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RESEARCH ARTICLE

Expression Levels of Intracellular Pathway Factors of B Lymphocytes in Patients with Multiple Sclerosis with and without Optic Neuritis Onset

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Abstract

Objective: Multiple sclerosis (MS) is a chronic, immune-mediated disorder of the central nervous system with a heterogeneous clinical course. Patients presenting with a first episode of optic neuritis (ON) generally exhibit a more favorable prognosis. Although T lymphocytes have traditionally been regarded as the primary drivers of MS pathogenesis, increasing evidence highlights the importance of B lymphocytes and their intracellular signaling pathways. This study aimed to investigate whether differences exist in B-cell-related intracellular pathway gene expression between patients with MS with and without ON onset and to assess their potential pathogenic implications.

Materials and Methods: A total of 26 patients with MS were enrolled, including 10 with ON onset and 16 without ON at disease onset. Disability was evaluated using the Expanded Disability Status Scale (EDSS), and cognitive performance was assessed using standardized neuropsychological testing. Peripheral blood samples were analyzed for B-cell-related gene expression [*B-lymphoid tyrosine kinase (BLK), B-cell scaffold protein with ankyrin repeats 1 (BANK1), transforming growth factor beta (TGFB), and ATPase Na^+/K^+ transporting subunit beta 3* (*ATP1B3*)] using quantitative polymerase chain reaction, and immune cell subset ratios were evaluated using flow cytometry.

Results: Although patients with ON-onset MS experienced a higher number of ON attacks during disease course, they demonstrated EDSS scores comparable to those of patients without ON onset. No significant differences were observed in immune cell subset ratios or in BLK, BANK1, or TGFB expression levels. However, ATP1B3 expression was significantly reduced in patients with ON onset compared with those without ON onset (p=0.011).

Conclusion: Reduced expression of *ATP1B3*, a gene implicated in B lymphocyte proliferation, appears to be associated with ON onset and increased frequency of ON attacks. These findings suggest that *ATP1B3* may be a potential biomarker associated with ON occurrence in MS. This hypothesis requires validation in larger longitudinal cohorts.

Keywords: Multiple sclerosis, optic neuritis, B lymphocyte, *ATP1B3*

Introduction

Multiple sclerosis (MS) is a demyelinating autoimmune disease of the central nervous system (CNS) that predominantly affects young adults and progresses through episodes of inflammation and myelin damage. Approximately 20% of patients with MS experience their first attack as optic neuritis (ON). Moreover, nearly half of patients with MS experience recurrent episodes of ON within 15 years of the initial attack (1).

In addition to genetic predisposition, environmental factors and infections are also implicated in the etiology of MS, presumably through the modulation of immune functions (2-5). Naïve $CD4^+$ and $CD8^+$ T-cells are believed to play a key role in the development of MS. After entering the CNS, T-cells induce an

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inflammatory milieu that leads to oligodendrocyte apoptosis, demyelination, and eventually neuronal degeneration (6-11). Although MS has long been considered a T-cell-mediated disease, growing evidence suggests that B-cells also play an important role. Memory B-cells and plasma cells are responsible for the rapid and abundant production of antibodies in response to antigen exposure. Analysis of the cerebrospinal fluid (CSF) of patients with MS has shown that elevated B-cell counts are associated with more rapid disease progression (12). Additional evidence supporting the role of B-cells in MS pathogenesis includes intrathecal immunoglobulin production, the presence of oligoclonal bands (OCBs) in CSF, clinical improvement following treatment with monoclonal antibodies targeting B lymphocytes, and correlations between CSF plasmablast and immunoglobulin M levels with clinical progression and the number of contrast-enhancing lesions in MS (13,14).

