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SILENT CENTRAL NERVOUSSYSTEM FFECTION INCASES OF SUB CLINICAL HYPOTHYROIDISM

By

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ABSTRACT

Background: Hypothyroidism is one of the greatest endocrinal disorders that can affect the central nervous system

Objective: To assess silent affection of central nervous system among cases of subclinical hypothyroidism.

Patients and methods: A group of Fifty cases of sub clinical hypothyroidismreferredfrom outpatients' clinic of Internal Medicine Department to Neurophysiology unit of Neurology Department of Al-Azhar University hospital in new Damietta, and another euthyroid group of fifty, age and gender matched healthy persons. The electrophysiological study of both groups was done including Electroencephalography and evoked potentials (auditory and visual).

Results: As regard to EEG, Eighteen patients (36%) had EEG abnormalities. thir teen patients (26%) had diffuse slowness of background activity formed mainly of theta wave activity with or without paroxysmal high voltage theta or delta wave activity (16%).Auditory evoked potentials (ABR)showed significant prolongation, of III &V wave latencies , and inter peak latencies of I-V, & III-V among the subclinical group on comparison with the control group, and also of significant prolonged latency of wave I of left ear and without correlation with thyroid stimulating hormone serum level. Visual evoked potentials (VEP) showed a significant prolongation of P100 latency in-group of sub clinical hypothyroidism on comparison with control group. There was no correlation between the TSH serum level and evoked potential latencies (ABR and VEP)

Conclusion: The central nervous system can be early affected in sub clinical hypothyroidism and the follow up electrophysiological assessment is recommended

Keywords: subclinical hypothyroidism, Auditory brainstem evoked response (ABR), Visual evoked potential (VEP), and Electroencephalograph (EEG).

INTRODUCTION

Thyroid disorders are the most common disorder among the endocrinal disorders that can affect the nervous system. Hypothyroidism is one of the insidious diseases, and has significant comorbidity. Subclinical hypothyroidism ((SCH) is defined when Thyroid Stimulating Hormone (TSH) exceeds the upper normal serum level with normal serum free T4 level **(Silva and Costa, 2013).**

The sub clinical hypothyroidism prevalence is 4-10% **(Al Eidanet al., 2018)**. The subclinical hypothrodism commonly affecting the elderly and more among females than males **(Silva and Costa, 2013).** Central nervous system is frequently affected in hypothyroidism with documentation of central delays as abnormal auditory brainstem evoked potential delayed latencies. And abnormal delayed visual evoked potentials latency and short amplitude **(Gupta et al., 2016) , and** (**Gupta et al., 2017).**

Thyroxin deficiency affects the brain function, and the first and prominent manifestations is impairment of vision and slow thinking **(Davis and Tremont, 2007)**

Hearing affection iscommon in cases of hypothyroidism, but the actual incidence is uncertain. It may affect 25% in cases of acquired and 35-50 % of cases with congenital hypothyroidism **(Kowsalya et al.,2011)**.

The evoked potentials is an objective and reliable measurements of the related sensory function and tracts. In addition,it is sensitive to detect silent lesion in these tracts. The Visual Evoked Potential (VEP) can assess the visual pathway up to visual cortex (**Dubey et al., 2022).**

Thyroid hormones have essential roles in neurotransmission,axonal transportation, and myelin formation. Thyroid hormone deficiency cause disturbance in impulse conduction and perception **(Jayanthi and Vinodha, 2016).**

Evoked potentials are principally appropriate for a noninvasive assessment of a numeral of afferent paths in nervous system**(Dubey et al., 2022).**

The furthermost prevalent disorder forgoing the manifest hypothyroidism is subclinical hypothyroidism**.** This can be identified when normal titraiodothyroxin (T3) and free thyroxin (T4) serum levels but thyroid stimulating hormone of high serum level. The thyroid hormonesare essential in development, growth of neurons and myelination**(Jaiswal and Dhankad, 2020).**

The neurophysiological studies showed abnormal measurements in cases of subclinical hypothyroidism, and the studies in valuation of nervous system (central and peripheral) in patients with sub clinical hypothyroidism is insufficient and contra-versed **(Jaiswal and Dhankad, 2020)**.Sub clinical hypothyroidism representation is common in outpatient clinic by a symptoms like sexual dysfunction, paresthesia, chronic fatigue, myalgia, psychiatric symptoms, and mild cognitive impairment or asymptomatic **(Silva and Costa, 2013).**

The aim of the present study was to assess objectively the silent changes of central nervous system function among cases of subclinical hypothyroidism.

