Int J Endocrinol Metab 2006; 4: 78-83

ORIGINAL ARTICLE

Peripheral Nerve Function in Subclinical Hypothyroidism: A Case-Control Study

Jalilzadeh SH, Bahrami A, Eftekharosadat B, Mobasseri M, Pezeshki Z.

Department of Physical Medicine and Rehabilitation, Endocrinology and Metabolism, and Community-Based Medicine, Tabriz University of Medical Sciences, Tabriz, I.R.Iran

Peripheral nerve dysfunction is a well documented feature of clinical hypothyroidism. Only a few studies have evaluated the functional alterations in central and peripheral nervous systems in subjects with subclinical hypothyroidism and results obtained have been controversial. The purpose of the present study was to investigate the effects of subclinical hypothyroidism on peripheral nerve function.

Materials and Methods: Twenty-eight individuals (25 females and 3 males) with subclinical hypothyroidism (defined biochemically as high serum TSH with simultaneously normal serum free T_4) as the study group and 30 age and sex matched subjects (27 females and 3 males) with normal thyroid function tests as the control group were enrolled into the study. None of the patients or controls had history of diabetes mellitus, neuromuscular, metabolic, vasculitic or rheumatologic diseases or were taking medications that may alter central or peripheral nerve function. Standard electrodiagnostic methods were used to study motor parameters including motor nerve conduction velocity, distal motor latencies, compound muscle action potential amplitude from median, ulnar, tibial and deep peroneal nerves, minimal-F-response from tibial, median and ulner nerves and sensory parameters including sensory nerve conduction velocity, sensory nerve action potential amplitude and distal sensory latencies from median, ulnar and sural nerves. In all patients and controls, values were obtained from both right and left sides. Values from patients were compared with those of controls by unpaired student's t-test.

Results: Motor and sensory nerve function values obtained from this electrophysiological study yielded no significant differences between patients with subclinical hypothyroidism and those with normal thyroid function.

Conclusion: The results of this study show that there are no significant alterations in peripheral nerve function in patients with subclinical hypothyroidism.

Key Words: Subclinical hypothyroidism, Peripheral neuropathy, Electrophysiologic parameters

Received: 08/07/2006- **Accepted**: 19/08/2006

Correspondence: SH Jalilzadeh, Department of Physical Medicine and Rehabilitation, Tabriz University of Medical Sciences, Tabriz, I.R.Iran
E-mail: t.u.end.d@tbzmed.ac.ir

Introduction

Thyroid hormones exert multiple effects on neural development and function.[1] Overt hypothyroidism is associated with significant alterations both in neuromuscular system and brain functions.[2] The neurological manifestations of clinical hypothyroidism in adults are varied and include peripheral neuropathy, en-

trapment neuropathy, mental dysfunction, hearing loss, seizures, possibly cerebellar ataxia and myxedema coma.[2,16-19] In some patients with clinical hypothyroidism, peripheral nerves dysfunction may be the main and presenting manifestation. Obviously, the frequency and severity of neuromuscular disease in overt hypothyroidism depend upon the severity and duration of thyroid hormone deficiency.

Subclinical hypothyroidism defined as a biochemical state characterized by an elevated serum TSH concentration with concomitant normal serum free thyroid hormone levels is a common disorder with an overall prevalence of 4-10 % in large general population screening surveys[3-6] and 7-26% in studies of the elderly.[1,2,7-9] Some believe that subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical and biochemical consequences.[10] In response to a validated survey regarding symptoms of subclinical hypothyroidism, subjects who were identified as having the disorder, more often reported having dry skin, poor memory, slow thinking, muscle weakness, fatigue, muscle cramps, constipation and cold intolerance.[4] Biochemically, subclinical hypothyroidism has been reported to be associated with abnormalities in serum lipids,[4,11] endothelial dysfunction,[12] accelerated atherosclerosis and coronary artery disease.[13]

Features of neuromuscular dysfunction attributable to subclinical hypothyroidism include abnormal myocardial contractility, skeletal muscle dysfunction and sensory and motor neurological impairment.[14,15] Electrodiagnostic studies have shown low conduction amplitude in peripheral nerves[20] and abnormal stapedial reflex[21] in patients with subclinical hypothyroidism. However, only a limited number of studies evaluated the functional alterations in central and peripheral nervous systems in patients with this disorder and the results obtained from these studies were controversial.[20-22] Thus, the effect of subclinical hypothyroidism on the function of peripheral nerves remains mainly uncertain. The aim of the present study was to evaluate the possible adverse effects of subclinical hypothyroidism on peripheral nerve function.

