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Iron, transferrin and ferritin concentrations in the cerebrospinal fluid of multiple sclerosis patients in comparison to controls

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ABSTRACT

Multiple Sclerosis (MS) is one of the most common neurological diseases. It seems that in addition to common risk factors, other factors such as minerals like iron have effects in the development or clinical course of the disease. The aim of the present study was to determine the ferritin, transferrin and iron levels in the cerebrospinal fluid (CSF) of patients with multiple sclerosis in comparison to the control group. In this case - control study we studied 120 patients in the two groups. Based on clinical examination and paraclinical results, diagnosis of MS was confirmed (Polman2010 and McDonald 2006 Criteria). All patients referred to hospital who required lumbar puncture(LP) as a part of making diagnosis entered the study; new MS patients in the case group, and patients with headache, neurodegenerative diseases e.g. Parkinson and Alzheimer diseases, diseases without inflammatory process such as peripheral neuropathy, pseudotumor cerebri, venous sinus thrombosis, and brain diseases of unknown etiology were included in the control group. After obtaining consent, CSF specimens were collected and iron, ferritin and transferrin levels were measured. Mean ferritin levels in the CSF of patients with MS was lower than the control group (14.94 ± 10.84 µg/l) but there was no statistically significant difference between the two groups (p=0.07). Mean transferrin and iron levels in MS patients were 1.34 ± 0.38 µg/l and 6.18 ± 4.45 mg/dl respectively; no statistically significant difference between the two groups was observed as well (p=0.31 and p=0.13, respectively). The findings showed that iron and transferrin levels in the CSF of patients with MS are higher than in control group, but without significant difference of opinion between the two groups. The ferritin levels were lower than control group, but this difference also was not statistically significant. Thus, the present study does not support the theory of role of iron in the pathogenesis of MS.

Keywords: Ferritin, iron, transferrin, cerebrospinal fluid, multiple sclerosis

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INTRODUCTION

Multiple sclerosis (MS) is characterized by triple features of inflammation, destruction of myelin, gliosis (scarring) and neuronal damage. Although there is disruption at the site of blood-brain barrier inflammation, but no signs of vasculitis exist and vessel wall is completely intact. The disease affects the central nervous system and its course may be relapsing-remitting and/or progressive. MS lesions begin with the infiltration of white matter and around venules by mononuclear cells, mostly T cells and macrophages and they are typically disseminated in time and space. There is also evidence of the involvement of the humoral immune system so that a small number of B

lymphocytes penetrate to the nervous system, and myelin-specific autoantibodieshave been found in degenerated myelin (1).

MS affects approximately 350,000 individuals in the United States and 2.5 million individuals worldwide, and is second only to trauma as a cause of neurologic disability beginning in early to middle adulthood. MS is approximately threefold more common in women than men. The age of onset is typically between 20 and 40 years (slightly later in men than in women), but the disease can present across the life span. In about 10% of cases it begins before age 18 years and a in a small percentage it begins before the age of 10 years. One proposed explanation for the latitude effect on MS is that there is a protective effect of sun exposure. The prevalence of MS is associated with latitude and sun exposure is one of the reasons. At high latitudes, the amount of UVB radiation reaching the earth's surface is often insufficient, and consequently, low serum levels of vitamin D are common. Prospective studies have confirmed that vitamin D deficiency is associated with an increase in MS risk. Manifestations of MS may vary from a benign disease to rapidly progressive and debilitating disease that leads to a significant change lifestyle [1].

Despite many studies on the causes of the disease, there is no consensus yet. Genetic factors, viral infections, autoimmune disorders are just some of the theories discussed. Some recent studies have shown that salts may have effects on development of the disease or its course [2]. Accused salts have a wide spectrum and iron, copper and zinc are among the most important [3]. The level of effect of these salts is not known however, and the results are diverse in literature. For example, Johnson in his article in 2000 has impacted the effect of gradual accumulation of copper and iron,and depletion of zinc on the pathogenesis of the disease [4]. Alimonti and colleagues also found serum iron levels are significantly lower in MS patients in their study [2].Visconti and colleagues reported changes in serum levels of iron, copper and zinc, although these changes were not statistically significant [3]. Moreover, some studies have indicated some role for nutritional supplements containing minerals in pathogenesis of MS. The results of a research in Belgium showed that the dietary Zn intake of MS patients is less than the recommended daily amount. Also, in patients with secondary progressive MS, the amount of dietary Fe was less than in other cases of MS [5].

To identify the possible role of Fe in pathogenesis of MS, we conducted this case-control study to determine the levels of ferritin, transferrin and Fe in the cerebrospinal fluid (CSF) of patients with MS compared with controls.

MATERIALS AND METHODS

This is a clinical trial research. This clinical investigation has conducted according to the principles expressed in the Declaration of Helsinki. Written informed consent have obtained from the subjects.In this research 120 patients were enrolled in bothcase and control groups. Diagnosis of MS was made based on physical examination and paraclinical results (Polman 2010 and McDonald 2006 criteria).Patients with relapsing-remitting MS, new MS patients based on McDonald criteria, and patients treated with the disease modifying drugs were entered the case group; and patients who had indication for lumbar puncture (LP) reasons other than MS such as headache, neurodegenerative diseases such as Parkinson's and Alzheimer's diseases, diseases without inflammatory process such as peripheral neuropathy, pseudotumorcerebri, venous sinus thrombosis, and brain diseases of unknown etiology were included in the control group.Clinically asymptomatic MS patients were excluded.After obtaining informed consent, CSF specimens were collected and level of iron, ferritin and transferrin were measured. The level of iron in the CSF specimens was examined by atomic absorption method. Samples were kept in the freezer at -70 °C until testing. The data were analyzed anonymously and reported.

