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RESEARCH ARTICLE

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The Relationship Between Neurofilament Light Chain and B Lymphocyte Chemoattractant and Cognition in Multiple Sclerosis

Ezgi BAKIRCIOGLU-DUMAN[1,2], **Fatma Belgin PETEK-BALCI**[1], **Nurcihan CALISKAN-DOLU**[3], **Ayse Ozlem COKAR**[1]

[1]Haseki Training and Research Hospital, Department of Neurology, Istanbul, Türkiye
[2]Nuffield Department of Clinical Neurosciences, University of Oxford, Oxford, UK
[3]Haseki Training and Research Hospital, Department of Biochemistry, Istanbul, Türkiye

ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, demyelinating disease of the central nervous system that is often associated with cognitive impairment. This study aims to investigate whether Neurofilament light chain (NfL) and B Lymphocyte Chemoattractant (CXCL13) are potential biomarkers for detecting cognitive impairment in MS.

Methods: 57 patients with Radiologically Isolated Syndrome (RIS), Clinically Isolated Syndrome (CIS) or Relapsing-remitting MS (RRMS) and 70 healthy controls were studied. NfL and CXCL13 were measured by ELISA (the Enzyme-Linked ImmunoSorbent Assay) in the patients' cerebrospinal fluid (CSF) and serum samples. The Turkish-validated version of Brief International Cognitive Assessment for MS (BICAMS) test was applied. Serum biomarker levels and cognition tests were compared between the control and patient groups.

Results: Serum NfL and CXCL13 values were significantly higher in the patient group ($p = 0.043$ and $p < 0.001$, respectively) compared to healthy controls. BICAMS were lower in the patient group ($p<0.001$). CSF CXCL13 levels demonstrated a significant negative correlation ($p = 0.034$) with California Verbal Learning Test-2 (CVLT-II) subtest scores, while CSF NfL levels showed a trend towards a negative association ($p=0.067$) with this subtest. There were no significant relationships between the serum or CSF biomarkers and the BICAMS total scores.

Conclusion: NfL and CXCL13 potential biomarkers may not be associated with cognitive impairment in MS patients. The limitations of this study include the absence of CSF data from healthy individuals and the lack of stratification by clinical MS subtypes (RIS, CIS, or RRMS). Since they have been seen as promising biomarkers in MS, further studies are needed to determine this potential relationship.

Keywords: Biomarker, cognitive ımpairment, CXCL13, multiple sclerosis, neurofilament light chain

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INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory, autoimmune, demyelinating disease of the central nervous system (CNS) and one of the most common causes of neurological disability in young adults worldwide (1,2). Due to the variability and unpredictability of the disease process, advanced biomarkers are being investigated to help early diagnosis and prognosis in MS (3).

Neurofilament light chain (NfL), one of the structural proteins of the neuronal cytoskeleton, has been associated with axonal damage in MS (4). NfL levels are measured in cerebrospinal fluid (CSF) and serum with the Enzyme-Linked ImmunoSorbent Assay (ELISA) method, but the sensitivity is low in serum measurement with this method (3). The "Single molecular array-SIMOA" method is recommended for serum NfL (5). CSF NfL measurement is thought to be an early predictive biomarker in terms of long-term clinical course, and conversion from RRMS to Secondary Progressive MS (SPMS) (6). A recent study suggested that higher serum NfL levels are linked to both current and future cognitive processing speed performance in people with MS (7).

Highlights

- **CXCL13 levels showed a significant negative correlation with CVLT-II scores.**
- **Serum NfL and CXCL13 levels were significantly elevated in MS patients.**
- **A significant positive correlation was found between serum and CSF NfL levels.**

The importance of B cells in MS pathogenesis has become increasingly clear in recent years. It was shown that clonally expanded B cells in MS originate and undergo affinity maturation in cervical lymph nodes before migrating to the CNS, demonstrating the critical role of B cells in MS immunopathology alongside T cell-mediated mechanisms (8). A very recent study demonstrated that a specific subset of pro-inflammatory

Correspondence Address: Ezgi Bakırcıoğlu-Duman, Department of Neurology, Haseki Training and Research Hospital, İstanbul, Türkiye • **E-mail:** ezgi.bakirciogluduman@ndcn.ox.ac.uk
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B cells (T-bet+CXCR3+) plays a key role in driving immune responses both in the peripheral system and CNS, contributing to early and chronic stages of the disease (9).

