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Interleukin-33 plasma levels in patients with relapsing-remitting multiple sclerosis

Abstract: Cytokines are implicated in the immunopathogenesis of multiple sclerosis (MS). Interleukin (IL)-33, one of the recently discovered members of the IL-1 superfamily, is a dual functional cytokine involved in various autoimmune disorders. In a case-control study, venous blood was collected from healthy subjects categorized as control group (n = 44) and MS patients (n = 44). All recruited patients were clinically diagnosed with relapsing-remitting MS (RRMS), including patients without treatment (new identified cases, n = 16) and those treated with interferon beta (IFN-β) (n = 28). The plasma levels of IL-33 in subjects were measured with ELISA. Significantly elevated IL-33 plasma levels were observed in RRMS patients ($p = 0.005$). Furthermore, IFN-β-treated MS patients had lower levels of IL-33 compared to the untreated patients ($p < 0.001$). Increased IL-33 plasma levels in the patient group might be associated with development of MS. These results could contribute to our better understanding about the role of IL-33 in the immunopathogenesis of MS.

Keywords: cytokines; immunopathogenesis; interleukin-33 (IL-33); multiple sclerosis (MS); neuroinflammatory diseases.

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Introduction

Multiple sclerosis (MS) is a neuroinflammatory disease of the central nervous system (CNS), identified by lesions in the brain's white matter and progressive disability in neuronal function (1). The age of onset of MS has been reported to be varying between 20 and 40 years (2). Some studies report that MS might slightly develop in either children or people above 60 years (3–5). Researchers have conflicting ideas on whether MS is a pathological disease, as MS presents with a variety of signs and symptoms (6, 7). Clinical investigations have demonstrated the role of immune cells in the progression of neural lesions during the acute early phase of MS, where relapses occur in the white matter of neurons and inside tracts in the gray matter, mainly because of inflammatory reactions. The main pathologic sign of MS is plaque in the demyelinated neurons, with immunocytological activity of resident immune cells during the course of the disease (8–11). Numerous clinical studies have shown that MS lesions are initiated by leukocyte cell types, including lymphocytes, macrophages and dendritic cells through various immunological mechanisms such as cytokine production (10, 12).

Cytokines have various functions in health and diseases, especially in MS (13–16). One of the most important cytokines that directly contributes to the immunopathogenesis of MS is IL-33 (17), a recently discovered cytokine, taking part in various inflammatory and autoimmune diseases like psoriasis, lupus erythematous, ulcerative colitis and MS (17–20). ST2L, a receptor of IL-33, is expressed on the surface of various subsets of leukocytes and conducts signals to activate the MAPK and nuclear factor κB (NF-κB) pathways by TNF receptor-associated factor 6 (TRAF6) (21, 22). The IL-33/ST2 pathway is pivotal to inflammatory responses and autoimmune disorders (23). It has been reported that ST2L is principal for the inflammatory activity of IL-33 because of expression on several immune cells like endothelial cells, mast cells, macrophages, basophiles and dendritic cells (18, 19, 24–28).

Isfahan is one of the highest MS reported rate areas in Oceania and Asia (5, 29–33). Regarding the possible

role of IL-33 in MS progression, we assessed IL-33 plasma levels in MS patients in comparison with healthy subjects.

Materials and methods

Patient selection

Venous blood samples (3–5 ml) were collected and plasma was isolated from 44 relapsing-remitting multiple sclerosis (RRMS) patients and 44 gender, race and age-matched healthy subjects with no previous neurological problem history. All patients were clinically diagnosed with RRMS according to the McDonald criteria (7) and no one used steroids or other medication to alleviate clinical symptom. The patient group was divided into two subsets, interferon beta (IFN-β)-treated and newly diagnosed MS patients with no treatment initiation. None of our patients underwent clinical worsening in the preceding weeks. The study was approved by the Ethical Committee on Human Research in Isfahan University of Medical Sciences and informed consent was obtained from patients participating in this study. Details of data gathering and sampling have already been published (34, 35).

Table 1: Comparison of mean IL-33 plasma levels in different factors within each group.

