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RESEARCH ARTICLE

Subclinical Hypothyroidism: behavioral and psychophysiological characteristics. A pilot study

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Abstract

Background: Clinical hypothyroidism affects various aspects of cognitive and affective brain function. The most severe hypothyroidism may also mimic a picture of melancholic depression and dementia. Subclinical hypothyroidism (SHT) is characterized by elevated TSH levels despite normal thyroid hormone concentrations. The aim of this research is to verify the presence of a typical psychophysiological pattern in SHT patients.

Methods: Since 1998 fifty patients who underwent surgeries at the Department of Endocrinology, University of Pisa, diagnosed with SHT, were subsequently recruited. Subjects underwent an inspection of the reported symptoms using the Crown & Crisp Experiential Index, and a psychophysiological assessment with a simultaneous recording of the parameters Skin Conductance Level/ Response (SCL/SCR), Surface Frontal Electromyogram (EMG), Peripheral Temperature (PT), Heart Rate (HR). As a control group, fifty subjects without endocrine disorders were subsequently recruited.

Results: Data shows little difference in levels in hormonal assays except for TSH. There is also a significant elevation of some of the CCEI subscales: Anxiety, Depression, and Somatic Complaints. At the autonomic level, there is a general pattern of excessive arousal with significant differences in SCL/SCR, HR, and PT.

Conclusions: A first data interpretation is that in sub-clinical hypothyroidism, the body tries to support and integrate the general lack of energy with an acceleration of the autonomic activity. This condition of initial arousal could be a useful indicator in order to monitor the treatment course and its effectiveness on the pathological evolution.

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INTRODUCTION

Subclinical hypothyroidism (SHT) occurs when serum TSH concentrations are raised and serum thyroid hormone concentrations are normal; it occurs in 4–20% of the adult population and may have various causes. In about 60–80% of cases, the disorder is associated with antithyroid peroxidase antibodies, a marker of chronic lymphocytic (Hashimoto's) thyroiditis. Thyroid hormones exert important effects on the adult brain and it is widely accepted that overt hypothyroidism is associated with psychological disorders and neuropsychiatric symptoms. Neuropsychiatric symptoms refer to a spectrum of emotional and cognitive problems directly related to changes in the brain of multiple factors (Cooper, Biondi, 2012; Almeida et al., 2007; Monzani et al., 1991; Monzani et al, 1993 May; Chueire et al., 2007; Davis et al.,

2003; De Jongh et al., 2011 ; Demartini et al., 2010).

Hypothyroidism affects various aspects of cognitive and affective brain function. The most severe hypothyroidism may also mimic a depiction of melancholic depression and dementia. The patient is frequently characterized by dysphoria, anxiety, restlessness, emotional lability and impaired concentration (Gulseren et al., 2006; Ge et al., 2013).

In hypothyroid patients, everything seems to move in slow motion, frequent mood is depressed and typical symptoms of major depression may be present (DSM-V, APA, 2013). They are apathetic, and they report fatigue and loss of interest in sex. Some have suicidal thoughts, and many complaints of memory loss and have symptoms such as difficulty sustaining attention even for short periods and a slowing of thought processes, which suggest the presence of cognitive impairment. A gradual increase of dysphoric reactions and irritability, isolation from friends or family members, and suspiciousness may also indicate changes in personality.

The majority of studies support the existence of a relationship between the state of thyroid function and cognition, in particular its relationship to the phenomena of reduced speed of cognitive processes, reduced efficiency in executive functions and reduced learning. Hypothyroidism is, in fact, associated with significant neurocognitive deficits involving attention and concentration, memory, perceptual function, defective language, executive functions, , disorientation in space and time, loss of autonomy, emotional depersonalization and other mental defects. Low thyroid function irrespective of age has been found to have a detrimental effect on cognitive functions because hypothyroidism prevents the brain from adequately sustaining the energy (glucose)-consuming processes needed for neurotransmission, memory and other higher brain functions (Reuters et al., 2012).

Also the cardiovascular system is directly affected; in overt hypothyroidism, vital signs reveal bradycardia, diastolic hypertension and in severe cases hypotension as a result of the depressed cardiac output. Overall cardiac output is decreased, due to the slower heart rate and decreased contractility (Liappas et al., 2009).

Neuropsychiatric symptoms tend to improve with therapy and with the restoration of a euthyroid state; although the response is variable and full recovery is not entirely certain.

It's in dispute, however, the extent of the effects that subclinical hypothyroidism actually exercises on mood or cognitive function, as well as the effect of therapy on neuropsychiatric symptoms in these cases (Sharma et al., 2014; Dubbs et al., 2014 ; Almeida et al., 2007 ; Ergür et al., 2012 ; Joffe et al., 2013; Feb; Parle et al., 2010).

