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Assessment of IL-17 in multiple sclerosis and its relationship with disease severity in Egypt

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Abstract

Central nervous system (CNS) demyelination and neurodegeneration are hallmarks of multiple sclerosis (MS). The pathophysiology of MS is related to the inflammatory cytokine interleukin-17 (IL-17), and there may be an association between IL-17 levels and disease severity. In order to find a non-invasive biomarker for disease progression, serum IL-17 levels in MS patients were measured in comparison to a matched control group. Additionally, the relationship between serum IL-17 levels and MS activity was examined. This case-control study included 31 MS patients who were diagnosed using the 2017 updated McDonald's criteria and a control group consisted of 20 apparently healthy individuals, matched for both age and sex. Serum samples were collected and analyzed for IL-17 concentrations using ELISA commercial kits. Clinical evaluations included demographic data, medical history, and an assessment of disease severity using the Expanded Disability Status Scale (EDSS). The study assessed serum levels of IL-17, and found significantly higher levels in MS patients (38.79± 37.36) in comparison to controls (1.47± 0.49). Levels of IL-17 were increased in secondary progressive MS patients than in relapsing-remitting MS patients, but did not reach statistical significance. No significant associations were identified between IL-17 levels and the duration of the MS disease or the frequency of relapses. In conclusion, the study pointed to increased IL-17 levels as a potential MS biomarker.

Keywords: MS, IL-17, Inflammation, demyelization, CNS

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Introduction

Multiple sclerosis (MS) immunopathogenesis is being under extensive studies, epidemiological data including twin and family approaches described an interaction between genes and environment.[1] MS presents with irregular episodes of disability and recovery, with a more progressive increase in neurological degeneration depending on the part of central nervous system (CNS) affected.[2]

The interleukin-17 (IL-17) inflammatory cytokine family comprises six members: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, with IL-17A being a key component, initially identified as cytotoxic T-lymphocyte-associated antigen 8 (CTLA-8). The protein was cloned following the discovery in 1993 of the gene encoding IL-17A, which was found to be an RNA transcript resembling a Herpesvirus Saimiri gene.[3] In 2005, two research teams identified a new subset of T helper 17 (Th17) CD4+ cells that produced IL-17A.[4] While it was initially believed that T helper CD4+ cells were the primary source of IL-17, subsequent research revealed that CD8+ cells are also capable of producing this cytokine. Additionally, IL-17 is synthesized by various innate immune cells referred to as "Type 17 cells," which include γδ T cells, natural killer T (NKT) cells, TCRβ+ natural Th17 cells, and Type 3 innate lymphoid cells (ILC3).[5]

Multiple genetic, epigenetic, and environmental variables interact to determine the complicated hereditary predisposition to MS.[6] Myelin antigen-specific auto-reactive CD4+ T cells are thought to be the cause of MS. An inflammatory response brought on by auto-reactive T lymphocytes causes demyelination and axonal degeneration.[7] Various immunopathological mechanisms contribute to the development of MS, which has a heterogeneous clinical course. Cytokines and other inflammatory mediators contribute to the pathophysiology of MS.[8]

One of the main contributors to autoimmune inflammatory illnesses, such as MS is thought to be Th17 cells.[9] Autopsy-collected MS plaques have been shown to express IL-17 transcripts.[10] Research has also shown that a specific single nucleotide polymorphism (SNP) in the IL-23R gene is linked to various human autoimmune disorders, suggesting that IL-23 signaling plays a vital role in the development of Th17 cells, which in turn promote the production of pro-inflammatory cytokines. Moreover, IL-17 was identified as the most prominently expressed gene in the CNS of patients with MS during autopsy examinations.[10,11] A study revealed that IL-17 is higher in MS patients' relapses and remissions than in healthy controls.[12] Th17 cells that produce interferon gamma (IFN-γ) infiltrate the blood-brain barrier and accumulate in the CNS during periods of disease activity in MS.[13] The genetic predisposition to MS is intricate and is influenced by the interaction of various genetic, epigenetic, and environmental elements, in addition to CD4+ cells. Understanding the role of IL-17 in MS helps to indicate the magnitude of immunopathogenic MS processes and help physicians to provide better care and disease management.

Subjects and Methods

This was a case-control study. MS patients were recruited from the Department of Neurology in Suez Canal University Hospital and from Al-Azhar University. This study included 31 MS patients diagnosed according to the 2017 revised McDonald's criteria[14] and a control group consisting of 20 normal individuals, who were recruited from the blood bank and coming for blood donation, matched for both age and sex. Controls were genetically unrelated friends or spouses of the patients who had no objective clinical signs of neurological disease, no diagnosis of MS, and no known case of MS in the family. They were normal donors coming to the blood bank in Suez Canal University hospital.

