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EFFECT OF LEVOTHYROXINE ON CARPAL TUNNEL SYNDROME IN PRIMARY HYPOTHYROIDISM

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ABSTRACT

Context: The prevalence of carpal tunnel syndrome(CTS) in hypothyroidism varies greatly in different studies ranging from 7 – 90%. There are very few studies evaluating the effect of levothyroxine on CTS in hypothyroidism. Aims: To estimate the prevalence of CTS in primary hypothyroidism(PH) at diagnosis and to compare the electrophysiological findings before and after levothyroxine replacement therapy(LRT).

Materials and methods: 54 subjects aged above 18 years diagnosed with PH were included. Subjects were divided into mild, marked subclinical hypothyroidism(SCH) and overt hypothyroidism based on T4 and TSH. Nerve conduction studies including median motor and sensory nerves were performed at the onset of the study and after 3 months of LRT.

Results: At the onset, electrophysiological evaluation revealed CTS in 11(20.4%) subjects of whom 10 had bilateral CTS. Of these 11 subjects, 7 were obese, 8 had marked SCH and 9 had TPOAb (thyroperoxidase antibody) positivity. After LRT only 5 had CTS. The differences between values of median motor distal latency, median sensory distal latency and conduction velocity before and after treatment were statistically significant.

Conclusion: CTS was bilateral in 90%. CTS was more common in subjects who were obese and had marked SCH and TPOAb positivity. Normalisation of TSH with LRT significantly reversed the electrophysiological abnormalities.

KEYWORDS : Primary hypothyroidism, levothyroxine, nerve conduction studies, carpal tunnel syndrome

INTRODUCTION

The prevalence of carpal tunnel syndrome(CTS) in hypothyroidism varied greatly in different studies ranging from 7-90%(Faraz, Singhal, Hossain, & Siddiqui, 2017; Karne & Bhalerao, 2016; Kececi & Degirmenci, 2006; Rao, Katiyar, Nair, & Misra, 1980). CTS may be symptomatic or asymptomatic. CTS is progressive and nerve conduction studies(NCS) help us to diagnose asymptomatic CTS early. Appropriate levothyroxine replacement therapy(LRT) reverses the findings related to entrapment neuropathy and polyneuropathy in hypothyroidism(Kececi & Degirmenci, 2006). Though there are many studies regarding prevalence of CTS in hypothyroidism, there are only very few studies evaluating the effect of levothyroxine on CTS in hypothyroidism. This study was performed to find out the prevalence and the effect of LRT on CTS in newly diagnosed primary hypothyroidism(PH).

PATIENTS AND METHODS

This was a prospective follow up study from April 2017 to Dec 2018. Newly diagnosed PH subjects, aged 18 - 60 years attending the outpatient departments of Endocrinology, King George Hospital(KGH), Visakhapatnam were enrolled in the study. Informed consent was taken from every subject. Study was approved by Institutional Ethics Committee / KGH. Exclusion criteria being subjects with known causes of neuropathy like diabetes mellitus, alcoholism, liver or kidney diseases, rheumatoid arthritis, malignancy, megaloblastic anaemia, pregnancy, any abnormal clinical presentation known to produce neuropathy, subjects using drugs known to produce neuropathy ,above and below the specified age limit.

A detailed history, general and neurological examination was performed. Subjects were classified into underweight < 18.5 kg/m2 , normal 18.5 – 22.9 kg/m2 , overweight 23-24.9 kg/m2 , obese >= 30 kg/m2 according to WPRO(western pacific region of WHO) classification of obesity in Asia. All subjects underwent haematological, T3 , T4, TSH and TPOAb testing. Reference values for our laboratory for TSH is 0.3 - 4.5 mIU/L , T4 is 4.5 – 12.6 mcg/dl, T3 is 60-180 ng/dl and TPOAb is positive if value is >60 IU/L. All the thyroid function tests were done using CLIA (chemiluminiscent immunoassay) method with Beckman Coulter Access 2 machine.

Subjects were classified according to American thyroid association guidelines into overt hypothyroidism (OH) with high TSH and low T4, Mild subclinical hypothyroidism (SCH) with TSH >4.5 - <=10 mIU/L and normal T4, Marked SCH with TSH >10mIU/L and normal T4. After confirming PH, all the subjects underwent NCS at baseline. NCS was done with Nicolet Viking machine in bilateral median nerves as per our laboratory standards. Distal latencies(DL), CMAP amplitudes, SNAP amplitudes, conduction velocity(CVs) were recorded. NCS was considered abnormal if there was any reduction of CMAP/SNAP amplitudes, reduction in CV, increased DL of more than two standard deviations. Table 2 shows normal limits(NL) for median motor and sensory NCS, which were established earlier in the laboratory.

