Factors associated with Autism Spectrum Disorder: a case-control study in the Lebanese population

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DOI: ***10-2427/13218***
Accepted on February 27, 2020

ABSTRACT

Background: Genetic factors represent the major etiological contributor in Autism Spectrum Disorders (ASD) but several studies also support the involvement of environmental factors. This last hypothesis is reinforced by the evident increase in the prevalence of this disorder in the last decades. Thus, in our study, we aimed to identify the correlation between factors related to sociodemographic elements, to child and mother's health and ASD in order to dress a best detailed profile of the patients.
Methods: We conducted a case-control study including 64 Lebanese patients with ASD and 67 matched controls recruited from all the Lebanese districts. Our data has been analyzed by SPSS 23.0 and the statistical tests carried out were the Independent Sample t-test and the Chi-Square test. In addition, a multivariate logistic regression analysis has been carried out using variables that showed a $p<0.05$ in the bivariate analysis.
Results: Our findings suggest that consanguinity (OR=4; 95% CI [1.3-12.04]), familial history of ASD (6.7 [1.1-39.3]), stress during pregnancy (3.6 [1.5-8.2]) and fetal prematurity (6.3 [1.2-33.01]) were significantly associated with increased odds of ASD. However, our results have shown no association between siblings suffering from diseases such as mental retardation, child's infections and ASD.
Conclusion: This pilot study carried out in all the regions of Lebanon allowed us to shed the light on factors associated with ASD which might be preventable.

Key words: Autism Spectrum Disorders, Consanguinity, Familial ASD history, Stress, Prematurity

INTRODUCTION

Autism Spectrum Disorders (ASD) are a group of complex, neurodevelopmental disorders characterized by impaired communication and social interaction, as well as restricted, repetitive and stereotypical behavior [1]. The prevalence of ASD worldwide is estimated to affect 1 out of 160 children [2]. Prevalence is also estimated to be 1 out of 66 children in Beirut and Mount-Lebanon regions in Lebanon [3].

To date, a range of studies have been performed to identify the etiological factors of ASD, which have shown that ASD is a multifactorial disorder involving a strong genetic component and environmental contributors, as well [2,4]. In fact, exposure to harmful environmental components can alter the expression of developmental genes essential to

critical periods of embryonic development, increasing the risk of developmental disorders, such as ASD [5]. Several studies have suggested that advanced age at parenthood, maternal prenatal medication, low weight at time of birth and prenatal infections [6–8]) could be considered as risk factors for ASD [9]. However, no one element was consistently reported for ASD among these studies.

Moreover, the environmental causes of ASD are not completely understood. It is also noteworthy that most of the studies conducted to determine the etiological factors of ASD were based on Western populations. Therefore, studies performed in different geographical areas or on other ethnic backgrounds to identify the possible environmental factors associated with ASD could help to better understand this disorder and to determine the optimal approach to reducing the risks for health issues.

Thus, in our study we focused on a Middle-Eastern, Lebanese population with the aim of identifying the possible factors related to socio-demographic status, the child and mother's health and ASD.

METHODS

In our case-control study, 64 patients with ASD and 67 controls matched for age and geographic location (Beirut, North, South, Mount Lebanon and Beqaa) were recruited from all Lebanese districts. Patients were selected from non-governmental organizations (NGOs) and institutions specializing in the care of disabled children, with ASD in particular, which support their medical, social, educational and rehabilitative needs.

Autistic patients were diagnosed in the study by the medical team of each association using Diagnostic and Statistical Manual of Mental Disorders, 5th edition (DSM-5) criteria [1]. Patients with Fragile X syndrome were excluded from the study. Controls were chosen from non-specialized schools located in all Lebanon districts. All parents/guardians of the children included in this study provided informed consent.

Sample size calculation

Using the Epi-info software for the calculation of the minimal sample size needed for our study, the results showed that this study required 47 cases versus 47 controls. This was calculated by implementing a power of 1-β=0.8, a confidence interval of 95%, a percentage of infection during pregnancy of 33.9% among controls and an odds ratio OR=3.3 based on previous research [6]"container-title":"Journal of Autism and Developmental Disorders","page":"2010-2021","volume":"48","issue":"6","source":"PubMed","abstract":"This case-control study explores the association between pregnancy/birth complications and other factors with Autism Spectrum Disorder (ASD, and considering a ratio of one control for every case.

