Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ

Cukurova Med J 2024;49(4):901-907
DOI: 10.17826/cumj.1463251

RESEARCH

Evaluation of neurofilament light chain levels in multiple sclerosis during acute attack periods

Multipl sklerozda akut atak dönemlerinde nörofilament hafif zincir düzeylerinin değerlendirilmesi

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Abstract

Purpose: The aim of this study is to evaluate how the serum neurofilament light chain (sNfL) was influenced in the multiple sclerosis (MS) patients before and after treatment of an acute attacks, and to determine the relationship of it with clinical findings.

Materials and Methods: Thirty eight patients with a definite diagnosis of relapsing-remitting MS (RRMS) and who had a clinical acute attack between December 2019 and November 2020 were included in the study. The sNfL levels were studied before and after the treatment of an acute attacks. The relationship of sNfL levels with the patients' clinical characteristics and treatment of acute attack was analyzed.

Results: The sNfL levels of a total of 38 RRMS patients were evaluated. The mean age of the patients were 35.8 ± 9.68 years (19-55 years). The sNfL level before and after treatment of acute attack were 3.55 pg/mL (3.09-4.54 pg/mL) and 3.36 pg/mL (3.01-3.86 pg/mL), respectively. No statistically significant difference was found between the sNfL levels before and after treatment. Likewise, no relationship between the before and after treatment sNfL levels with clinical findings such as gender, age, duration of disease, and biochemical findings were detected.

Conclusion: In our study, we found that the sNfL level, which is a biomarker of the prognosis and neuronal degeneration in the long-term, did not influenced by the high dose corticosteroid treatment.

Keywords: Attack treatment; corticosteroid; multiple sclerosis; neurofilament; neurofilament light chain.

Öz

Amaç: Bu çalışmanın amacı, multipl skleroz (MS) hastalarında serum nörofilament hafif zincir (sNfL) düzeylerinin atak tedavisi öncesi ve sonrasında akut dönemde nasıl etkilendiğinin incelenmesi ve klinik bulgular ile ilişkisinin değerlendirilmektir.

Gereç ve Yöntem: Aralık 2019-Kasım 2020 tarihleri arasında kesin olarak relapsing-remitting MS (RRMS) tanısı olan ve klinik atak geçiren 38 hasta çalışmaya dahil edildi. Hastaların demografik ve klinik verileri kayıt altına alındı. Atak öncesi ve tedavisi sonrasındaki sNfL düzeyleri çalışıldı. sNfL düzeylerinin hastaların klinik özellikleri ve atak tedavisi ile ilişkisi analiz edildi.

Bulgular: Toplam 38 RRMS hastasını sNfL örnekleri değerlendirildi. Hastaların yaş ortalaması 35.8 ± 9.68 yıl (19 – 55 yıl) idi. Hastaların atak tedavi öncesinde ortanca sNfL düzeyi 3.55 pg/mL (3.09 – 4.54 pg/mL), sonrasında ise 3.36 pg/mL (3.01 – 3.86 pg/mL) idi. Atak tedavisi öncesi ve sonrasındaki sNfL düzeyleri arasında istatistiksel olarak anlamlı fark saptanmadı. Atak tedavisi öncesi ve sonrasındaki sNfL düzeyleri ile hastaların cinsiyet, yaş, hastalık süresi gibi klinik bulgular ve laboratuvar bulguları arasında anlamlı ilişki gösterilemedi. Atak tedavisi sonrasında immünglobülin G indeksi yüksek olan grupta sNfL düzeyinin daha fazla azaldığı gösterildi, ancak istatistiksel anlamlık saptanmadı.

Sonuç: Prognostik ve uzun dönemde nöronal dejenerasyon belirteci olan sNfL'in yüksek doz kortikosteroid tedavisinden etkilenmediği çalışmamızda gösterilmiştir.

Anahtar kelimeler: Atak tedavisi; kortikosteroid; multipl skleroz; nörofilament; nörofilament hafif zincir

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Received: 05.04.2024 Accepted: 17.11.2024

