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Developmental, Behavioral and Genetic Factors in Correlation with Attention Deficit Hyperactivity Disorder in Egyptian Children

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Twenty two cases diagnosed as Attention Deficit Hyperactivity Disorder (ADHD), aged 6-10 years, chosen to study the correlation between developmental, behavioral and genetic factors in relation to some biochemical parameters. Another group of 22 healthy normal children of the same matched age and sexes were collected as control group. All cases and control children were subjected to full clinical and neurological history and examination, anthropometric measurements and behavioral assessment. Levels of folic acid, vitamin B_{12} and T_3, T_4 were estimated, for both cases and controls. Cytogenetic examination of peripheral blood lymphocytes were done for cases only. Chromosomal abnormalities were detected in 6 cases out of 22 cases. There was a significant decrease in the weight and BMI, as compared with controls, these decrease was highly significant among those with chromosomal abnormalities. Regarding the behavioral assessment, a significant decrease in three of the four components of Vineland Adaptive behavior scale: (communication, daily living skills and socialization), as compared with controls, this decrease in the three components was highly significant among those with chromosomal abnormalities. A non significant increase in the score of the motor skills, as compared with controls, while significant increase in it`s score was found among those with chromosomal abnormalities. Biochemical studies showed no significant decrease in T_3 and T_4 levels as compared with controls, while levels of Folic acid and Vitamin B_{12} showed significant decrease as compared with controls, this decrease in their levels showed highly significant decrease among those with chromosomal abnormalities. We concluded that this study is the first study in our knowledge examining the correlation between developmental, behavioral and genetic factors among children with ADHD in the same subject group. ADHD is multifactorial and is associated with a remarkable increase in chromosomal abnormalities, which affect behavior and anthropometric measurements.

Key words: ADHD, child health, cytogenetics, biochemistry

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INTRODUCTION

Attention Deficit Hyperactivity Disorder (ADHD) is the most commonly diagnosed behavioral disorder of childhood, estimated to affect between 3 and 5% of school-aged children, it is increasingly recognized as afflicting in adults as well (Field *et al*., 1998). Symptoms include inattention, hyperactivity and impulsivity. According to several sources, the causes are currently unknown and it is thought that the term covers a variety of related disorders. ADHD is a challenge with increasing interest for researchers as it represents a medical problem for children specially at school age. There is no single medical test that can accurately diagnose ADHD, though there are assessment tools. (American Academy of Pediatrics, 2000). There is a complex body of information suggesting multiple, heterogeneous, biochemical etiologies for ADHD.

Studies that support the notion that diet influences behavioral problems have focused on the role of sugar, preservatives and artificial dyes as well as food allergies (Rowe and Rowe, 1994). Nutritional therapies are the most commonly used alternative treatment among American children with ADHD. Dietary management of ADHD takes two basic forms: restriction and supplementation (Baumgaertel, 1999).

Dietary supplements potentially increase catecholamine (dopamine, norepinephrine and epinephrine) synthesis by precursor loading (tyrosine is the precursor to dopamine and norepinephrine) and delivering B-vitamins (vitamins B_3, B_6 and folic acid) and mineral (iron and copper) cofactors. Vitamin C is also a cofactor for the synthesis of the neurotransmitter norepinephrine, imbalances of which are also linked to ADHD (Arnold and Jensen, 1995). Deficiency of folate and vitamin B_{12} had been correlated with impairment of cognitive profile (Malouf *et al*., 2003), while reduction within normal level of thyroid hormones in hyperactive children were observed (Bereket *et al*., 2005). Supplementing the diet with amino acid precursors, in addition, with vitamin and mineral co-factors for neurotransmitter formation were of great value for ADHD (Grant, 1999).

