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Original Article

Autism Spectrum Disorder and Associated Risk Factors: A Matched Case-Control Study

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Abstract

Background and aims: Despite substantial advances in the etiology of autism spectrum disorder (ASD), the environmental risk factors have not yet been well understood. The present study investigated the association between ASD, and maternal and perinatal risk factors.

Methods: This matched, case-control study was conducted in Hamadan, the west of Iran, from November 2015 to May 2016. We enrolled 41 children with ASD aged 3-17 years. We selected four controls per one case from the same hospital where patients were born. Controls were separately matched with cases for sex, age, and birth year.

Results: We compared 41 ASD cases with 164 controls. After adjusting the odds ratio (95% CI), ASD was significantly associated with third-degree relatives consanguinity [3.29 (1.39, 7.75)], short birth length [4.99 (1.15, 21.60)], short head circumference [7.87 (1.48, 41.76), respiratory distress syndrome at birth 3.97 (1.91, 8.22)], respiratory assistance at birth [2.92 (1.39, 6.10)], birth hypoxia [2.85 (1.35, 5.99)], and low 1-minute Apgar score [3.65 (1.04, 12.75)].

Conclusions: Our findings suggest that ASD may be associated with multiple maternal and perinatal risk factors. Evidence based on large prospective multicenter cohort studies is required to indicate the impacts of maternal and perinatal exposures.

Keywords: Autism Spectrum Disorder; Risk Factors; Case-Control Studies

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Introduction

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by impaired social communication, restricted and repetitive behaviors, and language impairment. The symptoms usually become apparent in early childhood, typically during the first three years of childhood.[1] ASD incidence is approximately four times higher in boys than that in girls.[2,3] ASD was previously thought to be a relatively rare disease, but its prevalence has increased in recent decades. According to the evidence from different parts of the world, the prevalence of ASD varies from 2 to 20 per 1000, or approximately 1/50 to 1/500 in children.[2,4-6]

The pathogenesis of ASD has not yet been well understood. The general consensus is that genetic factors play an important role in the etiology of ASD and exposure to environmental factors such as toxic substances, teratogens, and perinatal events may contribute to variable expression of the disease.[7,8] A meta-analysis of 40 studies addressed over 60 perinatal and neonatal risk factors for ASD and reported that evidence is not sufficient to raise any single factor in the etiology of the disease.[9] However, evidence based on epidemiological studies has suggested that maternal, perinatal, and neonatal factors such as hypoxia, low Apgar score, abnormal presentation, low birth weight, meconium aspiration, advanced maternal age, diabetes, obesity, and hypertension may increase the risk of developing ASD.[10-16]

Despite substantial advances in the etiology of ASD and maternal, perinatal, and neonatal exposures which have been the focus of epidemiologic studies, the environmental risk factors for this disorder have not yet been properly investigated, particularly in developing countries. Until reliable information on the modifiable risk factors for ASD is collected, it is difficult to design and conduct preventive measures. The present study sought to assess the association between ASD and several potential maternal and perinatal risk factors for the disorder.

Methods

This matched, case-control study was conducted in Hamadan, the west of Iran, from November 2015 to May 2016. The case group included children with ASD and the control group included children without ASD.

We enrolled children with ASD aged 3-17 years whose birth medical records were available. The patients who were born in other cities or their medical records were incomplete or had congenital anomalies were excluded from the study. The diagnosis of ASD was made clinically by a clinician, based on the children's complete histories, physical and neurological examinations as well as the assessment of their social, lingual, and cognitive development. The parents were also interviewed. Final diagnosis was made by clinical judgment of the clinician aided by Gilliam Autism Rating Scale, 2nd edition (GARS-2). The GARS-2 is a norm-referenced instrument that consists of 42 items helps clinicians identify and diagnose autism in individuals aged 3-22 years. The items of the GARS-2 are based on the definitions of autism adopted by the DSM-IV. The instrument addresses the typical behaviors of a person with autism, including communication and social interaction.[17]

Because the number of cases was small, four controls were selected from the same study population per each case. The controls were selected from among children who were born in the same hospital where patients were born. Controls were separately matched with cases by sex, age, and birth year.

Additional data, which were needed for this study but were not recorded in the birth medical records, were collected through interviews with parents after explaining the objectives of the study for them. Since no intervention was carried out in this study, we just took parents' verbal informed consent to participate in this study and answer to our questions.

Perinatal and neonatal information was drawn from birth medical records available at the hospital using a checklist of items according to the context of the medical records. The checklist included data on consanguinity, birth weight (g), head circumference (cm), respiratory distress syndrome at birth, respiratory assistance at birth, birth hypoxia, pathologic jaundice, gestational age (w), interval between pregnancies (year), the mother's body mass index (kg/m^2), mother's age at pregnancy, gravidity, the type of childbirth (normal vaginal delivery versus cesarean section), number of previous live births, history of stillbirth, history of abortion, having prenatal care, and using supplementary drugs during pregnancy (vitamin D, folic acid, and ferrous sulfate).