B cell chemoattractant (CXCL13), which has pro-inflammatory characteristics due to its functions in the immune system, is a member of the CXC subtype of the chemokine superfamily (10). CXCL13 expression in CSF has been shown to increase in MS, and both serum and CSF CXCL13 levels are higher while in active disease (11,12). CXCL13 is supposed to be a predictor of conversion from CIS to MS (13,14).

Cognitive impairment, which is seen in approximately 40-70% of MS patients, can develop in all stages and subtypes of MS (15). Information processing speed slowdown and episodic memory decline are the most common cognitive impairments in MS, often accompanied by difficulties in executive function, verbal fluency, and visual-spatial analysis (16,17). Cognitive impairment occurs in 20–30% of CIS cases and may help predict conversion to MS, influencing treatment decisions (18).

In this study, the relationship between NfL and CXCL13 levels, which are neurodegeneration-related biomarkers, and cognitive impairment measured using the Brief International Cognitive Assessment for MS (BICAMS) method and its prognostic significance were studied in MS patients.

METHODS

Patients and Samples

This study included 57 patients who were diagnosed with RIS, CIS, RRMS and 70 healthy controls. Informed consent statements were obtained from all the study participants, explaining the study's objectives and content. Ethical approval for the study was obtained From the Ethics Committee of Haseki Training and Research Hospital on July 8, 2020, under the approval number 2020-119.

Inclusion criteria for the patient group;

- Being between the ages of 18-55,
- Not having an additional neurological and/or neurodegenerative disease,
- Diagnosis of CIS or RRMS according to McDonald criteria,
- Diagnosed with RIS according to Okuda criteria,
- Absence of any signs of infection, fever or malignancy.
- Participants with normal results for routine blood parameters, including thyroid function, vitamin B12 levels, and hemoglobin, were included to rule out potential medical conditions that could affect cognitive performance.

Inclusion criteria for the control group;

- Being between the ages of 18-55,
- Not having any known chronic disease,
- Absence of any known neurological disease, complaint and/or finding,
- No previous infection and/or malignancy of the CNS,
- No known autoimmune and/or neurodegenerative disease.

Cognitive Testing

The Turkish-validated version of BICAMS was performed to 50 patients and 70 control participants (19). Information processing speed and working memory were evaluated with the Symbol Digit Modalities Test (SDMT), verbal learning with the California Verbal Learning Test-2 (CVLT-II), and visuospatial memory with the Brief Visuospatial Memory Test-Revised (BVMT-R). Cognitive assessments in the MS group were conducted during remission, 3–6 months after the attack.

ELISAs

Neurofilament light chain and CXCL13 were studied only in the serum samples of 36 control participants since there were limitations on the number of kits, and LP was not performed in the control group. Lumbar punctures were performed on 55 patients and the CSF biomarker levels were measured. The biomarker and BICAMS results of the groups and the relationships were investigated. The correlation between serum and CSF biomarker levels and their relations with cognition tests were examined.

Biomarker measurements for CXCL13 (CLOUD-CLONE CORP., SEB601Hu, Houston, USA; Detection Range: 15.6–1,000 pg/mL) and NfL (CLOUD-CLONE CORP., SEE038Hu, Houston, USA; Detection Range: 15.6–1,000 pg/mL) were conducted in both CSF and serum samples using ELISA kits according to the manufacturer's instructions. The intra-method coefficient of variation was <10%, and the inter-method coefficient of variation was <12% for both kits. All samples were stored under appropriate conditions and analysed collectively.

The Expanded Disability Status Scale (EDSS) was not included in the present analysis as the majority of patients were at an early stage of the disease.

Statistical methods

SPSS 25 statistical package program was used for data analysis. The conformity of the data to the normal distribution was checked using the Kolmogorow-Smirnow test. Indicative statistics such as mean, standard deviation, median and frequencies were used. The Chi-square test was used to compare categorical variables. Independent t-test was used for two-group comparisons of normally distributed variables, and the F-ANOVA test was used for variables with more than two groups. Mann-Whitney-U and Kruskall-Wallis-H tests were used for data with the same characteristics that did not show normal distribution. The correlation degrees of the variables were examined using Pearson Correlation. In patient-control group comparisons, the One Sample t-test was used for normally distributed data, while the One-Sample Wilcoxon Signed test was used for non-normally distributed variables.

RESULTS

57 patients (40 female, 17 male) and 70 controls (44 female, 26 male) were included in the study. The average age was 33.7 ± 10.5 years in the patient group and 36.3 ± 9.4 years in the control group. There was no significant difference between the patient and control groups regarding age, gender (p=0.113; p=0.386, respectively), or educational status (p=0.159).