Materials and Methods

Twenty-eight subjects (25 females and 3 males) with newly discovered subclinical hypothyroidism (mean age 46.7 years) and 30 age and sex matched individuals (27 females and 3 males) without any history of thyroid disease and with normal TFTs (mean age 45 years) were enrolled into the study from among people who were admitted at ENT and ophthalmic outpatients' clinics of Sina medical center. Verbal informed consent was obtained from all subjects in the case and control groups. Demographic, clinical and laboratory characteristics of patients and controls are shown in table 1.

Table 1. Clinical and laboratory characteristics of patients and controls

	Patients (N: 28)	Controls (N: 30)	P value
Sex (female to male ratio)	25 F: 3M	27 F: 3M	
Age (mean ± SD)	46.7 ± 6.8	45 ± 8.6	NS
Serum TSH (mIU/mL)			
(mean ± SD)	9.56 ± 1.96	2.58 ± 1.96	< 0.001
(range)	6.9 – 13.5	0.7 – 4.2	
Serum free T4 (ng/dL)			
(mean ± SD)	1.33 ± 0.27	1.42 ± 0.9	NS
(range)	0.9 – 1.5	1.1 – 1.8	

Clinical Examination with more attention on neurological evaluation and thyroid size and consistency was performed in all patients and controls by an endocrinologist. A questionnaire for information regarding symptoms, medical history, demographic features, medications, personal and family history of thyroid disease was completed for both patients and controls. Patients with history of taking medications for thyroid problems, those with diabetes, alcoholism, renal failure, rheumatologic, metabolic or peripheral vascular disease, known neuromuscular disorders, or any other systemic diseases, pregnant women and those with abnormal neurologic findings were excluded from the study.

Thyroid function tests including serum TSH and free T_4 measurements were carried out by radioimmunoassay methods using reagents from Kavoshiar diagnostics commercial kits (Iran) for all patients and controls. Antithyroid peroxidase antibodies (anti-TPO) were determined with reagents from Kavoshiar in the 15 females in the patient group in whom the etiology of subclinical hypothyroidism was obscure and serum TSH was repeated to confirm elevated levels in this group. Subclinical hypothyroidism was defined as a state of elevated serum TSH with concomitant normal free T4 levels. The normal values for serum TSH and free T_4 were considered to be 0.3-4.5 uIU/mL and 0.8-1.9 ng/dL respectively. The etiologies of subclinical hypothyroidism were chronic autoimmune thyroiditis (diagnosed by positive anti-TPO antibodies) in 11 patients, radioiodine induced (radioactive iodine treated Graves' hyperthyroidism or toxic multinodular goiter) in 5 patients, subtotal thyroidectomy for Graves' disease in 2 and for multinodular goiter in 3 cases. Amiodarone, external neck radiation, and postpartum thyroiditis were responsible in 3 patients. In the remaining 4 cases the etiologies were unknown.

Electrodiagnostic studies were performed in all patients and controls using Biomid 2008 EMG-system equipment. The examination was done in (room temperatur 22-24^{o}C). During the study period the skin temperature was kept above 32^{o}C with a heating lamp. Motor nerve conduction velocity (MNCV), motor distal latency (MDL), and compound muscle action potential amplitude (CMAP Amplitude) were determined from median, ulnar, tibial and deep peroneal nerves bilaterally, using surface recording electrodes (needle size, 0.5×5 mm and interelectrode distance of 40 mm) and bipolar surface electrode for stimulation (interelectrode distance of 25 mm). The median and ulnar nerves were stimulated 8 cm above the active recording electrode at the wrist and elbow. The evoked muscle potentials were recorded from abductor pollicis brevis and abductor digiti minimi respectively. The tibial nerves were stimulated 8 cm above active recording electrode posterior to the medial malleolus and popliteal fossa. The evoked muscle potentials were recorded from the abductor hallucis muscle. The deep peroneal nerve was stimulated 8 cm above the active recording electrode at the ankle and head of fibula and the evoked muscle potentials were recorded from the extensor digitorum brevis muscle.