Groups	Factors	Mean ± SEM[a]	p-Value[b]
Case	Sex		
	Male (n = 6)	106.91 ± 64.08	0.688
	Female (n = 38)	195.28 ± 131.18	
	Age (years)		
	15–25 (n = 4)	33.39 ± 4.22	0.417
	26–35 (n = 17)	66.20 ± 24.51	
	36–45 (n = 13)	97.29 ± 63.69	
	Greater than 45 (n = 10)	57.07 ± 23.60	
	History of viral disease		
	Yes (n = 10)	69.03 ± 20.10	0.261
	No (n = 34)	75.79 ± 26.87	
	Family history of MS		
	Yes (n = 11)	43.91 ± 14.69	0.630
	No (n = 33)	84.37 ± 27.68	
Control	Sex		
	Male (n = 6)	22.50 ± 6.32	0.808
	Female (n = 38)	24.30 ± 3.38	
	Age (years)		
	15–25 (n = 1)	40.49 ± 0	0.816
	26–35 (n = 12)	21.84 ± 2.34	
	36–45 (n = 29)	26.28 ± 10.69	
	Greater than 45 (n = 2)	19.73 ± 4.95	

[a]Mean ± SEM (pg/ml).
[b]p-Values are two-tailed.

Table 2: Mean IL-33 plasma levels in MS and control groups.

	Control (n = 44)	Case (n = 44)	p-Value[a]
Total	24.05 ± 3.02[b]	74.25 ± 21.15	0.005
Treated (n = 28)	–	55.87 ± 24.26	0.031[c]
Untreated (n = 16)	–	84.76 ± 9.35	0.018[c]

[a]p-Values are two-tailed.
[b]Data are shown as mean ± SEM (pg/ml).
[c]Compared with control group.

Cytokine ELISA

The plasma levels of IL-33 were measured by an enzyme-linked immunosorbent assay (ELISA) kit (BOSTER Immunoleader, CA, USA) according to the manufacturer's instructions.

Statistical analysis

In order to check the normal distribution of plasma levels, a Kolmogorov-Smirnov Z-test was performed. Assessment of association between mean plasma levels and various subjects' factors was carried out by ANOVA and independent t-tests in the control subjects and Mann-Whitney and Kruskal-Wallis tests in the patient group (Table 2). The comparison of IL-33 plasma concentrations between the case and healthy groups was evaluated by the Mann-Whitney test. Data was demonstrated as mean ± SD for age and sex (Table 1) and mean ± SEM for comparison of IL-33 plasma level with various subjects' characteristic factors (Table 2). p-Values of less than 0.05 were considered as statistically significant and all p-values were two-tailed. Statistical analysis was executed using SPSS version 16.

Results

Main characteristics of patients and healthy controls

Information on age and gender of patients and healthy controls showed that both groups were matched for gender and age ($p > 0.05$).

Characteristic features of subjects and correlation with IL-33 plasma level

The association between various characteristic features of patients and the healthy group and IL-33 plasma levels was assessed. As shown in Table 1, no factors were correlated with IL-33 level.
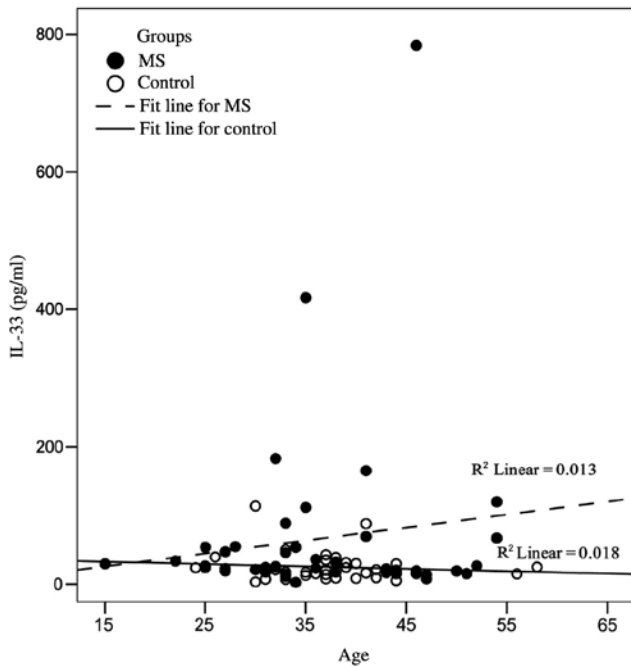
Figure 1: Plasma IL-33 levels based on age in the case and control groups.

