

Elevated Serum Neurofilament Light Chain in Hemodialysis Patients with Pruritus

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ABSTRACT

Background: Hemodialysis-related pruritus is a widespread, troubling issue with a complex pathogenesis, including neuropathy. The neurofilament light chain (NfL) is a neurocytoskeleton component that increases in neurodegenerative and polyneuropathy illnesses. **Objectives:** The aim of the current study was to evaluate the serum levels of NfL in pruritic hemodialysis patients. **Patients and methods:** Sixty patients receiving regular hemodialysis were selected, and divided into 2 equal groups (30 patients with pruritus, and 30 patients without pruritus), and a control group of 20 healthy individuals who were age and sex matched. With the help of the Visual Analogue Scale (VAS), pruritus intensity was evaluated. Hemoglobin, urea, creatinine, calcium, phosphorus, and parathormone laboratory tests were performed. Additionally, the serum NfL level was determined using ELISA.

Results: Serum NfL levels varied significantly between the study groups ($P=0.001$), with pruritic hemodialysis patients having the highest median level, followed by those without pruritus, and the control group having the lowest level. There was a significant positive correlation between the duration and intensity of itching and blood NfL ($P=0.001$). **Conclusion:** Increased NfL levels in hemodialysis patients with pruritus support the neuropathy hypothesis as a source of pruritus in end-stage renal disease.

Keywords: Neurofilament light chain, Hemodialysis, Pruritus.

INTRODUCTION

Patients with advanced chronic kidney disease (CKD) frequently have pruritus, which affects 15% to 49% of patients prior to dialysis and 50% to 90% of patients during dialysis⁽¹⁾. Uremic pruritus still has an unclear pathogenesis. Among the many possibilities that were taken into consideration was neuropathy⁽²⁾.

Neurofilaments are neuronal cytoskeletal proteins that include neurofilament light (NfL), medium, and heavy chains. NfL is involved in axonal development and stability⁽³⁾. Neuroaxonal injury in peripheral nerves causes the release of NfL into the extracellular space and peripheral circulation⁽⁴⁾. The aim of the current study was to evaluate the serum levels of NfL in pruritic hemodialysis patients.

PATIENTS AND METHODS

A case-control study was conducted and included 80 subjects recruited from Outpatient Clinics of Dermatology & Andrology Department and the Hemodialysis unit, Benha University Hospitals, during the period from January 2022 to July 2022.

Participants were divided into 3 groups: a first group of 30 hemodialysis patients with chronic pruritus, a second group of 30 hemodialysis patients without pruritus, and a third group of 20 healthy, age- and sex-matched controls. Patient groups comprised patients who had been receiving regular hemodialysis for more than 6 months. Patients with chronic illnesses, such as those related to the nervous system, the liver, the biliary system, cancer, other pruritic skin conditions, or those who were pregnant or lactating were not included.

All participants were subjected to a full and detailed clinical history with a focus on the relation of itching to dialysis sessions and the duration of dialysis. The severity of itching was estimated using the Visual Analog Scale (VAS) categories: 0 = no itching, <4 =

mild itching, $\geq 4 - < 7$ = moderate itching, $\geq 7 - < 9$ = severe itching, and ≥ 9 = very severe itching⁽⁵⁾.

Laboratory assay:

Blood samples were taken for analysis of hemoglobin concentration, parathormone, calcium, phosphorus, urea, creatinin. Serum NfL levels were measured using ELISA kits (supplied by Sinogeneclon Biotech Co., Ltd).

Ethical Approval:

The Ethical Institutional Review Board at the Faculty of Medicine at Benha University (MS 32-12-2021) approved the study. After explaining our research objectives, written informed consent was obtained from each participant. This study was conducted in compliance with the code of ethics of the world medical association (Declaration of Helsinki) for human subjects.

Statistical Analysis

The collected data were introduced and statistically analyzed by utilizing the Statistical Package for Social Sciences (SPSS) version 20 for windows. Qualitative data were defined as numbers and percentages. Pearson coefficient, Fisher's exact test and Chi-Square for Linear Trend were used for comparison between categorical variables as appropriate. Quantitative data were tested for normality by Kolmogorov-Smirnov test. Quantitative variables were described as mean and standard deviation (SD) or median and interquartile range (IQR), and independent sample t-test/Mann-Whitney test was used for comparison between 2 groups. Analysis of variance test "ANOVA" or Kruskal Wallis test was used to compare more than 2 groups with each other. P value ≤ 0.05 was considered to be statistically significant.

