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RESEARCH ARTICLE

Carpal tunnel syndrome in Egyptianhypothyroid patients : Prevalence and relation with clinical , laboratory and electrophysiological findings

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Abstract

Background : Carpal tunnel syndrome (CTS) is the most common peripheral nerve entrapment syndrome. Hypothyroidism is included as an important risk factor for CTS , however, this association is still unclear.
Objective : To assessthe prevalence of CT in patients with hypothyroidism and to evaluate the relation between occurrence of CTS in these patients with clinical , laboratory and electrophysiological findings.
Patients & Methods : The study included 200 females, divided into 2 groups: 120 patients with primary hypothyroidism , and 80 healthy age - matched controls. All subjects were subjected to full history taking, thorough clinical examination (general and neurological), calculation of body mass index (BMI) and electrodiagnosis for CTS. Laboratory investigations were performed for all patients including measurement of serum levels of thyroid stimulating hormone (TSH) , free thyroxine (FT4) , free tri-iodothyroxine (FT3) , anti-thyroid peroxidase antibodies (anti-TPO) and anti-thyroglobulin antibodies (anti-TG).
Results : Hypothyroid patients had a significantly higher prevalence of CTS (35.8 %) as compared to the control group (8.8 %) ($p<0.001$). There was a significant relation between occurrence of CTS and patients' age and BMI ($p<0.001$). Patients not taking adequate thyroxine replacement therapy had significantly higher frequency of CTS in comparison to those receiving this therapy ($p<0.05$). There was a significant difference in serum levels of TSH, FT4, FT3, anti-TPO and anti-TG between hypothyroid patients with CTS andthose without CTS ($p<0.001$). **Conclusion** : CTS can be considered a common manifestation associated with hypothyroidism. Initial evaluation (clinical & electrophysiological) and regular checking for CTS in hypothyroid patients are recommended.

INTRODUCTION

Hypothyroidism is defined as failure of the thyroid gland to produce sufficient thyroid hormone to meet the metabolic demands of the body. Data derived from the National Health and Nutrition Examination Survey (NHANES III) suggest that about one in 300 persons in the United States has hypothyroidism**(Hollowell et al., 2002).**The prevalence increases with age, and is higher in females than in males **(Boucai et al., 2011)**.

Primary hypothyroidism may occur as a result of primary gland failure which can result from congenital abnormalities, autoimmune destruction (Hashimoto disease), iodine deficiency, and infiltrative diseases. Autoimmune thyroid disease is the most common etiology of hypothyroidism**(Gaitonde et al., 2012)**.The best laboratory assessment of thyroid function, and the preferred test for diagnosing primary hypothyroidism, is a serum TSH test. If the serum TSH level is elevated, testing should be repeated with a serum free thyroxine (T_4) measurement. Overt primary hypothyroidism is indicated with an elevated serum TSH level and a low serum free T_4 level**(Baskin et al., 2008).**

Carpal tunnel syndrome (CTS) is a median entrapment neuropathy that causes paraethesia , pain and numbness in the distribution of the median nerve due to its compression at the wrist in the carpal tunnel**(Mc Carten et al., 2005).**CTS accounts for about 90 % of all nerve compression syndromes **(Ibrahim et al., 2012)**. CTS is an increasingly recognized cause of work disability **(Katz et al., 1998)** and is associated with considerable health care and indemnity costs **(Feuersteinet al., 1998).**

Most cases of CTS are of unknown causes **(Stembach, 1999)**.However , CTS can be associated with any condition that causes pressure on the median nerve at the wrist. Some common conditions that can lead to CTS include diabetes mellitus , hypothyroidism and connective tissue diseases **(Katz and Simmons ,2002).**

The present study was conducted to determine the prevalence of CTS in patients with primary hypothyroidism and to evaluate the relation between development of CTS in these patients with clinical , laboratory and electrophysiological findings.

