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Research Article

Evaluation of Nerve Conduction and Cognitive Function in Hypothyroidism and their Correlation with Serum Neurofilament Light Chain

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Abstract

Background: Hypothyroidism is an endocrine disorder defined by insufficient amounts of thyroid hormone. It can affect the peripheral nervous system, evaluated using electrodiagnostic studies and serum neurofilament light chain (NfL), a biomarker of neuronal injury. Cognitive function, including memory and attention, may also be impaired and assessed using the Montreal Cognitive Assessment (MoCA) tool. ***Objectives***: To assess peripheral neuropathy and cognitive dysfunction in hypothyroid patients and to evaluate their association with serum NfL levels. ***Methods***: A case-control study was conducted at Ghazi Al-Hariri Hospital in Baghdad from August 1, 2024, to April 1, 2025, involving 40 hypothyroid patients and 40 controls. All participants underwent sensory and motor nerve conduction studies and MoCA assessment. Serum NfL levels were measured in 20 patients and 20 controls using the ELISA technique. ***Results***: Hypothyroid patients showed significantly higher serum NfL levels (26.49±8.18pg/mL) compared to controls (9.6±1.64pg/mL; $p<0.001$). Nerve conduction studies revealed slower conduction velocities and prolonged latencies, particularly in the median and sural nerves ($p<0.001$). Cognitive dysfunction (MoCA < 26) was found in 47.5% of hypothyroid patients and was associated with higher NfL levels (30.23±7.49pg/mL *vs.* 20.87± 5.77pg/mL; $p=0.008$). ***Conclusions***: Hypothyroidism is associated with peripheral neuropathy and cognitive impairment; both linked to elevated serum NfL levels. NfL may serve as a non-invasive biomarker for neurological complications in hypothyroid patients.

Keywords: Enzyme-linked immunosorbent assay, Hypothyroidism, Montreal cognitive assessment, Nerve conduction study, Serum neurofilament light chain.

تقييم التوصيل العصبي والوظيفة المعرفية في قصور الغدة الدرقية وارتباطهما بالسلسلة الخفيفة للخيوط العصبية في الدم

الخلاصة

الخلفية: قصور الغدة الدرقية هو اضطراب في الغدد الصماء يعرف بكميات غير كافية من هرمون الغدة الدرقية. يمكن أن يؤثر على الجهاز العصبي المحيطي، ويتم تقييمه باستخدام دراسات التشخيص الكهربائي والسلسلة الخفيفة للخيوط العصبية في الدم (NfL)، وهي علامة حيوية لإصابة الخلايا العصبية. قد تضعف الوظيفة المعرفية، بما في ذلك الذاكرة والانتباه، وتقييمها باستخدام أداة مونتريال للتقييم المعرفي (MoCA). **الأهداف**: تقييم الاعتلال العصبي المحيطي والخلل الوظيفي المعرفي لدى مرضى قصور الغدة الدرقية وتقييم ارتباطهم بمستويات NfL في الدم. **الطرائق**: أجريت دراسة حالة وشواهد في مستشفى غازي الحريري في بغداد من 1 أغسطس 2024 إلى 1 أبريل 2025، شملت 40 مريضا بقصور الغدة الدرقية و 40 ضابطا. خضع جميع المشاركين لدراسات التوصيل الحسي والحركي للأعصاب وتقييم MoCA. تم قياس مستويات مصل NfL في 20 مريضا و 20 ضابطا باستخدام تقنية ELISA. ***النتائج***: أظهر مرضى قصور الغدة الدرقية مستويات أعلى بكثير من NfL في الدم (26.49±8.18 بيكوغرام/مل) مقارنة بالمجموعة الضابطة (9.6±1.64 بيكوغرام/مل. $p<0.001$). كشفت دراسات التوصيل العصبي عن سرعات توصيل أبطأ وزمن انتقال طويل ، خاصة في الأعصاب المتوسطة والسورالية ($p<0.001$). تم العثور على الخلل الوظيفي المعرفي (MoCA < 26) في 47.5٪ من مرضى قصور الغدة الدرقية وارتبط بمستويات أعلى من NfL ($p = 0.008$). **الاستنتاجات**: يرتبط قصور الغدة الدرقية بالاعتلال العصبي المحيطي والضعف الإدراكي؛ كلاهما مرتبط بارتفاع مستويات NfL في الدم. قد يكون NfL بمثابة مؤشر حيوي غير جراحي للمضاعفات العصبية لدى مرضى قصور الغدة الدرقية.

