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The relationship between thyroid hormone levels and cognitive functions in Graves' disease might be influenced by a history of mild traumatic brain injury

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Abstract

Background: The aim was to investigate the relation between cognitive functions and thyroid hormone levels among patients with untreated Graves' disease and to explore the influence of mild traumatic brain injury (mTBI) on the results.

Patients: A cohort of forty-four patients (mean age: 39.3 ± 10.2) with untreated Graves' disease were investigated and compared to a healthy control group (n=31, mean age: 36.7 ± 8.8). Six patients had a history of mTBI.

Methods: Neuropsychological tests were used to assess cognitive functions of attention, memory, executive and psychomotor performance.

Results: Within the patient group high free triiodothyronine levels were associated with higher cognitive performance. This was particularly the case if patients with a history of mTBI were excluded. However, the patients showed lower performance on several tests compared to the control group.

Conclusion: At the same time as cognitive dysfunction in untreated Graves' disease is present it parallels with a positive relation between thyroxine hormone levels and cognitive performance. This may explain previous conflicting research results. A history of mTBI, however, seems to prevent these positive thyroxine effects, indicating that an mTBI might be related to a subtle persistent impact on cognition.

Introduction

Thyroid hormones have a crucial influence on the growth and development of the central nervous system. In adults, thyroid dysfunction is associated with somatic, neurological and psychiatric abnormalities [1,2]. Graves' disease (GD) is a common thyroid disease, and in Sweden, the estimated incidence is 21/100,000 individuals [3]. It can cause a variety of physical and psychiatric symptoms, such as fine motor tremor, weight reduction, heat intolerance and anxiety [4]. GD is diagnosed by clinical signs together with suppressed thyroid stimulating hormone (TSH), and elevation of free thyroxine (fT4) and free triiodothyronine (fT3). A majority of patients have measurable thyroid receptor autoantibodies (TRAb) as well. Autoantibodies to thyroid peroxidase (TPO Ab) are also common [4]. There are indications of a genetic predisposition for the disease, but what triggers the onset of GD is unknown [5].

The relations between cognition and untreated Graves' disease (GD) have only been studied in a handful of studies, where some investigators have found attention problems [5], decreased memory functions and poorer problem-solving abilities [6] and others have found no cognitive dysfunctions [7].

In clinical praxis, highly elevated fT3 and fT4 levels have been associated with severity of disease and thyroid storm, but there is a lack of correspondence between thyroid hormone levels, symptoms and cognitive findings in GD [5,7]. However, the studies differ on whether T3 or T4 has been included, and if the hormones are measured in their free or bound forms. Another contributing cause for divergent results may be other factors, unrelated to the disease but still a possible components in conflicting results. One of these factors may be mild traumatic brain injury (mTBI). It has been estimated that the incidence of hospital-treated mTBI is to 100 – 300 per 100.000/ year in the industrialized world and over 600 per 100,000 when those not seeking emergency medical care are included [8]. Hence the prevalence of mTBI is expected to be relatively high in the population. Long-term effects of mTBI are controversial and large meta-studies have not found convincing evidence that patients have residual symptoms [9,10], while others claim that meta-analyses may mask individual symptoms in small sub groups [11]. If mTBI patients are fully recovered there should be the same results in studies on GD regardless if mTBI patients are excluded or not. Studies investigating such population differences in GD has not, to our knowledge been published earlier.

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In the present cohort study, the aim was to explore the relation between cognitive functions and thyroid hormones in patients with newly diagnosed and yet untreated GD and to investigate if a history of mTBI could influence the results.

