Psychiatria Danubina, 2024; Vol. 36, No. 3-4, pp 333-339 https://doi.org/10.24869/psyd.2024.333 *Original research*

THE RELATIONS BETWEEN THYROID HORMONES AND CLINICAL FEATURES OF TURKISH CHILDREN AND ADOLESCENTS WITH ADHD AND ADHD-NOS: A PRELIMINARY STUDY

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received: 26. 1. 2018; revised: 12. 12. 2023; accepted: 19. 1. 2024

Summary

Background: *The aim of this study was to compare the levels of thyroid hormones in children with ADHD and ADHD-NOS and to assess the relationship between ADHD symptom severity, anxiety symptom severity and thyroid hormone levels.*

Subjects and Methods: *The study was planned as a cross-sectional, retrospective study. The records of patients who applied to the study center in between January 2012 and January 2013 were screened and 205 ADHD and ADHD-NOS cases' records were evaluated. Both groups were compared according to thyroid hormon levels. The diagnosis of 205 patients' records and their comorbid psychiatric disorders was made clinically. ADHD symptom severity was assessed by Turgay DSM-IV–Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S). Anxiety symptom severity was assessed by The Screen for Anxiety Related Emotional Disorders (SCARED). Groups were compared with parametric or non-parametric methods according to assumptions of normality. P was set at 0.05 (two-tailed).*

Results: *Among the whole sample, 99 (48.3 %) patients were ADHD, and 106 (51.7 %) patients were ADHD- NOS. The average age of the children in the ADHD group was 10.88 ± 3.02 years, and the average age of the children in the NOS-ADHD group 9.93 ± 2.49 years. Thyroid hormone levels were detected in 81 of 205 patients participating in the study. We found statistically significantly higher T4 levels in the ADHD group compared to the ADHD-NOS group (p=0.006). A statistically significant negative correlation between the total number of diagnoses and T4 level was noted (p=0.001). TSH levels correlated significantly with T-DSM-IV-S total score and symptom counts in the Hyperactivity subscale of this measure.*

Conclusions: *Thyroid hormone levels may be affected in children with impairing ADHD symptoms and increased comorbidities. Our results should be supported with future studies.*

Keywords: *ADHD, ADHD-NOS, thyroid hormones*

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INTRODUCTION

Attention-Deficit Hyperactivity Disorder (ADHD) is an early-onset childhood neuropsychiatric disorder with age inappropriate and impairing symptoms of inattention, hyperactivity, and impulsivity. It is also frequently associated with cognitive deficits (APA 2013). Prevalence of ADHD is reported as 7.2 % in recent review (Chaulagain et al 2023.). In Turkey, the prevalence of ADHD was determined to be 12.4% (Ercan et al. 2019). Attention- Deficit Hyperactivity Disorder Not Otherwise Specified (ADHD-NOS) was reserved for disorders with prominent symptoms of inattention/ hyperactivity-impulsivity that do not meet criteria for ADHD in DSM-IV-TR (APA 2000). ADHD-NOS which is replaced with ADHD- Unspecified in DSM-5 (APA 2013) appears to be used as a diagnosis for situations in which children may be experiencing moderate attention problems in school that might be better characterized as learning or executive-functioning difficulties (APA 2000). ADHD is classified in ICD-10 as hyperkinetic disorder (F90) among behavioral disorders and affective disorders occurring in childhood and adolescence, whereas in ICD-11 it is classified as neurodevelopmental disorders called Hyperactivity Disorders and Attention Deficit Disorder (Pajević et al. 2020).

The etiology of ADHD is complex and not clearly understood yet. Although there is no definite identifiable factor, there are several hypotheses that ADHD is multi-factorial (Chaulagain et al.. 2023). Heritability rate of ADHD was reported to differ between 76.0 % and 80.0 %, making it one of the most highly heritable neuropsychiatric disorders (Franke et al. 2012). Although the exact reason still remain unknown, several prenatal and perinatal factors including exposure to toxins and heavy metals,

socio-psychological stress, diet, gene variants and structural/ functional abnormalities of the brain, neurotransmitter deficiency and dysregulation in the frontostriatal as well as fronto-cerebellar catecholaminergic circuits were reported to contribute to the etiology (Chaulagain et al. 2023, Kavanagh et al 2022). Many studies have examined the role of biomarkers in pathophysiology of ADHD. Biomarkers investigated for ADHD have ranged from genes, neurotransmitters, inflammatory markers, and environmental factors to nutritional and hormonal markers (Scassellati et al. 2012, Altun et al. 2018).

