The effect of interferon-beta on oxidative stress in patients with multiple sclerosis

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ABSTRACT

Objective: To assess the effect of interferon–beta on oxidative stress and total antioxidant status in patients with multiple sclerosis (MS).

Design: Case-control study.

Setting: College of Medicine and Ibn-Sina Teaching Hospital, Mosul.

Methodology: The study included 40 female patients with MS. They divided into 2 groups of 20 patients each. Group one included newly diagnosed MS patients and group 2 with relapsing–remitting multiple sclerosis (RRMS) in remission phase, who were on interferon therapy. Another twenty apparently healthy females, age matched with the patients, were considered as a control. Malondyaldehyde (MDA) and total antioxidant status (TAS) were measured in all groups.

Results: MDA values of both patients groups (1.48±0.59 µmol/l and 1.00±0.49 µmol/l, respectively), were significantly higher than those of the control group (0.60±0.18 µmol/l) ($p<0.001$). MDA values were significantly higher in newly diagnosed group than of RRMS 0.001). The TAS values of both patients groups (0.91±0.26 mmol/l and 1.43±0.20 mmol/l, respectively) were significantly lower than those of the control group (2.14±0.21 mmol/l), ($p<0.001$). TAS values of the newly diagnosed patients were significantly lower than those of the patients group with RRMS on interferon thera patients group ($p<0.001$).

Conclusion: MS patients have higher levels of MDA and lower levels of TAS than the control group. The newly diagnosed patients have significantly higher levels of MDA and lower TAS than RRMS patients on interferon-beta therapy. This result may give a new insight about interferon being effective in management of MS by acting as antioxidant.

Keywords: Multiple Sclerosis, Oxidative Stress, Interferon-Beta.

تأثير إنترفيرون- بيتا على حالة الإجهاد التأكسدي في مرضى تصلب الأعصاب المتعدد

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الخلاصة

الهدف: لتقييم تأثير إنترفيرون- بيتا على حالة الإجهاد التاكسدي وحالة مضادات الأكسدة لمرضى تصلب الأعصاب المتعدد.

العينات وطرق العمل: تم إعتماد تصميم دراسة حالة مقارنة لأربعين مريضا مشخصين بداء تصلب الأعصاب المتعدد إرتجاعي- إنحساري وتم تقسيمهم الى مجموعتين: المجموعة الأولى تضم عشرين مريضا حديثي التشخيص, والمجموعة الثانية تحت علاج إنترفيرون- بيتا في حالة الإنحسار, ومجموعة أخرى تضم عشرين من الأصحاء كمجموعة سيطرة، شملتهم الدراسة.

لكل شخص من مجموعتي المرضى والسيطرة تم قياس مستوى المالونديهايد, حالة مضادات الأكسدة الكلية.

أشارت النتائج الى إرتفاع معنوي في مستوى المالونديهايد مع إنخفاض معنوي في حالة مضادات الأكسدة الكلية في مجموعتي المرضى بالمقارنة مع مجموعة السيطرة. كما أظهرت الدراسة بأن مستوى المالونديهايد في مجموعة حديثي التشخيص أعلى معنويا وحالة مضادات الأكسدة الكلية أقل معنويا من مجموعة تصلب الأعصاب المتعدد إرتجاعي-إنحساري تحت علاج الإنترفيرون-بيتا.

الإستنتاجات: إن مرض تصلب الأعصاب المتعدد لديهم إرتفاع في مستوى المالونديهايد وإنخفاض في مستوى مضادات الأكسدة الكلية بالمقارنة مع مجموعة السيطرة، وفي مجموعة حديثي التشخيص مستوى المالونديهايد أعلى معنويا وحالة مضادات الأكسدة الكلية أقل معنويا من مجموعة تصلب الأعصاب المتعدد إرتجاعي-إنحساري تحت علاج الإنترفيرون- بيتا. أعطت هذه النتائج أفاق جديدة بأن الإنتيرفيرون- بيتا محتمل أن يؤدي دوره في معالجة تصلب الأعصاب المتعدد كعامل مضاد للأكسدة.

