organs such as the liver, spleen, kidney, heart and lungs. The average Mg content of MS patients in the CNS tissues, as well as in visceral organs except the spleen, was significantly lower than in the control group (Durlach et al. 2004, Johnson 2000).

Additionally, it is also alarming that as many as 35% of MS patients had an incorrect serum Mg concentration, of which 27% had concentrations above the norm, which may indicate a deregulated Mg metabolism.

Disorders in the Mg balance in the human body are well known. Primary magnesium deficiency in the nervous system appears to be the best descriptive model for the analysis of symptomatology, aetiology, pathophysiology, diagnosis and treatment of the most common forms of Mg deficit (Tarasov et al. 2015). The Mg imbalance is associated with such symptoms as hyperventilation, spasmophilia, chronic fatigue syndrome, neurocirculatory asthenia and idiopathic Barlow's disease (Durlach et al. 1997, Tarasov et al. 2015). Our research showed that patients with abnormal levels of Mg suffered from a poor function of the bowel and bladder, which was also demonstrated by Caddell (1996), who detected shock and tissue injury, especially of the intestine. Tissues from animals deficient in Mg are more susceptible to oxidative injury and lipid peroxidation than tissues from animals with normal Mg levels. Mg deficiency impairs antioxidant defence through decreased synthesis of glutathione and reduced activity of Cu/Zn superoxide dismutase. Consequences of Mg deficiency may include increased synthesis or activity of injurious mediators: IL-1, IL-6, TNF, endothelin, and oxygen free radicals (Caddell 1996).

Epidemiological investigations have demonstrated that environmental factors may contribute to the pathogenetic processes in MS (Nieves et al. 1994, Hanwell et al. 2008, Salzer et al. 2010, Handel et al. 2011, D'hooghe et al. 2012). In our study, no correlation was found between the serum levels of Mg and Mg provided with a diet. Bitarafan et al. (2014) showed that an average intake of Mg by MS patient was approximately 240 mg/day/person, while lower Mg diets were correlated with higher fatigue scores in these patients. Very similar results were obtained by Ramsaransing et al. (2009). Mg supplied from natural sources reached on average 250 mg d^{-1}. Both authors mentioned above showed an insufficient supply of Mg with a diet, a result which is slightly divergent from our data.

CONCLUSIONS

Our research shows that both patients with a deficiency and an excess of serum Mg concentrations presented with worse clinical condition. Therefore, Mg supplementation should be preceded by a biochemical examination of the concentration of this element in the serum.

Competing interests

Authors declare that they have no conflict of interest.

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