Cross-sectional area of the median nerve is increased in primary autoimmune hypothyroidism and decreases upon treatment with thyroxine

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Abstract

Background: The purpose of this study was to assess changes in the cross-sectional area (CSA) of nervus medianus by ultrasound in newly diagnosed primary hypothyroid patients after thyroxine replacement treatment.

Patients and methods: The cohort comprised 30 patients with newly diagnosed primary autoimmune hypothyroidism. These were subsequently compared with 30 controls, matched for sex, BMI and age. Ultrasound evaluation, including measurement of CSA at the level of the pisiform bone or tunnel inlet was performed at baseline and after 3 months. A CSA threshold of more than 10 mm² was considered pathological.

Results: CSA was increased in patients compared with controls (9.8 ± 0.7 mm² vs 7.2 ± 1.1 mm²; $P < 0.001$). Thyroxine substitution increased fT₄ levels (baseline, 11.0 ± 0.6 pmol/L vs 15.5 ± 0.4 pmol/L; $P < 0.001$) and decreased TSH (baseline, 23.9 ± 6.0 mIU/L vs 2.7 ± 0.2 mIU/L; $P < 0.001$). Thyroxine treatment decreased CSA to 8.4 mm² $\pm$ 0.3 mm² ($P = 0.033$). Before treatment, four patients experienced distal paresthesia in the median nerve distribution area. Increased CSA pathognomonic for carpal tunnel syndrome found in two symptomatic patients normalized after 3 months. No clinical symptoms were observed after 3 months. A positive correlation was found between TSH and CSA ($R = 0.155$, $P = 0.05$) before treatment.

Conclusion: Our study demonstrates that increase in median nerve CSA caused by primary autoimmune hypothyroidism can be fully reversible after achieving target levels of TSH and fT₄.

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Introduction

Thyroid hormones are involved in many functions of the central and peripheral nervous systems and, as a result, hypothyroidism may cause various neurological signs and symptoms (1). Chronic autoimmune thyroiditis is the most prevalent organ-specific autoimmune disease characterized by the presence of antibodies against thyroglobulin (anti-TG) and thyroid peroxidase (anti-TPO) (2). Autoimmune diseases have a broad spectrum of clinical manifestations. Among them, neurologic involvement, from both the central and the peripheral nervous systems, is one of the most challenging

manifestations, regarding the diagnosis and treatment of autoimmune diseases (3). Several studies that have examined nerve conduction parameters in hypothyroid patients reported that deficiency of thyroid hormones causes motor neuropathy by affecting different peripheral nerves, but, more commonly, the median nerve (4, 5, 6). A number of retrospective studies reported the prevalence of neuropathy to be between 10 and 70% in patients with hypothyroidism (1, 7, 8, 9). The most common form of peripheral entrapment neuropathy is carpal tunnel syndrome (CTS) (10). According to the

