

RESEARCH PAPER

The Effect of Sex Differences and Family History as a Genetic Factors related to Autism Spectrum Disorder among Group of children in Erbil city, Kurdistan Region- Iraq.

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ABSTRACT:

The expanding incidence of autism spectrum disorders (ASD) in the last years has led researchers to focus on the factors for identification and diagnosis that are linked with autism. ASDs are a group of early-onset and heterogeneous neurodevelopmental disorders of the brain. The aim of the recent study was to assess the family history and sex differences as factors related to ASD among Kurdish children in Erbil city. Two hundred and nineteen subjects with ASD and one hundred nineteen healthy children were included in the study. Depending on the type of data and the objective of the assessment, "Chi-square tests, Likelihood Ratio, Linear-by-Linear Association, Pearson Correlation, and Fisher's Exact Test" were used to compare dissimilarities between autistic groups and healthy groups. In the study group consisting of children with ASD, in terms of sex differences, about 75.8% of the children in the Autism group were male compared to 57.1% in the control group and 24.2% of the offspring in the autistic group were female compared to 42.9% in the control group, which means the ratio is (3:1, male: female) and if someone to be autistic in the family in future will be mostly male and this is highly significant in our study, the p-value about (0.002). This study concludes that Sex Differences and Family History as genetic risk factors for developing autism among the Kurdish population.

KEY WORDS: Autism Spectrum Disorder; Factors; Sex Differences; Family History.

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1.INTRODUCTION

Autism Spectrum Disorders (ASD) are a group of early-onset and heterogeneous neurodevelopmental disorders of the brain, that was first described by Kanner in 1943 in a detailed report of 11 children with similar anomalous tendencies (Kanner, 1943). According to the World Health Organization, Autism spectrum disorder (ASD) refers to a range of conditions characterized by some degree of impaired social behavior communication, and language, and a narrow range of interests and activities that are both unique to the individual and carried out repetitively (WHO, 2013).

The number of autism cases has been raised remarkably during the last 40 years as a comparison with the current epidemiology, a review of the latest global autism epidemiological survey conducted on the general population,

Estimates of autism prevalence have risen from less than 0.4% in the 1970s to stable Current estimates are 1-2% (Havdahl et al., 2021, Fombonne et al., 2021).The cause of ASD is still under research, however in the most recent study discovered that the etiopathogenesis of autism is multifactorial (Linnsand et al., 2021). as well as it is a highly heterogeneous disease in terms of pathogenesis, neurobiology, and symptomology (Hegarty et al., 2020). because according to most studies this disorder associated with the effects of interaction between genetic factors (Rylaarsdam and Guemez-Gamboa, 2019, Griesi-Oliveira et al., 2021). and non-genetic factors (Environmental factors) on various neurobiological pathways (Ohashi et al., 2021). The most frequently tested non-genetic factors associated with autism are socio-demographic characteristics for example (child's birth order, and parents' old age), physiological factors (grouping of pregnancy and childbirth complications, e.g.: Chemical factors

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such as diabetes, trauma, cesarean section, pre-eclampsia, intrauterine hypoxia or birth choking, neonatal jaundice, preterm birth, and low-birth weight) and traffic-related air pollutants, however understanding the role of factors of environmental in the pathogenesis of autism is till now in its beginning, and upcoming study needs to be continue to investigate how these factors are related (Linnsand et al., 2021). At the same time, Genetics plays a major role in triggering ASD (Huang et al., 2021). It is associated with both common and rare hereditary and *de novo* genetic variations that contribute to the pathogenesis of ASD (Bralten et al., 2018). The *de novo* defined as A genetic alteration that is present for the first time in one family member as a result of a variant (or mutation) in a germ cell (egg or sperm) of one of the parents, or a variant that arises in the fertilized egg itself during early embryogenesis. Also called *de novo* variant, new mutation, and new variant (Goldmann et al., 2019). However, cumulatively, the contribution of frequently inherited variants to the etiology of ASD is estimated to be 15% and 50% (Ohashi et al., 2021).

According to this studies ASD prevalence remains highly biased toward males (Werling and Geschwind, 2013). Actually, some studies recommends that male are mostly possible to be diagnosed with several neurodevelopmental conditions, like ASD, attention deficit hyperactivity disorder (ADHD), Tourette syndrome, and specific language impairment (Schaafsma and Pfaff, 2014, Ferri et al., 2018). However, the result of this study showed that there is an association between family history with neurological and mental disorder to autism, and by the presence or absence of co-occurring ID the association may differ (Xie et al., 2019). Of course, much more research is needed in this area to further establish associations and investigate the mechanisms underlying all these findings, was conducted to determine the association with between autism and two independent variables (sex differences and family history. The recent study investigated the following two important risk factors: which are Sex Differences and Family History among Kurdish children studying in autism centers of Erbil- Kurdistan Region-Iraq.

