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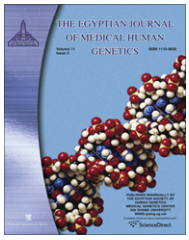

ORIGINAL ARTICLE

Risk factors for autism: An Egyptian study

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Abstract This study has been conducted to determine the possible risk factors of autism. This case control study was conducted at pediatric hospital, Ain Shams University on, 100 autistic patients who were subjected to the followings tools: Confirmation of diagnosis using DSM-IV-TR criteria, IQ assessment using Stanford–Binrent intelligence scale, and assessment of severity of autistic symptoms using childhood autism rating scale (CARS). Full clinical examination, neurological examination, EEG and audiological assessment were also done. Forty-six percent of our patients with autistic symptoms presented at the age of one and half years and 32% at the age of 2 years. Fifty-five percent of our patients had mild to severe retardation (IQ = 20–70), 36% below average mentality (IQ = 71–89) and 9% with normal mentality (IQ = 90–109). High maternal age (mother, $\geqslant$35 years) at birth was found in 23% of autistic children in comparison to 9.5% of controls. Also advanced paternal age (father, $\geqslant$35 years) at birth was found in 91% of cases in comparison to 83.5% of control group and the difference was statistically significant. Positive family history was found to be statistically significantly associated with the risk of autism (16% of cases versus 1% of control). All studied developmental milestones were delayed among autistic children than control group (p = 0.000). As regards natal factors, a history of low birth weight, delivery by cesarian section were significantly higher among cases than controls. Also postnatal factors as history of

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hypoxia, resuscitation and history of jaundice were considered significantly risk factors for autism ($p = 0.000$).

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1. Introduction

Autism is defined as severe psychiatric disorder of childhood marked by severe difficulties in communication and forming relationships with other people, in developing language, repetitive, and limited patterns of behaviours and obsessive resistance to small changes in familiar surrounding [1].

Autism is a chronic disorder with an onset before the age of 3 years, characterized by the following three main sets of behavioral disturbances: social abnormalities, language abnormalities and stereotyped repetitive patterns of behaviour [2]. It is considered one of the pervasive developmental disorders which represent a group of clinical syndromes that have two fundamental elements: developmental delays and developmental deviations [3]. The number of reported cases of autism increased dramatically in the 1990s and early 2000s. This increase is largely attributable to changes in diagnostic practices, referral patterns, availability of services, age at diagnosis, and public awareness [4] .Outward appearance of autistic child may not indicate a disorder .Diagnosis typically comes from a complete patient history, physical and neurological evaluation.

The possible causes of autism include perinatal factors as neonatal anemia, high incidence of respiratory distress syndrome and high incidence of medication usage during pregnancy in the mothers of autistic children, also maternal bleeding after the 1st trimester and meconium in the amniotic fluid [5]. It was also found that autism has an important genetic component although how many genes may be involved remain unclear [6].The most frequently described are the structural and numerical abnormalities of sex chromosomes, anomalies of chromosome 15 and chromosome 17q21 [7]. Environmental components are another important aspect of research in ASDs. Environmental factors such as mercury and radiation have been proposed as possible causes of autism spectrum disorders (ASDs) [8]. Several studies provided strong evidence against the hypothesis that MMR vaccination causes autism [9]. Combination of vaccines as MMR and DPT may also overstimulate children immune system that start the autistic biomedical cascade [10]. Prior research suggests that parental characteristics, such as age and level of education, may be associated with a risk of autism. Parental age has been shown to be associated with many disorders, such as schizophrenia, childhood cancer and fetal death, however, results from studies of parental age and autism are inconsistent [11]. Studies focusing on single perinatal risk factor have reported a positive association for low birth weight (<2, 500 g), gestational age at birth of less than 37 weeks, and congenital malformations. A gender stratification in one study indicated an increased risk of autism among boys, but not girls of low birth weight (<2, 500 g) [12]. The causes of autism are still unclear, although results from twin and family studies provide evidence for a strong genetic contribution, with the probability of multiple genetic loci involved. Less than complete concordance in monozygotic twins reveals the necessary role of non-genetic factors in the aetiology of autism [13]. Despite significant research on prenatal, perinatal, neonatal, and other risk factors in autism, the causal nature of these associations is still disputed due to several current methodological limitation of studies [14].

The aim of this work was to describe epidemiological, clinical and psychometric aspects of a group of Egyptian autistic children in order to determine the possible risk factors of autism.

