

High autism risk in children

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Background

Autism is a chronic and lifelong pervasive neurodevelopmental disorder that affects children's social, language/communication, and behavioral development. Risk factors for autism include prenatal, perinatal, and neonatal factors, whereas early detection of autism includes impairment of language and communication characteristics.

Aim of the study

The aim of the study was to identify the risk factors for autism.

Patients and methods

This study included 43 autistic children collected from psychiatric and pediatric clinics in Al-Ahsa Hospital (Al-Ahsa City, KSA). Autistic children were diagnosed clinically and confirmed by application of Autism Diagnostic Observation Schedule-Generative. The study also included 43 age-matched children who came for vaccination as a control group. Unfavorable prenatal, perinatal, and neonatal events and language and communication difficulties were examined and compared in both groups.

Results

The majority of the autistic group were boys 34 (79.07%) in comparison with 24 boys (55.81%) in the control group ($P=0.0213$). The maternal age above 35 years was found in 17 (39.53%) patients in the study group versus five (11.63%) in the control group ($P=0.0030$). Among the autistic children, the rate of uterine bleeding 17 (39.53%), prolonged labor 18 (41.86%), low birth weight 11 (25.58%), and birth hypoxia 12 (27.91%) was significantly more than in the control group [4 (9.3%), 7 (16.28%), 3 (6.98%), and 4 (9.3%), respectively]. In the autistic group, family discord 23 (53.49%) and family move 17 (39.54%) were more frequent than in the control group [12 (27.91%) and 5 (11.63%), respectively]. Reciprocal social skills were less frequent in autistic children 17 (39.54%) than in the control group children 31 (72.09%), whereas lack of social smile, poor eye contact, and language delay were more frequent among autistic children [23 (53.49%), 21 (48.84%), and 35 (81.4%), respectively] than in the control group children [9 (20.93%), 7 (16.28%), and 8 (18.61%), respectively].

Conclusion

Study of risk factors for autistic disorder and follow-up assessment enable early diagnosis of autism in younger children, leading to earlier intervention and assistance for an improved prognosis and long-term outcome.

Keywords:

autism, childhood, high risk

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Introduction

Autism is a severe developmental disorder that involves impaired social interaction and social withdrawal, verbal and nonverbal communication deficits, and stereotypic/repetitive patterns of behavior or interests [1,2]. It is a complex, behaviorally defined, static disorder of the immature brain, which is of great concern because of an astonishing reported increase in prevalence to be higher than that of spina bifida, cancer, or Down syndrome, and this jump is probably attributable to heightened awareness and changing diagnostic criteria rather than to new environmental influences [3].

The complex nature of autistic disorders, coupled with a lack of biologic markers for diagnosis and changes in

clinical definitions over time, creates challenges in monitoring the prevalence of autism. The age at identified peak prevalence of autism in children was 8 years [4]. Because autistic disorder is one of the major challenges in child mental health, it is extremely important to get more understanding of its causes [5].

Although autism is a global disorder, relatively little is known about its presentation and occurrence in many developing countries, such as Saudi Arabia [6]. Over the past decades, much research has been conducted to elucidate a single etiological factor and effective pharmacotherapeutics to address the core symptom domains of autism with limited success [7]. Neuropsychiatric research should capitalize on the tendency of particular

abnormalities of behavior, such as autism, to run in families [8]. Psychiatric problems are common in autistic disorders, but the reasons are poorly understood [9].

Progress has recently been made in the earlier identification of children with autistic disorder. Early diagnosis and referral to treatment before age of 3 years improve the prognosis of children with autism. However, autism is often not diagnosed until an age of 3–4 years, and medical providers may lack training to offer caregivers evidence-based treatment recommendations [10].

The American Academy of Pediatrics' recommendations should be applied in Saudi Arabia to help improve the average age at diagnosis and make a positive effect on children with autism and their families [11].