We used the chi-square test to compare categorical variables and the *t* test to compare the continuous variables. We also performed the conditional logistic regression analysis to examine the association between ASD and associated risk factors, adjusted for age, sex, and year of birth. All statistical analyses were performed at a significance level of 0.05, using Stata software, version 11 (StataCorp, College Station, TX, USA).

Results

We identified 86 ASD cases, of whom 32 subjects were born in other cities, and because their birth medical records were not available, 10 were excluded from the study because their birth medical records were not available, and 3 refused to participate in the study. The analysis was performed on data from the remaining 41 ASD cases and 164 matched controls.

The details of cases and controls, including demographic characteristics, personal information, and perinatal events are shown in Table 1. There were statistically significant differences between the case and control groups with respect to consanguinity ($P=0.001$), birth length ($P=0.016$), head circumference ($P=0.003$), infant respiratory distress syndrome at birth ($P=0.001$), respiratory assistance at birth ($P=0.005$), birth hypoxia ($P=0.007$), and low 1-minute Apgar score ($P=0.025$). There was no statistically significant difference between the two groups in terms of birth weight ($P=0.323$), pathologic jaundice ($P=0.684$), gestational age ($P=0.276$), interval between pregnancies ($P=0.558$), mother's body mass index ($P=0.929$), and advanced maternal age ($P=0.545$).

In addition, there was no significant difference between the case and control groups with respect to parity , type of delivery, number of live births, history of stillbirth, history of abortion, having prenatal care, and using supplementary drugs. These variables are not listed in Table 1. There was no positive family history of autism among cases and controls.

As shown in Table 2, after adjusting the odds ratio (95% CI) for sex, age and year of birth, ASD was found to be significantly associated with third-relatives consanguinity [3.29 (1.39, 7.75)], short birth length [4.99 (1.15, 21.60)], short head circumference [7.87 (1.48, 41.76)], respiratory distress syndrome at birth [3.97 (1.91, 8.22)], respiratory assistance at birth [2.92 (1.39, 6.10)], birth hypoxia [2.85 (1.35, 5.99)], and low 1-minute Apgar score [3.65 (1.04, 12.75)] and not significantly associated with pathologic jaundice [1.17 (0.54, 2.56)], previous term labor [3.37 (0.45, 25.00)], short interval between pregnancies [0.95 (0.08, 11.36)], high maternal body mass index [1.73 (0.10, 30.76)], and advanced maternal age [0.76 (0.31, 1.85)].

Discussion

According to our findings, ASD was associated with a number of maternal and perinatal risk factors, including consanguinity, short birth length, short head circumference, respiratory distress syndrome at birth, ventilation assistance at birth, birth hypoxia, and low

Table 1. Comparison of the Characteristics of Control Group and Case Group Using Chi-Square Test

Variables	Controls (n=164)[a]		Cases (n=41)[a]		P Value
	No.	%	No.	%	
Consanguinity					0.001
Unrelated	140	88.6	26	63.4	
Third relatives	13	8.2	10	24.4	
Fourth relatives	5	3.2	5	12.2	
Birth weight (g)					0.323
Normal (2500 to 4500)	150	99.6	36	87.8	
Low birth weight (<2500)	12	7.4	5	12.2	
Birth length (cm)					0.016
Normal (45.7 to 60.0)	136	96.5	31	86.1	
Short birth length (<45.7)	5	3.5	5	13.9	
Head circumference (cm)					0.003
Normal (32.2 to 38.5)	134	97.8	31	86.1	
Small head circumference (<32.2)	3	2.2	5	13.9	
Respiratory distress syndrome at birth					0.001
No	136	83.4	22	53.7	
Yes	27	16.6	19	46.3	
Ventilation assistance at birth					0.005
No	113	69.8	19	46.3	
Yes	49	30.2	22	53.7	
Birth hypoxia					0.007
No	116	71.2	20	48.8	
Yes	47	28.8	21	51.2	
Pathologic jaundice					0.684
No	125	76.2	30	73.2	
Yes	39	23.8	11	26.8	
Gestational age (wk)					0.276
Term (37 to 41)	143	87.2	32	78.0	
Preterm (<37)	18	11.0	7	17.1	
Post term (≥42)	3	1.8	2	4.9	
Interval between pregnancies (y)					0.558
≥2	78	97.5	19	95.0	
<2	2	2.5	1	5.0	
Maternal BMI (kg/m²)					0.929
Underweight (<18.5)	3	8.3	1	6.7	
Normal weight (18.5 to 24.9)	27	75.0	12	80.0	
Overweight/obese (≥25.0)	6	16.7	2	13.3	
Mother's age at pregnancy (y)					0.545
<35	129	78.7	34	82.9	
≥35	35	21.3	7	17.1	
1-minute Apgar score					0.025
≥8	156	96.3	34	87.2	
<8	6	3.7	5	12.8	

[a] Sum of subgroups are less than total number due to missing data.

1-minute Apgar score.

