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The SDF-1 3′A Genetic Variation of the Chemokine SDF-1α (CXCL12) in Parallel with its Increased Circulating Levels is Associated with Susceptibility to MS: A Study on Iranian Multiple Sclerosis Patients

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Abstract Immune system-related factors are important in pathogenesis of multiple sclerosis. The CXC chemokine SDF-1α (CXCL12) is involved in the immune responses. Hence, the aim of this study was to investigate the association between serum levels of SDF-1α (CXCL12) and its gene polymorphisms at position +801 with multiple sclerosis. In this experimental study, blood samples were collected from 100 multiple sclerosis patients and 100 healthy controls on EDTA pre-coated tubes. DNA was extracted and DNA samples were analyzed for SDF-1α (CXCL12) polymorphisms using PCR–RLFP in patients and controls. The serum levels of SDF-1α (CXCL12) were measured by ELISA. Demographic data were also collected by a questionnaire which was designed specifically for this study. Our results showed a significant difference between the *A/A*, *A/G*, and *G/G* genotype and *A* and *G* alleles of polymorphisms at position +801 of SDF-1α (CXCL12). Our results also showed that serum levels of SDF-1α (CXCL12) were markedly higher in patients than healthy controls, but no association was observed between SDF-1α (CXCL12) polymorphism and its serum levels. The results of this study might suggest the serum levels of SDF-1α (CXCL12) and its polymorphism play an important role in pathogenesis of multiple sclerosis. It is also worth noting that these factors could probably use as pivotal biological markers in the diagnosis of MS.

Keywords Multiple sclerosis · SDF-1α (CXCL12) · Polymorphism

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Introduction

Multiple sclerosis (MS) is a progressive, neurodegenerative central nervous system (CNS) disease that occurs most frequently in relapsing/remitting form in which a phase of demyelination is followed by a period of functional improvement (O'Keeffe et al. 2008; Weiner 2009). Recant loss of myelin and CNS inflammation are both common symptoms of MS. The responsible mechanisms of myelin degeneration in MS have yet to be identified (Lindvall and Kokaia 2006). Recent literature database stated that immune system-related parameters play key roles in the pathogenesis and complications of MS (Baker et al. 2009); in fact, immune regulatory factors might influence the pathogenesis of MS. Chemokines are low molecular weight proteins (8–17 kDa) (Hassanshahi et al. 2009). Increasing evidences have indicated the existence of a chemokine network in the CNS which is involved in physiological responses, under certain circumstances, pathological and repair processes subsequent to neurological injury (Arababadi et al. 2010a, b). The CXCR4 and CXCL12 are of high interest as therapeutic target in different pathological situations including different types of cancer (Terasaki et al. 2011), AIDS (Patrussi and Baldari 2011), systemic autoimmune and neuroinflammatory disorders (e.g., MS, stroke, and Alzheimer's disease) (Kohler et al. 2008) as well as stem cell biology (Ratajczak et al. 2004). Additionally, based on the significant role that CXCR4/CXCL12 axis plays in hematopoiesis including hematopoietic cell differentiation and survival and homing of hematopoietic progenitors to the bone marrow and regulation of neuronal progenitor cell migration in the CNS (Li and Ransohoff 2008; Klein and Rubin 2004), thus, genetic factors that lead to elevated expression of this chemokine enable the immune system to induce a vigorous immune response against CNS antigens in MS patients. Previous studies showed that the expression of SDF-1α (CXCL12) can be affected by its polymorphisms at position +801 region (Soriano et al. 2002). Therefore, the aim of this study was to investigate the relation between MS and functional polymorphisms of SDF-1α (CXCL12) gene (SDF-1–3′A), as well as the serum levels of this chemokine. We also studied the association between these polymorphisms and serum levels of SDF-1α (CXCL12) as a biological marker of MS.

Materials and Methods

Subjects

Specimens were collected from 100 relapsing–remitting MS patients and 100 healthy controls during 2008–2009 in Rafsanjan University of Medical Sciences. An expert neurologist confirmed the occurrence of MS, according to the clinical and paraclinical findings (MRI study, oligoclonal bands in CSF, and evoked potentials) based on McDonald's criteria (McDonald et al. 2001). All of the patients were under treatment with Cinnovex (a betaferon component) and the last attack happened 3 months before sampling. They also were matched regarding the stage of the disease (all of them were in silent stage). Healthy control cases were selected from Rafsanjan population with same sex, age, and socio-economical status following approval by Rafsanjan University of Medical Sciences ethical committee. Written consent forms are filled out by both patients and controls prior to sample collection.

DNA Extraction

Peripheral blood was collected on EDTA pre-coated tubes and then genomic DNA was extracted by a commercial kit (Bioneer, South Korea). Extracted DNA samples were stored at −20°C for further use.

