

## Clinical Manifestations, Blood Serotonin Level, Electroencephalography and Brain Magnetic Resonance Imaging in Autistic Children

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### Abstract

**The Aim of the Study:** Identification of the common clinical manifestations and types of autism in children Identification if there is a correlation between the clinical manifestations and blood serotonin level, electroencephalography (EEG) changes, and Brain Magnetic Resonance Imaging (MRI) changes.

**Subjects Methods:** Two groups of children were included in this study :The first group included autistic patients of various The second group included the control group: All children (cases and controls) were subjected to the following: History & examinations ,measurement of plasma level of serotonin, neurophysiological assessment by using conventional EEG Brain magnetic resonance imaging (MRI)

**Results:** The study was carried out on 22 autistic children and 10 healthy control children matched for age and sex. Highly statistically significant difference between study groups as regard EEG abnormality which higher in patients than control group  $P < 0.01$ . Statistically significant difference between the studied children in frontal horn widths ( $P < 0.05$ ). (Autistics were higher than controls). Statistically significant difference among study groups in diameter of inner table of clavium ( $P < 0.05$ ).

**Conclusion:** Hyperactivity are a significant co-morbid conditions associated with autism. There is a positive correlation between epilepsy and severity of autism. There is high blood serotonin level in about one-third of autistic children with positive correlation between high serotonin level and severity of autistic features. There is a positive correlation between brain MRI measurement abnormalities and severity of autism.

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### I. Introduction

Autism is a neurodevelopmental disorder with a range of clinical presentations. These presentations vary from mild to severe and are referred to as autism spectrum disorders. The most common clinical sign of autism spectrum disorders is social interaction impairment, which is associated with verbal and non-verbal communication deficits and stereotyped and repetitive behaviors (Zilbovicius M. et al., 2006).

There is no one specific cause of autism. Research has focused on whether chemical imbalances, differences in the brain, genetics, or problems with the immune system play a role in causing the disorder (Rutter M., 2005) .

Abnormal Electroencephalography (EEG) is obtained in 13% to 83% of autistic children, the varying percentage rate between the studies are probably explained by the different criteria used for the clinical diagnosis of autism (Chugani D., 2002).

Magnetic Resonance Imaging (MRI) may be helpful as part of a neurological assessment in the presence of focal neurological findings or severe developmental delay, but it cannot be used for diagnosis of Autism (Salmond H. et al., 2003).

Two of the most consistently observed biological findings in autism are increased serotonin levels in the blood and immunological abnormalities (including auto reactivity with tissues of the central nervous system) (Germano E. et al., 2006)

### The Aim of the Study:

1. Identification of the common clinical manifestations and types of autism in children.
2. Identification if there is a correlation between the clinical manifestations and blood serotonin level, electroencephalography (EEG) changes, and Brain Magnetic Resonance Imaging (MRI) changes. These may help in early detection and early intervention of the autistic disorder.

### Subjects:

- The study was carried out during the period between beginning of January 2007 and end of August 2008.

**Two groups of children were included in this study:**

- The first group included autistic patients of various types attending the Pediatric Neurology Clinic at Al-Azhar University Hospitals.
- The second group included the control group which had children with no medical or neuropsychiatric illness, and matched with age and sex with patient group.

**Inclusion Criteria:**

- The included children were fulfilling the criteria for autistic disorder according to the DSM-IV TR (*American Psychiatric Association, 2000*).
- Apparent healthy children (regarding motor and hearing function).
- Age from 2 to 13 years. No gross or major MRI brain abnormalities (like apparent brain congenital abnormalities, tumors, infections, or hypoxic/ ischemic insult)

**Exclusion Criteria:**

1. Patients with specific pervasive developmental disorder syndromes as Rett's syndrome and childhood disintegrative disorder.
2. Focal or generalized neurological abnormalities.
3. Children with chronic medical disorders as (Hypertension , chest diseases, gastrointestinal tract disorders or endocrinal diseases)

**Methods:**

**All children (cases and controls) were subjected to the following:**

1. Prenatal, Developmental and Neuropsychiatric History.
2. General and Neuropsychiatric Examinations.
3. Complete assessment of hearing.
4. Diagnosis and evaluation of autism was based on :
  - I. The criteria listed in 4th edition of diagnostic and statistical manual of mental disorder Text Revision (DSM-IV-TR).
  - II. Childhood Autism Rating Scale (CARS).

**According to CARS, the patients were divided into 2 groups:**

- **Group 1:** mild to moderate autism or (high functioning autism) [CARS score from 30 to less than 39].
  - **Group 2:** severe autism or (low functioning autism) [CARS score from 39 to 60].
5. Measurement of plasma level of serotonin.
  6. Neurophysiological assessment by using conventional EEG
  7. Brain magnetic resonance imaging (MRI) for:
    - A. Detection of any minor structural abnormalities associated with autism.
    - B. MRI measurements of certain brain areas: (Frontal horn, caudate nucleus, inner table of clavium and corpus callosum).

**Statistics.**

All data are collected, summarized, presented and analyzed by using an appropriate statistical package program (SPSS version, 13). All quantitative data are summarized by mean and standard deviation. Qualitative data are summarized by number and percentage. Test of significance for qualitative data is chi square Test of significance for quantitative data for 2 groups is t test, for more than two groups is F test, Post hoc test (LSD) used to detect differences between groups (*Armitage P., 1989*).