Methods

Participants

Patients between 18 – 55 years of age with newly diagnosed GD were invited to participate in the study. Exclusion criteria were: medication possibly interfering with neuropsychological test results (such as tranquillizers. SRRI accepted), dementia, seizures, a history of moderate to severe traumatic brain injury (concussion accepted), severe psychiatric diseases, difficulties understanding instructions in Swedish, planned or ongoing pregnancy, severe ophthalmopathy requiring corticosteroids at inclusion, or other systemic or serious disease. Also, patients with a previous treatment with antithyroid drugs were excluded, to avoid potential cognitive impairment in such a cohort. Patients typically had developed symptoms during two to three months. Fifty-four consecutive patients were invited to participate. Of these, eight patients declined, one patient had an indication for surgery and one patient was missed due to administrative reasons. Forty-four patients were included in the study. Six patients had a history of mTBI, defined according to the definition of mTBI by the American Congress of Rehabilitation Medicine [12].

Demographic data are presented in Table 1. All participants had elevated peripheral thyroid hormones and suppressed TSH. All but one had elevated TRAb. Only the patient who was TRAb negative underwent a radionuclide scan. This patient had an increased even diffuse distribution on a radionuclide scan confirming the GD diagnose. Nine patients were TPO Ab negative (<35 kl/L), 33 were TPO positive, and information was missing in 2 cases. Serum concentrations of thyroid hormones are presented in Table 2.

For comparison of the neuropsychological test results we used a control group of 31 healthy individuals with no history of mTBI. The control group consisted of controls in another study on mTBI, conducted by MCM, CNdB, and AB during the same time and where recruited via advertisement from the same geographic region as the patients. These individuals performed the same test battery as the participants in this study but were not matched to gender and also no hormone samples were drawn from the control group (Table 2).

Procedure

All patients were referred to an endocrine department in any of the three local county hospitals in Sörmland, Sweden. Patients were informed of the study at the diagnostic visit, and informed consent was obtained at this time. The neuropsychological assessment took place in an outpatient setting within seven days from the diagnostic visit. Subsequently, treatment with anti-thyroid medication and thyroxine (T4) was initiated. However, in cases of tachycardia and/or tremor beta-blockers were allowed, and 25 patients (57%) used beta-blockers at the time of neuropsychological assessment. One patient had hypertension and used an ACE-inhibitor; three were on antidepressant pharmacotherapy. At inclusion, none of the patients was addicted to alcohol or illicit drugs. In the control group, two persons were on antidepressant, and three were on asthma medication. At inclusion, none of the participants or control group were addicted to alcohol or illicit drugs.

Table 1. Demographic information for the total group of patients with Graves' disease (GD) (n=44), for the GD group where mTBI patients were excluded (n=38), for the GD group with a history of mTBI (n=6), and for the control group (n=31). Mean and (SD) are presented. Mann-Whitney U-test and Chi^2 test were used for comparison

Characteristics	Total GD population	GD/ mTBI exclusion	GD with mTBI	Control group
Gender: F/M, n (% F)	35/9 (80 %)*	30/8 (79 %)	5/1 (83 %)	18/13 (42 %)
Age: years	39.3 (10.2)	38.3 (10.1)	45.5 (9.3) *	36.7 (8.8)
Education: years	12.1 (2.3) *	12.0 (2.2) *	12.4 (3.0)	13.1 (1.9)
Beta blocker: Y/N, (% Y)	25/19 (57 %)***	22/15 (60 %)***	3/3 (50 %)**	0/31 (0 %)
Rey 15 item	14.9 (0.3)	14.9 (0.3)	15 (0.0)	14.5 (1.3) #

#One missing,
*a significant difference between patient population and control group of p <0.05
**a significant difference between patient population and control group of p <0.01
***a significant difference between patient population and control group of p <0.001

Table 2. Serum concentrations of thyroid stimulating hormone (TSH), free triiodothyronine (fT3), free thyroxine (fT4), thyroid receptor antibodies (TRAb) and thyroid peroxidase autoantibodies (TPO-Ab, two missing), for the total group of patients with Graves' disease (GD) (n=44), for the GD group where mTBI patients were excluded (n=38), and for the GD group with a history of mTBI (n=6). Mean and (SD) are presented