Hyperactivity is characterized by behaviors such as fidgeting, squirming, running about when inappropriate and talking excessively (APA, 1994). ADHD is likely to be associated with a number of impairments in many different domains, for instance, these children often exhibit decreased nonverbal and verbal working memory, impaired planning ability and a poor sense of time, (Barkley, 1998). Studies on ADHD children frequently report deficient performance on IQ measures in comparison to control children and other studies have found hyperactivity to be negatively related to achievement and IQ measurements (Sonuga-Barke *et al*., 1994). Although many studies comparing ADHD children to normal controls have conducted analyses controlling for IQ, doing so may be questionable in that deficient performance on IQ measures may be directly related to ADHD and the associated impairments in executive functioning (Barkley, 1997). Furthermore, hyperactivity have shown positive relations to problem behaviors (Barkley, 1998).

Genetic factors have been postulated as one of the major contributors to the development of ADHD (Wolraich and Baumgaertel, 1997). Many studies were performed as Cornish *et al*. (2004) and Borghgraef *et al*. (1990) they demonstrated the presence of attention deficit and hyperactivity among Fragile-X patients during evaluation of their behavior.

Briegel and Cohen (2004) and Niklasson *et al*. (2002) observed that 22q11.2 deletion syndrome which is the most common deletion syndrome in humans. Patients with this syndrome can show a variety of somatic symptoms together with disturbance in motor language, cognitive and social development mostly attention deficit hyperactivity. However, Bastain *et al*. (2002) performed a study on 100 children with ADHD and observed no difference exceeds those expected by chance.

MATERIAL AND METHODS

Subjects: This study was carried out on twenty two (22) cases (14 males and 8 females) with age ranged between 6-10 years old who provisionally diagnosed as ADHD based on the DSM-IV criteria (APA, 1994), from those attending the outpatient clinic of pediatrics Abo-El-Riesh student hospital and referred to the Department of Nutrition and Food science, NRC, over a period of 28 months (December 2003 to January 2005). Another group of 22 healthy normal children of the same matched age and sexes with no history of hyperactivity nor other neuropsychiatric troubles were collected as control group. All cases and control children involved in this study were subjected to full clinical and neurological history and examination. Anthropometric measurements as weight, height and calculation of body mass index BMI according to Roche *et al*. (1981) were assessed.

Behavioral assessment: It was done for each case and control using Vineland Adaptive Behavior Scale VABS. The purpose of the test is to assess social competence. The areas of assessment include four areas of adaptive behavior:communication, daily living skills, socialization

and motor skills. Parents were asked to complete a rating scale that measures four areas of adaptive behavior and one general area of maladaptive behavior. Scale assesses ability of individuals from newborn to adult to perform developmentally appropriate life-skills (Hean and Hosterman, 1989).

Biochemical analysis: For both cases and control group blood samples were centrifuged at 4°C for 15 min (3500×g) and stored at 80°C until analysis. Quantitative determination of free T_3 and T_4 concentration in plasma by a micro plate enzyme immunoassay -ELIZA (Biotec Laboratories Ltd., cat.No:7/324, 7/320). Concentration of folic acid, Vitamin B_{12} in serum were determined by DPC`s solid phase no boil dualcount, by means of a master trace with two isotopes, cobalt 57 (^{57}Co) and iodine 125 (^{125}I), which are easily separated by most dual-channel Gamma counters.

Cytogenetic examination of peripheral blood lymphocytes were done only for each patient (22 cases). Slides were G-banded according to the method described by Seabright (1971) and Verma and Babu (1995). High resolution banding according to the method of Yunis *et al*. (1984) using Methotrexate 17 hours before stopping the culture then Thymidine is added and continue incubation for 6 h before harvesting (method of synchronization). Metaphases were analyzed, any structural or numerical anomalies recorded then photographed and karyotyped according to the ISCN (1995).

Statistical analysis: All data obtained were statistically analyzed by using Student t-test according to Hill (1979).

RESULTS

Regarding the anthropometric measurements in our study we found that there was no significant differences in height between those with ADHD and controls. While there was a significant decrease in weight as well as BMI among children with ADHD as compared with controls, this decrease in weight and BMI was more significant among those with chromosomal abnormalities (Table 1).