Treatment with levothyroxine was started according to the standard guidelines and were followed up monthly with TSH. Subjects with OH and marked SCH received LT4 at a dose of 1.6 mcg/kg/day, while mild SCH were started with LT4 25 mcg/day. The dose was titrated at monthly follow up until biochemical euthyroidism was achieved. After achieving biochemical euthyroidism with normalisation of TSH, at the end of 3 months from starting treatment all subjects underwent NCS. Statistical analysis was done using IBM SPSS Statistics for Windows, Version 21.0. Descriptive statistics were expressed as means and percentages. Inferential statistical analysis was done using chi-square tests for nominal and ordinal variables, and paired "t" test for comparision of means. P-value of <0.05 was considered statistically significant.

RESULTS

A total of fifty four subjects with newly diagnosed PH were enrolled in the study . The baseline characteristics of study population is showed in table 1. Three of all subjects had symptoms and signs suggestive of upper extremity neuropathy. All subjects completed follow-up.

Table 1 : Baseline characteristics of study population

Variable	Range	Mean
Age(yrs)	19-60	35.12
BMI(kg/m2)	15.11-36.44	25.15
T3(ng/dl)	19-178	108.05
T4(mcg/dl)	0.42-10.73	5.43
TSH(mIU/L)	6.18-150	4.44
TPOAb (IU/ml)	1.8-1300	470.88

Of all subjects, 46 (88.88%) were female and 8 (11.12%) were male. 22 (40.74%) of subjects belong to 19-30 years, 19 (35.18%) belong to 31-40 years, 11 (20.37%) belong to 41-50 years, 2 (3.71%) belong to 50-60 years. Of all subjects, 11 (20.38%) were overweight, 21 (38.88%) were obese and 22 (40.74%) belonged to normal weight at baseline. In obese 17 were female and 4 were male, in overweight 7 were female and 4 were male and 22 of normal weight were female (P value – 0.017). At baseline 35.18% (n=19) subjects had OH, 65% (n=35) had SCH of which 11% (n=6) had mild SCH and 54% (n=29) had marked SCH. Of total 54 subjects, 36 (66.66%) were TPOAb positive and 18 (33.34%) were TPOAb negative. 4,19 and 13 subjects had TPOAb positivity in mild SCH, marked SCH and OH respectively.

Based on initial electrodiagnostic evaluation, 11(20.4%) subjects had evidence of CTS, of which 10 had bilateral CTS. All the three subjects who were clinically symptomatic had bilateral CTS. 5(45.45%), 4(36.36%), 2(18.19%) of CTS subjects belong to 30-40, 40-50, 50-60 years respectively. 72.72%(n=8) of CTS subjects were female and 27.28%(n=3) were male(p value – 0.337). 7(63.63%) were obese and 1(10.1%) was overweight(p value- 0.161). 8 of the 11 CTS had marked SCH and 3 had OH. 9 of the 11 subjects(81.8%) were TPOAb positive(P value 0.082).

After treatment at the end of 3 months, mean TSH was 2.13 mIU/L(p value – 0.000).

Two subjects had symptomatic neuropathy even after TSH normalisation. Of 11(20.4%) CTS at baseline, only 5(9.25%) had CTS at the end of three months and all these five had bilateral CTS. Of the two symptomatic patients after treatment , one had normal NCS and one had persistant CTS findings. Of 5 CTS patients after treatment, 4 were TPOAb positive and obese, 4 had marked SCH and one had OH.

Table 2 shows mean DL, amplitudes and CVs of median motor and sensory nerves before and after treatment.

Differences between mean DL of right median motor nerve(p value- 0.011) , left median motor nerve(p value- 0.043), right median sensory nerve(p value- 0.013) , left median sensory nerve (p value- 0.008) and CV of right median sensory nerve(p value- 0.005), left median sensory nerve (p value- 0.012) before and after treatment were statistically significant. Mean CMAP, SNAPs and CV of median motor nerves had no statistical significance.

