WORLD JOURNAL OF ADVANCE HEALTHCARE RESEARCH

SJIF Impact Factor: 5.464

ISSN: 2457-0400
Volume: 7.
Issue: 5
Page N. 64-68
Year: 2023

Original Article

www.wjahr.com

RİSK FACTORS ASSOCİATED WİTH AUTİSM SPECTRUM DİSORDERS

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Received date: 03 March 2023 **Revised date:** 24 March 2023 **Accepted date:** 14 April 2023

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ABSTRACT

Background: Autism spectrum disorder(ASD) is one of the most prevalent neurodevelopmental disorders which can affect the health related quality of life outcomes of the affected children and their families. **Objective:** The aim of this study was to identify the significance of certain risk factors for autism. **Materials and Methods:** An Analytic Case Control study was conducted in 148 patients with autism and 148 children diagnosed with other neurological conditions aged 2-10 years. They are selected from pediatric neurology clinic, Tishreen University Hospital and Centers Specialized in caring for children with autism, Syria between June 2021 and June 2022. **Result**: A total of 296 children, 215 males (72.6%) and 81 females (27.4%) with mean age 5.48± 2.1 years were included in the study. The prevalence of autism was increased significantly with decreasing of gestational age (p:0.001). Parental factors that associated significantly with autism were: paternal age older than 45 years(p:0.02), presence of consanguinity(p:0.003), family history of autism(p:0.001), parents' autoimmune disease(p:0.01), and smoking during pregnancy(p:0.001). Gestational age <37 week (OR 2.2), paternal age older than 45 years (OR 2.7), family history of autism (OR 4.3), presence of parents' autoimmune disease (OR 2.9), and smoking during pregnancy (OR 2.2) were independent factors that associated significantly with the risk of progression autism. **Conclusion:** There is an important prevalence of autism, and presence of prematurity, advanced age of father, family history of disorder, parents' autoimmune diseases, and smoking during pregnancy are all warning flags that may predispose to autism.

KEYWORDS: Autism, neurodevelopmental, risk factors, Syria.

1. INTRODUCTİON

Autism spectrum disorder(ASD) represents neurodevelopmental disorder characterized by deficits in social communication and repetitive patterns of behavior.[1] ASD is a life-long condition in most cases, and often severely affecting quality of life of both patients and their family.[1] Estimates indicate that prevalence of ASD is approximately 1 in 100 children worldwide, and the incidence in many low and middle income countries is unknown.[2] Prevalence has increased over the past five decades, and it is unclear whether this increase is related to an expansion of the diagnosis, increased awareness of disorder, important role of certain risk factors, and a true increase in the frequency of autism.[3]

There is no certain etiology that is responsible for ASD, and studies have shown that both genetic and environmental factors probably play a role, and affect brain development in early stages.[4] Although the pathogenesis of ASD is incompletely understood, studies reported high frequency of ASD in twins and consanguineous which supported the genetic bases for ASD.[5] Given the incomplete concordance for monozygotic twins, it is likely that genetic factors and exposure to environmental modifiers contribute to the ASD. Up to 15 percent of cases of ASD are associated with a genetic cause, whereas environmental and perinatal factors account for other cases of ASD.[6]

Diagnosis of ASD is considered difficult due to the absence of diagnostic medical investigations, and is established based on child behaviors and neurodevelopmental history.[7] The American Academy of Pediatrics(AAP) recommends that all children should be screened for ASD at ages 18 and 24 months. ASD can be determined at 18 months of age, but most cases are diagnosed in the age group 3 to 6 years.[8] Early diagnosis of ASD is crucial to improve the final outcome of patients, and it is essential to identify risk factors for

autism in children and develop effective prevention strategies.[9] We conducted this study due to the high prevalence of ASD and absence of the local studies. Therefore, the aim of this study was to investigate the risk factors for autism.

2. PATİENTS AND METHODS

2.1. Study Population

After approval by local research ethics committee, an Analytic Case Control study was conducted in 148 patients with ASD and 148 children with other neurological disorders aged 2-10 years seen at Pediatric Neurology Clinic, Tishreen University Hospital and Centers Specialized in caring for children with autism over a period of one year from June 2021 to June 2021.

Inclusion Criteria were as follows: Children aged 2-10 years old with diagnosed ASD, and age –matched groups with other neurologic disease.