Certain intracellular signaling pathways are preferentially involved in B-cell activation. The *B-cell scaffold protein with ankyrin repeats 1 (BANK1)* gene, located on chromosome 4, encodes a B lymphocyte-specific scaffold protein involved in B-cell receptor-mediated calcium mobilization within the intracellular space. B-lymphoid tyrosine kinase (BLK), a non-receptor tyrosine kinase belonging to the Src family of protooncogenes, participates in the regulation of cell proliferation and differentiation (15,16). The *BLK* gene has been implicated in the pathogenesis of autoimmune diseases, including rheumatoid arthritis and systemic lupus erythematosus (SLE) (17,18). Sodium, potassium-adenosine triphosphatase (Na^+/K^+-ATPase) is a major membrane protein involved in ion transport and provides the electrochemical gradient necessary for action potential generation in nerve and muscle cells. Among genes encoding membrane channel proteins, *ATPase Na^+/K^+ transporting subunit beta 3 (ATP1B3)* encodes the beta subunit of the Na^+/K^+-ATPase complex and is involved in lymphocyte activation (19). This gene contributes to Na^+/K^+-ATPase function, which increases intracellular sodium levels required for clonal expansion of T and B lymphocytes following antigen presentation (20-23). Reduced Na^+/K^+-ATPase activity has been suggested to trigger B-cell lymphoma-2 mediated apoptosis in cells. Thus, failure to suppress Na^+/K^+-ATPase activity may theoretically allow the persistence of autoreactive B-cells, thereby contributing to B-cell-mediated tissue damage (24). Transforming growth factor beta (TGFB) is expressed by regulatory B-cells, and selective inhibition of TGFB in B cells has been shown to increase the proportion of autoreactive B-cells (25,26). This cytokine has also been implicated in the development of gliosis, particularly in demyelinating plaques of the spinal cord (27).

Previous reports suggest that MS presenting with ON may involve heterogeneous disease mechanisms, which may influence long-term outcomes (28). Therefore, given the established importance of B cells in MS pathogenesis, we aimed to investigate whether patients with MS with and without ON onset exhibit differences in B-cell-mediated mechanisms by assessing peripheral blood B-cell subsets and measuring the expression levels of intracellular B lymphocyte pathway factors (*BANK1, BLK, ATP1B3,* and *TGFB*).

Materials and Methods

Participants and Neuropsychological Assessment

This study included 26 patients diagnosed with MS who were followed at the same MS outpatient clinic. The patients were divided into two groups: those with ON as the initial clinical manifestation of MS (n=10) and those without ON onset (n=16). An episode of ON was defined as painful vision loss or visual blurring lasting at least 24 hours, with no other identifiable cause. Demographic data, Expanded Disability Status Scale (EDSS) scores, number of ON relapses, type of first relapse (optic nerve or other region), and disease duration were recorded for all patients. None of the participants had coexisting systemic, neurological, autoimmune, or infectious disorders. No patients had experienced a relapse or received immunosuppressive treatment within 3 months prior to blood sample collection. In addition, none had received B-cell-depleting therapies before their current treatment. All patients were receiving immunomodulatory therapy, including interferon-β, fingolimod, dimethyl fumarate, or teriflunomide. To evaluate cognitive function, participants underwent standardized neuropsychological assessments in Turkish, including the Selective Reminding Test, 10/36 Spatial Recall Test, and Symbol Digit Modalities Test (SDMT), which assess verbal memory, visual memory, and sustained attention/information processing speed, respectively. Test selection and interpretation followed Turkish MS cognitive assessment literature, based on Brief Repeatable Battery of Neuropsychological Tests related norms and validated Turkish adaptation procedures (29). For the SDMT, Turkish validation studies support standardized administration in MS, including the oral version, with the number of correct responses recorded over 90 seconds (30). All neuropsychological assessments were performed by an evaluator blinded to clinical diagnosis and magnetic resonance imaging findings. Motor function was additionally assessed using the 9-Hole Peg Test and the timed 8-meter walk test. Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkiye, Haydarpasa Numune Education and Research Hospital, (decision no: HNEAH-KAEK2018/KK/31, date: 12.03.2018). Written informed consent was obtained from all participants.

