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Professional paper

MINIMAL F-LATENCY IN PATIENTS WITH NEWLY DISCOVERED PRIMARY HYPOTHYROIDISM AND THE ROLE OF BODY WEIGHT INDEX

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Abstract

Introduction. Electrodiagnostic testing of F-wave latency plays a significant role in the early detection of peripheral neurogenic processes. The relationship between Body Mass Index (BMI) and the integrity of the peripheral nervous system in hypothyroidism is not extensively studied.Aim. To investigate the relationship between minimal F-wave latency and BMI in newly diagnosed hypothyroid patients and to determine if early peripheral nervous system dysfunction is present.Materials and Methods. A clinical prospective study was conducted on 74 patients with newly diagnosed, untreated primary hypothyroidism. Inclusion criteria excluded patients with a history of peripheral nervous system disorders. BMI, thyroid-stimulating hormone (TSH), free thyroxine (fT4), and anti-thyroperoxidase antibodies (aTPO) were measured. Neurological assessments included self-evaluation, clinical examination, and electromyography (EMG) of minimal F-wave latency in the median and peroneal nerves. Statistical analysis was performed using SPSS software (version 26.0).Results. Of the 74 patients, 32.43% were male, and 67.57% were female, with a mean age of 43.13±8.21 years and a mean BMI of 27.21±3.19 kg/m². A statistically significant moderate correlation was found between BMI and minimal F-wave latency: n. medianus (r=0.432, p=0.0001) and n. peroneus (r=0.548, p=0.0001).Conclusion. Patients with untreated primary hypothyroidism and elevated BMI have an increased risk of peripheral nerve damage. Further research is necessary to enhance the predictive value of F-wave characteristics analysis for the early detection of peripheral neuropathy.

Keywords: primary hypothyroidism, minimal F-wave latency, Body Mass Index, electromyography, peripheral neuropathy

Introduction

The trend of scientific interest in regenerative and reparative medicine has brought new insights and insights into various mechanisms responsible for faster return to the physiological state of the damaged nerve. The data obtained from experimental studies on the power of locally applied thyroid hormones in the repair of damaged peripheral nerves, manifested through different modalities in the expression of regenerative factors, could have a common direction with the hypothesis that early in a state of thyroid hormone deficiency, discrete changes occur at the cellular level in the peripheral nervous system, which remain clinically latent for a longer period.

Electrodiagnostic studies of the minimum latency of the F wave are a sensitive parameter and have a significant role in the early detection of polyneuropathy because of the data they provide on the condition of the proximal segments of the peripheral nerves (1). Routine electrodiagnostic examination cannot always determine proximal pathology, which is why, in addition to measuring the minimum latency of the F wave (2, 3), it is suggestedanalysis of other parameters that may be more sensitive in detecting proximal lesions (4)

In addition to polyneuropathy, the minimum F-wave latency has also been used in the evaluation of carpal tunnel syndrome, especially in moderate and severe forms (5) , but sensitivity is reduced in cases with mild forms of the disease (6) .

Unlike numerous studies on the impact of increased body mass index (BMI) on other organ systems, the connection with the peripheral nervous system has not been sufficiently studied.

Electrophysiological studies have shown that obese patients have a disturbance in the homeostasis of action potentials and an increased pain threshold in experimental conditions. The most commonly cited metabolic theory postulates the existence of a disequilibrium between the secretion of pro-inflammatory and anti-inflammatory cytokines from adipose tissue, which can result in a systemic inflammatory response. In such a constellation, central and peripheral neuronal sensitization is triggered, which is the mechanism responsible for the occurrence of pain and other phenomena related to it. In conditions of nerve damage, coexisting proinflammatory cytokines promote, favor, and aggravate axonal damage and the demyelination process, and in addition, there is evidence for the pathogenetic role of lipotoxicity, impaired fat oxidation, circulatory disruption at the microvascular level, and neurogenic inflammation (7, 8).
In this regard, early electrodiagnostic study with F-wave examination can provide significant data for timely detection of nerve damage in patients with untreated hypothyroidism, without clinical symptoms of polyneuropathy.

Purpose

The aim of the study is to discover the relationship between the value of the minimum F-latency and the body mass index in patients with newly discovered and untreated hypothyroidism and to indirectly determine whether there is an early affection of the peripheral nervous system of the type of diffuse damage along the entire length of the nerves, as well as to determine whether there is a correlation of the pathological findings with some anthropometric variables.