2. Patients and methods

The present study was designed to be a case control type. It enrolled 100 cases with autism diagnosed by DSM-IV-TR criteria (American psychiatric association, 1994 diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised) [15,16]. The patients were 82 males (82%) and 18 females (18%). Their age ranged from 2 to 13 years (mean 6.75, SD ± 3.26 years).They were recruited from the Psychiatric Clinic, Pediatric hospital, Ain Shams University during the period from June 2008 to May 2010. Two hundreds healthy children comprised the control group. They were 144 males (71.3%) and 58 females (28.7%). Their ages ranged from 2 to 11(mean 5.53, SD ± 2.75 years).They were recruited from different outpatient clinics. Two control subjects were matched for each case, in age, gender, environment and habitate. Control group were referred to psychiatric clinic to exclude the presence of ASD.

I All cases were subjected to the following

Detailed history taking with special emphasis on; onset, course and duration of the disease and age, sex of the patient, consanguinity.

- Antenatal or maternal history: age at patient's birth, history of threatened abortion, any fetal loss, parity, chronic illness as hypertension, Diabetes mellitus (DM), infections or hospitalizations during pregnancy, medications (e.g.: antiepileptic drugs, anti-thyroid drugs, anti-D injection ……..).
- Natal and postnatal history including, gestational age, complication during Labour or delivery, history of prematurity or intrauterine growth retardation, gestational age at birth, birth weight, perinatal problems and postnatal course especially occurrence of neonatal hypoxia, resuscitation, pallor and jaundice.
- Developmental history (both mental and motor): age of sitting up without support, walking unassisted, first spoken word, combining words, accurate details of cognitive abilities, gross and fine motor functions, feeding disorders, abnormal sleep patterns and history of vaccination.
- Past history including: major childhood illnesses, any previous therapies used to treat the child's condition.
- Family history for any similar conditions, any genetic diseases and other psychological or mental disorders in the family.

Through clinical examination with laying stress on neurological examination.

2.1. Psychiatric evaluation

- Confirmation of diagnosis using DSM-IV-TR criteria of autism, i.e., impairments of language, social skills, and restricted stereotyped interest or activity.
- Assessment of mental age using Stanford-Binet intelligence scale (1986) [17], to calculate the intelligence quotient (IQ). This test is used to measure the child cognitive abilities. It is suitable for children aging from 2 to 16 years. The test has two items, the verbal and the performance and the test item is chosen according to the child abilities. IQ was calculated by dividing the mental age by the chronological age multiplied by 100. Subnormal intellectual function is diagnosed when IQ is below 70.
- Assessment of severity of autistic symptoms using childhood autism rating scale (CARS) [18] which rates the child on a scale from one to four in each of fifteen areas (relating to people, emotional response, imitation, body use, object use, listening response, fear or nervousness, verbal communication, non-verbal communication, activity level, and consistency of intellectual response, adaptation to change, visual response, taste, smell, touch response and general impression).

Others: include, EEG (electro encephalogram) and audiological assessment by brain stem auditory response.

***II** Statistics analysis*:

By using SPSS version 16, the differences in categorical variables between cases and control were compared with χ^2 statistics. Logistic regression analyses was used to determine the most risk factors associated with the occurrence of autism.

- For inclusion in the study, an informed written consent was obtained. The study protocol was approved by the hospital's ethical committee.

3. Results could be summarized in the following points

3.1. Sociodemographic factors

High parental age (mothers, $\geqslant$35 years; fathers, $\geqslant$35 years) at birth was found in 23% of autistic children in comparison to 9.5% of control group and the difference was statistically significant (Table 1).

3.2. The age of onset of autism

Forty six percent of our autistic patients presented at age of one and half years, 32% at age of 2 years, 18% at age of 3 years and 4% at age of 4 years.

3.3. Presenting symptoms

In 72% of our patients, the condition presented with delayed speech, in 11% started with tendency to play alone, in 9% with inattention to mother, and in 8% with loss of eye contact (Fig. 1).