Real-Time (RT)-Quantitative Polymerase Chain Reaction (qPCR)

Peripheral blood mononuclear cells (PBMCs) were isolated by Ficoll density gradient centrifugation, resuspended in freezing medium, and stored in liquid nitrogen (1×10^6 cells in fetal bovine

serum supplemented with 10% dimethyl sulfoxide). Total RNA was extracted from frozen PBMCs using the RNeasy Mini Plus Kit (Qiagen, Hilden, Germany) according to the manufacturer's instructions. RNA purity and concentration were assessed using a spectrophotometer. Samples with an optical density ratio at 260/280 nm between 1.9 and 2.1 were included in the analysis. Total RNA was reverse-transcribed into complementary DNA (cDNA) using the Transcriptor First Strand cDNA Synthesis Kit (Roche, Basel, Switzerland). RT-qPCR was performed using the Agilent Technologies Mx3005P qPCR system with SYBR Green Master Mix (LightCycler® 480 SYBR Green I Master, Roche, Basel, Switzerland) and gene-specific primers obtained from DNA Technology® (DN-10) (Table 1). Relative gene expression was calculated using the $2^{-\Delta\Delta CT}$ method, with glyceraldehyde 3-phosphate dehydrogenase (GAPDH) serving as the internal normalization control.

Flow Cytometry

To identify the proportions of major immune cell subsets in peripheral blood, frozen PBMCs were thawed and washed in complete medium (supplemented with 10% fetal calf serum, 1% minimum essential medium vitamins, 1% L-glutamine, 1% sodium pyruvate, 1% non-essential amino acids, and 1% penicillin-streptomycin). Cells were stained with fluorescently labeled monoclonal antibodies [anti-human CD3-FITC, CD16/CD56-PE, CD19-APC (Becton Dickinson (BD), Multitest™), CD27-FITC, CD24-PerCP, CD38-Alexa Fluor 700, IgD-APC/Cy7, and CD138-PE (BioLegend)]. Subsequently, six-color immunofluorescence analysis was performed using a BD FACSAria II flow cytometer (Becton Dickinson, Franklin Lakes, NJ, USA). Data were analyzed using CellQuest and FlowJo v7.6.5 software. The gating strategy for flow cytometry analysis is shown in Supplementary Figures 1 and 2.

Table 1. Primers used in real-time PCR studies

Gene	Primer sequence
BLK F	TAGATCACAGGGTCGGAAGG
BLK R	GGCAGCGGATCTTATAGTGC
TGFB F	GTACCTGAACCCGTGTTGCT
TGFB R	CAACTCCGGTGACATCAAAA
BANK1 F	GTTCAGACCCCGCACATATT
BANK1 R	CCTTCCCCTTCCATTTCATT
ATP1B3 F	AATCGCTACCAGGAACGCAA
ATP1B3 R	CGATCTCCACTCCTTCCAGC
GAPDH F	CCATCAATGACCCCTTCATT
GAPDH R	TTGACGGTGCCATGGAATTT

BLK: B-lymphoid tyrosine kinase, BANK1: B-cell scaffold protein with ankyrin repeats 1, TGFB: Transforming growth factor beta, ATP1B3: ATPase Na+/K+ transporting subunit beta 3, F: Forward, R: Reverse, PCR: Polymerase chain reaction

Statistical Analysis

Data distribution was assessed using the Kolmogorov-Smirnov test to evaluate normality. Because most variables were non-normally distributed, the Mann-Whitney U test was used for comparisons of continuous variables. Categorical variables were analyzed using the chi-square test. Spearman's rank correlation coefficient was used to assess associations between variables. The Bonferroni correction was applied for multiple comparisons. Statistical significance was set at $p<0.05$.