The role of hormonal markers for the diagnosis of ADHD has been increasing in recent years. A spectrum of thyroid pathologies has been recognized in ADHD from hypothyroidism to hyperthyroidism to Generalized Resistance to Thyroid Hormone (GRTH), a disease caused by mutations in the thyroid receptor gene and characterized by reduced responsiveness of peripheral and pituitary tissues to thyroid hormone (Millichap 2007). Even transient disruptions in developmental thyroid homeostasis could lead to manifestations of ADHD (Siesser et al. 2006). Furthermore, hyperthyroidism may cause symptoms like ADHD, such as anxiety, irritability, nervousness, and physical hyperactivity (Ahmed et al. 2008). Findings in the literature point to a possible relationship between thyroid dysfunction and ADHD in children.

In this study, we aimed to compare the levels of thyroid hormones (free tri idothyronine-T3, free tetra iodothyronine or thyroxine-T4 and thyrotropin-TSH) in children with ADHD and ADHD-NOS. We also aimed to assess the relationship between ADHD symptom severity, anxiety symptom severity and thyroid hormones levels.

SUBJECTS AND METHODS

Study center and timeframe

The study was planned as a cross-sectional, retrospective study. It was conducted at the outpatient department of Child and Adolescent Psychiatry in Abant Izzet Baysal University Medical Faculty. The records of patients who applied to the study center in between January 2012 and January 2013 were screened and 205 ADHD and ADHD-NOS cases' records were evaluated. The diagnosis of 205 patients' records and their comorbid psychiatric disorders was made clinically by the consensus of child psychiatry residents and the clinical supervisor according to DSM-IV-TR criteria (APA 2000). Ethics committee approval of the study was obtained from Bolu Abant İzzet Baysal University Clinical Trials Ethics Committee (Date: 16.05.2018, Number: 164).

Inclusion criteria were a primary diagnosis of ADHD or ADHD-NOS according to DSM-IV-TR criteria, adequate information on laboratory values and psychometric measures in patient records, application to the outpatient department between the specified time-frame. Patients with comorbid medical and psychiatric disorders were included. Patients with inadequate records were also excluded.

Measurements

Turgay DSM-IV–Based Child and Adolescent Behavior Disorders Screening and Rating Scale: This parent and teacher-reported scale was developed by Turgay by transforming the DSM-IV criteria (T-DSM-IV-S) into questions without changing their meanings and includes 9 items for attention deficit, 6 items for hyperactivity, 3 items for impulsivity, 8 items for Oppositional Defiant Disorder (ODD), and 15 items for Conduct Disorder (CD). Each item is rated on a scale of 0 = none, 1 = occasional, 2 = much, and 3 = very much. When subscales are evaluated, 2 to 3 points per item are assessed as symptomatic (1), while 0 to 1 are assessed as no symptomatic (0). A score of 6 or above is accepted as cut off (Turgay 1995). The validity and reliability study of this scale was established previously (Ercan et al. 2001)

The Screen for Anxiety Related Emotional Disorders (SCARED): This instrument consists of 41 items asking the parent (or caregiver) to indicate how often a descriptive phrase regarding how their child may have felt over the course of the previous three months is true. Respondents may select from the options of ''Not True or Hardly Ever True (0 point)'', ''Somewhat True or Sometimes True (1 point)'', and ''Very True or Often True (2 point)'' (Birmaher et al. 1997). When subscales are evaluated, 2 point per item are assessed as symptomatic (1), while 0 to 1 are assessed as no symptomatic (0). Both child and parent's report were used. The scale also includes somatic/ panic, generalized anxiety, separation anxiety, social anxiety and school fear subscales. A total score of ≥ 25 may indicate the presence of an anxiety disorder. Scores higher that 30 are more specific (Birmaher et al. 1997). SCARED Turkish forms' validity and reliability was established by Cakmakci (2004).