Table 1: Mean values±SE of the anthropometric measurements, (height, weight and BMI, in hyperactive children (with/without chromosomal abnormalities) in comparison with control group

Groups		Height (cm)	Weight (kg)	BMI (kg m^{-2})
Control subjects	Range	111-152	22.3-49.7	16.28-21.13
	Mean	136.8	36.4	19.45
(22 Children)	±SE	12.53	10.54	1.02
ADHD without chromosomal	Range	112.5-142	20.5-38.9	16.197-19.291
abnormalities	Mean	134.8	31.8	17.5
(16 Children)	±SE	7.04	6.1	1.04
ADHD with chromosomal	Range	113-148	21.4-40.5	15.059-17.804
abnormalities	Mean	136	28.7	15.517
(6-Children)	±SE	10.3	5.72	0.153

Fig. 1: Case (1): Paracentric inversion 22 (q12;q13.2)

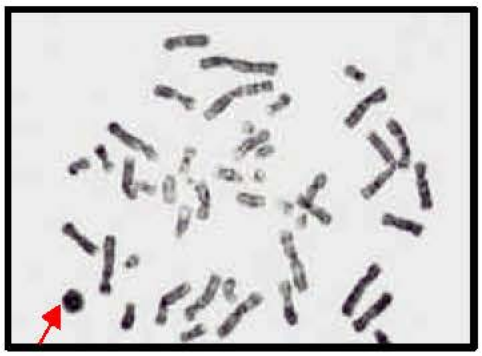

Fig. 2: Case (2) : Ring of chromosome 6

Fig. 3: Case (3): Paracentric inversion 19(q13.1;q13.4)

Table 2: Mean values±SE of Vineland Adaptive Behavior Scale: (Communication, Daily Living Skills, Socialization, Motor Skills), in hyperactive children (with/without chromosomal abnormalities) in comparison with control group

Groups		Communication	Daily living skills	Socialization	Motor skills
Control	Range	98-126	96-118	100-122	102-119
Subjects	Mean	114.3	108.3	114.6	115.2
(22 Children)	±SE	9.58	6.45	5.86	3.1
ADHD	Range	94-114	98-115	93-109	106-123
with out chromosomal	Mean	111.4	108.4	105.8	115.6
abnormalities (16 Children)	±SE	2.435	6.24	2.09	4.76
ADHD with	Range	94-112	98-105	93-106	106-123
chromosomal	Mean	108.2	100.2	103.4	119.4
abnormalities					
(6-Children)	±SE	3.05	1.03	1.89	2.05

Table 3: Mean values±SE of levels of Vitamin B_{12}, Folic acid, T_3 and T_4 in hyperactive children (with/without chromosomal abnormalities) as compared with control group

Groups		Vit. B_{12} (Pg dL^{-1})	Folic acid (ng mL^{-1})	T_3 (ng dL^{-1})	T_4 (ng dL^{-1})
Control	Range	450-1346	5.7-19.6	0.8-3.3	0.3-2.03
Subjects	Mean	937	9.9294	2.1882	1.1194
(22 Children)	±SE	215.66	2.08	0.27	0.66
ADHD	Range	427-1219	4.8-12.7	0.8-3.14	0.36-2.06
without	Mean	686.25	6.555	2.1083	0.91
chromosomal					
abnormalities					
(16 Children)	±SE	213.8	1.04	0.16	0.31
ADHD with	Range	398-1085	3.05-9.6	0.76-3.06	0.38-1.99
chromosomal	Mean	407.5	3.383	1.916	0.9333
abnormalities					
(6-Children)	±SE	6.48	0.012	1.03	0.74