Recruitment

Our research team contacted the organizations working with children with ASD, explaining the objectives of the study in the form of a letter in both Arabic and English sent to all the families. Nearly 70% of the families accepted to take part in our study. Afterwards, the families of the children were invited to a meeting in which at least two members of our group explained the aim of the study and answered any questions, if need be. Following informed consent regarding the individuals with ASD who would be the subjects of the study and under the supervision of the members of the research team, one or both of the parents filled out the questionnaire designed for the study. Genuinely, the highest standards of confidentiality were upheld.

Our questionnaire (Appendix 1) was based on the risk factors highlighted in previous studies [9,10]. It included questions with regard to socio-demographic elements, including age and gender of the subject, age of both parents, proximity of the household to industrial plants and education level of both parents. Furthermore, questions concerning consanguinity, vaccination, infections during childhood, the presence of ASD or other diseases in the family, smoking and/or the use of any drugs during pregnancy and any forms of stress were posed to the subjects.

For the recruitment of healthy children, the members of the team approached non-specialized schools from the same regions in which the children with ASD were recruited. After receiving signed approval of each family, the surveys were answered by one or both of the parents in the presence of one member of our team.

Data Analysis

The data was analyzed using the SPSS 23.0 (IBM SPSS Inc., Chicago, IL, USA) statistical analysis software. A p-value of <0.05 was considered significant. The statistical tests carried out were the Independent Sample t-test to compare one continuous and one dichotomous variable (to compare the means between two groups) and the Chi-Square test to assess the relationship between two categorical variables. A multivariable conditional logistic regression analysis was carried out using variables that showed a p-value of <0.05 in the bivariate analysis; potential confounders were eliminated only with a p-value of >0.2, in order to prevent residual confounding [11] investigators frequently employ a strategy that uses the data to help them decide whether to adjust for a variable.

The authors compared the performance of several such strategies for fitting multiplicative Poisson regression models to cohort data: 1 . In the logistic regression, the dichotomous absence/presence of ASD was used as the dependent variable.

RESULTS

The mean age of the participants in our study was 8.61 ± 4.28 years. Most of ASD cases presented a moderate intellectual disability.

Table 1 shows a comparison of the sociodemographic characteristics between cases and controls. Within the patient group, we observed a male and female gender distribution of 73% and 26%, respectively. Furthermore, a significantly higher proportion of ASD children had mothers with a low education level (illiteracy, primary and secondary education) compared to controls (15.9% vs 6.1%). Likewise, a significantly higher proportion of ASD children had illiterate fathers compared to the controls (36.2% vs 7.6%). As for parental age, an independent sample t-test was performed to determine whether a significant statistical difference lied between two groups: 1. children either with or without ASD 2. the age of either the mother or the father at the time of their child's birth. The p-values for the variables were all above 0.05, signifying no significant statistical difference between the two groups. Our results also illustrated no statistical difference between proximity to industrial plants and ASD cases. This could be explained by the fact that the majority of the study subjects, both patients and controls, did not live in the vicinity of industrial plants. Table 2 describes the co-morbid disorders that were present in the ASD children of our study. The findings revealed that several disorders, such as epilepsy, deafness, hyperactivity, self-injurious behavior, bulimia and sleep disturbances are common in ASD children, with hyperactivity being the most common disorder (73.4%).

