Al-Azhar University Journal
for Medical and Virus Research
and Studies

Relationship Peripheral Nerves Affection in Hypothyroidism

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Abstract

The most prevalent endocrine condition is hypothyroidism. There is disagreement over the occurrence of hypothyroid neuropathy and the nature of its etiology. To evaluate the affection of subclinical motor or sensory peripheral nerve among hypothyroid subjects. A total of 60 hypothyroid cases with no neurological symptoms were included and 60 healthy individuals were considered as controls. All subjects were investigated for medical history, full general and neurological examination, radiological and laboratory assessments and neurophysiologic nerve conduction study. Polyneuropathy was found mainly sensorimotor among 73.3% of the cases either axonal or demyelination affection. Sural and median nerves were the commonly affected nerves. Patients experienced a high rate of entrapment neuropathy, with carpal tunnel syndrome (CTS) accounting for 60%. In sensorimotor neuropathy, hypothyroidism is linked to polyneuropathy, primarily of the axonal affection type of motor nerve or demyelination affection in sensory neuropathy. Even in asymptomatic hypothyroid individuals, routine nerve conduction testing should be carried out early in the course of the disease to reduce the risk of structural damage and impairment.

Keywords: Hypothyroidism, Nerve Conduction Study, Neuropathy.

1. Introduction

Numerous nervous system activities and processes are influenced by thyroid hormones. Through their involvement in gene expression, myelin synthesis, and their impacts on the neurotransmitter system and axonal transport, they have an impact on both the central and peripheral nervous systems [1]**.** Reduced hormone production causes hypothyroidism, a frequent medical illness in the general population that manifests as common systemic symptoms such fatigue, constipation, cold sensitivity, weight gain, hair loss, dry skin, irregular menstrual cycles, and hoarseness [2] Additionally, individuals with hypothyroidism frequently

experience a range of symptoms related to the central and peripheral neurological systems, including myxedema coma, peripheral neuropathy, cerebellar ataxia, carpal tunnel syndrome, tarsal tunnel syndrome, and cognitive impairment.[3,4]
Laboratory testing is used to diagnose hypothyroidism: High levels of serum thyroid stimulating hormone (TSH) +/- low levels of serum free thyroxine (FT4) +/-low levels of serum free triiodothyronine (FT3) [5].
Axonal degeneration with shrinkage of axons, disruption of neurotubules and neurofilaments, aggregates of glycogen granules, mitochondria, diminished frequency of large, myelinated fibers with segmental demylination, lipid droplets, lamellar bodies, and remyelination are among the various pathologic descriptions of the hypothyroid neuropathy's pathogenesis [1]**.**
Because electrophysiological symptoms of neuropathy can be detected even subclinically, nerve conduction studies (NCS), which combine motor and sensory nerve conduction together (median, ulnar, tibial, and peroneal nerves), can be very helpful in the diagnosis of peripheral neuropathy [6].
The aim of the Work was assessing sub clinical peripheral nerves affection in hypothyroid patients through NCV study. To determine the type of neuropathy among affected nerves. To know the most commonly affected nerves in patients' groups.

2. Patients and Methods

2.1 Design

This case control research assessed sub clinical peripheral nerves affection in hypothyroid patients through NCS in comparison to control group.

2.2 Participants

This research encompassed 120 individuals with age range of 25-50 years. Cases with hypothyroidism were recruited from Rheumatology and Rehabilitation department outpatient clinic & endocrinology outpatients' clinic at Al Zahraa Hospital during the period from July 2022 to January 2023. Diagnosis of hypothyroidism was according to Dayan [5].

2.3 Inclusion criteria:

60 hypothyroidism subjects with high TSH +/- low serum free T4 and free T3 concentration according to Dayan [5].

2.4 Exclusion criteria:

Pregnant women, malignancies, DM,renal and hepatic failure, hyperlipidemia, hereditary sensory neuropathy, lumbar or cervical radiculopathy and subject on the following medications; contraceptive tablets, agents causing edema or polyneuropathy as steroids) or others causing PN were excluded from this work.

2.5 Ethical consideration:

A written informed consent has been obtained from all subjects following an explanation of the study. Our study was approved by the medical ethics and committee of the Faculty of Medicine for Girls at Al-Azhar University.

2.6 The following procedures were performed on all of the patients:

- Full History taking personal history, complain, general symptoms associated hypothyroidism.