Patients' demographic information, medical history, EDSS score, and assessment of relapse symptoms were gathered by a structured interview questionnaire. Commercial enzyme linked immunoassay (ELISA) kits (AssayPro, USA), (code PHI33083,3211805111) that use an antibody specific for human IL-17 coated on micro plates were used to measure the serum level of MS-relevant IL-17, according to the

manufacturer's instructions. The color of the final product indicated the amount of IL-17. The color was measured at wavelength 450 nm using an ELISA reader (Statfax ELISA Reader, USA).

Results

Table 1 shows no statistical difference in age and sex between the MS group and control group (p>0.05).The clinical characteristics of the disease in the study group are presented in tables 2 and 4. Table 3 shows the details of each MS attack among the study group. Table 5 shows the comparison of serum level of human IL-17 between the MS group and control group. Table 6 and table 7 illustrate the relationship between serum levels of IL-17 and the clinical characteristics of MS within the study group.

Table 1. Comparison of demographic data between the two studied groups.

	Cases (n = 31)	Control (n = 20)	*p* value
Sex			
Female no (%)	24 (77.4%)	15 (75.0%)	χ^2, FE NS
Male no (%)	7 (22.6%)	5 (25.0%)	
Age			
Min. – Max.	17.0 – 48.0	17.0 – 40.0	
Mean ± SD.	28.65 ± 9.08	25.0 ± 5.46	t NS
Median (IQR)	27.0 (22.0 – 33.50)	24.50 (22.0 – 28.50)	

IQR: Inter quartile range SD: Standard deviation t: Student t-test. χ^2: Chi square test; FET (Fisher Exact test), p > 0.05 is not significant (NS).

Table 2. Descriptive analysis of clinical data in the 31 MS cases.

	Min. – Max.	Mean ± SD.	Median (IQR)
Age at onset	16.0 – 41.0	23.76 ± 6.63	21.0 (20.0 – 26.50)
Disease duration in years since 1st attack	0.0 – 20.0	4.82 ± 4.45	4.0 (2.0 – 6.0)
Disease duration since diagnosis	0.0 – 12.0	2.84 ± 3.44	2.0 (0.25 – 3.50)
Latency	0.0 – 10.0	1.98 ± 2.20	1.0 (0.75 – 3.0)
Number of relapses	1.0 – 5.0	2.52 ± 1.09	2.0 (2.0 – 3.0)

IQR: Inter quartile range SD: Standard deviation

Table 3. Distribution of the 31 MS cases according to details of each attack in cases group.

	1st	2nd	3rd	4th	5th
Details of each attack					
Optic Neuritis	16 (51.6%)	11 (40.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Motor	5 (16.1%)	2 (7.4%)	4 (33.3%)	1 (16.7%)	0 (0.0%)
Sensory	2 (6.5%)	7 (25.9%)	2 (16.7%)	4 (66.7%)	2 (100.0%)
Cerebellar	3 (9.7%)	5 (18.5%)	6 (50.0%)	1 (16.7%)	0 (0.0%)
Brain Stem	4 (12.9%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Sensory & Cerebellar	1 (3.2%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Cerebella & Brain Stem	0 (0.0%)	1 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 4. Distribution of the 31 studied cases according to different parameters.

Parameter	No. (%)
EDSS	
Min. – Max.	1.0 – 5.0
Mean ± SD.	2.50 ± 1.07
Median (IQR)	2.50 (1.75 – 3.0)
DMT History	
TTT naïve	14 (45.2%)
On DMT	17 (54.8%)
MS Phenotype	
RRMS	26 (83.9%)
SPMS	5 (16.1%)
T2 lesions	
Min. – Max.	3.0 – 20.0
Mean ± SD.	8.39 ± 4.27
Median (IQR)	7.0 (5.50 – 10.50)
Cortical/Juxta cortical	19 (61.3%)
Periventricular	30 (96.8%)
Infratentorial	21 (67.7%)
# of enhanced lesions	
0	28 (90.3%)
2	2 (6.5%)
3	1 (3.2%)
Cervical MRI	
0	16 (51.6%)
1	12 (38.7%)
2	3 (9.7%)

IQR: Inter quartile range SD: Standard deviation. EDSS; Extended disability scale score. DMT; Disease modifying therapy RRMS; Relapsing remitting MS, SPMS; Secondary progressive MS.