Polymorphism Genotyping

SDF-1α (CXCL12) gene polymorphism at position +801 (SDF-1–3′A) was analyzed by polymerase chain reaction–restriction length polymorphism (PCR–RFLP) method. PCR reaction mixture was made up of addition of the following reagents to a 0.2-ml microcentrifuge tube on ice: 2.5 μl of Taq DNA polymerase buffer (10×), 0.5 μl of $MgCl_2$ (stock concentration 1.5 mM), 0.5 μl of each dNTP [dATP, dCTP, dGTP, and dTTP (stock concentration of 10 mM)], 1 μl of each primer [forward—CAGTCAACCTGGGCAAAGCC and reverse—AGCTTTGGTCCTGAGAGTCC (stock concentration of 25 ng/μl)], 1 μl of prepared DNA, and sterile double-distilled water to a final volume of 25 μl. The amplification was performed with the following program: one cycle of 93°C for 2 min, 93°C for 1 min (denaturation), 1 min at 57°C for annealing of SDF-1α (CXCL12), 72°C for 40 s (elongation) followed by 30 cycles of 93°C for 20 s, 55°C for 20 s, and 72°C for 40 s. During the last 45 s of the first stage, 0.3 μl of Taq DNA polymerase was added to the mixture. The amplified PCR product of SDF-1α (CXCL12) gene covers +801 region with a molecular size of 302 bp. The Sac-1 (Fermentase, Finland) restriction enzyme has merely a restriction site on this region, thus, the fragment will be digested into two 202- and 100-bp fragments following digestion. In case of heterozygotic form (A/G), three different fragments with 302, 202, and 100 bp are then visible. In homozygotic form, a 302-bp fragment [without any digestion (A/A)] or two 202 and 100 bp [digesting both alleles (G/G)] was then observed. The digested products were electro-

phoresed on a 2.5% agarose gel after adding 4 μl of loading buffer (Cinnagen, Iran) and studied on Chemi-Doc model XRS (Bio-Rad, USA) after staining with ethidium bromide.

Chemokine Assay

The serum levels of SDF-1α (CXCL12) were measured by ELISA (R&D systems, UK) in patients and healthy controls immediately after blood collection. Assays were performed as per manufacturer's guidelines. The sensitivity of kits was 2 pg/ml and inter- and intra-assay assessments of reliability of the kit were conducted.

Statistical Analysis

Hardy–Weinberg equilibrium was assessed using genotype data. Allele and genotype frequencies were calculated in patients and healthy controls by direct gene counting. Statistical analysis of the differences between groups was determined by χ^2 test using EPI 2000 and SPSS software version 13. P values less than 0.05 were considered significant. The study power was also calculated for each allele and genotype.

Results

Statistical analysis of demographic parameters indicated that the mean age, gender, and socio-economical status of the participants had no marked differences which was as follows: the mean age of patients was 40±9 years and of the control group was 40±7 years (P=0.85), the gender variation of patients was 59 (59%) female and 41 (41%) male, and for control group was 60 (60%) female and 40 (40%) male (P=0.9). There was no significant difference between groups regarding socio-economical status (Table 1) (P=0.90). Our results indicated significant increased levels of SDF-1α (CXCL12) in serum of MS patients compared to their related control (Fig. 1) (P<0.05). The mean concentration of SDF-1α (CXCL12) in patients and controls were 101.48± 25.58 and 37.31±5.58, respectively.

Evaluation of the polymorphisms in +801 of SDF-1α (CXCL12) by *S*ac-1 restriction enzyme showed that the prevalence of *A/A* genotype was nine (9%) in patients and 11 (11%) in controls. Our results also revealed that the frequency of *A/G* genotype was 25 (25%) and 45 (45%) in patients and controls, respectively. The frequency of the *G/G* genotype in patients was 66 (66%) and in controls were 44 (44%) (Fig. 2). Statistical analysis of our data confirmed a significant difference between the two groups (P<0.001). The frequency of *A* allele was 43 (43%) and 67 (67.5%) in patients and controls, respectively. Fifty-seven (57%) cases of *G* allele were observed in patients but the frequency of this allele was 32 (32%) in controls (Fig. 3). Statistical analysis of alleles also exhibited a significant difference between patients and controls (P<0.001).

