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Working memory and executive functions in hyperthyroid patients with Graves' disease

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Summary

Aim. Assessment of working memory and executive dysfunctions, as well as the intensity of depressive symptoms in hyperthyroid patients with Graves' disease, compared to healthy subjects.

Material and methods. Thirty (30) patients with Graves' disease (20 female, 10 male), aged 18-55, participated in the study. The control group consisted of 31 healthy subjects, matched by age, gender and educational level with patients in the examined group. The assessment of working memory and executive functions was estimated by the Wisconsin Card Sorting Test and the N-back test. The intensity of depressive symptoms was assessed by Beck Depression Inventory.

Results. Significant disturbances of working memory and executive functions were noted in hyperthyroid patients with Graves' disease in comparison to healthy subjects. Longer disease duration was associated with worse results in psychological tests, while higher educational level of the patient resulted in better test outcomes. In the group of patients with Graves' disease, 1/3rd of them presented with significant intensity of depression symptoms; additionally, the intensity of depression symptoms correlated with cognitive function impairments in the whole group of examined patients.

working memory / executive functions / hyperthyroidism

INTRODUCTION

Disorders of cognitive functions in thyroid diseases have been drawing a vivid interest of many research teams. It has, so far, been demonstrated that both hyper- and hypothyroidism are associated with specific changes in the functionality of the central nervous system (CNS) [1]. It appears from to-date's observations that even mild disturbances of thyroid functions may induce mood changes and affect cognitive functions [2].

Cognitive functions, such as concentration, memory, visual-spatial processes, linguistic skills or executive functions are the processes which help adapt to environmental conditions, while their efficacy depends on the functionalities of particular brain areas. Memory of one of the most important cognitive processes, which enables coding, storage and retrieval of acquired information. Short-term memory is necessary to maintain information for short period of time,

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while long-term memory enables storage of data acquired in the learning process.

Working memory is a special type of short-term memory. It is responsible for proper switching of data, depending on a given situation, what is provided by the, so-called, "on line" processes, building a specific bridge between incoming data and the actual situation. With this type of memory, we may flexibly modify our actions and adapt reactions to changing situations. The working memory is connected with the functionality of the dorsal-lateral parts of the pre frontal cortex. Effective working memory is the key basis for executive functions, responsible – among others – for the integration of complex psychological activities, such as planning or conceptual thinking.

Recently, researchers' attention has been drawn into the relationships between disorders in thyroid hormone secretion and the activity of neurotransmitter systems, first of all, of the dopamine, noradrenaline and serotonin systems as well as depressive and cognitive dysfunctions [3]. Disturbed cognitive functions, observed in persons with thyroid self-regulation, may reveal some reference to abnormal functionalities of the above-mentioned neurotransmitter systems in the brain [4]. Thyroid hormones play an important role in the development and proper functioning of the CNS [1]. Some researchers express an opinion that it is the hormones of the hypothalamic-pituitary-thyroid axis which play the key role of neurotransmitters in the CNS [5]. Experimental studies on animals [6] have provided some evidence for disturbed explorative and decision making functions, as well as for suppressed apparatus of responses to new stimuli, all in result of thyroid dysregulation.

The results of to-date's neuropsychological studies in hyperthyroid patients indicate disturbances of cognitive functions in these patients, such as problems with attention, in particular, with concentration ability, together with fresh memory disorders [7, 8, 9, 10]. It is assumed that the disturbances of cognitive functions, observed in hyperthyroid patients, may probably result from long-term, central effects of thyroid hormones, exerted in their elevated concentrations [11]. Another problem, observed in hyperthyroid patients, includes also psychopathological symptoms, such as phobia (morbid fear), fatigability, mood liability and, first of all, affective disturbances. It has been demonstrated that in as many as in 40% of patients with hyperthyroidism, depressive symptoms may occur with various degrees of intensity [12].

Hyperthyroidism is a syndrome of clinical symptoms, resulting from exposition of tissues to high concentrations of thyroid hormones in the systemic circulation. In the majority of cases, hyperthyroidism is caused by excessive secretory activity of the thyroid gland[13].

Graves' disease is an autoimmunological disorder, being the most frequent cause of hyperthyroidism. It may be found at any age but is most frequently diagnosed in middle-aged subjects [14]. Disorders of cognitive functions, such as memorising, concentration, spatial and verbal functions, as well as working memory and executive functions in Graves' disease have, so far, been a rather rare subject of investigation. In neuropsychological examinations of hyperthyroid patients in the course of Graves' disease, Trzepacz et al. have observed mild deficits of memory, concentration and complex problem solution [15], while Hutto [16] mentions, first of all, deterioration of concentration, attention and memory, especially of fresh memory.