Increased plasma levels of IL-33 in RRMS patients

The plasma levels of IL-33 were assessed in RRMS patients and in the control group. From Table 2 and Figure 3, the mean plasma levels of IL-33 in the RRMS patients were significantly higher than in the healthy subjects ($p < 0.05$). We also classified case groups into the two subgroups treated and untreated patients, and after final assessment, the results revealed a significant difference in IL-33 levels between the control group and both subgroups of MS patients. Besides, the mean levels of IL-33 in treated patients were significantly lower than those in the new diagnosed cases ($p > 0.001$).

Discussion

Cytokines have a crucial role in the immunopathogenesis of MS. Many studies have demonstrated increased infiltrating leukocytes in the brain, which consequently lead to CNS lesions through inflammatory cytokines and activated transcription factors like NF-κB (36, 37), signal transducer and activation of transcription 1 (STAT1) (37–39) and STAT6 (40, 41). The provocative cytokines result in the over-expression of inflammation-mediated genes and accordingly release toxic molecules, which increase demyelination (42–44). Activation of NF-κB and Toll-like receptor signaling pathways stimulates TNF-α or IL-1β, which mediates IL-33 transcription (21, 27, 45, 46).

The alterations of IL-33 in various age ranges in MS patients and healthy subjects are shown in Figure 1. According to the Pearson correlation coefficient analysis, the relationship between mean IL-33 plasma level and increase in age was weak and direct in the MS group and was feeble and inverse in the control group ($\rho_{(MS)} = 0.11$ and $\rho_{(Control)} = 0.13$).

Also, after separating the subjects based on gender, we observed a significant difference in female plasma IL-33 levels between both healthy and patient sub-groups ($p = 0.01$), but not in the male subsets (Figure 2).
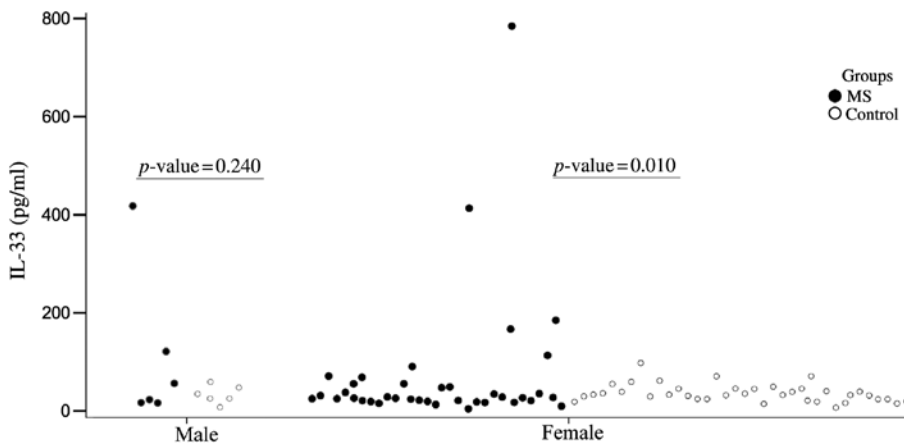
In the current study, we compared the plasma levels of IL-33 in RRMS patients with those in the healthy subjects. We did not find any significant association among various factors of MS patients and healthy control groups and
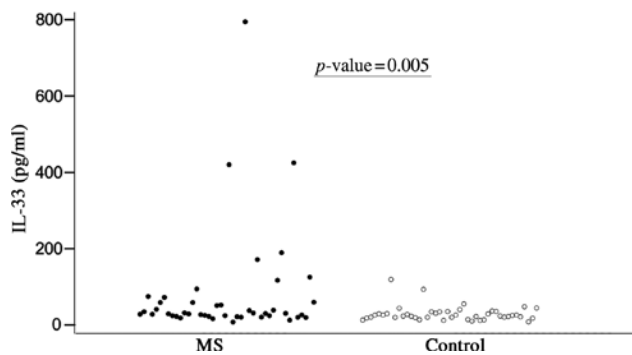

Figure 2: Plasma IL-33 levels in each of the case and control groups based on gender.