Hormones	Total population	GD/mTBI exclusion	GD with mTBI	Ref values
TSH	0.01 (0.0)	0.01 (0.0)	0.01 (0.0)	0.4-5.0 mIU/L
fT3	17.0 (6.2)	17.0 (6.3)#	16.8 (6.5)	3.3-6.0 pmol/L
fT4	43.3 (20.3)	43.3 (20.2)	43.7 (22.5)	10-22 pmol/L
TRAb*	10.8 (10.4)	11.0 (10.8)	9.9 (8.1)	< 1.0 IE/L
TPO-Ab	686.6 (1080)	490.9 (651.0)	1860.8 (2199.0)	< 35kI/L

*one patient was TRAb negative but was positive on technetium scintigraphy.
#five missing

Measures

Neuropsychological tests

The Color-Word Test (CWT, Stroop Test) is a test of executive functions measuring inhibition [13]. A Swedish version of the CWT test was used [14]. The discrepancy between the total time required to perform a pretest and the total time required to perform the main test is presented as the "Stroop effect" [13]. A low score indicates less Stroop effect and better performance.

The Controlled Oral Word Association Test (COWAT) evaluates the spontaneous production of words under restricted conditions as a test of the capacity to generate words fluently in an effortful, phonemic format. The scores reflect the total number of accurate words produced [13]. Higher scores indicate better performance.

The Grooved Peg Board Test (GPBT) measures motor precision and motor speed [13]. In this study, a mean score (seconds) of the right and left hand is presented. A low score indicates faster performance.

The Rey 15-item Test is a test of a participant's motivation and effort during the assessment. Patients with a score less than nine were excluded [13].

Ruff 2&7 Selective Attention Test, measures visual automatic detection speed (2&7 ADS), accuracy and controlled search speed (2&7 CSS) and accuracy [15]. In this study only the speed measures were used. Higher scores indicate better performance.

The Trail Making Test (TMT) – A measures attention, perceptual organization, and speed, while the Trail Making Test (TMT) – B measures attention, perceptual organization, speed, and mental flexibility [13]. The time to perform the test is measured. A low score indicates better performance.

The WAIS-III Digit Symbol Substitution Test (DSST) is a multi-factorial subtest used for measuring psychomotor processing speed

[16]. As memory capacity could influence the results, this was controlled for by also measuring incidental learning of symbols (DSST memo) [17].

The WAIS-III Digit Span (DS) measures verbal attention span with forward repetition of digits, and verbal working memory with backward repetition of digits. The latter involves executive functions [13,16]. Sum scores for forward and backward repetition are presented separately.

Laboratory assays

Venous blood samples were collected at baseline before the neuropsychological assessment and have been published elsewhere [18]. Concentrations of serum FT4 and FT3 were measured by chemiluminescent methods on an ADVIA Centaur (Siemens Healthcare Diagnostics, Tarrytown, USA). Total coefficient of variation (CV) for FT4 was 1.4% at 4.0 pmol/L, 5.2 % at 15 pmol/L and 6.0% at 54 pmol/L. For FT3, CV was 3.1% at 3.4 pmol/L and 3.0% at 14.9 pmol/L.

Statistics

SPSS 23 was used for statistical analyses. Median and range are presented. Due to the small sample size and skewed hormonal data, non-parametric methods were used: The Spearman correlation was used to investigate the relationship between hormone levels and performance on the cognitive tests; the Mann-Whitney U-test was used to investigate the difference between the patients and the control group; and Cochran Q test was used to investigate correlation difference whether mTBI patients were included or not. As the sample size was small, thus inferring a risk of beta errors, the Bonferroni correction was not applied. Two-tailed p-values were used with a critical significance level of $p < .05$. A power calculation was performed on the attention measure Trail Making Test, as attention has been reduced in at least one study [5]. For between-group effects (patient group vs control group) of 5.0, a SD of 5.6, an alpha level of 0.05, and a power of 0.80 a sample of 21 participants in each group would have been sufficient.

Ethics

All participants gave informed consent to take part in the investigation. The research was carried out in accordance with the Declaration of Helsinki (2000) and was approved by the Regional Ethical Board in Stockholm. It was registered at ClinicalTrials.gov DLL-159361.

