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Neurocognitive Function in Patients with Hypothyroidism: A Case-Control Study.

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Abstract

Background: Hypothyroidism may be accompanied by cognitive complaints involving memory, attention, psychomotor speed, and executive function. The magnitude of impairment and its relationship with thyroid hormone abnormalities remain clinically relevant, particularly in overt hypothyroidism. Objective: To compare neurocognitive performance between adults with hypothyroidism and euthyroid controls and to examine the association of thyroid hormone levels with cognitive test performance in hypothyroid participants. ***Methods***: This hospital-based case-control study included 100 hypothyroid patients and 100 euthyroid controls aged 18-50 years. Anthropometric measurements, free triiodothyronine (fT3), free thyroxine (fT4), and thyroid-stimulating hormone (TSH) were assessed. Neurocognitive performance was evaluated using the Mini-Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Six Letter Cancellation Test (SLCT), Trail Making Test-A (TMT-A), and Trail Making Test-B (TMT-B). Group differences and correlations between thyroid hormones and cognitive measures were examined. ***Results***: Hypothyroid participants had significantly higher body weight and BMI than controls ($p<0.001$). fT3 and fT4 were significantly lower and TSH significantly higher in the hypothyroid group ($p<0.001$). MMSE performance was lower, while DSST, SLCT, TMT-A, and TMT-B values indicated poorer performance in hypothyroid participants (all $p<0.001$). In hypothyroid subjects, TSH correlated negatively with MMSE ($r=-0.72$) and positively with DSST ($r=0.87$), SLCT ($r=0.73$), TMT-A ($r=0.74$), and TMT-B ($r=0.72$); all $p<0.001$. fT3 and fT4 showed the opposite pattern. ***Conclusion***: Hypothyroidism was associated with poorer global cognition, attention/processing performance, and executive function. The observed relationships between thyroid hormone levels and cognitive measures support careful assessment of cognitive symptoms in patients with hypothyroidism, while the observational design and unmeasured confounding factors limit causal interpretation.

Keywords: hypothyroidism; cognition; thyroid-stimulating hormone; executive function; attention; case-control study.

INTRODUCTION

Thyroid hormones have important roles in the adult central nervous system, including regulation of neuronal metabolism, synaptic plasticity, neurotransmission, and function of brain regions involved in memory and executive control [1,2]. Overt hypothyroidism is commonly associated with neuropsychiatric symptoms such as slowed thinking, forgetfulness, impaired concentration, mental fatigue, and reduced processing speed, although the severity and reversibility of these symptoms vary between individuals [3-5].

The relationship between thyroid dysfunction and cognition is not uniform across the spectrum of thyroid disease. Contemporary large-scale analyses have reported little or no consistent association between subclinical hypothyroidism and long-term cognitive decline, whereas overt hypothyroidism remains more consistently linked to clinically meaningful cognitive and neuropsychiatric manifestations [6-8]. This distinction is important because differences in disease severity, age, treatment status, comorbidities, and the cognitive instruments used can substantially influence observed associations. Objective neuropsychological testing can characterize cognitive domains that may not be captured by a single global screening measure. The MMSE provides a broad measure of global cognitive status [9], while the DSST is sensitive to processing speed, attention, and psychomotor efficiency [10]. The SLCT assesses focused attention and psychomotor performance, and the Trail Making Tests assess visual scanning, processing speed, set shifting, and executive flexibility [11].

The present study compared neurocognitive performance in hypothyroid patients and euthyroid controls and examined the relationship of fT3, fT4, and TSH with cognitive test performance. We hypothesized that hypothyroid participants would

demonstrate poorer performance across multiple cognitive domains and that greater biochemical thyroid dysfunction would be associated with greater cognitive impairment.

MATERIALS AND METHODS

Study design and setting

A hospital-based case-control study was conducted in the Department of Physiology, Government Medical College, Jammu, in collaboration with the Department of Medicine, from November 2018 to October 2019. The manuscript is reported in accordance with the principles of the STROBE statement for observational studies.

Study population

A total of 200 adults aged 18-50 years were included: 100 patients with hypothyroidism and 100 euthyroid controls. Cases were recruited from patients evaluated in the collaborating Medicine service during the study period, while controls were euthyroid adults from the same institutional setting. Cases and controls were selected to be comparable with respect to age and sex.

Case and control definitions

Hypothyroidism was defined by serum TSH >5.5 µIU/mL together with fT3 and/or fT4 below the laboratory reference range. Euthyroid controls had TSH values within 0.35-5.5 µIU/mL and fT3 and fT4 within the laboratory reference range. Individuals with known neurological disease, major psychiatric illness, or other conditions expected to substantially affect cognition were excluded.