The Clinical Global Impression-Severity Scale (CGI-S): CGI-S is the most widely used clinician-rated measure of treatment-related changes in functioning (Guy 1976). The CGI-S score rates illness severity on a 7-point scale, ranging from 1 (''normal'') to 7 (''among the most severely ill patients''). CGI-S is usually used in Turkish Child and Adolescent outpatient and inpatient clinics. It is also used frequently in clinical studies from

Turkey with established reliability and validity (Koroglu and Aydemir 2012). CGI-S was used to indicate symptom severity in present study.

Statistical Analysis

The data were evaluated using the Statistical Package for the Social Sciences (SPSS) version 22.0 (IBM Inc., Armonk, NY). Continuous variables are presented by means of summary statistics. This (unless otherwise stated) refers to the number of patients (n), mean, standard deviation (SD). Categorical data are presented using either absolute and relative frequencies. Demographic data were compared using Chi square tests. Yates' and Fisher's corrections were applied when required. The distribution of the data was evaluated by the Kolmogorov-Smirnov method. As the data were distributed normally, between group comparisons were evaluated by Student's t test or one-way ANOVA depending on group numbers. Pearson correlation analysis was used to determine the relationship between continuous variables. All tests were two tailed with p values < 0.05 considered significant.

RESULTS

The records of 205 patients were analyzed. Of these, 99 48.3 %) patients were diagnosed with ADHD and 106 (51.7 %) patients were diagnosed with ADHD- NOS. The average age of the children in the ADHD group was 10.88 ± 3.02 years, and the average age of the children in the ADHD-NOS group 9.93±2.49 years. The groups differed significantly in terms of age with children in the ADHD group being older (p = 0.015). Thirty-four children in the ADHD group were female, and 34 children in the ADHD-NOS group were female. No statistically significant difference was determined between the groups in terms of sex (p = .73). There were 45 cases having positive family history for psychopathology and 51 cases having medical disease history in the ADHD group. In the ADHD- NOS group, there were 54 cases having positive family history for psychopathology and 48 cases having medical disease history. Both family history and medical disease history between two groups did not display statistically significant difference. (respectively p=0.095, p=0.958) (Table-1). T- DSM-IV-S-parent subscales, SCARED subscales, and CGI_S scores between two groups are presented in Table-2.

Comorbid psychiatric disorder was detected in 144 (70.24%) of 205 cases included in the study. It was found that CD (28.29%) and specific learning difficulties (21.95%) were the most common comorbid psychiatric disorders. While 71 of these 144 cases had one comorbid psychiatric disorder, others had multiple comorbid psychiatric disorders. It was found that 76 cases in the ADHD group and 68 cases in the ADHD-NOS group had comorbid psychiatric disorders. No statistically significant difference was determined between the groups in terms of comorbid psychiatric disorders (p=0.531).

Thyroid hormones were detected in 81 of 205 patients participating in the study. While the average levels of thyroid hormones were T3: 4.16 ±0.73, T4: 1.23 ±0.20 , and TSH: 2.6 9±1.13 in the ADHD group (n:47), they were 4.13 ±1.66, 1.07 ±0.29, 2.34 ±1.17 in the ADHD-NOS group (n:34); respectively. When we compared to ADHD and ADHD-NOS groups, we found statistically significant difference between the both groups in terms of T4

Table 1 Comparison of Sociodemographic data of the ADHD-NOS and ADHD groups

	ADHD-NOS group (n:99)	**ADHD group (n:106)**	***p***
Age	10.88±3.02	9.93±2.49	.015
Gender			
Male	65	72	.73
Female	34	34	
Family history			
Positive	54	45	.095
Negative	45	61	
Medical disease history			
Positive	48	51	.958
Negative	51	55	

Table 2 Comparison of T-DSM-IV-S-parent subscales, SCARED subscales and CGI-S scores of the ADHD-NOS and ADHD groups

	ADHD-NOS group (n:99)	**ADHD group (n:106)**	***p***	***t***
T-DSM-IV-S-parent				
Attention	2.41±1.72	6.28±2.15	<.001	-14.657
Hyperactivity	1.40±1.85	4.52±3.18	<.001	-8.389
Opposition-defiance	1.45±2.02	3.56±2.99	<.001	-5.896
CD	0.11±0.46	0.56±1.22	0.001	-3.339
Total score	21.34±11.41	42.37±17.02	<.001	-10.588
SCARED				
Somatic/panic	1.85±2.31	2.29±2.47	.441	-.065
Generalized anxiety	1.32±1.98	3.11±2.64	.001	-3.067
Separation anxiety	1.43±1.68	2.68±1.92	.003	-3.015
Social anxiety	2.09±1.95	2.85±2.22	.106	-1.104
School phobia	0.53±1.31	1.15±.142	.050	-1.583
Total score	25.89±12.86	34.00±12.89	.007	-2.044
CGI-S	3.39±0.74	4.55±0.64	<.001	-6.634