Results

All participants demonstrated sufficient motivation on the test of motivation, and all test results were judged valid (Table 1). Those patients receiving beta-blockers did not differ in cognitive performance from those not receiving beta-blockers. However, patients receiving beta-blockers had higher fT4 levels $Z=2.95$, $p=0.003$. There were no significant differences in age, length of education, or hormone levels between those with a history of mTBI and those without mTBI (Table 2).

Two separate correlation analyses were performed – one where all patients were included (n=44) and one where patients with a history of mTBI were excluded (n=38). When all patients were included three of the eleven neuropsychological tests (27%) correlated significantly with f T3 levels (TMT-A, Ruff 2&7 ADS, and CWT). However, when patients with a history of mTBI were excluded seven of eleven of the tests (64%) correlated significantly with fT3 levels. Besides the three tests above, also performance on GPBT, Ruff 2&7 CSS, DS backward, and DSST memo correlated significantly to fT3 levels when the mTBI patients were excluded. In all occurrences the higher f T3 levels the better performance (Table 3) and Cochran Q Test showed that there was a significant difference in number of correlations, whether patients with a history of mTBI were included or not, $p=0.046$. Age did not correlate with hormone levels, and age only showed a weak correlation to TMT-A among the patients ($r_{GD}=0.314$, $p=0.038$). We also found that fT3 seems to be more sensitive to cognitive performance compared to fT4 as there were more neuropsychological test results correlating to fT3 (Table 3).

Compared to the control group, the patients with GD performed significantly less well on tests of visual organization speed (TMT-A), incidental memory (DSST memo), verbal working memory (DS backward) and verbal fluency (COWAT) (Table 4). There were no significant differences whether mTBI patients were included or not in the statistical analyses, except for motor functions were mTBI patients were significantly slower than the control group. There were no gender differences in the cognitive variables.

Discussion

In the present study, we aimed to examine the relation between cognitive performance and thyroid hormone levels among patients with newly diagnosed and yet untreated GD, and also to explore the influence of mTBI on the results. Within the patient group, elevated fT3 levels were associated with better performance in cognitive domains of attention, processing speed, and executive and motor functions. Still, the patients performed less well compared to the healthy control group on tests of visual organization speed, incidental memory, verbal working memory, and on tests of verbal fluency. Our results fail to acknowledge previous findings where no relationship have been found between thyroid hormone levels and symptoms [19] and cognition [5,7] in GD, but are in line with other studies were high thyroid levels have been associated with poorer test performance [5,6].

The fact that patients with GD perform less well than the control group but still seem to benefit from high thyroid hormone levels is puzzling, and the findings are conflicting in this area. One explanation for the conflicting results may be the fact that GD decreases the level of cognitive functioning as compared to healthy individuals, but

Table 3. Spearman's rank correlations between fT3 (five missing) and fT4 levels and cognitive functions for all patients (n=44) and when mTBI patients were excluded (n=38)

Test results	Total GD population		GD/mTBI excluded	
Tests	fT3	fT4	fT3	fT4
GPBT	-0.297	-0.207	**-0.380***	-0.238
DSST (120 sec)	0.153	0.2	0.311	0.317
TMT – A	**-0.364***	-0.226	**-0.461****	-0.244
Ruff 2&7 ADS	**0.322***	**0.318***	**0.378***	**0.340***
Ruff 2&7 CSS	0.212	0.109	**0.374***	0.198
DSST memo	0.228	0.23	**0.420***	**0.361***
DS - forward	0.205	0.141	0.329	0.191
DS – backward	0.289	0.113	**0.446****	0.179
COWAT	0.224	0.185	0.195	0.138
CWT	**-0.445****	**-0.332***	**-0.559****	**-0.351***
TMT - B	-0.041	-0.081	-0.119	-0.119

Abbreviations: DMF (dynamic motor functions), GPBT (Grooved Peg Board Test), TMT-A (Trail Making Test – A),
COWAT (Controlled Oral Word Association Test), DSST memo (WAIS-III Digit Symbol Substitution Test – memory
for symbols), BSRT-(Buschke Selective Reminding Test), CWT (Color Word Test – Stroop effect).
*correlation significant at the .05 level
**correlation significant at the .01 level