INTRODUCTION

Multiple sclerosis (MS) is a chronic neurodegenerative autoimmune disease characterized by a clinical course that can vary from severe, rapidly remitting attacks occurring months after onset to progression towards permanent disability[1–5]. In recent years, biomarkers that reflect tissue damage and enable the monitoring of preclinical disease activity have been utilized to evaluate therapeutic responses and predict disability, both in clinical trials and in the management of individual patients[2]. The serum neurofilament light chain (sNfL) is the most commonly used biomarker in MS. This biomarker is released as a breakdown product into the interstitial space and cerebrospinal fluid (CSF) since there is axonal injury and neuronal degeneration[3,4]. In MS studies that were performed in recent years, it was reported that the sNfL would a beneficial biomarker in regard to the prediction of prognosis and evaluation of the response to treatment[5-7]. Although sNfL has been proposed as a potential biomarker due to its increase during early diagnosis, sNfL levels rise across all stages of MS. However, these levels may fluctuate depending on the clinical course and active imaging findings[6]. In follow-up studies, it was also shown that the sNfL level would predict the severity of disease and conversion to MS[7-9]. Because it can be high at the time of diagnosis, it would be an early biomarker. Despite variations in methodological approaches across studies, the sNfL level is widely regarded as a reliable indicator of neuroaxonal damage resulting from acute inflammation[7-10]. Additionally, it has been claimed that the rise in the sNfL level during the attack period would specifically give information about the course of the disease in the long term[8,10]. The literature has reported a significant increase in sNfL levels following attacks or gadolinium-enhancing lesions; however, the duration of this elevation and the dynamics of sNfL prior to disease activity remain unclear.

Intravenous high dose methylprednisolone (IVMP) is an anti-inflammatory treatment used in the treatment of MS attacks, and there is primary evidence that it accelerates clinical improvement in attacks. Additionally, although it was determined that IVMP treatment applied in acute attacks of MS would decrease sNfL levels and that it has a considerable predictive value in regard to morbidity in the long term, the topic in the literature remains under debate[11].

The objective of this study was to examine the relationship between sNfL changes during the attack phase and the clinical and demographic characteristics of MS patients. This was achieved by comparing sNfL levels within the first 24 hours of the attack to the changes in sNfL levels observed during the first 24 hours following IVMP treatment in patients with clinical and radiological relapses

MATERIALS AND METHODS

Sample

A total of 38 patients, who experienced an acute attack of MS and had been followed-up in our out-patient clinic from December 2019 through November 2020 with the definitive diagnosis of relapsing remitting MS (RRMS), were included in the study. An attack of MS was defined as a new or deteriorating clinical symptoms lasting more than 24 hours where there is no fever, infection, or other medical condition[12]. The data of the patients in regard to the Expanded Disability Status Scale (EDSS) before attack, oligoclonal band (OCB), immunoglobulin G (IgG) indexes, follow-up periods, initial symptoms and findings, and ongoing immunomodulator treatments (IMTs) were recorded from the patients' records and archive. Patients under the age of 18 or over 60 were not included in the study. Additionally, those with chronic conditions such as heart, respiratory, liver, or renal failure were excluded. Individuals with other endocrine or psychiatric disorders, as well as patients receiving MS-specific treatments other than IMTs and those who had undergone corticosteroid treatment within the last three months, were similarly excluded from the study.

Procedure

The management of an acute attack was standardized as IVMP 1,000 mg/day for five consecutive days. All the management and interventions were performed in the hospital. None of the patients were given oral corticosteroids with the aim of decreasing the dose or continuing regimen. From all of the patients with attack, who were included in the study, blood samples were collected for sNfL levels just before initiation of and immediately at the end of IVMP treatment.

The current study was approved by the Ethical Commission of the Izmir University of Health Sciences Tepecik Education and Research Hospital

(Approval number: 2019/10-12). The written informed consent was obtained from the patients according to the Declaration of Helsinki by the World Medical Association and the instructions of Good Medical Practice.

Data acquisition

Blood samples of 5 mL for sNfL analysis were collected from a peripheral vein within the first 24 hours of admission to hospital and between 7:00 and 8:00 a.m. at the end of a five-day-long treatment of IVMP. Blood samples from each patient were collected in a clot-activating tube containing gel separator (BD Vacutainer® SST II Advance tube, 5 mL, 13 x 100 mm; Becton, Dickinson and Company, Franklin Lakes, NJ, USA). The tubes were centrifuged at 1,500 rpm for 10 minutes, and the serum was separated and stored at −80°C until analysis. The sNfL levels were measured by the enzyme-linked immunosorbent assay (ELISA)method using commercially available kits (Human Neurofilament protein L ELISA kit; Sunred Biotechnology, Shanghai, China).