- Clinical examination involving general, musculoskeletal examination: General examination with the focus on arterial blood pressure (ABP), pulse, anthropometric measurements that include Body Mass Index (BMI) evaluation (BMI=Weight (in Kg)/ height (m) ^{2} [7], waist to hip ratio, body weight,

height and finally full neurological examination to detect any deficits.

- Laboratory assessment.
- Radiological assessment: Plain x-ray of lumbar and cervical spines was carried out for exclusion criteria.
- Electrophysiological study (NCS).

They were done in a quiet room with a constant temperature using a thermostat of air condition at 26 to31 ºC. The subject was in lying or sitting position, the full text including purpose, procedure and importance was explained to the subjects before the test, the device used was Nihon Kohden Neuropak (Nihon Kohden Corporation, Tokyo, Japan) was used to perform the electrophysiological studies of this work.
Including determination of bilateral motor median, ulnar, posterior tibial and common peroneal nerves conduction studies.Sensory conduction study of both median, ulnar nerves and sural nerves.

2.7 Testing method

- Motor nerve conduction assessments were carried out in line with Weiss [8]. Surface electrodes were employed for recording as well as stimulation. Supramaximal stimulus, or 20% more intense than what was required to elicit the maximum amplitude of the recorded evoked motor response, was used for stimulation.
- An antidromic sensory nerve conduction study was performed for ulnar, median, and sural nerves in agreement with Weiss [8].

3. RESULTS

3.1 Demographic data

This study was carried out on 60 subjects with primary hypothyroidism, the age of the studied group ranged from 25-50 years with illness duration of 6 months to 10 years with mean 5.02±4.05 and Lthyroxin as replacement therapy.
In addition to 60 participants of age and sex-matched healthy volunteers as controls, the age of the studied group ranged from 25-50 years with a mean of 40.58±8.36. Male cases were 4(6.7%) while female cases were 56 (93.3%) cases, age of the control group ranged from 26 to 50 years with a mean of 39.30±7.22. Male subjects were 9 (15.0%) while the female was 51 (85.0%), their BMI ranged from (18.5 -30) with a mean of 24.17±4.25 while that of the control group ranged from (18-28) with a mean of 23.18±3.3.

3.2 laboratory data

- There was **a** highly significant variation between cases and controls regarding TSH and free T4, whereas no significance was found regarding free T3.
- TSH of the Patient group ranged from 1-10 mIU/ml with mean value 4.56±2.04 mIU/ml, TSH of control group ranged from 1.5-4 mIU/ml with mean value 2.82±0.67 mIU/ml è p value (<0.001**).
- Free T4 of Patient group ranged from 0.4-1.4 ng/dl with mean value 0.91±0.31 ng/dl, free T4 of control group ranged from 0.8-1.4 with mean value 1.32±0.14 ng/dl è p value (<0.001**).
- Free T3 of Patient group ranged from 1.6-4.1pg/ml with mean value 2.97±0.68 pg/ml, free T3 of control group ranged from 1.7-4.5 pg/ml with mean value 3.12±0.97 pg/ml è p value (0.334).

As shown in Table .1 regarding the number of neuropathies among our patient group 44 cases (73.33%) were polyneuropathy, 16 cases (26.66%) were normal & none of the cases displayed mononeuropathy, as regards type of neuropathy; Sensorimotor

affection was 31 case (70.5 %). Sensory affection was 13 cases (29.6 %), and isolated motor affection was zero. As shown in Figure .1 regarding the distribution of affected lateral nerves among our patients; the total lateral affected nerves equal 210 nerves distributed; 68 Median sensory (56.7%,), 35 Median motor nerves (29.2%) affected nerve and 33 sural affected nerves (27.%), were more commonly affected, 13 Ulnar sensory affected nerve (10.8%), 32 ulnar motor nerve (26.7%), 17 Peroneal nerve (14.2%) and 10 Tibial nerve (10%). As shown in Table .2 pathological affection in sensorimotor neuropathy; Motor nerves showed that axonal affection was the most dominant pathology in 73 nerves (34.67 %), demyelination affection was in 21 nerves (10 %) & mixed affection were 5 nerves (2.38%). Sensory nerves showed that demylination affection was the most dominant pathology 44 nerves (20.95%), axonal affection was 7 nerves (3.33%) & mixed affection was 26 nerve (12.3%), while pathological affection in pure sensory neuropathy; Demyelination affection was the most dominant pathology 15 nerve (7.14 %), axonal was 8 nerves (3.8%) & mixed affection was 11 nerve (5.2 %). As shown in Tables (3&4) nerve conduction of both median (motor & sensory), and sural nerves there were motor nerve conduction for median nerves at amplitude, sensory nerve conduction for (median, & sural nerves) at peak latencies, amplitudes and conduction velocities showed a significant effect on the patient's group ($p<0.05$); while the rest showed non-significant findings ($p>0.05$). As shown in Table .5, there is a considerable correlation (positive and negative) between NCS parameters of the sensory median nerve with replacement therapy, disease duration (years), TSH level and free T4. As shown in Table 6 nerves exceeding upper normal limit of DSL and DML that appear as entrapment pathology among total patients group there were: median nerve entrapment (CTS), a- sensory =60 % while b- motor =13.33 %, ulnar nerve entrapment a- sensory =13.3 % while b- motor =10%, posterior tibial nerve entrapment showed 13.33 %, Common peroneal nerve entrapment showed 00 and Sural nerve entrapment showed 26.6.

