Study of Thyroid Function in Children with Attention Deficit Hyperactivity Disorder and Aggressive Behavior

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ABSTRACT

Background: Attention deficit hyperactivity disorder (ADHD) is a well recognized psychiatric disorder of childhood. Its cause is unknown, but there is evidence of familial predisposition. Symptoms suggestive of the disorder have been reported in patients with generalized resistance to thyroid hormones (GRTH), a disease caused by a mutation in the thyroid receptor beta gene and characterized by reduced responsiveness of peripheral and pituitary tissues to thyroid hormone actions.

Aim of the Work: This study was conducted to assess the frequency of thyroid hormone abnormalities in children with ADHD and/or aggressive behavior and to relate these abnormalities to the type of behavioral disorder.

Patient and Methods: Thirty cases with behavioral disorders (ADHD and/or aggression) diagnosed by DSM-IV classification were studied in comparison to 10 age-and sex-matched healthy controls. Clinical examination and psychiatric evaluation including IQ and psychosocial assessment were done to all patients. Measurement of serum free triiodothyronine (fT3), free tetraiodothyronine (fT4) and thyrotropin (TSH) was done to cases and controls.

Results: There was a significantly lower IQ ($p<0.05$) among patients (84.2±16.4%) when compared to controls (100.9±5.4%). Significantly higher mean fT3 and TSH levels ($p<0.05$) were detected among cases (5.96±2.9 pg/ ml and 6.53±3.2 uIU/ml respectively) when compared to controls (2.96±0.82 pg/ml and 2.28±1.28 uIU/ml respectively) while a non significant difference ($p>0.05$) in the fT4 level was detected. Twelve out of our 30 studied cases (40%) had thyroid hormone resistance among whom 7 (23.3%) had high fT3 and high TSH levels while 5 (16.7%) had high fT3 and normal TSH. Among the ADHD group, 3/16 (18.8%) had high fT3 and high TSH levels and 1/16 (6.3%) had high fT3 and normal TSH levels. Among those with aggression, 2/8 (25%) had high fT3 and high TSH and a similar percentage had high fT3 and normal TSH. Among those with both ADHD and aggression, 2/6 (33.3%) had high fT3 and high TSH and a similar percentage had high fT3 and normal TSH. In the 3 groups of behavioral disorders, none of the cases had high fT4 levels above the age-matched controls.

Conclusion: A significant number of patients meeting the diagnostic criteria for ADHD have associated RTH. Therefore, measurement of TSH and fT3

should be incorporated in the work up of children in families having ADHD and/or aggression. In children with ADHD and concomitant RTH, particularly those who exhibit hyperactivity, liothyronine (L-T3) in supraphysiological doses could be beneficial in reducing hyperactivity and impulsivity and thus decreasing the need for psychostimulants. Further studies are warranted regarding the role of RTH in the pathophysiology of ADHD.

Key Words:

ADHD, aggression, thyroid, resistance.

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INTRODUCTION

Attention deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder which can not be explained by a single etiology. So, it is thought to be caused by a complex combination of environmental, biological and genetic factors.[1] ADHD is subgrouped into: ADHD-inattentive type, hyperkinetic (H) and impulsive (I) type and ADHD-combined type (ADHD-HI type). The core symptoms of this condition are short attention span, distractability, impulsivity and overactivity.[2] The treatment of ADHD requires expertise in many different treatment modalities. The components of treatment plan for ADHD include education, medical interventions; most important of which are psychostimulants; and psychosocial interventions.[3]

ADHD was found to be associated with generalized resistance to thyroid hormone (GRTH) (70% in youths and 40% in adults) which might suggest a common pathogenetic mechanism.[4] GRTH is a rare autosomal dominant disorder caused by a mutation in the thyroid receptor beta gene on chromosome 3.[5] The mutant thyroid receptor molecules have either reduced affinity for T3 or impaired interaction with one of the cofactors involved in the mediation of thyroid hormone action.[6] These mutant thyroid receptors interfere with the function of the normal thyroid receptors, which explains the dominant mode of inheritance.[7]

The clinical presentation of RTH is highly variable.[8] The most likely explanation for the variable clinical manifestations of this apparently monogenic condition is the genetic heterogeneity of many cofactors (coactivators and corepressors)[9] that modulate the receptor-dependent action of thyroid hormones.[10] Characteristic thyroid function tests are elevated free thyroxine (fT4) and free triiodothyronine (fT3) concentrations with non suppressed thyrotropin (TSH). The doses of thyroid hormones required to suppress TSH and to produce metabolic effects on peripheral tissues are higher than normal.[8]

With this background, we were stimulated to assess the frequency of thyroid hormone abnormalities in children with ADHD and/or aggressive behavior and to relate these abnormalities to the type of behavioral disorder.