الكلمات المفتاحية: تصلب الأعصاب المتعدد، جهد الأكسدة، إنترفيرون بيتا.

INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune disease of the central nervous system (CNS), characterized by inflammation, demyelination, oligodendrocyte loss, axonal injury and oxidative stress.[1] It affects the myelin sheath,[2] the fatty tissue that surrounds the nerve fibers protecting and allowing them to conduct electrical impulses.[3] Although the reasons for the autoimmune demyelinization are not clear,[4] one of these reasons is the neuronal imbalance between oxidants and antioxidants products in favor of the former.[5]

Prevalence of MS worldwide is estimated at one million cases; in the United States (US) it is 250,000- 350,000. Although not generally considered life threatening, this disease attributes in about 3,000 deaths each year in the US.[6]

Oxidative stress is defined in general as excess formation and/or insufficient removal of highly reactive molecules such as reactive oxygen species (ROS).[7] In the absence of adequate antioxidant defenses, ROS can cause oxidative damage to macromolecules resulting in oxidation of lipids, proteins and deoxyribonucleic acid (DNA).[8]

Central nervous system is susceptible to ROS-induced damage, because the brain consumption of oxygen is high, and the concentration of endogenous antioxidants is low.[9] Great number of evidences indicate that oxidative stress plays a major role in the pathogenesis of MS.[3,10]

Mitochondrial proteins and DNA are highly vulnerable to oxidative damage,[11] and therefore it is expected that free radical-mediated mechanisms may cause mitochondrial injury in MS.[12-15] The exact mechanisms responsible for increased oxidative stress in MS patients need further exploration.[16]

Immunomodulatory therapies have shown to reduce the rate of relapse significantly, and delay the progression of neurological disability in patients with relapsing-remitting multiple sclerosis (RRMS).[17] Interferons are considered to be members of the cytokine family of proteins,[18] interferon beta (IFN-β) is a first line treatment for (MS),[19] and as key component of the innate immune system.[18] It can cause complex immunomodulatory effects, but its mechanism of action as an immuno-modulator in the treatment of multiple sclerosis is not fully understood.[18,20] IFN-β has been shown to inhibit endothelial nitric oxide synthetase (NOS) activity and suppress endogenous nitric oxide (NO) free radical production.[21]

The present study aimed to assess the effect of IFN-β on oxidative stress and total antioxidant status in patients with (MS**).**

SUBJECTS AND METHODS

The study had approval from College of medicine, University Mosul. Forty female patients with MS (according to Mc Donald criteria), with age range between 25 & 45 years, were divided into 2 groups of twenty patients each. Group one included newly diagnosed MS patients and group 2 included patients with RRMS in remission phase on interferon therapy. The patients were registered in the Neurology Outpatient Department at Ibn Sina Teaching Hospital. Another twenty apparently healthy females, age matched with the patients, were considered as a control.

Pregnant and lactating women, individuals receiving trace elements, antioxidants or vitamin B complex, patients with acute or chronic illness other than MS, smokers and alcohol users were excluded from the study.

The studied groups were subjected to measurement of weight and height to derive body mass index (BMI), according to the equation:
BMI= weight (kg) /height (m).[22] Expanded Disability Status Score (EDSS) was assessed in MS patients group.

Serum MDA level, which is the consequence of lipid peroxidation and a marker of oxidative stress

was measured using thiobarbiturc acid (TBA) assay.[23] TAS was measured using Randox TAS kit (London–UK) following the instructions included in the leaflet of the kit.[24]

Statistical Analysis

Computer feeding was conducted by prepared computer program SPSS version 18. ANOVA Test (Analysis Of Variance) was used to identify the variation in the different variables. All values expressed as Mean± SD and P value of <0.05 was considered to be statistically significant.[25]

RESULTS

The individuals in the MS and control groups were comparable in terms of age and BMI as shown by non statistically significant differences between the groups (p > 0.5), **Table 1.**

Table 2 shows the comparison of MDA and TAS in the studied groups. MDA values of both patients group were higher than those of the control group (p<0.001), and MDA values were higher in newly diagnosed patient group than those of RRMS patients group on interferon therapy (p<0.001).

