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ORIGINAL ARTICLE

Assessment of Thyroid Hormones Level in Attention Deficit Hyperactivity Disorder Children

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ABSTRACT

Background: The relationship between ADHD and thyroid hormones has been controversial and widely debated. A range of thyroid abnormalities have been noted in relationship with ADHD. This study was conducted to assess thyroid hormones level in children with ADHD and compare them with healthy controls.

Methods: A sample of 46 participants (23 cases, 23 controls) was taken, cases satisfied the diagnosis of ADHD according to Diagnostic and statistical manual of mental disorder (DSM-5) and fulfills the inclusion criteria, diagnosis of ADHD was confirmed by ADHDT (The Attention-Deficit/Hyperactivity Disorder Test OF James E. Gilliam). Stanford-Binet Intelligence Scales- 5th edition (SB5) was performed to assess intelligence quotient (IQ) of the selected children.

Results: There was statistically significant difference between the case and control groups regarding child abuse and being have family history. Also, there was statistically significant difference between the case and control groups regarding performance, total IQ, they were lower in cases than control. On comparing between three subtypes of ADHD, there was statistically significant difference between them regarding child abuse being 100% in hyperactive, 66.7% in combined and 0.0% in inattentive subtype. Also, total T4 was significantly lower in inattentive subtype.

Conclusion: Total T4 level was lower in inattentive subtypes than other subtypes. But, thyroid hormones level showed no difference between ADHD children and control. Also, they have lower total and performance IQ than healthy ones. Children with ADHD were exposed to abuse more than healthy children especially in hyperactive and combined subtypes.

Keywords: ADHD, Thyroid function, IQ, Zagazig, Egypt.

INTRODUCTION

The DSM-5 characterizes attention deficit hyperactivity disorder as “persistent pattern of inattention and/or hyperactivity-impulsivity that interferes with functioning or development”. The categorization of ADHD as a neurodevelopmental disorder was made to reflect “brain developmental correlates with ADHD”^[1]. Studies found important association between ADHD and Dopamine system gene, especially DRD4 and DRD5^[2]

There is little research regarding the biological biomarkers although the cost estimates of ADHD and the prevalence rates. Biomarkers are important because they may be beneficial in early diagnosis and hence early treatment seeking as well as provide objective markers^[3]. One of the important biomarkers is the hormonal one; one of them is thyroid hormones. Thyroid hormones insufficiency during 28 early development causes structural and functional abnormalities in brain leading to cognitive dysfunction. A

spectrum of thyroid abnormalities have noted in ADHD from hypothyroidism to Hyperthyroidism to Generalized Resistance to Thyroid Hormone (GRTH) suggesting thyroid hormone deregulation / dysfunction in association with ADHD [4]. This study was conducted to assess thyroid hormones level in children with ADHD and compare them with healthy controls.

SUBJECTS & METHODS

Written informed consent was obtained from all participants and the study was approved by the research ethical committee of Faculty of Medicine, Zagazig University. The work has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for studies involving humans. The study was conducted from February to September 2018.

A case control study was done and sample of 46 participants from both sexes Assuming mean SD of T4 in ADHD children versus control group (7.24±2.73 versus 13.6±9.34) [5]. Sample was calculated to be 46 subjects using open Epi program with level of confidence 95 % and test power 80 % [6], in the age group from 6-12 years old, “New” cases fulfilling the diagnostic criteria for ADHD according to DSM–5 criteria [1] were screened for inclusion in the study group. Controls were selected from children of non-biological relatives or acquaintances visiting Psychiatry outpatient clinic. The controls were screened for psychiatric illness before inclusion in the study through clinical interview. The inclusion criteria for controls were age matched (± 2 years) with a minimum age of six years and maximum age of twelve years old. Inclusion criteria were: Age 6-12 years old, both sexes will be included and newly diagnosed cases, with exclusion criteria of participants with: Age below 6 or above 12, history or present symptoms of comorbid conduct, autistic disorder or other psychiatric disorders, IQ less than 70 and any medical illness interprets with the diagnosis.