Material and methods

A clinical, prospective study of 74 subjects was conducted in the neurophysiological laboratory of the GOB " 8-mi Septemvri " in Skopje, RNM. Ethical approval for the study was obtained from the local ethics committee of the hospital and the Ethics Committee of the Faculty of Medicine in Skopje. Written informed consent to participate in the study was obtained from all subjects. 74 hypothyroid patients (24 men and 50 women) were included . Inclusion criteria included: age 30-60 years, positive history, clinical findings and biochemical results in support of the diagnosis of overt or subclinical hypothyroidism, duration of endocrinological history of at most one year prior to diagnosis, negative history of symptoms and signs of peripheral nervous system lesions, standard neurological examination excluding signs of focal neurological deficits and/or the existence of irritative phenomena, normal serum vitamin B12 levels. Subjects with: a family history of peripheral nervous system diseases, a history of previous symptoms and signs of peripheral nervous system lesions (including in early childhood, patients with hyperglycemia, elevated glycosylated hemoglobin values without a diagnosis of diabetes mellitus, patients with a confirmed diagnosis of diabetes mellitus (regardless of medication compliance), patients with any other type of endocrinopathy, patients with elevated values of degradation products or elevated values of hepatic enzymes and/or with known liver or kidney disease, patients with connective tissue disease, patients with malignant disease, 9) patients who are or have been on chemotherapy and radiotherapy, pregnancy and breastfeeding, patients who are alcohol abusers, patients with active tuberculosis and/or who are on any regimen of therapy with tuberculostatics, patients with epilepsy and placed on any antiepileptic drug, patients who have been exposed to toxic noxious agents (lead, mercury, thallium, arsenic, gold, organophosphates, acrylamide, carbon disulfide, ethylene oxide, hexacarbons), patients who are chronically (for at least one month) on therapy with: amiodarone, metronidazole, misonidazole, chloroquine and hydroxychloroquine, colchicine,

podophyllin, thalidomide, disulfiram, dapsone, leflunomide, isoniazid, ethambutol, antinucleoside drugs, phenytoin, lithium.
The diagnosis of hypothyroidism is made based on the clinical picture and biochemical parameters that are examined using the immunochemiluminescent method on a Centaur device in the laboratory ofGOB September 8th . The reference values for biochemical thyroid status in the local laboratory are: for TSH = 0.4-4.0 IU/mL; for F T4 = 0.89-1.76 ng/dL; for F T3 = 2.3-4.2 pg/mL and for aTPO< 60U/mL
For each patient, the following were examined and entered: general demographic data: age, gender, nationality; anthropometric characteristics: body weight, body height and Body Mass Index (BMI) values; Biochemical parameters of thyroid status: levels of FT3, FT4, anti TPO and TSH; values obtained from electromyoneurographic recording and their electrophysiological characteristics.
Neurological evaluation was conducted in several stages: evaluation of inclusion and exclusion criteria, self-evaluation using the Michigan Questionnaire (9), assessment of neurological symptoms (10) , and neurological examination with examination of neurological disability, examination of gross motor strength, and examination of myotatic reflexes (11, 12).
The EMG recording was performed on a digital Nemus machine (EBN Spa Firenze, Italy). The conditions in the recording room, the temperature of the extremities, the standard sites for recording action potentials through the active and reference electrodes, the sites of electrical stimulation and their distances expressed in centimeters are in accordance with the recommendations in the protocol recommended by AANEM (13) and the nomogram from it was used to interpret the results obtained, except for the F latencies for which reference values according to Preston and Shapiro (14) were used. The neurographic measurement included the following motornerves: median nerve (n.medianus) andperoneal nerve (n.peroneusprofundus). For each nerve, the following were examined: distal minimum latency (DML), compound motor wave amplitude (CMA) and conduction velocity (CV). The F-wave was obtained from: n.medianus and n.peroneus profundus and its minimum latency (minimum F-wave latency, mlFb) was analyzed.

Statistical analysis

The data obtained during the research were statistically processed using the SPSS software package, version 2 6 .0 for Windows (SPSS, Chicago, IL, USA). Qualitative series were analyzed by determining the coefficient of relationships, proportions and rates. Quantitative series were analyzed with measures of central tendency (mean, median, 25% and 75% percentiles, minimum and maximum values), as well as with measures of dispersion (standard deviation). Shapiro - WilkW test was used to determine the regularity of the frequency distribution of the examined variables .Mann-Whitney U Testwas used to compare age and BMI between genders. Independent t-test was used to compare F-lat between n.medianus (m) and n.peroneusprofundus (m). Difference test was used to compare proportions. Pearson's correlation coefficient was used to determine the strength and direction of the association between ITT height and the values obtained for the minimum latency of the F-wave of n.peroneusprofundusor the values obtained for the minimum latency of the F-wave of n.medianus (m). Two-sided analysis of significance was used with a significance level of $p < 0.05$.

