

## Risk Factors of Autistic Spectrum Disorders (ASDs) among Egyptian children patients Attending Psychiatric Clinic of Postgraduate Childhood Studies Institute, Ain Shams University

Shaimaa S. Yousef \*, Ghada E. Amin \*, Olueya M. Abdel Baky \*\*, Samia I. El-Damaty \*.

\*Department of Community, Environmental and Occupational medicine, Faculty of medicine- Ain Shams University; \*\* Postgraduate Childhood Studies Institute - Ain Shams University

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### Abstract

Autism spectrum disorder (ASD) is characterized by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviours. ASD is caused by a combination of genetic and environmental factors. **Objective:** to identify possible risk factors of ASD. **Methods:** The current study is a case-control study. We recruited 142 caregivers of the children to complete an interview questionnaire about risk factors for ASD. Seventy one (71) cases of autistic children were recruited from Postgraduate Childhood Studies Institute affiliated to Ain Shams University, and 71 normal children from outpatient pediatric clinics of the Ain Shams University hospital. Cases and controls were matched regarding age and sex. **Results:** Advanced paternal age at the time of conception, hypertension during pregnancy, postnatal hypoxia, positive family history of psychiatric diseases, and artificial feeding are risk factors for ASD. Also, folic acid supplementation during 1<sup>st</sup> trimester is found to be protective from autism. **Recommendations:** Folic acid supplementation to the mother before pregnancy and at the first trimester of pregnancy (at least 600 mcg per day) is mandatory.

**Key words:** Autism spectrum disorder, ASD, social interaction, communication, repetitive behaviors, advanced paternal age.

**Corresponding author:** Shaimaa S. Yousef Email: shaimaasamy37@yahoo.com, phone

### Introduction

Autism spectrum disorder (ASD) and autism are both general terms for a group of complex disorders of brain development. These disorders are characterized, in varying degrees, by difficulties in social interaction, verbal and nonverbal communication and repetitive behaviors. The most obvious symptoms and signs of autism tend to emerge between 2 and 3 years of age. Early intervention with behavioral therapies can improve outcomes<sup>1</sup>. ASD affects over 3 million individuals in the United States and tens of millions worldwide<sup>2</sup>. Autism statistics from the CDC reveal that around 1 in 68 American children have ASD. This

increase is explained by improved diagnosis and public awareness. Studies also show that autism is four to five times more common among boys than girls. An estimated 1 out of 42 boys and 1 in 189 girls are diagnosed with autism in the United States<sup>3</sup>. In Egypt, there are no statistics showing the proportion of autistic children due to the considerable confusion between this group of children and a lot of different disabilities<sup>4</sup>.

The exact cause of autism is still unclear. It is now believed that the mechanism underlying autism etiology is most likely polygenic and that environmental factors may interact

with genetic factors to increase risk<sup>5</sup>. The role of genetics in autism risk is suggested by the higher recurrence rate in siblings of children with autism than in siblings of normal children, and the greater concordance rate of monozygotic twins (36–96%) as compared with same-sex dizygotic twins (0–30%)<sup>6</sup>. A striking finding on ASD is the strong tendency for the risk to increase with the age of the parents, particularly the father, at the time of conception<sup>5</sup>. Croen and his colleagues (2007)<sup>7</sup> found the relative risks of ASD associated with advanced maternal and paternal age to be 1.18 and 1.34, respectively. Moreover, positive family history of psychiatric diseases is a significant risk factor for ASD<sup>8</sup>.

