ORIGINAL ARTICLE
Oman Medical Journal [2016], Vol. 31, No. 1: 40–42

Increased Concentrations of Interleukin–33 in the Serum and Cerebrospinal Fluid of Patients with Multiple Sclerosis

Abdollah Jafarzadeh[1,2], Roya Mahdavi[2], Mitra Jamali[2], Hossain Hajghani[2]*, Maryam Nemati[2,3] and Hossain-Ali Ebrahimi[4]

[1]Department of Immunology, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[2]Department of Immunology, Kerman University of Medical Sciences, Kerman, Iran
[3]Department of Laboratory Sciences, Kerman University of Medical Sciences, Kerman, Iran
[4]Neurology Research Center, Kerman University of Medical Sciences, Kerman, Iran

ARTICLE INFO

Article history:
Received: 11 February 2015
Accepted: 7 September 2015

Online:
DOI 10.5001/omj.2016.08

Keywords:
Multiple Sclerosis; IL33 protein, human; Treatment.

ABSTRACT

Objectives: Interleukin (IL)–33 is a cytokine with both pro- and anti-inflammatory effects involved in the pathogenesis of some inflammatory diseases. The purpose of this investigation was to evaluate the serum and cerebrospinal fluid (CSF) IL–33 concentrations in patients with multiple sclerosis (MS). ***Methods:*** Blood specimens were obtained from 140 patients with MS (46 males and 94 females) with various disease patterns and treatment plans and 140 healthy subjects (47 males and 93 females), who acted as a control group. CSF samples were collected from 20 MS group and 20 sex- and age-matched patients with other neurological diseases of nonautoimmune etiology. The serum and CSF concentrations of IL–33 were measured by the enzyme-linked immunosorbent assay. ***Results:*** The serum and CSF IL–33 levels were significantly higher in the MS group compared to the control group ($p<0.001$ and $p<0.050$, respectively). The serum IL–33 concentrations were also significantly higher in newly diagnosed (untreated) patients and patients treated with methylprednisolone or with interferon-β and methylprednisolone compared to the healthy patient group ($p<0.007$, $p<0.002$, and $p<0.010$, respectively). Moreover, the serum IL–33 concentrations in patients with relapsing-remitting (RRMS), primary progressive (PPMS), and secondary progressive (SPMS) forms of the disease were significantly higher than in the healthy control group ($p<0.006$, $p<0.001$, and $p<0.020$, respectively). ***Conclusions:*** Our results showed increased concentrations of IL–33 in patients with MS including both untreated and treated MS patients and patients with the RRMS, SPMS, and PPMS forms. This suggests that IL–33 may be involved in the pathogenesis of all MS forms and treatment with methylprednisolone or both interferon-β plus methylprednisolone has no influence on IL–33 concentrations.

Multiple sclerosis (MS) is an autoimmune-mediated demyelinating disease of the central nervous system (CNS). The disease has four clinical forms: relapsing-remitting (RRMS), progressive relapsing (PRMS), primary progressive (PPMS), and secondary progressive (SPMS).[1]

Autoreactive pathogenic helper T cells (Th) play a prominent role in the pathogenesis of MS. Experimental autoimmune encephalomyelitis (EAE) is the most frequently used animal model system for studying MS.[2] Upon antigenic stimulation, naïve Th cells are activated and undergo several proliferations before finally differentiating into several subsets (i.e., Th1, Th2, Th17) and regulatory T cells (Treg), which are characterized by the production of particular cytokine profiles. Th1 cells that release inflammatory cytokines (e.g., interferon (IFN)-γ, tumor necrosis factor (TNF)-α) as well as Th17 cells that secrete interleukin (IL)–17 play central role in the pathogenesis of MS and EAE diseases.[3] Treg cells, which secrete transforming growth factor (TFG)-β, and Th2 cells, which release IL–4, were thought to be important in diseases amelioration.[4] Macrophages may also play a pivotal role in the pathogenesis of MS and EAE diseases.[5] In our previous studies, higher levels of a Th17–related chemokine (CCL20) and lower levels of a Th2/Treg-related chemokine (CCL22) were observed in patients with MS.[6,7]

IL–33 is a new member of the IL–1 family. The IL–33 receptor is a heterodimer comprised of ST2L (or ST2) and IL–1R accessory protein (IL–1RAcP).