TABLE 1. Sociodemographic characteristics of the sample set

Variable	Healthy children	Children with ASD	p-value
Gender			0.19
Male	42 (62.7%)	47 (73.4%)	
Female	25 (37.3%)	17 (26.6%)	
Industrial plants in the vicinity (Carpentry)			0.14
Yes	0 (0%)	2 (3.1%)	
No	67 (100%)	62 (96.9%)	
Industrial plants in the vicinity (Waste collection)			0.9
Yes	1 (1.5%)	1 (1.4%)	
No	66 (98.5%)	63 (98.4%)	
Industrial plants in the vicinity (Food industry)			0.073
Yes	0 (0%)	3 (4.7%)	
No	67 (100%)	61 (95.3%)	
Mother's age at the child's birth			0.23
Average ± Standard deviation	28.6 ± 5.04	29.8 ± 6.65	
Father's age at the child's birth			0.35
Average ± Standard deviation	35.0 ± 6.6	36.1 ± 7.4	
Mother's educational level			0.001*
Illiterate / Primary	4 (6.1%)	10 (15.9%)	
Secondary	13 (19.7%)	26 (41.3%)	
University	49 (74.2%)	27 (42.9%)	
Father's educational level			<0.0001*
Illiterate / Primary	5 (7.6%)	21 (36.2%)	
Secondary	26 (39.4%)	22 (37.9 %)	
University	35 (53%)	15 (25.9%)	

**significant p-value <0.05*

TABLE 2. ASD and associated disorders/symptoms

VARIABLE	ASD CHILDREN
Epilepsy	
Yes	11 (17.2%)
No	53 (82.8%)
Deafness	
Yes	21 (32.8%)
No	43 (67.2%)
Hyperactivity	
Yes	47 (73.4%)
No	17 (26.6%)
Self-injurious behavior	
Yes	36 (56.2%)
No	28 (43.8%)
Bulimia	
Yes	8 (12.5%)
No	56 (87.5%)
Sleep disturbances	
Yes	19 (70.3%)
No	45 (87.5%)

Table 3 shows the comparisons with respect to the mother's health-related factors, the child's characteristics, consanguinity and other aspects between cases and controls. A significantly higher percentage of ASD children exhibited the following compared to controls: ASD cases in their families (14.1% vs 3%), siblings suffering from diseases including mental and growth retardation (12.5% vs 1.5%), fetal prematurity (15.6% vs 4.5%) and the mother's self-reported stress during pregnancy (65.6% vs 29.7%) compared to the controls. Our findings demonstrate that a clear majority of the subjects were vaccinated against the rubella, mumps and measles viruses (MMR) in the two groups. Therefore, there was no association between this vaccination and ASD. However, a significantly higher percentage of children with autism had first-degree consanguineous parents compared to controls (25% vs 10.4%).

Multivariable analysis

Table 4 shows a multivariate analysis of risk factors for ASD using logistic regression, which was performed with variables having a p-value <0.05 in the bivariate analysis. The results of the logistic regression, defining the presence/absence of ASD as the dependent variable, presented that consanguinity (OR=4.022), fetal prematurity (OR=6.293), familial history of ASD (OR=6.732) and self-reported stress of the mother during pregnancy (OR=3.579) were significantly associated with an increased risk for ASD in the child. However, no association of the child's history of infections and siblings suffering from diseases with ASD were found.

DISCUSSION

A male predominance of ASD represented by 73% of the cases in our study is in accordance with the data reported in the literature, which overall sets the male-to-female ratio at 4:1 [12] (Table 1).

The study displayed an association between consanguineous marriage and ASD in the offspring. Moreover, a study within an Indian population showed that consanguinity increases the risk for ASD by an odds ratio of 3.22 [13]. In various Middle Eastern ethnic groups and political conflicts, the frequency of consanguineous marriage can reach 50% [14]. In fact, consanguinity could be associated with the increased incidence of multifactorial diseases, such as mental disorders. It is known that the main consequence of consanguinity is increased homozygosity for autosomal recessive disorders. The small number of epidemiological studies in consanguineous populations confirms that there exists a significant association between consanguinity and mental disorders among the resulting offspring [15] throughout the Middle East and South-East Asia. According to available data, couples of second cousins or closer and their offspring currently represent 10.4% of the world's population, thus resulting in increased frequencies of autosomal recessive disorders. Furthermore, consanguinity may be implicated in the increased frequency of multifactorial pathologies such as mental disorders. The few existing epidemiological studies in consanguineous and/or geographically isolated populations confirm that there is a significant association between consanguinity and mental disorders and a higher risk of schizophrenia or bipolar disorders among offspring from consanguineous couples. There exists a strong and complex genetic component in the predisposition to psychotic disorders that has been confirmed in numerous studies. However, the genetic basis of these disorders remains poorly understood. GWAS studies (Genome Wide Association Studies. Of the major populations studied so far, the highest rates of consanguineous marriage have been associated with low socioeconomic status. A study performed in suburb dwellings of Beirut reported that women working in the home and a low educational level demonstrate the highest rates of consanguinity [16]and its associated factors in different subgroups. The cross-sectional study was performed on a convenience sample of married women in Lebanon. The women were administered a standardized questionnaire in a face-to-face interview by independent enquirers. Among 1556 women, the overall prevalence of consanguineous marriages was 35.5%, and the consanguinity coefficient was 0.020; 968 marriages (62.2%.