PATIENTS AND METHODS

This case-control study was conducted on 30 cases with behavioral disorders (ADHD and/or aggressive behavior) diagnosed by DSM-IV classification[11], attending the Psychiatry Clinic, Pediatric Hospital, Ain Shams University during the period from January 2006 to January 2007. They were 20 males and 10 females with a male: female ratio of 2:1. Their ages ranged between 5 to 13 years with a mean age of 8.67±2.5 years. The control group enrolled 10 age-and sex-matched apparently healthy children from Pediatric Outpatient Clinic of Ain Shams University Childrens Hospital. An informed written consent of participation in the study was signed by the parents or legal guardians of the studied subjects.

All patients were subjected to the following:

1. Detailed history taking laying stress on neuropsychiatric and behavioral manifestations.

2. Thorough clinical examination with special emphasis on neurological examination, manifestations of hypothyroidism as well as neck examination to detect goiter if present.

3. Psychiatric evaluation including:

a. IQ assessment using Stanford-Binet Intelligence Scale.[12]
IQ was calculated using the formula: mental age/chronological age x 100. The IQ ranges were categorized as follows: 20-34 severe mental retardation, 35-49 moderate mental retardation, 50-69 mild mental retardation, 70-89 below average IQ, 90-109 normal IQ, 110-125 above average IQ, 125-140 genius.

b- Revised Child Behavior Checklist (RCBC):[13]
It is a score that indicates psychosocial dysfunction in children from preschool age through adolescence. It does not generate diagnosis, but instead suggests cutoff scores for problems in the "clinical range". The number of items is 88 items in which score 0 (Not true), 1 (sometimes true) or 2 (always true). The scales are: aggression scale and attention problem scale. The score of each scale is obtained by the summation of the scores of all items of the scales, so we get two scores: attention problem>8 and aggression problem≥9.

c- Diagnosis of psychiatric disorders using the Diagnostic and Statistical Manual of Mental Disorders, 4th edition.[11]

4. Quantitative measurement of serum fT3, fT4 and TSH (for patients and controls) with the Immulite 2000 Analyzer using chemiluminescent immunometric assay.[14]

STATISTICAL ANALYSIS

The data were statistically analyzed using SPSS statistical package version 10 (Echosoft Corp, USA, 2006). Description of quantitative variables was in the form of mean±SD and range while that of qualitative variables was given as frequency and percentage. Student t-test of 2 independent samples was used to compare quantitative variables. Chi-square test was used to compare 2

qualitative data. Pearson correlation coefficient (r-test) was used to relate different variables to each other. A value of $p<0.05$ was considered significant.

RESULTS

Out of the 30 studied cases with behavioral disorders, 16 (53.5%) had ADHD, 8 (26.7%) had aggression while 6 (20%) had both ADHD and aggression. Among patients with ADHD, 9/16 (56.2%) were males and 7/16 (43.8%) were females and boys were more hyperactive (5/9, 55.5%) and more inattentive (1/9, 11.2%) than girls (3/7, 42.8% and 0/7, 0% respectively) while combined hyperactive-inattentive ADHD was found in 3/9 (33.3%) of boys and in 4/7 (57.1%) of girls. Also, 75% of patients with aggressive behavior were males and 25% were females. There was a significantly lower IQ ($p<0.05$) among patients (84.2±16.4 %) when compared to controls (100.9±5.4%, Figure 1) but there was a non significant difference ($p>0.05$) in the mean IQ according to the type of behavioral disorder. None of the cases had goiter on clinical examination of the neck and all of them were neurologically free.