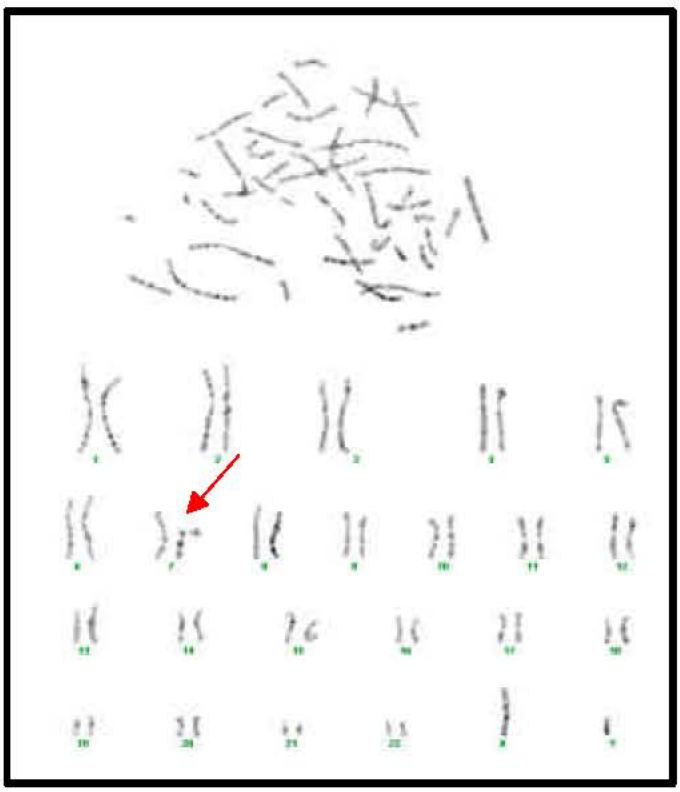

Fig. 4: Case (6): Deletion 7(q11.21; p22)

Table 4: Chromosomal study according to sex and age for cases with chromosomal abnormalities

Chromosomal analysis	Age (year)	Sex	Case No.
46, XX paracentric inversion. (q 21; q 22.2)	7	F	1
46, XY increase breakage and ring formation (ring chromosome No. 6)	10	M	2
46, XX paracentric inversion. 19(q 13.3;q13.4)	8.5	F	3
46, XY paracentric inversion. 22 (q 12; q13.2)	9	M	4
46, XX duplication 22q 12.2	7	F	5
46, XY translocation (4;8)(q13;q24.3) and deletion 7 (q 11.21; p 22)	6.5	M	6

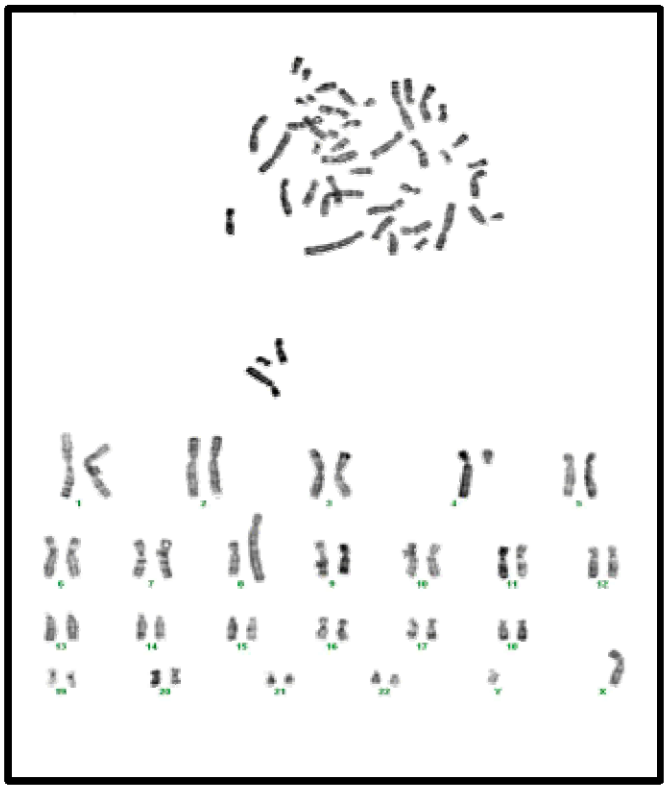

Fig. 5: Case (6): t(4;8)(q13;q24.3)