American Academy of Orthopedic Surgeons (AAOS), CTS is defined as a symptomatic median nerve compression neuropathy at the level of the wrist (11). The pathogenesis of abnormalities in peripheral nerves in patients with hypothyroidism include endoneurial accumulation of aminoglycane, as well as mucinous deposits in soft tissue surroundings of the peripheral nerves. These contribute to increased pressure on the median nerve at the wrist level (1, 9). Hypothyroidism produces alterations of fluid balance and peripheral tissue edema, which may lead to CTS development (1, 12). However, there are no data how autoimmunity plays a role in CTS pathogenesis. Consequently, treatment of hypothyroidism may help to minimize or cure CTS complaints (1, 12, 13, 14). Diagnosis is usually based on clinical symptoms and physical examination maneuvers, and is supported by nerve conduction studies (NCSs). In the literature review by the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) on the diagnosis of CTS, the sensitivity and specificity of NCS was 85 and 95% respectively (15). Ultrasonography (US) has been used as an alternative to NCS in the diagnosis of CTS (16). Despite some limitations, US of median nerve has not only been considered for the diagnosis of CTS, but also for the identification of the severity of median nerve damage. In comparison with NCS, US measurements from different sites were most consistent, and best sensitivity and specificity was reported for measures of cross-sectional area (CSA) of median nerve at the level of os pisiforme (17). Various studies have demonstrated that CSA of the median nerve at the carpal tunnel inlet and carpal tunnel outlet is significantly greater in CTS patients than in the normal population (15, 18, 19, 20). The CSA of the median nerve at the carpal tunnel inlet (at the level of the pisiform) is the most sensitive and specific US finding in patients with CTS. The cut-off value of CSA at the tunnel inlet in patients with CTS ranges from 6.5 to 15 mm² (19, 20, 21, 22). This difference in the cut-off point values of the tunnel inlet is due to the heterogeneity of study designs, different sample sizes, patient's characteristics and operator experience (21). Median nerve enlargement (CSA ≥ 10 mm² at the level of the pisiform bone or tunnel inlet) is the most commonly used parameter to diagnose CTS on US, and sensitivity has been reported to be as high as 97.9% using this parameter (16). To our knowledge, there have been no studies performed investigating autoimmune hypothyroidism and CSA using US. This study aims to provide novel information concerning US evaluation of CTS.

The primary objective of the study was to assess median nerve entrapment in patients with newly diagnosed and untreated autoimmune hypothyroidism in comparison with healthy adults. Furthermore, we assessed changes in the CSA by US before and following thyroxine treatment.

Patients and methods

Patients

We performed a cross-sectional, prospective follow-up study on 30 consecutive patients newly diagnosed with primary autoimmune hypothyroidism at the 5th Department of Internal Medicine, Medical Faculty of Comenius University, University Hospital Bratislava. The control group comprised age-, sex-, and BMI (Body mass index)-matched healthy controls. The control subjects had no history of any thyroid disorders and had a normal serum TSH and free T₄. The study protocol was approved by the ethics committee of the University Hospital Bratislava, and informed consent was obtained from all patients and controls according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh.

Inclusion criteria were as follows: newly diagnosed and untreated autoimmune hypothyroidism defined by thyroid-stimulating hormone (TSH) levels greater than 4.78 mIU/L and aTG plasma levels greater than 60 kIU/L and/or aTPO plasma levels greater than 60 kIU/L. No prior history or presence of any thyroid disorder or other conditions that may cause compressive neuropathy (e.g. diabetes mellitus, acromegaly, paraneoplastic, inflammation, alcoholism, liver and kidney disease, as well as mechanical overload) documented in patients cohort.

Laboratory investigations including complete blood count, serum glucose, creatinine, electrolytes, liver and kidney enzymes, vitamin B12 and folic acid were performed for all patients at baseline to eliminate other possible causes of neuropathy.

All patients received thyroxine treatment (mean: 83.5 µg, range: 25–125 µg) for hypothyroidism, and TSH and fT₄ levels were monitored for 3 months following baseline. Patients in control group underwent US evaluation at baseline and following 3 months.

Outcome measures

Thyroid function was assessed by measuring the concentration of TSH using a solid-phase, monoclonal

antibody-labeled chemiluminescent immunoassay (CLIA) (ADVIA Centaur and ADVIA Centaur XP; Tarrytown, NY, interassay coefficient of variability (CV), 3.55–5.51%); fT_4 using a solid-phase, polyclonal antibody-labeled CLIA (ADVIA Centaur and ADVIA Centaur XP; Tarrytown, NY, USA, interassay CV, 3.44–4.16%); thyroid peroxidase antibodies (TPO-Ab) using an electrochemiluminescence immunoassay (ECLIA) (Elecsys a cobas e analyzers, Basel, Swiss; interassay CV, 5.6–8.9%); and thyroglobulin antibodies (TG-Ab) using ECLIA (Elecsys and cobas e analyzers, Basel, Swiss; interassay CV, 5.8–6.0%).