All participants enrolled in the study (case and control subjects) were subjected to the following:

1. **Semi structured questionnaire including:** Socio-demographic data

including name, age, sex, The academic achievement, socioeconomic status using modified El Gilany [7], exposure to abuse (we asked in the questionnaire about exposure to physical, emotional, sexual abuse or neglect), consanguinity, family history of psychiatric illness (like, anxiety, depression and ADHD symptoms in family), mode of delivery, breast feeding or perinatal problems (smoking , fever, medication, uterine discharge during pregnancy, difficult labor, respiratory problems, low birth weight and intrauterine bleeding. Also, clinical data like: age of onset of the disorder, duration of illness and severity of symptoms and information about past history of any systemic illness or medication that could interfere with diagnosis.

2. **ADHDT (Attention Deficit Hyperactivity Disorder Test of Gilliam):** In this study, the ADHD symptoms in children were assessed with the 36- item ADHD interview test [8]. Mothers completed the interview, which is based on the Diagnostic and Statistical Manual of Mental Disorders (DSM- IV) criteria for ADHD. The instrument is designed to identify and evaluate ADHD in ages 3–23 years and contains three subscales: hyperactivity, inattention and impulsivity.

3. **Stanford–Binet Intelligence Scales:** It is a cognitive ability and intelligence test that is used to diagnose developmental or intellectual deficiencies in young children [9].

4. **Blood samples** were collected by a technician in anticoagulant free tubes, via a venipuncture of the antecubital vein and analyzed at Zagazig university hospitals laboratories. Serum levels of total Triiodothyronine (T3), total Thyroxine (T4), Thyroid Stimulating Hormone (TSH) were measured using fully-automated auto-analyzer Cobas e602 [10].

Statistical Analysis

After data collection, data were coded, entered and analyzed using SPSS (Statistical Package for Social Science) version 25. Qualitative data were presented as frequencies and percentages while, quantitative data were presented as mean, standard deviations and median. Qualitative independent variables were compared using chi-square test while

quantitative data of multiple independent groups were compared using analysis of variance (ANOVA test) for normally distributed data and the student "t" test for comparison of means of two independent groups. P value (≤ 0.05) was considered statistically significant difference.

RESULTS

In our study, majority of cases were males (78.3%) with mean age (8.4 ± 1.8) and most of cases were from low socioeconomic class (56.5%). 65.2% of cases were of combined subtype of ADHD [Table 1]. There was statistically significant difference between the case and control groups regarding child abuse and being have family history. But there was no statistically significant difference in birth weight, breast feeding, consanguinity and mode of delivery [Table 2]. Also, there was statistically

significant difference between the case and control groups regarding performance, total IQ, they were lower in cases than control. But regarding verbal IQ and thyroid functions, there was no statistically significant difference [Table 3]. On comparing between three subtypes of ADHD, the mean age of inattentive subtype was 10 ± 2.1 while in hyperactive one was 7.5 ± 1.9 and of combined one was 8.3 ± 1.5 , and as regarding sex all cases of hyperactive subtype were male and 73.3 % of combined one also there was statistically significant difference between them regarding child abuse being 100% in hyperactive, 66.7% in combined and 0.0% in inattentive subtype. But regarding other variables, there was no statistically significant difference [Table 4]. Also, total T4 was significantly lower in inattentive subtype [Table 5].

Table (1): Comparing socio-demographic characteristics between case and control groups:-

Variable	Case (23)		Control (23)		t Test	p-value
Age mean \pm SD (Range)	8.4 ± 1.8 (6-12)		8.9 ± 1.9 (6-12)		0.3	0.6
Variable	Case No(23)	%	Control No(23)	%	χ^2	p-value
Sex						
Male	18	78.3%	17	73.9%	0.1	0.7
Female	5	21.7%	6	26.1%		
Residence					0.3	
Rural	15	65.2%	13	56.5%		0.5
Urban	8	34.8%	10	43.5%		
Socio-economic class					2.2	
Very low						0.3
Low	0	0%	0	0%		
Moderate	13	56.5%	9	39.1%		
High	7	30.5%	12	52.2%		
	3	13.0%	2	8.7%		