Non – Inclusion Criteria: Children with presence one of the following: Rett syndrome, cerebral palsy, and chromosomal syndromes. Complete history, review of systems, and physical examination were performed for all children, and certain factors were compared between two groups.

2.2. Statistical Analysis

Statistical analysis was performed by using IBM SPSS version20. Basic Descriptive statistics included means, standard deviations(SD), median, Frequency and percentages. Chi-square test was used to study the relation between categorical variables. Multivariate logistic regression analysis was performed to estimate independent risk factors. This model included risk factors first identified through univariate analysis. All the tests were considered significant at a 5% type I error rate($p<0.05$), β:20%, and power of the study:80%.

3.RESULTS

The study included a group of 296 children who were assigned as follow; 148 children who were diagnosed as having an autistic disorder and 148 children with other neurological conditions. Ages ranged from 2 to 10 years, with mean age of 5.48±2.1 years. Males represented 72.6% of the patients and females 27.4% with male to female ratio was 2.6:1. A shown in table (1), 34(29.1%) of the cases and 20(13.5%) of controls were with gestational age <37 weeks, whereas 105(70.9%) of the cases and 128(86.5%) of controls were with gestational age≥37 weeks, p:0.001. In cases group, 129(87.2%) of the children born at a normal birth weight, 5(3.4%) were born at a high weight and 14(9.5%) born at a low birth weight versus 103(69.6%), 6(4.1%), and 39(26.4%) in the control group respectively, p:0.001. Seizures in neonatal period were reported in 5 patients (3.4%) of cases group versus 22 patients (14.9%) of control group, p:0.001.

Table 1: Comparison of neonatal characteristics of the study population.

Variable	Cases (148)	Control (148)	p value
Gestational age(weeks)			
<37	43(29.1%)	20(13.5%)	0.001
≥ 37	105(70.9%)	128(86.5%)	
Birth weight			
Normal	129(87.2%)	103(69.6%)	
High	5(3.4%)	6(4.1%)	0.001
Low	14(9.5%)	39(26.4%)	
Neonatal seizures			
Present	5(3.4%)	22(14.9%)	0.001
Absent	143(96.6%)	126(85.1%)	

For categorical age group analysis, we established 2 age groups of paternal age: ≤ 45 years (with 137 cases and 144 controls) and >45 years (with 11 cases and 4 controls), with presence of significant difference, p:0.02. In addition to, we established 2 age groups of maternal age≤40 years (with 142 case and 142 controls) and >40 years (with 6 cases and 6 controls) without presence of significant difference, p:1. The parents of 61(41.2%) of the cases group were consanguineous versus 33(22.3%) of the control group, p:0.003. In cases group, family history of autism was present in 21(14.2%) and absent in 127(85.8%), whereas family history in controls group was present in 5(3.4%) and absent in 143(96.6%), p: 0.001. Prevalence rate for parental autoimmune disease was 10.8% in the cases and 3.4% in controls, p:0.01. There were no significant differences between two groups regarding to hormone replacement therapy (23% versus 15.5%, p:0.1). Maternal smoking was present in 48 patients (32.4%) in cases group versus 24 (16.2%) in controls, whereas smoking was absent in 100(67.6%) versus124(83.8%) in controls, p:0.001. The rate of hospitalization during pregnancy was 23.6% in cases versus 20.3% in controls, p:0.4.

Table 2: Comparison of parental characteristics of the study population.

Variable	Cases	Controls	p value
Paternal age at birth(years)			
≤ 45	137(92.6%)	144(97.3%)	0.02
45>	11(7.4%)	4(2.7%)	
Maternal age at birth (years)			
≤ 40	142(95.9%)	142(95.9%)	1
40>	6(4.1%)	6(4.1%)	
Consanguinity			
Present	61(41.2%)	33(22.3%)	0.003
Absent	87(58.8%)	115(77.7%)	
Family history			
Present	21(14.2%)	5(3.4%)	0.001
Absent	127(85.8%)	143(96.6%)	
Parents' autoimmune disease			
Present	16(10.8%)	5(3.4%)	0.01
Absent	132(89.2%)	143(96.6%)	
Using of hormonal drugs			
Present	34(23%)	23(15.5%)	0.1
Absent	114(77%)	125(84.5%)	
Smoking during pregnancy			
Present	48(32.4%)	24(16.2%)	0.001
Absent	100(67.6%)	124(83.8%)	
Hospitalization during pregnancy			
Present	35(23.6%)	30(20.3%)	0.4
Absent	113(76.4%)	118(79.7%)	