Table 4. Neuropsychological test results for all study patients with Graves' disease (GD) (n=44), GD group with mTBI patients excluded (n=38) and GD group with a history of mTBI (n=6). Mean (SD) is presented. Mann-Whitney U-test was used for comparison between GD groups and control groups separately

Test results	Total GD popul.	GD/mTBI excl.	GD with mTBI	Control group
Motor functions				
GPBT (sec.)	67.8 (10.0)*	67.1 (10.4)	72.5 (5.5)**	62.7 (6.7)
DSST (scores)	75.9 (12.1)	76.0 (11.9)	75.2 (14.4)	82.0 (13.7)
Attention functions				
TMT – A (sec.)	27.5 (6.4)**	27.2 (6.3)**	29.3 (7.4)*	23.2 (7.3)
2&7 ADS (scores.)	142.8 (24.2)	145.3 (24.2)	126.7 (19.0)*	151.6 (25.4)
2&7 CSS (scores.)	122.3 (18.5)	124.0 (17.6)	111.8 (22.5)	125.3 (17.2)
Memory functions				
DSST memo (scores)	11.9 (4.9)*	11.5 (4.5)**	14.0 (7.0)	14.4 (3.2)
DS forw. (scores)	9.2 (1.8)	9.3 (1.7)	8.7 (2.4)	9.4 (1.8)
DS backw. (scores)	5.9 (2.0)*	5.9 (1.9)*	5.7 (2.2)	7.3 (2.1)
Executive functions				
TMT – B (sec.)	71.8 (25.4)	71.2 (25.0)	75.0 (30.3)	65.0 (18.9)
CWT Stroop (sec.)	39.8 (13.0) #	39.7 (14.9)	40.8 (12.9)	40.4 (15.4)
COWAT (scores)	36.3 (13.0)**	35.8 (12.2)*	40.0 (18.2)	47.2 (14.4)

Abbreviations: GPBT (Grooved Peg Board Test) DSST (Digit Symbol Test), 2&7 ADS (Ruff 2 & 7 Automatic Detection Speed), 2&7 CSS (Ruff 2 & 7 Controlled Search Speed), TMT – A (Trail Making Test – A), DSST memo (Digit Symbol Test incidental memory), TMT – B (Trail Making Test – B), CWT (Color Word Test), COWAT (Controlled Oral Word Association Test).
#One missing,
*a significant difference between patient population and control group of $p < 0.05$
**a significant difference between patient population and control group of $p < 0.01$
***a significant difference between patient population and control group of $p < 0.001$

elevated thyroid hormone levels could contribute to increasing mental arousal, and thus enhance the level of cognitive performance relatively in the diseased population. The effects of hormone levels can also be influenced by several confounding factors such as healthy or diseased individuals, primary or secondary hyper-/hypothyroidism, age, smoking and other co-morbid illnesses. Grigorova and Sherwin [20] have proposed that executive neuronal networks could be vulnerable to hormone changes in thyroid hormones associated with GD. In a healthy population of 122 euthyroid women between 25–75 years with a mean age of 51 years, higher levels of fT3 were associated with poorer performance on tests of attention and executive function [20]. In our study the patients performed less well on tests of attention and executive functions, but fT3 levels were associated to better functioning within the group. However, in Grigorova and Sherwin's study the patients were within normal hormone range and therefore not per se valid for patients with GD. Even though our study shows a positive correlation between hormones and performance level, this does not imply a higher performance level than before onset of GD.

