The Possible Role of Interleukin-6 as a Regulator of Insulin Sensitivity in Patients With Neuromyelitis Optica Spectrum Disorder

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Abstract

Background: The aquaporin 4- Immunoglobulin G (AQP4-IgG) is the disease-specific autoantibody that has a significant role in the pathogenesis of Neuromyelitis optica spectrum disorder (NMOSD). Circulating AQP4-IgG induces pro-inflammatory cytokines and may also trigger downstream signaling pathways leading to metabolic dysregulation.

Methods: We aimed to determine the risk association of hyperinsulinemia in NMOSD patients with seropositive AQP4-IgG and the serum levels of interleukin (IL)-6 and IL-17 compared with the control group.

Serum levels of metabolic (Insulin, Fasting Blood Sugar (FBS), lipid profile) and inflammatory (IL-6 and IL-17) markers were assessed in 56 NMOSD patients and 100 controls.

Results: Hyperinsulinemia was more prevalent in NMOSD patients independent of age, gender and body mass index (BMI) (48.2% vs. 26%, $p=0.005$). After adjusting age, sex and BMI, there was significant association between lower insulin sensitivity (IS) and NMOSD risk (95% CI: Beta=0.73, 0.62 to 0.86, $p=0.0001$).

The correlation between the duration of disease and circulating levels of insulin and FBS in NMOSD patients was not significant ($P>0.05$). Circulating levels of IL-6 and IL-17 were higher in NMOSD patients, and only IL-6 had an effect modifier for the association between lower insulin sensitivity and NMOSD risk.

Conclusions: Our data suggests that inflammatory pathogenesis of NMOSD leads to hyperinsulinemia and increases the risk of insulin resistance.

Background

Neuromyelitis optica spectrum disorder (NMOSD) is an astrocytopathy disease of the central nervous system (CNS) considered as a rare autoimmune disorder [1]. The prevalence of NMOSD is approximately 1–10 per 100,000 population. Through clinical, immunologic and magnetic resonance imaging (MRI) features, it can be distinguished from classic multiple sclerosis (MS) [2, 3]. The disease is characterized by “demyelination of optic nerve and/or transverse myelitis which is the result of inflammation in optic nerve and the spinal cord, respectively, leading to blindness and/or paralysis”[4].

The NMO-IgG, against aquaporin-4, is the disease-specific autoantibody that has a significant role in the pathogenesis of NMOSD as distinct from MS [5]. It specifically interacts with aquaporin-4 (AQP4) found all over the brain particularly spinal cord and optic nerves as sites of its accumulation [6]. AQP4 plays a critical role in water balance of the CNS. AQP4- IgG is produced by peripheral plasmablasts/ plasma cells and circulates in blood, crosses at the bridge of the blood brain barrier (BBB), and enters the central nervous system. In CNS, AQP4-IgG binds to AQP4 on astrocyte feet-ends, and then activates complement-

mediated astrocyte damage, and finally leads to BBB disruption and astrocyte loss with demyelination [7]. It has been suggested that the primary breakdown of the BBB due to the presence of AQP4-IgG and loss of AQP-4 in astrocyte promotes the secondary influx of plasma rich in AQP4-IgG, humoral or cellular immune components [7]. Also, sustained inflammatory cascades could raise the possibility of comorbidity of other autoimmune or inflammatory disorders [8]. Clinically, examining the pathogenesis of comorbid disorders is critical to treatment strategies for NMOSD patients.

Increasing evidence explains that circulating AQP4-IgG induces pro-inflammatory cytokines like interleukin (IL)-6, -17 and -2, tumor necrosis factor- α (TNF- α), interferon- γ (INF- γ), T helper (Th)-17, and Th2-related cytokines as described in the peripheral and CNS of NMOSD patients [9–11]. It may also trigger downstream signaling pathways leading to metabolic dysregulation such as insulin pathway [9–11].

Insulin is fundamental in glucose homeostasis, and its function depends on its secretion, the target tissue sensitivity, and its clearance that are affected by pro-inflammatory cytokines [12–14]. Most on humans have examined insulin sensitivity (IS) related to obesity and diabetes but some studies have implicated lower IS or higher insulin resistance (IR) concerning neurodegenerative and autoimmune disorders such as rheumatoid arthritis [15], systemic lupus erythematosus [16], Alzheimer's [17] and MS [18, 19]. These autoimmune disorders are linked to IR by impaired immune and inflammatory systems [20].