Results

Comparison of Clinical Features of the Study Groups

Patients were stratified into groups with and without ON at disease onset. No significant differences were observed between the two groups in age, sex, disease duration, treatment type, or EDSS scores. However, patients with ON onset had a significantly higher number of ON attacks during the disease course. Regarding cognitive and motor function tests, only SDMT scores differed significantly between groups (Table 2). After Bonferroni correction ($p<0.0062$), only the difference in the number of ON attacks remained statistically significant.

Flow Cytometry and PCR Results

In peripheral blood immunophenotyping of patients with MS, no clear association was observed between groups with and without ON onset in the proportions of T-cells, B-cells, NK-cells, regulatory B-cells (Bregs), plasmablasts, plasma cells, or memory B-cells (Figure 1).

In the next step, expression levels of B-cell-associated genes involved in B lymphocyte proliferation were measured using qPCR. No significant differences were observed in the mRNA expression levels of BLK, BANK1, or TGFB between the two groups. In contrast, ATP1B3 expression was significantly lower in patients with ON onset compared with those without ON onset ($p=0.011$) (Figure 2). This difference remained below the Bonferroni-adjusted significance threshold ($p<0.0125$).

Spearman's correlation analysis was performed to assess potential associations between clinical and cognitive parameters listed in Table 2 and expression levels of B-cell-associated intracellular molecules. A positive correlation was observed only between BLK expression and 8-meter walk test time ($p=0.009$, $R=0.644$). This correlation did not survive the Bonferroni-corrected threshold ($p<0.001$) and was therefore considered a chance finding. No significant correlations were observed between B-cell subset proportions and clinical or cognitive parameters in patients with MS.

Discussion

In our study, no significant correlations were observed between peripheral blood B-cell subset proportions and clinical measures of disability or cognitive performance in patients

Table 2. Comparison of MS patients with and without ON* at disease onset				
	With ON at disease onset (n=10)	**Without ON at disease onset (n=16)**	**p-value**	**Cohen's d-value**
Age	42.5 (11.2)	41.5 (6.7)	0.499	0.1
Gender (F/M)	7/3	13/3	0.508	NA
EDSS	2.5 (1.5)	3.0 (2.5)	0.128	0.4
Number of ON attacks	3.0 (2.2)	1.0 (2.0)	**0.006**	1.0
Disease duration	12.0 (6.5)	12.0 (5.0)	0.322	0.3
Immunomodulating treatment types **Interferon-β** **Fingolimod** **Dimethyl fumarate** **Teriflunomide**	 3 3 2 2	 4 5 4 3	0.988	NA
Selective recall test	9.0 (2.2)	8.0 (3.0)	0.069	0.5
Spatial recall test	4.5 (3.2)	4.0 (3.0)	0.477	0.0
Symbol Digit Modalities Test	44.0 (11.0)	32.0 (14.0)	**0.014**	0.9
9-hole peg test (seconds)	22.0 (7.0)	22.0 (7.7)	0.369	0.2
8-meter walk test (seconds)	7.5 (3.2)	8.5 (6.0)	0.108	0.4

Bold characters indicate statistically significant differences before Bonferroni correction. Continuous and categorical variables were compared with Mann-Whitney U and chi-square tests, respectively. Continuous variables are denoted as median (interquartile range)

*: Painful vision loss or blurring that lasts for at least 24 hours, with no other identifiable cause, was considered an episode of ON, ON: Optic neuritis, F: Female, M: Male, EDSS: Expanded Disability Status Scale, NA: Not applicable