Prenatal factors increasing the risk for ASD are maternal bleeding during pregnancy, gestational diabetes<sup>9</sup> and medications during pregnancy<sup>10</sup>. Also, studies have shown that folic acid demand is effective at reducing neural tube defect occurrence as Autism is a neurodevelopmental disorder that potentially originates during early pregnancy (first month) when folic acid is known to be critical<sup>11</sup>. Furthermore, Abd Elhameed and his colleagues (2011)<sup>12</sup> declared that the gestational hypertension was significantly higher in mothers of autistic children during pregnancy than in the control group. Moreover, Al-Ansari and Ahmed (2013)<sup>13</sup> found that caesarean section delivery may be associated with ASD in Bahrain. Neonatal factors which increase the risk for autism are like prematurity<sup>14</sup> and fetal hypoxia<sup>15</sup>. On the other hand, CDC (2015)<sup>16</sup> recommended that MMR vaccine is not responsible for the increase in the number of children with autism.

Although there is a significant number of researches on prenatal, perinatal, neonatal, and other risk factors of autism, the causal nature of

these associations is still disputed due to several current methodological limitations of studies<sup>9</sup>.

The aim of this study was to identify possible risk factors of autistic spectrum disorder.

## Subjects and methods

**Study design and setting:** A case-control study was conducted. The autistic children were recruited from Postgraduate Childhood Studies Institute affiliated to Ain Shams University, Egypt during the months of June, July, and August 2015. And the controls were recruited from outpatient pediatric clinics of Ain Shams University hospital, Egypt.

**Study sample:** The required sample size was 71 cases and 71 controls by using stata 10. Accordingly a total convenient sample of 142 was included in the study. Each group included 57males (80.3%) and 14 females (19.7%). Their age ranged from 3 to 12 years (mean 6.4, SD  $\pm$  2.5 years). Both cases and controls were matched regarding age and sex.

Children with ASD participating in the study have been diagnosed in the Postgraduate Childhood Studies Institute by the following: (1) Confirmation of diagnosis using DSM-V criteria of autism<sup>1</sup>, i.e. Impairments of language, social skills, and restricted stereotyped interest or activity. (2) Assessment of mental age using Stanford-Binet intelligence scale, 4<sup>th</sup> edition<sup>17</sup>, to calculate the intelligence quotient (IQ). This test is used to measure the child cognitive abilities. (3) Assessment of severity of autistic symptoms using childhood autism rating scale (CARS)<sup>18</sup>.

The control children were assessed by Childhood Autism Rating Scale (CARS) to exclude the presence of autistic features.

**Study tool:** Data was collected from all caregivers of children included in the

study using a structured interview questionnaire which was written in Arabic and included all the following items:

*Socio demographic data including:* For Child: name, gender, age, birth order & number of siblings. For Mother: age, marital status, level of education, occupation. For Father: age, level of education, occupation, smoking, consanguinity, income.

*Mother History including:* Antenatal history: age of mother during pregnancy of the child, induction of ovulation, presence of symptoms (bleeding during pregnancy, rubella, diabetes mellitus, hypertension, preeclampsia, convulsions), taking of medications (e.g. folic acid), exposure to radiation. Natal history: type of labor, breech presentation, place and time of birth. Postnatal history: birth weight, resuscitation, jaundice, admission to neonatal ICU, congenital anomalies.

*Child History including:* Developmental history: Age of knowing mother, knowing father, sitting unassisted, walking unassisted, saying a word, saying a sentence, admission to school. Vaccination history: BCG, oral polio, DPT, hepatitis B, MMR vaccines. Nutritional history: Breast feeding or artificial feeding.

*Family History including:* Family history for any psychiatric diseases in the family.

**Data management and analysis:** The collected data was revised, coded, tabulated and introduced to a personal computer using Statistical package for Social Science (SPSS 20 for windows). Suitable statistical analysis was done according to the type of data obtained for each parameter. The significance level was set at  $P < 0.05$ .

**Ethical consideration:** Administrative approval was obtained from the manager of Postgraduate Childhood

Studies Institute. Informed consents were obtained from caregivers including objectives, benefits, risks of the study and confidentiality of the individual data was assured.