In the multivariate logistic regression analysis**,** gestational age <37 week (OR 2.2,95% CI 1.1-7.2, p=0.01), paternal age older than 45 years (OR 2.7,95% CI 1.9-8.2, p=0.001), family history of autism (OR 4.3,95% CI 2.9-11.7, p=0.0001), presence of autoimmune disease of parents (OR 2.9,95% CI 1.1-7.8, p=0.0001), smoking during pregnancy (OR 2.2,95% CI 1.4-7.9, p=0.001), and presence of consanguinity(OR 2.3,95% CI 1.4-12.8, p=0.001) were factors that associated with the risk of progression autism, Table (3).

Table 3: Risk factors for autism of the study population.

Risk factors	OR b [CI95%]	OR a [CI95%]	p-value
Gestational age<37 week	2.6[1.4-4.7]	2.2[1.1-7.2]	0.01
Birth weight	1.1[0.6-2.2]	0.9[0.1-3.5]	0.8
Paternal age at birth older than of 45 years	2.8[1.3-6.7]	2.7[1.9-8.2]	0.001
Presence of family history of autism	4.7[1.7-12.9]	4.3[2.9-11.7]	0.0001
Parents' autoimmune disease	3.4[1.2-9.7]	2.9[1.1-7.8]	0.0001
Neonatal seizures	0.2[0.07-0.5]	0.2[0.09-2.7]	0.5
Smoking during pregnancy	2.6[1.3-8.6]	2.2[1.4-7.9]	0.001
Presence of consanguinity	2.4[1.3-6.9]	2.3[1.4-12.8]	0.001

4. DİSCUSSİON

To our knowledge, this study is the first in Syria to examine risk factors that related to ASD. Identifying risk factors for neurodevelopmental disorder will lead to earlier identification of children who might benefit from interventions that improve final outcome.

Males represented majority of the patients in the current study, which might be explained by the effects of sex steroid hormones on neurological peptides and transmitters that contribute in the pathogenesis of ASD.[10] This finding is agree with the result of Stokes et al study in which males represented 79% of the patients.[11] The result of the current study revealed that, compared with control group, autism was associated with a significant relationship with gestational age <37 week, advanced age of fathers, presence of a family history of autism, parents' autoimmune disease, smoking during pregnancy, and presence of consanguinity.

Predisposing factors for prematurity, perinatal circumstances, and postnatal complications such as intraventricular hemorrhage IVH and need for high frequency ventilation might be the explanation of the association between prematurity and the risk for autism.[12] This result agrees with Qian et al study that performed in USA.[13] Advanced ages of fathers were associated with increased risk of de novo spontaneous

mutations and alterations in genetic imprinting.[14] This result agrees with Stokes et al(2018) and Rickert et al(2015).[15]

The role of consanguinity and family history is supported by genetic bases of autism and role of consanguineous marriages in occurrence of autosomal recessive characteristics.[16] This result agrees with studies conducted by El-Baz et (2011) in Egypt and Boustany et al (2018) in Lebanon.[17,18]

In addition to, presence of autoimmune diseases leads to the circulation of autoantibodies that are harmful to brain tissue.[19] The association between autoimmune disease and autism agree with.[20]

Finally, nicotine has adverse effects on brain development via its function on nicotine acetylcholine receptors, and its role in placenta calcification.[21] These findings are comparable with the results of Kieltyka et al study (2013).[22]

5. CONCLUSİON

The current study demonstrated that gestational age <37 week, advanced age of fathers, presence of a family history of autism, parents' autoimmune disease, smoking during pregnancy, and presence of consanguinity play critical role in development of autism.

6-Recommendations

Prevention strategies must be taken regarding modifiable risk factors, and there is an important role for screening programs and early intervention.

Declarations

Competing of Interests

All the authors do not have any possible conflicts of interest.

Ethical consideration

After discussing the study with the parents, all of them gave a complete and clear informed consent to participate in the study. This study was performed in accordance with the Declaration of Helsinki.

Availability of data and materials

Most of the data was in the article, and other data can be asked from the corresponding author.

Funding

Not applicable.

Author contributions

All authors performed the measurements and wrote the article. Literature review was done by Dr.Nisreen Ali, and all authors performed analytic calculations and performed the numerical simulations.

ACKNOWLEDGEMENTS

We wish to thank all doctors in the pediatric department.

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