Regarding the behavioral assessment, there was a significant decrease in the scores of three of the four components of Vineland Adaptive behavior scale: (communication, daily living skills and socialization), among children with ADHD as compared with controls, this decrease in the three components was highly significant among those with chromosomal abnormalities. Regarding the score of the fourth component motor skills, there was a non significant increase in it`s value as compared with controls, while a significant increase in their score was seen among those with chromosomal abnormalities (Table 2).

Regarding the biochemical results, there was a significant low levels of Vitamin B_{12} and Folic acid as compared with controls, these levels showed a highly significant low levels among those with chromosomal abnormalities. Levels of T_3 and T_4, showed non significant decrease in their levels among children with ADHD, as compared with controls (Table 3).

Regarding the cytogenetic study, chromosomal abnormalities were detected in 6 cases (3 males and 3 females) out of 22 cases (27.2%). A wide range of abnormalities including chromosomal translocation, inversion, duplication and ring formation were recorded (Table 4 and Fig. 1-5).

DISCUSSION

Attention deficit hyperactivity disorder is the most commonly diagnosed behavioral disorder of childhood (Field *et al.*, 1998). Generally, symptoms appear before the age of 7 years and cause significant functional problems at home, in school and in various social settings. One- to two-thirds of all children with ADHD (somewhere

between 1 and 6% of the general population) continue to exhibit ADHD symptoms into adult life. Diagnosis is difficult but essential, as early treatment can substantially alter the course of a child's educational and social development (Daruna *et al*., 2000). From this point of view we start this research in order to study the correlation between developmental, behavioral and genetic factors in relation to some biochemical parameters in children with ADHD.

In the present study we found a significant low weight and BMI among hyperactive children as compared with control subjects, which is more low among cases with chromosomal abnormalities, this means that hyperactivity affecting weight gain and BMI. This finding may be explained and accepted by Fleming (2002), he reported that many individuals with ADHD report that they skip meals because they were busy and distracted. However, few studies have been undertaken to assess the prevalence of overweight in children with developmental disorders, such as attention deficit hyperactivity disorder (APA, 1994). Eunice (2005), stated that overweight also represents a problem a mong children with ADHD and according to his study he found that the prevalence of at-risk-for-overweight (BMI ≥ 85th percentile) and overweight (BMI ≥ 95th percentile) was 29 and 17.3% respectively in children with ADHD. We can explain this that individuals with ADHD their hunger becomes so intense that they swing in the opposite direction, overeating well beyond the point of reasonable intake because they don't know when to stop until they feel stuffed (Fleming, 2002).

Barkley and Murphy (1998), reported that probably the three most important components to a comprehensive evaluation of the client with Attention Deficit Hyperactivity Disorder are the clinical interview, the medical examination and the completion and scoring of behavior rating scales. In this study regarding the behavioral assessment, we found that there were a significant increase in the score of the motor skills in hyperactive children as compared with control subjects, while a significant decrease in the other three components including the communication, socialization as well as daily living skills in hyperactive children as compared with control subjects and this is accepted with APA (1994), they reported that in ADHD patients, behavior may severely affect school performance, family relationships and social interactions with peers, also agreed with Hill and Schoener (1996), they reported that ADHD is associated with multiple impairments and school failure. All of these findings are agreed with Barkley and Murphy (1998) as they reported that screening for intellectual ability and academic achievement skills is important in determining the presence of comorbid developmental delay or learning disabilities with ADHD. Furthermore these findings were more affected in cases with chromosomal abnormalities which means that not only hyperactivity affects the behavior of those children but chromosomal abnormalities played a more effect on the behavior of those children.