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INTRODUCTION

Thyroid hormones are essential for almost every human tissue and organ's growth, development, and metabolic regulation throughout life [1]. The thyroid gland, located in the anterior neck, produces hormones that are essential for sustaining growth, promoting metabolic processes, and permitting tissue development throughout life. Thyroxine (T4) and triiodothyronine (T3), the two main hormones secreted by the thyroid gland, are produced from iodine and the amino acid tyrosine [2,3]. Hypothyroidism, an endocrine disorder defined by inadequate thyroid hormone production, can be classified into primary, secondary, and tertiary types. Primary (overt) hypothyroidism is marked by elevated thyroid-stimulating hormone (TSH) levels and reduced free thyroxine (FT4) concentrations. Secondary hypothyroidism arises from insufficient TSH production, while central hypothyroidism encompasses both secondary and tertiary hypothyroidism due to pituitary or hypothalamic

dysfunction. Subclinical hypothyroidism, often representing an early stage of the disease, may either stabilize, resolve spontaneously, or progress to overt hypothyroidism over time. [4] Patients with subclinical hypothyroidism have TSH levels above the normal range (5-10 µIU/mL) but free T4 levels within the normal range [5]. Approximately 90% of hypothyroidism cases in iodine-sufficient areas are caused by Hashimoto's thyroiditis or thyroid failure after thyrotoxicosis surgery. Hypothyroidism affects more women than men [6], with prior research reporting prevalence rates of 3.2% in Baghdad and 12.5% in Basrah [7]. Thyroid hormones, particularly during late fetal and early childhood periods, are fundamental for nervous system development. They promote neural differentiation, axonal and dendritic growth, and synaptogenesis and stimulate enzymes involved in neurotransmitter production and receptor development. Furthermore, thyroid hormones regulate galactosyl sialyl transferase activity, crucial for myelin synthesis and effective nerve conduction [8]. Hypothyroidism adversely affects both the central and peripheral nervous systems, manifesting in a range of neurological symptoms. Cognitive dysfunction, such as memory deficits and reduced concentration, arises due to disrupted neuronal activity from thyroid hormone deficiency. Additionally, depressive symptoms and general fatigue are frequently reported, reflecting the hormones' role in neurotransmitter regulation and overall brain metabolism [9]. If left untreated, cognitive deficits associated with hypothyroidism—affecting attention, memory, abstract thinking, and problem-solving abilities—may progressively worse, increasing the risk of severe neurocognitive impairment and dementia [10]. The Montreal Cognitive Assessment (MoCA) is a widely utilized screening tool valued for its simplicity and clinical applicability in detecting cognitive alterations. It assesses multiple domains, including executive function, memory, language, attention, and visuospatial abilities, and is recognized as a reliable instrument across diverse neurological disorders [11]. Neuromuscular complications occur in approximately 20–80% of patients with thyroid dysfunction. Peripheral neuropathy is common, presenting with diminished reflexes, proximal muscle weakness, numbness, paresthesia, sensory loss, and delayed muscle responses. These manifestations are thought to result from dysfunction at the neuronal cell body, axonal, or myelin levels, contributing to slowed nerve conduction and reduced amplitudes. Distal sensory nerves, particularly the sural and median nerves, are often the earliest affected. Moreover, carpal tunnel syndrome, due to median nerve entrapment, is a significant cause of neuropathic symptoms in hypothyroid patients [12]. Many patients with thyroid disorders and associated neuropathy remain asymptomatic. Clinical presentations such as mononeuropathy and sensorimotor polyneuropathy have been linked to hypothyroidism, with the severity of symptoms correlating with both the duration and extent of hormonal deficiency [13]. Nerve conduction studies (NCS) are diagnostic tests used to evaluate the function of the peripheral nervous system by measuring the speed and strength of electrical signals in nerves [14]. Neurofilament light chain (NfL) is a cytoskeletal protein found in mature neuronal axons, providing structural stability and determining axonal diameter. It is released upon neuronal injury, serving as a biomarker for neuronal damage. NfL is more abundant in large, myelinated axons, facilitating a faster conduction velocity. It can be employed to evaluate disease progression and neuronal damage severity. NfL has been widely utilized as a biomarker for diagnosing central nervous system disorders such as dementia and multiple sclerosis. Recent studies have also demonstrated elevated serum NfL levels in various peripheral nervous system diseases, including amyloid neuropathy, HIV-associated neuropathy, and diabetic peripheral neuropathy. Given that axonal injury elevates circulating NfL levels, this biomarker offers a non-invasive tool to assess disease severity, monitor therapeutic response, and track the progression of peripheral neuropathies [15,16]. Studies support the use of serum NfL as a blood-based biomarker for neuronal injury in patients with peripheral neuropathies [17]. Additionally, research indicates a positive correlation between age and NfL concentrations, with serum levels increasing by approximately 3.1% for each additional year of life [18]. This study aims to assess the presence of peripheral neuropathy and cognitive dysfunction in patients with hypothyroidism and to examine their correlation with serum neurofilament light chain (NfL) levels. It also seeks to evaluate the potential utility of NfL as a diagnostic and prognostic biomarker for neurological complications associated with hypothyroidism.