**II. Results**

**The study was carried out on 22 autistic children and 10 healthy control children matched for age and sex. The children were subdivided into 3 groups:**

**Group 1:** included 8 cases with mild to moderate autism or “High functioning autism”.

**Group 2:** included 14 cases with severe autism or “Low functioning autism”.

**Group 3:** control group which included 10 healthy children.

**Table (1): Demographic data of study groups**

.0	<b>Group (1)</b> <b>N = 8</b> <b>Mild to moderate Autism</b>	<b>Group (2)</b> <b>N = 14</b> <b>Sever Autism</b>	<b>Group (3)</b> <b>N = 10</b> <b>Control</b>		
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<b>(1) Age</b>	$\bar{X} \pm (SD)$ 7.8 ± (3)	$\bar{X} \pm (SD)$ 7.2 ± (3.9)	$\bar{X} \pm (SD)$ 7.1 ± (3.5)	F – test 0.109	P = 0.999 P > 0.05 NS
<b>(2) Sex</b>	N %	N %	N %	X <sup>2</sup> 1.6	P = 0.435 P > 0.05 NS
Male	7 87.5	10 71.4	6 60		
Female	1 12.5	4 28.6	4 40		
<b>(3) Family history</b>	N %	N %	N %	X <sup>2</sup> 1.4	P = 0.019 P > 0.05 NS
Yes	2 25	0 0	0 0		
No	6 75	14 100	10 100		
<b>(4) Consanguinity</b>	N %	N %	N %	X <sup>2</sup> 1.4	P = 0.019 P > 0.05 NS
No	4 50	12 85.7	10 100		
1 <sup>st</sup> degree	1 12.5	2 14.3	0 0		
2 <sup>nd</sup> degree	3 37.5	0 0	0 0		

This table shows no statistically significant difference between study groups as regard age, sex, positive family history and consanguinity (P > 0.05).

**Table (2):** Classification of autistic children according to their CARS Score.

CARS score	Number (22)	%
Mild to moderate autism "High functioning" "Group 1"	8	36.4
Severe autism "Low functioning autism" "Group 2"	14	63.6

**Table (3):** Comparisons of medical history among study groups

	Group (1) N = 8 Mild Autism		Group (2) N = 14 Sever Autism		Group (3) N = 10 Control			
<b>Pregnancy</b>	N	%	N	%	N	%	X <sup>2</sup> 7.6	P = 0.464 P > 0.05 NS
- Normal	4	50	11	78.5	9	90		
- Twins	2	25	1	7.2	0	0		
- Health problem	2	25	2	14.3	1	10	X <sup>2</sup> 1.1	P = 0.785 P > 0.05 NS
<b>Delivery</b>	N	%	N	%	N	%		
- Normal	4	50	10	71.4	7	70		
- C.S	3	37.5	3	21.4	3	30	X <sup>2</sup> 1.3	P = 0.885 P > 0.05 NS
- ventouse delivery	1	12.5	1	7.2	0	0		
<b>Birth weight</b>	N	%	N	%	N	%		
- Normal	6	75	13	92.8	8	80	X <sup>2</sup> 3.4	P = 0.181 P > 0.05 NS
- Low	2	25	1	7.2	2	20		
<b>Type of feeding</b>	N	%	N	%	N	%	X <sup>2</sup> 8.8	P = 0.0112 P < 0.05 S
- Breast	6	75	13	92.8	10	100		
- Formula	2	25	1	7.2	0	0		
<b>History of Epilepsy</b>	N	%	N	%	N	%	X <sup>2</sup> 8.8	P = 0.0112 P < 0.05 S
- Yes	4	50	8	57.1	0	0		
- No	4	50	6	42.9	10	100		

This table shows no statistically significant difference between study groups as regard medical history except for history of epilepsy which is higher among sever autism than both mild and healthy one

**Table (4):** First observed symptom for the autistic children):

	Number (22)	%
Language defect	15	68.2
Social defect	5	22.7
Behavioral defect	2	9.1

**Table (5):** Blood serotonin levels of the studied children

Blood Serotonin	Group (1)	Group (2)	Group (3)
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	N = 8		N = 14		N = 10		X <sup>2</sup> 3.3 P= 0.183 (P>0.05) NS
	N	%	N	%	N	%	
Normal	6	75	9	64.3	10	100	
Increased	2	25	5	35.7	0	0	

**Table (6):** Comparison of EEG findings among study groups

	Group (1) N = 8		Group (2) N = 14		Group (3) N = 10		X <sup>2</sup> 21.5	P = 0.000 P < 0.01 HS
EEG	N	%	N	%	N	%		
- Normal	3	37.5	4	28.6	10	100		
- Focal epilepsy	3	37.5	5	35.7	0	0		
- Focal with secondary generalization	2	25	3	21.4	0	0		
- Generalized	0	0	2	14.3	0	0		

This table revealed highly statistically significant difference between study groups as regard EEG abnormality which higher in patients than control group P < 0.01

**Table (7):** Comparison of MRI measurements of frontal horn width among study groups

	Group (1) N = 8		Group (2) N = 14		Group (3) N = 10		F-test	P=0.35 P<0.05 S
	X'	(SD)	X'	(SD)	X'	(SD)		
<b>FH width</b>	3.4	(0.31)	3.4	(0.7)	2.9	(0.3)	3.7	

This table shows statistically significant difference between the studied children in frontal horn widths (P < 0.05).(Autistics were higher than controls).