Patients and Methods

Selection of patients:

The study included 120 patients with primary hypothyroidism diagnosed by thyroid hormones profile. These patients were selected from the outpatient clinics of Endocrinology, Neurology, Rheumatology and Rehabilitation , Zagazig University Hospitals, during the period from December 2013 to December 2014. All patients were females, their ages ranged from 18 - 65 years with a mean ± SD of 42.16 ± 10.22.

Eighty apparently healthy age-matched females served as a control group for the nerve conduction study.

Exclusion criteria: Pregnant women and patients with diabetes mellitus , other endocrinal diseases , connective tissue diseases , hepatic and renal disorders were excluded from the study. Patients with previous distal radius fracture and those with cervical radiculopathy or with a history of medication leading to neuropathy were also excluded. To avoid the risk factor of patient's sex and occupation , all subjects involved in this work were females and housewives.

The study was approved by Zagazig Medical Ethical Committee. Informed written consents were taken from all participants.

All patients and controls were subjected to the following:

- Detailed history taking including demographic data, disease duration , symptoms suggesting CTS , duration and dose of thyroxine replacement therapy , history of any other medications or other diseases.
- Full clinical examination (general and neurological) with stress on Phalen's sign **(Phalen , 1966)** , Hoffmann - Tinnel's sign **(Limke and Stien , 1997)**, pinprick sensation and pain was assessed using a visual analogue scale (VAS) **(Tay , 2006)**. Body mass index (BMI) was calculated.
- Radiological examination : Plain x-ray and magnetic resonance imaging (MRI) on cervical spines to exclude disc lesion if suspected.

Electrodiagnosis:

Electrodiagnosis of the upper limb was performed at room temperature for all patients and controls with a Viking Quest Nicolet electromyography apparatus. Conduction studies of the median and ulnar nerves and median nerve F-wave latencies were assessed in both upper extremities using standard methods **(Oh , 2003).**

Motor conduction studies were performed using an orthodromic method and superficial disc electrodes. Electrodes were placed over the abductor pollicis brevis muscle for the median nerve and the adductor digiti minimi muscle for the ulnar nerve. The active recording electrode was placed on the belly of the examined muscle and the reference electrode was placed on the tendon insertion. Compound muscle action potential (CMAP) was obtained by stimulating the median nerve at the wrist (5 cm proximal to the active recording electrode placed on the abductor pollicis brevis muscle) and antecubital fossa and the ulnar nerve at the wrist (5 cm proximal to the active recording electrode placed on the adductor digiti minimi muscle) and at the ulnar sulcus. Motor distal latency (DL) was measured from the beginning of the stimulus artifact to the onset of the action potential. Peak-to-peak CMAP amplitude was measured.

Sensory conduction studies were performed using antidromic method and ring electrodes. Digit2-wrist segment was used for median sensory nerve conduction studies and digit 5 - wrist segment was used for ulnar sensory nerve conduction studies. Sensory NCVs were calculated from the beginning of the stimulus artifact to the onset of the sensory nerve action potential (SNAP). Peak-to-peak amplitudes were measured.

F-wave study was performed for the median nerve by recording from the same muscle using the electrode placement mentioned above. Active stimulating electrode was placed proximally and at least 10 successive supramaximal stimulations were given. Minimum F-wave latency (F min) was recorded. CTS was diagnosed electrophysiologically if the median nerve sensory NCV was decreased and/or motor DL was prolonged.

Motor nerve conduction velocities below 50 m/s were considered abnormal **(Tan , 2004).**

Sensory nerve conduction velocities were considered abnormal if below 56.9±4 m/s for median nerve or below 57±5 m/s for ulnar nerve. Peak latencies of SNAPs of both median & ulnar nerves more than 3.2 ms were considered prolonged. F wave latencies above 29.1±2.3 for median nerve were considered prolonged **(De Lisa et al., 1994)**.