TABLE 3. ivariate analysis of factors associated with ASD

VARIABLE	HEALTHY CHILDREN	CHILDREN WITH ASD	P-VALUE
Consanguinity			0.029*
Yes	7 (10.4%)	16 (25%)	
No	60 (89.6%)	48 (75%)	
Familial ASD history			0.022*
Yes	2 (3%)	9 (14.1%)	
No	65 (97%)	55 (85.9%)	
Sibling suffering from diseases			0.013*
Yes	1 (1.5%)	8 (12.5%)	
No	66 (98.5%)	56 (87.5%)	
Infections during pregnancy			0.089
Yes	5 (7.5%)	11 (17.2%)	
No	62 (92.5%)	53 (82.8%)	
Antibiotics treatment during pregnancy			0.3
Yes	4 (6.2%)	7 (10.9%)	
No	61 (93.8%)	57 (89.1%)	
Self-reported stress during pregnancy			<0.001*
Yes	19 (29.7%)	42 (65.6%)	
No	45 (70.3%)	22 (34.4%)	
Abortion history			0.45
Yes	17 (25.4%)	20 (31.2%)	
No	50 (74.6%)	44 (68.8%)	
Prematurity			0.033*
Yes	3 (4.5%)	10 (15.6%)	
No	64 (95.5%)	54 (84.4%)	
Smoking during pregnancy			0.885
Yes	27	25	
No	40	39	
Child's infections			0.023*
Yes	18 (26.9%)	29 (46%)	
No	49 (73.1%)	34 (54%)	
MMR vaccine (Child)			0.073
Yes	66 (100%)	60 (95.2%)	
No	0 (0%)	3 (4.8%)	

**significant p-value <0.05; variables not shown in the table did not reveal a significant association.*

In addition, this study's results revealed that the mother's self-reported stress during pregnancy was strongly associated with ASD. It is, indeed, well known that prenatal exposure to such stress increases the risk for behavior and mental health complications, such as ASD, in the offspring [17]. In fact, several studies have investigated the effects of maternal stress on the neuro and cognitive development of the child [18]. Furthermore, several biological effects in the offspring, including abnormalities in functional/structural connectivity in the brain and aberrations in neurodevelopment/neurocognitive function, are linked to maternal psychological disturbance disorders, namely anxiety, during pregnancy [18]. For example, in response to stress stimuli, CRH (corticotropin-releasing hormone) is released by the hypothalamus; maternal serum CRH is able to cross the placenta, in addition to the high CRH levels

TABLE 4. Logistic regression with the presence vs absence of autism spectrum disorder defined as the dependent variable.

Variable	p-value	OR	95% Confidence Interval	
Consanguinity	0.013*	4.022	1.343	12.045
Child's infection history	0.228	1.707	0.715	4.072
Fetal prematurity	0.030*	6.293	1.200	33.010
Familial ASD history	0.034*	6.732	1.151	39.375
Self-reported stress during pregnancy	0.003*	3.579	1.558	8.22
Siblings suffering from diseases	0.067	8.193	0.860	78.004

-Variables entered in the model: consanguinity, child's infection history, medical treatment during pregnancy, fetal signs of prematurity, familial ASD, self-reported stress during pregnancy and siblings suffering from diseases.
** Significant p-value <0.05*

that could similarly be produced by the placenta itself, in response to external or intra-uterine stress. This will activate mast cells, which release a number of pro-inflammatory cytokines such as interleukin 6 (IL-6). This cascade of events might alter fetal blood-brain barriers, thus promoting the passage of antibodies and various molecules to the brain, leading to neuroinflammation. The pathogenesis of ASD could arise, as a result [19]. Additionally, maternal stress during pregnancy is considered a cause of prematurity.

