Short Communication

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Fibroblast Growth Factor-2 Levels Elevated in MS Patients' Serum

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ABSTRACT

Background: Various factors contribute to the pathogenesis of Multiple Sclerosis (MS), one of which is Fibroblast Growth Factor 2 (FGF2). The function of FGF2 is pleiotropic. The investigation of the role of this factor in the myelination has produced conflicting results.

Objective: To investigate the serum levels of FGF2 in patients with MS.

Material and Methods: Eighty patients with MS and eighty healthy volunteers with no history of inflammation or demyelinating disorders were included, and serum samples were collected to evaluate serum levels of FGF2 using the ELISA technique. Both groups had the same age and gender distribution. For analysis, the Mann-Whitney U test was used.

Results: Patients with MS had considerably greater serum FGF2 levels than the control group (P=0.005). There was no difference between the FGF2 level in men and women.

Conclusion: Our data indicate that FGF2 levels may be related to the susceptibility of Iranian patients with MS. Further studies are required to analyze the involvement of FGF2 in enhancing the inflammatory process in MS.

Keywords: Demyelination, ELISA, Fibroblast Growth Factor-2, Multiple Sclerosis, Serum

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INTRODUCTION

The autoimmune and demyelinating disease, Multiple Sclerosis (MS), is a highly variable disorder in which the myelin sheath in the central nervous system is invaded by the immune system. Traditionally, MS appears to be triggered by peripheral T cells being activated, and after the breakdown of the blood-brain barrier (BBB), they enter the brain and are reactivated by antigen-presenting cells, resulting in a sequence of inflammatory events (1, 2).

The myelin sheath is lost after the demyelination. This allows remyelination's natural regenerative response to create new sheaths from freshly generated oligodendrocytes. Once myelinated regions

of the CNS are damaged, the activation of oligodendrocyte progenitor cells triggers remyelination (3).

The precise mechanism of the disease is still unknown but several growth factors have been identified that affect the regenerative process and MS pathology. FGF2 is a member of the FGF family, extensively investigated in the context of MS. It binds to four transmembrane receptors (FGFR1-FGFR4). FGFR1-3 is expressed by oligodendrocyte cells (2). FGFR signaling regulates intracellular signaling pathways (4, 5).

More research is needed to develop stronger, more efficient, and less expensive treatment options owing to the obvious rising prevalence of MS and the huge expenses this disease imposes on society. Previously, we examined the correlation between various genes and MS (6-11). FGF-2 expression increased during myelin sheath repair in animal models with myelin damage, according to some studies (2, 12). Endogenous FGF2, on the other hand, has been found in some investigations to prevent remyelination in a demyelinating lesion (13-16). This disparity inspired us to compare the expression of this factor in MS patients and controls, and we concluded that more studies need to be conducted, especially in the genetic pattern of northeastern Iran.

SUBJECTS AND METHODS

Human samples were collected after obtaining the informed consent according to the Golestan University of Medical Sciences' ethical commission roles. The ethics commission of the Golestan University of Medical Sciences approved this investigation. Eighty RR-MS (Relapsing-Remitting MS) patients were included and enrolled at Golestan University of Medical Sciences. To minimize environmental effects, all of the patients and controls were drawn from the northeast of Iran. The average ages of the MS patients and controls were 319 and 33 8years, respectively. Expert neurologists diagnosed MS patients using the latest McDonald criteria, which were updated in 2017 (17). The control group comprised 80 healthy participants who were age and sex-matched and shared the same ethnic background as the MS patients. Nobody there had a history of autoimmune or inflammatory diseases. They originated from the Gorgan Blood Transfusion Organization in northeast Iran. Subjects who declined to take part in the study were excluded.

Serum Sample Analysis

10 mL of peripheral blood from each sample was taken in EDTA and the serum was isolated and kept at –70 °C. A sandwich ELISA kit from ZellBio GmbH (Ulm, Germany), was used to determine the amount of FGF-2 protein.

All the serum samples were analyzed in triplicate. FGF-2 was found to have a minimum detectable concentration of 7.5 pg/ml.