According to the criteria of **Padua et al., (1997)**, the severity of CTS was graded as negative (normal findings), minimal or very mild (abnormal sensory nerve conduction study of the palm–wrist segment), mild (abnormal sensory nerve conduction study of any of the finger–wrist (digits I–III) segments and normal motor DL), moderate (abnormal sensory nerve conduction study of any of the finger–wrist (digits I–III) segments and prolonged motor DL), severe (absence of the compound nerve action potential of any finger–wrist segment and prolonged motor DL), extreme (absence of compound nerve action potential of any finger–wrist segment and CMAP).

The palm wrist segment SNCV was calculated by subtracting the SNCV of third digit to the palm from the SNCV of third digit to the wrist **(Tan , 2004).**

Laboratory investigations:

Laboratory investigations were performed for all patients including:

I - Routine investigations : as complete blood picture, blood glucose level, liver and kidney function tests.

II- Thyroid hormones and thyroid antibodies:

Venous blood was extracted under aseptic conditions, and put into plain vacutainer tubes and allowed to clot .The samples were centrifuged for about 10 minutes then the serum was separated and kept at - 20˚C till the time of assay.

- Estimation of thyroid hormones:

Serum TSH , FT4 and FT3 were estimated using the Immulite 1000 system (Siemens Diagnostics) which is a fully automated solid-phase third generation immunoassay analyzer that has a chemiluminescent detection system.

Normal ranges for TSH is 0.3 - 4.0 uIU/ml , for FT4 is 0.71 - 1.85 ng / dl and for FT3 is 1.45 - 3.48 pg/ml

- Estimation of Anti-thyroid peroxidase antibodies (Anti-TPO):

This was done using Elecsys 2010 Immunoassay autoanalyzer (Roche diagnostics) by electro-chemiluminescence immunoassay (ECLIA) . Test principle: Samples are incubated with anti-TPO antibodies labelled with a ruthenium complex. After addition of biotinylated TPO and streptavidin-coated microparticles , the anti-TPO antibodies in the sample compete with the ruthenium conjugated anti-TPO-antibodies for the biotinylated TPO antigen. The immunocomplexes produced then bound to the solid phase. Chemiluminescence is induced when a voltage is applied to the electrode on which the microparticles are captured.

The results are calculated from a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the reagent bar code. Normal range is 0-35 IU/ml , so values greater than 35 IU/ml are considered positive.

- Estimation of Anti-thyroglobulin antibodies (Anti-TG):

It was done using the DRG-Anti-thyroglobulin ELISA kit (DRG International Inc., USA) . Test principle : Human autoantibodies to thyroglobulin in patient serum bind to the purified thyroglobulin on the microwells. After a washing step to eliminate the excess serum proteins , an enzyme labelled protein A is added to bind to the antigen-antibody complex in the microwells by its ability to bind to IgG antibodies. Excess enzyme is eliminated by a second wash step. After addition of a substrate the color is developed and its intensity is proportional to the amount of anti-TG in samples. The color is measured and quantitated by reading a dose response curve (DRC). Normal range is 0-100 U/ml, so values greater than 100 U/ml are considered positive.

Statistical analysis:

Data were analyzed using SPSS software package version 18.0 (SPSS, Chicago, IL, USA). Quantitative data were expressed using mean ± standard deviation , while qualitative data were expressed in frequency and percentage. Quantitative data were analyzed using Student's t-test to compare between the two groups. For comparing qualitative data , Chi square (X^2) test was performed. Fisher exact test was used when the expected frequency was less than 5. P value was considered significant at < 0.05 and highly significant at < 0.001.

Results

This study was carried out on 200 females, 120 patients suffering from primary hypothyroidism and 80 healthy age-matched volunteers were taken as a control group. There were non-significant differences between both groups as regard age and BMI (Table 1).