## Results

Table (1) shows that a statistically significant difference regarding education of mothers, age of fathers at conception and education of fathers, family income. Regarding family history, there was a statistically significant difference between cases and controls regarding family history of psychiatric diseases. Table (2) shows that a statistically significant difference between cases' and controls' mothers regarding hypertension during pregnancy and folic acid supplementation during 1<sup>st</sup> trimester of pregnancy. All mothers hadn't history of eclampsia, rubella infection, smoking or radiation during pregnancy. Table (3) shows that no statistically significant difference between cases' and controls' mothers regarding their natal history. Table (4) shows that a statistically significant difference between cases and controls regarding postnatal hypoxia, admission to NICU, period of admission, cause of admission and artificial feeding. Table (5) shows that after applying logistic regression model, the variables that affected ASD were positive family history of psychiatric diseases (OR=7.45), postnatal hypoxia (OR=4.64) and folic acid supplementation during 1<sup>st</sup> trimester of pregnancy (OR=0.199).

## Discussion

There is agreement amongst all professionals that autism is one of the most puzzling diseases. It is a neurodevelopmental disorder characterized by impairments in social and communication skills as well as restricted, repetitive, and stereotyped

patterns of behavior and movement. Its prevalence has surged in recent years<sup>1</sup>.

The findings of the current study showed that, mean age of studied children is 6.4 years old, This finding is in agreement with Elwardany and her colleagues (2013)<sup>19</sup> at Assiut City.

The present study showed that, most of children were males (80.3%). The findings of the present study are consistent with CDC (2014)<sup>3</sup> who declared that the estimated number of male to female children with ASD is approximately five times higher in boys than girls.

The current study showed that high paternal age (father  $\geq$  35 years) during pregnancy was found in 38.1% of autistic children in comparison with 15.5% of control group and the difference was statistically significant. Also the current study showed that high maternal age (mother  $\geq$  35 years) during pregnancy was found in 5.6% of autistic children in comparison of none of controls and the difference was statistically insignificant.

These results was in agreement with Reichenberg and his colleagues (2006)<sup>20</sup> who illustrated that there was an association between advancing paternal age and risk of ASD. They concluded that offspring of 40 years men or older were 5.75 times more likely to have ASD compared with offspring of men younger than 30 years, while advancing maternal age showed no association with ASD after adjusting for paternal age.

Regarding education, the current study showed that (64.8%) of fathers and (56.3%) of mothers of autistic children had university level of education; compared with (31%), (29.6%) for fathers and mothers of control group respectively. This may be due to the educated parents had awareness and good observation for any signs or change of child. These findings were

consistent with Elwardany et al. (2013)<sup>19</sup>.

Regarding the family income, (25.4%) of cases compared with (11.3%) of controls, their income was ranging between 3000 to 5000 LE, which was statistically significant. This may be due to high education among parents of autistic children.

The present study illustrated that (29.6%) of parents had consanguinity degree. This study agreed with Al-Salehi and his colleagues (2012)<sup>21</sup> in Saudi Arabia, but disagreed with El-Baz and her colleagues (2011)<sup>22</sup>. On the other hand, Sasanfar and his colleagues (2010)<sup>23</sup> reported that consanguinity had no role in a study done on the Iranian population.

According to family history of psychiatric diseases; the results of the present study showed that; (18.3%) of autistic children had family history of psychiatric diseases compared with (2.8%) of control group, this difference was statistically significant. This finding was in agreement with Sullivan and his colleagues (2012)<sup>8</sup> who found that presence of schizophrenia or bipolar disorder in first-degree relatives was a consistent and significant risk factor for ASD.

As regards prenatal factors; the present study found that cases' mothers had induction of ovulation more than controls' mothers and the difference was statistically insignificant. This finding was inconsistent with Hvidtj rn and his colleagues (2010)<sup>24</sup> who conducted a follow-up study in Denmark to assess the risk of ASD in children born after assisted conception. The difference may be due to different study populations and cultures.

