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Original Research Article.

Risk Factors Associated with Autism Spectrum Disorder at King Salman Armed Forces Hospitals - Autism Center in 2021

Rofayda Mansour Ahmed Mohamad[1], Rihab Taman[2], Aesha Alhewiti[3], Azza A Ballal[4], Samir Salah Eldin Mohamed Buraei[5], Waheed Ali Alshehri[6], Shatha Talal Alhakami[7], Manal Muhsen Alatawi[8], Sakeina Saleem Haroon[9], Sahar Hadi[10], Nouf Mohammed Abusalem[11], Abdullah Saeed Althobaiti[12]

[1]Preventive Medicine Supervisor of Training, Development and Research Unit of Preventive Medicine, Saudi Arabia.
[2]MD Psychiatry, Director of Autism Centre, Department of Psychiatry, Northwestern Armed Forces Hospital, Saudi Arabia.
[3]Bachelor in Special Needs Autism, Autism Educationalist,
Autism Centre, Department of Psychiatry, Northwestern Armed Forces Hospital, Saudi Arabia.
[4]Preventive Medicine Physician, Saudi Arabia.
[5,9]Registrar Family Medicine, King Salman Armed Forces Hospitals, Tabuk, Saudi Arabia.
[6]Head of Preventive Medicine Department, Saudi Arabia.
[7]Public Health Specialist Works in Training, Development and Research Unit of Preventive Medicine, Saudi Arabia.
[8]Registered Nurse, Preventive Medicine Department, King Salman Armed Forces Hospitals, Tabuk, Saudi Arabia.
[10,11,12]Preventive Medicine Department, King Salman Armed Forces Hospitals, Tabuk, Saudi Arabia.

ABSTRACT

Introduction: Autism spectrum disorder is a complicated neurological disorder that is characterized by behavioral and psychological problems in children. A wide spectrum of factors has been monitored in many studies, which are related to the autism spectrum, including genetic, environmental and parental factors, including those associated with pregnancy, obstetric diseases, and so on. Accordingly, this study aimed to determine the risk factors in Autism spectrum disorders in the Saudi population.

Methods: A case – control study covered 100 Autism spectrum disorders patients and 100 healthy group matched controls recruited from King Salman armed forces hospitals-autism center in 2021. The data was collected from the records and analyzed using SPSS 28.0.

Results: The study found that lower maternal education, rural residence, maternal unemployment, positive family history for autism, maternal stress and uptake of MMR vaccine uptake were identified as significant risk factors associated with autism in bivariable analysis (p values < 0.05 in all). In this study, multivariable / logistic regression analysis found that rural residence (AOR = 129.4, 95% CI 40.6 – 411.8, p < 0.001), positive family history of autism (AOR = 9.4, 95% CI 1.04 – 85.04, p = 0.046) and, and maternal distress (AOR = 2.8, 95% CI 1.53 – 5.1, p = 0.001) were identified as risk factors associated with ASD.

Conclusion: Our study suggested that maternal stress, rural residence and family history of autism are significant risk factors for ASD. Identifying these risks and protective factors associated with ASD will not only help us understand its prevalence but may also constitute important preventive measures.

Keywords: Risk Factors, Child, Autism spectrum disorder.

***Correspondence to:**

Dr. Rihab Taman,
MD Psychiatry,
Director of Autism Centre,
Department of Psychiatry,
Northwestern Armed Forces Hospital, Saudi Arabia.

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INTRODUCTION

ASD is a complicated neurological disorder that is characterized by behavioral and psychological problems in children. These children become distressed when their surrounding environment is changed because their adaptive capabilities are minimal.[1] Worldwide, the prevalence of ASD is estimated to affect 1/160 according to the World Health Organization (WHO).[2]

For instance, the prevalence of ASD in Saudi Arabia has not yet been accurately determined. One study stated that 42,500 cases were diagnosed with autism.[3] A more recent systematic review showed that the prevalence of ASD in Arabian Gulf countries, including Saudi Arabia, ranged from 1.4 to 29 per 10,000 population.[4] This is, in fact, lower than the prevalence rate

measured by studies conducted in developed countries (39–77 per 10,000).[5] The role of genetics in autism risk is suggested by the higher recurrence rate in siblings of children with autism than in siblings of typically developing children, and the greater concordance rate of monozygotic twins (MZ, 36–96%) as compared with same-sex dizygotic twins.[6] To date, several genetic and environmental factors have been mentioned for ASD [5, 6]. Exposure of the mother and the child to harmful environmental agents during central nervous system development can change the expression of some genes that are essential to embryonic development, leading to an increased risk of developmental disorders which are frequently associated with ASD.[7]