Serum and CSF NfL levels were raised in a proportion of MS sera and CSFs compared with control sera (for serum; p= 0.043) (Figure 1). Serum and CSF CXCL13 levels were raised compared to control sera (for serum; p value=<0.001) (Figure 2). As expected, serum CXCL13 levels were higher than CSF, whereas the opposite was the case for NfL levels.

The BICAMS subtests and total scores were found to be significantly lower in the patient group than in the control group (all p<0.001) (Figure 3).

Correlation analyses between biomarkers and BICAMS were performed in the patient group. A negative correlation was found between CSF Nfl and BICAMS (p = 0.030), with a Pearson Correlation (r) value of -0.308.

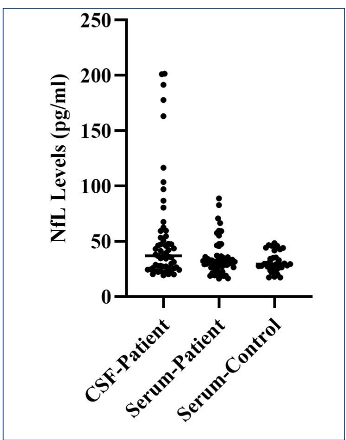

Figure 1. Comparison of CSF and serum NfL levels between the patient group and healthy controls.

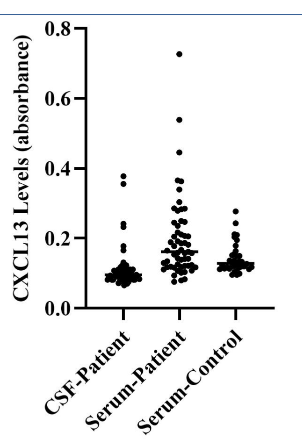

Figure 2. Comparison of CSF and serum CXCL13 levels between the patient group and healthy controls.

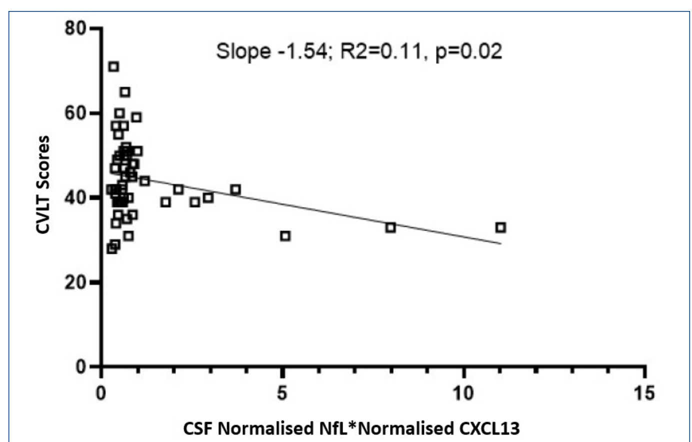

Figure 5. Association between the product of normalised CSF NfL and CXCL13 levels and CVLT-II scores.

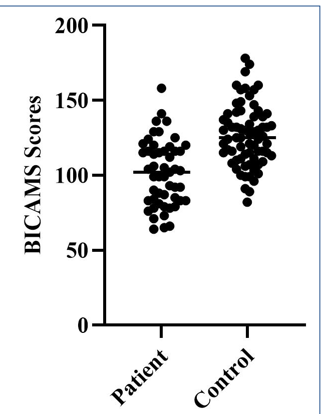

Figure 3. BICAMS scores in the patient group and healthy controls.

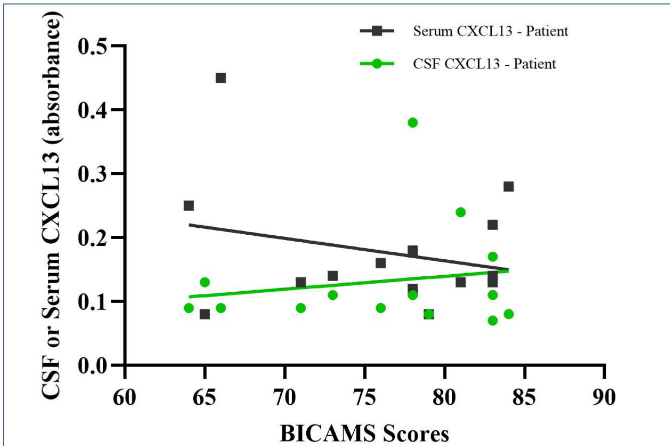

Figure 4. Distribution of BICAMS Scores in the Patient Group, Showing That Only 28% Scored Below the Normal Range (Mean−2*SD).

