Serum Neurofilament Light Chain as a Biomarker of Disease Activity in Multiple Sclerosis

Original Article

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ABSTRACT

Background: Neurofilament light chain (NFL) is a cytoskeletal protein found in neurons indicating neural damage resulting from neuroinflammation and degeneration related to multiple sclerosis (MS). Among the various subtypes of MS, the most prevalent is relapsing-remitting multiple sclerosis (RRMS).

Aim of the Work: The current study aimed to assess the prognostic value of serum NFL biomarker as a predictor of disease activity and clinical outcomes.

Materials and Methods: This case control study was performed on 44 relapsing remitting MS patients and 22 apparently healthy controls. The study was conducted at Ain Shams University Hospital in both the Neurology Department and the Clinical Pathology the Department in the period between August 2023 and January 2024.

Results: In comparison to controls, RRMS patients showed no statistically significant difference in serum NFL levels (p= 0.094). Patients were grouped into two categories, patients in a relapse phase and those in a remission phase. When comparing the patient groups, there were significant statistical differences as regard family history of MS (p= 0.046), EDSS score (p= 0.003), number of relapses (p= 0.025) and the duration of the disease (p= 0.018).

Conclusion: In this study, NFL was not a reliable biomarker in predicting disease worsening and activity among RRMS patients when measured by enzyme-linked immunosorbent assay (ELISA) as there is an overlap between NFL levels among patients and controls.

Key Words: Cerebrospinal fluid, enzyme-linked immunosorbent assay, multiple sclerosis, neurofilament proteins, relapsing remitting.

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INTRODUCTION

Multiple sclerosis is a chronic autoimmune disease of the central nervous system (CNS). The immune system mistakenly attacks the myelin sheath which is the protective covering around the nerve fibers. It affects approximately 2.8 million individuals globally. The most prevalent type of the disease is RRMS, comprising roughly 80% of cases where patients typically experience episodes of disease relapse. In 5–15% of cases the disease presents as primary progressive multiple sclerosis and identified by a steady increase in disability without relapses. After 10–15 years of RRMS the disease often transitions into secondary progressive multiple sclerosis which is marked by a gradual progression of symptoms and accounts for 5% of cases[1].

Neurofilaments (NF) are neuron-specific filaments with a diameter of 10 nm classified under the type IV family of intermediate filaments (IF), which are cytoskeletal building blocks within neurons. These neurofilaments are composed of three primary types collectively known as the NF triplet: the neurofilament light chain (NFL; approximately 60 kDa), the neurofilament medium chain (NFM; around 90 kDa), and the neurofilament heavy chain (NFH; roughly 115 kDa)[2]. The cytoskeletal protein component known as neurofilament light chain is only expressed in neurons. When neurons are damaged it is released into the extracellular fluids such as blood and the concentration of it indicates how quickly the neurons release it[3].

A precise and non-invasive MS biomarker might now be developed thanks to the strong association between

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CSF and NFL blood levels. When it comes to the clinical therapy of patients with multiple sclerosis, serum NFL is thought to be a sensitive biomarker that reveals neuroaxonal impairment. Serum NFL has been linked in the past to physical impairment, clinical exacerbations, response to disease-modifying agents and alterations in magnetic resonance imaging (MRI) associated with multiple sclerosis[4].

AIM OF THE WORK

The present study aimed to evaluate the prognostic value of serum NFL biomarker as a predictor of disease activity and clinical outcomes.

MATERIALS AND METHODS

Study design and Study population

This is a case control study that was conducted at Ain Shams University Hospital in both the Neurology Department (MS unit) and the Clinical Pathology Department (Immunology unit) in the period between August 2023 and January 2024. A total number of 66 subjects were included (44 patients and 22 controls); Forty-four patients suffering from RRMS diagnosed according to McDonald's criteria 2017 ***McDonald et al., 2001*** and twenty-two healthy controls. Patients were further divided into two groups based on clinical symptoms; patients in relapse (group A) and patients in remission (group B).

Inclusion criteria

Egyptian adult patients with RRMS diagnosed based on the McDonald's Criteria (2017). Patients having other demyelinating diseases were excluded.

ETHICAL APPROVAL

Before being enrolled in the present study each patient had consented to participate in the study after being aware of its purpose and methods. After reviewing the study protocol from an ethical perspective the research ethics committee at Ain Shams University authorized it with number MS 378/2023.