Table (1): Neuropathies Types.

Nerve	N.	%
Affected frequency (N=60)		
Mononeuropathy	0	0
Polyneuropathy	44	73.3
Normal	16	26.7
Type of neuropathy (N=44)		
Motor neuropathy	0	0
Sensory neuropathy	13	29.6
Sensorimotor	31	70.5

Table (2): Pathological affection sensorimotor and pure sensory neuropathy.

Pathology	N.	%
Motor (47.14 %)		
Demylination	21	10
Axonal	73	34.67
Mixed	5	2.38
Sensory (36.6%)		
Demylination	44	20.95
Axonal	7	3.33
Mixed	26	12.3
Pathology (pure sensory neuropathy)	No.	%
Demylination	15	7.14
Axonal	8	3.8
Mixed	11	5.2

N; number of affected nerve (210).

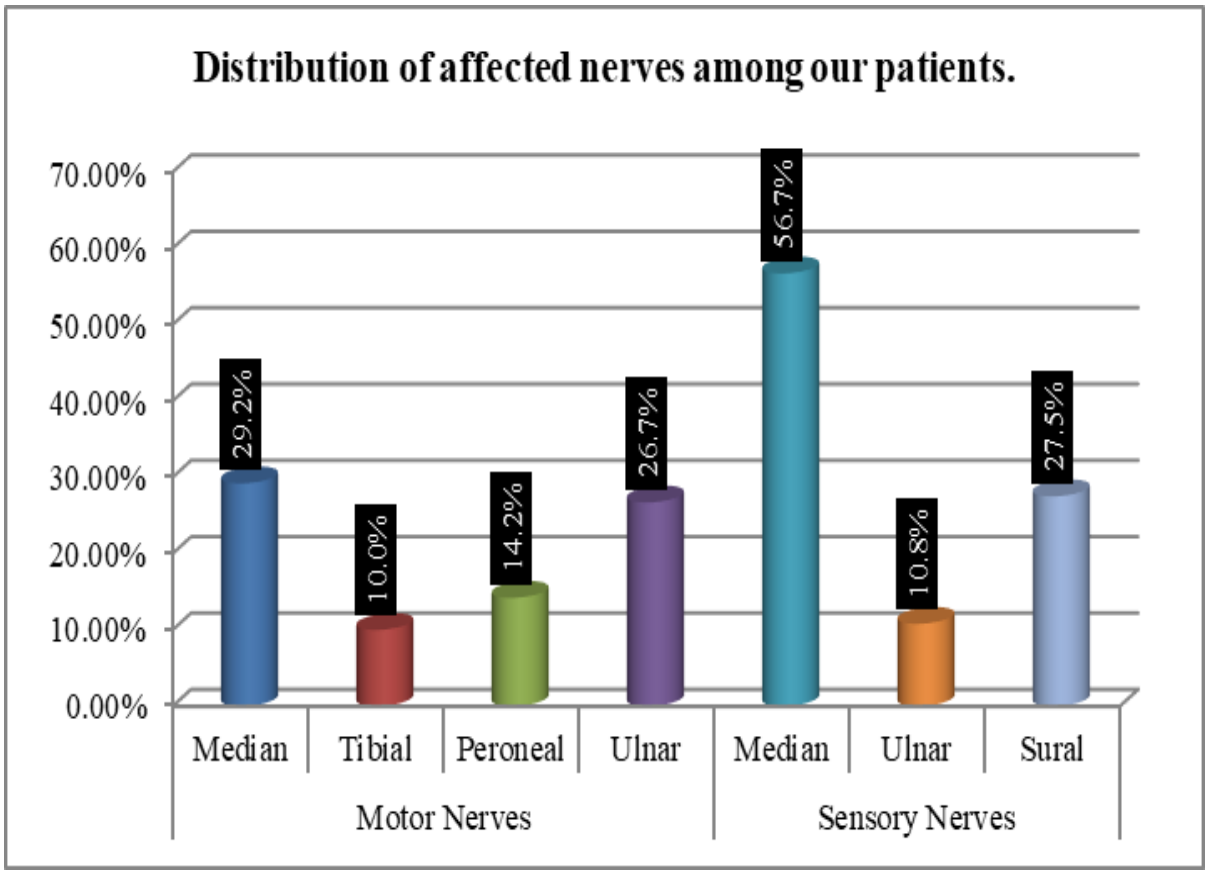

Figure (1): Affected nerves among the cases.

Table (3): Comparison between patient and control groups according to motor nerve conduction for median nerves.

Motor nerve conduction for Median nerves			Cases (n=60)	Controls (n=60)	Test value	P-value
DML (ms)	Right	Mean ± SD	3.19±0.50	3.23±0.69	-0.363	0.717
		Range	2-4.2	2-4		
	Left	Mean ± SD	3.38±0.76	2.75±0.53	5.264	<0.001**
		Range	2-5.5	2-4		
Amplitude W (mv)	Right	Mean ± SD	10.36±2.26	13.33±1.50	-8.472	<0.001**
		Range	6-15	10-15		
	Left	Mean ± SD	10.28±2.41	12.63±1.34	-6.620	<0.001**
		Range	5-14	11-15		
NCV (m/s)	Right	Mean ± SD	55.65±5.14	56.30±4.27	-0.753	0.453
		Range	43-65	49-65		
	Left	Mean ± SD	56.45±5.68	57.33±4.49	-0.945	0.346
		Range	49 -65	50-65		

t-test for Mean ± SD, p-value >0.05 is insignificant; **p-value <0.001 is highly significant, DML; distal motor latency, W; wrist, NCV; nerve conduction velocity.

Table (4): Comparison between patient and control groups according to sensory nerve conduction for median nerves.