Patients and Methods

Fifty consecutivesrecently diagnosed subclinical hypothyroid patients referred from outpatients' clinic of Internal Medicine Department to Neurophysiology unit of Neurology Departmentof Al-Azhar University Hospitalin new Damietta, and

50age and gender matchedeuthyroid healthy persons attended to the out patients as relatives to our stuffand students. The study was ethically approved by the Institutional Review Board of Damietta Faculty of Medicine, Al-Azhar University, and we excluded from our study the subject who have: (a) Other systemic sicknesses like: renalimpairment, diabetes, obstructive lung disease, liverimpairment, rheumatoidarthritis, dyslipidemia, malignancy, vitamin deficiency, historyofalcoholism,and manifest thyroid disease. (b) Patients with hearing problems as detected on history and examination, which interfere with auditory brain stem evoked potential (like multiple sclerosis, cerebellopontine angle lesions, brainstem stroke, or hearing loss). (c) Patients with visual diminishing as noticed on the history and examination, which affect the visual evoked potential (like glaucoma, cataract, marked visual impairment, vitreous opacities, multiple sclerosis, or any cerebral causes affecting the visual pathway).

Biochemical analysis of thyroid function included quantity TSH, free T3, and free T4 serum level. Subclinical hypothyroidism (SCH) was demarcated when serum level of thyroid stimulating hormone (TSH) beyond the high level of normal even with normal serum level of free thyroxine**(Silva and Costa, 2013).** The subclinical hypothyroidism was diagnosed when TSH level outdid the normal range (0.27-4.5 uIU/ mL), and FT4 within normal range (0.93-1.7ng/dL).

Evoked potentials (auditory and visual) Studies were piloted via Nihon Kohden machine, Model UT- 0800 J. Box BOARD (2CH) For JB-942BK, (made in Japan). Subjects scalp were washed with soap and water on the day of the record. We placed the disc electrodes according the 10-20 standard system using adhesive conducting paste.

Auditory brainstem evoked potentials (ABR):

The electrodes were placed as followed: Reference electrode on vertex(Cz), the active on mastoid of each stimulated ear, and the ground on forehead.
The earphone stimulators: The click stimulus at rate of 11 HZ of 90 dB intensity delivered to the stimulated ear, and on other non stimulated ear masking sound of 40 dB. The filter setting ranged from low cut (100 Hz) to high cut (3000 Hz). The sweep speed: 1 ms/division, and sensitivity at 0.5 μv/division.1000 auditory responses were summated and analyzed and displayed as ABR latencies and inter peak latencies (I,III,V,I-III,III-V, and I-V) measurements**(Karl etal., 2003 , and Ali & Al-Adl, 2021).**

Visual evoked potential (VEP):

VEPs were recorded by using a pattern reversing checkerboard. The filter frequency was 1–100 Hz, analysis time 300 ms, sensitivity 20 uV/division, rate of stimulation 1 Hz and averaging 200. The electrode placements: The reference electrode on the vertex (Cz), the active on occiput (Oz), and the ground on forehead. Stimulator: A pattern reversing checker board presented on a monitor 1 meter from a tested eye in semi dark room at rate 1-2 Hz , the subject instructed to fix the examined eye at fixation point and cover the other eye. The visual response were summated and analyzed and displayed as P100 latency among VEP response witch including negative wave latencies (N 75 and N 145) and positive wave latency (P100)**(Karl et al., 2003 , and Ali & Al-Adl, 2021).**

Conventional watchfulness EEGs were recorded consuming an 20-channel EEG system - Medicom MTD using scalp electrodes Placed according to the international 10-20 system with referential and bipolar montages. Photic and hyperventilation stimulation were done as

provoking tests.