Table (1): Demographic and clinical data of hypothyroid patients and controls

		Hypothyroid patients (No.= 120)	Controls (No.= 80)	P value	Sig.
Age (Years)		42.16 ± 10.22	40.09 ± 10.07	0.127	NS
BMI		32.38 ± 6.35	29.84 ± 6.14	0.089	NS
Disease duration (Years)		11.61 ±8.12	-	-	-
Thyroxine replacement therapy	With No. (%)	67 (55.83 %)	-	-	-
	Without No. (%)	53 (44.17 %)			

BMI : Body mass index
NS : Non-significant

Prevalence and severity of CTS in hypothyroid patients and controls:

By clinical examination, only 32 patients and 4 of control subjects had positive signs for CTS, in the form of positive Phalen's sign or Tinnel's sign or pinprick sensation.

By electrophysiological studies, the prevalence of CTS in hypothyroid patients was 35.8 % (n=43), while it was 8.8 % (n=7) in the control subjects (Table 2). This means that 11 hypothyroid patients and 3 control subjects had subclinical CTS and diagnosed electrophysiologically.

We compared the prevalence of CTS between patients and control subjects. Hypothyroid patients had a significantly higher frequency of CTS as compared to the control group (p<0.001). According to the criteria of**Padua et al., (1997).**Moderate CTS was more frequent among the patients (p<0.001). Table (2) demonstrates these findings.

Table (2): Comparison between hypothyroidpatients and controls as regard the frequency and severity of CTS

Degree of CTS	Hypothyroid patients (No.= 120)	Controls (No.= 80)	P value	Sig.
Minimal	7 (5.8 %)	4 (5 %)	0.865	NS
Mild	12 (10 %)	3(3.8%)	0.113	NS
Moderate	21(17.5%)	0 (0%)	< 0.001	HS
Severe	2 (1.7 %)	0 (0 %)	0.427	NS
Extreme	1 (0.8 %)	0 (0 %)	0.784	NS
No. of CTS	43 (35.8 %)	7 (8.8 %)	<0.001	HS

Values are expressed as numbers (percentages)
NS : Non-significant
HS : Highly significant

Through the questionnaire and clinical examination of the 43 hypothyroid patients with CTS , the predominant sensory symptoms were paraethesia and numbness present in 72.1 % and 65.1 % of patients respectively. By clinical examination , only 8 patients (18.6 %) had abductor pollicis brevis (APB) muscle wasting and 9 (20.9 %) had APB weakness. Phalen's sign and Tinnel's sign were positive in 35 (81.4 %) and 33 (76.7 %) respectively. Regarding the side of the affected limb , electrophysiological study showed that unilateral and bilateral involvement with CTS occurred in 37 (86 %) and 6 (14 %) respectively , however right and left hand involvement were 28 (65.1 %) and 9 (20.9%) respectively. These findings are shown in Table (3).

Relationship between occurrence of CTS and demographic & clinical data of hypothyroid patients:

In this study, there was a highly statistically significant relation between occurrence of CTS and patients' age and body mass index (BMI) ($p<0.001$). Patients not taking adequate thyroxine replacement therapy , for at least 3 months before enrolment in this study, had significantly higher frequency of CTS in comparison to those receiving this therapy ($p<0.05$). These results are shown in Table (4).

Relationship between occurrence of CTS and laboratory findings of hypothyroid patients:

In the present study , there was a highly statistically significant difference in serum levels of TSH , FT4 , FT3 , anti-TPO and anti-TG between hypothyroid patients with CTS and those without CTS ($p <0.001$) as shown in Table (5).
In the 120 hypothyroid patients, the frequency of anti-TPO positive cases was 63.3 % (76 patients) while the frequency of anti-TG positive cases was 35.0 % (42 patients).