Table (2): Comparing clinical history between case and control groups:-

Variable	Case No(23)	%	Control No(23)	%	χ^2	p-value
<u>Birth weight</u>						
<2.5 kg	10	43.5%	4	17.4%	3.6	0.05
>2.5 kg	13	56.5%	19	82.6%		
<u>Mode of delivery</u>						
vaginal	14	60.9%	15	65.2%	0.09	0.7
cesarean section	9	39.1%	8	34.8%		
<u>Consanguinity</u>						
Yes	7	30.4%	6	26.1%	0.1	0.7
No	16	69.6%	17	73.9%		
<u>Breast feeding</u>						
Normal	15	65.2%	17	74.0%	0.6	0.7
Artificial	5	21.7%	3	13.0%		
Combined	3	13.0%	3	13.0%		
<u>Perinatal problems</u>						
Yes					FET	0.6
No	4	17.4%	2	8.7%		
	19	82.6%	21	91.3%		
<u>Child abuse</u>						
Yes	14	60.9%	5	21.7%	7.2	0.007*
No	9	39.1%	18	78.3%		
<u>Family history</u>						
Yes	9	39.1%	2	8.7%	5.8	0.01*
No	14	60.9%	21	91.3%		

* Statistically significant difference ($P \leq 0.05$)

* FET: Fischer exact test, a type of Chi square test.

Table (3): Comparing IQ, thyroid functions and ADHDT scores between case and control groups:-

Variable	Case (23)	Control (23)	t-Test	p-value
<u>IQ performance</u>				
mean \pm SD	88.9 \pm 11.6	102.7 \pm 9.6	4.3	0.001**
(Range)	(70-111)	(80-120)		
<u>IQ verbal</u>				
mean \pm SD	102.2 \pm 10.5	105.8 \pm 9.6	1.2	0.2
(Range)	(80-119)	(84-119)		
<u>IQ total</u>				
mean \pm SD	95.6 \pm 11.2	104.2 \pm 9.2	2.8	0.007*
(Range)	(75-115)	(83-117)		
<u>TSH</u>				
mean \pm SD	2.4 \pm 0.8	2.3 \pm 0.9	0.3	0.7
(Range)	(1.18-4.44)	(1.18-4.44)		
<u>T4</u>				
mean \pm SD	106.2 \pm 13.6	112.1 \pm 21.4	1.1	0.2
(Range)	(78.4-133)	(75.9-167.3)		
<u>T3</u>				
mean \pm SD	2.6 \pm 0.3	2.6 \pm 0.4	0.07	0.9
(Range)	(2.1-3.3)	(1.84-3.4)		
<u>ADHDT</u>				
mean \pm SD	117.3 \pm 13.1	80.9 \pm 4.7	12.4	0.001**
(Range)	(94.1-137.3)	(75.3-91.9)		

* Statistically significant difference ($P \leq 0.05$)** Statistically highly significant difference ($P \leq 0.001$)

Table (4): Comparison between the three different subtypes of ADHD in the case group as regarding age, sex and clinical data finding:-

Variable	inattentive		hyperactive		combined		F test	p-value
	No(4)	%	No(4)	%	No(15)	%		
Age	10±2.1 (7-12)		7.5±1.9 (6-10)		8.3±1.5 (6-11)		2.2	0.1
Variable	inattentive		hyperactive		combined		χ^2	p-value
	No(4)	%	No(4)	%	No(15)	%		
Sex							1.3	
Male	3	75.0%	4	100.0%	11	73.3%		0.5
Female	1	25.0%	0.00	0.0%	4	26.7%		
Birth weight							1.7	
<2.5 kg	1	25.0%	1	25.0%				
>2.5 kg	3	75.0%	3	75.0%	8	53.3%		0.4
					7	46.7%		
Mode of delivery							1.1	
Vaginal	3	75.0%	3	75.0%				
cesarean section	1	25.0%	1	25.0%	8	53.3%		0.6
					7	46.7%		
Consanguinity							0.9	
positive	2	50.0%	1	25.0%	4	26.7%		
negative	2	50.0%	3	75.0%	11	73.3%		0.6
Breast feeding							8.7	
Normal	3	75.0%	1	25.0%	11	73.3%		
Artificial	0	0.0%	3	75.0%	2	13.3%		0.06
Combined	1	25.0%	0.00	0.0%	2	13.3%		
Perinatal problems								
positive	0.00	0.0%	0.00	0.0%	11	73.3%	2.3	
negative	4	100.0%	4	100.0%	4	26.7%		0.3
Child abuse							9.1	
Yes	0.00	0.0%	4	100.0%	10	66.7%		0.01*
No	4	100.0%	0.00	0.0%	5	33.3%		
Family history							1.1	
Positive	1	25.0%	1	25.0%	7	46.7%		0.5
negative	3	75.0%	3	75.0%	8	53.3%		