TAS values of both patients groups were significantly lower than those of the control group (p<0.001), and TAS values of the newly diagnosed patients group were significantly lower than those of the patients group with RRMS on interferon therapy (p<0.001). EDSS was higher in newly diagnosed patients group than patients group who is on interferon therapy (p<0.001).

Table 1. The age and BMI among studied groups.

Parameters	Mean ± SD			P-value
	The newly diagnosed (n=20)	The RRMS on IFN-β (n=20)	Control (n=20)	
Age (years)	35.35±8.22	34.90±8.03	34.55±6.19	NS
BMI (kg/m)	25.85±4.99	24.88±3.54	25.39±4.69	NS

Table 2. The serum level of MDA and TAS of MS patients and control groups, and EDSS in newly diagnosed and patients on interferon therapy.

Parameters	Mean ± SD			P-value
	The Newly diagnosed (n=20)	The RRMS on IFN-β (n=20)	Control (n=20)	
MDA (µmol/l.)	1.48±0.59*	1.00±0.49*	0.60±0.18*	<0.0001
TAS (mmol/l.)	0.91±0.26*	1.43±0.20*	2.14±0.21*	<0.0001
EDSS	3.10±1.08	1.77±0.57	--	<0.0001

** is the non-homogenous group*

DISCUSSION

The present study was performed to assess the oxidative stress in a newly diagnosed relapsing–remitting multiple sclerosis (RRMS) patients and in those who are in remission phase, who are on interferon therapy, by measuring plasma levels of a byproduct of lipid peroxidation, *i.e.* malondialdehyde (MDA), and the plasma antioxidant capacity, by measuring total antioxidant status (TAS) and in parallel way to assess the effect of interferon-beta (IFN-β) on the oxidant/ antioxidant status and its effect on the course of the disease using Expanded Disabling Status Score (EDSS).

The current study included 40 females divided into 2 equal groups. The groups were matched concerning the number and their ages as well as body mass index (BMI) as confirmed statistically by the absence of significant differences between the studied groups. This matching of individual group's number, age and BMI may exclude any effect of these parameters on the results of the study. The removal of the age and BMI factors interference with results of clinical trials were done in the majority of other trials concerning antioxidant field.[26- 29]

In this study serum MDA levels were found to be significantly higher in patients with MS of both groups compared to the healthy control subjects.

Increased MDA level in our patients, which is the consequence of lipid peroxidation and a marker of oxidative stress is an evidence of exaggerated oxidative stress in these patients. Several studies have demonstrated an increase in the levels of lipid peroxidation, evaluated by its measurement in plasma, serum and in cerebrospinal fluid (CSF) of

MS patients with respect to healthy subjects.[27, 30-31] Miller *et al,*[29] found that MDA levels were significantly higher in serum of MS patients than the control group. Karg *et al*[21] and Vinychuk *et al*[32] reported that the plasma lipid peroxides levels were increased followed by decreased vitamin E level in MS patients. These results are comparable to the results of this study.