Results

The research sample consisted of a total of 74 patients, of whom 24 (32.43 %) were male and 50 (67.57 %) were female, with a sex ratio of 0.48 : 1, and a significantly higher percentage of females compared to males - Difference 35.14 % [(19.16 – 48.67) 95% CI]; p=0.001) .
The mean age of the patients in the sample was 43.13 ± 8.21 years, with a min/max of 30/60 years and 50% of patients older than 42 years for Median IQR=42 (37-50). The mean age of men was 45.37 ± 8.58 years, with a min/max of 30/60 years, and for women 42.06 ± 7.88 years, with a min/max of 31/60 years. 50% of men were over 44 years old for Median IQR=44 (39-53), and 50% of women were over 41 years old for Median IQR=41 (36-47). There was no significant difference between the two sexes in terms of patient age - Mann-Whitney U Test: Z= 1.622; p= 0.1047 .
The distribution by nationality in the sample indicated that Macedonians dominated 57 (77.03%), Albanians were 11 (14.86%), and the representation of other nationalities was 6 (8.11%).
The average ITT in the entire sample was 27.21±3.19 kg/m ^{2}, with a min/max of 23.1/32.3 kg/m ^{2}and 50% of patients with ITT >26.85 kg/m ^{2} . In male and female patients, the average ITT was consistently 26.70±2.52kg/m ^{2} vs 27.45 ± 3.47 kg/m ^{2}with consequently 50% of them with ITT < 26.65 kg/m ^{2}vs.<26.95 kg/m ^{2} . There was no significant difference between the sexes in terms of ITT - Mann-Whitney U Test: Z= -0.779; p=0.4357.
There was no significant difference between the sexes in terms of the average value of F-lat of n.medianus (m) (p=0.164) or the minimum latency of the F-wave of n.peroneusprofundus (m) (p=0.221) (Table 1).

Table 1. Comparison of minimal F-wave latency of n.medianus and n.peroneusprofundus in the whole sample and by gender

Clinical parameters	N	Mean ± SD Mean±SD	Min/Max Min/Max	Median (IQR) Median (IQR)	p
n.medianus (m) ms					
F - lat (men)	24	29.18±1.50	26/ 31.8	29.4 (27.9-30.3)	t-test $_{(72)}$ = -1.406; p=0.164
F - lat (women)	50	28.52±2.05	24.3/ 33.1	28.7 (26.5-30.1)	
n.peroneusprofundus (m)					
F - lat (men)	24	50.61±2.83	46.5-57.9	50.6 (48.2-52.7)	t-test $_{(69)}$ = - 1, 236 ; p= 0.221
F - lat (women)	50	49.57±3.51	43.1/ 57.2	48.7 (47.1-52.1)	
ms - milliseconds; Independent t-test;*significant at p<0.05					

The correlation analysis indicated a significant linear moderate positive correlation between ITT and the values obtained for the minimum latency of the F-wave of n.medianus (m) ($r_{(74)}$ =0.4 32 ; p =0.0 001) as well as the values obtained for the minimum latency of the F-wave of n.peroneusprofundus(m) ($r_{(74)}$ =0.548; p =0.0 001) - with increasing ITT of the patients, the values of these two parameters also increased significantly (Graph 1).