In patient groups with thyroxine substitution, there have been studies indicating a positive relation between higher thyroxine doses and self-reported wellbeing. In a study reported by Samuels and coworkers [21], hypothyroid patients were treated with two doses of T4, the higher of which corresponded to subclinical thyrotoxicosis while the lower dose corresponded to euthyroidism. The higher dose was related to an increase in fT3 level and improvement in mood and motor learning, but not in other cognitive functions, such as working memory, verbal or nonverbal declarative memory [21]. Walsh et al studied patients with primary hypothyroidism given three different doses of thyroxine. The highest thyroxine dose resulted in fT4 and fT3 levels within the normal upper range and did not result in improved cognitive function or quality of life [22]. However in Walsh's study correlation analyses were not performed. In a more elderly population [23] and in patients with mild cognitive impairment [24], high fT3 and high total T3 levels respectively have been associated with impaired cognitive functions. On the contrary, de Jong et al. found no such relationship [25]. In an elderly population, dementia or other brain degeneration may influence the results [24]. Moreover, the relation between hormone levels and cognition does not have to be linear, and the balance between hormones could also be an influencing factor [26]. The fact that those who had more symptoms as tachycardia and/or tremor received beta-blockers and participants with beta-blockers had higher fT4 levels also suggests that there is some connection between hormones and symptoms.

Selection bias of patients might furthermore contribute to inconsistent results. In our study, the results differed whether patients with a history of mTBI were included in the study, as they were slower on attention and motor tests than the patients without a history of mild brain trauma. As the mTBI group consisted of only six patients, the power was too low to expect any significant results. There is a controversy about persisting effects of a mild brain injury. Psychological factors have been associated to worse outcome report [27], while meta-analyses have not been able to find residual cognitive impairment [9]. Still, while most return to normal levels at neuropsychological assessment within one year, fifty percent report three or more posttraumatic symptoms [28]. Symptom reports have been associated with other factors such as litigation [29] while studies on a large group of individuals might obscure small group or individual symptoms after an mTBI [11]. In this study the patients were consecutively included and a majority of the patients with a history of an mTBI, had their injury in childhood (the shortest span was 15 years). They were not subjects for rehabilitation or any litigation processes, but still when including them in the analyses results were influenced, particularly so the correlation between hormone levels and neuropsychological tests results. In another study on persisting fatigue among self-selected patients with mTBI, we found a reduced connectivity in the thalamus and middle frontal gyrus on fMRI leading to increased activation of cortical networks after a vigilance task [30]. To some extent patients are capable of functional compensation by activating larger brain areas, which also has been proven in patients with thyroid dysfunction [31]. Thus, the strain to compensate both for mTBI and GD could lead to a reduced ability to benefit from the arousal effect of high thyroxine levels. During the last 15 years, there have been developments in brain imaging, neuropathology and non-imaging biomarkers which have changed the opinion of mTBI as a completely reversible insult [32]. One could also speculate if a previous trauma to the head could lead to a more stressful life situation for some individuals, and subsequently trigger the onset of the disease in genetically vulnerable subjects [33].

Another important factor that might contribute to inconsistent results is whether fT4 or fT3 are included in the analyses. In our study, fT3 levels were more related to cognitive performance than fT4 levels. In the investigation by Vogel *et al.,* the total, though not fT3 alone, was measured [7], and in Alvarez's study [5], triiodothyronine resin uptake was measured [5]. T4 enters cells via thyroid hormone transporters, and in the next step deiodinases convert T4 to the more biologically active T3, or to inactive reverse T3 [34]. Moreover, serum levels might not reflect the hormone concentrations in the brain or the sensitivity of thyroid hormone receptors during hyperthyroidism [35]. As the thyroid receptor is a nuclear receptor, this might be of fundamental

importance as the relationship between T4 and T3 may be changed within the CNS in GD, due to deiodinase activity or by yet unknown mechanisms and might also be an explanation for the lack of positive effects of thyroxine for the mTBI patients. This hypothesis needs to be explored in other studies conducted specifically for this purpose.

In conclusion our study, indicates a positive correlation between thyroxine hormone levels and enhanced cognitive performance. A history of mTBI in combination with GD, however, seems to, due to still unknown CNS mechanisms, reduce these thyroxine effects on cognition. The results indicate that a history of an mTBI might not be as harmless as earlier believed [32]. As the population is small our findings have to be validated in larger studies.

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