The current study revealed that cases' mothers had hypertension during pregnancy more than controls' mothers and the difference was statistically significant. This result disagreed with El-Baz and his colleagues (2011)<sup>22</sup>

who revealed that no significant difference was found between cases and controls as regards hypertension during pregnancy.

This study showed that there were no statistically significance difference between cases' and controls' mothers regarding bleeding during pregnancy and gestational diabetes and autism. But, Gardner and his colleagues (2011)<sup>5</sup> reported that there was an association between maternal bleeding during pregnancy and gestational diabetes and autism. These differences might be explained by different study populations. All mothers of studied children hadn't history of rubella infection during pregnancy, eclampsia, smoking, exposure to radiation during pregnancy.

According to folic acid supplementation, (80.3%) of cases' mothers compared with (94.4%) of controls' mothers have received folic acid during 1<sup>st</sup> trimester of pregnancy, which was statistically significant. This finding was in agreement with Schmidt and his colleagues (2012)<sup>11</sup> who reported that folic acid intake was significantly greater for mothers of typically developing children than for mothers of autistic children with ASD. This finding is supported by the odds ratio (< 1), resulted by logistic regression model for the factors affecting ASD among studied groups, which means that folic acid supplementation in the 1<sup>st</sup> trimester is protective from ASD.

As regards natal factors, ceserian section delivery was (36.6%) in both groups, which was a statistically insignificant. This results was consistent with El-Sawy (2011)<sup>10</sup> who found that (59.1%) of cases' mothers and (43.2%) of controls' mothers delivered by caesarean section, yet it seemed to have no impact on the etiology of autism. But El-Baz and her colleagues (2011)<sup>22</sup> reported that

ceserian section was statistically significantly increased in mothers of autistic patients. This difference may be due to different causes of CS which may be lead to neonatal hypoxia.

As regards place of birth, most of mothers of cases and controls were delivered in hospital or special clinic, and the difference was statistically insignificantly. This finding is expected due to increased awareness of mothers to deliver under supervision of medical staff for better monitoring the progress in labor and checkup the baby after birth.

As regards prematurity, (9.9%) of cases versus (4.2%) of controls were delivered less than 37 weeks, this difference was statistically insignificantly. This finding was consistent with El-Baz and her colleagues (2011)<sup>22</sup> and also with Visser and his colleagues (2013)<sup>15</sup>.

As regards birth weight, (15.5%) of cases versus (11.3%) of controls had low birth weight at birth, which was statistically insignificant. This finding is in agreement with Visser and his colleagues (2013)<sup>15</sup>. On the other hand, El-Baz and her colleagues (2011)<sup>22</sup> who reported that low birth weight had statistically significant effect for ASD. The difference may explained by the subjective reporting of the birth weight by the caregivers of children.

As regards postnatal hypoxia, (21.1%) of cases versus (4.2%) of controls were exposed to postnatal hypoxia, and the difference was statistically significant. Therefore, regarding cause of admission to Neonatal Intensive Care (NICU), hypoxia represented (16.9%) of causes of admission to NICU among cases versus (4.2%) of controls. This finding is consistent with Visser and his colleagues (2013)<sup>15</sup> and El-Baz and her colleagues (2011)<sup>22</sup>.

The current study showed that there was no significant effect of

Hyperbilirubinemia for ASD which was consistent with El-sawy (2011) <sup>10</sup>. The present study shows that, equal percent of both groups (4.2%) had history of congenital anomalies, which was in agreement with Visser and his colleagues (2013) <sup>15</sup>.

The current study showed that (25.4%) of cases versus (8.5%) of controls were admitted to NICU after birth, the difference was statistically significant. This explained as the primary cause of admission was postnatal hypoxia, which is distressing sign for the child, so mostly needs admission to NICU as a life saving measure. Regarding period of admission to NICU, the cases were admitted more than controls and the difference was also statistically significant for autistic children. This explained as period of admission is according to the severity of condition.