Based on the cytokine theory of IR [21], activation of the immune system induces cytokines, chemokines, and other inflammatory signals that lead to lower insulin sensitivity [14, 22].

In this study, we aimed to investigate the circulating insulin levels in NMOSD patients and possible effect modifier roles of two important humoral immunity factors in NMOSD pathogenesis, IL-6 and IL-17, on insulin sensitivity in NMOSD patients.

Materials And Methods

Study design and population

This is a case-control study designed by the Multiple Sclerosis (MS) Research Center of Tehran University of Medical Sciences. The participants of this study were NMOSD patients who referred to MS clinic of Sina hospital as a pioneer MS referral center in Tehran, Iran. All NMOSD patients with seropositive AQP4-IgG met Wingerchuck et al. [23] criteria for the diagnosis. Patients who use steroidal drugs (prednisolone, dexamethasone, and other corticosteroids) within the last 3 months were not recruited in the present study. Medical history, the age of diagnosis of NMOSD and the medications and comorbidities of each patient were checked by the patient's medical record, and were confirmed by neurological examination.

Participants of the healthy group were recruited by announcing in health house centers from Tehran Municipality. The control group was the healthy people who had no history of inflammatory, autoimmune,

and neurological disorders, and family history of MS or NMOSD. They were referred to the MS research center of Sina hospital.

The study was conducted in accordance with the Declaration of Helsinki and Ethical Committee of the National Institute for Medical Research Development (IR.NIMAD.REC.1398.159) of Iran. Written informed consent was obtained from each participant.

Biochemical Analysis

Blood samples were drawn from an antecubital vein after at least 10 hours of overnight fasting for all study participants. Serums fasting blood glucose (FBS), low-density lipoprotein (LDL), high-density lipoprotein (HDL), total triglyceride (TG), and total cholesterol (TC) were assessed using enzymatic colorimetric assay (Pars-Azmun kits, Iran) by an auto-analyzer (Hitachi 902, Japan) with intra-assay precision: 0.63%-1.23% and inter-assay precision of 1.09–1.8%.

Serum levels of IL-17 and 6 were determined by ELISA kits (CUSABIO) according to the manufacturer's instructions, with intra-assay precision: CV < 8%, and inter-assay precision: CV < 10%. Serum levels of insulin were determined by ELISA kit (Monobind, Netherland) according to the manufacturer's instructions, with intra-assay precision: CV < 6.6%, and inter-assay precision: CV < 6%.

Definition Of Metabolic Syndrome Components

We used the modified definition of the WHO criteria [24], consisting of hyperglycemia (fasting glucose ≥ 110 mg/dl), waist circumference ≥ 94 cm, dyslipidemia (triglycerides ≥ 150 mg/dl or HDL cholesterol < 40 mg/dl), or blood Pressure (BP) $\geq 140/90$ mmHg or taking BP medication. Also, hyperinsulinemia was defined based on the upper fourth quartile of circulating insulin in healthy group.

As an insulin sensitivity index, we used the QUICKIE equation. $IS_{QUICKIE}$ is derived from the product of the fasting plasma glucose (FPG) and the fasting plasma insulin (FPI). $IS_{QUICKIE} = 1 / ((\log(\text{Fasting Insulin(mU/L)}) + \log(\text{Fasting Glucose(mg/dl)})))$

Long format of the International Physical Activity Questionnaire (IPAQ) was used to assess the physical activity. Following IPAQ's guidelines, frequency and duration of physical activity were converted to Metabolic Equivalent of Tasks (MET).

Statistical analysis

Data analysis was performed using SPSS 20.0 (SPSS Inc., Chicago, IL). Categorical and continuous variables are expressed as number (%) and mean $\pm$ standard deviation, respectively. Normality of data was examined using the Shapiro–Wilk test. Comparisons between study groups were performed using

the Student's t-test for continuous variables and χ^2 test for categorical variables (control as a reference group). Demographics and clinical parameters were presented by descriptive statistics.

Pearson's correlation was applied to determine the correlation between circulating metabolic and inflammatory markers.

A back-ward logistic regression model was used to determine the independent association of insulin resistance with NMOSD. Two-tailed P values < 0.05 were considered significant.

Results

Baseline characteristics

In the present case-control study, 56 NMOSD patients with seropositive AQP4-IgG and 100 controls without family history of MS or NMOSD were involved. Participants were recruited between December 2019 and Feb 2020.