SCARED: The Screen for Anxiety Related Emotional Disorders; CGI-S: The Clinical Global Impression-Severity Scale

Table 3 Comparison of thyroid hormones levels of the ADHD-NOS and ADHD groups

	ADHD-NOS group	ADHD group	p	t
T3, pg/mL (rr: 1.71-3.71 pg/mL)	4.13±1.66	4.16±0.73	.926	0.910
T4, ng/mL (rr: 0.7-1.48 pg/mL)	1.07±0.29	1.23±0.20	.006	-1.055
TSH, µIU/ ml (rr:0.51-4.3 µIU/ ml)	2.34±1.17	2.69±1.13	.204	0.873
rr: reference range				

Table 4 Examination of the relationship between ADHD symptoms and Thyroid hormones (Pearson correlation analysis)

		T3 level	**T4 level**	**TSH level**
T-DSM-IV-S-parent				
Attention	r	.025	.001	.137
	p	.849	.996	.284
Hyperactivity	r	.171	-.042	.251
	p	.181	.743	.047
Total score	r	.238	-.141	.264
	p	.060	.270	.037

levels, but there was no significant difference in terms of t3 and TSH levels in the both groups (Table-3).

When the relationship between total number of diagnosis and thyroid hormones was assessed, a statistically significant negative correlation was found between the total number of diagnosis and T4 levels (r: -386, p:0.001), but the same relationship with T3 and TSH levels was not obtained (p>0.05)

When the relationship between the symptoms of ADHD and thyroid hormones was evaluated, while there was a significant positive correlation between ADHD HA sub scores, ADHD total scores and TSH levels (p=.047, p=.037 respectively), no correlation was found between the symptoms of ADHD and T3 and T4 (p>.05) (Table-4). When the relationship between SCARED scores and thyroid hormones was evaluated, no relationship was found between thyroid hormones and SCARED subscales and total scores (p>.05, Table 4).

DISCUSSION

In this retrospective study, we aimed to compare the levels of thyroid hormones in children with ADHD and ADHD-NOS, and to assess the relationship between ADHD symptom severity, anxiety symptom severity and thyroid hormone levels. We have shown significant difference between ADHD and ADHD-NOS groups in terms of T4 levels. We found a statistically significant negative correlation between the total number of diagnosis and T4 level. We also found a significant positive correlation between TSH levels and ADHD total score and hyperactivity sub score.

The main outcome of this study is significant difference between ADHD and ADHD-NOS in terms of T4 levels being higher in the ADHD group. In studies assessing thyroid hormones and ADHD relations in the literature, mostly ADHD and healthy control groups were compared for thyroid hormone levels (El Rahman et al. 2014, Toren et al. 1997, Cakaloz et al. 2011, El Baz et al. 2008, Kuppili et al. 2017; Albrecht et al. 2020). The data comparing to ADHD and healthy control in terms of thyroid hormones was inconsistent. In a recent study, TSH and free T4 concentrations were significantly lower in children with ADHD compared to those without, while adolescents with a diagnosis of ADHD or ADHD symptoms had higher fT3 levels compared to controls (Albrecht et al. 2020). Kuppili et al. (2017) found that serum total T4 levels were significantly lower in cases of ADHD compared to controls with no difference in serum total T4 and TSH. Conversely, two previous studies found no significant difference in serum T3, T4 and TSH levels between ADHD and healthy control groups. (El Rahman et al. 2014, Toren et al. 1997). A previous study from Turkey and another one from Egypt found that free T3 and TSH levels were significantly lower in ADHD when compared to healthy controls (Cakaloz et al. 2011, El Baz et al. 2008). The discrepancies in those studies may be explained by sampling methods or due to lack of evaluation of patients for GTHR. Our results are novel in comparing thyroid hormone levels in groups with differing degrees of ADHD symptoms and suggest that T4 levels were elevated in those with more severe symptoms. Our results may also suffer from sampling bias and external validity should be evaluated with further studies on larger samples from multiple centers.