Figure 3: Comparison of IL-33 plasma levels in RRMS patients and healthy subjects.

mean IL-33 plasma levels. To the best of our knowledge, this is the first study describing the relationship between IL-33 and various features of investigated subjects.

Many findings have proved the involvement of immunity and imbalance between pro- and anti-inflammatory cytokines in the pathogenesis of MS (19, 47, 48). IL-33 has a contradictory function in immunity. It is well known that IL-33 induces mRNA expression of pro-inflammatory cytokines such as tumor necrosis factor-α (TNF-α) and IL-1β in the microglia. Binding of IL-33 to its receptor (ST2) induces activation of NF-κB and plays a critical role in the development of experimental autoimmune encephalomyelitis (EAE) (49–51). On the other hand, ST2 deficiency in dendritic cell surfaces leads to exacerbation of EAE (52). Furthermore, in response to IL-33, dendritic cells inhibit EAE (53). Interestingly, ST2 deficiency in BALB/C mice abrogates resistance to EAE (52). These are conflicting examples about the role of IL-33 in the immune system. Although clinical studies have shown that administration of IL-33 causes development of inflammation in the EAE model (54), other investigations have declared that IL-33 is not a necessary element for EAE pathogenesis (55). This is another evidence for the dual role of IL-33.

Previous studies have mentioned that IFN-β treatment could significantly suppress IL-33 plasma levels (56). In accordance with them, our assessments revealed that plasma levels of IL-33 in IFN-β-treated patients were significantly lower than in untreated patients ($p < 001$). It could be noticed that IFN-β therapy in RRMS patients can modulate MS development, which would be a favorite future therapeutic target for MS patients (57, 58). Today, it has been admitted that IFN-β can be used as disease-modifying therapy agent that, due to its anti-inflammatory properties, can boost remyelination indirectly. While there are many new medications to treat MS patients, such as glatiramer acetate, or various corticosteroids, IFN-β is still one of the most commonly used drugs as a desirable

and safe first-line treatment approach (59). Furthermore, follow-up studies have reported that using IFN-β can be beneficial for decreasing severity of disease (60).

It has been shown that IL-33 can biologically mediate several significant immune disorders, including rheumatoid arthritis, asthma, inflammatory bowel disease, dermatitis, cardiovascular disease and autoimmune hepatitis (18, 19). Moreover, the role of IL-33 in the immune system and the CNS is noticeable. In the immune system, the serum level of IL-33 that is elevated in response to the systemic inflammation results in the activation of various immune cells like dendritic cells, macrophages and lymphocytes. On the one hand, this initiation causes down-regulation of systemic inflammation. In the CNS, IL-33 stimulates vascular permeability in the blood-brain barrier (BBB) toward infiltrating immune cells, which consequently causes BBB disruption. Entry of immune cells into the CNS is responsible for beginning inflammation and promoting CNS resident immune cells like astrocytes to produce IL-33. It mediates infiltrating immune cells and/or CNS resident cells via binding to ST2 receptor, which causes cytokine and antibody generation and may modulate MS development. IL-33 also has a pivotal role in myelin damage/repair through its direct effect on oligodendrocytes (17) and glial activation, particularly astrocytes, and on induction of microglia proliferation, which causes the production of pro- and anti-inflammatory cytokines at the same time (61, 62).

Scientific attention has recently been directed toward the evaluation of IL-33 in the brain and immune-related diseases (63). There is enough evidence to show upregulated IL-33 expression by astrocytes and peripheral leukocytes in MS patients (64). Although it has been found that IL-33 induces pro-inflammatory type-2 responses, the anti-inflammatory properties of this cytokine have been thought to be beneficial in autoimmunity (65, 66) as well as in many other disorders (67).