**Table (8):** Comparison of MRI measurement of caudate nuclei among study groups

	Group (1) N = 8		Group (2) N = 14		Group (3) N = 10		F-test	
	X'	(SD)	X'	(SD)	X'	(SD)		
- Length of right caudate	2.1	(0.3)	2.2	(0.3)	1.9	(0.2)	2.8	P = 0.073 P>0.05 NS
- Length of left caudate	2	(0.3)	2.1	(0.3)	1.9	(0.2)	1.1	P = 0.322 P>0.05 NS
- Width of right caudate	1.09	(0.1)	1.09	(0.1)	0.96	(0.12)	3.1	P = 0.056 P>0.05 NS
- Width of Left caudate	1.06	(0.12)	1.05	(0.19)	0.93	(0.14)	2	P = 0.148 P>0.05 NS
- Area of right caudate	2.3	(0.51)	2.4	(0.45)	1.9	(0.4)	3.7	P=0.35 P<0.05 S
- Area of left caudate	2.1	(0.6)	2.2	(0.47)	1.7	(0.2)	3.1	P = 0.58 P>0.05 NS
- (IC) Inter caudate distance	0.75	(0.3)	0.70	(0.2)	0.84	(0.12)	2.9	P = 0.069 P>0.05 NS

This table shows no statistically significant difference between MRI measurement of caudate areas except Rt caudate area (P<0.05) but measurement is higher in autistic than control group except intercaudate distance which is lower in autistics than controls.

**Table (9):** Comparison of MRI measurements of frontal horn width among study groups

	Group (1) N = 8	Group (2) N = 14	Group (3) N = 10	F-test	
	X' (SD)	X' (SD)	X' (SD)		
<b>FH width</b>	3.4 (0.31)	3.4 (0.7)	2.9 (0.3)	3.7	P=0.35 P<0.05 S

This table shows statistically significant difference between the studied children in frontal horn widths ( $P < 0.05$ ). (Autistics were higher than controls).

**Table (10):** Comparison of MRI measurement of inner table of clavium among study groups.

	Group (1) N = 8	Group (2) N = 14	Group (3) N = 10	F-test	
	X' (SD)	X' (SD)	X' (SD)		
<b>IT Inner table of clavium</b>	13.2 (0.69)	12.8 (0.69)	12.5 (0.58)	2.1	P=0.139 P<0.05 S

This table shows statistically significant difference among study groups in diameter of inner table of clavium ( $P < 0.05$ ).

**Table (11):** Comparison of MRI measurements of corpus callosum among study groups:

	Group (1) N = 8	Group (2) N = 14	Group (3) N = 10	F-test	
	X' (SD)	X' (SD)	X' (SD)		
<b>(1)LCC Length of corpus callosum</b>	5.9 (0.33)	6.1 (0.5)	6.6 (0.56)	5.2	P=0.011 P<0.05 S
<b>(2) Genu</b>	0.81 (0.2)	0.82 (0.2)	1.03 (0.14)	3.1	P = 0.56 P>0.05 NS
<b>(3) Splenium</b>	0.88 (0.12)	0.82 (0.19)	0.88 (0.16)	0.446	P = 0.645 P>0.05 NS
<b>(4) Anterior part</b>	0.5 (0.11)	0.46 (0.1)	0.58 (0.1)	3.4	P=0.047 P<0.05 S
<b>(5) Posterior part</b>	0.43 (0.13)	0.4 (0.1)	0.47 (0.1)	0.846	P = 0.434 P>0.05 NS

This table shows no statistically significant difference between the 3 groups in corpus callosum measurements except length of corpus callosum and anterior part in which there were decreased values in autistics than controls ( $P < 0.05$ ).

### III. Discussion

In the present study, the autistic children's mean age at recognition of first symptom was 24 months. Two studies found the average age of recognition to be 14.9 months and 18.3 months (Volkmar F. et al., 1985; Siegel B. et al., 1998). Other studies, found the average age of symptoms arousing concern was 19.1 months using the Autism Diagnostic Interview (Lord C. et al., 1994; DeGiacoma A. and Fombonne E., 1998).

These studies suggest that parents first notice differences in their children fairly early, given the complexities of actual diagnosis (Daley T., 2004).

Age of first manifestation of autism is a matter of some dispute (Bailey A. et al., 1996). Probably the model age where parents become seriously concerned about autism is at two years of age when language delay becomes a concern (Adrien J. et al., 1992). However, several retrospective studies show that parents noticed abnormalities by 12 months of age or earlier. Examples are: Lack of anticipation for being picked up, eye to eye

gaze for social signaling, joint attention, reaching for a familiar person and imitating other people's actions, e.g., waving good bye or clapping hands. Retrospective studies of home movies at 9-12 months and at first birthday by Osterling J. and Dawson G., (1994) document these findings.

In the present study, the male to female ratio was 3.4:1.

Folstein S. and Rosen – Sheidley B. (2001) found the male to female ratio of idiopathic autism is 4-10:1.