Also, there was a negative correlation between CSF CXCL13 and CVLT-II (p=0.034, r= -0,300). Serum NfL reflected CSF NfL (p=0.002, r=0.4). Moreover, CSF NfL and CSF CXCL13 were correlated with each other (p=0.004, r=0.4).

BICAM scores fell below the control range (mean: 126; defined as 126 – 2*SDs) in only 14 out of 50 patients (28%). When this subgroup was analyzed separately, no strong associations with biomarkers were observed (Figure 4). However, when the NFL and CXCL13 levels were normalised to the mean value of the MS cohort, there was a trend towards significance for CSF NfL (p=0.067) and a significant relationship for CXCL13 (p=0.034) with the CVLT-II subtest scores. There was also a significant relationship between biomarkers and CVLT-II when normalised values were multiplied (Slope -1.54; R2 0.11; p=0.02) in order to test whether the combined effect of NfL and CXCL13 levels was strongly associated with cognitive performance (Figure 5).

DISCUSSION

Biomarkers in serum and CSF are being investigated expeditiously to make early diagnoses and predict prognosis in MS. In practical terms, there is no single biomarker that accurately predicts the course of the disease in MS (2). Early diagnosis and rehabilitation of cognitive impairment, which affects the quality of life and functionality, is essential. Although disease-modifying agents used in MS have been shown to affect cognition positively, there is no approved treatment for cognitive impairment yet (16,17,20).

In this study, the primary data that aims to be revealed is the relationship between the two biomarkers studied and cognition impairment in MS. Although we found a negative correlation between CSF NfL and the BICAMS total score, we could not find a significant relationship after considering only those with lower cognition compared to the control group.

The other main result of this study is that we found a negative correlation between CSF CXCL13 levels and CVLT-II in the patient group. This situation may reveal that verbal learning can be affected more in patients with high CSF CXCL13 levels. However, we could not find a significant relationship after considering only the ones with lower cognition compared to the control group. These results may be explained by the small number of groups, the absence of progressive MS, the absence of patients with long disease duration, and the use of ELISA rather than SIMOA.

One of the recent studies reported a more substantial decrease in CVLT-II scores in MS patients with high serum and CSF NfL levels in parallel to the present results in terms of CSF NfL (21). A retrospective study using BICAM stated that serum NfL levels were higher in patients with cognitive impairment, which was associated with the future information processing speed (7). Another study investigated the relationship between serum NfL and memory and executive functions in MS patients using the SIMOA method. It emphasised that cognitive impairment and high serum NfL

levels were correlated (22). We did not find a significant relationship between serum NfL and BICAMS. The possible reason is that we used the ELISA method for both CSF and serum NfL measurement since the SIMOA method is not yet available in our centre.

A study published in 2021 stated a strong correlation between CSF CXCL13 elevation and grey matter damage in newly diagnosed MS patients and that CXCL13 may help differentiate severe cognitive impairment from mild cognitive impairment (23).

To the best of our knowledge, no study directly investigates the relationship between CXCL13 levels and cognition impairment in MS patients has been published, making the present results significant in this respect.

Serum NfL and serum CXCL13 were both elevated, and the CSF NfL and CSF CXCL13 levels were positively correlated in MS patients. This supports that neurodegeneration and B cell-related inflammation are correlated in active disease. In addition, a strong positive correlation between CSF and serum NfL levels in the patient group was also found. Varhaug et al. showed that CSF and serum NfL levels were elevated in all subtypes and during attacks in MS patients. Increased NfL in active MS reflects inflammation and also neurodegeneration (24). As consistent with this research in our study, LP was performed in the majority of our patients at the time of admission to the hospital with an attack, and the biomarker levels were found to be high. Serum and CSF NfL levels showed a strong correlation, which is in line with the literature (25), (26).

The subtests and total scores of the BICAMS were found to be significantly lower in patients compared to the control group. It should be emphasised that although the mean disease duration of the patient group was only two years and some patients were in the early stage, the cognition test results of the patients were lower than the control group. This finding supports that cognitive impairment is affected even in the earliest stages of the disease. BICAMS has been used in this study because it can be applied quickly and allows the evaluation of the most frequently affected areas of cognitive impairment in MS.