In conclusion, in agreement with previous studies, our data confirmed that IL-33 levels were significantly higher in RRMS patients than in healthy controls, which suggested that IL-33 is a pro-inflammatory cytokine that might be involved in the pathogenesis of MS. Furthermore, IFN-β can modulate IL-33 production in RRMS patients and could be a new promising target for therapeutic strategies.

Highlights

– IL-33 is an important cytokine playing a critical role in autoimmune diseases, especially MS.

– Our assessment revealed a significant increase in IL-33 plasma levels of MS patients.
– There was a reduction in IL-33 levels in IFN-β-treated patients compared with untreated patients.

Conflict of interest statement: The authors declare no conflicts of interest.

References

1. Noseworthy JH, Lucchinetti C, Rodriguez M, Weinshenker BG. Multiple sclerosis. N Engl J Med 2000; 343: 938–52.
2. Kurtzke JF, Page WF, Murphy FM, Norman JE, Jr. Epidemiology of multiple sclerosis in US veterans. 4. Age at onset. Neuroepidemiology 1992; 11: 226–35.
3. Orton SM, Herrera BM, Yee IM, Valdar W, Ramagopalan SV, Sadovnick AD, Ebers GC, Canadian Collaborative Study Group. Sex ratio of multiple sclerosis in Canada: a longitudinal study. Lancet Neurol 2006; 5: 932–6.
4. Ramagopalan SV, Yee IM, Dyment DA, Orton SM, Marrie RA, Sadovnick AD, Ebers GC, For the Canadian Collaborative Study Group. Parent-of-origin effect in multiple sclerosis: observations from interracial matings. Neurology 2009; 73: 602–5.
5. Etemadifar M, Abtahi SH, Minagar A, Akbari M, Masaeli A, Tabrizi N. Late-onset multiple sclerosis in Isfahan, Iran. Arch Iran Med 2012; 15: 596–8.
6. Lassmann H. Acute disseminated encephalomyelitis and multiple sclerosis. Brain 2010; 133(Pt 2): 317–9.
7. McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY, Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. Ann Neurology 2001; 50: 121–7.
8. Frohman EM, Racke MK, Raine CS. Multiple sclerosis–the plaque and its pathogenesis. N Engl J Med 2006; 354: 942–55.
9. Lassmann H, Bruck W, Lucchinetti C. Heterogeneity of multiple sclerosis pathogenesis: implications for diagnosis and therapy. Trends Mol Med 2001; 7: 115–21.
10. Lucchinetti C, Bruck W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47: 707–17.
11. Wekerle H. Immune pathogenesis of multiple sclerosis. Neurol Sci 2005; 26(Suppl 1): S1–2.
12. Kornek B, Lassmann H. Neuropathology of multiple sclerosis-new concepts. Brain Res Bull 2003; 61: 321–6.
13. Vorob'eva AA, Ivanova MV, Fominykh VV, Zakharova MN, Zigangirova NA, Guliaeva NV. [Biomarkers in multiple sclerosis (a review and experimental data)]. Zhurnal nevrologii i psikhiatrii imeni SS Korsakova/Ministerstvo zdravookhraneniia i meditsinskoi promyshlennosti Rossiiskoi Federatsii, Vserossiiskoe obshchestvo nevrologov [i] Vserossiiskoe obshchestvo psikhiat 2013; 113(10 Pt 2): 23–31.
14. Katsavos S, Anagnostouli M. Biomarkers in multiple sclerosis: an up-to-date overview. Mult Scler Int 2013; 2013: 340508.