The baseline and clinical characteristics of study groups are summarized in Table 1. NMOSD patients did not use corticosteroid at least 3 months before sampling. Among NMOSD patients, 14.28% (n = 8) had at least a history of a chronic disorder; vitiligo (1 out of 56), SLE (1 out of 56), asthma (3 out of 56), type 1 diabetes (1 out of 56), arthritis (1 out of 56) and Crohn's disease (1 out of 56).

In our population study, there were no significant differences in age, gender, and body mass index (BMI) between the two groups ($P > 0.05$).

Serum levels of insulin were higher in NMOSD patients while serum levels of FBS were lower in NMOSD patients than the control group even after adjusting with age, sex and BMI ($p = 0.0001$, $p = 0.002$; respectively).

The data analysis showed no significant differences in lipid profile levels between the two groups ($p > 0.05$).

Table 1
Clinical and biochemical characteristics of the NMOSD and control groups under study

Baseline characteristics	NMOSD N = 56	Control N = 100	p-value
Age (years)	35.89 ± 9.39	37.40 ± 6.68	0.24
Sex (Female)	89.3% (50)	93.0% (93)	0.42
BMI (kg/m ²)	26.61 ± 5.15	26.82 ± 5.45	0.81
History of alcohol consumption (whisky and/or vodka)	3.57% (2)	1% (1)	0.26
History of smoking	5.35% (3)	6% (6)	0.86
Physical activity (Ln MET-min/week)	7.36 + 2.09	7.60 + 1.07	0.38
Duration of the disease (years)	4.16 ± 2.91	-	-
Age of onset (years)	32.28 ± 9.11	-	-
Medications	23.2% (13)	-	
Azathioprine	76.8% (43)		
Rituximab			
Comorbidity	14.28% (8)	-	
EDSS score*	3 (3.5)		
Biochemical and laboratory analysis			
FBS (mg/dL)	85.47 ± 6.93	90.42 ± 9.03	0.003
Ln.HDL (mg/dL)	3.89 ± 0.23	3.93 ± 0.20	0.29
LDL (mg/dL)	100.71 ± 71	105.97 ± 97	0.27
Ln.TG (mg/dL)	4.71 ± 0.46	4.57 ± 0.48	0.07
Chol (mg/dL)	171.75 ± 32.62	177.77 ± 34.67	0.29
Ln.Insulin (μU/L)	2.78 ± 0.88	2.12 ± 0.48	0.0001
Ln. SAT (U/L)	3.30 ± 0.28	3.24 ± 0.31	0.15
Ln.ALT (U/L)	2.94 ± 0.31	2.81 ± 0.45	0.038
Ln.IL-17 (pg/ml)	2.00 ± 1.18	1.11 ± 0.81	0.0001
Ln.IL-6 (pg/ml)	3.76 ± 0.74	3.34 ± 0.62	0.008

*median (IQR)

Numerical variables were expressed as the mean $\pm$ SD except for EDSS (median (IQR)). Categorical variables were presented as percentages. Values in bold indicate statistical significance ($P < 0.05$).

ALT, alanine aminotransferase; SAT, serum agglutination test, BMI, body mass index; EDSS, expanded disability status scale; FBS, fast blood sugar; Chol, total cholesterol; HDL, high-density lipoprotein cholesterol; IL-6, interleukine-6; IL-17, interleukine-17; LDL, low-density lipoprotein; Ln, natural log; MET, metabolic equivalent of task; TG, triglyceride.

Metabolic Syndrome Components:

The prevalence rates of metabolic syndrome components are presented in Table 2. Hyperinsulinemia was approximately 1.5 times higher in NMOSD patients than the control group (in women participants, 50% in NMOSD group and 26.9% in the healthy group).

Among other metabolic syndrome components, the data analysis showed no significant differences between the two groups.

In women participants, the prevalence rates of hyperglycemia, dyslipidemia, and hypertension were statistically similar to the control group ($p > 0.05$). There was no separate data analysis for the male subgroup because of its small size.

In the control group, the data analysis showed there was direct correlation between serum levels of insulin and FBS ($p = 0.02$, $r = 0.23$). However, in NMOSD group, there was not any significant correlation between serum levels of insulin and FBS ($p = 0.1$).