Statistical analysis: The collected data were analyzed using the SPSS version 25. The data were expressed as means and standard deviation. Numerical data were compared by student t test for means. Pearson Correlation Coefficient test was used for study the correlation between TSH level and parameters of evoked potentials (visual and auditory) within the subclinical hypothyroidism group. P< 0.05 was considered significant.

Results

On comparison of both groups as regard of age distribution and mean serum level of T4 no significant difference, and significant difference as regard of TSH mean serum level (Table1).

Table (1): comparison between group I(control) and group II (subclinical hypothyroidism) as regard of age, T4 and TSH serum level.

Groups / Parameters	Group I (n :50) Mean±SD	Group II (n :50) Mean± SD	P value
Age(mean±SD)	38.5 ±4.22	39.11±5.04	0.513
FT4(ng/dl)	1.1±0.21	1.2±0.31	0.062
TSH (uIU/mL)	3.25 ±0.36	5.91±0.54)	<0.001

FT4:free thyroxin . TSH: thyroid-stimulating hormone

Auditory brain stem evoked potential (ABR): Latencies and inter peak latencies of both ears showed significant prolongation of III&V wave latencies , and inter peak latencies of I-V, & III-Vamong the subclinical group on comparison with the control group, and also of significant prolonged latency of wave I of left ear.(Tables2&3).

Table (2): Comparison of absolute latencies and inter-peak latencies of group I (control) and group II(sub clinical hypothyroid patients) of right ear ABR

Groups / Waves	Group I (n :50) Mean± SD	Group II (n :50) Mean± SD	P value
Wave I	1.59±0.19	1.67±0.25	0.075
Wave II	2.74±0.24	2.76±0.3	0.241
Wave III	3.64±0.21	3.86±0.47	0.003*
Wave IV	4.7±0.4	4.91±0.51	0.241
Wave V	5.47±0.35	6±0.61	<0.001*
IPL I-III	2.05±0.22	2.17±0.42	0.077
IPL I-V	3.89±0.3	4.17±0.51	0.001*
IPL III-V	1.85±0.3	2.2±0.36	<0.001*

*P value<0.05. BAEP: Brainstem auditory evoked potential

Table (3): Comparison of left ear ABR absolute latencies and inter-peak latencies of control (group I) and sub clinical hypothyroid patients (group II)

Groups / Waves	Group I (n :50) Mean± SD	Group II (n:50) Mean± SD	P value
Wave I	1.55±0.16	1.75±0.31	<0.001*
Wave II	2.64±0.23	2.87±0.44	<0.002*
Wave III	3.65±0.28	3.98±0.8	<0.007*
Wave IV	4.66±0.39	5.08±0.72	<0.001*
Wave V	5.49±0.26	6.17±0.89	<0.001*
IPL I-III	2.1±0.3	2.24±0.61	0.149
IPL I-V	3.94±0.31	4.27±0.55	<0.001*
IPL III-V	1.84±0.34	2.08±0.32	<0.001*

*P value<0.05.

Visual evoked potential (VEP): There was a significant prolongation of P100 latency in group of sub clinical hypothyroidism on comparison with control group (Table4).

Table (4): Comparison of visual evoked potential (VEP) P100 latency of group I and group II

Groups / Parameters	Group I (n :50) Mean± SD	Group II (n :50) Mean± SD	P value
Rt eye P100 latency(ms)	98.72±0.89	109.47±1.71	<0.001*
Lt eye P100 latency(ms)	97.71±0.89	108.46±1.70	<0.001*

The correlation between mean serum level of TSH and evoked potential latencies (ABR & VEP): There was no significant correlation between TSH serum levels and various latencies of ABR and VEP waves (Table 5).