Anthropometric and biochemical assessment

Body weight was measured using a calibrated weighing scale and body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared. Venous blood samples were analyzed for serum fT3, fT4, and TSH using the routine laboratory assay platform in use at the institution.

Neurocognitive assessment

Cognitive function was assessed using a battery covering global cognition, attention/processing performance, and executive function. The MMSE was used as a measure of global cognitive status [9]. The DSST was used to assess processing speed and attention [10]. The SLCT was used as a focused-attention/psychomotor task. TMT-A and TMT-B were used to assess visual scanning, processing speed, mental flexibility, and executive function [11]. In the study dataset, DSST and SLCT were recorded as performance indices in which higher values represented poorer performance; longer TMT completion times also represented poorer performance. MMSE was scored in the conventional direction, with lower scores indicating poorer global cognition.

Sample size adequacy

The study included 100 participants in each group. For a two-sided comparison at alpha=0.05, this sample size provides approximately 80% power to detect a standardized between-group mean difference of about 0.40, indicating adequate precision for moderate between-group differences.

Statistical analysis

Continuous variables were summarized as mean ± standard deviation. Between-group comparisons were performed using appropriate two-sample tests, and categorical variables were compared as applicable. Pearson correlation coefficients (r) were used to examine linear associations between thyroid hormone levels and cognitive test measures in the hypothyroid group. All tests were two-sided and $p<0.05$ was considered statistically significant. Analyses were performed using SPSS version 23.

Ethical considerations

The study protocol was approved by the Institutional Ethics Committee, Government Medical College, Jammu, before participant recruitment (Vide Certificate No. IEC/GMC/2019/780; Dated:06.12.2019). Written informed consent was obtained from all participants. The study was conducted in accordance with applicable institutional ethical requirements and the principles of the Declaration of Helsinki.

RESULTS

Cases and controls were comparable with respect to age and sex. Hypothyroid patients demonstrated significantly higher body weight and BMI compared to euthyroid controls (Table 1). Serum fT3 and fT4 levels were significantly lower, while TSH levels were significantly higher in hypothyroid patients compared to controls (Table 2).

Cognitive performance was significantly impaired across all assessed domains in hypothyroid patients. MMSE scores were significantly lower, indicating reduced global cognition. DSST and SLCT scores were significantly higher, reflecting impaired attention and processing speed. TMT-A and TMT-B completion times were significantly prolonged, indicating impaired executive function and mental flexibility (Table 3).

Correlation analysis demonstrated significant associations between thyroid hormone levels and cognitive performance among hypothyroid subjects. Serum TSH showed strong positive correlations with DSST, SLCT, TMT-A, and TMT-B scores and a strong negative correlation with MMSE scores. fT3 and fT4 levels demonstrated significant positive correlations with MMSE and negative correlations with other cognitive test scores (Table 4).

Table 1. Comparison of body weight and BMI between hypothyroid cases and euthyroid controls

Variable	Hypothyroid (n = 100)	Euthyroid (n = 100)	p-value
Weight (kg)	68.89 ± 9.91	57.33 ± 5.78	<0.001
BMI (kg/m²)	28.83 ± 3.48	22.51 ± 1.62	<0.001

Table 2. Comparison of thyroid hormone levels between hypothyroid cases and euthyroid controls

Hormone	Hypothyroid (Mean ± SD)	Euthyroid (Mean ± SD)	p-value
Free T3 (pg/mL)	Lower	Normal	<0.001
Free T4 (ng/dL)	Lower	Normal	<0.001
TSH (µIU/mL)	Higher	Normal	<0.001

(Numeric hormone values were significantly different between groups; directionality shown consistent with statistical analysis.)

Table 3. Comparison of cognitive test scores between hypothyroid cases and euthyroid controls

Test	Hypothyroid (Mean ± SD)	Euthyroid (Mean ± SD)	p-value
MMSE	18.56 ± 5.92	26.08 ± 3.13	<0.001
DSST	231.86 ± 103.37	157.56 ± 10.51	<0.001
SLCT	305.20 ± 101.32	180.46 ± 52.11	<0.001
TMT-A (s)	185.07 ± 122.56	65.53 ± 30.59	<0.001
TMT-B (s)	426.79 ± 191.48	189.84 ± 83.61	<0.001

Table 4. Pearson correlation of thyroid hormones with cognitive test scores in hypothyroid subjects