METHODS

Study design and setting

This is a case-control study carried out at the Department of Neurophysiology in Ghazi Al-Hariri Hospital in Baghdad during the interval from August 1, 2024, to April 1, 2025. Forty apparently healthy individuals, who visited the neurophysiology department of the hospital for a Nerve Conduction Study (NCS), agreed to be included in the study as controls. A consultant neurophysiologist examined them to exclude any history of neuropathy or any disease that causes neuropathy. The study group included 40 patients with hypothyroidism who presented to the Department of Neurophysiology as referrals from the endocrine unit in Baghdad Teaching Hospital.

Inclusion criteria

Both genders (male and female). Hypothyroid patients who were already diagnosed and on treatment. Patients with low serum levels of total T3 and total T4 and high serum TSH level (newly diagnosed). Patients with normal serum levels of thyroid hormones and high serum TSH levels (subclinical hypothyroid).

Exclusion criteria

Post-menopausal females to exclude the effect of other hormonal imbalances. Pregnant women. Patients with renal insufficiency, liver disease, or any other medical conditions that might be a possible cause of neuropathy (i.e., diabetes mellitus, leprosy, drug-induced neuropathy, family history of neuropathy, malignancy, and neuromuscular disorders). Patients with psychological disorders, dementia, and Alzheimer's disease.

Evaluation and outcome measurements

All participants were evaluated first by taking their detailed past medical history, gender, and age, along with a neurological examination. Body mass index (BMI) in kg/m^2 was calculated for both groups, and their biochemical profile for total T3 (TT3), total T4 (TT4), and thyroid-stimulating hormone (TSH) levels was evaluated using an automated immunoassay analyzer (TOSOH AIA-2000). Normal ranges of serum concentration of TT3, TT4, and TSH were taken to be 0.79-1.58 ng/mL, 4.9-11.0 µg/dL, and 0.38-4.31 µIU/mL, respectively. The required questionnaire was recorded for each participant.

MoCA test

The Arabic version of the standard MoCA was used to conduct cognitive assessments. These tests are available in Arabic on the MoCA website, and we received permission to use them in our research from http://mocatest.org. On a scale of 0 to 30, scores below 26 indicate cognitive impairment, while lower scores indicate poorer cognitive function. Cognitive function is assessed using multiple domains such as visuospatial/executive, naming, memory, attention, language, abstract delayed recall, and orientation. The test was administered in a quiet, isolated section of the department. The assessments were completed in about 10-15 minutes [19,20].

Nerve conduction study

The nerve conduction studies were performed using Natus 2019 Ireland, at Neurophysiology department. The sensory nerve conduction study was performed bilaterally in median nerves of upper limbs and bilaterally in sural nerves of lower limbs, respectively. The nerves examined for the motor nerve conduction study were bilateral median nerves in upper limbs and bilateral common peroneal nerves in lower limbs, respectively. The motor nerve conduction studies included determination of distal motor latencies, motor nerve conduction velocity, and amplitude of the compound muscle action potentials. The sensory nerve conduction studies included determination of sensory latencies and amplitude of sensory nerve action potentials. Patients were lying in a supine position or sitting comfortably with their limbs relaxed, and the skin was adequately prepped with abrasive gel to reduce impedance. Surface electrodes were placed at the appropriate sites, initially nerves were stimulated with low voltage strength of current and gradually increased till we reached a maximal response curve.

Neurofilament light chain protein assessment

Blood samples were collected from 20 participants of each group (hypothyroid patients and controls). Standardized venipuncture procedures were performed in the morning by a trained laboratory technician, who collected 5 mL of venous blood from each participant in gel collection tubes and then allowed it to clot for 10-20 minutes at room temperature before centrifugation at 2000-3000 rpm for 20 minutes. The resultant samples were stored at -20°C until analysis to avoid repeated freeze-thaw cycles. Serum concentrations of neurofilament light chain protein (NfL) were measured using an enzyme-linked immunosorbent assay (ELISA) kit.