T-test was used for statistical analysis, and descriptive statistics to assess demographic data.

Ethics Committee of Zahedan University of Medical Sciences has approved this study (Approval Number: 539T). The authors have declared that no competing interests exist.Concerning ethical issues, The Committee of Zahedan University of Medical Sciences approved this study. This research is extracted form a research project (Approval Number: 539T) with allocated ethical code from Committee of Ethics. This clinical study has conducted according to the principles expressed in the Declaration of Helsinki. A letter of permission to conduct the study was taken from the School of Medicine of Zahedan University of Medical Sciences to seek permission from authorities. Ethical Clearance for the study was also obtained from the Zahedan University of Medical Sciences Ethical Review Board. Verbal consent was sought from participants because the patients were from different culture, ethnicity and

language. All consent form was documented and keep in archive. In this clinical trial, there were not patients under 18 years. The anonymity as well as confidentiality was assured participants prior to their inclusion in the study.

RESULTS

A total of 120 patients in the two groups, 59 cases and 61 controls, were enrolled with a mean age of 31.54 ± 13.51 years and the gender distribution of 48 males and 62 females without statistically significant difference between the two groups (p=0.07) (Table 1).

Table 1. Gender distribution of the participants in the study

Group	Male	Female	Total No (%)
Case	18	41	59 (49.2)
Control	30	31	61 (50.8)
P-value (Chi-square)	0.07		

Mean ferritin level of CSF of MS patients was lower than the control group (14.94 ± 10.84 µg/l) but there was no statistically significant difference between the two groups (p=0.07).Mean transferrin levels were 1.34± 0.38 µg/l and 1.25 ± 0.48 µg/l in the case and control groups, respectively. There was no statistically significant difference between the two groups (p=0.31). Mean iron levels in the CSF of patients with multiple sclerosis and control group were 6.18 ± 4.45 mg/dl and 5.05 ± 3.1 mg/dl, respectively. Also no significant difference among the two groups for Fe levels was observed (p=0.13). Table 2 demonstrates the details of findings.

Table 2. Mean iron, ferritin and transferrin levels in CSF of patients with multiple sclerosis compared with controls

Group / Index	Case	Control	P-value (T-test)
Iron (mg/dl)	6.18 ± 4.45	5.05 ± 3.1	0.13
Ferritin (µg/l)	14.94 ± 10.84	40.38 ± 25.32	0.07
Transferrin (µg/l)	1.34 ± 0.38	1.25 ± 0.48	0.31

DISCUSSION

Role of minerals such as iron in the occurrence or process of MS has been studied for a long time. In the present study, ferritin levels in MS patients was lower than controls, but this difference was not statistically significant (P = 0.07). Worthington and colleagues study (2010) also showed no association between baseline CSF ferritin levels and level of disability in patients with MS disease exists. Moreover, no changes in CSF ferritin levels over 3-year follow-up of these patients were observed. There were no association between velocity of disease progression and changes in CSF ferritin levels in primary progressive and relapsing remitting subtypes, but there was an indirect relationship with secondary progressive MS, that is similar to our study to some extents [6].

Given that the main target of MS is oligodendrocytes and myelin, Steven et al. (USA 1998), reported high concentrations of ferritin and Fe in these cells, and proposed that in times of stress, such as hypoxia, they increase ferritin synthesis due to its protective role against oxidative stresses by bonding iron, because iron in the free form or loose bonds can be toxic to cells. As a result iron was introduced as a cause of cellular damage in MS pathology. They also showed that CSF ferritin levels in chronic progressive active MS patients is higher than in normal subjects, that is inconsistent with our results [7].Rejdak et al. in 2008 studied 34 patients with relapsing remitting MS during the acute phase of relapse. Twenty of them were followed for 6 to 8 weeks for level of disability. They used ferritin as a marker for microglial activity, and found no significant correlation between ferritin levels and disease-related disability. But the relationship between ferritin and S100Bprotein (marker of astrocytes activities) was observed [8].Study of Levine et al. about levels of iron and ferritin in CSF of MS patients showed an increase in ferritin which is notproportional to our results [9].We found higher CSF iron and transferrin levels in MS casesthan the control group, although the difference was not significant statistically.

Johnson, in his study on MS patients has noted a gradual increase in the Fe [4], But Visconti in a study on 12 patients with first demyelination episode observed that neither in acute phase nor in six-month follow-up phase, serum iron has changed [3]. Sfagos et al. also showed that the level of iron in MS cases group did not differ from the

control group, which is fully consistent with our study [10].The results of the study of Abo-Krysha and colleagues showed that there is no difference between serum iron levels in cases compared with controls, but serum transferrin level was higher that indicates iron dysfunction [11], which is proportional to our results to some extents. Exley et al. in a study showed that the amount of iron excreted in the urine of MS patients is higher than controls [12]. Some studies indicated that decreased dietary iron intake is associated withincreased disease severity [2]. Role of Iron in occurrence of MS or its course still requires more investigations, but the most probable cause could be iron imbalance that can cause inflammation in the brain tissue and consequently lead to MS[11].

CONCLUSION

Overall, findings of the present study did not indicate significant difference in iron, ferritin and transferrin levels in CSF of MS patients compared with the control group.Our findings and the findings of other studies are not sufficient to reach a general conclusion about the impact of minerals like iron on the disease, thus it still remains a hypothesis. Hence, further studies in other regions as well as for other minerals are recommended.

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