Study procedures

1. Detailed medical history (age, gender, past, current medical history and family history of MS).
2. Collection of the following data from the medical records:
    a. Detailed medical examination using Kurtzke Expanded Disability Status Scale Score (EDSS score) (Kurtzke, 1983) for assessing disease disability of the patients.
    b. Cranial and spinal magnetic resonance imaging.
3. Measurement of serum NFL by quantitative ELISA.

Sample collection

Each participant had five milliliters (5 ml) of venous blood drawn while adhering to strict aseptic procedures. The samples were put into a sterile vacutainer equipped with a clot activator and allowed to coagulate for thirty minutes. The samples were centrifuged for 20 minutes at 2000–3000 rpm. To be utilized for the NFL test, the separated serum was kept in storage at -80°C. Recurring freezing and thawing of the samples was avoided and hemolyzed samples were disposed of.

Analytical methods

Neurofilament light chain was measured as instructed by the manufacturer using quantitative ELISA kit supplied by Elab Science (14780 Memorial Drive, Suite 108, Houston, Texas, 77079, USA); catalog number E-EL-H0741. The detection limit ranges (15.63-1000 pg/mL). Minimal detection limit was 9.38 pg/mL.

Statistical analysis

Data were collected, revised, coded and entered to the IBM statistical package for social science (SPSS) version 20.0 of the software into a computer system for analysis (IBM Corp, Armonk, NY). Data was presented and suitable analysis was done according to the type of data obtained for each parameter.

Descriptive statistics of the study participants

Table 1 summarizes the descriptive data of all subjects as regard demographic data (age, sex, family history and smoking).

Table 1: Descriptive data of all subjects as regard demographic data.

Group	Patients (*n* = 44)		Group A Cases in Relapse (*n*=22)		Group B Cases in Remission (*n*=22)		control	
Parameter	No.	%	No.	%	No.	%	No	%
Sex								
Male	7	15.9	2	9.1	5	22.7	5	22.7
Female	37	84.1	20	90.9	17	77.3	17	77.3
Age (years)								
Min. – Max.	18.0 – 45.0		22.0–45.0		18.0 – 45.0		18.0 – 45.0	
Mean ± SD.	32.0 ± 8.24		34.05±5.90		29.95 ± 9.78		31.36 ± 8.16	
Median (IQR)	32.50(25.0 – 39.0)		34.0(30.0–38.0)		29.0 (21.0 – 40.0)		33.50(24.0 – 38.0)	
Smoking								
No	39	88.6	19	86.4	20	90.9	-	
Yes	5	11.4	3	13.6	2	9.1	-	
Family history of MS								
No	36	81.8	15	68.2	21	95.5	-	
Yes	8	18.2	7	31.8	1	4.5	-	

IQR: Inter quartile range; SD: Standard deviation.

Results of NFL levels & clinical data:

Comparative statistics between patients and control groups revealed non-significant difference as regard serum level of NFL, sex and age variations.

The mean level of serum NFL in patients was 37.66 ± 31.46. Conversely in the control group the mean level of NFL was 22.36±6.99 (Table 2).

Table 2: Statistical analysis of NFL mean levels, sex and age among the cases and control groups.

Group	Patients (*n* = 44)		Control(*n* = 22)		Test of Sig.	*p*	Significance
Parameter	No.	%	No.	%			
Sex							
Male	7	15.9	5	22.7	χ^2=0.458	FEp=0.515	NS
Female	37	84.1	17	77.3			
Age (years)							
Min. – Max.	18.0 – 45.0		18.0 – 45.0				NS
Mean ± SD.	32.0 ± 8.24		31.36 ± 8.16		t=0.297	0.768	
Median (IQR)	32.50(25.0 – 39.0)		33.50(24.0 – 38.0)				
Serum NFL							
Min. – Max.	15.0 – 125.0		15.0 – 35.0				
Mean ± SD.	37.66 ± 31.46		22.36 ± 6.99		U=361.50	0.094	NS
Median (IQR)	24.0 (17.0 – 36.50)		19.50 (16.0 –29.0)				

IQR: Inter quartile range; SD: Standard deviation; t: Student t-test; χ^2 : Chi square test; FE: Fisher Exact; U: Mann Whitney test; NS: non significant

P: *p value* for comparing between the two studied groups.

Comparative statistics between group A and group B revealed significant statistical differences as regard family history of MS, EDSS score, number of relapses and disease duration. Conversely no statistically significant variations (p> 0.05) when comparing both groups in terms of serum NFL level and smoking (Tables 3,4).

Table 3: Comparison between relapse and remission according to clinical data.