RESULTS

There were no statistical significant differences among the study groups as regard to the age and sex (**Table 1**).

Table (1): Comparison between patients and healthy group regarding age and gender.

Variables		Patient Group (n=60)		Control Group (n=20)		Test value	P-Value
Age (years)	Mean ± SD	53.7 ± 10.9		50.9 ± 8.9		t= 1.1	0.3 (NS)
	Median (Min. - Max.)	53.5 (36-80)		49.5 (37-65)			
Gender	Male (n, %)	36	60	11	55	X ² = 1.5	0.7 (NS)
	Female (n, %)	24	40	9	45		

t independent t test, X² Chi Square test, NS non-significant.

The current study demonstrated highly significant differences among the three groups as regard to serum NfL concentrations, calcium, phosphorus, urea, creatinine and parathormone with the highest levels in patient with pruritus followed by patients on hemodialysis without pruritus and the least one was the control group (**Table 2**).

Table (2): Comparison of laboratory data among the studied groups.

Variable	Patients with Pruritus (n=30)			Patients without pruritus (n=30)			Control Group (n=20)			Test value	P value
	Median	IQR	Min-Max	Median	IQR	Min - Max	Media	IQR	Min-Max		
Serum NfL concentrations (pg/mL)	458.8	100.8	394-614.5	227.6	17.8	201.3-256	126	9.4	115-145	Kw = 55.4	0.001 HS
Patient with pruritus ≠ patient without pruritus= 0.001, Patient with pruritus ≠ control= 0.001, Patient without pruritus ≠ control= 0.001											
Calcium (md/dL)	7.9	1.5	6.3-9.2	9.2	1.3	6.7-10.2	9.1	1.4	8-10.3	Kw = 34.9	0.001 HS
Patient with pruritus ≠ patient without pruritus= 0.001, Patient with pruritus ≠ control= 0.001, Patient without pruritus ≠ control= 0.											
Urea (md/dL)	177	80.5	62-285	11.2	36	11.5-225	8.6	5.6	5.9-24	Kw= 34.2	0.001 HS
Patient with pruritus ≠ patient without pruritus= 0.001, Patient with pruritus ≠ control= 0.001, Patient without pruritus ≠ control= 0.001											
Creatinine (md/dL)	10.6	2.5	6.5-19.3	92.5	36	55-209	1	0.4	0.5-1.5	Kw= 3.3	0.001 HS
Patient with pruritus ≠ patient without pruritus= 0.001, Patient with pruritus ≠ control= 0.001, Patient without pruritus ≠ control= 0.001											
Parathormone (pg/mL)	354	348	106-950	216	184.3	60-617	22	10.8	12-50	Kw = 21.7	0.001 HS
Patient with pruritus ≠ patient without pruritus=0.02, Patient with pruritus ≠ control= 0.001, Patient without pruritus ≠ control= 0.001											
Hemoglobin (g/dL)	9.6	1.5	8.2-13	9.3	1.3	7.4-13.9	11.6	1.6	10-13	Kw = 4.3	0.2 NS
Phosphorus (md/dL) (Mean ± SD)	8.7 ± 1.7			8.2 ± 1.9			3.4 ± 0.74			F= 76.8	0.001 HS
Patient with pruritus ≠ patient without pruritus= 0.9, Patient with pruritus ≠ control=0.001, Patient without pruritus ≠ control=0.9											

Median, range, IQR(interquartile range): Non-parametric test.

KW kruskal wallis test, F ANOVA test, HS highly significant, NS non-significant.

There was significant difference between different grades of pruritus and control group regarding serum NfL concentrations (**Table 3**).

Table (3): Comparison between patients with different severity grades of pruritus and controls regarding serum NfL concentrations.