Table (5): Comparison between the three different subtypes of ADHD in the case group regarding IQ and thyroid functions:-

Variable	inattentive N (4)	hyperactive N (4)	combined N(15)	F test	p-value
<u>IQ performance</u>				1.5	
mean ± SD	91.3±6.9	97±11.1	86.2±12.3		0.2
(Range)	(83-98)	(84-111)	(70-110)		
<u>IQ verbal</u>				2.2	
mean ± SD	104±4.6	111±7.1	99.4±11.3		0.1
(Range)	(99-110)	(102-119)	(80-118)		
<u>IQ total</u>				2.1	
mean ± SD	98.3±6.2	104.3±8.9	92.6±11.7		0.1
(Range)	(90-104)	(93-115)	(75-114)		
<u>TSH</u>				0.1	
mean ± SD	2.5±0.9	2.6±0.3	2.3±0.8		0.8
(Range)	(1.18-3.35)	(2.2-3)	(1.2-4.4)		
<u>T4</u>				4.4	
mean ± SD	90.1±12.7	110.1±10.5	109.5±12.1		0.02*
(Range)	(78.4-102)	(100-121)	(92.8-133)		
<u>T3</u>				0.1	
mean ± SD	2.6±0.33	2.7±0.4	2.5±0.3		0.89
(Range)	(2.2-2.9)	(2.1-3.1)	(2.1-3.3)		

DISCUSSION

This study was conducted to evaluate hormonal biomarkers namely thyroid hormones in children with ADHD and compare them with healthy controls and to explore the relation of the thyroid biomarkers with severity of ADHD. The sample included: 23 children diagnosed as ADHD according to DSM-5 criteria and 23 healthy controls. Serum levels of total T3, total T4 and TSH were measured.

Majority of affected children were male (78.3%) These findings are consistent with previous studies that show that children diagnosed with ADHD are predominantly males^[11] and also in two Egyptian studies, one was performed at the psychiatry clinic, Pediatric Hospital, Ain Shams University^[12] and the other was performed at the Kasr Aini Pediatric Hospital outpatient psychiatry clinic^[13].

Compared to males with ADHD, females with ADHD are more prone to have difficulties with inattentive symptoms than hyperactive and impulsive symptoms, and females often receive a diagnosis of ADHD significantly later than do males^[14].

Most of the children in our study were from a low socioeconomic level and from rural areas. That is consistent with another study was performed in Egypt^[13]. Many authors have reported that children affected by psychological disorders tend to be of low socioeconomic status^[15]. Another studies in Saudi Arabia^[16] and India^[5] are showing that majority of affected children were from upper\ middle socioeconomic class. That could be explained by that our sample was taken from children attending outpatient clinic at general hospital, so most of were from low socioeconomic status.

This study shows significant proportion of family history that is consistent with another study on Egyptian sample^[17]. International studies noted the higher prevalence of psychopathology in the parents and other relatives of children and adolescents with ADHD^[18]. In particular, higher rates of ADHD, conduct problems, substance abuse, and depression were repeatedly observed in these studies.

As regard child abuse (physical, emotional, sexual or neglect), it shows significant difference between affected children and healthy ones. Also, there is a

significant difference between the three subtypes. Almost all hyperactive children and 66.7% of combined ones have been exposed to abuse either physically or verbally or both, but not sexually, in contrast to inattentive subtype have not exposed at all. The National Society for the Prevention of Cruelty to Children (NSPCC) describes types of child abuse as follows: a) Physical abuse: refers to every action causing injury to the child. b) Emotional abuse: refers to every type of action damaging self-respect of the child. c) Neglect: refers to disregard of basic needs of child (physical or emotional) ^[19].

One possibility is that a combination of abuse and ADHD results in aggressive behavior as an additive function of both risk factors. That is, a combination of parental stress and distress plus difficult child temperament may set the stage for failures in caregiving, leading to abusive parenting, which accentuates aggressive child tendencies.

In the current study, the most common ADHD subtype was combined subtype (65.2 %), followed by equal inattentive subtype (17.4%) and hyperactive/impulsive subtype (17.4%). In the present study, when investigating the frequency of ADHD subtypes according to gender, combined and hyperactive subtype more common in boys than girls while inattentive subtype has nearly no sex difference. Our results revealed that boys with ADHD are rated more hyperactive-impulsive, while girls are rated more inattentive and combined subtype. This is nearly similar to data obtained from ^[17] ^[20] ^[21].

