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The effect of interferon-β therapy on brain-derived neurotrophic factor serum concentration in relapsing—remitting multiple sclerosis: a randomized clinical trial

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Abstract

Introduction: Beta interferon (IFN-β) is known as the first-line therapy in relapsing-remitting multiple sclerosis (RRMS). Recent studies have shown different effects of IFN-β on brain-derived neurotrophic factor (BDNF) serum levels. Given the known role of BDNF in the restoration and conservation of the nervous system, this study was designed to investigate the possible effect of this drug through stimulating BDNF production.
Objectives: Impressible treatments for progressive multiple sclerosis (MS) are still being sought. Individual response to existing treatments for MS varies significantly among patients while the risk of serious adverse events remains an issue, especially for the novel drugs.
Patients and Methods: In this clinical trial, 96 patients newly diagnosed with RRMS were studied within three months, in 3 groups of 32 subjects. Each group received one of the foregoing drugs (Avonex, Rebif and Betaferon). BDNF levels were compared between different groups at the end.
Results: BDNF serum concentration in all groups was significantly different ($P<0.001$) compared to baseline after 3 months. And comparison between groups showed a significant difference between the groups receiving Betaferon (IFN-β1b) ($P=0.001$) and Rebif ($P=0.002$) compared to the other groups. Avonex compared with either control or Betaferon (IFN-β1b) and Rebif groups showed no significant difference. Also the correlation between the mean changes in expanded disability status scale (EDSS) and BDNF was not observed (r = -0.189, $P=0.065$).
Conclusions: Significant difference in BDNF levels were observed between groups.
Trial registration: Registration of trial protocol has been approved in the Iranian Registry of Clinical Trial (identifier: IRCT2013073114234N1; https://irct.ir/trial/13874).

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Introduction

Multiple sclerosis (MS) is the most common neurological disorder in young adults which is known as a chronic inflammatory, autoimmune and central nervous system demyelinating disease. Accordingly, the initial treatment strategy for these patients has been based on the regulation and control of immune-mediated disease-modifying drugs (DMDs) (1), particularly in patients with a course of relapsing-remitting multiple sclerosis (RRMS), which includes over 80% of patients with MS (2). One of the important categories of drugs is DMDs immunotherapy group (2). To date, several clinical trials have confirmed immunotherapy response (3). Interferon β1a (IFN- β1a), β1b (IFN- β1b), fingolimod and laquinimod are among this group. Different types of interferon beta (IFN- β), as first-line treatment for prevention of relapse of RRMS patients are used. However, the biological mechanisms of its therapeutic effects are not

Key point

Having any further information about interferon and following effective status can be useful to improve patients' disease course and their quality of life.

fully understood (4).

Oligodendrogenesis and myelination are regulated by various neurologic issues. Strategies for enhancing the production of factors associated with myelination can restore and facilitate demyelination forms such as RRMS (5). Evolution and survival of the nervous system is associated with the polypeptide growth factors called neurotrophic factors. Brain-derived neurotrophic factor (BDNF) is a member of the neurotrophin family (6,7), and is generated with cortical neurons (6). Several studies have shown damaging effect of inflammatory cells caused by disruption of the neurotrophin secretion of proteins, including BDNF (8). BDNF increases neuronal response to injury or destruction through inhibition of axonal damage and cell death, supporting oligodendrocytes, remyelination and stimulation of axonal growth (3,9). This protein is found in immune cells in MS lesions while its role in making oligodendrocyte myelin and glycoprotein has been shown in some studies (10). However, some other studies have reported functional inconsistent in BDNF protein isoforms (11).

Recently, several neuronal protective effects, due to the increase in BDNF serum levels in patients treated with immunomodulatory drugs for controlling MS (Fingolimod, laquinimod and glatiramer acetate) have been reported (9,12-14). In a study on patients with RRMS who were under treatment with interferon and did not have relapsed, serum BDNF levels showed a significant increase in the third month in comparison with baseline (15). The human immune cells can secrete BDNF, preventing from neuronal and axonal degradation subsequent a variety of pathological damages (16). In one study it was shown that peripheral mononuclear cells in RRMS patients treated with IFN-β1, secrete more BDNF compared to untreated patients (17). Studies that showed the effects of interferon on serum BDNF are limited and in some cases the results are controversial (18).

Objectives

According to the unknown superiority of any one of the three above-mentioned drugs in reducing the amount of patients' disability, this study was designed to compare the extent of the impact of each of these three drugs on the in expanded disability status scale (EDSS) and BDNF scale of treated patients.

Patients and Methods

Study design

The current study was designed as a double-blind randomized clinical trial which followed for 3 months on 96 patients with MS according to the McDonald criteria (19). Patients were referred to Ahvaz Golestan hospital MS clinic (2015 to 2016). The study was approved by the Ethics Committee of the Ahvaz University of Medical Sciences. Written informed consent was obtained from all participants prior to the enrollment.