There are no laboratory tests that can determine or exclude ADHD, but it might be important to rule out some other relevant causes of hyperactivity or attention problems. A blood test of the thyroid functions should be considered. This will be regularly done within a routine check of the patient (Martin, 2003). In our study although there was a non significant decrease in the levels of T_3, T_4, but this may correlates with symptoms of hyperactivity and this is agreed with Martin (2003), who explained that the correlation between thyroid hormones concentrations and symptoms of hyperactivity does not prove causality, What it does show is that thyroid hormones may provide a physiologic basis for the dichotomy between symptoms of inattention and symptoms of hyperactivity. On the other hand Hauser and Weintraub (2005) reported that positive correlation between elevated levels of certain thyroid hormones and hyperactivity/impulsivity in a selected group of patients was found. Martin (2003) reported that hyperthyroid or Hypothyroid problems can both trigger a number of attention-disruptive symptoms. Serum levels may, or may not be within a normal laboratory range, however false positives or false negatives with thyroid panels are not uncommon. Thyroid hormones may play a role in the hyperactive and impulsive symptoms of children with ADHD.

Folic acid (Vitamin B_9) helps tissue growth and cell function. In addition, it helps to increase appetite when needed and stimulates the formation of digestive acids. In our study Vitamin B_{12} and Folic acid were significantly decreased in hyperactive children as compared with controls, This finding is explained by Jeffrey *et al.* (2002) they reported that Vitamin B_{12} deficiency results in impairment of the activities of B_{12}-requiring enzymes. Impaired activity of methionine synthase may result in elevated homocysteine levels, traps folate in a form that is not usable by the body, resulting in symptoms of folate deficiency even in the presence of adequate folate levels. Thus, in both folate and vitamin B_{12} deficiency, folate is unavailable to participate in DNA synthesis. In our study we found that the decrease in the levels of folic acid and Vitamin B_{12} were highly significant among those with chromosomal abnormalities and this is explained by Jeffrey *et al.* (2002) they reported that folic acid works along with vitamin B_{12} and vitamin C to help the body digest and utilize proteins and to synthesize new proteins

when they are needed. It is necessary for the production of red blood cells and for the synthesis of DNA (which controls heredity and is used to guide the cell in its daily activities). So, in present study we recommend dietary supplementation of folic acid and vitamin B_{12} and this is agreed with Rowe and Rowe (1994) they reported several studies that support the notion that diet influences behavioral problems. Also agreed with Baumgaertel, 1999 he reported that nutritional therapies are the most commonly used alternative treatment among American children with ADHD.

Sandra *et al.* (2003) reported that twin and family studies suggest that genes, strongly indicated for ADHD. Four regions found on chromosomes 2p,10q,16p and 17q, showed suggestive evidence for linkage. Three of these locations (10q,16p, 17q) overlapped regions suggested from previous investigations of ADHD. In our study chromosomal abnormalities were detected in 6 cases (3 males and 3 females) out of 22 cases (27.2%). A wide range of abnormalities included inversion, increased breakage, band duplication and translocation were found, this finding is agreed with Bastain *et al.* (2002) whom also observed no consistant chromosomal abnormalities among patients with ADHD. These findings of chromosomal analysis showed no consistant aberrations as were observed by other authors Borghgraef *et al.* (1990), Wolraich and Baumgaertel (1997), Niklasson *et al.* (2002), Briegel and Cohen (2004) and Cornish *et al.* (2004) but it was an indicator about some anthropometric, behavioral aspects of these patients when they were compared by other cases with ADHD without any chromosomal aberrations.

CONCLUSIONS

This is the first study in our knowledge examining the correlation between developmental, behavioral and genetic factors among children with ADHD in the same subject group. According to the results of the present study we can propose that ADHD is associated with a remarkable increase in chromosomal abnormalities among the presented cases (27.2%), which are reflected on their anthropometric measurements as well as their behavior.

So, we can also conclude that neurodevelopmental disorders such as ADHD are multifactorial, with a number of different genes, likely to be of varying effect have been implicated and interacting with environmental influences, presumably contributing to the development of the observed phenotypes.

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