In the subclinical hypothyroidism all these cohorts of depression-like behavior, sometimes accompanied by subtle hyperactivity of Hypothalamic–pituitary–adrenal axis, as was evidenced in a trial conducted on rat model , are more nuanced but do not always occur with moderate seriousness (Samuels 2010).

Rather, there may be symptoms "patchy" and, among these, the most frequent is depression. Controlled studies suggest that the cognitive and mood symptoms respond to treatment, although the data is controversial and methodologically limited. In addition, functional neuroimaging data support the existence of cognitive and affective changes and the reversibility of these phenomena with the therapy, in subclinical hypothyroidism as well. This data, however, is not uncontroversial. Recent studies on the impact of subclinical hypothyroidism on cognition and mood and epidemiological studies designed to assess the normal range of TSH in the population have stimulated considerable debate on the identification of the real and appropriate normal range of TSH. In particular , the doubt arose that patients with overt hypothyroidism can be undertreated, and that patients with subclinical hypothyroidism may be substantially outside the range of normal thyroid function and should , in fact , be treated (Yamamoto et al., 2012).

Moreover, next to nothing has been studied about the autonomic characteristics of this clinical population.

The aim of this study is to assess psychopathological symptoms and autonomic nervous system activation in patients diagnosed with subclinical hypothyroidism, in order to possibly identify typical patterns that could be useful for treatment planning and evaluation.

Material and Methods

Since 1998, fifty patients who underwent surgeries at the Department of Endocrinology, University of Pisa, Italy, diagnosed with a form of SHT were subsequently recruited; at the moment it is impossible to distinguish between the different forms of SHT these patients happened to have. The clinical sample was composed by 50 people (17 males, 33 females) with a mean age of 40.7 years (sd: 7.3) while the control group was composed by 50 people (22 males, 28 females) with a mean age of 24.2 years (sd: 3.4) as shown in TABLE 1.

TABLE 1: Sample characteristics

	Subclinical HT	Controls	Totals
M (n/)	17	22	39
F (n/)	33	28	61
Totals	50	50	100
Mean Age (SD)	40.7 (7.3)	24.2 (3.4)	

In addition of routine blood tests and hormonal assays, subjects underwent an investigation of the reported symptoms by the Crown & Crisp Experiential Index (CCEI, Crown & Crisp, 1979). CCEI is a rating scale able to detect some psychopathological symptoms present in the last period in the patient's life, grouped in six scales: Anxiety, Phobic Anxiety, Obsessive Behaviors, Depression, and Hysteria as Emotional Dyscontrol. After the test administration, a psychophysiological assessment (PPA) with simultaneous recording of the parameters Skin Conductance Level/ Response (SCL/SCR), Surface Frontal Electromyogram (EMG), Peripheral Temperature (PT), Heart Rate (HR). The PPA was divided in the following 4 phases:

- *"Adaptation"* (4-5 minutes): Patients were led in a room with a temperature between 18° and 22° and a humidity not higher than 50%, and they were invited to seat in an armchair with headrest, wide arms and a reclining back. They were informed about the content and the meaning of the procedure and reassured about the fact that the procedure was not invasive or harmful.

At the same time, a psychologist took care of positioning electrodes and transducers, setting up the equipment for the registration and monitoring the value progress of the different physiological parameters examining their arrangement.

- *"Rest"* (6 minutes): the registration started, after telling the patients to close their eyes, to stay still and relaxed as much as possible and to signal eventual problems (i.e. need to cough) raising the first finger of the left hand (in that case, the registration was temporarily stopped)

- *"Stress"* (4 minutes): Patients were asked to perform a mental task consisting in the subtraction of 13 from 1007 and from every subsequent result (continuous subtraction)

- *"Recovery"* (6 minutes): at the end of the stress presentation patients were asked to stop performing the mental task and to rest and relax as much as possible.

During the PPA the following physiological parameters were recorded:

Electromyography of the frontal muscle (EMG), whose electric potential was detected using two active electrodes located about 1cm over the eyebrows lining with pupils, and one of reference, in the middle of the forehead.

Heart Rate (HR), detecting the electric potential of the cardiac muscle with the classical bipolar junction used for electrocardiograms and calculating the existing time between an R wave (ventricular contraction) and another (Heart Rate and Inter Beat Interval).

Peripheral Temperature (PT), applying a thermistor at the base of the thenar eminence of the dominant hand.

Skin Conductance Level/Response (SCL/SCR), letting a slight electric current pass between two electrodes located on the last phalanx of the dominant hand fingers (in this case, first and second finger).

All of the PPA was recorded using the Psycholab VD 13 equipment of the SATEM Company in Rome, interfaced with a PC.