Regarding the thyroid function tests, significantly higher mean fT3 and TSH levels ($p<0.05$) were detected among cases (5.96±2.9 pg/ml and 6.53±3.2 uIU/ml respectively) when compared to controls (2.96±0.82 pg/ml and 2.28±1.28 uIU/ml respectively) while a non significant difference ($p>0.05$) in the fT4 level was detected (Table 1). There was a non significant difference ($p>0.05$) in the mean levels of thyroid function tests between the 3 types of behavioral disorders (Table 2) and on comparing both sexes. Also, there was a non significant correlation ($p>0.05$) between age of cases and each of fT3 ($r=0.29$), fT4 ($r=0.23$) and TSH ($r=0.12$). Out of our 30 studied cases, 12 children (40%) had RTH among whom 7/30 (23.3%) had high fT3 and high TSH levels while 5/30 (16.7%) had high fT3 and normal TSH levels. Among the ADHD group, 3/16 (18.8%) had high fT3 and high TSH levels while 1/6 (6.3%) had high fT3 and normal TSH levels. Among those with aggression, 2/8 (25%) had high fT3

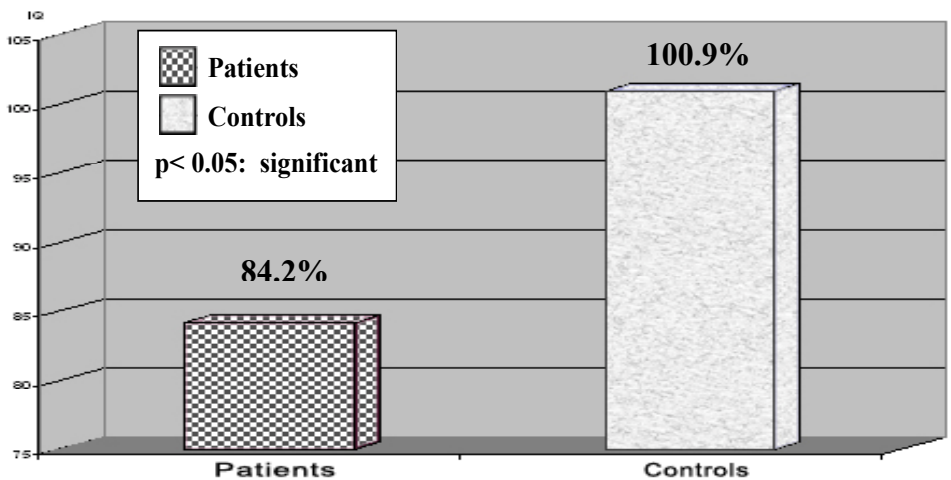

Fig. 1:. Statistical comparison between the mean IQ in patients and controls.

and high TSH and a similar percentage had high fT_3 and normal TSH levels. Among those with both ADHD and aggression, 2/6 (33.3%) had high fT3 and high TSH and a similar percentage had high fT3 and normal TSH levels. In the 3 groups of behavioral disorders, none of the cases had high fT4 levels above the age-matched controls (Table 3).

Table 1: Statistical comparison between mean thyroid hormone levels among patients and controls.

	Patients n= 30	**Controls** n = 10	**t**	**P**	**Significance**
fT_3 (pg/ml) $\bar{X}$ ± SD	5.96 ± 2.9	2.96 ± 0.82	2.2	0.03	Significant
Range	2.5 – 12.68	2.01 – 4.4			
fT_4 (ng/dl) $\bar{X}$ ± SD	1.23 ± 0.197	1.35 ± 0.2	1.6	0.11	NS
Range	0.989 – 1.7	1.05 – 1.6			
TSH (uIU/ml) $\bar{X}$ ± SD	6.53 ± 3.2	2.28 ± 1.28	2.14	0.036	Significant
Range	0.466 – 13.5	0.38 - 4.86			

p<0.05: significant, p>0.05: non significant, fT3: free triiodothyronine, fT4: free thyroxin, TSH: thyroid stimulating hormone, $\bar{X}$: mean, NS: non significant.

Table 2: Statistical comparison of the mean thyroid hormone levels according to the type of behavioral disorder.