Variable	Patient group				Control group	Test value	P Value
	No pruritus	Mild pruritus	Moderate pruritus	Severe Pruritus			
Serum NfL (pg/mL) Median (Min.- Max.)	227.4 (201.3-256)	456.9 (394-517.6)	465.5 (411.5-614.5)	465.4 (427.5-603)	126 (115-145)	KW = 69.6	0.001

No pruritus ≠ Mild pruritus= 0.001, No pruritus ≠ moderate pruritus= 0.001, No pruritus ≠ severe pruritus= 0.001, No pruritus ≠ Control group= 0.001, mild pruritus ≠ moderate pruritus=0.4, mild pruritus ≠ severe pruritus= 0.3, mild pruritus ≠ Control group= 0.001, moderate pruritus ≠ severe pruritus=0.8, moderate pruritus ≠ Control group=0.001
IQR(interquartile range):: Non-parametric test. KW: Kruskal Wallis test

ROC curve revealed cut-off value for serum NfL between pruritus patients and non-pruritus group was ≤427 pg/mL with sensitivity (86.7%), specificity (100%), AUC=0.8 and 95% CI (0.67-0.89) (**Table 4, Figure 1**).

Table (4): Specificity and sensitivity of serum NfL concentrations in detecting pruritus.

Variable	AUC	Cut- Off Point (pg/mL)	Sensitivity	Specificity	PPV	NPV	Accuracy	95% CI	P-Value
serum NfL	0.8	427	86.7	100	100	92.6	0.95	0.67-0.89	0.02 S

S significant

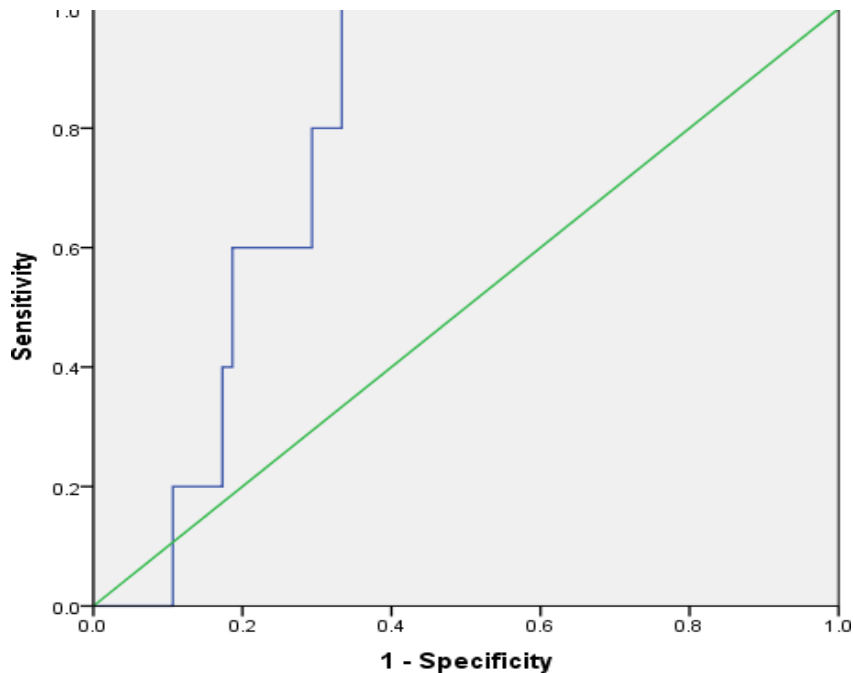


Figure (1): Roc Curve for serum NfL in detecting pruritus.

There was significant positive correlation between serum NfL and VAS score of pruritus (**Figure 2**).