Multidisciplinary diagnostic assessment of autism should include detailed information on developmental history, parents' descriptions of the everyday behavior and activities of the child, direct assessment of the child's social interaction style, including where possible with age peers, and formal assessment of communicative, intellectual, and adaptive functions [12]. Clinical assessments need to concentrate on the identification of impairments in early nonverbal social communication behaviors that characterize children with autism from the second year of life, including social orienting, imitation, play, and reciprocal affective behavior [13].

The particular pattern of symptoms that presents in a 2-year-old child with autism may differ from that seen at the more prototypic age of 4 or 5 years. In particular, overt repetitive and stereotyped behaviors may be less notable; although these are seen alongside the social and communicative impairments, they are highly indicative of autistic disorder [14]. Despite evidence for the association of some prenatal, perinatal, and neonatal risk factors with autism, it remains unclear whether these risks are causal or play a secondary role in shaping clinical expression in individuals with genetic vulnerability [15]. It is now believed that the mechanism underlying autism etiology is most likely polygenic and potentially epistatic and that the environmental factors may interact with genetic factors to increase the risk [16].

Aim of the study

The purpose of this study was to explore the possible risk factors in children with autistic disorder versus controls.

Patients and methods

A total of 43 autistic children, 32 boys and 11 girls between the age of 3–8 years, presented to the psychiatric and pediatric clinics in Al-Ahsa Hospital (Al-Ahsa city, KSA). The study design was approved by the institutional ethics committee and review board. Age-matched 43 children without any psychiatric or medical disorders or developmental delay who came for vaccination were collected as a control group. The

participants were enrolled in this cross-sectional study during the period from February 2010 to January 2012. All parents or guardians signed informed consent. All autistic and control group children and their parents were subjected to semistructured psychiatric interview and complete pediatric history. All studied children were subjected to thorough pediatric examination. Unfavorable prenatal, perinatal, and neonatal events in the birth records of all studied children were examined. Early social, language, and communication difficulties were reported. The rate of those factors was compared in both groups.

Diagnosis of autism was made according to the *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Text Revision (DSM IV-TR) and was confirmed by application of Autism Diagnostic Observation Schedule-Generic (ADOS-G), which is a semistructured, standardized assessment of social interaction, communication, play, and imaginative use of materials for individuals suspected of having autism. The observational schedule consists of four 30-min modules. During administration of the tool, only one module is given to an individual and module selection is based on the individual's expressive language level rather than the individual's age. Each item on the ADOS-G is scored on a three-point scale. A score of 1 indicates no evidence of abnormal behaviors related to autism, a score of 2 indicates that abnormal behaviors are present, and a score of 3 indicates the presence of severe abnormalities. ADOS-G provides cutoffs for behaviors consistent with autism, and children who score lower than these cutoffs are interpreted as not presenting behaviors consistent with a diagnosis of autism [17]. ADOS-G indicates excellent inter-rater reliability within domains and excellent internal consistency [18], with quite good sensitivity, specificity, and positive and negative predictive values [19].

Statistical analysis

All statistical calculations were performed using computer program Microsoft Excel version 7 (Microsoft Corporation, New York, New York, USA) and statistical package for the social science version 13 (SPSS Inc., Chicago, Illinois, USA) statistical program. Data were statistically described in terms of number and percentage. Comparison of the studied groups was carried out using the χ^2 -test to compare categorical variables. A *P*-value less than 0.05 was considered statistically significant.

Results

Following diagnostic assessment, the 43 children fulfilling the DSM IV-TR criteria for autism confirmed by application of ADOS-G were compared with the 43 children who were enrolled as a control group.