Ultrasound

All patients underwent high-resolution real-time US of the carpal tunnel before and after thyroxine therapy. Ultrasound measurements were performed by a single operator using a 12 MHz linear array transducer (GE LOGIQ e portable ultrasound machine, Willowick, OH, USA). The US examination was performed with the patient seated in front of the sonographer, with the forearm resting on the table and the palm facing up in the neutral position. We performed transverse imaging of the median nerve for the area of the carpal tunnel inlet, which is defined as the proximal margin of the flexor retinaculum between the scaphoid tubercle and the pisiform bone. A longitudinal view was used to confirm the correct identification of the median nerve. The median nerve was observed on the screen as an oval or ellipsoid hypoechoic reticular area with a hyperechoic rim beneath the flexor retinaculum (19). The median nerve CSA was measured by the direct method (tracing method). Each measurement was performed five times. To prevent measurement error, the highest and lowest values were eliminated, and the remaining three measurements were averaged. This is the most extensive methodology for measuring the median nerve encountered among the studies (23).

Statistics

Statistical analysis was performed using the statistics software SPSS version 19 (IBM SPSS Statistics, IBM). Categorical data were expressed as the mean $\pm$ standard error of the mean (S.E.M.). Unpaired *t*-tests were performed for comparisons between the hypothyroidism subject and his/her control subject who was matched for age, sex and BMI. Paired *t*-test was used to compare baseline and post-treatment results in the hypothyroid group. Pearson correlation coefficients were calculated to analyze the

correlation between TSH, thyroid autoantibodies and CSA of the nervus medianus.

Results

Study group

Thirty patients were included in the study at baseline and comprised 22 women and 8 men. In the control group, 22 women and 8 men were included. The mean age of patients was 49.2 years, and in the control group, 52.6 years. No significant difference in sex, BMI and age was found between both the patient and control groups. Before thyroxine treatment, a significantly greater median nerve CSA of patients in comparison with controls ($9.8 \pm 0.7 \text{ mm}^2$ vs $7.2 \pm 1.1 \text{ mm}^2$; $P < 0.001$) was observed (Table 1). In patients cohort, CSA $> 11 \text{ mm}^2$ in four patients was recorded. Significant differences were found between TSH levels at baseline ($23.9 \pm 6.0 \text{ mIU/L}$) and after 3 months ($2.7 \pm 0.2 \text{ mIU/L}$; $P < 0.001$). In the cohort of patients, a number of 16 had TSH $> 10 \text{ mIU/L}$ and 14 patients had normal levels of fT_4 . In those 14 subjects, median nerve CSA was greater in comparison with controls ($9.8 \pm 0.4 \text{ mm}^2$ vs $7.2 \pm 1.1 \text{ mm}^2$; $P < 0.001$). In entire study group after thyroxine treatment, median nerve CSA significantly decreased ($9.8 \pm 0.7 \text{ mm}^2$ vs $8.4 \pm 0.3 \text{ mm}^2$; $P = 0.033$). After treatment, no difference in BMI was observed ($24.5 \pm 0.8 \text{ kg/m}^2$ vs $24.4 \pm 0.7 \text{ kg/m}^2$) (Table 2). None of the patients had BMI $> 30 \text{ kg/m}^2$ at baseline and after treatment.

There was a relationship between hypothyroidism and median nerve CSA. At baseline, a positive correlation was observed between TSH and CSA ($R = 0.155$, $P = 0.05$) (Fig. 1), and a negative correlation was found between fT_4 and CSA ($R = -0.149$, $P = 0.001$) (Fig. 2). No correlation was

Table 1 Baseline characteristics of patients and control groups. Data is presented as means or mean $\pm$ S.E.M.