Statistical analysis

The data analysis was performed using the IBM SPSS Statistics version 25 software package (IBM Corp., Armonk, New York, USA). Descriptive statistics were presented as frequency and percentage (%), median, 25th percentile, 75th percentile, mean (*M*), and standard deviation (*SD*). Normality of continuous variables was evaluated with the Shapiro–Wilk test and Q-Q plots. The Wilcoxon signed rank test was used to compare pre-and post-treatment values. In the comparison of the post-treatment values, the percentage change (last value-initial value/initial value) was calculated and used in the comparisons. Independent samples *t*-test and Mann–Whitney *U* test were used to compare post-treatment values. Pearson or Spearman's rho correlation coefficients were used to determine the relationship between post-treatment level and age and disease duration. A *p*-value of <0.05 was considered statistically significant.

RESULTS

Of the included 38 patients with the diagnosis of RRMS, 29 (76.3%) were female and nine (23.7%) were male. While the mean age of the patients was 35.82 ± 9.68 years, the mean duration of disease was 7.39 ± 6.39 years. In all, 65.8% of the patients were under first-line IMTs, and two (5.3%) patients were not given IMTs. The clinical and demographic characteristics of the patients are shown in Table 1.

Table 1. Demographic and clinical characteristics of the patients.

Variables		n	%
Gender	Female	29	76.3
	Male	9	23.7
Medication	1st line IMTs	25	65.8
	2nd line IMTs	11	28..9
	No medication	2	5.3
OCB	Negative	9	23.7
	Positive	29	76.3
EDSS	<3.0	28	73.7
	≥3.0	10	26.3
Lesion site at episode	Cranial	25	65.8
	Spinal	13	34.2

OCB: Oligoclonal band; EDSS: Expanded Disability Status Scale IMTs: Immunomodulator treatments.

The median sNfL levels before and after the treatment of acute attack were 3.55 pg/mL (3.09 – 4.54 pg/mL) and 3.36 pg /mL (3.01 – 3.86 pg/mL), respectively. There was no statistically significant difference between the pre- and post-treatment median sNfL levels (p = 0.376). Since the pre-treatment median sNfL level in males and the patients who were under first-line IMTs were lower in comparison with their counterparts, and there was no considerable difference between the groups (p = 0.068 and p = 0.115, respectively). The pre-treatment sNfL level did not reveal statistically significant correlation with age (r = –0.289, p = 0.079) and duration of disease (r = 0.130, p = 0.436).

Additionally, there was no statistically significant relationship detected between pre-treatment sNfL level and OCB, IgG index, lesion site at episode, and EDSS values (Table 2).

Table 2. Comparison of demographic data with pre-treatment sNfL level

Variable		n	Pre-treatment sNfL level (pg /mL)	Test statistics	P-value*
Gender	Female	29	3.81 (3.14 – 4.87)	1.820	0.068
	Male	9	3.38 (3.02 – 3.52)		
OCB	Positive	29	3.53 (3.10 – 4.53)	0.052	0.973
	Negative	9	3.68 (2.71 – 4.74)		
IgG	≤0.69	9	3.68 (2.71 – 6.09)	-0.223	0.840
	>0.69	29	3.53 (3.10 – 4.44)		
EDSS	<3.0	28	3.57 (3.0 – 4.47)	0.414	0.683
	≥3.0	10	3.47 (3.10 – 5.72)		
Lesion site at episode	Cranial	25	3.68 (3.19 – 4.58)	-1.462	0.150
	Spinal	13	3.68 (2.98 – 4.40)		
Medication	1st line IMTs	25	3.38 (3.02 – 4.41)	1.597	0.115
	2nd line IMTs	11	4.39 (3.48 – 5.35)		

* indicates Mann Whitney U test.
OCB:Oligoclonal band; IgG:Immunoglobulin G; EDSS:Expanded Disability Status Scale; IMTs:Immunomodulator treatments.

One of the outcomes of the study indicated that there was a statistically significant decrease in sNfL levels in the group of patients who had a high IgG index after treatment, when compared with the group with a low IgG index (p = 0.021).The decrease of sNfL was more than 3% in the patients in whom the IgG index was higher after IVMP treatment. In terms of post-treatment sNfL, there was no statistically significant difference between genders, OCB, EDSS, and the patients who received IMTs or not (Table 3).

Table 3. Comparison of demographic data with post-treatment sNfL level.