Table 2
The prevalence of metabolic syndrome components based on modified WHO criteria in NMOSD and control groups

Metabolic syndrome component	NMOSD N = 56	Control N = 100	p-value
Hypertension ($\geq 140/90$ mmHg)	5.4% (3)	2% (2/100)	0.35*
Dyslipidemia (triglycerides ≥ 150 mg/dl or HDL cholesterol < 40 mg/dl)	37.7% (21)	26.0% (26)	0.13
Hyperglycemia (Fasting glucose ≥ 110 mg/dl)	0.0% (0)	4%(4)	0.29*
Hyperinsulinemia (forth Quartile)	48.2% (27)	26.0% (26)	0.005
waist girth ≥ 94 cm	35.0% (20)	16.0% (16)	0.063
IS _{QUICKI}	0.32 $\pm$ 0.04	0.35 $\pm$ 0.02	0.0001

Insulin Sensitivity In Nmosd Patients:

Insulin sensitivity (Quicki index) was calculated based on fasting serum levels of insulin and FBS. There was significant lower IS in patients with NMOSD compared with the control group (0.32 ± 0.04 vs. 0.35 ± 0.02 , $p = 0.0001$). In logistic regression model, after adjusting for age, sex and BMI, there was significant association between lower IS and NMOSD risk (95% CI: Beta = 0.73, 0.62 to 0.86, $p = 0.0001$).

In NMOSD patients, there were not any significant correlation between IS and duration of disease ($p = 0.08$) and EDSS score ($p = 0.27$). Also, there was not any significant difference in serum levels of insulin or insulin sensitivity in NMOSD patients with different type of medication; rituximab and azathioprine ($p = 0.91$, $p = 0.40$; respectively).

Inflammatory Markers:

The data showed that serum levels of IL-17 were significantly higher in NMOSD patients than the control group (mean Ln-IL17 $\pm$ SD: 2.00 ± 1.18 pg/ml vs. 1.11 ± 0.81 pg/ml, $p = 0.0001$, respectively) even after adjusting age, sex and BMI (95% CI, beta: 2.35, 1.63 to 3.37, $p = 0.0001$) (Fig. 1a).

The serum levels of IL-6 was significantly higher in NMOSD patients (mean Ln-IL6 $\pm$ SD: 3.76 ± 0.74 pg/ml vs. 3.34 ± 0.62 pg/ml, $p = 0.008$, respectively) (Fig. 1b) even after adjusting with age, sex and BMI (95% CI, beta = 2.39, 1.23 to 4.67, $p = 0.01$).

In NMOSD group, there was only significant direct correlation between IL-6 and TG ($P = 0.025$; $r: 0.341$). In the control group, there was only significant correlation between IL-6 and IL-17 with TG ($P = 0.04$; $r: 0.322$, $P = 0.001$; $r: 0.338$, respectively).

There were not any correlations between IL-6 and IL-17 with liver enzymes in each group (Table 3).

There was not any significant correlation between inflammatory markers and duration of diseases in NMOSD patients ($P > 0.12$) and EDSS score ($p > 0.34$).

Regarding to different type of medications, rituximab and azathioprine, there was not any significant differences in serum levels of IL-6, IL-17 and insulin in NMOSD patients ($p = 0.81$, $p = 0.91$, $p = 0.44$; respectively).

Also, there were not any significant correlation between IL-6, IL-17 with disease statues (duration of disease and EDSS) ($p > 0.12$).

Table 3

Correlation between biochemical and inflammatory markers in NMOSD patients and control group

	NMOSD				control			
	Ln. IL-6 (pg/ml)		Ln.IL-17(pg/ml)		Ln. IL-6 (pg/ml)		Ln.IL-17(pg/ml)	
	r	P-value	R	P-value	r	P-value	r	P-value
Ln.insulin (μ U/L)	0.32	0.03*	0.19	0.15	-0.05	0.75	-0.02	0.81
FBS (mg/dL)	0.11	0.54	0.003	0.98	0.07	0.66	0.16	0.10
Ln.TG (mg/dL)	0.34	0.02*	0.16	0.23	0.32	0.04*	0.34	0.001*
Ln.HDL (mg/dL)	-0.27	0.08	-0.02	0.88	-0.03	0.83	-0.06	0.56
LDL (mg/dL)	0.05	0.74	0.02	0.86	0.11	0.51	-0.008	0.93
Chol. (mg/dL)	0.003	0.98	0.03	0.84	0.16	0.34	0.10	0.32
Ln.AST (U/L)	0.12	0.44	0.19	0.18	-0.02	0.89	0.11	0.26
Ln.ALT (U/L)	-0.08	0.62	-0.03	0.81	0.06	0.73	-0.11	0.28

* After adjusting with BMI, age and sex, there was constant significant correlation.

ALT, alanine aminotransferase; SAT, serum agglutination test, Chol, total cholesterol; HDL, high-density lipoprotein cholesterol; IL-6, interleukine-6; IL-17, interleukine-17; LDL, low-density lipoprotein; Ln, natural log; TG, triglyceride.