One of the consistent findings in autism is the male predominance, with ratios ranging from 3:1 to 10:1 in high functioning autism (Gillberg C. and Coleman M., 2000; Baron-Cohen S., 2002; Fombonne E., 2003; Yeargin-Allsopp M. et al., 2003).

The preponderance of males suggests an X-Linked disorder, and recent genome-wide screens by 2 separate groups have found evidence of linkage to the X chromosome, but the data are inconsistent (Liu J. et al., 2001; Shao Y. et al., 2002).

In the present study, the rate of autistic children with history of autism in the family was 9%. In the study of Hanan H. (2006), the positive family history was 17.5% for families that have one child with autism; there is an increased risk of having another child with autism. This recurrence risk is estimated to be about 4% which is greater than that found in families that do not have a child with autism (Gillberg C., 1998).

In our study we found a considerable consanguinity rate of 22.27% and this is in agreement with the result of Hanan H., (2006), where the consanguinity was estimated as 20%.

Consanguinity is not often reported as a risk factor in western countries, since consanguineous marriages are banned (Filipek P. et al., 1999).

Twin studies reported 60% concordance for classic autism in monozygotic (MZ) twins versus none in Dizygotic twins. The higher MZ concordance supporting genetic inheritance as the predominant causative agent (Muhle R. et al., 2004). In the present study, three of the autistic group children were identical twins, 2 (25%) from group 1 (high functioning autism) and 1 (7.2%) from group 2 (low functioning autism).

In our study, maternal health problems during pregnancy were found in 4 cases (18.18%) (2 from group 1 and 2 from group 2); included one mother had oligohydraminos, two anaemia and one pyelonephritis.

In the study of Hanan H., (2006), 25% of mothers of the autistic children developed health problems during pregnancy including toxemia of pregnancy, gestational diabetes, hypertension, medical conditions and obstetrical conditions. .

In this study, 14 (63.6%) of the autistic children were delivered normally, while 6(27.3%) by caesarean section and 2 (9.1%) by ventouse "instrumental delivery". In the study of HananH., (2006), 47.5% of the autistic children were delivered normally while 52.5% were delivered by cesarean section.

In the present study, 3 (13.64%) of the autistic children were low birth weight. In the study of Hanan H., (2006), (12.5%) needed incubator care and (10 %) were either premature or developed neonatal convulsions.

A reduced fetal nutrient supply might be a consequence of poor placental function, and an outcome of a sub-optimal placental nutrient supply is exposure of the fetus to excess glucocorticoids, which act to restrict fetal growth and to programme permanent changes in the neural, cardiovascular, endocrine and metabolic systems. The role of poor placental function and sub-optimal placental nutrient supply in the pathogenesis of autism should be further investigated (Bertram C. and Hanson M., 2002).

In the present study, 19 (86.36%) of the autistic children were breast fed and 3 (13.64%) formula fed, and this is in agreement with the result of the study of Hanan H., (2006).

Social level was found to have no effect on the incidence of autism (Fombonne E., 1999; Larsson H. et al., 2005). In the present study, (13.64%) of the mothers were illiterate and only (4.56%) of fathers also illiterate, (63.63%) of the mothers were a level less than university and about the same percentage for fathers, (22.73%) of mothers were a level of university or higher and (31.81%) of fathers were the same level.

In the present study, the size of family of autistic children ranged from 3 to 7, and as regard birth order (50%) of autistic children were born further on. The result was statistically insignificant and this is in agreement of the result of the study of Hanan H., (2006).

In the present study, 12 (54.54%) of the autistic children were epileptic, 4 out of 8 (50%) from group 1 (High Functioning Autism), 8 out of 14 (57.1%) from group 2 (Low Functioning Autism). So, in our study, epilepsy was found higher among low functioning group than high functioning group.

Epilepsy occurs in 10-30% of individuals with autism. This association was mentioned in the first description of autism by Kanner. Therefore epilepsy should be suspected in children with autism who have paroxysmal events (Gabis L. et al., 2005).

The prevalence of epilepsy in autistic children has been estimated at 7 to 14%, whereas the cumulative prevalence by adulthood is estimated at 20% to 35%, seizures onset peaks in early childhood and again in adolescence. Mental retardation, with or without motor abnormalities and family history of epilepsy, was a significant risk factor for the development of seizures in autistic individuals (Gillberg C. and Steffenburg S., 1987; Tuchman R. et al., 1991; Wong V., 1993; Rapin I., 1996).

In our study, there is higher prevalence of epilepsy than previous studies, and low functioning autistic cases were higher than high functioning cases as regard prevalence of epilepsy, and thus there is a correlation between autism and epilepsy and therefore the prognosis may be bad with presence of epilepsy, and this is in agreement with the result of the study of **Rapin I., 1996**.

In our study, epilepsy was higher than other previous studies because of parents in our country give more attention and sought medical advice urgently when there is epileptic seizures rather than the autistic features. The first group of symptoms noticed by the parents of the autistic children in the present study was the language defect in (68.2%) of the cases. Language defects remain the focus of the parents even after diagnosis. Parents also tend to measure progress of treatment by the development of language. Language defects can be verbal or non verbal. In verbal defects, the child may have no spoken language or a few words that do not suit his/her chronological age or the child may have echolalia and other speech disorders. Non verbal language defects includes facial expressions and indicating wants using body parts, for example by pointing at a desired object, which is missing in most autistic children (**Green V. et al., 2006**).