Study population

Inclusion criteria included clinical evaluation and early diagnosis confirmation by two neurologists collaborating. The clinical course of relapsing-remitting, with active disease at presentation time was detected according to the patient's clinical criteria or MRI, lack of other neurological or autoimmune comorbidities. Accordingly, other clinical course of relapsing-remitting, are EDSS of less than 5.5, no record of receiving any of the drug groups (interferon, mitoxantrone or cyclophosphamide) used in this study and no history of corticosteroid use during the past three months. Exclusion criteria were changing the drug regimen of the patient, the diagnosis of other neurological or autoimmune diseases during the study, severe concomitant diseases such as metabolic and gastrointestinal diseases, fluctuations in drug dosage during the study, aspartate transaminase, alanine transaminase, or creatinine 1.5 times more than the upper normal limit or total bilirubin more than 1.8 mg/dL, not completing 3 months of treatment, discontinuation of therapy due to side effects or absence for survey by the end of the study. Totally, 130 eligible patients after selection were blocked at random. There were no statistically significant differences between groups at baseline. Also confounding factors such as other drugs in 3 groups were controlled since no significant difference between them was found.

Treatment protocol

Patients were randomly enrolled based on the block in one of the three groups receiving interferon Avonex (IFN-β1a), Rebif (IFN-β1a) and Betaferon (IFN-β1b) clusters. Two different recombinant IFN-β, IFN-β1a (Avonex® and Rebif®) and IFN-β1b (Betaferon®) are approved for the treatment of RRMS. Another researcher, encoded the packages containing the drugs (A, C and B). Distribution of packages containing drugs was based on coding and data analysis was done by someone else. Drug used during treatment did not change while the patients were instructed to take their usual diet and physical activity during the study and avoid fluctuation in drug dose without notice. Given the fact that all patients in our study sponsored by the MS Society, they monthly received medication. For adherence to treatment, patients were monitored through documents on the forum, since their relapse was recorded during 3 months. In addition, in the case of an acute attack, patients were treated with intravenous corticosteroids. Selection of these patients was random, while we tried to reduce the basic differences between groups, such as age, gender and EDSS.

After sterilizing arm with alcohol, with a 19-gauge needle (according to blood transfusion protocol) 10 mL of volunteer's blood was taken aseptically. Blood samples were then collected in heparinized tubes (15 IU/cc) and centrifuged at 300 rpm. To minimize the coefficient of variation between tests the plasma obtained from all samples were stored in a -70°C freezer until the final

analysis. Plasma BDNF concentration was measured in Ahvaz Golestan hospital laboratories using ELISA (enzyme-linked immunosorbent assay), with commercial kits BOSTER and ELISA READER TEfAKAN machine made in Austria, with the range of readings (assay range) 0-2000 pg/mL and sensitivity lower than 2 pg/mL. The tests were done by the same person. At the end of the study, serum levels of BDNF, the number of relapses and changes in EDSS of all patients were re-evaluated.

Ethical issues

This study was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (#ethical code; IR.AJUMS.REC.1391.652). This study is the result of the residential thesis by Shahram Tarahomi in neurology department (# U-91186). Registration of trial protocol has been approved in Iranian Registry of Clinical Trial (identifier: IRCT2013073114234N1; https://irct.ir/trial/13874).

Statistical analysis

Results were compared to investigate the effect of treatment protocol on EDSS and BDNF among and within the three treatment groups during 3-month period. Paired t-test and ANOVA were used to assess the statistical significance of the continuous variables, within and among groups, respectively. Statistical analyses were performed using SPSS18 (SPSS, Chicago, IL, USA). A value of $P \leq 0.05$ was used as a criterion for statistical significance.

Results

Overall 96 patients participated in this study and followed up for 3 months. The mean age of patients was 28.66 ± 7.51 years. There were 76 (79.17%) women and 20 (20.83%) men in the study. No significant difference was seen in age, gender or education level of participants among the three groups. The most common complaints were visual (73.5%) and motor disorders (60.3%).

Changes in EDSS, BDNF and relapse during 3 months are shown in Table 1. Prior to treatment no significant difference was observed in EDSS among three groups ($P=0.467$). Additionally, no changes were seen in final EDSS ($P=0.623$). According to ANOVA results, variation of EDSS had no significant changes during study time (Figure 1A).

Mean comparison in BDNF using the one-way ANOVA test showed no significant difference in primary BDNF among three intervention groups ($P=0.32$). But at the end of study a significant increase was observed in BDNF ($P<0.001$). Inter groups comparison indicated a significant variation in BDNF and a great improvement was seen in Betaferon (IFNβ 1b) group. In fact among the study groups, Betaferon (IFNβ 1b) had the best effect on MS patients followed by patients in Rebif and Avonex groups (Figure1.B).