Correlation between circulating levels of inflammatory markers and insulin sensitivity

In unadjusted data analysis, there were significant correlations between insulin levels and IL-6 ($p = 0.037$, $r = 0.31$) but not with IL17 ($p = 0.15$) in NMOSD patients.

In the control group, there was not any significant correlation between insulin levels and inflammatory markers, IL-6 ($p = 0.75$) and IL17 ($p = 0.81$).

In logistic regression model, after adjusting with age, sex, BMI, taking medicines and IL-6, there was only an independent direct association between IL-6 and NMOSD risk (95% CI: beta = 2.29, 1.06 to 4.96, $p = 0.035$). There was not any constant association between IS and NMOSD risk ($p = 0.08$).

To examine the effect modifier role of IL-17, logistic regression model was used. After adjusting with age, sex, BMI, taking medicines and IL-7, there was independent direct association between IL-17 (95% CI: Beta = 2.15, 1.42–3.26, $p = 0.0001$) and lower IS ($p = 95\%$ CI: beta = 0.8, 0.68 to 0.93, $p = 0.004$) with NMOSD risk.

Discussion

To consider the association between insulin resistance and NMOSD, all patients were seropositive AQP4-IgG. In our study, 48.2% of NMOSD patients were at risk of hyperinsulinemia compared with 26% in the control group with OR = 2.65. In line with our findings, a few studies have assessed insulin sensitivity or resistance in MS patients but not in the patients with NMOSD. Oliveira et al. revealed 40% prevalence of IR in MS patients compared with 21.1% in the control group with OR = 2.48[18]. In another study, Ruiz-Arguelles et al. reported that insulin resistance was more prevalent in patients with MS, especially in patients with the secondary progressive type of MS [19], which had direct association with the patients' disability levels. In newly diagnosed patients with MS, Penesova et al. observed lower insulin sensitivity in MS patients in comparison with controls [25]. They also considered other metabolic syndrome components. They found that MS patients had higher fasting and post-load glucose concentrations than the control group. However, they did not find any differences in plasma levels of lipid profile. In another study on MS patients, Soliman et al. reported higher prevalence of insulin resistance and a three-fold prevalence of metabolic syndrome in MS patients [26]. The authors mentioned that all components of metabolic syndrome were more prevalent in women with MS.

Of note, in our study population, only hyperinsulinemia was more prevalent in NMOSD patients and there were not any significant differences in other metabolic syndrome components between NMOSD patients and healthy people. As expected, hyperinsulinemia is primarily associated with impaired glucose homeostasis, but our data did not show any significant correlation between insulin levels and FBS in NMOSD patients. unlike the control group. It is likely that hyperinsulinemia is associated with impaired glucose tolerance in NMOSD patients, not with fasting blood sugar, that will be examined by oral glucose tolerance test. Nevertheless, more probably it is associated with inflammatory factors identified as pathogenesis of NMOSD.

Interlukine-6 is an interesting cytokine with several functions in the immune system and metabolic regulation of immune responses [27]. It has impairing effects on the insulin signaling which could result in adverse effects on glucose homeostasis [27, 28] via two main pathways: the janus kinase/signal transducer and activator of transcription (Jak/STAT) and the mitogen-activated protein kinase (MAPK) [28].

In the course of NMOSD, IL-6 as a humoral immune system factor plays an essential role in NMOSD pathogenesis [29–31]. Interleukin-6 supports plasma cell differentiation and survival and has a potential role in the induction of plasmablasts and/or plasma cells that produce autoantibodies against AQP4 and other relevant antigens [32, 33]. The elevated levels of IL-6 in serum or CSF of NMOSD patients is likely to facilitate survival of AQP4-specific antibody secreting cell (ASC) in the CNS of NMOSD patients [34, 35]. Activated IL-6 signaling may have direct effect on cell pathways like insulin in NMOSD patients. Direct targeting of IL-6 signaling may have a direct effect on plasma cell survival, autoantibody production and NMOSD pathology.