Social reactivity defects were the first group of symptoms noticed by (22.7%) of the parents of the autistic children in the current study. Social defects make the family of the autistic child suffer, because the child appears unable to recognize the caregivers, refuses to play or interact with people especially children prefers inanimate objects. In the present study, (9.1%) of the autistic children showed behavioral defects (body rocking, television [T.V] watching and playing with objects for hours) as the first group of symptoms noticed by the parents who either consider them normal behaviors and over look them, or these behaviors irritate the parents so much that they train the children to stop them or to reduce their frequency.

Stereotyped movements are a particularly interesting set of motor behaviors prevalent in about one third of people with autism. A significant proportion of stereotyped movements in autism are also self-injurious behaviors (SIB), such as head banging. SIB is a devastating disorder, the prevalence of which in autism is estimated from 10-40 percent. Both SIB and stereotyped behavior are manifested at very early age, in normal infants, however, they rapidly decrease by one year and are rarely seen beyond five years of age (**Schroeder S. et al., 2002**).

In the present study, there is no statistically significant difference between the two groups of the autistic children as regard first observed symptom. According to the previous result, any child with language defect or delay in development of speech, autism should be considered. In the current study (8 cases out of 22) 36.4% of the autistic children were mild to moderate autism, (high functioning group) and (14 out of 22) 63.6% were severe autism, or (low functioning group), the evaluation was by using Childhood Autism Rating Scale (CARS). CARS scores can be used for detection of severity of autism and follow up of the cases for evaluation of effect of treatment. Children with autism have a larger head circumference, only a small proportion have frank macrocephaly (**Bolton P., et al., 1994; Bailey A. et al., 1995; Woodhouse W. et al., 1996**). But in our study, number of cases below 5 years age was 5 only, and the number is so small to be compared with control group.

In the present study, there is no statistically significant difference between autistic and control groups as regard weight and height and this is in agreement with the result of the study of **Hanan H., 2006**. In the present study, the highly significant finding during the examination of autistic children was the presence of hyperactivity, (95.45%) the autistic children were hyperactive ( $P < 0.01$ ). Problems of inattention and hyperactivity affect one half of individuals with autistic disorder. Care must be taken to ensure that inattention and hyperactivity are not manifestation of other behavioral pathology seen in association with autistic disorders, as this will affect treatment decisions (**Hazell P., 2007**).

The high incidence of hyperactivity in the autistic children of our study can be explained by, parents sought medical advice because of hyperactivity was a distressing problem in their families and causing scholastic inachievement. In the present study, the blood serotonin level was higher in autistic than control group, the plasma serotonin level was elevated in (31.8%) of autistic children, and this is in agreement of the previous studies of (Anderson G. et al., 1990; Leventhal B. et al., 1990; Curraro M. et al., 1993; Leboyer M. et al., 1999; Chugani D., 2004; Muhle R., 2004; Cantor B., 2005).

In the present study, the blood serotonin level was higher in the low functioning group ( $2.6 \pm 0.531$ ) than high functioning group ( $2.5 \pm 0.8$ ), and there might be a relation between high plasma serotonin levels and lower verbal ability scores (Chugani D., 2004). From the previous result, there is a possibility of correlation between high plasma serotonin level and severity of the disorder. Many studies have consistently reported that about one-third of autistic individuals have hyperserotonemia (Anderson G. et al., 1990). Persons with autism have high levels of serotonin-ranging between 25 % and 50 %, higher than persons without autism, this higher serotonin level may result from problems with the serotonin transporter that arise from errors in the gene, high serotonin levels may explain why persons with autism have problems showing emotion and handling sensory information, such as sounds, touch and smells (Muhle R. et al., 2004, and Cantor B., 2005).

Serotonergic abnormalities have been reported in autism, specifically hyperserotonemia, as well as elevated blood serotonin in the first-degree relatives of children with autism (Leboyer M. et al., 1999). Serotonergic abnormalities during prenatal and early postnatal development might lead to reciprocal changes in thalamocortical connectivity, which results in a certain predisposition for autism, hyperserotonemia in autism may also involve a typical metabolism of the metabolic serotonin precursor tryptophan as a potential mechanism for alterations in serotonin availability (Chugani D., 2004).

In the study of Cuccaro M. et al., (1993), they conducted a study that looked at the level of blood serotonin and the verbal ability of individuals with autism and their immediate relatives. Using a well accepted IQ test (Wechsler Scales), these researchers found that individuals with high serotonin platelet or blood levels, had lower verbal ability scores. However, other measurements of intellectual abilities were not changed, including visual-spatial ability or memory. In the study of (Hranilovic D. et al., 2006), hyperserotonemia is the most consistent serotonin-related finding in autism. The basis of this phenomenon, and its relationship to the central serotonergic dysfunction remains unclear.

Platelet serotonin level (PSL) in 53 autistic adults and 54 healthy controls was measured. Mean PSL in autistic group ( $75.7 \pm 37.4$  ng/ml) was significantly higher than the control sample ( $59.2 \pm 16.2$  ng/ml) due to presence of hyperserotonemic subjects which comprised 32% of the patients. PSL of autistic subjects did not correlate with the severity of symptoms, as measured by total CARS score, or the degree of mental retardation. However, significant negative relationship was observed between PSL and speech development, indicating the relationship between the peripheral 5HT concentrations and verbal abilities in autistic subjects.