Minimal F-responses were measured in tibial, median and ulnar nerves bilaterally. The tibial nerve was stimulated 8 cm above active recording electrode posterior to medial malleolus with cathode proximal than anode and F-response was recorded from abductor hallocis muscle. The median and ulnar nerves were stimulated 8 cm above the active recording electrode at the wrist with cathode more proximal than the anode and F-responses were recorded from abductor pollicis brevis and abductor digiti minimi muscles respectively.

Sensory nerve conduction velocities (sensory NCV), sensory distal latency (sensory DL) and sensory nerve action potential Amplitudes (SNAPA) were measured antidromically from median, ulnar and sural nerves bilaterally, using a surface recording electrode (needle size, 0.5 × 5 mm and interelectrode distance of 40 mm) and bipolar surface electrode for stimulation (interelectrode distance

of 25 mm). Median sensory parameters were obtained from the third finger with stimulation of median nerve 14 cm proximal to wrist. Ulnar sensory parameters were obtained from the fifth finger with stimulation of ulnar nerve 14 cm proximal to the wrist. Sural sensory parameters were obtained from posterior to the lateral malleolus with stimulation of sural nerve 14 cm proximal lateral to Achilles tendon. The mean values of each electrodiagnostic parameter in patients with subclinical hypothyroidism and controls were compared using independent unpaired students t-test. $p<0.05$ was considered statistically significant.

Results

The mean±SD values for serum concentrations of TSH and FT_4 in patient and control groups have been documented in table 1. As shown there was no statistically significant difference between serum levels of free T_4 in both groups (1.33±0.27 vs.1.42±0.9 ng/dL, p=0.463) but TSH concentrations were significantly higher in patients than in controls (9.56±1.96 vs. 2.58±1.07 µIU/mL, $p<0.001$).

Table 2. Electrophysiological findings in patients with subclinical hypothyroidism and healthy controls

Electrodiagnostic parameter	Patients (n = 28)	Controls (n = 30)	P value
Tibial motor			
Amp cmap (m.v)	10.92 ± 2.5	10.97 ± 3.55	NS
Distal Latency (m/sec)	5.09 ± 2.5	5.17 ± 0.44	NS
NCV (m/sec)	45.59 ± 0.54	46.94 ± 4.27	NS
F (m/sec)	47.98 ± 4.26	46.56 ± 4.57	NS
H (m/sec)	28.29 ± 3.57	28.30 ± 1.78	NS
Peroneal motor			
Amp cmap (mv)	5.14 ± 1.15	5.16 ± 1.64	NS
DL (m/sec)	4.80 ± 0.40	4.70 ± 0.41	NS
NCV (m/sec)	46.87 ± 3.03	46.23 ± 3.83	NS
Median motor			
CMAP Amp (mv)	14.57 ± 4.90	14.85 ± 4.48	NS
DL (m/sec)	3.66 ± 0.20	3.67 ± 0.31	NS
NCV (m/sec)	55.73 ± 4.52	56.36 ± 4.70	NS
F (m/sec)	24.59 ± 1.95	24.72 ± 1.60	NS
Ulnar motor			
CMAP Amp (mv)	13.53 ± 4.07	13.30 ± 3.34	NS
DL (m/sec)	2.99 ± 0.33	3.09 ± 0.39	NS
NCV (m/sec)	57.92 ± 3.64	57.96 ± 4.26	NS
F (m/sec)	24.29 ± 1.90	24.94 ± 1.87	NS
Median Sensory			
SNAP Amp (µv)	40.79 ± 11.05	37.57 ± 11.55	NS
DL (m/sec)	2.69 ± 0.27	2.72 ± 0.23	NS
NCV (m/sec)	52.69 ± 4.51	51.83 ± 3.36	NS
Ulnar Sensory			
SNAP Amp (µv)	39.51 ± 12.19	36.61 ± 10.47	NS
DL (m/sec)	2.54 ± 0.21	2.60 ± 0.27	NS
NCV (m/sec)	54.21 ± 3.33	53.18 ± 3.78	NS
Sural Sensory			
SNAP Amp (µv)	16.92 ± 2.95	16.19 ± 3.84	NS
DL (m/sec)	2.69 ± 0.29	2.73 ± 0.30	NS
NCV (m/sec)	45.95 ± 3.02	46.40 ± 2.21	NS