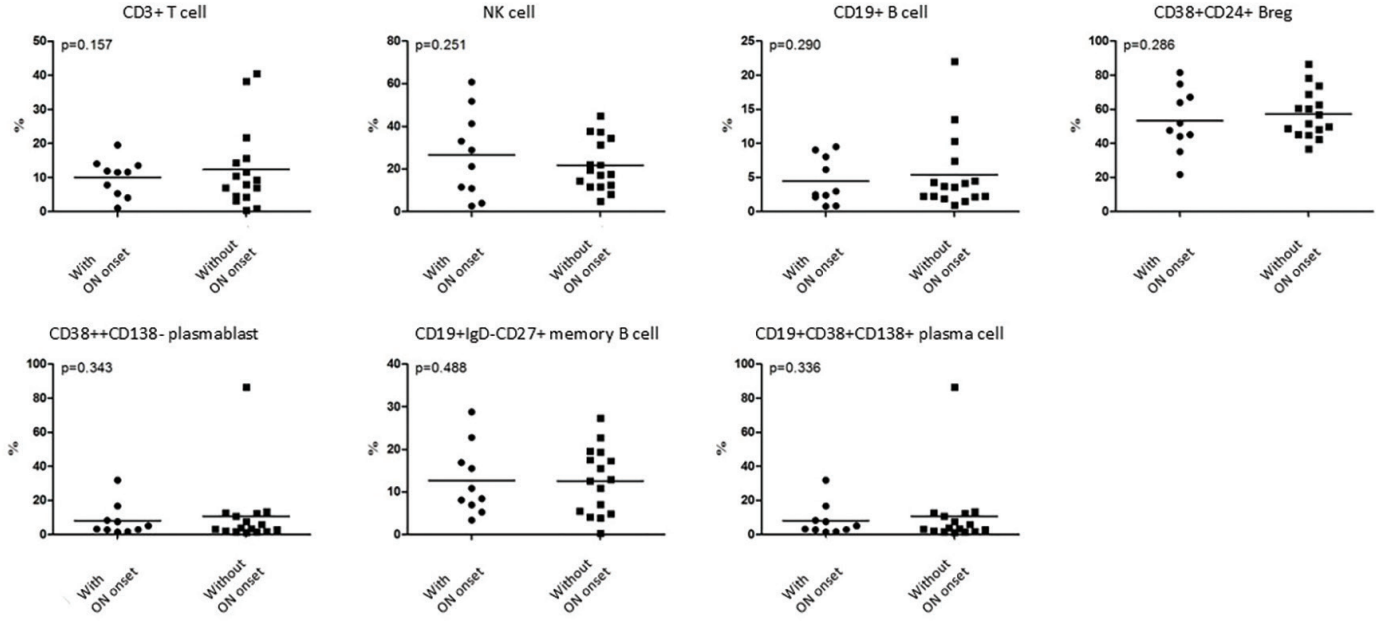

Figure 1. Comparison of peripheral blood immune cell subset ratios in patients with MS with and without ON onset. P-values are indicated in the upper left corner; horizontal lines represent median values