Variable	Patients (n=30)	Control (n=30)	P-value
Sex (M/F)	8/22	8/22	> 0.05
Age (year)	49.2 ± 2.3	52.6 ± 2.9	
M/F (mean)	55.9/46.7	59.4/49.4	> 0.05
BMI (kg/m^2)	24.5 ± 0.7	24.5 ± 0.5	
M/F (mean)	27.1/23.5	26.4/23.6	> 0.05
TSH (mIU/L)	23.8 ± 6.0	2.3 ± 0.2	
M/F (mean)	33.9/20.2	2.3/2.3	< 0.001
fT_4 (pmol/L)	11.0 ± 0.6	16.5 ± 0.4	
M/F (mean)	10.6/11.1	16.5/16.4	< 0.001
CSA (mm^2)	9.8 ± 0.7	7.2 ± 1.1	
M/F (mean)	10.3/9.7	8/7	< 0.001

Table 2 Body-mass index, levels of thyroid-stimulating hormone and free thyroxine, and cross-sectional area before and after treatment with thyroxine. Data are presented as mean $\pm$ S.E.M.

Variable	Baseline	Month 3	P-value
BMI (kg/m ²)	24.5 $\pm$ 0.8	24.4 $\pm$ 0.7	>0.05
TSH (mIU/L)	23.9 $\pm$ 6.0	2.7 $\pm$ 0.2	<0.001
ft ₄ (pmol/L)	11.0 $\pm$ 0.6	15.5 $\pm$ 0.4	<0.001
CSA (mm ²)	9.8 $\pm$ 0.7	8.4 $\pm$ 0.3	0.003

observed between TSH, ft₄ and CSA after normalization of thyroid function after 3 months. This result was expected as a common physiological finding.

In four hypothyroid patients, clinical signs (e.g. distal paresthesias with weakness, tingling and pain in the distribution of the median nerve) of CTS were reported. Two of them had a baseline CSA measurement greater than 11 mm², which is considered pathognomonic for CTS. Following 3 months of appropriate hormone replacement, CSA values were normalized in these patients, and their symptoms resolved.

Discussion

Previous studies of ultrasound assessment of median nerve confirmed greater median nerve CSA in patients with thyroid dysfunction in comparison with healthy

Figure 1

Trend in CSA – TSH relationship. At baseline, a positive correlation was observed between TSH and CSA ($R=0.155$, $P=0.05$). A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0397>.

Figure 2

Trend in CSA – ft₄ relationship. At baseline, a negative correlation was found between ft₄ and CSA ($R=-0.149$, $P=0.001$). A full colour version of this figure is available at <http://dx.doi.org/10.1530/EJE-16-0397>.

controls. However, no previous study on thyroid hormone replacement-mediated effect on CSA was reported.

In this study, we performed ultrasound measurement of the median nerve CSA in patients which are due to thyroid dysfunction at higher risk of developing CTS, followed by US measurements after 3-month thyroxine treatment. The strengths of the study are prospective study design of consecutively included hypothyroid patients with carefully matched control group and using of high-tech US performed by a single examiner. We are aware of some limitations e.g. smaller sample size with low number of patients with clinical signs of CTS and presence of subclinical hypothyroidism in some patients.

Recent studies have shown that US is effective in confirming the diagnosis of CTS (24, 25, 26). Ultrasound has several advantages compared with NCS. First, other lesions that display symptoms similar to CTS may be excluded from examination, and these include tenosynovitis, mass lesions and anatomic defects. Furthermore, US is cheaper, widely available, involves a short examination time and it is more sensitive and less invasive than NCS. The use of US can be recommended as the first-line method in the diagnosis of CTS (24).

In this study, all patients with hypothyroidism were found to have significantly higher TSH levels and lower ft₄ levels compared with the control group. At baseline,