Group	Group A Cases in Relapse (*n*=22)		Group B Cases in Remission (*n*=22)		Test of Sig.	*p*	Significance
Parameter	No.	%	No.	%			
Smoking							
No	19	86.4	20	90.9	χ^2=0.226	FEp=1.000	NS
Yes	3	13.6	2	9.1			
Family history of MS							
No	15	68.2	21	95.5	χ^2=5.500*	FEp=0.046*	S
Yes	7	31.8	1	4.5			
Duration of disease (months)							
Min. – Max.	2.0 – 168.0		1.0 – 156.0				
Mean ± SD.	41.64 ± 44.63		20.73 ± 34.60		U=141.50*	0.018*	S
Median (IQR)	30.0(12.0 – 60.0)		10.50(3.0 – 4.0)				
No. of relapses							
Min. – Max.	2.0 – 20.0		1.0 – 7.0				
Mean ± SD.	5.50 ± 4.25		3.27 ± 1.96		U=148.000*	0.025*	S
Median (IQR)	4.50 (3.0 – 6.0)		3.0 (2.0 – 5.0)				
EDSS score							
Min. – Max.	1.0 – 5.0		1.0 – 4.0				
Mean ± SD.	3.20 ± 1.12		2.23 ± 0.92		U=120.500*	0.003*	S
Median (IQR)	3.0 (2.0 – 4.0)		2.0 (2.0 – 3.0)				
Serum NFL							
Min. – Max.	15.0 – 85.0		15.0 – 125.0				
Mean ± SD.	26.55 ± 15.50		48.77 ± 39.09		U=165.0	0.070	NS
Median (IQR)	20.50(16.0 – 33.0)		29.50(17.0 – 87.0)				

IQR: Inter quartile range; SD: Standard deviation; χ^2: Chi square test; MC: Monte Carlo; FE: Fisher Exact; U: Mann Whitney test; t: Student t-test

P: *p value* for comparing between the two studied groups; NS: non-significant; S: significant; *: Statistically significant at $p \leq 0.05$

Table 4: Descriptive statistics of the cases groups and control group as regard NFL levels

Serum NFL (pg/dL)	Patients (*n* = 44)	Group A Cases in Relapse (*n*=22)	Group B Cases in Remission (*n*=22)	Control (*n* = 22)
Min. – Max.	15.0 – 125.0	15.0 – 35.0	15.0 – 125.0	15.0 – 35.0
Mean ± SD.	37.66 ± 31.46	26.55±15.50	48.77 ± 39.09	22.36±6.99
Median (IQR)	24.0 (17.0 – 36.50)	20.50 (16.0–33.0)	29.50(17.0 – 87.0)	19.50(16.0–29.0)

IQR: Inter quartile range SD: Standard deviation

To investigate the NFL association with different clinical parameters, correlation studies were done using Pearson's method between serum level of NFL and the various parameters examined in MS cases collectively and among each group (group A and B). There was in general positive correlation between serum level of NFL and the number of relapses, the duration of disease, age and EDSS score (r 0.007, r 0.084, r 0.277 and r 0.218) respectively. Among group A, the correlations between serum NFL level and age, number of relapses, EDSS score and disease duration were positive (r 0.272, r 0.353, r 0.382, r 0.505) respectively. In group B, positive correlation between NFL levels and age and EDSS score (r 0.350, r 0.486), no significant correlation was found between NFL levels and the duration of the disease or the number of relapses (Table 5).

Table 5: Correlation between Serum NFL and different parameters in each patient group.

Serum NFL		Age (years)	Duration of disease (months)	No. of relapses	EDSS score
Patients (*n*= 44)	r_s	0.277	0.084	0.007	0.218
	p	0.069	0.588	0.964	0.155
in Relapse (*n*=22) (Group A)	r_s	0.272	0.505	0.283	0.382
	p	0.221	0.017*	0.107	0.079
in Remission (*n*=22)(Group B)	r_s	0.350	-0.035	-0.005	0.486
	p	0.111	0.876	0.982	0.022*

DISCUSSION

For young individuals, multiple sclerosis is the most prevalent non-traumatic debilitating illness[5]. Multiple sclerosis relapse is characterized by recurring bouts of inflammatory demyelination in the brain and spinal column. These episodes can either stay asymptomatic (i.e., subclinical) or be accompanied by acute non-specific neurological symptoms like pain or tiredness. According to brain MRI measurements, the great majority (~90%) of localized inflammatory lesions in RRMS are caused by subclinical lesion activity rather than overt neurological symptoms[6,7].