The reported study aimed at evaluation of working memory and executive functions and at assessment of depression symptoms in patients with hyperthyroidism in the course of Graves' disease.

MATERIAL

Thirty (30) patients were involved in the study, all of them with fresh diagnosis of hyperthyroidism in the course of Graves' disease (20 female and 10 male) at the age between 18 and 55 years (the mean age: 40.9 ±11.2 years). The included patients were endocrinologically diagnosed at the Clinic of Endocrinology and Metabolic Diseases, Medical University of Łódź, at the Endocrinological Outpatient Clinic of The S. Sterling Teaching Hospital No. 3 and at the Clinic of Endocrinology and Diabetology of the Collegium Medicum (Bydgoszcz) of the M. Copernicus University in Toruń.

The diagnosis of hyperthyroidism was obtained on the basis of decreased thyrotropic hor-

mone (TSH) concentrations and of increased free thyroxine (FT_4) and free triiodothyronine (FT_3) concentrations. Graves' disease was confirmed on the basis of increased concentrations of anti-TSH receptor (anti-TSH-R) antibodies. The criteria of exclusion from the study included: addiction to psychoactive substances, as well as other severe somatic and neurological diseases and brain traumas revealed in anamnesis. All the qualified patients were submitted to psychological tests during 7 days of pharmacological treatment, administered for hyperthyroidism.

The control group included 31 healthy subjects (23 female and 8 male) at the age between 18 and 55 years (the mean age: 42.1 ± 7.0 years). None of the controls had even suffered from serious somatic or neurological diseases or had been addicted to psychoactive substances.

All the subjects were qualified to the study, following prior explanation of the study goal and character and of the principles of examination performance, completed by declaration of conscious written consent.

METHODS

Methods of examination

Neuropsychological evaluation

In the neuropsychological evaluation, the Wisconsin Card Sorting Test – (WCST) was applied for assessment of working memory and cognitive functions (a), while the N-back test was used for evaluation of visual-spatial working memory and of visual-motor coordination ability (b).

Ad a) The Wisconsin Card Sorting Test – (WCST) in Heaton's computer version [18]. In the evaluation, the following test parameters were taken into account:

- the number of perseverance errors (PE), indicating thinking rigidity;
- the number of non-perseverance errors (N-P), showing some tendency towards chaotic or incidental reactions;
- the number of correctly configured categories (CC), which provides for the index of thinking efficacy;
- the number of attempts, needed to configure the first category (1st cat.), which provides evidence for the ability to formulate logical concepts;
- the percent of reactions conformable with logical concept (concept %), showing evidence for the ability to utilise both newly perceived information and earlier recovered experience.

Ad b) N-back test in computer version [19].

It contains a set of 27 digits (i.e., repeating digits: 2, 4, 6, 8), appearing on the screen in 1.8 second intervals, where each stimulus is presented for 200 ms. Depending on selected option, an examined person is requested to memorise a stimulus, displayed before a certain number of other stimuli, i.e., 1-, 2-, 3, 4-back. In the reported study, the 1-back option was applied. Evaluation of test results takes into account the percent (%) of correct answers and the time of reaction (in milliseconds), i.e., the time during which the task is performed.

Psychometric evaluation

The Beck's Depression Inventory [BDI] [17] was applied for evaluation of the intensity of depression features. The Inventory consists of 21 questions, which are to be answered individually by an examined person, who assesses the intensity of experienced symptoms in a 0-3 scale. Any total score ≥ 12, being the sum of answers to all the questions, may be indicative of depression.

RESULTS

Tab. 1 presents the results of neuropsychological tests and the degree of intensity of depression symptoms in hyperthyroid patients in the course of Graves' disease, juxtaposed for comparison with the results of healthy subjects.

As it appears from Tab. 1, patients with Graves' disease in hyperthyroid status, when compared with the group of healthy subjects, presented with significantly worse results in both tests, evaluating working memory and executive functions. The hyperthyroid patients made significantly more errors of perseverance and non-perseverance in WCST, configured less categories, needed more time to configure the 1st category

Table 1. Results obtained in neuropsychological tests and the degree of intensity of depression symptoms in hyperthyroid patients in the course of Graves' disease, when compared with healthy subjects. Mean results ± SD. The differences with healthy subjects attain the level of significance, *p<0.05; **p<0.01, U-Mann-Whitney's test.