*Corresponding author: ✉hebrahimi@kmu.ac.ir

ST2 is expressed on some leukocytes particularly on mast cells and activated Th2 cells. It acts to increase the effector function of these cells.[8] The binding of IL–33 to its receptor induces the secretion of pro-inflammatory cytokines from mast cells and Th2 lymphocytes,[8] stimulates the migration of Th2 cells,[9] promotes the activation of the eosinophil, basophil, and natural killer (NK) cells,[10] potentiates the Th1- and Th2–related immune responses,[11] triggers IFN-γ secretion by invariant NK T cells (iNKT) and NK cells, and increases the count of iNKT cells in the spleen.[12] The importance of IL–33 has been suggested in the strengthening of innate immunity and may act as an alarmin to activate the immune system following cell necrosis or apoptosis.[13]

IL–33 is a nuclear cytokine that constitutively expresses in endothelial and epithelial cells.[13] Interestingly, the highest quantity of IL–33 expression in mice was found in the brain and spinal cord,[14] suggesting the possible specific actions of IL–33 in the CNS additional to its role in the immune system. Recent investigations have also demonstrated that IL–33 may contribute to the pathogenesis of some inflammatory diseases suggesting that IL–33 may have strong pro-inflammatory characteristics.[13,15] Although, there are a few studies regarding the association of IL–33 and MS, the influences of gender, MS patterns, and treatment program on IL–33 concentration have not been investigated. In this study, we sought to evaluate the concentration of IL–33 in MS patients and any association with gender, treatment programs, and disease patterns.

METHODS

Peripheral blood specimens were collected from two groups between January 2013 and February 2014. Group one was comprised of 140 patients with MS (46 men and 94 women) who were referred to the Shephah Hospital of Kerman (a city in southeast Iran). MS was diagnosed by specialist neurologists, according to the McDonald's criteria.[16] Of the 140 patients, 102 patients presented with RRMS, 28 with SPMS, eight with PPMS, and two with PRMS. The patients were also differentiated as newly (n = 51) and previously diagnosed (n = 89). Newly diagnosed patients were enrolled into the study before receiving any treatment. Previously diagnosed patients were treated with methylprednisolone, IFN-β, or IFN-β plus methylprednisolone. The treated MS patients received intravenous methylprednisolone 1000 mg/day for three to five days following an acute MS attack or 30 μg intramuscular IFN-β once weekly (Avonex, Biogen, Massachusetts, US or CinnoVex, CinnoGen, Iran) or 44 μg subcutaneously, three times weekly (Rebif, Merck Serono, Switzerland) for at least three months. Some MS patients were initially treated with IFN-β (during the silent stage of disease) and after the occurrence of an acute MS attack with methylprednisolone.

Cerebrospinal fluid (CSF) samples were obtained from another 20 patients with MS (four men and 16 women) and 20 sex- and age-matched patients (five men and 15 women) with other neurological diseases of nonautoimmune etiology (such as a tension headache or meningitis). The CSF samples were obtained during routine diagnostic work-up or for other clinical purposes. CSF specimens were collected from patients who were not under immunosuppressive medication and were stored at –70 °C.

Group two (considered the control group) comprised of 140 healthy subjects (47 men and 93 women) that were recruited among blood donors of the Kerman Transfusion Organization. All control subjects were in basic good health, with no history of CNS disease or any other relevant disorders. Those with a history of recurrent infections, asthma, allergy, and atopic diseases, any suspected immunological disorders, malignancy, surgery, smoking, drug use, and major trauma within six months before blood sampling were all excluded from the study. A peripheral blood specimen was taken from all subjects, and the sera were separated and stored at –70 °C.

Our study was evaluated and approved by the Ethical Committee of Kerman University of Medical Sciences. All participants gave their written informed consent before enrollment.

The serum and CSF IL–33 concentrations were determined using commercial enzyme-linked immunosorbent assay (ELISA) kits (BosterBio, California, US) according to the manufacturer's instruction. The sensitivity of the test was less than 10 pg/ml.

The Student's *t*-test, analysis of variance (ANOVA), and chi-square tests were performed for comparison of variables between groups. The data were analyzed by SPSS Statistics (Chicago,

Table 1: Serum levels of IL–33 in patients with MS patients and the control group according to gender.