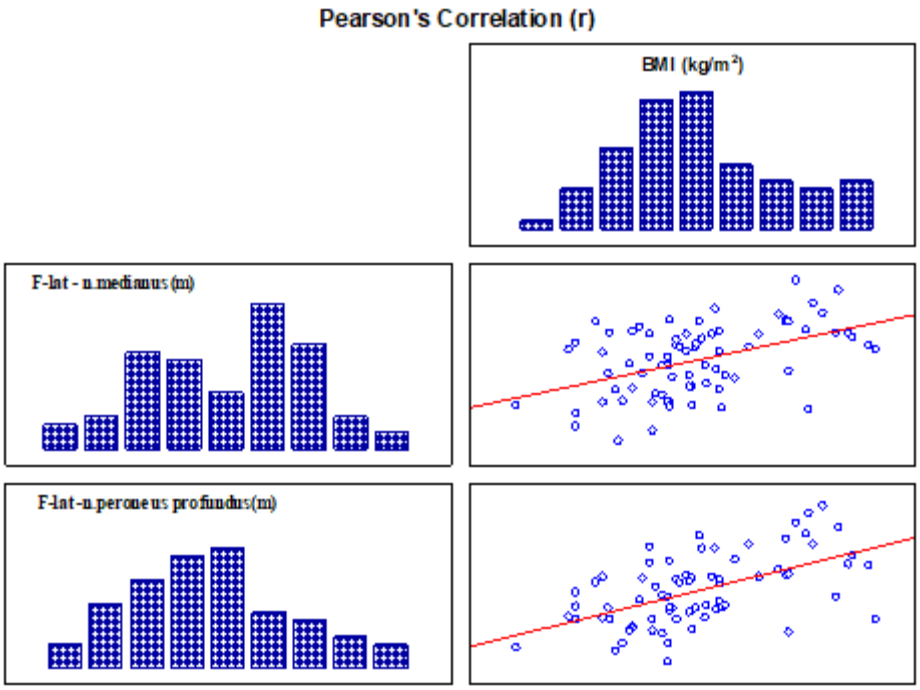

Chart 1. Correlation of BMI with F-lat of n.medianus (m) and F-lat of n.peroneusprofundus

Discussion

The alteration of the peripheral nervous system in conditions of hypothyroidism is based on several hypotheses about pathogenetic and pathophysiological mechanisms (15) , and on the other hand, there is a large body of evidence in scientific studies indicating that thyroid hormone substitution levels the clinical picture of the peripheral neurogenic syndrome (16). Our study analyzed several anthropometric variables and values of the minimum F latency measured from the median and peroneal nerves. In terms of gender, of the total number of respondents, a significant higher representation of the female gender. These findings are in line with the results obtained from previous studies. Extensive research has been published on the higher prevalence of hypothyroidism in females (17,18 , 19, 20, 21, 22, 23).

The mean age of the subjects was 43.13 years and there was no significant difference between the two sexes. This finding is similar to most studies that have investigated the relationship between age and the occurrence of hypothyroidism, and their results are consistent in indicating that hypothyroidism most often occurs after the 40th, or 45th year of life. (24, 25, 26, 27, 28)

The mean ITT value was 27.21 kg/m², with no significant difference between the two sexes. For the values of the minimum latency of the F wave individually for the median and peroneal nerves, no significant difference was found between the two sexes. Examination of the relationship between ITT and the minimum latency of the F wave between the subjects showed a moderate positive correlation for both nerves (n. medianus and n. peroneus profundus), indicating that with the increase in ITT, the values of the minimum latencies of the F wave are significantly prolonged. From the values for the analysis of the correlation of the two nerves: n. medianus ($r = 0.432$, $p = 0.0001$) and n. peroneus profundus ($r = 0.548$, $p = 0.0001$) , it was shown that the correlation is higher for the results for the peroneal nerve. The results of the correlation analysis between ITT and the minimum F-wave latency for a moderate positive relationship in both nerves suggest that increased ITT may affect the prolongation of F-wave latencies. These findings are consistent with data from previously published studies showing significantly prolonged F-wave latencies in hypothyroid patients .In the study by Abdelazeem et al., performed EMNG measurements in hypothyroid patients who did not have a clinical

picture of polyneuropathy and other peripheral nerve damage. The study found that there was no significant difference between hypothyroid patients and the control group in terms of F wave examinations in the median, ulnar, peroneal and tibial nerves, suggesting that there is no proximal lesion of the peripheral nerves in hypothyroid patients. However, this study did not state whether the patients were already on thyroid replacement therapy, which could correlate with the above discussion of the regenerative power of thyroid hormones (29). The study by Garg et al. focused on neurographic measurements in newly diagnosed patients with hypothyroidism that had not started hormone replacement therapy. The results showed that the minimum latency of the F wave was significantly prolonged in the median nerve and tibial nerve compared to the control group, which led them to conclude that the pathogenetic mechanism in hypothyroidism may lead to prolonged F wave responses, suggesting impaired conduction through peripheral nerves (30), but in contrast to our study, only 12% of patients were neurologically asymptomatic.