To assess any differences with the general population, fifty subjects without a personal history of mental and endocrine disorders were subsequently recruited (Ge et al., 2013; Davis, Tremont, 2007). This control group did blood test of basal values of TSH, total and free T3 and T4, filled out the CCEI questionnaire and underwent the psychophysiological examination. Volunteers were recruited from students in the last two years of the degree courses in Medicine and the Psychology, Master's or Ph.D. level.

Statistics

The Kolmogorov Smirnov normality test did not demonstrate any normal distribution of data, so statistical analysis has been processed using non-parametric statistics. For the descriptive statistics the Median and the first and third quartile have been used, and unpaired comparisons have been made employing the U-Mann Whitney statistical test.

Results

Data shows the same small difference in levels in hormonal assays: TT4 and TT3, FT3, FT4, TSH, but particularly elevated in TSH. Obviously values of Controls and Subclinical HT, are significantly different in the two groups, due to the presence of the classical pattern of the thyroid dysfunction, as shown in TABLE. 2.

TABLE.2: Median and quartiles (1st and 3rd) of the hormonal profiles in subclinical hypothyroidism (SHT) and control groups, in brackets reference values for the healthy population. Statistical significance between two groups was determined by U-Mann-Witney Test.

	Controls			SHT			P
	Median	1 st Quartile	3 rd Quartile	Median	1 st Quartile	3 rd Quartile	
TT4 (4,5-12 □g/dl)	8.47	7.21	9.30	7	5.57	8.17	<.01
TT3 (8-20 ng/dl)	15.77	13.75	16.75	11.80	9.65	13.28	<.001
FT3 (2-5,2 pg/ml)	4.09	3.68	4.65	2.99	2.85	3.44	<.001
FT4 (7-22 pg/ml)	10.8	8.73	12.79	5.80	5.18	7.42	<.001
TSH (0,3-4,2 mcUI/ml)	1.5	1.1	3	9.78	7.59	11.58	<.0001

As displayed in TABLE 3 and Figure 1, SHT group showed significant higher scores in all the CCEI subscales: Anxiety symptom (P<.0001, U-Mann Whitney), Phobia (P<.001, U-Mann Whitney), Obsessive symptoms (P<.001, U-Mann Whitney), Somatic Complaints (P<.0001, U-Mann Whitney), Depression symptoms (P<.0001, U-Mann Whitney), Hysteria (P<.001, U-Mann Whitney). Furthermore, patients affected by SCH, show a higher level of anxious and depressive symptoms and have more somatic complaints than control, and this could be seen as behavioral effect of their physiological status.

TABLE 3. CCEI scores (Median) Median and quartiles (1st and 3rd) of subclinical hypothyroidism (SHT) and control groups for the score of each Crown & Crisp Experiential Index (CCEI) category Legend: A=Anxiety symptoms; P=Phobia; O=Obsessive symptoms; S=Somatic Complaints; D Depression Symptoms; H=Hysteria-Emotional Discontrol.

	Controls			Subclinical HT			P
	Median	1st Quartile	3th Quartile	Median	1st Quartile	3th Quartile	
A	5	3	7	9	7	11	<0.0001
P	4	2	5	6	4	8	<0.001
O	6	4	7	9	6	10	<0.001
S	3	2	4	9	7	11	<0.0001
D	3	2	4	8	7	9	<0.0001
H	4	2	5	8	6	9	<0.001