	ADHD n = 16	**Aggression** n = 8	**ADHD & Aggression** n = 6	**f**	**P**	**Significance**
fT_3 (pg/ml) $\bar{X}$ ± SD	4.5 ± 2.9	5.4 ± 2.95	5.42 ± 3.3	0.29	0.75	NS
Range	2.5 – 10.68	3.0 – 10.46	2.51 – 9.84			
fT_4 (ng/dl) $\bar{X}$ ± SD	1.2 ± 0.143	1.31 ± 0.27	1.18 ± 0.2	0.879	0.57	NS
Range	0.99 – 1.47	1.02 – 1.7	0.989 – 1.5			
TSH (uIU/ml) $\bar{X}$ ± SD	4.6 ± 2.96	4.4 ± 3.5	4.6 ± 4.0	0.012	0.98	NS
Range	0.645 – 10.5	0.466 – 9.97	0.576 – 10			

P>0.05: non significant, $\bar{X}$:mean, ADHD: attention deficit hyperactivity disorder, fT_3: free triiodothyronine, fT_4: free thyroxin, TSH: thyroid stimulating hormone, NS: non significant.

Table 3: Frequency of thyroid hormone resistance according to type of behavioral disorder.

	ADHD n = 16		Aggression n = 8		ADHD & Aggression n = 6		X^2	P	Significance
	n	%	n	%	n	%			
High fT_3 & high TSH	3	18.8	2	25	2	33.3	0.54	0.76	NS
High fT_3 & normal TSH	1	6.3	2	25	2	33.3	5.92	0.2	NS

p>0.05: non significant, ADHD: attention deficit hyperactivity disorder, fT_3: free tri-iodothyronine, TSH: thyroid stimulating hormone, NS: non significant.

DISCUSSION

In our study, out of the 30 cases with behavioral disorders, 53.3% had ADHD, 26.7% had aggression and 20% had both ADHD and aggression. Males were more commonly affected by ADHD (56.2%) than females (43.8%) which was confirmed by other investigators.[15,16] The lower incidence of ADHD in girls might be related to having a relatively larger caudate nucleus than boys.[17]

In the current study, boys were more hyperactive (55.5%) and more inattentive (11.2%) than girls (42.8% and 0.0%, respectively) which goes with the results obtained by other researchers.[18,19] Other authors[3] found that girls tend to be inattentive rather than hyperactive/impulsive. In 2004, Quinn and Wigal[16] stated that ADHD often goes unrecognized in girls and that symptoms such as inattentiveness and poor school performance are seen as the hallmark signs of ADHD in girls. This is partly because girls' symptoms are not recognized as typical indications of ADHD and partly because these symptoms are less noticeable and less troublesome to adults than are boys symptoms. The tendency of girls to "Suffer silently" often means that they bear the burden of untreated ADHD for a much longer time than do boys.

Moreover, in our study, 75% of patients with aggressive behavior were males and 25% were females. This was confirmed by Pataki[20], who found that 7.9% of boys were aggressive in comparison to 2.3% in girls. This was explained by American Psychiatric Association in 1994[21] who stated that boys are more physically aggressive, whereas girls are more likely to threaten others without taking an action.

In our series, the mean IQ was significantly lower in patients than controls which was confirmed by other authors.[22] Some researchers[23,24] concluded that low IQ was related to antisocial behavior and chronically high levels of aggression.

In the current study, there was a significant increase in the mean fT3 and TSH levels among patients when compared to controls with a non significant difference in case of fT4. Twelve out of

our 30 studied patients (40%) had RTH among whom 7/30 (23.3%) had high fT3 and high TSH levels while 5/30 (16.7%) had high fT3 and normal TSH. Among the ADHD group, 3 out of 16 children (18.8%) had high fT3 and high TSH levels and one out of 16 (6.3%) had high fT3 and normal TSH levels. Among those with aggression, 2 out of 8 children (25%) had high fT3 and high TSH and a similar percentage had high fT3 and normal TSH. Among those with both ADHD and aggression, 2 out of 6 (33.3%) had high fT3 and high TSH and a similar percentage had high fT3 and normal TSH. In 1993, Weiss and his collegues[25] concluded that the prevalence of thyroid hormone abnormalities was higher in children with ADHD than in the normal population. They found that among their ADHD patients, 7 out of 14 (50%) had high fT3 and high TSH levels and 4 out of 14 (28.5%) had high T3 with normal TSH levels. In subjects with RTH, serum T4 and T3 concentrations are elevated and serum TSH concentrations are inappropriately normal or elevated reflecting the compensatory physiologic response of the pituitary-thyroid system to tissue resistance.[4]