15. Fernandez O, Martin R, Rovira A, Llufriu S, Vidal-Jordana A, Fernandez-Sanchez VE, Alvarez-Cermeno JC, Izquierdo G, Arroyo-Gonzalez R, Rodriguez-Antiguedad A, Casanova-Estruch B, Montalban X. Biomarkers in multiple sclerosis: an update for 2014. Rev Neurol 2014; 58: 553–70.
16. Fernandez O, Arroyo-Gonzalez R, Rodriguez-Antiguedad A, Garcia-Merino JA, Comabella M, Villar LM, Izquierdo G, Tintoré M, Oreja-Guevara C, Álvarez-Cermeño JC, Meca-Lallana JE, Prieto JM, Ramió-Torrentà L, Martínez-Yélamos S, Montalban X. [Biomarkers in multiple sclerosis]. Rev Neurol 2013; 56: 375–90.
17. Pei C, Barbour M, Fairlie-Clarke KJ, Allan D, Mu R, Jiang HR. Emerging role of interleukin-33 in autoimmune diseases. Immunology 2014; 141: 9–17.
18. Kurowska-Stolarska M, Hueber A, Stolarski B, McInnes IB. Interleukin-33: a novel mediator with a role in distinct disease pathologies. J Intern Med 2011; 269: 29–35.
19. Liew FY, Pitman NI, McInnes IB. Disease-associated functions of IL-33: the new kid in the IL-1 family. Nat Rev Immunol 2010; 10: 103–10.
20. Theoharides TC, Zhang B, Kempuraj D, Tagen M, Vasiadi M, Angelidou A, Alysandratos KD, Kalogeromitros D, Asadi S, Stavrianeas N, Peterson E, Leeman S, Conti P. IL-33 augments substance P-induced VEGF secretion from human mast cells and is increased in psoriatic skin. Proc Natl Acad Sci USA 2010; 107: 4448–53.
21. Funakoshi-Tago M, Tago K, Hayakawa M, Tominaga S, Ohshio T, Sonoda Y, Kasahara T. TRAF6 is a critical signal transducer in IL-33 signaling pathway. Cell Signal 2008; 20: 1679–86.
22. Funakoshi-Tago M, Tago K, Sato Y, Tominaga S, Kasahara T. JAK2 is an important signal transducer in IL-33-induced NF-kappaB activation. Cell Signal 2011; 23: 363–70.
23. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. Nat Rev Drug Discov 2008; 7: 827–40.
24. Aoki S, Hayakawa M, Ozaki H, Takezako N, Obata H, Ibaraki N, Tsuru T, Tominaga S, Yanagisawa K. ST2 gene expression is proliferation-dependent and its ligand, IL-33, induces inflammatory reaction in endothelial cells. Mol Cell Biochem 2010; 335: 75–81.
25. Espinassous Q, Garcia-de-Paco E, Garcia-Verdugo I, Synguelakis M, von Aulock S, Sallenave JM, McKenzie AN, Kanellopoulos J. IL-33 enhances lipopolysaccharide-induced inflammatory cytokine production from mouse macrophages by regulating lipopolysaccharide receptor complex. J Immunol 2009; 183: 1446–55.
26. Guo L, Wei G, Zhu J, Liao W, Leonard WJ, Zhao K, Paul W. IL-1 family members and STAT activators induce cytokine production by Th2, Th17, and Th1 cells. Proc Natl Acad Sci USA 2009; 106: 13463–8.
27. Schmitz J, Owyang A, Oldham E, Song Y, Murphy E, McClanahan TK, Zurawski G, Moshrefi M, Qin J, Li X, Gorman DM, Bazan JF, Kastelein RA. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. Immunity 2005; 23: 479–90.
28. Turnquist HR, Thomson AW. IL-33 broadens its repertoire to affect DC. Eur J Immunol 2009; 39: 3292–5.
29. Etemadifar M, Abtahi SH. Multiple sclerosis in Isfahan, Iran: past, present and future. Int J Prev Med 2012; 3: 301–2.
30. Etemadifar M, Abtahi SH, Akbari M, Murray RT, Ramagopalan SV, Fereidan-Esfahani M. Multiple sclerosis in Isfahan, Iran: an update. Mult Scler 2014; 20: 1145–7.