Table 1 shows the sociodemographic characteristics of autistic children and the control group and their parents. Children in both groups were age matched with a mean age of 3.7 ± 1.2 and 3.5 ± 1.3 years for autistic children and the control group, respectively. The number of boys was significantly higher in the autistic group than in the control group ($P = 0.0213$). History of autistic sibling was

Table 1 Sociodemographic characteristics of autistic children and controls and their parents

Sociodemographic characteristics	N (%)		P-value
	Autistic children (N=43)	Control group (N=43)	
Sex of the child			
Boy	34 (79.07)	24 (55.81)	0.0213*
Girl	9 (20.93)	19 (44.19)	0.0213
Other autistic sibling	11 (25.58)	1 (2.33)	0.0016
Parents socioeconomic status			
Low	16 (37.21)	17 (39.54)	0.8245
Moderate	15 (34.88)	13 (30.23)	0.6453
high	12 (27.91)	13 (30.23)	0.8122
Age of mother (> 35 years)	17 (39.54)	5 (11.63)	0.0030*
Age of father (> 45 years)	11 (25.58)	10 (23.26)	0.8018

P-value is considered significant if <0.05.

Table 2 Shows prenatal, perinatal, and neonatal factors in autistic children and in the control group

Factors	N (%)		P-value
	Autistic children (N=43)	Control group (N=43)	
Prenatal factors			
Smoking	6 (13.95)	5 (11.63)	0.7467
Gestational age <37 weeks	13 (30.23)	14 (32.56)	0.8162
Uterine bleeding	17 (39.54)	4 (9.3)	0.0011*
Pre-eclampsia	3 (6.98)	2 (4.65)	0.6449
Perinatal factors			
Breech presentation	7 (16.28)	1 (2.33)	0.0259*
Prolonged labor	18 (41.86)	7 (16.28)	0.0089*
Cesarean section	8 (18.61)	9 (20.93)	0.7865
Cord complication	6 (13.95)	1 (2.33)	0.0178*
Birth injury	5 (11.36)	2 (4.65)	0.2367
Neonatal factors			
Low birth weight	11 (25.58)	3 (6.98)	0.0194*
Oxygen requirement	12 (27.91)	4 (9.3)	0.0266*
Birth defect	5 (11.63)	4 (9.3)	0.7246
Hyperbilirubinemia	14 (32.56)	15 (34.88)	0.8195

P-value is considered significant if <0.05.

significantly more common in autistic children than in the control group ($P = 0.0016$). There was no statistically significant difference between both groups regarding the parent's socioeconomic status. The prevalence of mothers aged above 35 years was more in the autistic than in the control group ($P = 0.0030$), but there was no difference between both study groups regarding the prevalence of fathers aged above 45 years.

Table 2 shows prenatal, perinatal, and neonatal factors in autistic children and in the control group. With respect to the prenatal factors, there was no statistically significant difference between the study groups except in the incidence of maternal uterine bleeding ($P = 0.0011$). With respect to the perinatal factors, there was a higher incidence of breech presentation, prolonged labor, and cord complications in the autistic group than in the control group ($P = 0.0259$, 0.0089 , and 0.0178 , respectively), but there was no statistically significant difference between both groups regarding the rate of cesarean section or birth injury. With respect to the neonatal factors, in the autistic group, children with low birth weight and those who required oxygen were more

Table 3 Shows related environmental factors in autistic children and in the control group

Factors	N (%)		P-value
	Autistic children (N=43)	Control group (N=43)	
Child receiving skills	3 (6.98)	13 (30.23)	0.0056*
Psychosocial stress	12 (27.91)	11 (25.28)	0.6075
Family discord	23 (53.49)	12 (27.91)	0.0157*
Birth of a new sibling	13 (30.23)	13 (30.23)	1
Family move	17 (39.54)	5 (11.63)	0.0030*

P-value is considered significant if <0.05.

Table 4 Early behavioral and language characteristics of autistic children and the control group

Factors	N (%)		P-value
	Autistic children (N=43)	Control group (N=43)	
Reciprocal social skills (relatedness to parents and peers)	17 (39.54)	31 (72.09)	0.0023*
Lack of social smile	23 (53.49)	9 (20.93)	0.0018*
Poor eye contact	21 (48.84)	7 (16.28)	0.0013*
Anxiety due to disrupted routine	7 (16.28)	6 (13.95)	0.7633
Language delay	35 (81.4)	8 (18.61)	<0.0001*

P-value is considered significant if <0.05.

prevalent than in the control group ($P = 0.0194$ and 0.0266 , respectively). The frequency of birth defects or neonatal hyperbilirubinemia showed no statistically significant difference between the study groups.