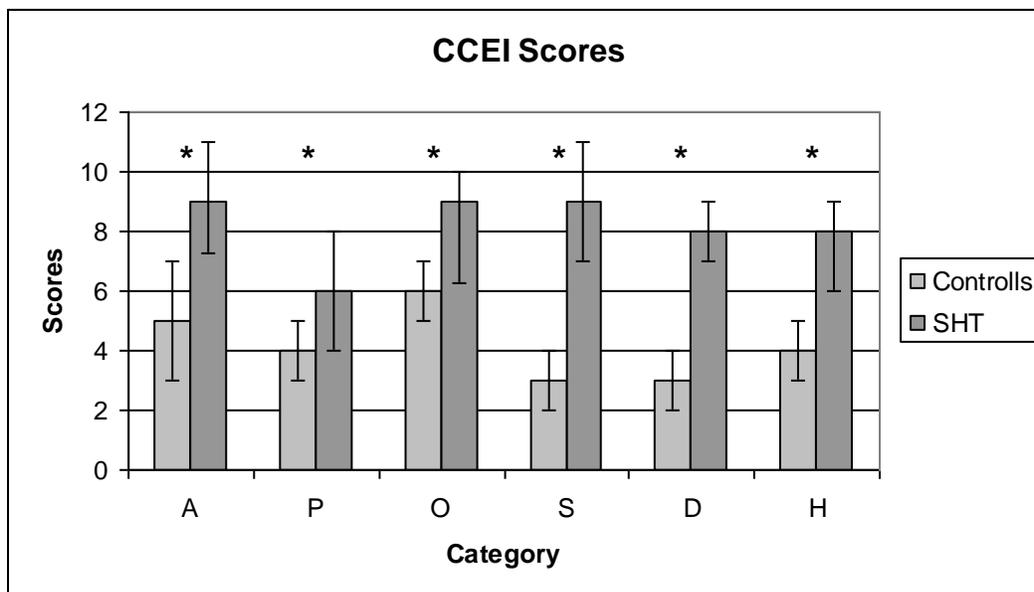


Figure 1: Median and quartile (1st and 3rd) of subclinical hypothyroidism (SHT) and control groups for the score of each Crown & Crisp Experiential Index (CCEI) category: **A** Anxiety; **P** Phobia; **O** Obsession; **S** Somatic Complaints; **D** Depression; **H** Hysteria (emotional discontrol). Statistical significance, U-Mann-Witney Test: (P<.0001), + (P<.001)

At the autonomic level, SHT subjects showed a general pattern of excessive arousal with statistically significant differences among groups in SCL/SCR, HR, and PT (always P<.0001, U-Mann Whitney). In particular, in SHT group there is a typical pattern of elevated values in HR, SCL, EMG, and lower values in PT, characteristic of a whole autonomic hyper arousal (TABLE 4) This result is completely unexpected, since the behavioral pattern of these patients is more depressive-like, and usually it is mirrored by an autonomic hypoactivated profile. This result is completely unexpected, since the behavioral pattern of these patients is more depressive-like, and usually it is mirrored by an autonomic hypoactivated profile.

TABLE 4. PPA Scores (Median) Legend: EMG= Frontal Muscle Surface EMG; SCL= Skin Conductance Level; PT =Peripheral Temperature; HR =Heart Rate. Median and quartiles (1st and 3rd) of PPA Scores. Statistical significance between two groups was determined by U-Mann-Witney Test.

	Controls			Subclinical HT			P
	Median	1st Quartile	3th Quartile	Median	1st Quartile	3th Quartile	
EMG	2.18	1.77	3.10	3.6	3	4.25	<0.0001
SCL	4.88	3.76	5.41	9.79	7.20	12	<0.0001
PT	33.8	33.35	34.40	30.4	29.40	31.7	<0.0001
HR	70	66	47	75	69	78	<0.0001

Discussion and Conclusion

Two different and important kinds of data seem to characterize the examined sample of subject with SHT: psychopathological reported symptoms and the pattern of autonomic arousal. The most relevant psychic symptoms seem to be anxiety and depression immediately followed by somatic complaints. If the last one could be partially explained by the recent medical diagnosis, and the presence of depressive symptoms is in total accord with the evidence collected in the literature on symptoms reported in overt hypothyroidism interestingly anxiety symptoms seem to have a prevalence on depressive ones. (Cooper, Biondi, 2012; Almeida et al.,2007; Monzani et al., 1991; Monzani et al, 1993 May; Chueire et al., 2007; Davis et al., 2003 ; De Jongh et al., 2011 ; Demartini et al., 2010).

This data is not supported by previous research, but the anxious symptomatology reported by these patients could be the cognitive and self-reported manifestation of the autonomic hyperactivation detected in this sample through the PPA.

In fact, despite one of the physical consequences of clinical hypothyroidism is a general low level of heart rate (HR) (Reuters et al., 2012) compared to people selected from the general population, the examined SHT sample revealed an autonomic unbalance characterized by moderate high values in $\frac{3}{4}$ of the parameters, among which, the HR.

A possible first interpretation of the results obtained is that in this kind of slight form of hypothyroidism, the body, especially during the first period of the endocrine dysfunction, tries to support and integrate the general lack of energy caused by the hypothyroidism, with an acceleration of the autonomic activity. If this data will be confirmed by other prospective studies, with groups of subjects that are more balanced, this data could represent a very important discovery with a useful fallout in the clinical practice. In fact, one of the most important clinical consequences of overt hypothyroidism, also slightly present in subclinical hypothyroidism, is the presence of depressive symptoms, asthenia, apathy, so often treated with antidepressants (Dubbs , Spangler, 2014).

If this solution could be helpful in general, in case of autonomic hyper arousal, antidepressant could cause several problems in the ménage of the case with negative consequences due, e.g., to the rising of hypo maniacal symptoms. A brief psychophysiological assessment seems therefore to be a good and low expensive methodology in order to better understand the clinical picture and better evaluate how far therapy should last. Moreover, the PPA could be a useful tool to model the treatment plan according to the patient's specific physiological necessities and a way to track a patient's autonomic balance, thus optimizing treatment effectiveness and preventing possible secondary effects linked to overt hypothyroidism, like depressive syndromes or heart failures.

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