3.4. The education level in autistic patients

One third of cases (36%) were in school of special needs, 25% were in normal schools with shadow, 17% were in kinder

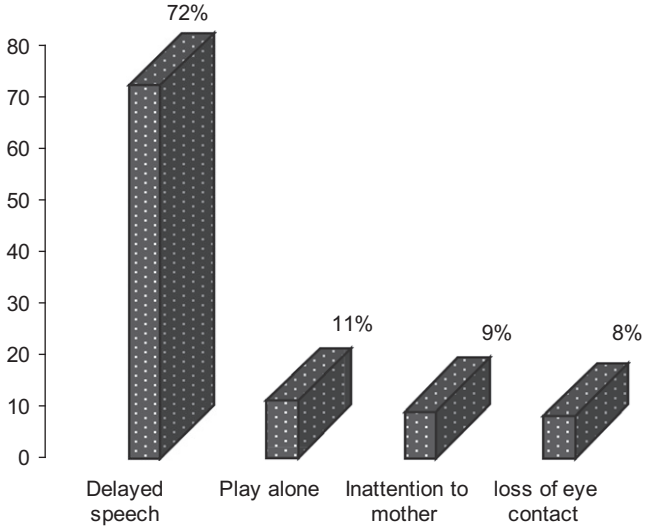

Figure 1 The specific presenting symptoms of autism.

Table 1 Comparison between cases and controls as regards some socio-demographic factors.

Item	Cases (No. 100)		Control (No. 200)		Chi square	*p*-value
	No.	(%)	No.	(%)		
Maternal age at birth						
> 35 years (35–42)	23	(23.0)	19	(9.5)	10.324	0.001*
Paternal age at birth						
> 35 years (36–62)	91	(91.0)	167	83.5)	31.447	0.000*
Sex						
Male	82	(82.0)	144	(72.0)	0.463	0.496
Family history of similar conditions						
Positive	16	(16.0)	2	(1.0)	26.886	0.000*
Consanguinity						
Positive	13	(13.0)	43	(21.5)	3.041	0.081

* Highly Sig.

garden, 9% were in normal school without shadow and 13% were not attached to school.

Clinical examination showed that few cases had congenital anomalies (1%) and dysmorphic features (2%), 5% had diminished motor power, 17% had abnormal gait in the form of toe walking, 18% had delay in bowel control (11% had enuresis and 7% had encopresis between ages of 4–7 years, 31% had a diffuse epileptogenic focus in EEG, 38% had abnormal sensations, 56% with stereotyped movements, and 70% were hyperactive (Fig. 2).

3.5. Developmental milestones

All studied developmental milestones were delayed among autistic children than control group. The difference was statistically significant ($p = 0.000$) (Table 2).

3.6. Prenatal, natal and postnatal factors

- No significant difference between cases and controls as regards prenatal factors, except history of threatened abortion which was reported in 11% of cases in comparison to 2.5% of controls and the difference was statistically significant ($p < 0.01$) (Table 3).
- As regards natal factors, a history of low birth weight and delivery by ceserian section or instrumental tools were significantly higher among cases than controls. Postnatal factors as history of hypoxia and neonatal jaundice were statistically significantly increased in cases than in controls, i.e., they carry a risk for autism ($p = 0.000$) (Table 3).

3.7. The degree of CARS in autistic patients

Fifteen of our patients (15%) had mild degree of autism with CARS (21–27), 28% with moderate degree of autism (28–33) and 57% with severe autism ($\geqslant 34$) (Table 4).

3.8. The degree of IQ in autistic group

There were 55% of our patients with mild to severe mental retardation (IQ = 20–70), 36% with below average mentality (IQ = 71–89) and 9% with normal mentality (IQ = 90–109) (Table 5).

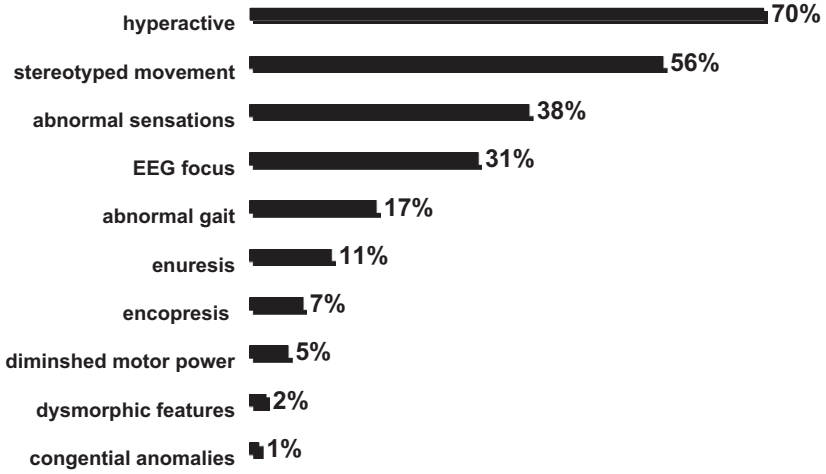

Figure 2 Clinical findings among autistic children.