Table (3) : Clinical and neuropathological findings in the 43 hypothyroid patients with CTS

Findings	No.	%
Sensory symptoms		
- Paraethesia	31	72.1
- Numbness	28	65.1
Motor symptoms		
- Muscle wasting	8	18.6
- Muscle weakness	9	20.9
Clinical signs		
- Phalen's sign	35	81.4
- Tinnel's sign	33	76.7
Nerve conduction studies		
- Unilateral	37	86.0
- Bilateral	6	14.0
- Right hand	28	65.1
- Left hand	9	20.9

Table (4): . Comparison of demographic and clinical data of hypothyroid patients with and without CTS

		Hypothyroid patients with CTS (N0. =43)	Hypothyroid patients without CTS (N0. =77)	P value	Sig.
Age (Years)		50.32 ± 11.72	36.19 ± 10.02	< 0.001	HS
BMI		37.41 ± 8.82	28.02 ± 7.47	< 0.001	HS
Disease duration (Years)		12.14 ±8.46	10.96 ±7.89	0.283	NS
Thyroxine replacement therapy	With (67)	14 (20.9 %)	53 (79.1 %)	< 0.05	S
	Without (53)	29 (54.7 %)	24 (45.3 %)		

BMI : Body mass index
NS : Non-significant
S : Significant
HS : Highly significant

Table (5) : Comparison of thyroid hormones and thyroid autoantibodies levels in hypothyroid patients with and without CTS

	Hypothyroid patients with CTS (N0. =43)	Hypothyroid patients without CTS (N0. =77)	P- value	Sig.
Serum TSH (uIU/ml)	22.14 ± 4.37	8.42 ± 1.24	< 0.001	**HS**
Serum FT4 (ng/dl)	0.46 ± 0.04	1.15 ± 0.07	< 0.001	**HS**
Serum FT3 (pg/ml)	1.22 ± 0.17	2.38 ± 0.29	< 0.001	HS
Anti-TPO (IU/ml)	82.16 ± 12.61	39.86 ± 7.42	< 0.001	HS
Anti-TG (IU/ml	129.49 ± 31.54	76.10 ± 18.26	<0.001	HS

Values are expressed as mean ± SD
TSH : Thyroid stimulating hormone
FT4 : Free thyroxine
FT3 : Free tri-iodothyronine
Anti-TPO: Anti-thyroid peroxidase antibodies
Anti-TG :Anti-thyroglobulin antibodies
HS : Highly significant

Discussion

Thyroid hormones are involved in many functions of the central and peripheral nervous system and as a result, hypothyroidism may cause various neurological signs and symptoms **(Khedr et al., 2000 and Yuksel et al., 2007).**

Nerve conduction parameters in hypothyroid patients were studied to observe the incidence of neuropathy and functional status of peripheral nerves in thyroid deficiency. Most of them had reported that deficiency of thyroid hormones cause neuropathy by affecting different peripheral nerves but more commonly the median nerve **(Yeasmin et al., 2007).**

The mechanism involved in the development of neuropathy in hypothyroidism still remains unclear. Mononeuropathies secondary to compression caused by deposition of mucopolysaccharide or mucinous deposits in the soft tissues surrounding peripheral nerves and
a polyneuropathy due to either a demyelinating process or primary axonal degeneration are the most commonly proposed mechanisms of peripheral nerve dysfunction in hypothyroidism **(Arikan et al., 2005).** Myelin structure abnormalities and dysfunction of axonal-oligodendroglial processes may also be responsible for neuropathy in patients with hypothyroidism **(Ferracci and Carnevale , 2006 and Galea et al., 2007)**.Also, hypothyroidism produces alterations of fluid balance and peripheral tissue edema, which may lead to CTS development **(Beghni et al., 1989).**

It has been reported that one third of patients with CTS have an underlying cause including hypothyroidism , diabetes mellitus and rheumatoid arthritis **(Atcheson et al., 1998)**.In the study of **de Riik et al., (2007)**, it was found that 6 % of patients with carpal tunnel syndrome had hypothyroidism and they concluded that systematic screening for hypothyroidism , diabetes mellitus and connective tissue diseases in patients with CTS who have not been diagnosed with these underlying diseases before leads to a limited number of newly detected patients.

Many other studies have been done investigating the association between CTS and hypothyroidism , however , these studies only looked at the prevalence of hypothyroidism in patients with CTS and not vice versa **(van Diik et al., 2003 and Ernest and Ian , 2004).**

Therefore, we designed this research to study the prevalence of CTS in patients with primary hypothyroidism and to evaluate the relation between development of CTS in these patients with clinical , laboratory and electrophysiological findings.