This differ from another studies that show the most common subtype was hyperactive subtype which was found in more than 50% cases followed by combined followed by inattentive subtype ^[5]. Other studies reported higher prevalence of the inattentive type ^[20] ^[23] ^[24], whereas another study reported the preponderance of the combined type ^[25].

In our study higher prevalence of hyperactive subtype than some studies could be explained by that mean age of this group is less than other subtypes (7.5±1.9). Individuals who meet criteria for hyperactive subtype in preschool may shift to combined subtype

early in elementary school, as increased attention demands in school make their symptoms of inattention more noticeable and impairing, leading to an increase in the prevalence of combined subtype and a decrease in the prevalence of hyperactive one. In the present study, no statistically significant differences were found between male and female children with ADHD as regard results of ADHDT, results only confirmed the diagnosis of ADHD.

Although the IQ scores, estimated by the Stanford-Binet 4th edition, for all ADHD children were above 75 (mean and SD for the total score of intelligence was 95.6 ± 11.2), it was still lower than that of the control group of normal children (104.2 ± 9.2); with statistically significant difference in performance IQ with mean and SD are (88.9±11.6) while mean and SD of the control group are (102.7±9.6).

These results were consistent with the findings from many other studies ^[26] ^[27] ^[28] ^[29] reporting significantly lower cognitive abilities in ADHD children as estimated through IQ tests and compared with matched controls. With regard to the results of the Wechsler intelligence quotient(WISC), results showed statistically significant differences between the ADHD group and the control group, indicating lower executive performance on WISC in all the test domains, a finding that was concluded by multiple other studies ^[30] ^[31]. Nevertheless, the literature demonstrates the possibility of having both ADHD and high IQ, which is an area of some controversy ^[32]. Previous studies by ^[33] ^[34] found a significant negative association between degree of ADHD and intelligence.

However, low IQ could be explained by ADHD symptoms that may directly cause an individual to perform poorly on the standard test of intelligence ^[35]. Also, the association between ADHD symptoms and low IQ cannot be fully attributed to inattentive test-taking behaviors. That the co-occurrence of ADHD and low IQ has genetic origins raises the possibility that specific genes may influence brain networks that underlie both ADHD and IQ ^[36].

As regard the thyroid profile (TSH, T3, T4), the levels of the three hormones in the study group with within normal; no thyroid dysfunction was detected. There was no statistically significant difference between the study group of ADHD patients and control group found in mean serum T, mean serum T4 and mean serum TSH between cases and controls. But, mean serum T4 level was lower in cases when compared to controls and statistically significant lower in inattentive subtype.

A stronger relationship was evidenced between lower concentrations of T4 and more frequent mood symptoms and more perhaps ADHD patients may have subtle abnormalities in the hypothalamic-pituitary-adrenal axis. T4 may contribute directly toward poor attention, as suggested by studies of children with hypothyroidism^[37]. A recent Indian case control study showed Mean serum T4 level was significantly lower in cases when compared to controls and no significant difference was found in mean serum T3 and mean serum TSH between cases and controls^[5].

In contrast to our study, another studies found no significant difference was found in serum T3, T4 and TSH levels between cases and controls^{[13] [38]}. However, free T3 and TSH levels were significantly lower in cases when compared to controls in two studies conducted in Egypt in 2008 and in Turkey in 2011^{[12] [39]}. The study findings are in contrast with findings of GRTH where there is decreased peripheral responsiveness characterized by high T3 and T4 levels^[40]. That difference might be explained by estimation of total thyroid hormones (Total T3 and Total T4) instead of free thyroid hormones also small sample size.

Limitations

The relatively small sample size that could limit certain interpretations.

CONCLUSIONS

Total T4 level was lower in inattentive subtypes than other subtypes. But, thyroid hormones level showed no difference between ADHD children and control. Also, they have lower total and performance IQ than healthy ones. Children with ADHD were exposed to

abuse more than healthy children especially in hyperactive and combined subtypes.

RECOMMENDATIONS

Thyroid hormones level shouldn't be neglected as total T4 level was significantly lower in inattentive subtype with having clinical implications on clinical characteristic of ADHD and on choice of the most appropriate treatment.

Conflict of Interest: Not declared.

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