Neurofilament light chain has the benefit of being abundant which represents the state of degeneration that happens at later stages of MS and neuronal damage from neuroinflammation. It may be employed as a quantifiable single biomarker and gives a prognostic value[8]. According to new recommendations "Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria" the importance of CSF diagnostic in MS diagnosis has decreased[9]. Blood-based biomarkers were therefore far more useful for routine long-term illness monitoring[10]. From that point we aimed to assess the diagnostic and prognostic value of serum NFL as a predictor biomarker of disease activity in patients presenting with RRMS in an attempt to throw light on a new easier accessible marker for MS patients. The present study is a case control study that was conducted at Ain Shams University Hospitals on 66 subjects further classified as 22 RRMS patients in remission, 22 RRMS patients in relapse and 22 age and sex matched controls who were neurologically free. All subjects in the study were subjected to the measurement of serum NFL by ELISA assay.

In our studied population, the serum mean level of NFL in patients is higher than control with no statistical significant variation between them (p= 0.094). This finding came in consistency with a meta-analysis done in 2019 by ***Renan Barros et al***., they reported that NFL could not be a promising candidate as an MS diagnosis biomarker owing to the significant overlap in the findings between patients and controls, this meta-analysis identified 10 studies comparing serum and CSF NFL between MS patients and controls[11].

When sNFL was measured using the Single Molecular Array method (SiMoA) ***Niiranen et al.*** (2024) revealed that no statistically significant difference was seen between patients with RRMS and healthy controls. They also emphasized that neither serum NFL nor CSF NFL appeared to be helpful in the diagnosis of multiple sclerosis. It was also mentioned that when combined with clinical and radiological data NFL levels may be a useful indicator of future disease activity. Its capacity to evaluate prognosis and track disease activity on an individual basis however still needs more clarification[12].

In contrast to these findings, ***Kuhle et al***. (2016) who assessed sNFL by Electrochemiluminescence (ECL) reported that sNFL levels at baseline in RRMS were significantly different from the control group. They also conducted a comparison between a commonly used conventional ELISA for NFL and two other methods; an Electrochemiluminescence-based assay and the SiMoA method using CSF and serum samples of clinical importance. The study found that multiple sclerosis patients exhibited significantly higher serum NFL levels compared to controls when measured with the SiMoA method but not when using the other platforms (ELISA and ECL)[13].

Alagaratnam et al. (2021) also reported that SimoA was the favored technique for measuring NFL particularly when dealing with low or normal levels as SimoA digital immunoassay is 126-folds and 25- folds more sensitive than ELISA and ECL assays respectively for quantification of NFL[14].

Although ***Pafiti et al***. (2023) assessed sNFL level in MS patients using ELISA and SiMoA assays they reported significant variation between MS patients and healthy

controls by ELISA ($p = 0.0006$). Moreover sNFL levels in MS patients were significantly higher than healthy controls by SiMoA ($p = 0.0014$)[15].

In our study patients, sNFL level comparison revealed higher levels in remitted patients than in relapsed patients. ***Barro et al***. (2018) and ***Cantó et al***. (2019) who assumed that the lack of data regarding the last relapse time of remission group as they could have a relapse in the duration before sampling could explain this elevation of sNFL in remitted patients[16,17]. In addition, multiple studies in CIS patients reported that increased NFL values in CSF or serum were a supplementary predictor of future disease activity[18].

Similarly ***Cantó et al.*** (2019) associated higher levels of serum NFL levels with relapse within 90 days; this reflected the benefit of sNFL as a retrospective biomarker for studying MS behavior in RRMS patients. Elevated levels of blood NFL following a relapse were detectable for as long as 60 days later. The continued high levels may be associated with a slower rate of breakdown in the blood or persistent release from the brain into the bloodstream[17].

The presence and quantity of new T2-weighted MRI lesions can elevate sNFL levels even in patients who do not exhibit symptoms. ***Bittner et al.*** (2021) demonstrated that sNFL levels linked to concurrent episodes of disease activity, the number of gadolinium-enhancing lesions as well as measures of brain volume and atrophy[19]. Also ***Johnsson et al***. (2024) found that RRMS or CIS in a relapse reached their peak concentration of sNFL levels 2-12 weeks after onset of relapse. Then it started a slow and steady decline, so they considered this duration protective against false negative results. In addition patients suffering from a relapse and no contrast-enhanced lesions had lower sNFL than patients suffering from a relapse with contrast enhanced lesions. The fluctuation in sNFL levels likely resulted from biological processes including metabolism and waste removal combined with the severity, duration, frequency of relapses and the extent of lesions visible on MRI scans[20].

The discrepancies between our results and others can be explained by the lack of baseline sNFL assessment and the follow up by serial prospective measurement of sNFL.