Table 1 Sex, economic status, and duration of treatment of MS patients

Variable	SDF-1α serum level
Sex	
Male	232±82.9[a]
Female	72.4±21.1
Economic status	
Good	119±58.5
Medium	91±24.1
Duration of treatment	
Under 3 years	143±39.2
Over 3 years	50.9±24.1

[a] Significant difference

Discussion

In this study, a case–control study was undertaken to examine the role of the SDF-1–3′A polymorphism in susceptibility to MS in southeastern Iranian MS patients. We have chosen MS patients and controls from the same ethnic background, and all were living in a common geographic area in the southeast region of Iran. All of the patients were also matched regarding the stage of the disease, types of treatment, and the last attack. We have demonstrated here that there was a significant association of the SDF-1–3′A polymorphism with MS in Iranian relapsing–remitting patients. To the best of our knowledge, this is the first study to report an association between the SDF-1–3′A polymorphism and MS. The significance of chemokines and their related receptors, which play a fundamental part in the starting and development of MS, has

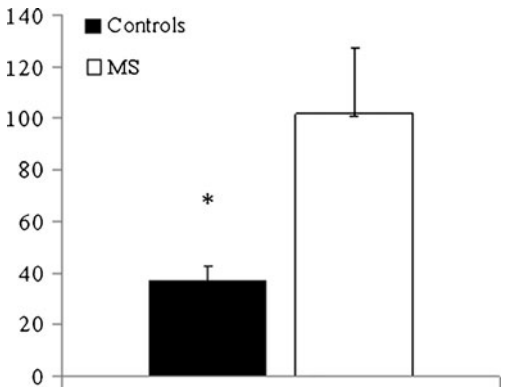

Fig. 1 Concentration of SDF-1α (CXCL12) circulating levels in MS patients and relative controls. The figure illustrates that serum levels of SDF-1α (CXCL12) were increased in MS patients

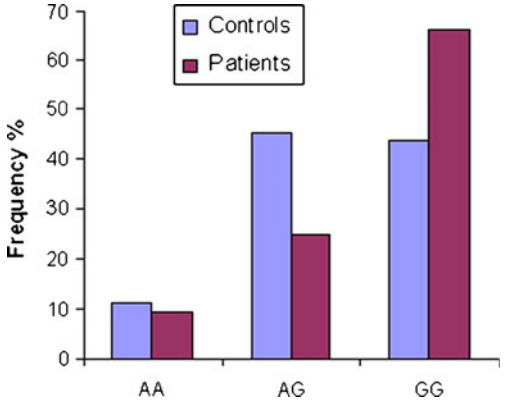

Fig. 2 Frequency of SDF-1α (CXCL12) genotype polymorphisms in the MS patients and relative controls. The frequency of GG genotype was increased in the patients compared to healthy controls

been explored over the last decade (O'Keeffe et al. 2008; Weiner 2009). In animal models, McCandless and colleagues using animal models indicated that polarized expression SDF-1α (CXCL12) at the blood–brain barrier (BBB) facilitated leukocyte extravasation into the CNS and the entrance of autoreactive leukocytes, hence, leading to an inflammatory reaction (McCandless et al. 2008). A transition at position 801 (G to A), SDF-1–3′A, is described as a common polymorphism in the 3′ untranslated region of the SDF-1α (CXCL12) gene (Kawasaki et al. 2004). In our study, we showed that nine (9%) cases of our patients had *A/A* genotype, 25 (25%) emerged with *A/G*, and ultimately 66% displayed *G/G* genotype variant. Although there are not much studies on the polymorphisms in different diseases, the association of SDF-1–3′A polymorphisms with HIV (Pourazar et al. 2005; Watanabe et al. 2003) and lung cancer (Razmkhah et al. 2005) have been reported. More recently, we also studied an association between the SDF-1–3′A polymorphisms with post-transfusion occult hepatitis B infection and type 2 diabetes (Hassanshahi et al. 2010; Derakhshan et al. 2011). SDF-1–3′A polymorphisms indicated to be associated with

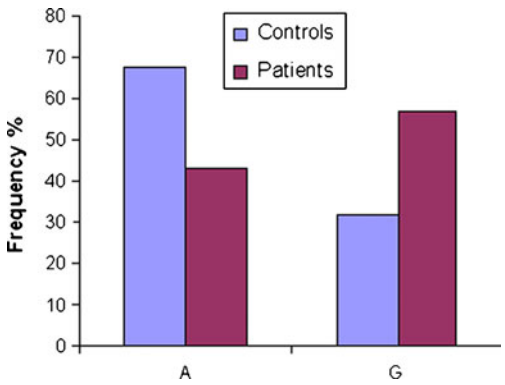

Fig. 3 Frequency of SDF-1α (CXCL12) allele polymorphisms in the MS patients and relative controls. The frequency of G allele was increased while A allele decreased in the patients compared to healthy controls