31. Etemadifar M, Maghzi AH. Sharp increase in the incidence and prevalence of multiple sclerosis in Isfahan, Iran. Multiple Sclerosis 2011; 17: 1022–7.

32. Etemadifar M, Sajjadi S, Nasr Z, Firoozeei TS, Abtahi SH, Akbari M, Fereidan-Esfahani M. Epidemiology of multiple sclerosis in Iran: a systematic review. Eur Neurol 2013; 70: 356–63.

33. Etemadifar M, Izadi S, Nikseresht A, Sharifian M, Sahraian MA, Nasr Z. Estimated prevalence and incidence of multiple sclerosis in iran. Eur Neurol 2014; 72: 370–4.

34. Shajarian M, Alsahebfosoul F, Etemadifar M, Sedaghat N, Shahbazi M, Firouzabadi FP, Dezashibi HM. IL-23 plasma level measurement in relapsing remitting multiple sclerosis (RRMS) patients compared to healthy subjects. Immunol Invest 2015; 44: 36–44.

35. Naderi S, Hejazi Z, Shajarian M, Alsahebfosoul F, Etemadifar M, Sedaghat N. IL-27 plasma level in relapsing remitting multiple sclerosis subjects: the double-faced cytokine. J Immunoassay Immunochem 2016; 37: 659–70.

36. Eggert M, Goertsches R, Seeck U, Dilk S, Neeck G, Zettl UK. Changes in the activation level of NF-κB in lymphocytes of MS patients during glucocorticoid pulse therapy. J Neurol Sci 2008; 264: 145–50.

37. Gobin SJ, Montagne L, Van Zutphen M, Van Der Valk P, Van Den Elsen PJ, De Groot CJ. Upregulation of transcription factors controlling MHC expression in multiple sclerosis lesions. Glia 2001; 36: 68–77.

38. Feng X, Petraglia AL, Chen M, Byskosh PV, Boos MD, Reder AT. Low expression of interferon-stimulated genes in active multiple sclerosis is linked to subnormal phosphorylation of STAT1. J Neuroimmunol 2002; 129: 205–15.

39. Frisullo G, Angelucci F, Caggiula M, Nociti V, Iorio R, Patanella AK, Sancricca C, Mirabella M, Tonali PA, Batocchi AP. pSTAT1, pSTAT3, and T-bet expression in peripheral blood mononuclear cells from relapsing-remitting multiple sclerosis patients correlates with disease activity. J Neurosci Res 2006; 84: 1027–36.

40. Christophi GP, Hudson CA, Gruber RC, Christophi CP, Mihai C, Mejico LJ, Jubelt B, Massa PT. SHP-1 deficiency and increased inflammatory gene expression in PBMCs of multiple sclerosis patients. Lab Invest 2008; 88: 243–55.

41. Zeis T, Graumann U, Reynolds R, Schaeren-Wiemers N. Normal-appearing white matter in multiple sclerosis is in a subtle balance between inflammation and neuroprotection. Brain 2008; 131(Pt 1): 288–303.

42. Rodriguez M. Effectors of demyelination and remyelination in the CNS: implications for multiple sclerosis. Brain Pathol 2007; 17: 219–29.

43. Scarisbrick IA, Blaber SI, Lucchinetti CF, Genain CP, Blaber M, Rodriguez M. Activity of a newly identified serine protease in CNS demyelination. Brain 2002; 125(Pt 6): 1283–96.

44. Scarisbrick IA, Linbo R, Vandell AG, Keegan M, Blaber SI, Blaber M, Sneve D, Lucchinetti CF, Rodriguez M, Diamandis EP. Kallikreins are associated with secondary progressive multiple sclerosis and promote neurodegeneration. Biol Chem 2008; 389: 739–45.

45. Nile CJ, Barksby E, Jitprasertwong P, Preshaw PM, Taylor JJ. Expression and regulation of interleukin-33 in human monocytes. Immunology 2010; 130: 172–80.

46. Zhang L, Lu R, Zhao G, Pflugfelder SC, Li DQ. TLR-mediated induction of pro-allergic cytokine IL-33 in ocular mucosal epithelium. Int J Biochem Cell Biol 2011; 43: 1383–91.

47. Amor S, Puentes F, Baker D, Van Der Valk P. Inflammation in neurodegenerative diseases. Immunology 2010; 129: 154–69.

48. Lassmann H, Bruck W, Lucchinetti CF. The immunopathology of multiple sclerosis: an overview. Brain Pathol 2007; 17: 210–8.