Table 2 : Mean latencies, amplitudes and CVs of all median nerves before and after treatment

NERVE	BEFORE THERAPY	AFTER THERAPY	NL	t	P
RIGHT Median motor					
DL	3.728	3.554	4.2	2.627	0.011
CMAP	12.98	13.561	4.4	-1.846	0.71
NCV	58.241	58.389	49	-0.805	0.424
LEFT Median motor					
DL	3.694	3.613	4.2	2.068	0.043
CMAP	13.072	13.470	4.4	-1.324	0.191
NCV	57.852	57.963	49	-0.383	0.704
RIGHT Median sensory					
DL	3.565	3.465	3.5	2.580	0.013
SNAP	52.574	53.519	20	-1.600	0.115
NCV	53.463	55.63	52	-2.964	0.005
LEFT Median sensory					
DL	3.652	3.509	3.5	2.769	0.008
SNAP	56.574	56.167	20	0.545	0.588
NCV	53.741	55.389	52	-2.618	0.012

DISCUSSION

The association between hypothyroidism and CTS was first reported in the medical literature in 1954 in a patient with CTS and myxoedema(Schiller & Kolb, 2012). The prevalence of CTS in PH in the present study was 20.4%. The reported prevalence of CTS in hypothyroidism was between 7% to as high as 92%(CREVASSE & LOGUE, 1959)(Purnell, 1961)(Schiller & Kolb, 2012). Although hypothyroidism is considered as an important risk factor for CTS, the nature of association between hypothyroidism and CTS is obscure(Purnell, 1961). The prevalence of CTS in our study was 20.4%, which was lower when compared to the earlier studies(Khedr, Toony, Tarkhan, & Abdella, 2000)(Karne & Bhalerao, 2016). The varying prevalence of CTS in all these studies could be due to differences in the sample size, baseline characteristics of the subjects, duration of disease and treatment regimens.

Our study showed significantly prolonged DLs and slowed CVs in median nerve, concordance with earlier studies(Kececi & Degirmenci, 2006)(El-Salem & Ammari, 2006). NCV denotes fastness with which nerve signal spreads, and is determined by myelination, diameter and length of the axon(Kennett & Aurangzeb, 2016). Decrease in the NCV in this study might be due to decrease in thyroid hormone levels leading to demyelination. This study showed a high prevalence of asymptomatic nature of CTS (66.6%) and NCS picks up CTS early, which helps us to intervene ealy. In this study, 90% of CTS were bilateral and all symptomatic CTS were bilateral. In contrast to studies showing that age increases risk of CTS(Blumenthal, Herskovitz, & Verghese, 2006)(Bland, 2005), in this study majority of CTS subjects belonged to 31-50 years and no association was seen with age. This may be because of less number of CTS subjects in our study.

In this study gender has no significant association with CTS. One study showed female gender and older age group were associated with more severe CTS, with a significant interaction between age group and BMI(Bland, 2005). CTS had no significant association with overweight or obese subjects in this study compared to previous studies(Agarwal & Gaur, 2015)(GOUVEIA, KOUYOUMDJIAN, MORITA, ROCHA, & MIRANDA, 2005)(Karne & Bhalerao, 2016). In our study, CTS was more common in marked SCH probably due to more number of subjects with marked SCH. A previous study showed that there are no significant alterations in peripheral nerve function in SCH(Jalilzadeh SH, Bahrami A, 2006) In this study, of 11 CTS, 9 had TPOAb positivity , but there is no statistical significance. There were no earlier studies correlating TPOAb with CTS. One study showed that TPOAb might be associated with acute demyelinating myeloneuropathy(Turkoglu & Tuzun, 2010).

The present study focused on the effects of PH on CTS and improvement in CTS following appropriate LRT. In our study, of 11 CTS only five (9.25%) still had electrophysiological evidence of CTS after LRT. There was statistically significant differences between mean DLs and CVs of median nerve at baseline and after treatment in our study. This suggests that the mechanisms leading to CTS in PH might be reversible at early stages. Irreversible cases might have longer duration of disease or hypothyroidism which led to permanent changes in nerves or might take longer time than 3 months to restore NCS abnormalities. So, there may be no need to carry out additional treatment for CTS especially in early stages. In our study, obese, TPOAb positivity and higher TSH had persistent CTS after treatment. In our study, two patients were symptomatic even after achieving biochemical euthyroidism. Previous studies revealed that despite obtaining biochemical euthyroidism, most patients with PH experience symptoms and electrophysiological signs of CTS(Katirji, 2012)(Purnell, 1961)(Shirabe, Tawara, Terao, & Araki, 1975). In contrary, earlier studies indicate that CTS symptoms improve with LRT(Cruz, Tendrich, Vaisman, & Novis, 1996)(Kececi & Degirmenci, 2006).

The majority of previous studies in hypothyroidism patients analysed NCS before treatment, in this study, we compared NCS before and after LRT. This gives the opportunity to evaluate the efficacy of levothyroxine therapy on CTS. The results of this study demonstrate that the abnormalities related to entrapment neuropathy in PH can be reversed within 3 months with LRT. Therefore, in the presence of CTS, a trial of medical therapy can be given to subjects before considering surgery in PH. Early detection of PH is important to treat with

levothyroxine as to prevent electrophysiological abnormalities.

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