Table 5. Comparison of IL-17 between the two studied groups.

	Cases (n = 31)	Control (n = 20)	^{U}p value
IL-17 (ng/dl)			
Min. – Max.	10.40 – 150.0	0.70 – 2.20	
Mean ± SD.	38.79 ± 37.36	1.47 ± 0.49	<0.001*
Median (IQR)	26.0 (15.30 – 42.0)	1.45 (0.98 – 1.85)	

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test. *$p \leq 0.05$ is significant.

Table 6. Comparison of IL-17 between the relapsing remitting MS and secondary progressive MS.

	RRMS (n = 26)	SPMS (n = 5)	^{U}p value
IL-17 (ng/dl)			
Min. – Max.	10.40 – 135.0	16.0 – 150.0	
Mean ± SD.	35.94 ± 33.76	53.60 ± 54.91	NS
Median (IQR)	25.50(14.50 –40.0)	34.0 (24.0 – 44.0)	

IQR: Inter quartile range SD: Standard deviation U: Mann Whitney test. $p > 0.05$ is not significant (NS).

Table 7. Correlation between IL-17 (ng/dl) with different parameters in the 31 cases group.

	IL-17 (ng/dl)	
	r_s	*p* value
Duration since 1st attack	0.050	NS
Duration since diagnosis	0.256	NS
Number of relapses	0.048	NS

rs: Spearman coefficient. $p > 0.05$ is not significant (NS).

Discussion

Axonal degeneration and neuronal demyelination are hallmarks of MS, a chronic autoimmune-mediated illness of the CNS that can cause a range of clinical impairments, including motor, sensory, and cognitive symptoms. According to the widely accepted theory of MS etiology, lymphocytes entering the CNS trigger a persistent pathogenic immune response that causes demyelination and activates CNS-endogenous immune cells, ultimately resulting in damage to neurons and axons.[15]

T-helper 17 lymphocytes are one of the immune cells that has been shown to play an immunopathogenic role during MS. Tumor necrosis factor alpha (TNF-α) and other Th17 lymphocyte-related cytokines cause matrix metalloproteinases to be expressed, which is crucial for breaking down the blood-brain barrier and entering the CNS. Additionally, Th17 cells generate a lot of pro-inflammatory cytokines, primarily IL-17, which act on immunological, glial, and neuronal cells' unique receptor (IL-17R).[16]

IL-17 can enhance endothelial inflammation by prompting the endothelium to release pro-inflammatory mediators, including IL-1, IL-6, TNFα, granulocyte-macrophage colony-stimulating factor (GM-CSF), monocyte chemoattractant protein-1 (MCP-1), granulocyte colony-stimulating factor (G-CSF), various chemokines, and macrophage inflammatory protein-2 (MIP-2). Furthermore, IL-17 significantly promotes the aggregation of neutrophils within inflamed tissue.[17] A substantial correlation between IL-17 and the early stages of MS disease has been proposed based on IL-17 features.[18] Here, we assessed the serum concentration of IL-17, its potential role in the pathogenesis of MS and its relation to MS activity and severity in order to help identify a noninvasive potential marker of on-going disease progression.

The study included two groups; a case group consisted of 31 MS patients (77.4% females and 22.6% males) with mean age of 28.65 ± 9.08 years and another control group of 20 normal subjects (75 % females and 25 % males) with mean age of 25.0 ± 5.46 years. There was no statistically significant difference in age and sex observed between the groups (p >0.05).

Our findings were nearly similar to those conducted by Ashtari, et al., 2019, in Iran who found that, among the 70 MS studied patients, 81.4 % were females and the mean age was 30.20 ± 1.42 years.[18] Also, Ghaffari, et al 2017, demonstrated that the mean age for MS patients was 35.70 ± 7.90 years and most of the studied MS patients were females (78.5%).[17] Furthermore, Slavov in Bulgaria, 2023, found that the majority of the MS patients evaluated were female (71.7%) and that their mean age was 37±1.83 years.[19] These findings revealed that MS is more common in females compared to men. Several factors contribute to this difference, with hormonal, genetic, and environmental influences playing significant roles.[18]

Regarding MS patients, our study revealed that the mean age of disease onset was 23.76 ± 6.63 years, the mean disease duration since the first attack with MS and since its diagnosis were 4.82 ± 4.45 years and 2.84 ± 3.44 years, respectively. Patients with MS in our study had average number of relapses of two times with average latency of one year (0.75 – 3 years).