Variable	n	Post-treatment sNfL level (pg /mL)	Test statistics	95% CI	p value
Gender					
Female	29	-0.05 ± 0.31	-8.891	-0.17 – 0.06	0.087*
Male	9	0.03 ± 0.17		-0.09 – 0.17	
OCB					
Positive	29	-0.07±0.25	-1.713	-0.17 – 0.01	0.094*
Negative	9	0.10±0.35		-0.16 – 0.37	
IgG					
≤0.69	9	0.19 (-0.12 – 0.50)	-2.283	-	**0.021****
>0.69	29	-0.03 (-0.31 – 0.09)		-	
EDSS					
<3.0	28	-0.05 ± 0.29	0.781	-0.17 – 0.05	0.440*
≥3.0	10	0.02 ± 0.28		-0.17 – 0.23	
Lesion site at episode	25	-0.09±0.25	1.732	-0,19;0,01	0,092*
	13	0.07±0.32		-0,12;0,26	
Medication					
1st line IMTs	25	0 ± 0.30		-0.11 – 0.13	0.105*
2nd line IMTs	11	-0.16 ± 0.20	-1.666	-0.29 – -0.02	

* indicates independent-samples t test and ** indicates Mann Whitney U test.
OCB: Oligoclonal band; IgG: Immunoglobulin G EDSS:Expanded Disability Status Scale; IMTs:Immunomodulator treatments.

DISCUSSION

In our study, sNfL levels before and after IVMP treatment during the acute inflammatory attack phase in MS patients showed no significant change. Furthermore, there was no significant correlation between sNfL levels and the demographic or clinical characteristics of the patients before and after IVMP treatment. The sNfL levels were found to be lower in male patients and in those receiving first-line IMTs. Additionally, the reduction in sNfL levels following IVMP treatment was statistically significantly greater in MS patients with a high IgG index.

The high sNfL levels were determined to indicate neuronal injury independent of the underlying pathological mechanism. In respect to higher sNfL levels in comparison with healthy controls, Disento et al.[13] reported a connection between sNfL levels and both localized lesions in the brain and spinal cord, as well as radiological activity. Moreover, it was also reported that the sNfL levels would be highly related to the relapses and disease deteriorations[13]. Likewise, other than being a good indicator in long-term prognosis, Kuhle et al.[14] showed the increased levels of sNfL throughout the course and in the acute attack phase of the disease in MS patients. In another study, the increased levels of sNfL in radiologically isolated syndrome patients were shown to increase the risk of the development of clinically isolated syndrome (CIS) and MS in the future[15]. In the studies in which CIS patients were included, independent of the other risk factors (such as age, OCB, and lesion count on T2), the high CSF or serum neurofilament levels were highlighted as an additional indicator of relapses in the future[10,13,14]. In the current study, we detected that the pre- and post-IVMP treatment sNfL levels did not reveal significant difference in the patients who were admitted as a result of attack.

In the event of an acute attack, injury of the blood–brain barrier eases the shift of the sNfL to the peripheral circulation and leads to higher measured levels of it in the serum[7,16]. Bergman and coworkers (17) reported that the cumulative relapse frequency for the last 12 months was in relationship with high sNfL levels. Along with the increase of sNfL levels in an attack of MS, it was shown that it would be related with the localization of the lesions[5,7,13]. Based on gadolinium enhancement on radiological imaging, it has been reported that sNfL levels may increase, with elevated levels persisting for some time, particularly in the presence of spinal cord lesions[6].

However, although the increase in sNfL levels was shown in acute attacks, it was argued that this increase was not prominent in the immediate but in the follow-up period[10,11]. In our study, the relationship between sNfL levels and the localization of the lesion responsible for acute attacks could not be shown. Furthermore, no significant difference between the pre-treatment and post-treatment sNfL levels was detected, which would be related to the fact that due to the effect of IVMP treatment, the breakdown of the sNfL would be decreased or halted, which would have resulted in no change in the sNfL levels. It should be kept in mind that the sNfL levels would reveal fluctuations due to the varied measurement modalities.

High dose corticosteroid is an effective treatment modality in an acute attack of MS. Since there are a variety of considerable changes at the cellular level in an attack of MS, the effects of corticosteroids on these changes were shown. In the MS patients who had had an acute attack and had a recurrent episode in the follow-up, Gawde et al.[11] examined the protein components of the cell membrane including the sNfL, urokinase plasminogen activator, mannose binding lectin 2, and FK506-binding protein 5. They showed a considerable decrease in the level of these cell membrane proteins after corticosteroid treatment. However, in addition to the increase in sNfL levels in an acute attack of MS, they also showed that the sNfL level was not accompanied by a significant decrease like other protein levels after treatment. As a result, they claimed that there is no direct effect of corticosteroid treatment on high levels of sNfL before an attack of MS. Compatible with the literature, our results did not reveal a direct effect of high-dose corticosteroid treatment on sNfL levels.