In the present study, fifteen cases out of 22 (68.2%) of the autistic children had abnormal EEG findings, 5 cases from group 1 (high functioning autism) and 10 cases from group 2, and EEG interpretation was as the following, in group 1, three cases had focal epileptogenic discharges and mainly temporal, two cases had focal epileptic discharges with secondary generalization; in group 2, five cases had focal discharges and mainly temporal, three cases had focal with secondary generalization and two cases had generalized epileptic discharges. The result was statistically highly significant ( $P < 0.01$ ), and this in agreement with the previous studies of Toshiaki H. et al., (2001) and Chugani D. (2002).

Our study revealed 9 cases out of 15 (60%) who had abnormal EEG findings were epileptics, and this is in agreement with the study of Rossi P. et al., (1995). EEG studies in autism, have revealed a high rate of epileptic EEG abnormalities, Small J., 1975 documented a relationship between EEG and IQ, in that the incidence of mental retardation was higher in the group with EEG abnormalities (Kawasaki Y. et al., 1997), reported that there was a significant relationship between the presence of epilepsy and the occurrence of spikes, although the focus of spike discharges has been reported to be the centro-temporal, temporal, or frontal region.

In an EEG study by Dawson G. et al., (1995) who compared the normally developing children with autistic children, they found EEG abnormalities in the frontal and temporal regions, but not in the parietal region, and that the differences were more prominent in the left than the Rt hemisphere, Harrison D. et al., 1998 presented an adult autistic patient with results suggestive of left anterior deactivation and right frontal activation.

From our mentioned results, this study pointed to a positive correlation between EEG with or without epilepsy and autism, as well as its severity.

In the present study, 3 cases (13.6%) had structural MRI brain abnormalities in the form of white matter affection "posterior dysmyelination", but the result was statistically insignificant. In general, both CT and MRI data indicated an absence of gross structural brain lesions in autism spectrum disorders (Bailey A. et al., 1998).

As regard caudate measurements in autistic children, our study revealed that there was increased area of the caudate nucleus, "Rt more than Lt", the result was statistically significant in Rt caudate area. On the other hand, caudate measurements were increased in autistic children than in control group, but the result was statistically insignificant. As regard, intercaudate distance there was decrement in the autistic group than in the control group, but also, the result was statistically insignificant.

In the present study, there is increased frontal horn widths in autistic children, and the result was statistically significant ( $P < 0.05$ ). Also, this study revealed that there was increased measurement of inner table of clavium, the result was statistically significant ( $P < 0.05$ ). This may agree with the study of Piven J. et al., (1996, 1997) on autistic children, by using volumetric MRI they found that there is increased volume of total brain, total tissue, lateral ventricle volumes, increased volume of parietal, temporal and occipital lobes. One MRI study of pair of MZ twins demonstrated decreased caudate, amygdale and hippocampus volumes as well as reduced volumes of the superior temporal gyrus and the frontal lobe relative to controls (Kates W. et al., 1998).

In the present study, decreased measurement of the corpus callosum in the autistic group than control group but the result was statistically insignificant. There was significance when comparing the length of corpus callosum and thickness of anterior part of corpus callosum in which decreased values in autistics than controls ( $P < 0.05$ ). The results agree with the results of Facundo M. et al., (1999) in which the areas of corpus callosum were examined on midsagittal magnetic resonance imaging scans of 27 low-IQ autistic individuals and 17 non



autistic individuals of comparable mental age, autistic individuals had a significantly smaller corpus callosum (most marked in the body). Results demonstrate that abnormalities of the corpus callosum reported in high-functioning autistic individuals are also present in autistic individuals with mental retardation. This controversy of the increment or decrement of some parts of the brain may be related to the age of the patients or duration and severity of the autistic patients.

So, various anatomical sites in the brain have been hypothesized as the primary source of pathology in autistic disorder, such as enlarged brain size, reductions in the area of corpus callosum, and the medial temporal lobe structure. According to recent MRI studies, slow and differential maturation of the brain does not happen in autism. There is a relatively brief period of overgrowth, followed by reduced or arrested growth (*Courchesne E., 2004*).

#### **IV. Conclusion**

- Language deficit is the first and the most common clinical presentation in autistic children.
- Autistic disorder is common in males than females.
- There are two apparent clinical types of autism, high and low functioning autism.
- Epilepsy and hyperactivity are a significant co-morbid conditions associated with autism.
- There is a positive correlation between epilepsy and severity of autism.
- There is high blood serotonin level in about one-third of autistic children with positive correlation between high serotonin level and severity of autistic features.
- Abnormal EEG finding is a significant result present in autistic children with a positive correlation between abnormal EEG findings and severity of autism.
- There are no specific structural brain MRI abnormalities in autism.
- There are differences in measurements of certain brain areas such as caudate and corpus callosum in autistic children and these differences can explain the autistic symptoms.
- There is a positive correlation between brain MRI measurement abnormalities and severity of autism

#### **From the present study, we can recommend the following:**

1. The pediatrician and neuropsychiatrist should give more attention to detect the early clinical manifestations of autism to minimize the social, communication and behavior abnormalities.
2. Screening and surveillance programs for early detection of autistic disorder.
3. Further study of serotonin levels in both blood and cerebrospinal fluid of autistic children and its effect on autistic symptoms.
4. Further study of volumetric MRI functional MRI, MRS and PET in autistic children.