In 1993, Hauser et al.[4] found that symptoms of ADHD have been reported in association with GRTH. This might suggest a common pathogenetic mechanism consisting either of reduced sensitivity of nuclear receptors to thyroid hormone (GRTH) or reduced availability of intracellular T3 for nuclear receptor binding. In addition to its important role in brain development, the thyroid receptor-thyroid hormone complex may influence catecholamine neurotransmitter systems which are thought to be involved in the pathophysiology of ADHD. There is also neurobiological evidence to support the role of thyroid hormones in the development of areas of the brain associated with learning.[26] Although the neuroanatomical mechanism for abnormalities in the human RTH patients is unknown, impaired T3 receptor binding during development could result in abnormalities in axonal and neuronal proliferation and migration, and the regulation of genes during critical peroids.[4] Any of these mechanisms could result in damage to brain structures that are critical for optimal learning.[26] Moreover, in 2006, Siesser and his collegues[27] suggested that even transient perturbations in developmental thyroid homeostasis can have longstanding behavioral and cognitive consequences, including producing the full spectrum of symptoms of ADHD.

In our series, none of the patients had goiter and all of them were neurologically free. The clinical presentation of RTH is highly variable. The majority of individuals are completely asymptomatic.[8] Some of them present with goiter and an euthyroid or mildly hypothyroid metabolic state (subtle hypothyroidism) or uncommonly hyperthyroid state.[28] Brucker Davis and his associates in 1995[29] stated that in GRTH, pituitary and peripheral tissues are not always involved to the same degree, and this creates a mosaic of hypothyroid and hyperthyroid symptoms in the patient. If the degree of resistance is similar in pituitary and peripheral tissues, high levels of thyroid hormones results in compensation, and patients are euthyroid due to near normal TSH levels. On the other hand, patients with selective pituitary resistance to thyroid hormone (PRTH) are predominantly hyperthyroid and have hypermetabo-

lism and tachycardia. This is because pituitary resistance results in hypersecretion of TSH, which compensates, at least in part, for hormone resistance in peripheral tissues.[28]

Some researchers[4,10] stated that in children with RTH and concomitant ADHD, particularly those that exhibit hyperactivity, liothyronine (L-T3) in supraphysiological doses may be beneficial in reducing hyperactivity and impulsivity thus reducing the need for psychostimulant medication. In the majority of children with ADHD who do not have RTH, L-T3 treatment has no effect. This suggests that one mechanism of ADHD in persons with RTH could be relative hypothyroidism, and this further supports the link between ADHD and RTH.[4] The optimal dose of thyroid hormone is variable among individuals, and doses of as high as 1,000 µg per day may be necessary to achieve the desired effects. Reduction of the serum TSH concentration to normal is a convenient guide to therapy.[30]

In contrast to our study, Valentine and his collegues[31], found no cases of RTH among patients with ADHD. Also, Toren et al.[32], found that total triiodothyronine (TT3) levels were slightly above the upper limit of normal among ADHD patients, but a non significant difference in TT3 values was noted between the ADHD and the control groups.

Among those with aggression, Eklund et al.[33], found significantly higher T3 levels in violent offenders with an early aggressive behavioral risk pattern. Similarly, Stalenheim[34], after follow-up investigation of a forensic psychiatric sub-population (6-8 years) and collection of data from criminal records at follow-up from the National Council for Crime Prevention, showed that criminal recidivists at follow-up had higher serum T3 levels than normal controls. The T3 levels in criminal recidivists correlated positively to psychopathy and aggression-related personality.

In our series, there was a non significant difference in the mean fT4 levels among patients when compared to controls. This goes with the results obtained by other authors[32,35] who found that thyroxin concentration was less strongly related to attentional functioning and was not related to hyperactivity. Also, among our 3 studied groups of behavioral disorders, none of the cases had high fT4 levels above the normal age-matched laboratory values. In contrast to our study, Hauser et al.[4], found that the mean serum T4 and fT4 were higher in the ADHD subjects with RTH.

In conclusion, a significant number of patients meeting the diagnostic criteria for ADHD have associated RTH. Therefore, measurement of TSH and fT3 should be incorporated in the work up of children in families having ADHD and/or aggression. Being a developing country, on a cost effective basis, measurement of fT4 is not essential. In children with ADHD and concomitant RTH, particularly those who exhibit hyperactivity, liothyronine (L-T3) in supraphysiological doses could be beneficial in reducing hyperactivity and impulsivity and thus decreasing the need for psychostimulants. Further studies are warranted regarding the role of RTH in the pathophysiology of ADHD.

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