Table (5): correlation between TSH serum level and various latencies of evoked potentials (ABR and VEP)

TSH / Parameters	Correlation coefficient (r)	P value
Rt Wave I latency	0.1	0.35
Lt Wave I latency	0.09	0.71
Rt Wave III latency	0.19	0.36
Lt Wave III latency	0,24	0.26
Rt Wave V latency	0.18	0.34
Lt Wave V latency	0.34	0.31
Rt IPL (III-V)	0.22	0.26
Lt IPL(III-V)	0.23	0.23
R t IPL (I-V)	0.2	0.2
Lt IPL (I-V)	0.21	0.22
Rt VEP P 100 latency	0.22	0,26
lt VEP P 100 latency	0,21	0.22

Electroencephalography EEG: Eighteen patients (36%) had EEG changes. Thirteen patients (26%) had diffuse slowness of background formed mainly of theta wave activity with or without paroxysmalhigh voltage theta or delta wave activity (16%) (Table 6).

Table (6): EEG changes among patients of sub clinical hypothyroidism::

variables	No of patients	% of patients
Normal EEG	32	64
Abnormal EEG	18	36
Diffuse slowness of back ground	13	26
Paroxysmal high voltege	8	16
Paroxysmal sharp activity	4	8

DISCUSSION

In our study, ABR and VEP results were suggestive of central nervous system affection in cases of subclinical hypothyroidism. P100 latency showed significant prolongation on comparison with control group and withoutsignificant correlation with thyroid stimulating hormone,and this co agreed with **Gupta et al. (2016)** and **Sankareswari et al. (2016)** who observed prolonged P 100 latency in patients with early stage of hypothyroidism which also reported improvement of P100 latency on treatment.**Tamburini et al. (1989)** noted that 3 patients of 9 recently diagnosed hypothyroid patients had aberrantly increased latencies, while 7 had a lesser than ordinary amplitude,and attribute these changes to metabolic derangement and not to structural abnormalities,where thyroid hormones have essential role in neurotransmission, axonal transportation and myelin formation. Thyroid hormone deficiency causes disturbance in impulse conduction, and perception lack of thyroid hormones affect the mitochondrial oxidation leading to lack of ATP and lack of proteins synthesisthat causing oxidative damage of myelin sheath and oligodendroglial cells resulting demyelination and latency prolongation of P100, and ABR wave latencies **(Jayanthi & Vinodha, 2015 and Jayanthi & Vinodha, 2016). .**

Khedr et al. (2000) also found a significant increased P100 latency and decrease of VEP amplitudes in hypothyroid cases on comparison with the healthy group. However, there wasno correlation between these findings and thyroid stimulating and thyroid hormonal serum levels. The ABR waves have different sources, and so each wave represented activity of its generator source. Wave I signify peripheral nerve but other waves II.III.IV and V signify cochlearnucleus,superior olivary nucleus, lateral lemniscus and inferior colliculus,correspondingly. I-III interpeak latency represent the conduction across the acoustic nerve throughsubarachnoidspace into the lower pons. I-V interpeak latency representsconduction across proximal acoustic nerve over pons to midbrain. III-V inter peak latency represent neural conduction across the lower pons to mid brain. Thus, ABR is useful for testing the hearing pathway in cases of subclinical hypothyroidism **(Sharma et al., 2015)**

In our study, latencies and inter peak

latencies of both ears showed significant prolongation of III &V wave latencies , and inter peak latencies of I-V, & III-V among the subclinical group on comparison with the control group, and also of significant prolonged latency of wave I of left ear and without correlation with thyroid stimulating hormone serum level.This reach agreement with **Sharma et al. (2015)** where they concluded that cases of subclinical hypothyroidism with normal hearing showed prolonged V wave latency in ABR of both ears that mean central auditory pathway was significantly affected in subclinical hypothyroid cases.**Gupta etal. (2016)**reported prolonged all ABR latencies and inter peak latencies of hypothyroid group on comparison with control group**.Ozata et al. (1995**) reported in their study no significant changes in BAEP in group of subclinical hypothyroidism on comparison with the control group.