Plasmablasts/ plasma cells have additional proinflammatory functions and may secrete factors such as IL-17[36, 37]. Thus, in the context of NMOSD, elevation of IL-17 levels may lead to enhanced recruitment of granulocyte to the CNS, and developing disease relapse. More investigations are needed to directly examine the phenotype, quantity, and activity of proinflammatory B cells and ASCs in NMOSD. In the context of metabolic regulation, IL-17 plays several roles in adipocyte differentiation, and insulin and glucose homeostasis [38]. In vivo studies propose IL-17 significant contribution in the systemic homeostasis of glucose as well. It is important to underline that lower IL-17 was related to a reduction in serum insulin. Reduced basal levels of insulin often represent improvement in insulin sensitivity, which may contribute to the more efficient glucose metabolism observed. Our data show that higher IL-6 and IL-17 in NMOSD patients with seropositive AQP4 while only IL-6 had a modulatory role in the course of lower insulin sensitivity. However, the effect modifier role of IL-6 does not imply a causality role for IL-6 in insulin resistance in NMOSD patients. It is possible that IL-6 in combination with other inflammatory markers links insulin resistance to NMOSD risk.

As far as we know, the present study is a first study shows insulin resistance in NMOSD patients. However, some limitations of our study are worth noting. Firstly, our patients have used corticosteroids intermittently during the course of the disease, which might have affected insulin secretion and sensitivity. However, not all patients were on the corticosteroid as a part of treatment strategy except patients on the Rituximab who received 100 mg methylprednisolone every 6 months in combination with Rituximab. To control the effect of using the corticosteroid on insulin levels, we included patients who did not use corticosteroid 3–4 months prior to sampling.

Secondly, this was a case-control study and considered only the association between lower IS and NMOSD risk. However, based on evidence, it is likely that the pathogenesis of NMOSD might have caused higher insulin level and insulin resistance as a result.

Thirdly, 14% of our NMOSD patients had comorbidities other autoimmune disorders, and because of the smaller sample size, it was not adjusted in the data analysis. Nevertheless, the data analysis in patients without comorbidities showed the same result (non-included).

Lastly, we evaluated only two cytokines in associated with insulin resistance. In patients who develop autoimmune responses associated with insulin resistance, additional cytokines could be useful in the evaluation.

Conclusion

The present study revealed the independent association between lower insulin sensitivity and NMOSD risk. The association was modified by higher circulating levels of IL-6 in NMOSD patients. Our data showed no association between insulin resistance and severity and duration of the disease. As immunosuppressive therapy is the main treatment in NMO patients, it seems that the treatment does not affect insulin resistance which needs additional independent treatment. There is enough evidence

demonstrating the positive effect of the blockade of some cytokines like IL-6 in the improvement of insulin sensitivity in autoimmune disorders. This line of treatment can be helpful for NMOSD patients.

List Of Abbreviations

ASC, Antibody secreting cell

BBB, Blood brain barrier

CNS, Central nervous system

EDSS, Expanded disability status scale

TNF- α , Tumor necrosis factor- α

IL-6, Interleukin – 6

IL-17, Interleukin – 17

INF- γ , Interferon- γ

IS, Insulin sensitivity

IR, Insulin resistance

IPAQ, International Physical Activity Questionnaire

MS, Multiple Sclerosis

MET, Metabolic Equivalent of Tasks

NMOSD, Neuromyelitis optica spectrum disorder

AQP4-IgG, The aquaporin 4- Immunoglobulin G

Th-17, T helper – 17

Declarations

Ethics approval and consent to participate: The study was conducted in accordance with the Declaration of Helsinki and Ethical Committee of the National Institute for Medical Research Development (IR.NIMAD.REC.1398.159) of Iran. Written informed consent was obtained from each participant.

Consent for publication: Not applicable

Availability of data and materials: The data that support the findings of this study are available from Multiple Sclerosis research center of Tehran University of Medical Sciences but restrictions apply to the availability of these data, which were used under license for the current study, and so are not publicly available. Data are however available from the authors upon reasonable request and with permission of research deputy of Multiple Sclerosis research center of Tehran University of Medical Sciences.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: ZM analyzed and interpreted the biochemical data. ARN, and MAS analyzed and interpreted patients' data regarding the NMOSD. AO, NR, TV, and ZM performed laboratory tests and collecting clinical data. ZM wrote the draft of article. All authors read and approved the final manuscript.

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Figures

Figure 1

Serum levels of IL-6 and IL-17 in NMOSD patients and control group. The serum levels of IL-17 were significantly higher in NMOSD patients than the control group (mean Ln-IL17 ± SD: 2.00±1.18 pg/ml vs. 1.11±0.81 pg/ml, p=0.0001, respectively) The serum levels of IL-6was significantly higher in NMOSD patients (mean Ln-IL6 ± SD: 3.76±0.74 pg/ml vs. 3.34±0.62 pg/ml, p=0.008, respectively).