CMAP Amp; Compound Muscle Action Potential Amplitude, DL; Distal Latency, NCV; Nerve Conduction Velocity, SNAP; Sensory Nerve Action Potential, NS; Not Significant

In the present work, a total of 25 electrophysiological parameters (the higher number studied so far) of peripheral nerves function, were studied in both patient and control groups. The obtained values (mean ± SD) in each group have been recorded and compared in table 2. Using independent unpaired student's t-test for comparison of obtained results, we found no statistically significant differences between the studied parameters in healthy controls and patients with subclinical hypothyroidism.

Discussion

Thyroid hormones exert multiple effects on neural development and function.[1] Overt hypothyroidism is associated with significant alterations in both the neuromuscular system and brain functions due to axonal damage or myelin abnormalities.[2] Peripheral nerve dysfunction in hypothyroid subjects may be clinical or subclinical. The subclinical neuropathies of hypothyroidism are detected by prolonged distal latencies in electrodiagnostic measurements. Prolonged distal latencies and slowing of motor and sensory functions of peripheral nerves have been shown in electrophysiologic evaluation of patients with overt hypothyroidism. Subclinical hypothyroidism defined as a biochemical state characterized by an elevated serum TSH concentration with concomitant normal serum free thyroid hormone levels is a common disorder.[3-6] Some believe that subclinical hypothyroidism represents mild thyroid failure and is a clinically important disorder that has adverse clinical and biochemical consequences.[10] Features of neuromuscular dysfunction attributable to subclinical hypothyroidism include abnormal myocardial contractility, skeletal muscle dysfunction and sensory and motor neurological impairment.[14,15] Electrodiagnostic studies have shown low conduction amplitude in peripheral nerves and abnormal stapedial reflex in patients with subclinical hypothyroidism.[20, 21] However, only a limited number of studies have evaluated the functional alterations in central and peripheral nervous systems in patients with this disorder and the results obtained from these studies were controversial.[20-22]

In the present investigation, 25 electrophysiologic sensory and motor parameters of peripheral nerves function were studied. The results showed no significant differences between values obtained for each parameter from patients with subclinical hypothyroidism and those from subjects with normal thyroid function. In agreement with the results of this study, Ozata and his co-workers assessed the principal electrophysiological parameters of peripheral nerves function in 27 patients with subclinical hypothyroidism and 20 age-and sex matched subjects without thyroid dysfunction. They were not able to find any significant differences between the measured electrodiagnostic parameters and interpeak latencies from patient and control groups. They concluded that subclinical hypothyroidism does not lead to alterations in peripheral nerve function.[22]

On the other hand, Misiunas et al studied electrophysiologic alterations in peripheral nerve function in 47 women. Subjects were divided into three groups: 1) Those with normal basal serum TSH but exaggerated TSH response to TRH, 2) Patients with high basal TSH and normal FT4 and 3) Those with normal thyroid function tests. Contrary to our results their findings showed incipient axonal alterations in patients with subclinical hypothyroidism (groups 1 and 2). The abnormality was more evident in patients with high basal levels of serum TSH. We were unable to explain the discrepancies between the two studies.[20] Deposition of glycosaminoglycans in nerves and soft tissues surrounding them with resultant axonal degeneration and secondary segmental demyelination forms the pathogenetic basis of alterations in peripheral nerve function in thyroid hormone deficiency, which is reversible with thyroxine replacement. In subclinical hypothyroidism

serum free thyroxine levels are maintained within normal limits by elevated TSH concentrations. Thus, it seems reasonable to find no significant impairment in peripheral nerve function in subclinical hypothyroidism.

In conclusion, the results of our investigation indicate that subclinical hypothyroidism does not lead to any degree of impairment of peripheral nerve motor or sensory functions.