Evaluating the relapse rate within and between groups revealed no significant statistical difference before treatment($P=0.29$); comparison between groups after intervention showed relapse rate decreased in three pharmaceutical groups, while patients in Betaferon (IFNβ 1b) group had a significant difference rate and no significant rate was observed in Rebif and Avonex groups.

Discussion

MS is the most common neurological disorder (3) which causes physical and cognitive disorders in young adults (1-3). DMDs are used for the treatment of these patients.

IFN-β group are an important category of DMDs drugs. IFN-β have been identified as one of the first drugs that partially affect the course of MS. The mechanisms of therapeutic effects of IFN-β in MS have not clearly known (20-24). Among which, there are immunomodulatory mechanisms of INFβ, which include stimulation, inhibition and activation of T lymphocytes, modulation of inflammatory mediators and cytokines and reduction of cell migration to the nervous system which increases

Table 1. Comparison of EDSS, BDN and relapse rate for each interferon (paired *t* test results)

	Avonex	Betaseron	Rebif	P-value
EDSS				
Primary EDSS	1.05 ± 0.34	1.11 ± 0.11	1.03 ± 0.09	0.467
Final EDSS	1.07 ± 0.14	0.99 ± 0.34	1.01 ± 0.36	0.623
Differences	0.02 ± 0.32^{ns}	-0.12 ±0.35^{ns}	-0.02± 0.32^{ns}	-
BDNF				
Primary BDNF	651.30 ± 1.12	699.20 ± 54.35	678.27± 25.30	0.32
Final BDNF	801.00 ± 0.81	1016.65 ± 40.23	903.08 ± 3.02	< 0.001
Differences	149.69 ± 1.44**	317.45 ± 67.53**	224.81 ± 26.35**	-
Relapse				
Baseline	2.1±0.16	2.6 ± 1.00	2.42±32	0.29
After therapy	1.89±0.31	0.8 ± 0.9	2.13±0.85	0.004
Difference	0.21±0.1^{ns}	1.8 ± 0.67**	0.29±0.12^{ns}	-

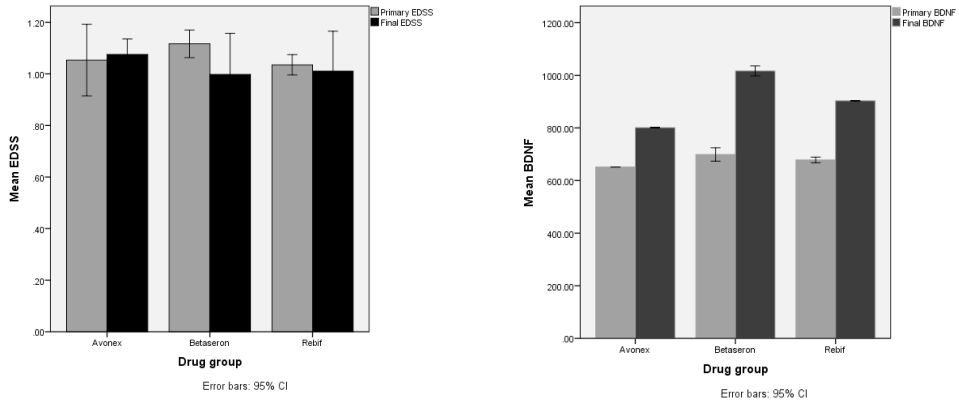

Figure 1. Comparison of the amount of patients' EDSS and BDNF for each interferon group, at the beginning and end of the study (Anova results)

the interleukin-10 levels which shifting the inflammatory cytokine response profiles of Th1 to Th2 (22-26).

Recent studies suggest a possible role of BDNF in the mechanism of action of DMDs. In several studies investigating treatment with Glatiramer acetate and laquinimod, BDNF levels were significantly increased in patients with MS and even increased the amount of healthy subjects. In a study investigating neuroprotective mechanism of Fingolimod, it was suggested that it is neuroprotective mechanism conducted through increasing the amount of neuronal BDNF (1,12,14,27). However, INFβ effects on serum BDNF is controversial. Some in vivo and in vitro studies reported that interferon has no effect on BDNF secretion (8,18,28,29). In contrast, other studies showed that BDNF secretion in MS patients treated with INFβ is higher than untreated patients (15,30).