MS: Multiple sclerosis, ON: Optic neuritis, IgD: Immunoglobulin D

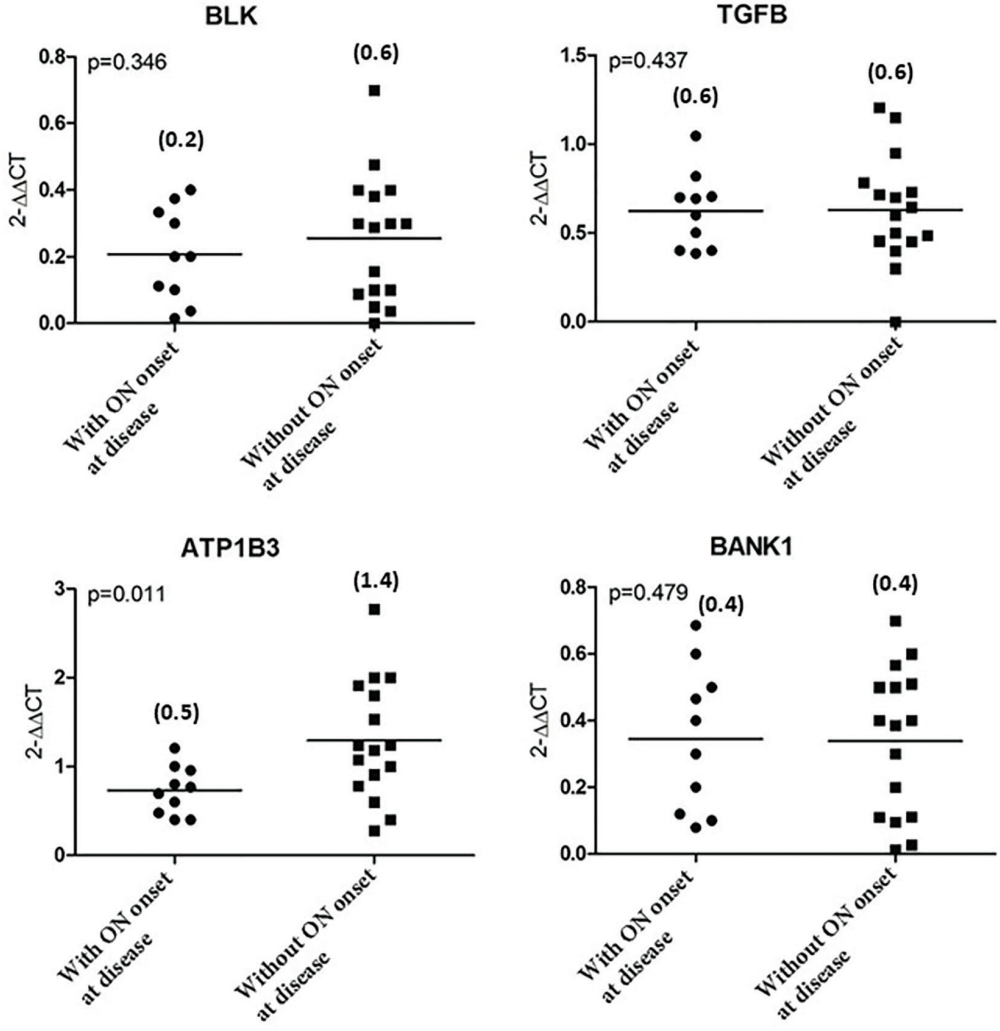

Figure 2. Comparison of expression levels of B-cell-associated genes in MS patients with and without ON onset. P-values are indicated in the upper left corner; horizontal lines represent median values, and values in parentheses indicate interquartile ranges

BLK: *B-lymphoid tyrosine kinase, BANK1: B-cell scaffold protein with ankyrin repeats 1, TGFB: Transforming growth factor beta, ATP1B3: ATPase Na^+/K^+ transporting subunit beta 3*, ON: Optic neuritis

with MS with ON-onset. These findings suggest that alterations in peripheral B-cell subset distribution do not directly reflect the degree of neurological or cognitive impairment in MS. Specifically, variations in the relative frequencies of naïve, memory, and regulatory B-cell populations in peripheral blood were not associated with EDSS scores or measures of cognitive processing efficiency.

Moreover, when participants were stratified according to disease onset type, no significant differences were observed in peripheral B-cell subset distributions between patients with ON-onset MS and those without ON-onset MS. Collectively, these findings indicate that peripheral blood immunophenotyping provides only a partial representation of the complex immune processes underlying disease activity and disability progression in MS.

In a previous study, significant differences were reported in the expression levels of *CR2, BLNK, RASGRP3*, and *BLK* genes between patients with MS and healthy controls. Correlation analysis further demonstrated that these genes had strong diagnostic utility (31). Another study reported that BLK expression was lower in patients with neuromyelitis optica compared with healthy individuals; however, during untreated acute attacks, BLK levels increased by 1.8-fold relative to healthy controls (32). In addition, reduced BLK expression has been associated with the development of immune complex-mediated glomerulonephritis in experimental models (33).