Sensory nerve conduction for median nerves			**Cases (n=60)**	**Controls (n=60)**	**Test value**	**P-value**
Peak latency(ms)	Right	Mean ± SD	3.60±0.97	2.92±0.56	4.681	<0.001**
		Range	1-5	2-4		
	Left	Mean ± SD	3.43±1.02	2.89±0.69	3.379	<0.001**
		Range	1-5	1-4		
Amplitude (mv)	Right	Mean ± SD	16.53±8.78	23.18±6.13	-4.809	<0.001**
		Range	4-25	11-35		
	Left	Mean ± SD	19.05±7.69	22.25±7.95	-2.198	0.030*
		Range	6-35	10-35		
Conduction velocity (m/s)	Right	Mean ± SD	50.97±9.85	65.73±6.45	-9.713	<0.001**
		Range	34-65	55-75		
	Left	Mean ± SD	50.37±10.26	65.73±4.45	-9.826	<0.001**
		Range	34-65	55-70		
Sensory nerve conduction for Sural			**Cases (n=60)**	**Controls (n=60)**	**Test value**	**P-value**
DSL (ms)	Right	Mean ± SD	3.86±0.98	3.53±0.79	2.031	0.045*
		Range	2.5 -6	2-4		
	Left	Mean ± SD	3.90±1.36	3.60±0.83	1.462	0.147
		Range	3-10	2-5		
Amplitude (mv)	Right	Mean ± SD	7.93±4.90	9.53±2.19	-2.310	0.023*
		Range	4-18	7-20		
	Left	Mean ± SD	8.30±4.23	9.28±2.16	-1.608	0.110
		Range	2-17	7-19		
Conduction velocity (m/s)	Right	Mean ± SD	52.35±7.20	55.55±6.88	-2.489	0.014*
		Range	39-65	45-66		
	Left	Mean ± SD	51.22±8.44	54.82±7.00	-2.543	0.012*
		Range	35-65	45-65		

t-test for Mean±SD, p-value >0.05 is non-significant; *p-value <0.05 is significant; **p-value <0.001 is highly significant.

Table (5): Correlation between thyroxin dose, Disease duration (years), TSH, Free T4 & Free T3 with Sensory nerve conduction for median nerves, using Pearson Correlation Coefficient among the study group.