In our study,the common EEG abnormality was diffuse slowness of background with and without paroxysmal high voltage activity that can be interpreted by cerebral hypoperfusion and this co agreed with **Frochetti et al. (1997**) and **Khedr et al. (2000)** who studied patients with rapidly progressive dementia, and using EEG and single photon emission tomography subclinical hypothyrodism which were reversed with treatment.

Conclusion:The subclinicalhypothyroidism can affect the central nervous system sub clinically and so the electrophysiological examination must be done for all cases of subclinical hypothyroidism for early diagnosis and early treatment.

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تأثر الجهاز العصبي المركزي الصامت في حالات قصور الغدة الدرقية تحت الإكلينيكي

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خلفيــة البحــث : يعتبــر قصــور الغــدة الدرقيــة أحــد أكثــر اضــطرابات الغــدد الصــماء التــي يمكــن أن تــؤثر علــى الجهاز العصبي المركزي

الهــدف مــن البحــث: تقيــيم التــأثير الصــامت للعصــب المركــزي بــين حــالات قصــور الغــدة الدرقيــة تحــت الإكلينيكي.

المرضى وطرق البحث : تمت إحالة خمسين مريض من مرضى القصور السريرى للغدة الدرقية الذين تم تشخيصهم حديثًا من العيادة الخارجية لقسم الباطنية العامة إلى وحدة الفسيولوجيا العصبية فيقسم المخ والأعصاب بمستشفى الأزهر الجامعى بدمياط الجديدة , ومجموعة ضابطة من الاصحاء من نفس اعمار المرضى وكان عددهم خمسون. وتم إجراء الدراسة الفيسيولوجية الكهربية لكلتا المجموعتين بما في ذلك تخطيط كهربية الدماغ والجهود المستحثة للعصب السمعى البصرى لجميع المجموعات المدروسة .

نتــائج البحــث: بالنســبة للتخطــيط الكهربــائي للــدماغ ، كــان 36٪لــديهم نشــاط غيــر طبيعــى فــي مخطــط كهربيــة الــدماغ: (26 ٪) عــانوا مــن تبــاطؤ منتشــر فــي نشــاط الخلفيــة يتكــون أساسًــا مــن نشــاط موجــة ثيتــا مــع أو بدون الانتيابي

نشــاط موجــة ثيتــا أو دلتــا ذات الجهــد العــالي ' 16٪. أظهــرت الإمكانــات الســمعية المحفــزة إطالــة كبيــرة فــي زمــن انتقــال V فقــط بــين المجموعــة الســريرية الفرعيــة بالمقارنــة مــع المجموعــة الضــابطة: وقــد أظهــرت الإمكانــات المرئيــة المحرضــة إطالــة معنويــة فــي زمــن انتقــال P100 فــي مجموعــة قصــور الغــدة الدرقيــة الســريري مقارنــة بمجموعــة الــتحكم', لــم يكــن هنــاك ارتباطــا بــين مســتوى الهرمــون المحفــز للغــدة الدرقيــة فــى الــدم وزمــن الكمــون للموجــات III&V وايضــا الــزمن البينــى بــين المجــات V-I & V-III و وزمــن الكمون للموجة P100 وتغييرات التخطيط الكهربى للدماغ.

الاســتنتاج: يمكــن أن يتــأثر الجهــاز العصــبي المركــزي مبكــرًا بقصــور الغــدة الدرقيــة الســريري ويوصــى بالمتابعتــة المبكــرة مــن خــلال التقيــيم الفســيولوجي الكهربــائي (تخطــيط كهربيــة الــدماغ والجهــود المســتحثة للعصب السمعى البصرى) .

الكلمــات الدالــة: قصــور الغــدة الدرقيــة تحــت الإكلينيكــي ، الفيســيولوجيا الكهربيــة ، كهربيــة الــدماغ والجهــود المستحثة للعصب السمعى والبصرى .