Table 3 shows related environmental factors in autistic children and in the control group.

The children who received social skills were more prevalent in the control group than in the autistic group ($P = 0.0056$). There was no statistically significant difference between both groups regarding psychological stresses and birth of a new sibling. Family discord and history of family move were significantly more frequent in the autistic group than in the control group ($P = 0.0157$ and 0.0030 , respectively).

Table 4 shows early behavioral and language characteristics of autistic children and the control group. Reciprocal social skills were less common in the autistic group than in the control group ($P = 0.0023$), whereas lack of social smile, poor eye contact, and language delay were more common in the autistic group than in the control group ($P = 0.0018$, 0.0013 , and 0.0001 , respectively). Anxiety due to disrupted routine in the autistic group and in the control group was near to each other, with no statistically significant difference.

Discussion

The increasing recognition of the benefits of early intervention for children with autism stresses the importance of risk factors identification and early detection of signs and symptoms of autistic disorder.

The present study demonstrated that the mean age at autism diagnosis was 3.7 ± 1.2 years, parallel to the results of Planche *et al.* [20] who found that most children with autism would be reported to be diagnosed around the age of 3–4 years. Some possible reasons for a delay in diagnosis are: professionals may be concerned about the strong emotional reaction of parents when they are told that their child has autism, fear of negative consequences from labeling the child, and hope that the symptoms will reverse.

Data from this study revealed that the prevalence of autism is much more common in boys (79.07%) than in girls (20.93%), consistent with the results of previous studies [21,22].

In the current study, autistic siblings were markedly involved in the autistic group (25.58%) compared with the control group (2.33%), supporting the data of Simonoff *et al.* [9] who mentioned that multiple lines of evidence have supported a substantial heritable component of autism etiology for decades, including sibling studies. Abrahams and Geschwind [23] also mentioned that autism has a strong genetic basis, although complex and unclear, but is explained more by rare mutations or by rare combinations of common genetic variants.

The results of this study revealed no role for the parents socioeconomic class to be considered as a risk factor in autistic children [low (37.21%), moderate (34.88%), and high (27.91%)] versus control children [low (39.54%), moderate (30.23%), and high (30.23%)], similar to the description by Volkmar *et al.* [21] who said that, over the past 25 years, no epidemiological studies have demonstrated an association between autistic disorder and any socioeconomic status. Contrary findings have been observed by Kogan *et al.* [24] who stated that children with autism were more likely to live in families that report financial problems. Those contradictory findings may be explained by cultural and socioeconomic differences.

In our results, it is common to find mothers of autistic children above the age 35 years (39.54%) compared with the control group (11.63%), which is in agreement with the findings of Sandin *et al.* [25] who reported in their meta-analysis that there is an association between advancing maternal age, especially above the age of 35 years and risk for autism. However, the role of paternal age in autism in our study was null in comparison with the control group (fathers above the age of 45 years in the autistic and control group were 25.58 and 23.26%, respectively), but the reverse was found in the study by Hamlyn *et al.* [26] who said that advanced paternal age was considered a risk factor for autism.

Data from this study denoted that there is no significant difference in the frequency of smoking mothers in the autistic group (13.95%) and in the control group (11.63%), whereas contradictory results were obtained by Visser *et al.* [27] who observed that there is maternal higher exposure to smoking during pregnancy in autistic disorder children compared with the normal group.

On the basis of the present study, we recognized that the gestational age was less than 37 weeks in 30.23% of the autistic group and 32.56% of the control group, with no significant difference, whereas reverse data gathered by Leavey *et al.* [28] confirmed the role of shortened gestation in autism risk.