Such findings, emphasizing the contribution of the environment in the etiology of ASD, strengthen the importance of identifying risk and protective factors in order to minimize the deleterious interaction between environmental and genetic factors. Several studies have proven that some parental, prenatal and postnatal factors increase the risk of ASD.[8,9]

For example, a significantly higher incidence of ASD has been observed in children having mothers without folic acid supplementation during pregnancy compared to whom their mothers had supplemented.[10] As for iron, it has been reported that its deficiency, especially during breastfeeding, could lead to an increased ASD risk.[11] To date, there is no curative treatment for ASD. However, associated comorbidities could be reduced by prenatal measures and early behavioral interventions.[12,13]

Findings include significantly higher incidence of bleeding during pregnancy[14], breech presentation and low Apgar scores, cesarean delivery[15] and gestational age at birth <35 weeks.[16] In general, several studies report that prenatal and perinatal risk factors are associated with autism.[17]

Moreover, maternal nutrient deprivation has been associated with strong increases in risk of schizophrenia, neural tube defects.[18] Short interpregnancy interval (IPI) is another proxy strongly associated with ASD in two very large cohort studies.[19] other explanations [cultural, family planning or lifestyle factors], short IPI may indicate maternal depletion of essential nutrients including folate, as these become depleted during pregnancy and can remain low for up to a year postpartum.[20]

A number of investigations have assessed maternal smoking in association with ASD, each with limitations, and overall producing inconsistent findings.[21] Moreover, the association between maternal antidepressant use during pregnancy and ASD is more controversial. Studies found a 50% increase in risk of ASD of mothers who took SSRIs during pregnancy; the estimate was imprecise but consistent.[16] Low Apgar scores as well as conditions requiring neonatal special follow-up are important risk factors for childhood autism. These findings suggest that fetal distress is a potential risk factor for these disorders.[22]

All these factors were examined individually; thus it was still unclear that whether these factors are causal or play a secondary role in the development of autism.[23]

Some family history studies found that the relatives of propends with ASD were more likely to have a history of schizophrenia.[23] Many studies findings suggest that intrauterine and neonatal factors related to deviant intrauterine growth or fetal distress are important in the pathogenesis of autism.[24] Considering that the maternal, paternal, pregnancy and neonatal factors of ASD are not fully elucidated, our study which was conducted in the Saudi population focused on identifying protective and risk factors that can help in designing future studies aiming for ASD prevention or risk attenuation.

METHODS

A hospital based case–control study was conducted in Autism Centre affiliated to Prince Mohammed Bin Salman Program for Autism and Developmental Disorders, King Salman Armed Forced Hospital located in North Western Area of Saudi Arabia in 2021. The study included 100 children diagnosed with autism spectrum disorder and 100 typically developing normal children, who are age and sex matched between 18 months and 6 years.

The sample is a comprehensive sample that include all children who are attending the autism center of the hospital. The control group was recruited from the children who attend to well-baby clinic for their vaccination doses. The eligibility criteria if one of their parents is employed full-time or military inclusion criteria for the case group is to be diagnosed as a case of autism spectrum disorder case and his age is less than 6 years and attend the center for follow-up.

The two groups were selected by physicians and nurses working in Autism Center. Subsequently, a definitive database was constructed. The variables for the study based on socioeconomic, environmental, perinatal, natal and post-natal risk factors including: Several socio-economic factors, environmental.

Descriptive statistics were done to describe the data. For categorical variables, frequencies and percentages were reported. Differences between groups were measured using: Bivariate analyses to compare case and control groups by chi-square tests for categorical variables with SPSS 28.0.

Moreover, multivariable analysis / logistic regression was used to adjust the analysis to obtain the measured of associations with odds rations and confidence intervals value of less than 0.05 was considered as significant. Data entry, analysis and result interpretation were done by researchers. Informed consent was obtained from all participants' caretakers.

The study was approved by the research ethical committee of the hospital. The personal information was discarded so as to guarantee confidentiality.

RESULTS

Our case-control study included 100 ASD patients and 100 healthy group matched controls recruited from King Salman armed forces hospitals- autism center in 2021.

The data collected from the records was analyzed using SPSS 28.0. In bivariable analysis, independent Student T-test and Chi-Square test were carried out for the bivariate analysis of the data. Lower maternal education, rural residence, maternal unemployment, positive family history for autism, maternal stress and uptake of MMR vaccine uptake were identified as significant risk factors associated with autism in bivariable analysis (p values < 0.05 in all) as detailed in tables 1,2.