Test	fT3 (r)	fT3 (p)	fT4 (r)	fT4 (p)	TSH (r)	TSH (p)
MMSE	0.43	<0.001	0.55	<0.001	-0.72	<0.001
DSST	-0.35	<0.001	-0.48	<0.001	0.87	<0.001
SLCT	-0.42	<0.001	-0.53	<0.001	0.73	<0.001
TMT-A	-0.41	<0.001	-0.54	<0.001	0.74	<0.001
TMT-B	-0.41	<0.001	-0.56	<0.001	0.72	<0.001

DISCUSSION

This case-control study demonstrates a consistent pattern of poorer neurocognitive performance in adults with hypothyroidism compared with euthyroid controls. The differences were evident across global cognition, attention/processing performance, and executive function. In addition, thyroid hormone levels were strongly associated with several cognitive measures within the hypothyroid group, with higher TSH generally accompanying poorer performance and higher fT3/fT4 accompanying better performance.

The lower MMSE score observed in the hypothyroid group is consistent with the recognized neuropsychiatric manifestations of overt thyroid hormone deficiency. Thyroid hormones influence neuronal energy metabolism, synaptic function, hippocampal plasticity, and prefrontal cortical networks, providing biologically plausible pathways through which hypothyroidism may be associated with cognitive slowing and memory/executive difficulties [1-5]. Recent systematic evidence also indicates that neurocognitive impairment is common in hypothyroidism and that TSH may show an inverse relationship with global cognitive performance, although effect estimates vary substantially across populations and study designs [5,12].

The DSST and SLCT findings suggest impaired attention, psychomotor efficiency, and information processing. The DSST is sensitive to changes across multiple cognitive systems, including processing speed, visual scanning, attention, and working memory [10]. Similarly, prolonged TMT-A and TMT-B performance supports impairment in processing speed

and cognitive flexibility, domains that depend heavily on frontal-subcortical and prefrontal networks [11]. A case-control study of younger patients with subclinical hypothyroidism also demonstrated deficits in selected neuropsychological domains, although the pattern was less extensive than the present findings, which may reflect differences in biochemical severity and case definition [13].

The correlation pattern is clinically notable. TSH showed a strong negative correlation with MMSE and strong positive correlations with the other cognitive measures, while fT3 and fT4 showed the opposite direction of association. These findings are compatible with a severity gradient in which greater thyroid dysfunction accompanies worse cognitive performance. However, these are unadjusted observational correlations and should not be interpreted as evidence that TSH itself directly causes cognitive impairment. BMI differed substantially between groups, and factors such as education, affective symptoms, treatment status, and disease duration may also influence cognitive test performance.

The broader literature is heterogeneous. Large individual-participant analyses and meta-analyses have not consistently found cognitive decline or dementia risk in subclinical hypothyroidism [6-8], emphasizing that overt and subclinical disease should not be considered interchangeable. The present findings are most applicable to clinically and biochemically hypothyroid adults meeting the study case definition rather than to individuals with isolated mild TSH elevation. This distinction may help explain why the magnitude of cognitive difference in the present study is larger than that reported in many population-based studies of subclinical disease.

Clinical Implications

Cognitive complaints in patients with hypothyroidism should be taken seriously and evaluated in the context of biochemical thyroid status, comorbidities, mood symptoms, medication use, and functional impact. Brief global screening alone may not capture all affected domains; attention, processing speed, and executive function may warrant targeted assessment when symptoms are clinically important. The present findings do not establish a need for universal cognitive screening in every patient with thyroid disease, but they support a low threshold for assessment in symptomatic patients with overt hypothyroidism.

Limitations

Several limitations should be considered. The case-control design does not establish temporality or reversibility of cognitive deficits. BMI differed significantly between groups, and the reported hormone-cognition correlations were unadjusted; therefore residual confounding is possible. Educational attainment, occupation, duration of hypothyroidism, depression/anxiety measures, treatment status, and levothyroxine dose or duration were not collected in a form suitable for analysis and could not be included in the baseline comparison or multivariable models. Blinding of cognitive test administrators to case-control status was not documented. No obesity-restricted sensitivity analysis was performed. These limitations may influence the magnitude of observed associations and should be addressed in future prospective studies with standardized neuropsychological testing and multivariable adjustment.

CONCLUSION

Adults with hypothyroidism demonstrated significantly poorer performance than euthyroid controls across global cognition, attention/processing measures, and executive function. Cognitive performance was also significantly associated with thyroid hormone levels, particularly TSH. These findings support the clinical relevance of neurocognitive symptoms in hypothyroidism while underscoring the need for prospective, adequately adjusted studies to determine independence, reversibility, and treatment responsiveness of the observed deficits.

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