Our findings indicated that consanguinity may increase the risk of ASD by more than threefold. Genetic factors play a fundamental role in etiology of ASD.[7,8] Evidence has shown that consanguinity can increase familial clustering of multiple hereditary diseases within the same family.[18] However, it is not clear whether consanguinity can really increase the risk of ASD. Some epidemiological studies reported a positive association between consanguinity and the risk of developing ASD[19,20] but some studies have not confirmed such association.[21,22] It is estimated that the observed association may be confounded by other factors. Evidence based on large studies is required to approve the association between consanguinity and ASD.

We observed that hypoxia, respiratory distress syndrome, and ventilation assistance at birth were significantly associated with ASD. Similar finding has also been reported by several epidemiological studies.[23-25] The reason is that poor fetal oxygenation during labor and impaired respiratory gas exchange at birth may result in permanent damage to the brain and neurological impairment in the future.[26,27] Experimental evidence suggests that hypoxia-ischemia-induced cerebral atrophy and corpus callosum injury contribute to the development of learning and memory deficits.[28]

Our results suggest that children with an Apgar score of

Table 2. Association Between Autism Spectrum Disorder and Demographic, Personal, and Clinical Characteristics Using Conditional Logistic Regression Analysis

Variables	Controls (n = 164)	Cases (n = 41)	Adjusted OR (95% CI)[a]	P value
Consanguinity				
Unrelated	140	26	1.00	
Third relatives	13	10	3.29 (1.39, 7.75)	0.006
Fourth relatives	5	5	5.23 (1.19, 23.02)	0.029
Birth weight (g)				
Normal (2500 to 4500)	150	36	1.00	
Low birth weight (<2500)	12	5	1.80 (0.58, 5.57)	0.580
Birth length (cm)				
Normal (45.7 to 60.0)	136	31	1.00	
Short birth length (<45.7)	5	5	4.99 (1.15, 21.60)	0.032
Head circumference (cm)				
Normal (32.2 to 38.5)	134	31	1.00	
Small head circumference (<32.2)	3	5	7.87 (1.48, 41.76)	0.015
Respiratory distress syndrome at birth				
No	136	22	1.00	
Yes	27	19	3.97 (1.91, 8.22)	0.001
Ventilation assistance at birth				
No	113	19	1.00	
Yes	49	22	2.92 (1.39, 6.10)	0.004
Birth hypoxia				
No	116	20	1.00	
Yes	47	21	2.85 (1.35, 5.99)	0.006
Pathologic jaundice				
No	125	30	1.00	
Yes	39	11	1.17 (0.54, 2.56)	0.685
Gestational age (wk)				
Term (37 to 41)	143	32	1.00	
Preterm (<37)	18	7	1.99 (0.65, 6.09)	0.227
Post term (≥42)	3	2	3.37 (0.45, 25.00)	0.241
Interval between pregnancies (y)				
≥2	78	19	1.00	
<2	2	1	0.95 (0.08, 11.36)	0.967
Mother's body mass index (kg/m^2)				
Normal weight (18.5 to 24.9)	27	12	1.00	
Underweight (<18.5)	3	1	No data	-
Overweight/obese (≥25.0)	6	2	1.73 (0.10, 30.76)	0.708
Mother's age at pregnancy (y)				
<35	129	34	1.00	
≥35	35	7	0.76 (0.31, 1.85)	0.549
1-minute Apgar score				
≥8	156	34	1.00	
<8	6	5	3.65 (1.04, 12.75)	0.043

[a] Odds ratio adjusted for sex, age, and year of birth.

less than 8 had an OR of 3.65. Low Apgar score may lead to intellectual disability and ASD.[29,30] Although ASD has a genetic basis and exposure to maternal and perinatal risk factors has also been reported to be causal in some cases, it is unlikely that ASD is caused by a single obstetric factor.[31] Gardener et al conducted a meta-analysis to examine the association between over 60 perinatal and neonatal factors and ASD. They concluded that evidence is not sufficient to implicate any single perinatal or neonatal factor in autism etiology, but a wide spectrum of conditions during perinatal and neonatal period may increase the risk.[9]

The main limitation of this study was the small number of cases of ASD. In order to overcome this limitation, we increased the number of controls per every case to improve the statistical power. Furthermore, detailed information about some of the risk factors had not been recorded in the birth medical records. This caused certain limitations to perform data analysis and decreased the statistical power of the study. Despite these limitations, the current study shows some maternal and perinatal risk factors for ASD in a middle-income country. The results may be helpful for policymakers who plan for preventive programs and prioritize risk factors in order to reduce the burden of ASD.

Conclusion

Based on our findings, ASD may be associated with no single, but several maternal and perinatal risk factors. Although our results were statistically significant for some risk factors, evidence based on large prospective multicenter cohort studies is required to indicate whether maternal and perinatal exposures may increase the risk.

Ethical Approval

The Ethic Committee of the Hamadan University of Medical Sciences approved this study (IR.UMSHA.REC.1394.466).

Conflict of Interest Disclosures

None.

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