Measuring TAS is better than measuring individual antioxidant enzymes, because TAS gives a more precise indication of the relationship between antioxidants and disease.[3] In this study TAS concentration was lower in MS patients of both groups, than that of the control group. This result is in accordance with the results of previous studies that compared the concentrations of TAS and individual antioxidant enzymes in MS patients.[3,29,33-34] Choi *et al,*[35] reported that glutathione (GSH) levels were lower in patients with MS, while Miller *et al,*[36] found a low level of superoxide dismutase (SOD) in patients with MS. Jimenez-Jimenez *et al,*[26] Besler *et al,*[27] and Salemi *et al*[37] compared the serum levels of vitamin E in patients with MS and matched controls. They found that the serum level of vitamin E was significantly lower in patients with MS than controls (P<0.05).The decrease of the concentration of vitamin E, the major lipophilic chain-breaking antioxidant, confirms the possible involvement of this vitamin in MS pathogenesis.[37]

In this study serum MDA levels were found significantly higher in newly diagnosed patients than in RRMS. TAS levels were found to be significantly lower in newly diagnosed patients than in patients with RRMS on interferon therapy. This indicates that the oxidative stress is enhanced in non-treated patients, and lower oxidative stress in treated patients which be may attributed to the effect of IFN-β therapy.

Koch *et al,*[38] measured blood plasma lipid peroxidation in different types of MS; they found significantly higher levels in all types compared with the control.

Oxidative stress is very high during active progression of multiple sclerosis when compared to those individuals whose multiple sclerosis is in remission or when compared with normal controls.[39] Ferretti *et al,*[40] report an increase in plasma lipid peroxidation in patients in an early stage of the disease.

In a follow-up study, 14 patients with RRMS were followed for 6 months with interferon-beta treatment. It was reported that erythrocyte vitamin E level was reduced (P < 0.001) before treatment, but had regained the same level as in controls after 6 months of IFN-β therapy. The authors concluded that interferon treatment seemed to exert a sparing effect toward the erythrocyte vitamin E content.[41]

In this study, EDSS was higher in newly diagnosed patients group than the patient group on interferon therapy (p<0.001), indicating the beneficial effect of IFN-β on the progression of the disease. Immunomodulatory therapies have shown to reduce the rate of relapse significantly, and delay the progression of neurological disability in patients with RRMS.[17] Interferon-beta reduces the overall frequency of MS attacks by approximately 30% compared with placebo in therapeutic trials.[42,43]

One of the greater challenges facing researchers trying to explain the mechanism of action of interferon in MS is the complex pathological process in this disease.[44] It is now generally agreed that initial step in MS episode is an inflammatory process initiated by activation of T cells that cross blood brain–barrier (BBB) and target specific myelin antigens within CNS, the activated T cells will respond by producing cytokins that will stimulate inflammatory process leading to tissue injury.[45]

Review of literature provides limited conflicting data concerning the mechanism of interferon-beta in the management of MS, since its exact mechanism of action is not completely understood.[19] IFN-β appears to be directly involved in increasing the expression and concentration of anti-inflammatory agents while down regulating the expression of proinflammatory cytokines.[46] Therefore the proposed mechanism of action of IFN-β in MS is immune modulation via its effects on T cells, (decreasing immune cell entering across the BBB, inducing apoptosis of auto-reactive T cells, promoting T regulatory cell activity, and inducing a shift to anti-inflammatory cytokines).[17]

It is well known that inflammation raises reactive oxygen species (ROS) levels leading to oxidative stress (OS).[2] Excessive release of free radicals may play an important role in MS pathogenesis,[9]

and may promote transendothelial leukocyte migration and free radicals generation that contribute to oligodendrocyte damage and axonal degeneration.[47] According to this information, and the results obtained in this study, a new insight may be drawn that interferon- beta may exhibit its effect in management of MS by acting as antioxidant through its anti inflammatory effect. Ongoing and future studies will increase our understanding of the actions of IFN-β on the immune system and the CNS, which will in turn aid advances in the management of MS.

CONCLUSION

Patients with multiple sclerosis have higher levels of MDA and lower levels of TAS than the control group. This high value of MDA reflects enhancement of oxidative stress in MS patients, and low value of TAS may be due to development of oxidative stress that reduces the concentration of the antioxidant status of the body.

The newly diagnosed patients have higher levels of MDA and lower TAS than RRMS patient group. This indicates that IFN-β in management of MS may be via its antioxidant property.

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