In addition, the variables revealing a p-value < 0.05 were used for the multivariate logistic regression analysis; rural residence (AOR = 129.4, 95% CI 40.6 – 411.8, p < 0.001), positive family history of autism AOR = 9.4, 95% CI 1.04 – 85.04, p = 0.046) and, and maternal distress (AOR = 2.8, 95% CI 1.53 – 5.1, p = 0.001) were identified as risk factors associated with ASD as detailed in tables 1 – 3.

Table 1: The relation between maternal factors with the occurrence of autism (n = 100 autism case + 100 healthy controls)

Maternal factors		Frequency		Bivariable analysis (unadjusted)		Multivariable analysis / Logistic regression (adjusted analysis)			
		Case	Control	Odds ratio	P value	Odds ratio	P value	95% confidence intervals	
								From	To
Maternal education	Not educated	12	2	1.00	0.008	1.00	0.547	-	-
	Before university	33	27	0.20		0.11		0.00	20.33
	University	55	71	0.13		0.28		0.00	48.53
Social status	Married with child father	88	14	1.00	0.159	1.00	0.343	-	-
	Married not child father	1	78	0.01		0.01		0.00	0.02
	Divorced	9	8	0.18		0.47		0.10	2.22
	Widowed	2	0	-		-		-	-
Residency	Rural	87	5	127.15	< 0.001	129.39	**< 0.001**	40.65	411.84
	Urban	13	95						
Maternal employment	Yes	25	45	0.41	0.003	0.36	0.113	0.10	1.27
	No	75	55						
Use of anti-depressant	Yes	2	1	2.02	0.561	4.29	0.497	0.06	288.87
	No	98	99						
Family his. Autism / M. illness	Yes	31	4	10.78	< 0.001	9.40	**0.046**	1.04	85.04
	No	69	96						

Table 2: The relation between pregnancy factors with the occurrence of autism (n = 100 autism case + 100 healthy controls)

Pregnancy factors		Frequency		Bivariable analysis (unadjusted)		Multivariable analysis / Logistic regression (adjusted analysis)			
		Case	Control	Odds ratio	P value	Odds ratio	P value	95% confidence intervals	
								From	To
Nutrition during pregnancy	Normal	33	26	1.40	0.278	1.37	0.350	0.71	2.68
	With problems	67	74						
Antepartum hemorrhage	Yes	8	6	1.36	0.579	0.96	0.950	0.23	3.95
	No	92	94						
Threatened abortion	Yes	14	13	1.09	0.836	0.67	0.468	0.23	1.96
	No	86	87						
Prematurity	Yes	13	13	1.00	1.00	0.86	0.749	0.34	2.17
	No	87	87						
Maternal stress	Yes	60	36	2.67	0.001	2.79	**0.001**	1.53	5.10
	No	40	64						
Viral infection	Yes	2	3	0.66	0.651	0.59	0.599	0.08	4.15
	No	98	97						
Gestational diabetes	Yes	16	9	1.93	0.134	2.44	0.064	0.95	6.28
	No	84	91						
Neonatal infection	Yes	4	1	4.13	0.174	5.22	0.151	0.55	49.81
	No	96	99						
Pathological meconium	Yes	4	7	0.55	0.352	0.44	0.265	0.10	1.86
	No	96	93						
Mode of labor	Yes	52	60	0.72	0.254	0.72	0.276	0.39	1.31
	No	48	40						

Table 3: The relation between neonatal factors with the occurrence of autism (n = 100 autism case + 100 healthy controls)

Neonatal factors		Frequency		Bivariable analysis (unadjusted)		Multivariable analysis / Logistic regression (adjusted analysis)			
		Case	Control	Odds ratio	P value	Odds ratio	P value	95% confidence intervals	
								From	To
Child sex	Male	69	72	0.87	0.642	0.81	0.746	0.23	2.87
	Female	31	28						
Aspiration syndrome	Yes	1	5	0.19	0.097	0.17	0.440	0.00	15.63
	No	99	95						
Fetal hypoxia	Yes	8	5	1.65	0.39	2.14	0.516	0.22	21.14
	No	92	95						
NICU stay	Yes	20	17	1.22	0.585	1.82	0.487	0.34	9.80
	No	80	83						
Genetic syndrome	Yes	4	2	2.04	0.407	0.41	0.790	0.00	299.34
	No	96	98						
Birth asphyxia	Yes	1	5	0.19	0.097	0.19	0.135	0.02	1.67
	No	99	95						
Low birth weight	Yes	13	10	1.34	0.506	0.60	0.630	0.08	4.69
	No	87	90						
MMR vaccine uptake	Yes	86	72	2.39	0.015	1.00	0.997	0.28	3.61
	No	14	28						

DISCUSSION

This case control study was conducted to determine the maternal, paternal, pregnancy and neonatal familial factors related to ASD in Saudi individuals. Our study uncovered significant risk factors that could easily be modified with the objective to reduce the risk of ASD.