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### الملخص العربي

المظاهر الإكلينيكية ومستوى السيروتونين بالدم وتخطيط الدماغ الكهربائي والتصوير بالرنين المغناطيسي على المخ في حالات التوحد عند الأطفال

إضطرابات النمو النمطية المنتشرة حديثاً هي مجموعة من الأمراض تتميز بعيوب في اللغة، والتواصل الاجتماعي وتكرار السلوك والعادات بصورة نمطية.

يعتبر التوحد من أكثر الاضطرابات النمائية شيوياً ويعد من الاضطرابات الدائمة التي تستمر طوال فترة الحياة وهناك العديد من الصعوبات التي تظهر عند تشخيص التوحد. ومن هذه الصعوبات أن التوحد يظهر من خلال سلسلة من الدرجات المتداخلة من اضطرابات النمو ونتيجة لتفاعل عدد من العوامل، ويصبح التشخيص أكثر صعوبة لدى الأطفال الذين يقعون في طرفي متصل التوحد ذوى الإصابة البسيطة والذي يطلق عليه التوحد ذو المستوى الوظيفي المرتفع وكذلك ذوى الإصابة الشديدة والذي يطلق عليه التوحد ذو المستوى الوظيفي المنخفض. حيث لا توجد علامات أو خصائص فسيولوجية أو جينية ثابتة مميزة لهم كما هو موجود في بعض الإعاقات الأخرى.

اضطراب التوحد هو مرض ناشئ عن خلل وظيفي في المخ خاصة الجزء المسئول عن التطور السلوكي والتواصل الاجتماعي، وسببه غير معروف حتى الآن. ونظراً لوجود زيادة ملحوظة في معدل انتشار المرض حديثاً، فإن البحث عن مسبباته أصبح شينياً ضرورياً. تم إجراء الدراسة الحالية أثناء الفترة من بداية يناير 2007 إلى آخر أغسطس 2007 بوحدة أعصاب الأطفال - بقسم الأمراض العصبية- بمستشفيات جامعة الأزهر، وشملت الدراسة مجموعتين من الأطفال:

المجموعة الأولى: تتكون من 22 طفلاً من الذين يعانون من اضطراب التوحد، والمجموعة الثانية: تتكون من 10 أطفال أسوياء كمجموعة مقارنة. تم تشخيص الحالات عن طريق تطبيق العلامات الفارقة لمرض التوحد باستخدام الدليل الإحصائي التشخيصي الرابع النسخة المراجعة لعام 2000.

وتشمل خصائص الانضمام على:

- (1) أطفال أصحاء ظاهرياً طبيياً وعصبياً.
- (2) يتراوح العمر من 2 إلى 13 سنة.
- (3) عدم وجود خلل كبير بالمخ عن طريق التصوير بالرنين المغناطيسي.

وتشمل خصائص الاستبعاد على:

- (1) الأطفال المصابون بالاضطرابات الارتقائية المصنفة مثل اضطراب ريت.
- (2) وجود خلل جزئي أو كلي ظاهر إكلينيكيّاً بالجهاز العصبي.
- (3) الأطفال المصابون بأمراض عضوية مزمنة مثل أمراض الصدر أو ضغط الدم.

وفد تم إجراء الآتي للأطفال:

- (1) أخذ التاريخ المرضي الطبي والعصبي الكامل.
- (2) الفحص الكامل خاصة على الجهاز العصبي والنفسي.
- (3) التقويم الكامل للسمع.
- (4) مقياس تقدير التوحد في مرحلة الطفولة (اختبار كارز).

وباستخدام هذا الاختبار تم تقسيم الحالات إلى مجموعتين:

- (1) المجموعة الأولى: هي مجموعة التوحد البسيط والمتوسط أو التوحد ذو المستوى الوظيفي المرتفع. واشتملت هذه المجموعة على 8 حالات وكانت درجاتهم في اختبار كارز تتراوح من 30 إلى أقل من 39.
- (2) المجموعة الثانية: هي مجموعة التوحد الشديد أو التوحد ذو المستوى الوظيفي المنخفض. واشتملت هذه المجموعة على 14 حالة

و درجاتهم في اختبار كارز تراوحت من 39 إلى 60.

وفي الدراسة الحالية كانت المجموعة الثالثة هي العينة الضابطة التي اشتملت على 10 أطفال أسوياء .

- (5) قياس نسبة السيروتونين بالدم.
- (6) تخطيط الدماغ الكهربائي.
- (7) التصوير بالرنين المغناطيسي على المخ بهدف:
- (أ) وجود آفة بسيطة بالمخ مرتبطة بالتوحد.
- (ب) قياس بعض المناطق بالمخ وتشمل (القرن الأمامي، نواة المذنب، السطح الداخلي للكلافرين والجسم الجاسي).