Strengths of the study; this is a comprehensive study comparing two different biomarkers, NfL and CXCL13, with cognition in MS patients. It is also the first study to directly investigate the relationship between serum and CSF CXCL13 and cognition impairment in MS. The study's limitations were the subgroups' small sample size, the lack of long-term follow-up and regular repetitive cognitive evaluation, and the inability to use the SIMOA method for NfL. Lastly, the biomarker measurements were obtained during the attack period, which may have affected their levels independently of baseline disease activity.

As a result, both NfL and CXCL13 may be potential predictive biomarkers of cognitive impairment. This study did not find a significant relationship between NfL and CXCL13 and cognitive impairment in MS patients. Serum NfL levels are higher in MS patients, and CSF and serum NfL levels are correlated. In addition, the correlation of CSF NfL and CXCL13 in the patient group suggests that neurodegeneration and B cell activation are together in MS patients. There is a need for studies with higher sample sizes, prospective long-term follow-ups, and advanced technology measurement methods. When the SIMOA method becomes widespread, it will be possible to obtain information about the cognition and disability progression of MS patients by checking the NfL level from serum at regular intervals. Future studies should focus on MS patients in the early stages of the disease, where those biomarkers could predict cognitive impairment and, therefore, help to prevent cognitive disability by implementing early immunotherapies.

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Conflict of Interest: The authors declare no conflict of interest and received no financial support for this study.

Author Contributions: Concept: EBD, FPBB; Design: EBD, FPBB; Supervision: FPB, AOC; Materials: EBD, ECD; Data collection/processing: EBD, FPB, NCD; Analysis and interpretation: EBD, FPB; Literature Search: EBD, FPB; Writing: EBD, FPB; Critical Review: EBD, AOC.

REFERENCES

1. Kaminska J, Koper OM, Piechal K, Kemona H. Multiple sclerosis - etiology and diagnostic potential. Postepy Hig Med Dosw (Online). 2017;71(0):551–563. [Crossref]
2. Oh J, Vidal-Jordana A, Montalban X. Multiple sclerosis: clinical aspects. Curr Opin Neurol. 2018;31(6):752–759. [Crossref]
3. Ekmekci Ö. Multipl skleroz; prognoz ve belirteçler. Duman T, editör. Multipl Skleroz. 1. Baskı. Ankara: Türkiye Klinikleri; 2020. p. 41–47.
4. Housley WJ, Pitt D, Hafler DA. Biomarkers in multiple sclerosis. Clin Immunol. 2015;161(1):51–58. [Crossref]
5. Kuhle J, Barro C, Andreasson U, Derfuss T, Lindberg R, Sandelius Å, et al. Comparison of three analytical platforms for quantification of the neurofilament light chain in blood samples: ELISA, electrochemiluminescence immunoassay and Simoa. Clinical Chemistry and Laboratory Medicine (CCLM) [Internet]. 2016;54(10). [Crossref]
6. Bhan A, Jacobsen C, Myhr KM, Dalen I, Lode K, Farbu E. Neurofilaments and 10-year follow-up in multiple sclerosis. Mult Scler. 2018;24(10):1301–1307. [Crossref]
7. Jakimovski D, Zivadinov R, Ramanthan M, Hagemeier J, Weinstock-Guttman B, Tomic D, et al. Serum neurofilament light chain level associations with clinical and cognitive performance in multiple sclerosis: A longitudinal retrospective 5-year study. Mult Scler. 2020;26(13):1670–1681. [Crossref]
8. Stern JNH, Yaari G, Vander Heiden JA, Church G, Donahue WF, Hintzen RQ, et al. B cells populating the multiple sclerosis brain mature in the draining cervical lymph nodes. Sci Transl Med [Internet]. 2014 Aug 6 [cited 2025 Jun 24];6(248). [Crossref]
9. Jelcic I, Naghavian R, Fanaswala I, Macnair W, Esposito C, Calini D, et al. T-bet+ CXCR3+ B cells drive hyperreactive B-T cell interactions in multiple sclerosis. Cell Reports Medicine. 2025;6(3):102027. [Crossref]
10. Iwanowski P, Losy J, Kramer L, Wójcicka M, Kaufman E. CXCL10 and CXCL13 chemokines in patients with relapsing remitting and primary progressive multiple sclerosis. J Neurol Sci. 2017;380:22–26. [Crossref]
11. Festa ED, Hankiewicz K, Kim S, Skurnick J, Wolansky LJ, Cook SD, et al. Serum levels of CXCL13 are elevated in active multiple sclerosis. Mult Scler. 2009;15(11):1271–1279. [Crossref]
12. Stilund M, Gjelstrup MC, Petersen T, Møller HJ, Rasmussen PV, Christensen T. Biomarkers of inflammation and axonal degeneration/damage in patients with newly diagnosed multiple sclerosis: contributions of the soluble CD163 CSF/serum ratio to a biomarker panel. Reindl M, editor. PLoS One. 2015;10(4):e0119681. [Crossref]
13. Brettschneider J, Czerwoniak A, Senel M, Fang L, Kassubek J, Pinkhardt E, et al. The chemokine CXCL13 is a prognostic marker in clinically isolated syndrome (CIS). Kleinschnitz C, editor. PLoS One. 2010;5(8):e11986. [Crossref]
14. Khademi M, Kockum I, Andersson ML, Iacobaeus E, Brundin L, Sellebjerg F, et al. Cerebrospinal fluid CXCL13 in multiple sclerosis: a suggestive prognostic marker for the disease course. Mult Scler. 2011;17(3):335–343. [Crossref]
15. Oreja-Guevara C, Ayuso Blanco T, Brieva Ruiz L, Hernández Pérez MÁ, Meca-Lallana V, Ramió-Torrentà L. Cognitive dysfunctions and assessments in multiple sclerosis. Front Neurol. 2019;10:581. [Crossref]
16. Benedict RHB, Cookfair D, Gavett R, Gunther M, Munschauer F, Garg N, et al. Validity of the minimal assessment of cognitive function in multiple sclerosis (MACFIMS). J Inter Neuropsych Soc [Internet]. 2006 Jul [cited 2021 Oct 12];12(04). [Crossref]