While the sNfL level was shown to reveal a weak but important correlation with EDSS score before treatment in some studies, other studies have not shown as significant of a relationship as was shown in the current study[13,14]. The reason for this different result was possibly related to the number of patients, the duration of disease, the clinical characteristics of the patients, and specificity of the method applied to do measurement in serum. A short period of a high course of sNfL levels after an acute attack was related with higher risk of a recurrent attack within three years and deterioration of EDSS[5,13,18]. Also, in comparison to the clinically stable patients with lower

EDSS scores, higher sNfL levels were found in the advanced stages of disease.

To this point, the information regarding the influence of gender on sNfL levels is scant[10,11,13,14]. In their cross-sectional and longitudinal study, in which a comparison of sNfL levels was made between a control group and a patient group with MS, Disanto et al. (13) did not report a considerable difference. Likewise, the same inquiry in 31 RRMS patients in whom CSF and serum neurofilament levels at the time of an acute attack was evaluated by Kuhle et al.[14] did not reveal a significant difference between males and females. On the contrary, in the meta-analysis of all neurology patients, Brider et al.[19] reported a higher level of sNfL level in males than in females, and they emphasized the need for determination of the normal values of sNfL according to gender. In our study, since the sNfL levels were found to be higher in females both before and after an acute attack, the difference was not significant.

A low or stable sNfL level would exclude existence of an activity of clinical or subclinical disease. The index studies in this regard have shown the variability of sNfL levels in different treatment groups[19,23]. While all IMTs revealed an effect on sNfL levels, the strong IMTs such as fingolimod, natalizumab, and rituximab were shown to result in a significant decrease in sNfL levels in the long term[20,21,23]. A decrease in the sNfL level with an effective medical treatment would be considered as a bioindicator of an effective treatment[22]. In our study, the sNfL level was lower in the patients who received first-line IMTs, but there was no statistically significant difference between the treatment groups. The reason for this finding was possibly highly related to the fact that the patients were both clinically and radiologically stable before an attack and their sNfL levels were not evaluated longitudinally, which was within the limitations of our study.

The importance of intrathecal B cells in the pathophysiology of MS has been put forward in recent years[18]. The sNfL level of the patients who have OCB has been reported to be higher in comparison with OCB negative patients[24]. In a study comprising 142 patients, a considerable relationship between sNfL level and CD80+ (B and myeloid cells) and CD19+ (B cells) levels was reported[25]. However, Uher et al[8] and Dalla Costa et al.[25] reported that sNfL level was unrelated to positive OCB. Likewise, we could not show a relationship between sNfL and the existence of OCB in our study. However, the drop in sNfL level in the patients who had a high IgG index as an indicator of activated B cell state was higher after acute attack treatment. This situation is generally related to the corticosteroid dependent suppression of inflammation

The small number of patients and control groups, the lack of equal distribution of patients based on the utilized medications, the examination of sNfL being conducted using serum and not being able to examine it in the CSF, and the utilization of the ELISA method, which is less sensitive compared with single molecule array (SiMoA) which was not available at the time of planning the study, were the limitations of the current study.

The current study showed that there was no effect of high dose corticosteroid treatment on pre-and post-treatment sNfL levels. In our opinion, inclusion of the measured sNfL levels in the decision-making progress would provide an individualized approach to treatment and more rapid management of MS. In view of all these findings, it can be concluded that prospective, long-term, longitudinal, multi-centered, and more extensive studies are needed. We conclude that inclusion of a bioindicator in drug studies in particular would enable us to observe the effect of the current and ongoing developing treatments on these bioindicators much more clearly, which would clarify their position in clinical practice.

Author Contributions: Concept/Design : AS, AÇ, UŞ, LÖ; Data acquisition: AS, LÖ; Data analysis and interpretation: LÖ, AS, İK; Drafting manuscript: LÖ, AS, İK; Critical revision of manuscript: LÖ, AS, İK, AÇ, UŞ; Final approval and accountability: AS, LÖ, İK, AÇ, UŞ; Technical or material support: AS, İK, AÇ; Supervision: LÖ, AS, İK; Securing funding (if available): n/a.
Ethical Approval: This study was approved by the Izmir University of Health Sciences Tepecik Education and Research Hospital Ethics Committee with the Approval number: 2019/10-12..
Peer-review: Externally peer-reviewed.
Conflict of Interest: The authors declare that they have no potential conflict of interest regarding the investigation, authorship, and/or publication of this article.
Financial Disclosure: This study received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

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