Ethical consideration

All patients and controls verbally agreed to participate in the study after being given a detailed explanation of the study plan. The study was approved by the ethics committee of the University of Baghdad's College of Medicine.

Statistical analysis

The collected data were analyzed using Statistical Package for Social Sciences (SPSS) software version 26.0 (Chicago) and Quantspy.org. The continuous data were presented mainly as mean and standard deviation and with median and range for some variables, as they were analyzed for normality of distribution using Shapiro Wilk test. The comparison between means was done using an unpaired t-test and analysis of variance (ANOVA). While categorical variables are presented as frequencies with percentages, the comparison was done using Fisher's exact test and the chi-square test. A *p*-value less than 0.05 was considered a level of statistical significance.

RESULTS

A total of 80 participants were enrolled in this study, including 40 patients with hypothyroidism and 40 apparently healthy controls. As shown in Table 1, the mean age and BMI were slightly higher in patients than in controls, with BMI demonstrating a statistically significant difference. A marked predominance of females was observed in the hypothyroid group (80%), while males were more prevalent among controls (55%). Educational levels also varied significantly between the groups. Thyroid function analysis showed significantly elevated TSH levels and decreased T4 values in the hypothyroid group compared to controls (TSH: 18.74 ± 25.32 *vs.* 2.71 ± 0.82 mIU/mL; T4: 4.69 ± 1.93 *vs.* 7.79 ± 1.53 µg/dl; both $p < 0.001$). T3 levels were marginally lower in patients but did not reach statistical significance ($p = 0.17$).

Table 1: Comparison of demographic data between patients and controls (n=40 in each group).

Parameter		Patients	Controls	*p*-value
Age (year)	Mean±SD	36.33±8.78	34.13±6.91	
	22-30	14(35.0)	15 (37.5)	0.293*
	31-40	11(27.5)	17 (42.5)	
	40-51	15(37.5)	8 (20.0)	
BMI (kg/m^2)	Mean±SD	29.8±4.88	26.4±2.8	
	Normal	6(15.0)	14 (35.0)	<0.001*
	Overweight	9(22.5)	21 (52.5)	
	Obese	25(62.5)	5 (12.5)	
Sex	Male	8(20.0)	22 (55.0)	0.002**
	Female	32 (80.0)	18 (45.0)	
Education	Not educated	7(17.5)	2 (5.0)	
	Primary school	19(47.5)	7 (17.5)	0.009***
	Secondary school	6(15.0)	15(37.5)	
	College	8(20.0)	16(40.0)	

Values were expressed as frequency, percentage and mean±SD. * Chi square test, ** Fisher exact test *** Yates Chi square test.

Neurophysiological studies revealed alterations in nerve conduction parameters. Patients demonstrated significantly slower conduction velocities and prolonged latencies across the motor median, peroneal, and sensory median nerves. For instance, the right motor median nerve conduction velocity was markedly lower in patients than in controls, while proximal latency was prolonged. Similar patterns were observed in left-sided and additional peripheral nerves. (Table 2).

Table 2: Comparison of neurophysiological parameters of the motor and sensory median nerves between patients and controls by unpaired t-test (n=40 in each group)

Parameter	Patients	Controls	*p*-value
Rt. MMN Distal Latency (ms)	3.38±0.81	3.2±0.38	0.201
Rt. MMN Distal Amplitude (mV)	7.65±2.77	9.03±1.03	0.005
Rt. MMN Proximal Latency (ms)	7.45±1.18	6.53±0.46	<0.001
Rt. MMN Proximal Amplitude (mV)	6.91±2.26	8.29±0.93	0.001
Rt. MMN Conduction Velocity (m/s)	51.74±3	65.38±4.15	<0.001
Lt. MMN Distal Latency (ms)	3.47±0.71	3.16±0.31	0.014
Lt. MMN Distal Amplitude (mV)	7.77±2.04	9.03±1.37	0.002
Lt. MMN Proximal Latency (ms)	7.58±0.86	6.53±0.63	<0.001
Lt. MMN Proximal Amplitude (mV)	7.18±1.87	8.24±1.22	0.004
Lt. MMN* Conduction Velocity (m/s)	52.12±3.38	65.29±4.93	<0.001
Rt. SMN* Peak Latency (ms)	3.42±0.65	2.94±0.19	<0.001
Rt. SMN Amplitude (mV)	35.19±17.74	41.84±11.28	0.049
Lt. SMN Peak Latency (ms)	3.42±0.63	2.83±0.18	<0.001
Lt. SMN Amplitude (mV)	37.18±19.38	42.82±11.4	0.118

Values were expressed as mean±SD. *MMN: Motor median nerve, SMN: Sensory median nerve.