When gene expression levels were compared between patients with and without ON-onset MS, only *ATP1B3* expression was significantly lower in patients with ON-onset MS. In other autoimmune diseases, such as SLE, Na^+/K^+-ATPase activity

has been associated with increased B-cell survival and B-cell-mediated tissue damage (34). ATP1B3 has also been shown to enhance interferon-α production in lymphocytes (35). However, there is insufficient evidence to suggest that ATP1B3 is involved in antigen presentation or proinflammatory cytokine production, which are additional key functions of B-cells in autoimmune conditions. The reduced expression of this gene, which is implicated in B lymphocyte expansion, in patients with ON-onset MS may therefore suggest a less prominent B-cell-mediated pathophysiology in this subgroup of MS. This interpretation is supported by reports emphasizing the predominance of T-cells in ON (36,37). However, these findings should be interpreted with caution, as peripheral blood lymphocyte expression profiles may not accurately reflect those of lymphocytes in the CNS, which are more directly relevant to the pathophysiology of ON and MS. Therefore, further studies—preferably using CSF lymphocytes—are needed to validate these hypotheses regarding the role of ATP1B3 in MS pathogenesis.

However, ATP1B3 expression may potentially serve as a prognostic biomarker in patients with MS. Many currently used MS biomarkers are either B-cell derived (e.g., OCBs and kappa free light chains) or involved in B-cell chemotaxis to the CNS (e.g., CXCL13) (38,39). Thus, if future studies with larger MS cohorts reproduce our findings, ATP1B3 may be considered for inclusion in panels of B-cell-related biomarkers used to support MS diagnosis and prognosis assessment.

Study Limitations

We acknowledge several limitations of this study, including the small sample size (particularly for a gene expression study aimed at identifying prognostic biomarkers), the absence of healthy controls, and the single-center, cross-sectional design, all of which may limit the generalizability and interpretation of the findings. Therefore, our results should be considered preliminary observations suggesting a potential association and highlighting the need for validation in larger, independent cohorts. Additionally, due to the cross-sectional design, we were limited to correlating current gene expression levels with the type of first attack, which occurred in the past. Because gene expression may vary significantly throughout the disease course, we cannot confidently conclude that ATP1B3 expression levels were altered at disease onset. Longitudinal gene expression studies are therefore needed to address this limitation. Finally, although immunomodulatory treatment type may act as a potential confounder, this effect could not be statistically assessed due to the small number of patients per treatment group, resulting in limited statistical power.

Conclusion

Our preliminary findings suggest a putative association between ATP1B3 expression and ON onset in MS. This supports the notion that future research should integrate peripheral immunophenotyping with CSF analyses, neuroimaging markers, and longitudinal clinical data to provide a more comprehensive understanding of the immune mechanisms underlying disability accumulation. Validation of these findings in larger cohorts, including both MS patients and healthy controls, will be essential to confirm their relevance and clarify their potential as prognostic biomarkers.

Supplementary Figures 1 and 2: https://d2v96fxpocvxx.cloudfront.net/dd8262ff-66e6-418e-b233-a064eb1ea82f/content-images/d37ee4e4-3c98-493e-8c05-62d3236a8a3a.pdf

Ethics

Ethics Committee Approval: Ethical approval for the study was obtained from the Ethics Committee of University of Health Sciences Turkiye, Haydarpasa Numune Education and Research Hospital, (decision no: HNEAH-KAEK2018/KK/31, date: 12.03.2018).

Informed Consent: Written informed consent was obtained from all participants.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Z.F., D.O.Y., R.T., E.A., Concept: Z.F., V.Y., R.T., E.T., Design: Z.F., V.Y., R.T., E.T., Data Collection or Processing: Z.F., D.O.Y., R.T., E.A., Analysis or Interpretation: Z.F., V.Y., E.T., E.A., Literature Search: Z.F., D.O.Y., Writing: Z.F., D.O.Y. Z.F., D.O.Y., V.Y., R.T., E.T., E.A.

Conflict of Interest: No conflict of interest was declared by the authors.

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