To gain more insight to the role of uterine bleeding in autistic disorder, in our results, history of uterine bleeding was much more common in the autistic group (39.54%) than in the control group (9.3%), which goes hand in hand with the results of Juul-Dam *et al.* [29] who mentioned that autistic children have a significantly higher incidence of uterine bleeding when compared with the general population.

With respect to the perinatal factors, there was a higher incidence of breech presentation, prolonged labor, and cord complications in the autistic group than in the control group ($P = 0.0259$, 0.0089 , and 0.0178 , respectively), but there was no statistically significant difference between both groups regarding the rate of cesarean section or birth injury. This goes along with the results of other studies [15,30,31].

Data gathered from the present study revealed no significant difference between the frequency of birth injury among the autistic group (11.36%) and the control group (4.65%), whereas the reverse was recognized by May-Benson *et al.* [32] who reported that birth-related injury is one of the risk factors for autism.

Children with low birth weight and those who required oxygen were more prevalent in the autistic group than in the control group ($P = 0.0194$ and 0.0266 , respectively), which is consistent with the meta-analysis study that found low birth weight as well as exposure to hypoxia at birth as risk factors for autism [31].

We did not find any significant difference between the rates of birth defects in the autistic group (11.63%) and the control group (9.3%), whereas Guinchat *et al.* [15] reported that it is common to identify birth defect in autistic children compared with general population.

This study suggests no significant difference in the frequency of hyperbilirubinemia among the autistic group (32.56%) and the control group (34.88%), whereas Juul-Dam *et al.* [29] showed a higher incidence of hyperbilirubinemia in autistic children when compared with the general population.

One of the plausible hypotheses to interpret the previous results is that improvements in obstetric and neonatal management have led to an increased rate of survivors with pre-existing brain damage.

The current study revealed that the rate of children receiving skills among the autistic group (6.98%) was significantly lower than that of the control group (30.23%), which is in agreement with the finding of Grindle *et al.* [33] in that the children who learned new skills by the end of 1 year and additional skills during the second year were associated with positive changes regarding social interaction and communication.

Our findings revealed that family discord was more common among the autistic group (53.49%) compared with the control group (27.91%), similar to the results of Hastings and Johnson [34] who noticed that the level of family discord is high, up to 70% of mothers and 40% of fathers of autistic children.

Our study denoted that the rate of family move among the autistic group (39.54%) was more frequent than the control group (11.63); however, Sadock *et al.* [35] mentioned that children with autistic disorder can respond with exacerbated symptoms to a family move.

The present study identified that the autistic children have poor reciprocal social skills (39.54%) compared with the control group (72.09%), a finding that goes along with another study which found that autistic children do not exhibit the expected level of subtle reciprocal social skills that demonstrate relatedness to parents and peers [36].

On the basis of our gathered data, lack of social smile, poor eye contact, and language delay were more common in the autistic group than in the control group ($P = 0.0018$, 0.0013 , and 0.0001 , respectively), which is in agreement with findings of other studies [37,38].

Interpretation of the meaningfulness of many results of this study is difficult, as the specific complications that carried the highest risk of autism represented various forms of pathologic processes with no presently apparent unifying feature; however, methodological variations including diagnostic criteria, comparison groups, sample size, and exposure-assessment methods were also likely sources of heterogeneity of risk factor effects across studies.

Conclusion and recommendations

Our findings support several prenatal and infantile risk factors for autism; therefore, it is recommended to perform follow-up assessment to children who were exposed to prenatal, perinatal, and neonatal adverse events.

Early detection of children with autism enables them to be evaluated and entered into treatment programs at the earliest possible opportunity, as many studies show that these children benefit from beginning intensive early intervention as soon as possible.

Diagnosis of autism in children several months after birth may give the chance to design interventions that will arrest the disorder before it develops; however, having a solid enough diagnostic marker for early diagnosis of the disorder is still a far cry.