Serum neurofilament light chain (NfL) concentrations were significantly higher among hypothyroid patients compared to controls (Table 3).

Table 3: Comparison of serum neurofilament light chain between patients and controls by unpaired t test (n=20 in each group)

Parameter	Patients	Controls	*p*-value
S. NfL chain (pg/mL)	26.49±8.18	9.6±1.64	<0.001

Values were expressed as mean±SD.

Correlation analysis revealed significant associations between serum NfL and various parameters. In patients, NfL correlated negatively with T4 (r = -0.521, *p*= 0.018) and positively with latencies in both the right and left MMN and SMN nerves. (Figure 1).

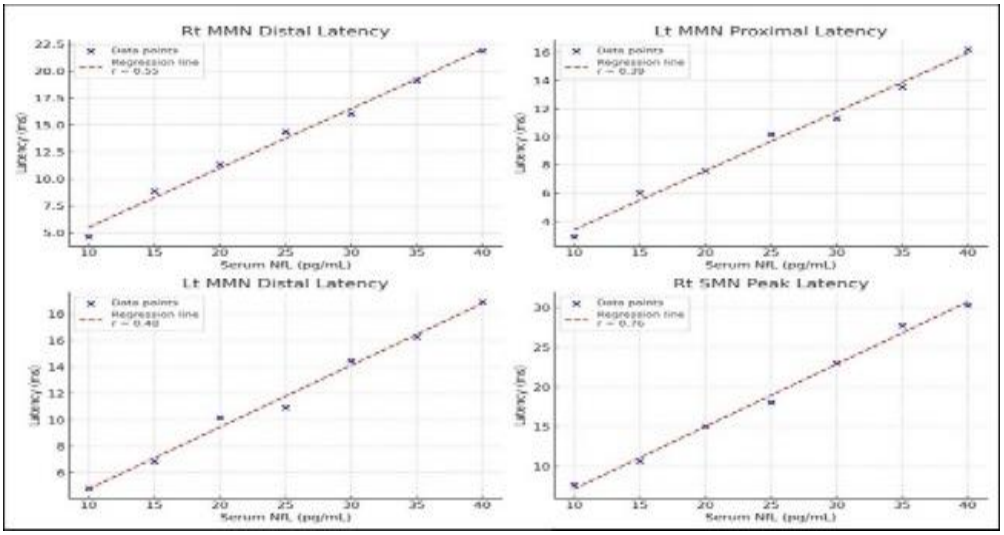

Figure 1: Correlation between serum neurofilament light chain (NfL) levels and nerve conduction latencies of both right and left motor median nerves and right sensory median nerve in hypothyroid patients.

Among controls, NfL was positively associated with age (r = 0.845, $p< 0.001$) and BMI (r = 0.529, $p= 0.016$). Sex-related comparisons within the patient group revealed higher NfL levels in males (34.87 ± 7.04 pg/mL) than females (23.69 ± 6.58 pg/mL; $p= 0.005$). Reflex assessment showed higher NfL concentrations in patients with depressed reflexes (33.7 ± 6.52 pg/mL) compared to those with normal reflexes (24.08 ± 7.34 pg/mL; $p= 0.018$). Cognitive dysfunction was associated with lower T3 concentrations ($p< 0.001$) and higher NfL levels (30.23 ± 7.49 pg/mL in patients with low MoCA scores *vs.* 20.87 ± 5.77 pg/mL in those with normal scores; $p= 0.008$) (Figure 2).

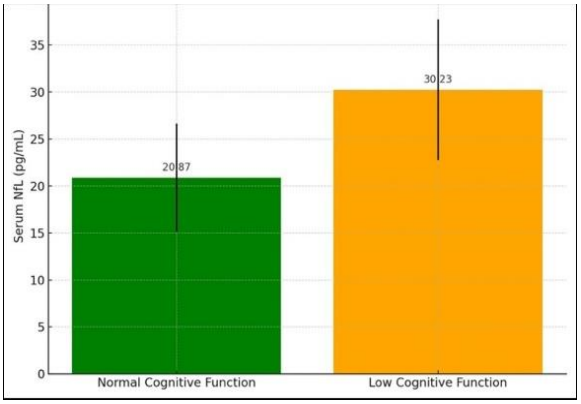

Figure 2: Comparison of serum neurofilament light chain (NfL) levels based on cognitive function in hypothyroid patients.