Table 2 Comparison between cases and controls as regards developmental milestones.

Item	Cases (No. 100)		Control (No. 200)		Chi square	*p*-value
	No.	(%)	No.	(%)		
Afraid	41	(41.0)	36	(18.0)	18.917	0.000*
No wave bye-bye	58	(58.0)	3	(1.5)	1.325	.000*
NO Recognition of mothers	53	(53.0)	0	(0.0)	1.298	.000*
Delayed developmental milestones						
• Delayed walking	22	(22.0)	0	(0.0)	47.932	.000*
• Delayed sitting	13	(13.0)	0	(0.0)	28.682	.000*
• Delayed head support	12	(12.0)	0	(0.0)	25.243	.000*
Hand writing						
• Rt.	91	(91.0)	172	(86.0)	2.158	.340
• Lt.	6	(6.0)	22	(11.0)		
• No writing	3	(3.0)	8	(4.0)		

Table 3 Comparison between cases and controls as regards some prenatal, natal and post natal risk factors.

Item	Cases (No. 100)		Control (No. 200)		Chi square	*p*-value
	No.	(%)	No.	(%)		
Prenatal maternal factors						
• Threatened abortion	11	(11.0)	5	(2.5)	9.688	.002*
• Hypertension	4	(4.0)	11	(5.5)	.296	.586
• DM	0	(0.0)	7	(3.5)	3.548	.060
• Drug	8	(8.0)	24	(12.0)	1.064	.302
• Anti-D	2	(2.0)	15	(7.5)	3.707	.054
• Rash (mother)	1	(1.0)	5	(2.5)	.748	.387
• Infection	1	(1.0)	4	(2.0)	.395	.530
Natal						
• Pre-term (< 37 weeks)	6	(6.0)	13	(6.5)	.022	.883
• *Delivery method*						
Normal vaginal	54	(54.0)	151	(75.5)	19.535	.000*
Cesarean section	39	(39.0)	50	(25.0)		
Instrumental	7	(7.0)	1	(0.5)		
• *Birth weight*						
Normal	86	(86.0)	182	(91.0)	7.057	.029*
High birth weight	4	(4.0)	13	(6.5)		
Low birth weight	10	(10.0)	6	(3.0)		
Post natal factors						
• Hypoxia	12	(12.0)	3	(1.5)	15.667	.000*
• +ve resuscitation	11	(11.0)	2	(1.0)	16.270	.000*
• Neonatal jaundice	24	(24.0)	10	(5.0)	24.295	.000*
• Pallor	0	(0.0)	3	(1.5)	1.500	.221
• Routine vaccine	84	(84.0)	183	(91.5)	7.045	.028*

* Highly Sig.

Table 4 Classifications of the patients according to CARS Scores.

Groups	Cases	
	No.	(%)
Mild (21–27)	15	(15%)
Moderate (28–33)	28	(28%)
Severe (⩾34)	57	(57%)
Total	100	(100%)

Table 5 The degree of IQ in autistic group.

Groups	Cases	
	No.	(%)
Mild to severe retardation	55	(55%)
Below average mentality	36	(36%)
Normal mentality	9	(9%)
Total	100	(100%)

3.9. The electroencephalography (EEG) abnormalities

Thirty one of cases had diffuse epileptogenic focus in EEG (Fig. 2).

Table 6 Significant risk factors of autism by using logistic regression model.

	Wald	Sig.	95.0% CI	
			Lower	Upper
Family history	12.674	.000*	3.643	86.467
Instrumental delivery	5.264	.022*	1.478	144.397
Jaundice	14.610	.000*	2.329	13.679
hypoxia	10.521	.001*	2.480	39.708
Paternal age > 35	11.730	.001*	2.445	26.740
Maternal age > 35	4.134	.032	1.079	5.443
Constant	2.352	.125		

* Highly Sig.

3.10. Significant risk factors of autism

By using logistic regression model, positive family history, instrumental methods of delivery, high paternal and maternal age (> 35), postnatal hypoxia and jaundice were associated with a statistically significantly increased risk of autism (Table 6).

