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№ 8291

Decreased Levels of Soluble Fractalkine as an Early Biomarker Distinguishing Secondary Progressive from Relapsing Remitting Multiple Sclerosis

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June 18, 2022

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Abstract

Secondary Progressive Multiple Sclerosis (SPMS) differs from Relapsing Remitting Multiple Sclerosis (RRMS) in clinical, immunological, pathological, radiological charecteristics and response to treatment. A spesific biomarker for the transition from RRMS to SPMS have not yet been reported, so our aim in this study is to evaluate the role of soluble fractalkine (sFKN)as an early biomarker for disease progression in distinguishing between SPMS and RRMS.Fractalkine is a unique chemokine with direct relationship with its receptor to reduce expression of pro-inflammatory genes in activated microglia.In our study,serum levels of sFKN levels were found to be decreased in SPMS compared to RRMS and healty controls.As a result,the decrease in serum sFKN levels support the development of neurodegeneration and promote the transition from RRMS to SPMS.thus sFKN can be used as an early biomarker and in future it will be a promising new therapeutic target.

Introduction

In generally, MS starts relapsing remitting course (RRMS), at later times,may transform into SPMS. Two types of inflammation have been reported in MS patients. The first is the focal invasion of T and B lymphocytes which affect the white matter and causes active demyelinated lesions.The other type is associated with the formation of subpial demyelinated lesions, a slow accumulation of T and B cells and with diffuse neurodegeneration in the white or gray matter. Neurodegeneration is associated with progressive clinical disease(1).Cortical lesions in SPMS are charecterised by activated microglia and inflammatory infiltrates. Meningeal lymphocytic aggregates have been found in patiennts with SPMS.Risk factors associated with progression to SPMS inlude longer disease duration,male sex,higher baseline EDSS score, lower brain volume, spinal cord involvement. There is no definitive laboratory test indicative of progressive disease, however, measures of disability progression widely used in clinical practise(2). Barbour C et al, reported CSF biomarkers are able to separate RRMS from progressive forms, CSF biomarker-based approaches are not yet integrated into neurological examination(3). On the other hand,in our previous study, in acomparison of the MS patients and controls, we found that the median values of the EDSS scores among genotype of the V2941 polymorphism in the fractalkine gene receptor were statistically higher in genotype II than genotype VI. Also RRMS was statistically higher in genotypeVI than in genotypeII,where as the frequency of SPMS was statistically higher in genotypeVV than in the genotypeVI for the same polymorphism.(4).In another study,it was shown that the CX3CR1 I(249) T(280) haplotype has a protective effect when transforming into the SPMS(5).To date,no spesific clicnical,immunologic,patholodi,radiologic marker to determine when RRMS transform into SPMS. There is a need for biomarkers to support early detection of SPMS.For this reason,we searced previously unstudied sFKN for its ability to be an early biomarker distinguishing SPMS from RRMS.

Materials and Methods

Our study consisted of 24 SPMS, 38 RRMS and 30 healty controls. SPMS and RRMS were diagnosed according to Mc Donald 2017 criteria(6) and were not taken any drug at the time of the study. The degree of neurologicaldeficits were assessed by Expanded Disability Status Scale (EDSS). All individuals in the patient and control group were informed about the study and consent of the patients was obtained. Serum levels of sFKN were tested by Enzyme Linked Immunosorbent Assay(ELISA) method. 5cc peripheral blood samples were taken from the patient and healty controls, centrifuged at 5000 rpm for 10 minutes, and the serum was separated and stored at -20 degrees until analysis. Fractalkine concentration was determined spectrophotometrically.
Absorbances read at 450 nm.Statistical analysis were performed using the IBM SPSS 21.0 Differences among SPMS and RRMS patients groups were assessed with Chi-square,Mann-Whitney and Fisher exact test.

Results

Clincal charecteristics of the paeticipants of this study is presented in Table 1. According to this table,in the SPMS group, there were 15 women with a mean age of 38.02, a total of 24, in the RRMS group, there were a total of 38 patients, 28 of whom were women with a mean age of 31.06. Disease duration 12.21 in the SPMS group, 4.67 in the RRMS group, EDSS was 5.5±1.7 in the SPMS group and 1.5±1.6 in the RRMS group. The patients and healty control groups were similar in terms of age and gender. No statistically significant differences was found in terms of the mean age,gender distribution and disease duration between the groups. As assessed by the chi-square test serum sfractalkine mean values did not show a statistically significant and difference in terms of genders($p=0.253$). Although there was a weak negative correlation between serum fractalkine levels and age and disease duration,but this relationship was not statistically significant ($p=0.614$,$p=0.086$). Serum fractalkine levels of patients and healty controls are shown in Table 2. Serum Fractalkine levels of SPMS group were significantly lower than RRMS group and controls ($p<0.05$).

Table 1.Clinical charecteristics of the participants

	SPMS	RRMS	CONTROL
Age	37.02±3.72	31.06±2.68	34.18±4.0
Sex			
a.Female	15	28	20
b.Male	9	10	10
Duration of disease (year)	12.21	4.67	---
EDSS	5.5±1.7	1.5±1.6	---

Table 2: Serum Fractalkine levels of patients and healty controls.

	Fractalkine (pg/ml)
SPMS (n=24)	0.52±2.14
RRMS (n=38)	
a:During the attack	1.2±0.32
b:After the attack	0.98±0.16
Controls (n=30)	0.74±3.32

Discussion

Cytokines and chemokines are konown to play important role in the immunopathogenesis of MS. Among chemokines serum levels of FKN was reported to be elevated in RRMS patients (7). However, it has not been observed in patients with SPMS. FKN is a chemokine that can exist i a soluble form, as chemotactie cytokine, or in a membrane-attached form that arts a binding molecule. FKN dose dependently suppressed the production of nitric oxide (NO), interleukine-6 (IL-6), tumor negrosis factor alpfa (TNF- α) with activated microglias. It is also significantly suppressed neuronal cell death induced by microglia activated with lipopolisaccarides (LPS) and interferon- gamma (INF- γ) in dose dependent manner. These possible functions of fractalkine as on intrinsic inhibitor against neurotoxicity by activated microglia and may be an intrinsic neuroprotective chemocine in the CNS. However, due to its dual effects, FKN exerts numerous effects on pathophysiological conditions that have both negative and positive consequences on immunopathogenesis (8-13).

FKN is a unique chemokine with direct relationship with its receptor (CX3CRI) to reduce expression of proinflammatory genes in activated microglia (14). According to the results of our study, the decrease in sFKN level supports the development of neurodegeneration by increasing neuroinflammation in CNS. It may contribute to the neurodegenerative mecanisms of progression and promote the transition from RRMS to SPMS. As a result our research shows that sFKN can be used as an early biomarker associated with disease progression in distinguishing between SPMS and RRMS, Additionally in future it will be a promising new therapeutic target.

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