DISCUSSION

In this study, participants with hypothyroidism had a higher mean age compared to controls, though this was not statistically significant (p=0.293). In contrast, the body mass index (BMI) among hypothyroid patients was more elevated than controls (p<0.001) and consistent with prior literature findings that suggest hypothyroidism, even in its subclinical form, is a known risk factor for gaining weight through decreased basal metabolic rate and altered lipid metabolism. Ibraheem et al. found elevated BMI, waist circumference, and waist-to-hip ratios for patients with both clinical and subclinical hypothyroidism [21]. The sex distribution varied significantly across groups, as more hypothyroid patients were female (80%) as compared to the male (55%) control group (p = 0.002), which was consistent with a regional study indicating that the burden of thyroid disorders differs based on sex, with more women than men exhibiting thyroid dysfunction [22]. The education levels were also significantly different across hypothyroid patients and controls, as hypothyroid patients had a large proportion of patients with a lower education level, which could be a contributing factor for delayed diagnosis and ultimately poorer disease outcomes [23]. The demographic differences also illustrated biological and socioeconomic factors that interact to influence hypothyroidism, emphasizing the importance of early screening and health education initiatives directed towards education levels of patients. This study found significant associations between hypothyroidism and impairment of both peripheral and central neurological functions. Serum neurofilament light chain (NfL) was identified as a sensitive biomarker of neuroaxonal injury and found in higher levels among hypothyroid individuals. Taken together, it would seem that the neuroaxonal injury was due to damage caused by thyroid hormone deficiency, and the high levels of NfL would correlate with that injury. The associations are consistent with prior studies that have highlighted the importance of thyroid hormones for maintaining neuronal structure and functions [24]. The marked slowing of nerve conduction velocities and prolongation of latencies observed in this study represent the impact of thyroid hormone deficiency on peripheral nerve function. The abnormalities of electrophysiological studies are consistent with findings reported by Bhat et al., who demonstrated impaired myelination and nerve conduction in individuals with hypothyroidism [25]. Moreover, the relationship identified between serum NfL and impaired cognitive performance in hypothyroid patients indicates involvement of the central nervous system, for patients with hypothyroidism who exhibited cognitive dysfunction, as assessed by lower MoCA scores, also showed significantly higher serum NfL concentrations. These results underscore the possibility that hypothyroidism plays a significant role in cognitive dysfunction. Mishra et al. found that neuroinflammation is elicited by deficits in thyroid hormones and can impair synaptic signaling and trigger a cascade that impacts cognition [26]. Additionally, the parallel elevation of serum NfL in these patients supports its role as a biomarker for neuronal injury linked to cognitive impairment. The observed reductions in T3 levels and elevated levels of corresponding serum NfL in cognitively impaired patients are supportive of the proposed mechanism. Male patients had elevated levels of serum NfL compared to female patients, which may reflect a differential susceptibility to neurodegenerative processes that could be influenced by sex hormones. The presence of elevated NfL levels in newly diagnosed patients suggests early axonal stress preceding the initiation of treatment, comparable to trends observed in other neurodegenerative disorders [27,28]. Overall, these results enhance the potential use of serum NfL as a non-invasive and clinically relevant biomarker for assessing neurological involvement in patients with hypothyroidism. The link with both objective neurophysiological abnormalities and subjective cognitive symptoms further supports its use in early diagnosis, risk estimation, and tracking disease progression.

Study limitations

This study is limited in its small sample size, especially for serum NfL analysis, which may impact the ability of the findings to generalize. Future research with larger cohorts is warranted to clarify these associations and to study longitudinal trends in NfL levels following initiation of thyroid hormone therapy.

Conclusion

Our study shows strong evidence indicating hypothyroidism is associated with both peripheral neuropathy and cognitive dysfunction. Serum neurofilament light chain (NfL) level elevation is associated with underlying neuronal injury, which correlates with nerve conduction abnormalities and cognitive impairment. These findings lend support to NfL being a non-invasive biomarker for potential early detection and ongoing monitoring for neurological complications in patients with hypothyroidism. There is a need for longitudinal studies to determine the prognostic utility of NfL and the response to treatment.

Conflict of interests

The authors declared no conflict of interest.

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Data sharing statement

Supplementary data can be shared with the corresponding author upon reasonable request.

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