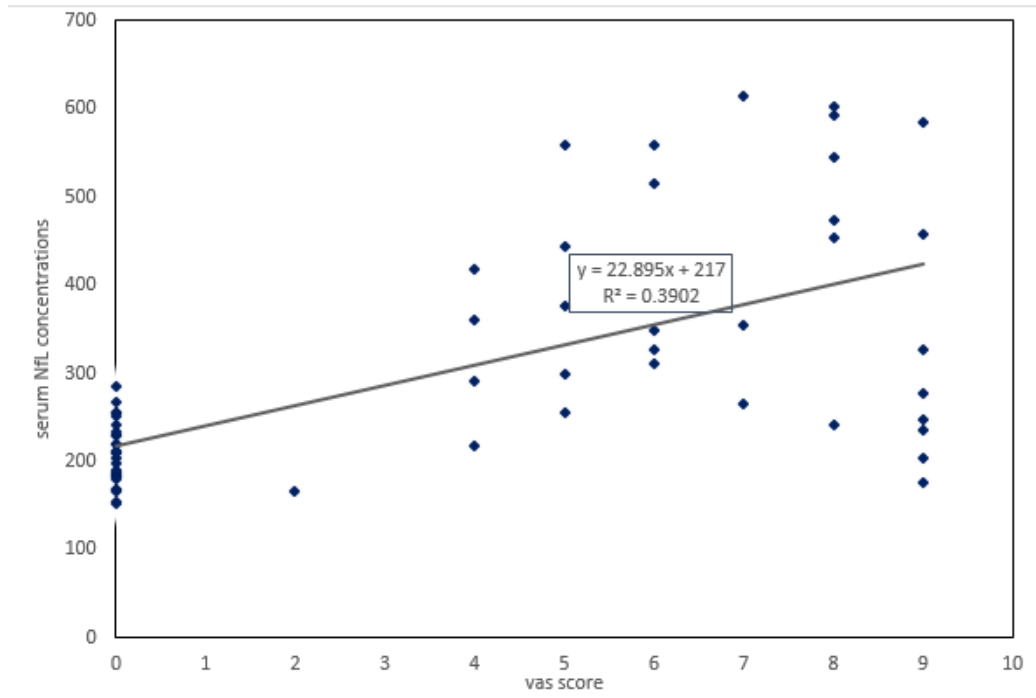


Figure (2): Scatter plot showing significant positive correlation between serum NfL concentrations and VAS score (P=0.001).

Significant positive correlations were observed between serum NfL concentrations and duration of dialysis, duration of pruritus, VAS score of pruritus, calcium, phosphorus, Parathormone, urea and creatinine (Table 5).

Table (5): Correlation between serum NfL and the different clinical and laboratory variables among studied groups.

Variable	Serum NfL concentration	
	Rho	P –value
Age (years)	0.7	0.5
Duration of dialysis (years)	0.6	0.001(HS)
Duration of pruritus (months)	0.8	0.001(HS)
Vas score	0.9	0.001(HS)
Calcium (md/dL)	-0.47	0.001(HS)
Phosphorus (md/dL)	0.73	0.001(HS)
Urea (md/dL)	0.7	0.001(HS)
Creatinine (md/dL)	0.7	0.001(HS)
Parathormone (pg/mL/)	0.7	0.001(HS)

HS: highly significant

DISCUSSION

Neuropathic itching is caused by neural injury without any skin changes. It accounts for 8-19% of chronic pruritus cases (6). There are numerous causes of peripheral neuropathy (PN), including nutritional

deficits and toxic neuropathies (7). PN occurs in 60-100% of patients who are submitted to dialysis due to CKD (8).

A systematic review and meta-analysis settled that blood level of NfL may be a beneficial indicator of neuronal injury in patients with PN (9). Louwsma et al. (10) revealed that NfL levels are increased in patients with polyneuropathy in amyloidosis. Maalmi et al. (11) indicated that higher NfL levels are associated with diabetic sensorimotor polyneuropathy. Furthermore, the concentration of NfL increases in parallel with the serum creatinine (12).

According to the current study, hemodialysis patients have considerably higher serum NfL levels than the control group. At the same time, NfL is positively correlated with laboratory changes that occur with renal failure. In the same context, Korley et al. (13) showed that worse renal function was linked to increased serum NfL levels. On the other hand, Hermansson et al. (14) observed that among patients with HIV infection, plasma NfL level is not linked with serum creatinine levels.

Although the exact method by which renal function impacts blood NfL dynamics is unknown, there are some theories. One theory is that the kidneys clear blood NfL (12). Another explanation is the decline in renal function, which leads to low levels of erythropoietin and active vitamin D and the loss of its neuroprotective properties (15).

According to our findings, hemodialysis patients who experienced pruritus had considerably higher NfL than hemodialysis patients who did not. Additionally, hemodialysis patients showed a substantial positive link between NfL and the degree of pruritus, with a

cut-off point (427pg/mL) at which there is a higher probability of developing pruritus.

LIMITATIONS

Small size of study groups, single hemodialysis center, and lack of neurological assessment were the main defective points in the current research.

CONCLUSION

The elevated serum NfL in hemodialysis patients who experience pruritus gives support to the idea that neuropathy plays a role in the development of pruritus.

Financial support and sponsorship: Nil.

Conflict of interest: Nil.

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