In our study this issue was evaluated by comparing the effects of treatment with various forms of IFN-β on serum levels of BDNF in patients during 3 months. At the end of third month, the comparison between serum levels of BDNF with the baseline showed a significant increase in all groups. Following the pairwise comparison among the groups, no significant difference between interferon beta-1a (Avonex and Rebif) with interferon beta-1b (Rebif) was observed. The Avonex group compared with two other interferon groups showed an intermediate effect on serum BDNF levels of patients. It means that the mean changes had a significant difference in Avonex group compared to Betaferon (IFNβ 1b) or Rebif groups. This suggests that after three-month administration of Rebif and Betaferon (IFNβ 1b), BDNF levels were significantly increased, while this increase was significantly greater than Avonex.

The effects of physical activity on the central nervous system are complex and not fully understood. Also there are different reports about the association between physical activity and BDNF, some of which have shown increase (31-33), decrease (34), and no change (35) in BDNF following physical activity. So, all the patients participating in our study were asked not to change their daily activity during 3 months of study.

In recent years, special attention has been focused on the possible role of BDNF in the central nervous system (31). It plays a crucial role in the maintenance and growth of multiple nervous systems (7,39), including regulation of neurogenesis (10), neuroplasticity and cellular debris (3,9,11,38). On the other hand, by stimulating the synthesis of anti-apoptotic factors such as BCL-2, it prevents cell death in culture media (40,41).

Cellular origin of human BDNF is not completely understood but it has been shown that a wide variety of immune cells outside the nervous system, such as T cells, B cells, monocytes and hematogenic precursor cells produce and secrete BDNF (42-44).

The roles of neurotrophins are varied according to the receptor they bind to. According to the binding receptors, neurotrophins act are varied.so that, the rate of neurothrophin increased when nerve injury happened or; when they bind to P75 receptor they would have regulatory role in cellular death program (45), while in connection with the tyrosine kinase A (TrK-A) they would preserve neurons. Thus, they determine both ends of the spectrum of cellular life and death (46). The inflammation leads to increased BDNF protein expression in cells of the central nervous system. Also during inflammation, tyrosine kinase receptor of BDNF is upregulated (47).

Neurotrophins may act as paracrine or autocrine agents in the inflammatory response. It is shown that expression levels of BDNF in the nervous system in neuropathic injury, autoimmune diseases and inflammatory would change (48-50). Several studies have suggested that the damaging effects of the inflammatory cells in the CNS are the result of potentially detrimental activities of these cells on secretion of neurotrophins such as BDNF (16,43,51,52).

Peripheral blood mononuclear cells (PBMCs) in RRMS patients secrete fewer BDNF compared to healthy individuals. This may be caused by changes in serum levels of neurotrophic factors and/or their receptors expression rate (53-55).

In another study it was found that patients with MS have high levels of BDNF in their brains (43).

Increased production of BDNF by immune cells isolated from MS lesions has been also reported. Studies on MS patients treated with interferon β represents that the production of BDNF is greater in these patients (9,11). Azoulay et al showed that a possible direct neuroprotective mechanism of INFβ by inducing secretion of BDNF from lymphocytes which are sensitive to this drug (13). Although previous studies were mentioned that interferon β can facilitate the production of BDNF from endothelial cells (13), the secretion of BDNF by immune cells in MS is low (16,56). In MS, regulation of BDNF secretion is lost by the interactions between CD40 cells. The findings reported by Azoulay et al showed that peripheral mononuclear cells in MS patients treated with interferon β1, compared to untreated patients, secrete more BDNF. Likewise, they found that stimulation of peripheral mononuclear cells in patients treated with antibodies against CD40 cell, increases BDNF levels. Decreased secretion of BDNF and CD40-induced dysregulation, in untreated patients may be reversed by administration of interferon β1. These effects are due to INFβ ability to upregulate BDNF secretion (57,58). It is worth mentioning that INFβ treatment did not increase the number of monocytes expressing CD40, but also increase the number of CD40 copies on the surface of each monocyte (59). So INFβ treatment would increase availability of many monocytes to stimulate CD40.

Conclusion

The results may introduce BDNF as a biomarker to predict the behavior of the disease and to monitor response to treatment. Therefore further studies with larger sample size, investigating the presence of neutralizing antibodies in patients whose BDNF levels would not increase, as well as studying other types of MS, is recommended.

Limitations of the study

Despite the strong point of this study, short time of follow up and lack of control group were important limitations. More studies with larger sample size and longer follow up period need to demonstrate the neuroprotective of IFN-β, secondary to the increase of BDNF.

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Authors' contribution

All authors passed four criteria for authorship contribution based on recommendations of the International Committee of Medical Journal Editors. NM, MB designed the protocol of study. ST and HH developed the protocol and performed it. Critical revision of the manuscript for important intellectual content was performed by SMTM and MB. Analysis of data was performed by FJ.

Conflicts of interest

The authors declare that they do not have any conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, double publication) have been completely observed by the authors. This article does not contain any studies with animals performed by any of the authors.

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