US measurement of the CSA at the level of the pisiform bone demonstrated a mean value of 9.8mm^2 in the patient group compared with 7.2mm^2 in the control group, which is comparable to results from previous studies (15, 19, 25, 26, 27). In the study group, 14 patients had fT_4 levels in normal range. Accumulation of mucopolysaccharides in the tendon sheaths and synovial membranes may cause CTS by loading pressure on the median nerve. It is obvious that this condition is more common in long-standing disease (28). Some studies have shown that the neuromuscular signs of hypothyroidism may be present in the subclinical forms as well (29, 30, 31). Despite this fact, a similar study by Jalilzadeh *et al.* indicated that there were no neuropathic or myopathic changes in patients with subclinical hypothyroidism, besides CTS (32). Study by Shiri using neuromuscular studies showed that symptoms of CTS are also seen in patients with hypothyroidism when they are euthyroid or they are on thyroid replacement therapy, but CTS was not a consequence of subclinical hypothyroidism (33). However, this study was aimed to detect the median nerve thickening measured by ultrasound regardless of clinical manifestation of thyroid disease or CTS. When statistical analysis was performed in subset of patients with normal fT_4 levels and increased TSH, the results for median nerve CSA still remain significantly elevated in comparison with healthy controls.

Changes in the BMI may potentially affect the integrity of the nerve. Werner *et al.* demonstrated that obese individuals ($\text{BMI} > 29$) are 2.5 times more likely to complain of CTS than slender individuals ($\text{BMI} < 20$) (34). The correlation between the CSA of the median nerve with BMI may exist. In this study, no significant difference in BMI was observed between patients and the control group; hence, our results do not appear to be influenced by this factor.

In our patient cohort with hypothyroidism, the CSA of the median nerve was greater in men ($10.3 \pm 0.4\text{mm}^2$) compared with women ($9.7 \pm 0.5\text{mm}^2$). The CSA of the median nerve was greater in men compared with women in control group as well. This result is similar to the study of 49 patients, who reported the CSA of the median nerve proximal to the carpal tunnel to be 2.2mm^2 higher in men than in women, although these patients did not have hypothyroidism (35).

To the best of our knowledge, there is no study comparing the effect of thyroxine treatment on the CSA in patients with primary hypothyroidism. We have performed a prospective follow-up study of patients treated with thyroxine over a 3-month period. The results

confirmed a significant decrease in TSH levels and CSA values after thyroxine treatment, with no change in BMI. At baseline, a significant correlation was observed between TSH, fT_4 levels and CSA values, although this relationship was not observed following normalization of TSH and fT_4 . This relationship confirmed that the CSA values in patients with overt hypothyroidism are directly influenced by levels of thyroid hormones.

Furthermore, at baseline, four patients were reported to have distal paresthesia in the distribution of median nerve, with weakness, tingling and pain. Pathologically increased median nerve CSA values (greater than 11mm^2) were documented in two of these patients. At 3 months, CSA values and clinical symptoms of CTS become normal in these four patients. This additional evaluation provides the opportunity to evaluate the efficacy of replacement therapy on the enlargement of the CSA of the median nerve, and aids in the prevention of unnecessary surgery in primary hypothyroidism patients with clinical signs of CTS. Follow-up of these patients demonstrated that the abnormalities related to entrapment neuropathy in hypothyroid patients can be reversed with adequate treatment.

This study demonstrated the influence of autoimmune hypothyroidism on structural alterations of the nerve, represented by US determinants of median nerve CSA, and thus evaluated the adverse effect of hypothyroidism on the median nerve. This study provides coherent data on the effect of primary hypothyroidism on the enlargement of the median nerve CSA. The data were evaluated with respect to median nerve CSA measurements and compared with BMI-, age- and sex-matched controls. Patients with untreated primary hypothyroidism were found to have a significantly greater CSA compared with healthy controls. In addition, the presence of entrapment neuropathy in hypothyroidism decreased after replacement treatment in newly diagnosed patients. The study provided a support to a well-known clinical observation that adequate treatment helps to prevent surgical decompression in CTS induced by hypothyroidism. Early treatment of hypothyroidism may impede the progression of neuromuscular complications or minimize their occurrence. Autoimmunity may potentially play an important role in the pathogenesis of nerve thickening associated with hypothyroidism; however, this has not yet been investigated. Ultrasound is a sensitive, noninvasive method for the diagnosis of CTS associated with hypothyroidism providing a metric which improves with substitution treatment of hypothyroidism, thus supporting the pathophysiology and clinical findings.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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