Group	Sex	Number	IL–33 levels*	*p*-value
MS	Male	46	268.8±67.5	0.050
	Female	94	492.2±77.6	
	Total	140	408.0±55.3	
Control	Male	47	121.2±25.7	0.310
	Female	93	192.3±65.9	
	Total	140	156.8±35.4	

**Values expressed as mean±SD. The serum levels of cytokine are expressed as pg/ml. IL–33: interleukin–33; MS: multiple sclerosis; SD: standard deviation.*

Illinois, US) version 18. A *p*-value less than 0.050 was considered statistically significant.

RESULTS

The mean age of patients with MS was 35.0±8.3 years and 36.1±8.1 years in the control group. There were 94 (67.1%) female patients with MS and 46 (32.9%) males. In the control group, there were 93 (66.4%) females and 47 (33.6%) males. There was no significant difference between the MS group and control group in age and gender distribution ($p = 0.260$ and $p = 0.500$, respectively).

CSF samples were obtained from 20 patients with MS and 20 age- and sex-matched control patients. The mean age was 33.6±9.3 years in the MS group and 35.3±7.0 years in the control group. There were 16 (80.0%) female and four (20.0%) male patients with MS and 15 (75.0%) female and five (20.0%) males in the control group. There was no significant difference between the patients with MS and the control group in mean age and gender distribution ($p = 0.430$ and $p = 0.700$, respectively).

The mean serum IL–33 concentration was 408.0±55.3 pg/ml in the MS group and 156.8±35.4 pg/ml in the control group. The serum IL–33 concentration was significantly higher in the MS group compared to the control group ($p<0.001$) [Table 1]. In the control group, the difference in the serum IL–33 concentrations between males and females was not significant. However, cytokine levels were found to be higher in females. In female MS patients, the serum IL–33 concentrations were significantly higher compared to male patients ($p<0.050$). In both male and female patients with MS, the serum IL–33 concentrations were significantly higher compared to patients in the control group of the same gender ($p<0.050$ and $p<0.010$, respectively) [Table 1].

Table 2: CSF levels of IL–33 in MS patients and control group according to gender.

Group	Sex	Number	IL–33 levels*	*p*-value
MS	Male	4	66.6±37.0	0.700
	Female	16	79.1±13.0	
	Total	**20**	**76.6±12.3**	
Matched controls	Male	5	38.4±7.3	0.500
	Female	15	45.9±8.2	
	Total	**20**	**44.1±6.4**	

**Values expressed as mean±SD. The CSF levels of cytokine expressed as pg/ml. CSF: cerebrospinal fluid; IL–33: interleukin–33; MS: multiple sclerosis; SD: standard deviation.*

The mean CSF concentrations of IL–33 were 76.6±12.3 pg/ml in the MS group and 44.0±6.4 pg/ml in the control group. The CSF concentrations of IL–33 were significantly higher in the MS group than in the control group ($p<0.050$) [Table 2]. In the MS and control group, the difference in the mean CSF concentrations of IL–33 between men and women were not significant. In female patients with MS, the CSF concentrations of IL–33 were significantly higher compared to the control group ($p<0.040$). In males, this difference was not significant [Table 2].

Table 3: Serum levels of IL–33 in newly (untreated) and previously diagnosed (treated) patients with MS according to gender.

Group	Sex	Number	IL–33 levels*	*p*- value
Untreated	Male	25	289.3±83.1	0.320
	Female	26	452.4±140.9	
	Total	**51**	**372.4±82.6**	
Treated	Male	21	244.4±112.1	0.100
	Female	68	512.8±93.3	
	Total	**89**	**433.4±628.9**	
Control	Male	47	121.2±25.7	0.310
	Female	93	192.3±65.9	
	Total	**140**	**156.7±35.4**	

**Values expressed as mean±SD. The serum levels of cytokine expressed as pg/ml. IL–33: interleukin–33; MS: multiple sclerosis; SD: standard deviation.*

Serum IL–33 concentrations in newly diagnosed (untreated) and previously diagnosed (treated) MS patients are given in Table 3. Overall, the serum IL–33 concentrations in untreated and treated patients were significantly higher than the control group ($p<0.007$ and $p<0.001$, respectively). However, there was no significant difference between untreated and treated patients. In both untreated and treated

Table 4: Serum levels of cytokine IL–33 in MS patients according to treatment.