Statistical Analysis

The data were recorded in IBM SPSS Statistics for Windows, version 23 (IBM Corp., Armonk, N.Y., USA), and the means of parametric variables were calculated. For parametric variables, data is provided as means±SD. Normal distribution was checked using Skewness, Kurtosis statistics, and Shapiro-Wilk and Kolmogorov–Smirnov tests. To compare quantitative data, the Mann-Whitney U test was utilized. A statistically significant difference was determined to have P value 0.01.

RESULTS

The research recruited 160 people (80 sick and 80 healthy controls). For patients and controls, the average age was 31±9 and 33±8, respectively. A significant difference was found between the patients and the controls in the serum level of FGF-2 ($P<0.005$) (Figure 1). Male/female ratios in patients did not differ

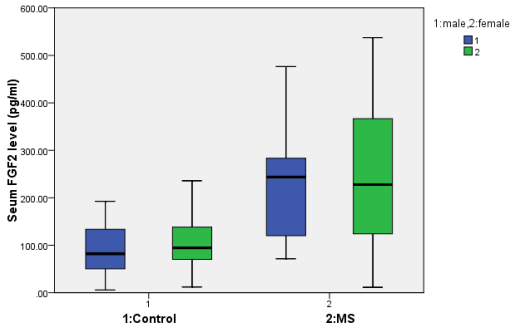

Figure 1. Comparison of FGF-2 level between MS patients and the control group separately for males and females.

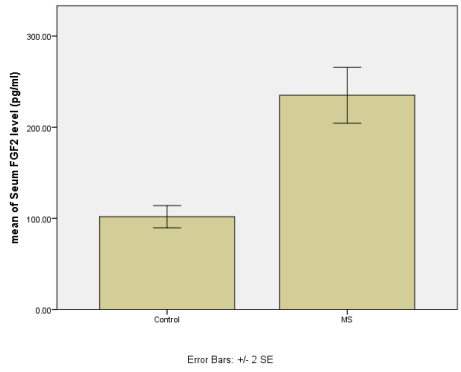

Figure 2. Histogram of serum level of FGF-2 in the control group.

significantly (20/60) compared with the controls (25/55). The Expanded Impairment Status Scale (EDSS) is a tool for measuring MS disability and tracking changes in disability over time. The Mean±SD EDSS was 3.4±1.9, and the mean±SD age at onset 26±7 was years. Men and women did not vary in terms of age, EDSS, or onset age. The normality tests and normal distribution graph are shown in Tables 1, 2, and Figures 2, 3 respectively. So the analysis was performed using the non-parametric Mann-Whitney U test (Table 3). The serum FGF2 expression level in MS patients was significantly higher than in the control group (P<0.005). There was no discernible gender difference.

Our study revealed a significant increase in serum FGF-2 levels in MS patients (P<0.005) (Figure 3). Our results are consistent with Sarchielli et al. (18). We found no difference in FGF-2 levels between the male and female patients. The level of FGF2 seems to indicate a severe inflammatory process in MS.

Table 3. Mann-Whitney U test

Test statistics	
	Serum FGF2 level (pg/ml)
Mann-Whitney U	1258.000
Wilcoxon W	4498.000
Z	-6.627
Asymp. Sig. (2-tailed)	0.000

a. Grouping Variable: 1: Control, 2: MS

DISCUSSION

In MS patients, the disease affects FGF2 and

Table 1. Descriptive Statistics for MS patient and the control group

	N		Mean		Std. Deviation	Variance	Skewness		Kurtosis	
	Male	Female	Statistic	Std. Error	Statistic	Statistic	Statistic	Std. Error	Statistic	Std. Error
Control	25	55	101.8559	6.09414	54.50764	2971.082	0.408	0.269	-0.327	0.532
MS	20	60	237.0621	15.29052	136.76259	18704.007	0.303	0.269	-0.816	0.532

Table 2. Tests of Normality. If (sig) P<0.05, the distribution is not normal.