Similarly, Meshram K. et al. in patients with early diagnosed hypothyroidism and clinical neurological symptoms and signs, but not treated with levothyroxine, found pathological features of the sensory nerves, but without a focus on the characteristics of the motor nerves (31). Neurographic measurements in patients with newly diagnosed subclinical hypothyroidism who were not treated with hormone replacement therapy with TSH values between 6.9 and 13.5 μ IU/mL, showed that there was no significant difference in the F wave parameters between the subclinical hypothyroidism group and the control, which may be correlated with the normal T4 level and it can be assumed that at the beginning of the disease the peripheral nervous system evaluated by EMG functions in a physiological range.(32).

In contrast to our study, Sadinedra et al. found that patients with newly diagnosed hypothyroidism had prolonged minimum, maximum and mean F wave latencies compared to healthy subjects. These findings were characteristic of the median nerve, which could also suggest distal neuropathy of the median nerve, probably at the level of the radiocarpal region, and given that there was no significant difference between the F wave measurements in the ulnar nerve and the control group, they suggested that the median nerve is more frequently affected in conditions of hypothyroidism. Although these subjects were newly diagnosed, no specific insight could be found into whether they received hormone replacement therapy or grouped F wave values in patients with neurological clinical symptoms and signs and those who were neurologically asymptomatic (33). Abas et al. examining neurographic electromyographic findings in newly diagnosed patients with hypothyroidism found that peripheral nerve damage begins early in the course of the disease, with sensory fibers being more severely damaged than motor fibers, more in the lower extremities than in the upper extremities, and that the presumed mechanism is mixed axonal and segmental demyelination. They emphasized that demyelination is more common than axonopathy (34). Similarly, a predominant sensory involvement of the peripheral nerves was found by Balaraman et al. in a study of neurographic findings in newly diagnosed hypothyroid women, indicating subclinical damage to the sural nerve in the setting of early hypothyroidism, while there were no significant abnormalities in the motor nerves. Their study lacks data on whether the patients were neurologically asymptomatic (35).

In contrast, Akarsu et al. found that motor nerves were more damaged than sensory nerves in patients with clinically overt and subclinical hypothyroidism, but no F wave measurements were reported. In contrast to our study, these patients had neurologically overt clinical symptoms and signs, and it was not specified whether they had newly diagnosed hypothyroidism or were on treatment for it (36).

In recent studies investigating the relationship between obesity, hypothyroidism, and peripheral nervous system damage, several factors acting at different levels have been identified. The main emphasis is on the inflammatory effect, which is systemic and local and interacts with the mechanical, compressive effect of adipose tissue on the nerve, and in addition, the role of

hormonal dysregulation and metabolic imbalance has been established (37, 38, 39, 40). EMG studies in patients with hypothyroidism and pathological ITT have found that obesity may significantly participate in the deterioration of nerve conduction in newly diagnosed patients. In the study by Sharma et al. predominantly more pathological values were obtained in the conduction velocity of sensory nerves, but prolonged minimal F latencies were also found for the median and tibial nerves, which these authors linked to the potential aggravating effect of overweight on the existing metabolic imbalance . In addition, they suggested that in patients with hypothyroidism, especially those with pathological ITT, there is a tendency to develop carpal tunnel syndrome, which could be a cumulative effect of metabolic changes within the framework of thyroid hormone deficiency, the mechanical effect of increased pressure on the median nerve in conditions of obesity, inflammation and deposition of fatty products around the nerve (41) . Therefore, references to findings of carpal tunnel syndrome are more frequent in the literature and they most often affirm the thesis of multifactorial pathogenetic factors in its occurrence in patients with hypothyroidism and obesity (42). Increased ITT was positively correlated with abnormal peripheral nerve findings with a predilection for motor nerves in the study by Singh et al.The minimum latency of the F wave was prolonged, but it is noteworthy that, unlike ours, 88% of the participants in this study were neurologically symptomatic patients (43). Such insights emphasize the importance of rigorous treatment of obesity in order to reduce the risk of developing peripheral neuropathy or attenuate its clinical picture (44).
In order to more precisely objectify the degree of sensitivity and specificity of the F-wave in patients with increased ITT and untreated hypothyroidism, in the future we propose conducting new studies that, in addition to the minimum latency, will examine its other parameters such as chronodispersion, tachydispersion, F-wave index and others, which could increase its level of reliability for prediction in the early and latent stages of polyneuropathy.

Conclusion

The presented results suggest that increased ITT in patients with primary untreated hypothyroidism may contribute to early peripheral nerve damage, compared to those with normal ITT. Although statistically insignificant, the results indicate the need for further research to determine the clinical implications, especially in patients at risk for developing polyneuropathy .

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