	Subjects with Graves' disease N=30	Healthy subjects N=31
WCST		
WCST PE	12.4 ± 9.4**	7.6 ± 1.6
WCST N-P	11.7 ± 5.9*	7.9 ± 3.0
WCST CC	5.5 ± 1.1*	6.0 ± 0.2
WCST 1st cat	14.5 ± 7.9*	12.9 ± 3.3
WCST % conc.	70.1 ± 16.8**	80.8 ± 6.3
N-back		
% of correct answers	78.1 ± 20.7**	92.4 ± 232.5
Reaction time	923.4 ± 392.6*	574.5 ± 285.7
BDI	8.8 ± 8.1**	2.1 ±1.7

and provided for a lower index of answers, conformable with the logical conception, than healthy subjects. In turn, the results, obtained in the N-back test, demonstrate that those patients demonstrated a lower percent of correct reactions and with longer reaction time. All this indicates significant disorders of executive functions, associated with prefrontal cortex impairment in hyperthyroid subjects in the course of Graves' disease.

The intensity of subjectively evaluated depression symptoms, observed in the group of 20 subjects, was not significantly elevated, being at the borderline of the subdepression syndrome. However, in 10 subjects, i.e., in 1/3rd of the patients, the intensity of the symptoms was really significant and evaluated at score 12-37.

Tab. 2 presents results of the correlation between the age or education and the results of neuropsychological tests in both groups (the group of patients with Graves' disease and the group of healthy subjects) and between the duration of the disease or the intensity of depression features in Beck's scale and the results of neuropsychological tests in the examined patients with Graves' disease.

The age of examined patients did not correlate with values of any of the WCST subtests. In turn, a certain association was observed between the age and the N-back test results, namely a negative correlation was found between the of patients age and the percent of correct answers, while a positive correlation was demonstrated between the age and the reaction time. It may then be stated that, with growing age, patients with Graves' disease during hyperthyroidism period present with steady progression of visual-spatial working memory disorders, while age has no effect on the degree of deterioration of executive functions.

Among the patients with Graves' disease, the level of education, measured recorded in years of school education, correlated negatively with the number of perseverance errors, while positively with the number of correctly configured categories and the percent of answers compatible with logical concept in WCST. Education was also related to N-back test solution levels, namely, a positive correlation was observed between the number of years at school and the percent of correct answers, while a negative correlation occurred between the number of education years and the time of reaction. It may indicate that intellectual training favourably improves the efficacy of cognitive functions in Graves' disease.

Table 2. Spearman's correlations between age and education and the results of WCST and N-back tests in both studied groups and between disease duration and the intensity of depression symptoms (BDI) and the results in WCST and N-back tests in the group with Graves' disease. *p < 0.05

	Subjects with Graves' disease N=30				Healthy subjects N=31	
	Age	Years of education	Disease duration	BDI	Age	Years of education
WCST						
WCST PE	0.27	-0.41*	-0.02	0.19	0.01	-0.15
WCST N-P	0.10	-0.09	0.24	-0.09	0.25	0.05
WCST CC	-0.08	0.43*	0.06	0.04	0.07	-0.12
WCST 1 cat	0.07	0.13	0.27	-0.01	0.22	-0.15
WCST % conc.	-0.16	0.36*	-0.08	-0.15	-0.38	-0.02
N-back						
% of correct answers	-0.55*	0.29*	0.08	-0.21*	-0.06	0.04
Reaction time	0.41*	-0.04*	0.39*	0.13	0.04	0.04

While in the group of healthy subjects, no statistical correlations were observed between the age and education of the examined patients and the results of WCST or N-back tests.

In the group of ill patients, disease duration did not correlate with the values of the majority of studied neuropsychological parameters; except the time of reaction in the N-back test, a positive correlation was observed between disease duration and the reaction time. There was also a negative correlation between the degree of intensity of depression symptoms in Beck's scale and the percent of correct answers in the N-back test. It is then demonstrated that the occurrence of depression symptoms in hyperthyroid patients in the course of Graves' disease deteriorates the efficacy of working memory and of executive functions.