Group	Treatment	Number	IL–33 levels*	*p*-value
MS	IFN-β	6	285.1±153.0	0.620
	MP	16	511.8±187.6	
	IFN-β+MP	65	426.0±88.2	
	No treatment	51	372.5±82.6	
Control	-	140	156.8±35.4	

**Values expressed as mean±SD. The serum levels of cytokine expressed as pg/ml. IL–33: interleukin–33; MS: multiple sclerosis; SD: standard deviation; IFN-β: interferon-β; MP: methylprednisolone*

Table 5: Statistical comparison of the serum IL–33 levels in patients with MS patients, according to their treatment program.

Treatment	IFN-β	MP	IFN-β +MP	No treatment
IFN-β	-	0.492	0.446	0.725
MP	0.492	-	0.649	0.443
IFN-β+MP	0.446	0.649	-	0.658
No treatment	0.725	0.443	0.658	-
Control	0.346	0.002	0.006	0.007

IFN-β: interferon-β; MP: methylprednisolone

patients, no significant differences were observed between males and females concerning the IL–33 concentrations [Table 3].

The serum IL–33 concentrations in treated MS patients with methylprednisolone or both of IFN-β plus methylprednisolone were significantly higher than the control group ($p<0.002$ and $p<0.01$, respectively). However, no significant difference was observed in patients treated with IFN-β and the control group. The serum IL–33 concentrations in patients treated with IFN-β was lower compared to untreated patients, but the difference was not significant [Table 4 and Table 5]. No significant differences were observed in the mean serum levels of IL–33 between patients treated with methylprednisolone, IFN-β, or both IFN-β plus methylprednisolone [Table 5].

No significant differences in serum IL–33 concentration were observed between patients with various MS patterns. However, the serum IL–33 concentrations in patients with RRMS, SPMS, and PPMS were significantly higher than the control group ($p<0.006$, $p<0.001$, and $p<0.020$, respectively) [Table 6].

Table 6: Serum levels of IL–33 in MS patients according to disease patterns.

Group	Diseases form	Number	IL–33 levels*	*p*-value
MS	RRMS	102	364.1±61.3	0.530
	SPMS	28	567.2±155.3	
	PPMS	8	486.6±127.51	
	PRMS	2	374.6±375.1	
	Total	140	408.0±55.3	
Control	-	140	156.7±35.4	

**Values expressed as mean±SD. The serum levels of cytokine expressed as pg/ml. IL–33: interleukin–33; MS: multiple sclerosis; SD: standard deviation; PPMS: primary progressive multiple sclerosis; PRMS: progressive-relapsing multiple sclerosis; RRMS: relapsing-remitting multiple sclerosis; SPMS: secondary progressive multiple sclerosis.*

DISCUSSION

We observed increased concentrations of IL–33 in both serum and CSF samples from patients with MS, which suggests that IL–33 contributes to its pathogenesis. In both male and female patients with MS, the serum IL–33 concentrations were significantly higher compared to the control group subjects with the same gender. Accordingly, the elevated IL–33 concentrations may contribute to the pathogenesis of MS in both genders.

In female patients with MS disease, the mean CSF IL–33 concentration was also significantly higher compared to women in the control group. In male patients with MS disease, the mean CSF IL–33 concentration was also higher compared to men in the control group, but the difference was not statistically significant. This was probably due to a low sample size of men. The use of a suitable sample size of CSF from men in any future studies could clarify this association. Recent investigations have also indicated that IL–33 may be involved in the pathogenesis of chronic inflammatory diseases such as asthma, rheumatoid arthritis, and anaphylaxis suggesting that IL–33 may have potent pro-inflammatory characteristics.[13,17]

Attention has been focused on the role of IL–33 in the pathogenesis of immune-mediated CNS diseases due to very high levels of IL–33 mRNA expression in the brain and spinal cord.[14] The IL–33 is produced by some cells such as keratinocytes, dendritic cells, activated macrophages, endothelial cells, epithelial cells, smooth muscle cells, and fibroblasts.[18] Furthermore, IL–33 is mainly produced

by astrocytes in murine spinal cord[19] and human CNS tissues.[20] This suggests that IL–33–producing astrocytes may contribute to innate immune responses in the CNS. Astrocytes also express the IL–33 receptor, and IL–33 expression by astrocytes was increased in response to inflammatory stimuli and toll-like receptor ligation.[21] IL–33 levels were elevated in the periphery and CNS of MS patients, indicating that IL–33 may participate in the pathogenesis of MS disease.[20]