Several studies have reported a higher prevalence of ASD in pre-term than in full-term infants [20,21]. Likewise, our survey illustrated an association between prematurity and ASD. Indeed, premature birth, as for all placental, neurological, and neurodevelopmental issues, has constituted a risk factor for ASD development [22]. More specifically, due to an immature nervous system, pre-term children are at risk for poor neurodevelopment [23].

This case-control study also showed that a familial ASD history was more common within the ASD group, which suggests a genetic aspect to ASD. In fact, studies have found that the possibility of a child being diagnosed with ASD is increased by a factor of 10 if he/she already has a first-degree relative (sibling) suffering from the disorder and by a factor of 2 if he/she has a third-degree relative (cousin) with ASD [24].

We must recognize the multiple shortcomings of this pilot study. First, it exhibited a limited sample size, which might not be indicative of the whole population. Second, this is a case-control survey including retrospective reports and, consequently, a low degree of evidence. Furthermore, it is possible that recall bias influenced the outcomes of the study due its retrospective nature. The effect of the recall bias could be differential and lead to the over-estimation of the outcomes of some known risk factors. The questionnaire used in this investigation had not been previously validated. Nevertheless, it was based on previous international studies. Future studies containing more details regarding social conditions and personal elements are necessary to examine the limitations mentioned herein. However, our results suggest the presence of several factors that are significantly associated with ASD.

CONCLUSION

This survey carried out on a Lebanese population showed that the identifiable risk factors for the development of ASD were consanguinity, prematurity, self-reported stress of the mother during pregnancy and a familial history of ASD. Identifying these risk factors associated with ASD will help to increase our understanding of this disorder, to determine how these factors affect the prevalence of ASD in Lebanon, and to establish the optimal methods in reducing the risk of debilitating health. This will also improve personalized prognoses and strategies to decrease the frequency of ASD occurrences as much as possible.

Acknowledgments

This project has been funded with the support from the National Council for Scientific Research in Lebanon (CNRSL) and the Higher Center for Research of the Holy Spirit University of Kaslik (HCR-USEK).We thank all the NGOs and associations that care for patients with autism and graciously shared their data with us.

Compliance with Ethical Standards

The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments, and the Holy Spirit University Ethical Committee has approved the study protocol.

Conflict of interests

The authors declare that they have no conflict of interests

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APPENDIX 1

Survey

NGO:
Caza:
Phone number:

VARIABLE	CHILDREN
Gender	
Male	
Female	
Industrial plants in the vicinity (Carpentry)	
Yes	
No	
Industrial plants in the vicinity (Waste collection)	
Yes	
No	
Industrial plants in the vicinity (Food industry)	
Yes	
No	
Mother's age at the child's birth	
Father's age at the child's birth	
Mother's educational level	
Illiterate / Primary	
Secondary	
University	
Father's educational level	
Illiterate / Primary	
Secondary	
University	

2. ASD AND ASSOCIATED DISORDERS/SYMPTOMS FOR ASD CHILDREN:	
VARIABLES	
Epilepsy	
Yes	
No	
Deafness	
Yes	
No	
Hyperactivity	
Yes	
No	
Self-injurious behavior	
Yes	
No	
Bulimia	
Yes	
No	
Sleep disturbances	
Yes	
No	

VARIABLE	CHILDREN
Consanguinity	
Yes	
No	
Familial ASD history	
Yes	
No	
Sibling suffering from diseases	
Yes	
No	
Infections during pregnancy	
Yes	
No	
Antibiotics treatment during pregnancy	
Yes	
No	
Self-reported stress during pregnancy	
Yes	
No	
Abortion history	
Yes	
No	
Prematurity	
Yes	
No	
Child's infections	
Yes	
No	
MMR vaccine (Child)	
Yes	
No	
Smoking during pregnancy	
Yes	
No	