A developmental 'window' – that is, the readiness of the brain for a specific learning – is open only for a certain period; when that opportunity is missed, the learning is likely to be limited despite the best efforts. Hence, the earlier the diagnosis, the better the prognosis.

The public should learn and receive more information about risk factors and early manifestation of autism for the sake of early diagnosis and intervention.

A larger sample size, from multiple sites, is needed to improve the statistical power of such studies and to validate or refute their findings.

Given the variety of risk factors, we propose that future studies should investigate combinations of multiple factors rather than focusing on a single factor.

Limitations

- (1) Overreporting an error could occur when we relied on parent reports (retrospective parental recall) or health records, which have been shown to inflate estimates.
- (2) Small sample size.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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المخلص العربي

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**قسم طب الأطفال – كلية الطب – جامعة أسيوط

المستخلص:

الخلفية: التوحد هو اضطراب مزمن مدى الحياة ومتغلغل في نمو الجهاز العصبي و الذي يؤثر علي اجتماعيات الطفل وكلامه وتواصله مع الاخرين وكذلك نموه السلوكي.ان عوامل الخطر لمرض التوحد تشمل عوامل ما قبل الولادة،وأثناء الولادة وبعدها بينما الكشف المبكر عن مرض التوحد يشمل اضطراب خصائص اللغة والتواصل.

الهدف من البحث: تحديد عوامل الخطر لمرض التوحد.

المرضى والطرق: لقد اشتملت هذه الدراسة علي 43 طفل تم تجميعهم من العيادات النفسية والأطفال في مستشفى الأحساء مدينة الأحساء-المملكة العربية السعودية.و تم تشخيص الأطفال المصابين بالتوحد سريريا، وتأكد ذلك من خلال تطبيق الجدول الزمني العام لمراقبة و تشخيص التوحد (ADOS-G). وشملت الدراسة أيضا 43 طفل اعمارهم متطابقة جاؤا للتطعيم كمجموعة تحكم. تم فحص الأحداث غير المواتية قبل الولادة،وأثناء الولادة وبعدها والصعوبات اللغوية والتواصل و تم مقارنة كلتا المجموعتين.

النتائج : وكان غالبية المصابين أولاد 34 (79.07%).وكانت أعداد الأمهات اللاتي بلغن فوق سن 45 سنة اكثر في مجمعة أطفال التوحد 17 (39.53%) عنهم في مجموعة التحكم 5 (11.63%). وكان بين الأطفال الذين يعانون من التوحد، كانت نسبة نزيه الرحم 17 (39.53%)، و طول فترة الولادة 18 (41.86%)، وانخفاض الوزن عند الولادة 11 (25.58%) ونقص الأكسجين عند الولادة 12 (27.91%) أكثر من مجموعة التحكم 4 (9.3%) و 7 (16.28%)، و 3 (6.98%)، و 4 (9.3%) على التوالي]. وفي مجموعة المصابين بالتوحد كانت المشاكل الأسرية 23 (53.49%) وتنقل الأسرة 17 (39.54%) أكثر تكرارا من مجموعة التحكم 12 (27.91%) و 5 (11.63%) على التوالي]. كانت المهارات الاجتماعية المتبادلة أقل تكرارا في الأطفال المصابين بالتوحد 17 (39.54%) من أطفال مجموعة التحكم 31 (72.09%)، في حين عدم وجود الابتسامة الاجتماعية، وسوء التواصل البصري وتأخير اللغة كانت أكثر شيوعا بين الأطفال المصابين بالتوحد 23 (53.49%)، 21 (84.48%) و 35 (81.4%) على التوالي]. من أطفال مجموعة التحكم 9 (20.93%)، و 7 (16.28%) و 8 (18.61%) على التوالي].

الخلاصة: دراسة عوامل الخطر لاضطراب التوحد ومتابعة التقييم تساعد علي التشخيص المبكر لاضطراب التوحد في الأطفال الأصغر سنا، مما يؤدي إلى التدخل والمساعدة في وقت سابق لتحسين التكهن بالنتائج على المدى الطويل.