Sensory nerve conduction for median nerves		**Thyroxin dose**	**Disease duration (years)**	**BMI**	**TSH**	**Free T4**	**Free T3**
Peak latency (ms)	R-value	-0.130	.445**	-0.085	0.143	-.393*	0.009
	p-value	0.320	<0.001	0.520	0.276	0.002	0.946
Amplitude (mv)	R-value	.320*	-0.001	0.112	-0.145	0.178	0.173
	p-value	0.013	0.993	0.393	0.269	0.173	0.185
Conduction velocity (m/s)	R-value	0.044	-.324*	-0.001	-.385*	.505**	-0.022
	p-value	0.740	0.011	0.994	0.002	<0.001	0.869

r-Pearson Correlation Coefficient.

Table (6): Nerves exceeding the upper normal limit of DSL and DML.

DSL (ms)	Control limit	Total number of cases			
		Unilateral cases	Bilateral cases	Total N	Percentage %
Median	≤ 4	10	26	36	60 %
Sural	≤ 4	7	9	16	26.6 %
Ulnar	≤ 4	6	2	8	13.3 %
DML (ms)	Control limit	Total number of cases			
		Unilateral cases	Bilateral cases	Total. N	Percentage %
Median	≤ 4	8	0	8	13.33 %
Ulnar	≤ 3	3	3	6	10 %
Tibial	≤ 5	8	0	8	13.33 %
Peroneal	≤ 5	0	0	0	00

N; Total number of cases (60), DML; distal motor latency, DSL: distal sensory latency.

4. Discussion

In the present study, we found no statistically significant differences between both groups as regards age and BMI as the groups were matched almost in the same age and BMI. Our results were in agreement with Mai et al. [9] who conducted NCS on 30 hypothyroid cases with no neurological symptoms and 10 healthy individuals were enrolled as a control, their BMI with a mean of 25.1±4.0. While the controls their BMI with a mean of 22.9±3.8 and found no statistically significant difference as regards BMI. However, Karne and Bhalerao [10] discovered that 8% of people 55 years of age and older had peripheral neuropathy, indicating that neuropathy rises with age. The same association between neuropathy in hypothyroidism and a high BMI was also mentioned. Their enrollment of numerous patients beyond the age of 55 may be the cause of this discrepancy. Additionally, 25% of their samples had obesity. In the current study, polyneuropathy was evident in 73.3% & none of our patients showed mononeuropathy. Also, 70.5 % had Sensorimotor neuropathy, 29.6 % had pure Sensory neuropathy & none had pure motor neuropathy. Our results are in agreement with Mai et al. [9] who found that (57.7 %, and 86.6%) of sensorimotor polyneuropathy was the predominant finding respectively. The type of neuropathy determined among hypothyroid cases has been a point of debate among several previous kinds of literature, Sensorimotor polyneuropathy was the dominant finding in many studies Arikanoglu A et al. [11]. On the other hand, Ajeena I [12] detected a high prevalence of sensory neuropathy (44%), followed by sural mononeuropathy (43%). In addition, Balaraman et al. [13] found a potential reduction in sensory nerve conduction

(latency, amplitude, duration, area, conduction velocity) in sural and median nerves as well as 10% purely motor neuropathy.

It is evident that despite a few small differences between the research, sensorimotor and sensory neuropathy—a conclusion we have verified—remain the fundamental result in hypothyroid patients. The length of the condition, whether it is treated or not, the dosage of elastin and appropriate control, the patient's age and BMI, and other variables could all affect the variances.

In the current study, as regards pathological presentation, sensorimotor neuropathy showed that (34.67 %) was axonal pathology affecting the motor part of the nerve, followed by (20.95%) was demylination pathology affecting the sensory part of the nerve.

Also, as regards pathological presentation in pure sensory neuropathy we found that (7.14%) was demylination pathology that affects sensory nerves. Our results in agreement with Duyff et al. [14] who conducted NCS and EMG on 24 hypothyroid patients and found that pure axonal sensorimotor was a major finding among their cases.