In the present study , the prevalence of CTS (detected electrophysiologically) was higher in hypothyroid patients (35.8 %) than in control subjects (8.8 %). The difference was highly statistically significant (P < 0.001). The same finding was also reported by **Palumbo et al., (2000).**This finding supports the hypothesis that hypothyroidism is considered a risk factor for development of CTS.

Also , our results were in agreement with **Kececi and Degirmenci(2006)** who found that electrophysiological evaluation revealed CTS in 15 out of 40 hypothyroid patients (37.5 %).

Prevalence of CTS in hypothyroid patients was variable in different studies. It was 30.4 % (7 out of 23 patients) in the study of **Samanci et al., (2003)** , and 29 % (7 out of 24 patients) in the study performed by **Duffy et al., (2000)**.However **, Palumbo et al., (2000)**reported a relatively lower prevalence 23.1 (%). They found that 6 out of 26 hypothyroid patients had electrical studies that supported the diagnosis of CTS.

The difference in percentages of prevalence of CTS in hypothyroid patients in different studies may be due to the different number of patients included , and also may be attributed to the different inclusion and exclusion criteria applied in each study.

Patient's sex and occupation may be risk factors for development of CTS . To avoid this, all subjects in the present work were females and housewives. We performed ulnar nerve conduction studies and median nerve F-wave latencies in this research to exclude patients with peripheral neuropathy and root affection.

In our study , the majority of patients with CTS presented with right hand involvement more than left hand or bilateral. These findings were in accordance with many studies **(Tay , 2006 , Abd-Elaty et al., 2002 and Zeid et al.,2003).**

We reported a highly statistically significant relation between the occurrence of CTS and patients' age and body mass index (BMI) (p<0.001). This finding was also reported by Kouyomdjan et al., (2002) who concluded that presence of CTS was significantly related to increasing age and high BMI.

Regarding effect of hormone replacement therapy on the occurrence of CTS, we found that patients not taking adequate thyroxine replacement therapy, for at least three months before enrolment in our study, had significantly higher frequency of CTS in comparison to those receiving this therapy. Our finding agrees with Bland (2005) who stated that the risk of developing CTS increases when thyroid disease is untreated. This result is also supported by Kececi and Degirmenci (2006) who concluded that the findings related to CTS in hypothyroid patients can be reversible in a period of three months of appropriate hormone replacement treatment. They stated also that the chance of medical treatment must be given to patients before considering surgical treatment. Also , Kasem et al., (2014) reported that with hormone replacement therapy , CTS can be reversed in patients with hypothyroidism within three months.

Laboratory investigations in the present study showed that there was a highly statistically significant difference in serum levels of TSH , FT4 , FT3 , anti-TPO and anti-TG between hypothyroid patients with CTS and those without CTS (P <0.001) . To our knowledge, there are no previous researches studying the relationship between occurrence of CTS in hypothyroid patients and levels of thyroid hormones and thyroid autoantibodies.

In our 120 hypothyroid patients, the frequency of anti-TPO positive cases was 63.3 % (76 patients) while the frequency of anti-TG positive cases was 35 % (42 patients). These percentages are in agreement with **Saravanan and Dayan (2001) and Sapin et al., (2003)** who stated that in patients with hypothyroidism, 50% to 90% have detectable anti-TPO antibodies while 30% to 50% have detectable anti-TG antibodies.

In conclusion , the present study demonstrated that CTS can be considered a common manifestation associated with hypothyroidism , and there is a strong association between development of CTS and serum level of thyroid hormones and autoantibodies.
Initial evaluation (clinical & electrophysiological) and regular checking for CTS in hypothyroid patients are recommended. Further studies are required to establish the role of other diagnostic procedures in diagnosis of CTS in hypothyroid patients. Plan for rehabilitation studies is needed to improve the health of hypothyroid patients with CTS.

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