4. Discussion

There is agreement amongst all professionals that autism is one of the most puzzling diseases. It is a neurodevelopmental

disorder characterized by impaired social interaction; its prevalence has surged in recent years [19].

Autism spectrum disorders (ASDs) are prevalent neurodevelopmental disorders. ASDs diagnoses are characterized by impairment in social interaction and communication, repetitive behaviours, abnormal movement patterns, and sensory dysfunction [20]. A kid who has autism has trouble in linking words to their meaning, doesn't like changes in routines, and acts in unusual ways [21]. There is increasing suspicion that autism doesn't have a single cause but it is a complex disorder with a triad of (social impairment, repetitive behaviour, communication difficulties) that have distinct causes but often co-occur [22].

Increased prevalence would suggest directing more attention towards changing environmental factors instead of continuing to focus on genetics-environmental factors that have been claimed to contribute to autism or exacerbate its symptoms. They include, certain foods [23], infectious diseases, heavy metals, solvents, diesel exhaust, and phenols used in plastic products, pesticides, alcohol, smoking, and vaccines [21]. So autism is considered one of the pervasive developmental disorders which represent a group of clinical syndromes that have two fundamental elements, developmental delay and developmental deviations [24].

Our results pointed to the higher risk of autism in boys than girls. This finding was consistent with that reported by Itzchak et al. [25] who found 461 children (81%) out of 564 participants were male autistic patients. Shu et al. [26] said that autism is more than twice as common in boys as girls, and this ratio increases to 5:1 at the high-ability end of the autism spectrum.

Our results revealed that 48 cases of autistic patients were of high social class as most of their parents are professional (doctors and engineers). According to CARS Scores 57% of our cases had severe degree of autism, 28% had moderate degree, and 15% had mild degree. Ninety one percent of our patients are right handed. Most of parents of our patients (87%), are non consanguineous. Similar findings were reported by many authors. [27,28]. Family history of autism was reported in 16% of cases versus 1% of control. Muhle et al. [29] suggested that families of individuals with autism tend to demonstrate a set of cognitive disorders that are not seen in other family groups.

In the current study most of our patients presented at age of 18–36 months, where 46% of our patients presented at age of 18 months, 32% at age of 2 years, 18% at age of 3 years and only 4% presented at age of 4 years. These findings are in agreement with Gray and Tonge [30] who found that parents become concerned about autistic behaviour at the age of 12–30 months. On the other hand, Mandell et al. [31] found that there is often wide variation in the age which children present for diagnosis or to obtain necessary therapy, in different socioeconomic groups. Paul et al. [32] reported that the median age of identification was 5.7 years. Parametric survival models revealed that several factors were associated with a younger age of identification: being male, having an IQ of 70 or lower. Katazyna et al. [33] reported that the earliest symptoms of autism often appear before a child's second birthday, but most children with autism are not diagnosed until they are in preschool or elementary school.

In seventy two percent of our patients the condition presented with delayed speech, in 11% symptoms started with like to play alone, in 9% the condition presented with inattention to mother, and in 8% with loss of eye contact. Noens et al. [34] reported that about a third to a half of individuals with autism do not develop enough natural speech to meet their daily communication needs. Also Volkmar and klin [2] concluded that social impairments were recognizable in ASDs diagnosed children as poor eye contact, inability to utilize nonverbal gestures, and inability to play the same way as typically developing children. Another study by Zhongguo [35] reported that children with autism presented a series of abnormal behaviours, including no social smile, no eye contact, no respond to own name and delay in language.

Thirty Six percent of our patients were attached to schools of special needs, 25% were in normal schools with shadow, 17% in kinder garden, 13% not attached to any school and 9% in normal schools without shadow. Treatment and education of autistic and related communication handicapped children (TEACCH) is a service, training, and research program for individuals of all ages and skill levels with autism spectrum disorders. Kielinen et al. [36] found that 43.9% of 187 children with autism aged between 3- and 18-years-old in their study in northern Finland were receiving TEACCH. Some improvement was reported, and were further compromised by the fact that 82.9% of those in the study were receiving more than one intervention. In general, children with autism perform best in closely supervised curriculum, which is structured, involve a degree of repetition and has small teacher: student's ratio.