Also, Asia A and Warkar A [15] stated that sensory demyelinating polyneuropathy was commonly encountered. On the other hand, Mai, et al. [9] found that sensorimotor mixed neuropathy was the most frequent pathological sign followed by sensory axonal then least likely demylination neuropathy. According to our findings, thyroid hormones may be to blame. These hormones have a significant impact on protein synthesis and degradation, mitochondrial oxidative activity, and catecholamine sensitivity. In addition to interacting with several key growth factors, neural development may control microtubule assembly to influence axonal growth. This could point to a potential axonal degradation process Mai, et al [10]

Additionally, the increased pressure brought on by the infiltration of mucopolysaccharide-protein complexes causes focal demyelination in the sensory nerves. Furthermore, because the metabolism of carbohydrates is reduced, glycosaminoglycans cannot be broken down and instead accumulate in the entrapment regions, which results in entrapment neuropathies Magri F etal.[16]

Early in the course of the disease, when motor nerve conduction velocity is still within a normal range, the clinical and electrophysiological neuropathies in hypothyroidism may result in diminished sensory nerve action potentials Donofrio PD et al. [17]

In our present study, the most affected nerves were median (sensory & motor) and sural nerves, were more commonly affected nerves with percentage of (56.7%, 29.2% and 27.5% respectively).

Our results in agreement with Salim et al. [18] revealed that he most affected nerves was median sensory nerve followed by sural nerve.

On the other hand, Mai et al. [9] found that the most two affected nerves were median nerve and peroneal nerve.

The length of the disease, whether it is treated or not, the patient's age, BMI, and the dosage and appropriate management of thyroxin could all affect the variations.

Regarding nerves exceeding upper normal limit of DSL and DML (60%) of cases were CTS (sensorimotor and pure sensory CTS), (26.6 %) of cases were sural entrapment and

(10 %) of cases were ulnar entrapment, (13.3%) of cases were posterior tibial entrapment (tarsal tunnel syndrome).

Our results in agreement with Mai et al. [9] [that] found that 66.67% was CTS. Also, Karne and Bhalerao [10] found that 60% was CTS.

On the other hand, Ajeena[12] and Asia & Warkar [(15)] didn’t establish the same high percent. Again, this might be the result of the many neurophysiological approaches that were employed.

In current study, as regard motor nerve conduction; the motor nerve conduction for

median nerves at amplitude, motor nerve conduction for ulnar nerves at amplitude, motor nerve conduction for tibial nerves at amplitude & conduction velocity, motor nerve conduction for peroneal nerves at amplitude & conduction velocity, have a significant effect on the patient's group while the rest showed insignificant relation. Our results in agreement with Mai et al. [9] who found that there was a significant variance between cases and controls regarding DML, distal amplitude and NCV of both median, tibial and peroneal nerves. On the other hand, Balaraman et al. [13] found no considerable variation between cases and controls in terms of all motor parameters. This discrepancy might be attributed to the fact that all their cases were newly diagnosed.

In the current study, we noticed that 26.7% of hypothyroid cases displayed no abnormal electrophysiological outcomes.

This result is in agreement with Jalilzadeh S et al. [19] and Yeasmin et al. [20] who found normal electrophysiological results in subclinical hypothyroidism.

That was a reference to the pathogenetic foundation of peripheral nerve function changes associated with hypothyroidism, which can be reversed with thyroxine replacement therapy. Elevated TSH concentrations in subclinical hypothyroidism keep serum free thyroxine levels within normal bounds. It may therefore be acceptable to conclude that subclinical hypothyroidism does not result in a major decrease of peripheral nerve function. Consequently, the proportion of patients with normal results may represent those who have subclinical hypothyroidism (Jalilzadeh S et al. [19].

Since the majority of his hypothyroid participants were receiving hormone therapy, normal electrophysiological findings may be the result of almost normal values of TT3 and TT4, and the thyroid shortage may be a factor contributing to the decline in nerve conduction characteristics Yeasmin etal.[20]

In current study showed that significant correlation (positive and negative) between NCS parameters of all examined nerves more at sensory median and sural nerves with replacement therapy, disease duration (years), TSH level and free T4.

5. Conclusion

In our study, we have done NCS to assess subclinical peripheral neuropathy in hypothyroid patients compared to controls, we have detected that hypothyroid patients have statistically significant differences as regard NCS parameters._Polyneuropathy with hypothyroidism is mainly sensorimotor, in (73.3% &70.5%) respectively of the patients either axonal or demyelination affection in pure sensory neuropathy. Median and sural nerves were the dominantly affected nerves. A high incidence of entrapment neuropathy was encountered among the patients, especially carpal tunnel syndrome 60 %.

ACKNOWLEDGMENTS

We would like to thank all the patients included in this study for their time and cooperation.

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