17. Rao SM, Leo GJ, Bernardin L, Unverzagt F. Cognitive dysfunction in multiple sclerosis.: I. Frequency, patterns, and prediction. Neurology. 1991;41(5):685–691. [Crossref]
18. Zipoli V, Goretti B, Hakiki B, Siracusa G, Sorbi S, Portaccio E, et al. Cognitive impairment predicts conversion to multiple sclerosis in clinically isolated syndromes. Mult Scler. 2010;16(1):62–67. [Crossref]
19. Ozakbas S, Yigit P, Cinar BP, Limoncu H, Kahraman T, Kösehasanoğulları G. The Turkish validation of the brief international cognitive assessment for multiple sclerosis (BICAMS) battery. BMC Neurol. 2017;17(1):208. [Crossref]
20. Benedict RHB, DeLuca J, Enzinger C, Geurts JJG, Krupp LB, Rao SM. Neuropsychology of multiple sclerosis: looking back and moving forward. J Int Neuropsychol Soc. 2017;23(9-10):832–842. [Crossref]
21. Friedova L, Motyl J, Srpova B, Oechtering J, Barro C, Vodehnalova K, et al. The weak association between neurofilament levels at multiple sclerosis onset and cognitive performance after 9 years. Mult Scler Relat Disord. 2020;46:102534. [Crossref]
22. Mattioli F, Bellomi F, Stampatori C, Mariotto S, Ferrari S, Monaco S, et al. Longitudinal serum neurofilament light chain (sNfL) concentration relates to cognitive function in multiple sclerosis patients. J Neurol. 2020;267(8):2245–2251. [Crossref]
23. Pitteri M, Magliozzi R, Nicholas R, Ziccardi S, Pisani AI, Pezzini F, et al. Cerebrospinal fluid inflammatory profile of cognitive impairment in newly diagnosed multiple sclerosis patients. Mult Scler. 2021;135245852110325. [Crossref]
24. Varhaug KN, Torkildsen Ø, Myhr KM, Vedeler CA. Neurofilament light chain as a biomarker in multiple sclerosis. Front Neurol. 2019;10:338. [Crossref]
25. Disanto G, Barro C, Benkert P, Naegelin Y, Schädelin S, Giardiello A, et al. Serum Neurofilament light: A biomarker of neuronal damage in multiple sclerosis: Serum NfL as a Biomarker in MS. Ann Neurol. 2017;81(6):857–870. [Crossref]
26. Kuhle J, Barro C, Disanto G, Mathias A, Soneson C, Bonnier G, et al. Serum neurofilament light chain in early relapsing remitting MS is increased and correlates with CSF levels and with MRI measures of disease severity. Mult Scler. 2016;22(12):1550–1559. [Crossref]