References

1. Boyages SC, The neuromuscular system and brain in hypothyroidism, In: Braverman LE, Utiger RD editors. Werner & Ingbar's the thyroid: a fundamental and clinical text. 8th ed. Philadelphia: Lippincott Williams & Wilkins 2000. p. 803-10.
2. Tonner DR, Schlechte JA. Neurologic complications of thyroid and parathyroid disease. Med Clin North Am 1993; 77: 251-63.
3. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham survey. Clin Endocrinol (Oxf) 1977; 7: 481-93.
4. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000; 160: 526-34.
5. Rivolta G, Cerutti R, Colombo R, Miano G, Dionisio P, Grossi E. Prevalence of subclinical hypothyroidism in a population living in the Milan metropolitan area. J Endocrinol Invest 1999; 22:693-7.
6. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995; 43: 55-68.
7. Bagchi N, Brown TR, Parish RF Thyroid dysfunction in adults over age 55 years. A study in an urban U.S. community. Arch Intern Med 1990; 150: 785-7.
8. Sawin CT, Chopra D, Azizi F, Mannix JE, Bacharach P. The aging thyroid. Increased prevalence of elevated serum thyrotropin levels in the elderly. JAMA 1979; 242: 247-50.
9. Parle JV, Franklyn JA, Cross KW, Jones SC, Sheppard MC. Prevalence and follow-up of abnormal thyrotrophin (TSH) concentrations in the elderly in the United Kingdom. Clin Endocrinol (Oxf) 1991; 34: 77-83.
10. McDermott MT, Ridgway EC. Subclinical hypothyroidism is mild thyroid failure and should be treated. J Clin Endocrinol Metab 2001;86:4585-90.
11. Diekman T, Lansberg PJ, Kastelein JJ, Wiersinga WM. Prevalence and correction of hypothyroidism in a large cohort of patints referred for dyslipidemia. Arch Intern Med 1995; 155: 1490-5.
12. Lekakis J, Papamichael C, Alevizaki M, Piperingos G, Marafelia P, Mantzos J, et al. Flow-mediated, endothelium-dependent vasodilation is impaired in subjects with hypothyroidism, borderline hypothyroidism, and high-normal serum thyrotropin (TSH) values. Thyroid 1997; 7: 411-4.
13. Hak AE, Pols HA, Visser TJ, Drexhage HA, Hofman A, Witteman JC. Subclinical hypothyroidism is an independent risk factor for atherosclerosis and myocardial infarction in elderly women: the Rotterdam Study. Ann Intern Med 2000; 132: 270-8.
14. Monzani F, Caraccio N, Siciliano G, Manca L, Murri L, Ferrannini E. Clinical and biochemical features of muscle dysfunction in subclinical hypothyroidism. J Clin Endocrinol Metab1997; 82: 3315-8.
15. Monzani F, Caraccio N, Del Guerra P, Casolaro A, Ferrannini E. Neuromuscular symptoms and dysfunction in subclinical hypothyroid patients: beneficial effect of L-T4 replacement therapy. Clin Endocrinol (Oxf) 1999; 51: 237-42.
16. Torres CF, Moxley RT. Hypothyroid neuropathy and myopathy: clinical and electrodiagnostic longitudinal findings. J Neurol 1990; 237: 271-4.
17. Beghi E, Delodovici ML, Bogliun G, Crespi V, Paleari F, Gamba P, et al. Hypothyroidism and polyneuropathy. J Neurol Neurosurg Psychiatry 1989; 52: 1420-3.
18. Dyck PJ, Lambert EH. Polyneuropathy associated with hypothyroidism. J Neuropathol Exp Neurol 1970; 29: 631-58.
19. Meier C, Bischoff A. Polyneuropathy in hypothyroidism. Clinical and nerve biopsy study of 4 cases. J Neurol 1977; 215: 103-14.
20. Misiunas A, Niepomniszcze H, Ravera B, Faraj G, Faure E. Peripheral neuropathy in subclinical hypothyroidism. Thyroid 1995; 5: 283-6.
21. Goulis DG, Tsimpiris N, Delaroudis S, Maltas B, Tzoiti M, Dagilas A, et al. Stapedial reflex: a biological index found to be abnormal in clinical and subclinical hypothyroidism. Thyroid 1998; 8: 583-7.
22. Ozata M, Ozkardes A, Corakci A, Gandogan MN. Subclinical hypothyroidism does not lead to alteration either in peripheral nerves or in Brain stem Auditory evoked potentials. Thyroid 1995; 5: 201-205.