We also observed a significant negative correlation between the total number of psychiatric disorder diagnosis and T4 level for both groups. This means that as the vitamin T4 level decreases, the number of psychiatric diagnoses increases. Thyroid hormone (TH) changes, even within the normal range, have been related to the risk of developing common psychiatric disorders (Soheili-Nezhad et al. 2023). El Rahman et al. (2014) compared ADHD patients with one or no comorbid diagnosis and ADHD patients with at least two comorbidities in terms of thyroid hormones. They found no statistically significant differences in the thyroid hormones of the two groups. They also found that thyroid hormones were within normal ranges in the two groups (El Rahman et al. 2014). In another study, it was found high concentrations of T4 levels were related to mood lability, preoccupations, and lower ratings of attention problems (Stein and Weiss 2003). Due to scarcity of the literature focusing on thyroid hormones and psychiatric comorbidity/ symptom loads in patients with ADHD our results should be deemed preliminary and require replication.

Another finding we have in our study that there is a significant positive correlation between TSH levels and ADHD total score and hyperactivity sub score. This means that as TSH and T4 levels increase, ADHD total and hyperactivity scores increases. The data assessing the relationship between ADHD symptom severity and thyroid hormone levels was inconsistent. Albrecht et al. (2020) found serum TSH, fT3, and fT4 with risk for ADHD diagnosis or symptom. Kuppili et al. (2017) found no significant correlation between serum T3, T4,TSH levels and Conners' Parent Rating Scale –Revised short (Conners 1997) scores (Kuppili et al. 2017). Hauser et al (1997) found significant correlation between among the thyroid hormone levels only T3 levels and hyperactivity and impulsivity symptoms of ADHD (Hauser et al. 1997). In another study in our country, thyroid functioning and its behavioral correlates were evaluated using Child

Behavior Check List (CBCL) in children with ADHD with or without ODD comorbidity. This study found significant negative correlations between attention problems, delinquent behaviors, aggressive behaviors, internalizing, externalizing subscores, total scores of CBCL and TSH levels (Cakaloz et al. 2011).

Our findings should be evaluated within the context of limitations. Firstly, the study was retrospective and depended on information recorded routinely in clinical records. This dependence led to a missing data which may have affected the results. Secondly, the study was conducted on a clinical sample evaluated at a single center and may not reflect patient populations in other centers or in the community. Thirdly, the laboratory evaluations were conducted as part of the baseline examination prior to commencing pharmacotherapy at the study center but due to dependence on patient charts we could not ascertain whether the patients were drug naive or were receiving treatment at the time of evaluations. Despite those limitations this is the only study that we are aware of evaluating psychometric features and laboratory values of children diagnosed with ADHD and ADHD- NOS.

CONCLUSION

We showed a significant difference between ADHD and ADHD-NOS groups in terms of T4 levels, statistically significant negative correlations between the total number of diagnoses and T4 levels and a significant positive correlation between TSH levels and ADHD total scores and hyperactivity sub scores in our study. Those results suggest that TSH and T4 levels may be associated with ADHD symptoms and that assessing thyroid hormone levels (especially TSH levels) may be beneficial in children with ADHD and elevated psychiatric comorbidity. Further studies on larger samples characterized according to ADHD symptom loadings and psychiatric comorbidities are needed to evaluate the contribution of thyroid functioning and neurodevelopmental disorders.

Ethical Considerations: Does this study include human subjects? YES
Authors confirmed the compliance with all relevant ethical regulations.
Conflict of interest: No conflict of interest
Funding sources: The authors received no funding from an external source
Authors contributions: Dr. Yusuf Ozturk: study design, data collection, first draft, approval of the final version, statistical analysis, writing of the manuscript. Dr. Zehra Hangül: study design, data collection, first draft, approval of the final version, statistical analysis, writing of the manuscript. Dr. Nuran Demir: study design, data collection, first draft, approval of the final version, statistical analysis, writing of the manuscript. Dr. Ali Evren Tufan: study design, data collection, first draft, approval of the final version, statistical analysis, interpretation of data.

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