Higher expression of IL–33 mRNA in the CNS of EAE mice has been observe.[22] Within the CNS, microglia cells are the main target of IL–33, which induces microglia proliferation, phagocytosis, and the secretion of inflammatory cytokines and chemokines.[19] IL–33 induces the synthesis of IL–6, IL–13, and monocyte chemoattractant protein (MCP)–1 in microglia, and this induction is increased by IL–33–activated mast cells.[21] The activated microglia cells have been introduced as important effector cells that contribute to the demyelination process in MS.[23] IL–33 is also a potent endothelial activator that increases endothelial permeability in vitro and induces vascular leakage in mouse skin.[24] As the breakdown of the blood-brain barrier (BBB) is an essential step for the subsequent CNS inflammation, IL–33 may contribute to MS and EAE inflammation by disrupting the BBB in addition to modulating the immune system. Importantly, IL–33 may also facilitate recruitment of leukocytes into the CNS.[25]

Our results showed no significant differences in IL–33 serum levels between untreated patients and treated patients with methylprednisolone or both IFN-β plus methylprednisolone. The serum IL–33 concentrations in MS patients treated with methylprednisolone or both interferon-β plus methylprednisolone were significantly higher than the control group. However, there was no significant difference between patients treated with IFN-β and the control group on serum IL–33 concentrations. These findings indicate that treatment with IFN-β is more effective than treatment with methylprednisolone or both of IFN-β plus methylprednisolone in reducing serum IL–33 concentrations. Accordingly, the immunomodulatory effects of IFN-β may perform, in part, through the suppression of the IL–33 production. In agreement with our results, it has also been reported that treatment with IFN-β decreases IL–33 expression in the plasma and peripheral blood mononuclear cells of patients with MS.[20] In the absence of methylprednisolone, treatment with IFN-β may have reducing effects on the IL–33 levels whereas, in the presence of methylprednisolone, the IFN-β effects on IL–33 levels disappeared. Therefore, methylprednisolone may influence the IFN-β effects on IL–33 levels. The insignificant change in IL–33 levels observed between treated and untreated MS patients seems to indicate that this cytokine may not be associated with the immunomodulatory effect of methylprednisolone in MS. Moreover, it should be noted that the immunotherapeutic effects of IFN-β and methylprednisolone on the MS disease may be performed through their modulating effects on the other inflammatory and immunopathological parameters. Our results encourage further studies to investigate the influences of IFN-β and methylprednisolone on the IL–33 production.

IL–33 may be involved in the pathogenesis of all MS forms. We saw higher levels of IL–33 in patients with RRMS, SPMS, and PPMS forms of MS compared to the control group. The levels of IL–33 were also higher in patients with PRMS, but valid statistical analyzes require bigger sample size for this MS disease pattern.

Although high expression of IL–33 mRNA in the CNS of mice was also demonstrated,[14] studies of its role in the development of EAE as an animal model of MS are controversial.[26] IL–33 may have a preventive role in EAE at the initial (inducible) stage of the disease. However, after the establishment of EAE, it may have an enhancing role in the disease development due to the presence of some inflammatory cells in CNS. It has been reported that IL–33 induces both Th1- and Th2–related immune responses depending on the presence of certain conditions (i.e., the cytokine environment and cellular types).[27] For example, IL–33 has synergistic effects with IL–1 and IL–18 to increasing Th1/Th17–related response in experimental arthritis.[28] It has been also demonstrated that IL–33 stimulates IFN-γ synthesis by iNKT and NK cells.[26] IL–33 also reinforces Th1/Th17–related immune responses in some experimental models of immune disorders.[29] In IL–33–treated mice, the antigen-stimulated draining lymph nodes produce more IL–17 and IFN-γ.[14] Accordingly, IL–33 may be involved in the pathogenesis of the EAE and MS through the reinforcement of Th17 and Th1 cell functions.

CONCLUSION

Our study showed increased concentrations of IL–33 in patients with MS. This included both untreated and treated patients, and those with RRMS, SPMS, and PPMS form of the disease. Accordingly, IL–33 may be involved in the pathogenesis of all MS forms, and treatment of MS patients with methylprednisolone or both IFN-β plus methylprednisolone have no influence on IL–33 concentrations.

Disclosure
The authors declared no conflicts of interest. No funding was received for this study.

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