49. Smith DE. The biological paths of IL-1 family members IL-18 and IL-33. J Leukocyte Biol 2011; 89: 383–92.

50. Miller AM. Role of IL-33 in inflammation and disease. J Inflamm (Lond) 2011; 8: 22.

51. Ali S, Mohs A, Thomas M, Klare J, Ross R, Schmitz ML, Martin MU. The dual function cytokine IL-33 interacts with the transcription factor NF-kappaB to dampen NF-κB-stimulated gene transcription. J Immunol 2011; 187: 1609–16.

52. Milovanovic M, Volarevic V, Ljujic B, Radosavljevic G, Jovanovic I, Arsenijevic N, Lukic ML. Deletion of IL-33R (ST2) abrogates resistance to EAE in BALB/C mice by enhancing polarization of APC to inflammatory phenotype. PLoS One 2012; 7: e45225.

53. Le H, Kim W, Kim J, Cho HR, Kwon B. Interleukin-33: a mediator of inflammation targeting hematopoietic stem and progenitor cells and their progenies. Front Immunol 2013; 4: 104.

54. Jiang HR, Milovanovic M, Allan D, Niedbala W, Besnard AG, Fukada SY, Alves-Filho JC, Togbe D, Goodyear CS, Linington C, Xu D, Lukic ML, Liew FY. IL-33 attenuates EAE by suppressing IL-17 and IFN-gamma production and inducing alternatively activated macrophages. Euro J Immunol 2012; 42: 1804–14.

55. Oboki K, Ohno T, Kajiwara N, Arae K, Morita H, Ishii A, Nambu A, Abe T, Kiyonari H, Matsumoto K, Sudo K, Okumura K, Saito H, Nakae S. IL-33 is a crucial amplifier of innate rather than acquired immunity. Proc Nat Acad Sci USA 2010; 107: 18581–6.

56. Christophi GP, Gruber RC, Panos M, Christophi RL, Jubelt B, Massa PT. Interleukin-33 upregulation in peripheral leukocytes and CNS of multiple sclerosis patients. Clin Immunol 2012; 142: 308–19.

57. Kanda T. Interleukin-33/suppression of tumorigenicity 2 system: can it be a future therapeutic target for neuroimmunological disorders? Clin Exp Neuroimmunol 2013; 4: 255–6.

58. Wang S, Ding L, Liu S-S, Wang C, Leng R-X, Chen G-M, Fan YG, Pan HF, Ye DQ. IL-33: a potential therapeutic target in autoimmune diseases. J Investig Med 2012; 60: 1151–6.

59. Georgiou AM. Therapeutic strategies for multiple sclerosis: current data. Int J Health Allied Sci 2015; 4: 3.

60. Syrmos C, Orologas A. Efficacy of interferon in multiple sclerosis. PJNS 2013; 8: 15–8.

61. Yasuoka S, Kawanokuchi J, Parajuli B, Jin S, Doi Y, Noda M, Sonobe Y, Takeuchi H, Mizuno T, Suzumura A. Production and functions of IL-33 in the central nervous system. Brain Res 2011; 1385: 8–17.

62. Hudson CA, Christophi GP, Gruber RC, Wilmore JR, Lawrence DA, Massa PT. Induction of IL-33 expression and activity in central nervous system glia. J Leukocyte Biol 2008; 84: 631–43.

63. Theoharides TC, Petra AI, Taracanova A, Panagiotidou S, Conti P. Targeting IL-33 in autoimmunity and inflammation. J Pharmacol Experim Therap 2015; 354: 24–31.

64. Zhang F, Tossberg JT, Spurlock CF, Yao SY, Aune TM, Sriram S. Expression of IL-33 and its epigenetic regulation in multiple sclerosis. Ann Clin Transl Neurol 2014; 1: 307–18.

65. Hardman C, Ogg G. Interleukin-33, friend and foe in type-2 immune responses. Curr Opin Immunol 2016; 42: 16–24.

66. Zhao Q, Chen G. Role of IL-33 and its receptor in T cell-mediated autoimmune diseases. Biomed Res Int 2014; 2014: 1–10.

67. Arshad MI, Khan HA, Noel G, Piquet-Pellorce C, Samson M. Potential therapeutic aspects of alarmin cytokine interleukin 33 or its inhibitors in various diseases. Clin Therap. 2016; 38: 1000–16. e1.