autoimmune disorders such as type 1 diabetes and autoimmune thyroid disease (Kawasaki et al. 2004); hence, in the present study, we report an association between MS and SDF-1–3′A gene polymorphisms. Therefore, based on our polymorphism results, it could be concluded that SDF-1–3′A heterozygote and homozygote gene types are more susceptible to MS, and the genotypes may play a crucial role in the development of MS. These findings may also apply for differential diagnosis of MS from the other neurological disorders. In our study, we also showed enhanced serum levels of SDF-1α (CXCL12) in MS relapsing–remitting patients compared to control. The overexpression of SDF-1α (CXCL12) protein in relapsing–remitting patients in this study probably could be a result of SDF-1α 3′A polymorphisms and has regulatory effects on SDF-1α (CXCL12) at this gene because Winkler et al. showed that this polymorphisms have regulatory effects on SDF-1α (CXCL12) expression (Winkler et al. 1998). In contrast to our observations, Sellebjerg and co-workers reported the increased levels of CXCL13 but not SDF-1α (CXCL12) in different types of MS (Sellebjerg et al. 2009). This discrepancy between our findings and Sellebjerg's results could probably be explained by the fact that all of our patients were in relapsing–remitting phase of MS, while Sellebjerg in parallel with relapsing–remitting patients analyzed other phases of MS as well. Furthermore, these results may probably aid in roughly speculating the occasion of the entering of a patient to this phase based on the SDF-1α (CXCL12) serum levels. However, McCandles and colleagues elucidated that rodent but not human SDF-1α (CXCL12) is increased in earlier phase of MS even before BBB disruption that is via IL-1β which is produced by T-helper and T-cytotoxic immigrant lymphocytes (McCandless et al. 2008). Monocyte infiltration to the brain tissue is believed to be essential for progression and development of MS inflammatory reactions, and the crucial role of SDF-1α (CXCL12) in the recruitment of these cells is of paramount importance. On the other side of this scenario, it has been indicated that attachment of monocytes to the ICAM-I is facilitated by SDF-1α (CXCL12) induced by TNF-α and IL-1β (Malik et al. 2008). Taken together, our result may explain a mechanism by which the induced levels of SDF-1α (CXCL12) in MS patients is a progression of a story of indirect regulation by TNFα shown to be increased in MS patients. In the other disorders and type cell such as hepatitis B and hepatoma cells, we have previously showed increased levels of SDF-1α and other CXC chemokines like IP-10 in response to TNF-α (Hassanshahi et al. 2007). Histochemical studies demonstrated that SDF-1α (CXCL12) is involved in homing of CXCR4 [SDF-1α (CXCL12) receptor] infiltrated cells in pre-vascular regions of MS patients and blocks their infiltration to the parenchymal tissues of CNS (McCandless et al. 2008). Importantly, evidences showed that the

migration and recruitment of leukocytes which express CXCR4 [one of SDF-1α (CXCL12) receptors] in response to SDF-1α (CXCL12) may lead to development of MS. A transition at position 801 (G to A), SDF-1–3′A, was described as a common polymorphism in the 3′ untranslated region of the gene. Therefore, our results in a way shows that the serum levels of SDF-1α (CXCL12) could probably be used as a key biomarker in MS prognosis, and it may be concluded that elevated SDF-1α (CXCL12) levels assist the progression of MS, and a relation could be postulated between the levels of the chemokine and CNS involvement and also increased level of autoimmunity in the patients (Poggi et al. 2007). SDF-1α (CXCL12)/CXCR4 axis plays an important role in some autoimmune pathogenic conditions such as rheumatoid arthritis (Pablos et al. 2003). These days, it has been demonstrated that stem cells are present in periphery, in fact regarding the notion of involvement of SDF-1α (CXCL12) in homing of stem cell. The increased levels of this chemokine in MS patients in our study could also be due to the critical role of SDF-1α (CXCL12) in recruitment of these cells to the MS, and could help neurogenesis and angigenesis in MS patients for its neurogenetic and angiogenesis properties (Hess and Borlongan 2008). It may be related to the prominent role of SDF-1α (CXCL12) and its receptor, CXCR4, in development, recruitment of neural progenitors, and homeostasis of neural progenitors in developing CNS tissues (Li and Ransohoff 2008). In the secondary lymphoid organs and CSF of MS patients, the presence of B cells bearing (BCL-2, KIG^{7+}, $Cd77^{+}$, $CD19^{+}$) phenotype and T cells with ($CD45RO^{+}$–$CCR7^{+}$–$CD27^{+}$) phenotype and increased SDF-1α (CXCL12) and CXCL13 as micro-environmental factors has been documented (Corcione et al. 2004; Giunti et al. 2003). Therefore, collectively our findings with Coercion and Glutei findings may probably mean that increased levels of SDF-1α (CXCL12) in relapsing–remitting phase could be regarded as a reason for induction of an immune response for recruitment of CXCR4-expressing cells. Again, the presence of memory phenotype T cells accompanying $CXCR4^{+}$ and also increased levels of SDF-1α (CXCL12) together could be considered as a new insight for further studies because it seems that memory T cells are important in the maintenance of MS patients in the relapsing–remitting status.

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