DISCUSSION

The results, obtained in the course of the reported study, indicate disturbances of cognitive functions, associated with impaired prefrontal cortex functionality in hyperthyroid patients with Graves' disease, which is not observed in healthy subjects. The ill subjects presented with results, indicative of enhanced disturbances of working memory and executive functions, demonstrated, among others, by increased thinking rigidity, a tendency towards reaction perseverance, lower thinking efficacy and worse visual working memory, measured by the N-back test, when compared with healthy subjects. Those results confirm the earlier studies of Bhatara et al. [20] who demonstrated that hyperthyroid patients in the course of Graves' disease did show significantly worse outcomes of neuropsychological tests, involving a certain role of the prefrontal cortex, such as, for example, the Wisconsin Card Sorting Test. Also other authors ascertain that, in subjects with Graves' diseases, disorders within various cognitive areas may be observed, e.g., the processes of concentration, memorising and, first of all, those regarding the executive functions [9, 21].

We demonstrated in our studies that in patients with Graves' disease with hyperthyroidism, changes of the frontal functions demonstrated age-related increases, while no such relationship was observed among healthy subjects. Studies of other authors indicate though that certain aspects of working memory may be weakening with age [22, 23] but, as it appears from the present studies, the degree of these changes is really lower than in subjects with Graves' disease.

In the examined group of patients, there was also a significant relationship between education, measured by the number of years at school(s) and the results of neuropsychological tests. The persons, who had studied for longer time periods, were given much better scores in the performed tests. It may thus indicate that higher education and – most probably – higher intellectual activity in persons with higher education levels have some protective role with regards to the frontal functions in Graves' disease. It then speaks in favour of intellectual training activities, e.g., neuropsychological therapy in persons with Graves' disease.

It was observed in the reported study that 1/3rd of the examined patients presented with significantly increased depression symptoms which could have greatly influenced the clinical picture of the disease, while also deteriorating cognitive functions. Following the results of present studies, depression symptoms and disorders of cognitive functions are a consequence of abnormal activities of such brain structures as the prefrontal cortex and the hippocampus. It may also be at the base of frequently observed neuropsychiatric symptoms in patients with Graves' disease, the symptoms including anxiety, irritability, phobia and depression symptoms, connected with abnormal functionality of the CNS [21, 24, 25].

As it has already been mentioned, affective disorders and cognitive functions may result from changing levels of thyroid hormones, which may significantly affect the functionality of the prefrontal cortex, as well as of other structures, connected with emotional and cognitive data processing. It is also shown by the results of previous studies, performed for more than forty years, and concerning the relationship between secretion disorders of thyroid hormones and mood changes [26]. This relationship has also been confirmed by our studies in which associations were distinguished between the intensity of depression symptoms and the degree

of disorders of frontal functions, mainly visual-spatial working memory and psychomotor efficacy in the examined subjects with Graves' disease. The results also correspond with the studies, performed on a group of patients with depression, indicating a clear relationship between the enhancement of depression symptoms and the degree of deterioration of working memory and executive functions [27, 28].

Both psychic dysfunctions and disorders of cognitive functions in hyperthyroidism in the course of Graves' disease may, sometimes, require psychiatric intervention as well as psychotherapeutic management [29]. The results of recently attempted studies demonstrate that these dysfunctions bring about psychic discomfort, significantly decreasing the quality of life and social functioning of hyperthyroid patients [3, 12, 30]. In the present study, depression was evaluated by means of Beck's Depression Self-Report Inventory, which allows obtaining information, concerning the subjective evaluation of general feeling and functioning of the studied person. In case of the examined subjects with Graves' disease, it is an important index of subjective attitude towards disease and functioning in a difficult situation.

The studies, undertaken in the reported study, have been among the first attempts in Poland to evaluate disorders of cognitive functions, associated with the functionality of the frontal cortex in patients with Graves' disease. The obtained results indicate the occurrence of depressive symptoms and disorders of frontal cortex functions in hyperthyroid patients in the course of Graves' disease. It is advisable to undertake further studies, regarding disorders of cognitive functions and depression in various stages of thyroid function dysregulation in the course of Graves' disease.

CONCLUSIONS

1. Patients with hyperthyroidism in the course of Graves' disease, when compared with healthy subjects, present significant disturbances regarding working memory and executive functions, associated with deteriorated functionality of the brain prefrontal cortex.
2. The age of patients with hyperthyroidism in the course of Graves' disease deteriorates the frontal functions, while the years of completed education improve the same functions. This is not observed in healthy subjects; additionally, the duration of the disease unfavourably affects the frontal functions of patients with Graves' disease.
3. Manifestation of depression in hyperthyroid patients in the course of Graves' disease is a contributive factor to impairment of cognitive functions.

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