Our study showed that high parental age (mother $\geqslant$35 years, father, $\geqslant$35 years) at birth was found in 23% of autistic children in comparison to 9.5% of control group and the difference was statistically significant. Reichenberg et al. [37] 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. In agreement to these results Kolevzon et al., [8] found that the parenteral characteristic associated with an increased risk of autism and autism spectrum disorders include advanced maternal age, and paternal age. Another study by Marissa et al. [38] concluded that advanced maternal age, rather than paternal age, may pose greater risk for autism.

All studied developmental milestones were delayed in our autistic children than control group. The difference was statistically significant. In agreement to our findings, Filipek et al. [39] reported some of noted behaviours in autism which include: delayed speech and language skills, doesn't point or wave "bye-bye". Mc Partland [40] found that children with autism may be delayed in acquiring motor activity, such as bicycle riding. They may be poorly coordinated or have an abnormal gait or posture, poor hand writing. Also our results are in agreement with June et al. [41] who said that about 96% of autistic children had motor developmental delay. Qualitative impairment in social interaction and communication was also more commonly observed than restricted interests and activities.

As regards natal factors, history of low birth weight and using instrumental tools during delivery were significantly higher among our cases than controls .Our results dealing with postnatal factors as history of hypoxia, resuscitation, history of neonatal jaundice were also statistically significantly

increased in autistic patients ($p = 0.000$). Kolevzon et al. [8], suggested the presence of nonheritable prenatal, and perinatal risk factors for autism. A possibility supported by study Bolton et al. [42] demonstrated an association between autism and obstetric complications, prenatal or intrapartum use of medications. Burd et al. [43] reported that perinatal risk factors as breech presentation, low Apgar score ($\leqslant 7$) at 5 min, low birth weight ($\leqslant 2500$ g), gestational age at birth of less than 35 weeks, and being small for gestational age were associated with a statistically significantly increased risk of autism.

Also Rikke et al. [44] conducted a population-based matched case-control study of 473 children with autism and 473 matched controls. They found an almost fourfold risk for infantile autism in infants who had hyperbilirubinemia after birth (OR 3.7 [95%CI1.3,10.5]). Their findings suggest that hyperbilirubinemia in the neonatal period is an important factor to consider when studying causes of infantile autism. However, Lisa et al. [45] reported that neonatal hyperbilirubinemia is not a risk factor for Autism Spectrum Disorders.

In our study, 55% of our patients presented with mild to severe mental retardation, 36% with below average mentality and 9% with normal mentality. This is in accordance with Baron-Cohen et al. [46] who reported that autistic children have spectrum of IQ ranged from 0 to 60.

In the current study, 31% of autistic children had epileptic focus in EEG, with and without a history of convulsions .In accordance with Kagan-kushnir et al. [47] who found that seizures are common in ASD, occurring in approximately 20–30% of patients. A research by Blatt [48] explaining the reason of the high seizure rate in individuals with autism is that because of the decreased of GABA which is an important inhibitory neurochemical in the CNS. Also in accordance to our results Ballaban and Tuchman [49] found that 64 patients with autism out of 316 children evaluated for ASD had EEG findings. These findings confirm the importance of ongoing medical follow-up for children with ASDS, especially for those with abnormal EEG results. Hara [50] said that, seizures occur in autistic children most commonly of generalized type and reported that epilepsy is one of the negative factors of cognitive, adaptive and behavioral outcomes for individuals with autism.

5. To conclude

Autism is one of five disorders that falls under the umbrella of Pervasive Developmental Disorders (PDD), a category of neurological disorders characterized by "severe and pervasive impairment in several areas of development." Evidence to suggest that male children, high parental age, consanguinity, positive family history, being small for gestational age, postnatal hypoxia, jaundice and obstetric conditions are associated with an increased risk of autism and ASDs. Although not proven as independent risk factors for autism, these variables should be examined in future studies that use large, population-based birth cohorts with precise assessments of exposures and potential confounders.

6. Recommendations

- Early detection of cases of autism through:
- National screening program (CHAT) for preschoolers and increase the awareness of populations and families by the early symptoms and signs of autism as delayed speech and loss of eye to eye contact.
- All children should be screened with a standardized developmental tools at specific intervals (at the 9–18–24–30 months) for early detection of ASDs.
- Proper management of autistic children including behavior, educational, cognitive and pharmacotherapy through expanding and fortifying the autism specialized rehabilitation centers.

7. Conflict of interest

The authors declare that there is no conflict of interest.

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