وقد أظهرت هذه الدراسة النتائج التالية:

- (1) سادت نسبة الذكور على الإناث حيث بلغت نسبتهم (77.28%) من حالات التوحد.
- (2) كانت عيوب اللغة أول الأعراض الملحوظة من قبل الأهل في (68.2%) من الحالات.
- (3) بلغت نسبة زواج الأقارب في (22.27%) من حالات التوحد، ووجد أفراد آخرون مصابون بالتوحد في العائلة في (9%) من الحالات.

- (4) بلغت نسبة الأطفال المصابين بالصرع (54.54%) من حالات التوحد، وكان أكثر انتشاراً في الأطفال ذوي المستوى الوظيفي المنخفض عن ذوي المستوى الوظيفي المرتفع مع وجود دلالة إحصائية.
- (5) كانت نسبة الأطفال ذوي المستوى الوظيفي المرتفع 36.4% والأطفال ذوي المستوى الوظيفي المنخفض 63.6% وتم تقسيم حالات التوحد إلى هذين النوعين السابقين بواسطة اختبار كارز (مقياس تقدير التوحد في مرحلة الطفولة).
- (6) وجود نشاط حركي زائد في نسبة (95.45%) من حالات التوحد مع وجود دلالة إحصائية عالية.
- (7) كانت نسبة السيروتونين بالدم عالية في أطفال التوحد عن العينة الضابطة، حيث وجدت بنسبة (31.8%) من حالات التوحد، وكانت النتيجة مرتفعة في أطفال التوحد ذوي المستوى الوظيفي المنخفض عن ذوي المستوى الوظيفي المرتفع.
- (8) نسبة وجود بؤر صرعية في المخ بواسطة استخدام تخطيط الدماغ الكهربائي في (68.2%) من حالات التوحد مع وجود دلالة إحصائية عالية.
- (9) زاد وجود البؤر الصرعية في الأطفال ذوي المستوى الوظيفي المنخفض عن الأطفال ذوي المستوى الوظيفي المرتفع. كما كانت نسبة (60%) من الأطفال الذين لديهم بؤر صرعية في المخ يعانون من حدوث نوبات متكررة من التشنجات، وبالتالي وجدت علاقة إيجابية بين التوحد والصرع، كما وجدت علاقة إيجابية بين شدة التوحد ووجود بؤر صرعية في المخ.
- (10) وجود اختلاف في قياسات بعض المناطق بالمخ باستخدام التصوير بالرنين المغناطيسي على المخ مثل عظمة الكلافريم واتضح أيضاً نقص في قياسات الجسم الجاسي (الجامد) في أطفال التوحد عن العينة الضابطة، وهذه الاختلافات في القياسات قد تفسر أعراض التوحد المختلفة.
- ومن هذه الدراسة نستطيع أن نستنتج الآتي:**
- عيوب اللغة أول الأعراض الملحوظة وأشهرها حدوثاً في أطفال التوحد.
  - اضطراب التوحد يزداد في الذكور عن الإناث.
  - وجود نوعين واضحين من التوحد إكلينيكيًا، التوحد ذو المستوى الوظيفي المرتفع والتوحد ذو المستوى الوظيفي المنخفض.
  - الصرع والنشاط الزائد عبارة عن اضطرابات مصاحبة للتوحد ومرتبطة بشدة المرض.
  - وجود زيادة في نسبة السيروتونين بالدم في حوالي ثلث حالات التوحد مع وجود علاقة إيجابية بين شدة المرض وارتفاع نسبة السيروتونين بالدم.
  - وجود بؤر صرعية في المخ باستخدام تخطيط الدماغ الكهربائي ذو دلالة إحصائية عالية مع التوحد مع وجود علاقة إيجابية بين شدة التوحد ووجود البؤر الصرعية المخية.
  - وجود اختلاف في قياسات مناطق المخ المختلفة باستخدام الرنين المغناطيسي مع وجود علاقة إيجابية بين شدة التوحد وهذه القياسات المختلفة.
- وقد خرجنا من هذه الدراسة بمجموعة من التوصيات:**
- 1- التنبيه على أخصائي الأطفال والأعصاب والطب النفسي بإعطاء الاهتمام البالغ بعمل برنامج مسح ورصد على مجال واسع في التشخيص المبكر للتوحد بهدف التدخل العلاجي والتأهيلي المبكر لتقليل حدة الأعراض.
  - 2- التعرف على حالات التوحد ذو المستوى الوظيفي المرتفع وإعطاء العلاج المناسب لها من أجل الحصول على مستقبل جيد.
  - 3- العلاج المبكر للأمراض المصاحبة للتوحد مثل الصرع والنشاط الزائد وذلك لسبب ارتباطها الإيجابي بشدة المرض.
  - 4- الدراسة المستقبلية لمستوى السيروتونين بكل من الدم والسائل النخاعي في أطفال التوحد ودراسة تأثير التغيير في مستوى السيروتونين على أعراض التوحد.
  - 5- عمل تخطيط دماغ كهربائي لكل حالات التوحد وذلك كفحص روتيني.
  - 6- الدراسة المستقبلية باستخدام الرنين المغناطيسي الحجمي على عدد كبير من الحالات وعلاقة ذلك بالأعراض الإكلينيكية في حالات التوحد عند الأطفال.
  - 7- الدراسة المستقبلية باستخدام الرنين المغناطيسي الوظيفي في حالات التوحد عند الأطفال.