	Kolmogorov-Smirnov[a]			Shapiro-Wilk		
	Statistic	df	Sig.	Statistic	df	Sig.
Control	0.096	80	0.065	0.976	80	0.138
MS	0.114	80	0.012	0.965	80	0.029

a. Lilliefors Significance Correction

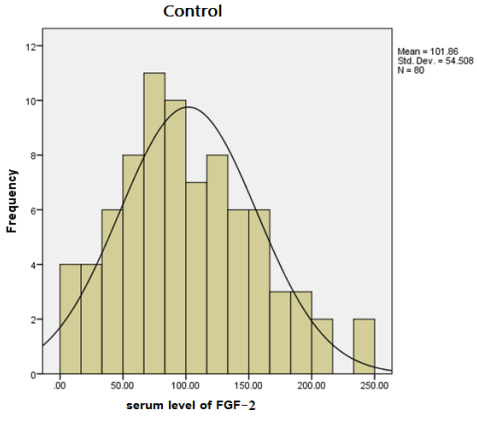

Figure 3. Histogram of serum level of FGF-2 in the MS patient group.

its receptors, which suggests an important role in this factor. FGF2 levels are particularly high in the cerebrospinal fluid (CSF) and serum of MS patients (18-20). Mori et al, on the other hand, did not identify any significant alterations in FGF2 (21). FGF2 levels in MS patients were higher than in the control group, according to the study (22). FGF2 is found in active lesions as well as the periphery of chronic lesions in the brain. The findings are in line with the demyelination models, which reveal elevated levels of FGF2 and FGFRs in lesion sites (14, 23, 24). The significance of those increases were assessed by increasing the FGF2 level following demyelination (12).

Some experiments which examine the levels of FGF2 indicate that FGF2 helps to repair (2). On the contrary, Endogenous FGF2 has been found in some investigations to prevent remyelination in a demyelinating lesion. Oligodendrocytes and myelin are recovered in FGF-/- mice (13-16). Also, histological examination of patients with progressive MS showed that FGF2 expression was more prominent in demyelinated lesions (25). Astrocytes, and by secreting FGF-2, increase the proliferation and survival of OPC but prevent OPC maturation to become myelinating oligodendrocytes. Therefore, it may be inferred that astrocytes releasing too much FGF2 hinder myelination (1).

FGF2 appears to have a pleiotropic function and may play a positive role in intrinsic repair at first, which helps the recruitment and proliferation of oligodendrocytes but later inhibits oligodendrocyte differentiation. FGF2 may cooperate in a pro-inflammatory microenvironment, in which neuroprotective autoimmunity is present but can cause damage if exacerbated (5). Murtie et al. examined the role of FGF2 in the response of oligodendrocytes to demyelination, and their findings may support our results (15).

There is a significant enhancement of multiple FGFR types in response to demyelination and also FGF2 has different effects according to different signaling pathways regulating oligodendrocyte lineage differentiation and myelination (13, 24). Because many FGFR types are expressed within and surrounding the demyelinated lesions, interpreting the action of FGF2 is difficult (13).

A new FGFR1-selective agonist can bypass FGF2-induced myelination inhibition, reducing tissue damage and speeding up the lesion healing (25). The anti-inflammatory and neuroprotective effects of cell-specific deletion of FGFR2 in oligodendrocytes are accompanied by alterations in FGF/FGFR signaling and downregulation of remyelination inhibitors SEMA3A and TGF-beta, as well as FGF2 (26).

As a result, FGF-2 levels that are higher imply more severe demyelination (2). Given the importance of FGF/FGFR signaling in neuroinflammation, the regulation of FGF2/FGFR signaling could be a therapeutic strategy for neurodegenerative diseases like MS (27). Targeted FGFR inhibition could be a potential strategy for improving remyelination It is also urged that this study be broadened to incorporate various ethnicities.

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AVAILABILITY OF DATA AND MATERIALS

The dataset used to support the conclusions of this paper is supplied in the article (along with any extra files).

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ETHICAL APPROVAL AND CONSENT TO PARTICIPATE

The present study was approved by the ethics committee of The Golestan University of Medical Sciences.

Conflict of Interest: None declared.

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