Our study reported that positive family history of autism (AOR = 9.4, 95% CI 1.04 – 85.04, p = 0.046) is associated with ASD. Likewise, in Lebanon, Gerges et al indicated that familial ASD history is more common among ASD group compared to controls.[27]

Also, Chaaya et al[28] revealed that having ASD and ADHD patients in the family are risk factors related to ASD, which support the role of genetics in ASD. In fact, a study conducted on a large cohort of Swedish children showed that the heritability of the disorder is approximately 50% and the risk of ASD increases 10-fold if a sibling has the disease and 2-fold if a cousin is diagnosed with ASD.[29]

However, this result was concordant with the finding of two studies from Middle East countries showing that familial history of mental illness and ASD are significantly associated with ASD onset in children.[30,31]

Our study reported that rural residence (AOR = 129.4, 95% CI 40.6 – 411.8, p < 0.001) was significantly associated with autism. In general, the association of rural housing with higher rates of autism can be explained by several directions, most of which are related to the status of surveillance systems for autism, in addition to the different social, cultural and genetic backgrounds in some countries, which are directly or directly related to autism spectrum disorders. On contrary, similar rates of ASD prevalence are reported in both rural and urban and areas.[32]

Hartley et al added that there are specific factors which contribute to barriers in diagnosis and services for affected individuals and families in rural settings. They reported that rural settings are characterized by lessened availability of services per capita and low socioeconomic status and education levels. Moreover, Cohen et al stated that there are significant differences in rural versus urban parent-report on how doctors respond to concerns and doctors are more likely to suggest that the parent discuss the concern with the school for rural (40%) versus urban (28%) areas.[34]

Furthermore, Green et al realized that[35] the increased geographic distance between practitioners and affected individuals for rural areas further compounds this specific demand for strong and direct links between practitioners and central community areas. Accordingly, reduced awareness and diminished screening in rural areas may lead to a certain segment of ASD cases to be undetected, specifically cases in which there is no co-occurring intellectual or language impairment.

Studies[31-35] agreed that the geographic distance from central resources in addition to low socioeconomic status, may create a specific burden for affected families in rural areas, as travel costs can deter them from seeking services.

The current study found that the presence of maternal distress (AOR = 2.8, 95% CI 1.53 – 5.1, p = 0.001) was identified as risk factors associated with ASD. In similar context, Van den et al agreed that the effects of prenatal exposure to maternal stress on the behavior and mental health of the offspring.[25]

They added that these effects include abnormalities in neurodevelopment, neurocognitive function, and cerebral processing which lead to changes in both the hypothalamo–pituitary–adrenal axis (HPA) and the autonomic nervous system.[25]

Moreover, Angelidou et al[26] added that corticotropin-releasing hormone (CRH) secretion from the hypothalamus is a result of stress and correlated with the level of stress during pregnancy.

Maternal CRH can easily cross the placenta, and the placenta itself can produce considerable amounts of CRH due to external or intrauterine stress and has an immune-modulatory role; it stimulates the activation of mast cells to release pro-inflammatory cytokines, such as interleukin 6 (IL-6), that increase blood–brain barrier (BBB)'s permeability. These events lead to the action of auto-antibodies against brain peptides, which cause brain inflammation, thus contributing to ASD pathogenesis.[26]

CONCLUSION

ASD is one of the prevalent childhood neurodevelopmental disorders around the world. Currently, many of the Saudi epidemiological studies conducted on ASD patients have a limited sample size compared with other countries. Subsequently, ASD epidemiological investigation on the Saudi population should be improved in order to achieve more robust conclusions.

In short, our study suggested that maternal stress, rural residence and family history of autism are significant risk factors for ASD. Identifying these risk and protective factors associated with ASD will not only help us understand its prevalence but may also constitute important preventive measures.

Future studies with large and heterogeneous sample sizes should be done to identify the time of the exposure to environmental factors and its relationship with critical developmental phases.

LIMITATIONS

Despite the limited sample size of our case-control study, we were able to suggest wade range of risk factors for ASD. However, our study was of the retrospective type based on the information given from the parents, which leads to the possibility of memory bias and low conclusiveness. Another limitation was the difficulty to verify the diagnosis criterion because it was not done by the research team. Thus, taking into consideration the fact that our results come from an observational/correlational non-experimental work, causality is not inferred, and readers are warned to avoid formulating the study results into quick intervention guidelines.

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