As regards nutritional history, (31%) of cases versus (15.5%) of controls had artificial feeding, which was statistically significant. This results were in agreement with Schultz and his colleagues (2006)<sup>25</sup> who declared that, babies who were not breastfed had a four times higher risk of autism than babies who were breastfed due to essential fatty acids are necessary for the proper development of the brain and nervous system, are present in breast milk.

Logistic regression model of the factors affected ASD among studied groups (N= 142) showed that folic acid supplementation during 1<sup>st</sup> trimester of pregnancy (OR=0.21, 95% CI= 0.06, 0.71) was protective, while positive family history of psychiatric diseases (OR=8.26, 95% CI= 1.71, 39.98) and postnatal hypoxia (OR= 4.79, 95% CI= 1.22, 18.83), were significant risk factors for ASD.

**Conclusion:** Folic acid supplementation during 1<sup>st</sup> trimester of pregnancy is protective from ASD, positive family history of psychiatric

diseases and postnatal hypoxia, were significant risk factors for ASD. ASD was also significantly associated with advanced paternal age at conception, hypertension during pregnancy, admission to NICU, duration of admission to NICU and artificial feeding.

**Recommendations:** Increase public awareness about the risk factors and early signs of ASD. Folic acid supplementation before pregnancy and at the first trimester of pregnancy and/or eating a diet rich in folic acid (at least 600 mcg per day) is mandatory for prevention of ASD. All children should be screened with standardized developmental tools at specific intervals at the 9–18–24–30 months for early detection of ASD. Proper management of autistic children including behavior, educational, cognitive and pharmacotherapy through expanding and fortifying the autism specialized rehabilitation centers to improve the lives of those children.

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**Table (1): Socio- demographic characteristics of studied groups and family history:**

Item		Cases N=71		Controls N=71		P- value
		N	%	N	%	
Marital status	Married	67	94.4	66	93	0.555
	Divorced	4	5.6	3	4.2	
	Widow	0	0	2	2.8	
Education of mother	Illiterate	3	4.2	12	16.9	0.003*
	Read and Write	0	0	4	5.6	
	Primary	1	1.4	3	4.2	
	Preparatory	7	9.9	10	14.1	
	Secondary	20	28.2	21	29.6	
Age of mother at conception of autistic child in years	University	40	56.3	21	29.6	0.101
	< 20	4	5.6	11	15.5	
	20-	28	39.4	29	40.8	
	25-	25	35.2	24	33.8	
	30-	10	14.1	7	9.9	
Education of Father	35 or more	4	5.6	0	0	0.000*
	Illiterate	3	4.2	15	21.1	
	Read and Write	1	1.4	1	1.4	
	Primary	1	1.4	0	0	
	Preparatory	4	5.6	6	8.5	
	Secondary	16	22.5	27	38	
Age of father at conception of autistic child in Years**	University	46	64.8	22	31	0.006*
	<30	21	29.6	35	49.3	
	30-	23	32.4	25	35.2	
Income/ month (in Egyptian pounds)	≥ 35	27	38.1	11	15.5	0.001*
	< 1200	14	19.7	34	47.9	
	1200-	39	54.9	29	40.8	
Consanguinity	3000- 5000	18	25.4	8	11.3	1.00
	No	50	70.4	50	70.4	
Family history of psychiatric diseases	Yes	21	29.6	21	29.6	0.003*
	No	58	81.7	69	97.2	
	Yes	13	18.3	2	2.8	

*\*Statistically significant, \*\* No fathers of autistic children were below 25 years at time of conception.*