A study conducted by Kostic, et al, 2014, demonstrated that both the average duration of the disease and annualized relapse rate was one year.[20] Also, Slavov, 2023 in Bulgaria found that

the mean age at first manifestations was 30±1.29 years. The majority of patients had been diagnosed with MS for duration of up to five years, accounting for 57% of the cohort. By the conclusion of the first month, all patients experienced an additional relapse, with the highest percentage occurring by the end of the third week, which was 76.08%.[19] Khaibullin et al., 2017, in Russia found that the average duration of the MS disease was 48.4 months (2.5–185.6 months).[21]

Our study demonstrated that the Expanded Disability Status Scale (EDSS) score among MS patients was 2.5 (1.75 – 3.0). Regarding MS phenotypes, most of the patients (83.9%) had RRMS and only 16.1% had SPMS. The majority of MS lesions (96.8%) were periventricular, 67.7% of the lesions were infratentorial and 61.3 % were cortical/Juxta cortical.

Our results coincide with those reported by Perrone, et al., 2022, in Italy who revealed that the majority of MS patients (88 %) were RRMS while only 12 % were identified as SPMS.[22] Similarly, Mina et al., 2021 in USA found that 58 %, 19 % and 23 % of MS patients were identified as RRMS, SPMS and primary progressive multiple sclerosis (PPMS), respectively. The EDSS score was 1.5, 6.5 and 6, respectively among the three phenotypes.[23] Also, Bose, et al., 2023, stratified the MS patients in their study into RRMS (72.8%); PPMS (5.1%) and SPMS (22.1%) and found that the EDSS scores were higher for SPMS (5.9±1.8) and PPMS (5.9±1.8) than for RRMS (1.9±1.5; p<0.001).[24] In addition, Khaibullin, et al., 2017, revealed that 80 % of MS patients were identified as RRMS, 15 % as SPMM and only 5 % as PPMS and the EDSS score was 3.2 (1.5–7.5).[21] In Germany, a study conducted by Willing, et al., 2018 found that the average disease duration in RRMS patients was 56 months (2–244) months and the EDSS score was 1.4.[25]

In our study, it was found that the mean serum level of IL-17 was significantly higher in MS patients (38.79 ± 37.36 ng/dl) compared to the control group (1.47 ± 0.49 ng/dl) (p < 0.001). However, the mean serum level of IL-17 was higher among SPMS patients (53.60 ± 54.91 ng/dl) than in RRMS patients (35.94 ± 33.76 ng/dl) with no statistically significant difference between two groups (p=0.305). There were no significant correlations between serum level of IL-17 and disease duration since first MS attack (rs=0.050, p=0.790), duration since MS diagnosis (rs=0.256, p=0.165) and number of relapses (rs=0.048, p=0.799) in all study subjects.

The study by Ghaffari et al., 2017, showed that MS patients had greater serum IL-17 concentrations than controls (p < 0.001), which is consistent with our study findings. Additionally, their research showed no appreciable variations in serum IL-17 levels across MS patients with various illness types.[17] Ashtari et al., 2019, found that the mean serum level of IL-17 in MS patients was substantially greater than in control subjects (p<0.001), and that age and serum level of IL-17 in MS patients were positively correlated (r=0.28, p=0.012).[18] Additionally, Kostic et al., 2014 observed that the CSF of MS patients had a substantially higher IL-17A level than that of the control group (p=0.003), whereas the duration of the MS disease was inversely correlated with the IL-17A level.[20]

Contrary to our results, the study by Slavov, 2023,[19] and Khaibullin et al., 2017[21] found that MS patients had greater mean serum levels of IL-17 than the control group, but the difference did not reach statistically significant differences (p >0.05). In summary, the current study's findings demonstrated that MS patients, particularly those with RRMS and SPMS patterns, had greater IL-17 concentrations. IL-17 showed potentials as a biomarker for detection of MS disease. Finding the levels of IL-17, CSF, diagnosing MS, and figuring out the molecular mechanisms underlying this cytokine could help to create targeted therapy plans for MS.

Author Contributions

All authors contributed with same effort in writing and reviewing the manuscript.

Declaration of Conflicting Interests

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Ethical approval

The Research Ethics Committee of the Faculty of Medicine, Suez Canal University reviewed and approved the protocol of the study (Research 5277#, approval dated May 2023).

Informed consent

Prior to being enrolled in the study, all study subjects gave written informed consent.

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