In our study, a significant correlation was evident in the serum level of NFL between the two patients groups as regard EDSS score. This matches a study done by ***Barro et al***. (2018) who studied 259 patients and reported significant positive associations of sNFL with EDSS as well as with occurrence of a relapse within 120 days from sampling[16].

Similarly Canto et al. (2019) who measured serum NFL in different clinical subtypes of MS at baseline and annually every 5 years for up to 12 years, found that baseline sNFL levels showed significant associations with EDSS score. There was no association between sNFL levels and future EDSS worsening, this could be resulted from the delay in the development of disability following nerve damage[17].

In accordance with the previous finding, ***Bittner et al***. (2021) ran larger studies on 814 RRMS and CIS patients who were assessed at baseline and up to four years follow-up and 607 RRMS and progressive patients with a median of 6.5 years follow up clarified that the EDSS score and sNFL levels were weakly, yet significantly associated[21].

However ***Jabbar et al***. (2024) disclosed that there were no significant correlations between serum neurofilament light and heavy chains levels and EDSS, disease activity, type, and duration. So it cannot be considered a biomarker for MS disease activity and severity[22].

CONCLUSION AND RECOMMENDATIONS

Based on our analysis we are not able to conclude a significant diagnostic or even prognostic performance for sNFL among RRMS patients when measured by ELISA. Our recommendations for NFL assessment to be done in serial dynamic manner both baseline and longitudinal changes are necessary in validation of sNFL predictive power reflected on patients' early treatment optimization. Further studies on larger scale using SiMoA assay are recommended for better understanding of disease behavior and subsequent changes in the marker level which can aid to establish a normative database containing a reference range for sNFL among all age groups.

CONFLICT OF INTEREST

There are no conflicts of interest.

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None.

AUTHOR CONTRIBUTION

We declare that all listed authors have made substantial contributions to all of the following three parts of the manuscript:

- Research design, or acquisition, analysis or interpretation of data.

- Drafting the paper or revising it critically.

- Approving the submitted version.

We also declare that no one who qualifies for authorship has been excluded from the list of authors.

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مستوي بروتين الخيوط العصبية (السلسلة الخفيفة) في الدم في مرضى التصلب المتعدد كدليل على نشاط المرض

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الخلفية: سلسلة الخيوط العصبية الخفيفة هي بروتين عصبي هيكلي يعكس حالة الإصابة العصبية الناتجة عن التهاب الأعصاب والتنكس الذي يحدث في التصلب المتعدد. توجد أنواع فرعية مختلفة من التصلب المتعدد، وأكثرها شيوعًا هو النمط الانتكاسي-المتحسن.

هدف الدراسة: تهدف الدراسة الحالية إلى تقييم القيمة التنبؤية للعلامة الحيوية الخيوط العصبية الخفيفة في الدم كمؤشر لنشاط المرض والنتائج السريرية.

المواد والطرق: تم إجراء دراسة حالة-ملاحظة على 44 مريضًا بالنمط الانتكاسي-المتحسن من التصلب المتعدد و22 فردًا سليمًا في الظاهر. تم إجراء الدراسة في مستشفى جامعة عين شمس، في كل من قسم الأعصاب (وحدة التصلب المتعدد) وقسم التشريح المرضي (وحدة المناعة)، وذلك خلال الفترة ما بين أغسطس ٢٠٢٣ ويناير ٢٠٢٤.

النتائج: بالمقارنة مع المجموعة الضابطة، لم يظهر مرضى النمط الانتكاسي-المتحسن من التصلب المتعدد اختلافًا إحصائيًا مهمًا في مستوى الخيوط العصبية الخفيفة في الدم (p=0.094). تم تقسيم المرضى إلى مجموعتين وفقًا للأعراض السريرية، الى المرضى في نوبة الانتكاس والمرضى في مرحلة التحسن. كشفت الإحصائيات المقارنة بين مجموعة المرضى عن فروق إحصائية مهمة فيما يتعلق بتاريخ العائلة من التصلب المتعدد (p=0.046)، ودرجة الإعاقة البدنية بسبب المرض (p=0.003)، وعدد الانتكاسات (p=0.025)، ومدة المرض(p=0.018).

الخلاصة: تشير الدراسة الحالية إلى أن مستوى الخيوط العصبية الخفيفة في الدم ليس علامة حيوية مفيدة في التنبؤ بتفاقم المرض ونشاطه بين مرضى النمط الانتكاسي-المتحسن من مرض التصلب المتعدد. أيضا يوجد تداخل بين مستويات الخيوط العصبية الخفيفة في المرضى والمجموعة الضابطة.