**Table (2): Comparison between cases and controls as regard Antenatal history of the mother:**

	Item	Cases N=71		Controls N=71		P-value
		N	%	N	%	
<b>Induction of ovulation</b>	<b>No</b>	60	84.5	66	93.0	0.111
	<b>Yes</b>	11	15.5	5	7.0	
<b>Bleeding</b>	<b>No</b>	64	90.1	65	91.5	0.77
	<b>Yes</b>	7	9.9	6	8.5	
<b>Gestational DM</b>	<b>No</b>	69	97.2	67	94.4	0.68
	<b>Yes</b>	2	2.8	4	5.6	
<b>Hypertension during pregnancy</b>	<b>No</b>	59	83.1	67	94.4	<b>0.034*</b>
	<b>Yes</b>	12	16.9	4	5.6	
<b>Preeclampsia</b>	<b>No</b>	65	91.5	70	98.6	0.12
	<b>Yes</b>	6	8.5	1	1.4	
<b>Folic Acid supplementation</b>	<b>No</b>	14	19.7	4	5.6	<b>0.012*</b>
	<b>Yes</b>	57	80.3	67	94.4	

*\* Statistically significant*

**Table (3): Comparison between cases and controls as regard natal history of the mothers:**

Item		Cases N=71		Controls N=71		P-value
		N	%	N	%	
<b>Type of labor</b>	<b>VD</b>	45	63.4	45	63.4	1.00
	<b>CS</b>	26	36.6	26	36.6	
<b>Place of birth</b>	<b>Home</b>	1	1.4	4	5.6	0.055
	<b>Hospital</b>	59	83.1	47	66.2	
	<b>Special Clinic</b>	9	12.7	19	26.8	
	<b>Others (in car)</b>	2	2.8	1	1.4	
<b>Time of birth</b>	<b>Full Term</b>	64	90.1	65	91.5	0.12
	<b>Preterm</b>	7	9.9	3	4.2	
	<b>Post Term</b>	0	0	3	4.2	

Table (4): Comparison between cases and controls as regard neonatal history:

Item		Cases N=71		Controls N=71		P-value
		N	%	N	%	
Birth WT	VLBW (< 1500 gm.)	2	2.8	0	0	0.196
	LBW (1500 - 2500 gm.)	11	15.5	8	11.3	
	NBW (2500 - 4000gm.)	51	71.8	60	84.5	
	HBW (> 4000 gm.)	7	9.9	3	4.2	
Hypoxia	No	56	78.9	68	95.8	0.002*
	Yes	15	21.1	3	4.2	
Admission to NICU	No	53	74.6	65	91.5	0.007*
	Yes	18	25.4	6	8.5	
Period of admission	< 1 Week	8	11.3	4	5.6	0.035*
	1 Week- 1 Month	7	9.9	2	2.8	
	> 1 Month	3	4.2	0	0	
Cause of admission	Hypoxia	12	16.9	3	4.2	0.023*
	Hyperbilirubinemia	4	5.6	3	4.2	
	Others**	2	2.8	0	0	
Occurrence of jaundice	No	40	57.7	39	54.9	0.74
	Yes	30	42.3	32	45.1	
Congenital anomalies***	No	68	95.8	68	95.8	1.00
	Yes	3	4.2	3	4.2	
Breast feeding	No	8	11.3	4	5.6	0.23
	Yes	63	88.7	67	94.4	
Artificial feeding	No	49	69	60	84.5	0.029*
	Yes	22	31	11	15.5	

\*Statistically significant, \*\*Others are like septicemia, prematurity and pneumonia.  
 \*\*\*Congenital anomalies are like cardiac anomalies, hypospadias, polydactyl and anal anomalies.

**Table (5): Logistic Regression model for the Factors affecting ASD among studied group:**

Item	B	S.E.	P value	Odds ratio	95% C.I.	
					Lower	Upper
Age of father	0.83	0.52	0.098	2.3	0.85	6.45
Age of mother	0.104	0.64	0.904	1.1	0.31	3.76
Folic acid during pregnancy	-1.62	0.62	<b>0.012</b>	0.21	0.06	0.71
Postnatal hypoxia	1.53	0.70	<b>0.025</b>	4.79	1.22	18.83
Positive family history of psychiatric diseases	2.01	0.81	<b>0.009</b>	8.26	1.71	39.98
Constant	-4.25	1.23	0.001	0.014		