2.MATERIALS AND METHODS

2.1 Ethical approval:

Ethical approval was granted from the Council of Ministry / Ministry of higher education & scientific research - Salahaddin university – Erbil / College of Education-Higher Education/directorate postgraduate no (3/1/5/1548) issued (06/9/2021), to all of the centers of Autism Spectrum Disorder in Erbil city, Kurdistan Region- Iraq, for example (Emarate, Hana, Amal, Gashbin, Lana, Bahoz, Zhyan, Sima, and Chra), As well as approval from autistic parents to collect data or to get information from them. Before the study began, in order to preserve the research participants' dignity, rights, safety, and well-being.

2.2 Study design

According to the centers for Autism Spectrum Disorder study was conducted in Erbil city to determine the associations among ASD and the two factors: Sex Differences, Family History. A questionnaires form was used to get info from the parents of autistic in the recent study. The questionnaires form consists from two parts: the first part to get some characteristics of autistic parents for example age, confirmed with their birth dates. While the second part of the questionnaire included that information about children for example age, gender, birth date and family history in their family. For autistics, healthcare personnel who made the diagnosis was noted. The original questionnaires form was written in Kurdish and was content confirmed by an expert panel because mostly of them do not speak English. After that the validated questionnaire was then translated into the English language.

2.3 Study ASD and Control Groups

The study consisted of 339 children in Erbil city, Kurdistan Region- Iraq. Validation of the identification was questioned from the principals of those centers, the person who approved the child's registration with a certificate from a doctor. An over-all of 219 was autistics and 120 healthy group were planned for this study, as well as the group of control presence in the similar environmental location as the autistic group.

2.4 Data collection

Questionnaires were distributed over the parents of the autistic children through the principal of the respective centers. The parents were informed that the participation in this study

was voluntary and written consent was obtained from consenting parents.

2.5 Statistical analysis

All the data analyses were performed using SPSS version 26 software. Frequencies, means, and standard deviations were used to summarize the data. Chi-square tests, Likelihood Ratio, Linear-by-Linear Association, and Fisher's Exact Test were used to compare differences between cases and controls. Associations between Sex Differences, Family history, and ASDs were tested by using logistic regression analyses.

3.RESULTS

In the over-all 500 questionnaires form, when we distributed in all centers of autism in Erbil city were the answers rate about 67.6%. So the exact number of participants answered

Table (1) Shows the statistical results of studied parameters (Age, Sex differences, and Family History) of Cases and Controls.

completely were 219 autistics and 119 healthy individual. The main character of offspring's and their mothers and fathers like (age, gender, and family history) has been studied as shown in Table 1. Generally, the offspring in autistic group and healthy group were statistically significant in the terms of association between sex differences and family history on the bases of ASD. The mean of mothers' age and Fathers' age in the autistic groups was higher than Control group. As well as in the term of sex differences 75.8% of the offspring in the Autism groups were male and about 57.1% in the control group were male, while 24.2% of the children in the group of autistic were female and about 42.9% in the group of control were female. As well as in the term of family history about 59 (26.9%) in 219(100.0) of autistic children have family history.

Variable	Overall (n =338)	ASD (n =219)	Non-ASD (n =119)	P-value
Age				
Child's age in years Mean (SD)	7.41 (2.9)	7.0 (3.00)	8.0 (3.00)	.004
Mother's age in years Mean (SD)	27.26 (5.583)	28.11 (5.549)	26.41 (5.618)	.678
Father's age in years Mean (SD)	31.78 (6.471)	32.08 (6.395)	31.48 (6.548)	.604
Sex Differences				<0.001
Male	234 (66.45%)	166 (75.8%)	68 (57.1%)	
Female	104 (33.55%)	53 (24.2%)	51 (42.9%)	
Family History				<0.001
Family history/ Mean (SD)	1.115 (0.323)	0.27 (0.445)	1.96 (.201)	
Yes	64 (15.55%)	59 (26.9%)	5 (4.20%)	
No	274 (84.45%)	160 (73.1%)	114 (95.8%)	

As shows in the table 3 the associations between Sex Differences and Family History on the bases of related to autism, were tested and using logistic regression analyses, that the variables of healthy group were not used in this model. When we did cross tabulation (correlation) between sex differences and family history were statistically highly significant. As well as the rate autism was higher in male than female as showed in Figure1.

Table (2) Shows the Number and Percentage of participants from Cross tabulation between sex difference and family history.

Sex Differences * Family History (Cross tabulation)					
		Family History		Total	
		No	Yes		
Gender	Male	Count	130	36	166
		% of Total	59.4%	16.4%	75.8%
	Female	Count	30	23	53
		% of Total	13.7%	10.5%	24.2%
Total		Count	160	59	219
		% of Total	73.1%	26.9%	100.0%

Table (3) Shows the statistical results from cross tabulation between gender and family history with level of Significant.

Sex Differences * Family History (Cross tabulation)					
Name of tests	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	9.620 ^a	1	.002		
Continuity Correction ^b	8.548	1	.003		
Likelihood Ratio	9.054	1	.003		
Fisher's Exact Test				.004	.002
Linear-by-Linear Association	9.576		.002		
N of Valid Cases	219				

a. 0 cells (0.0%) have an expected count less than 5. The minimum expected count is 14.28.

b. Computed only for a 2x2 table

As shown in this bar chart the ratio of autism from male to female and showed the male had more exposed to be autistic in the family in future.

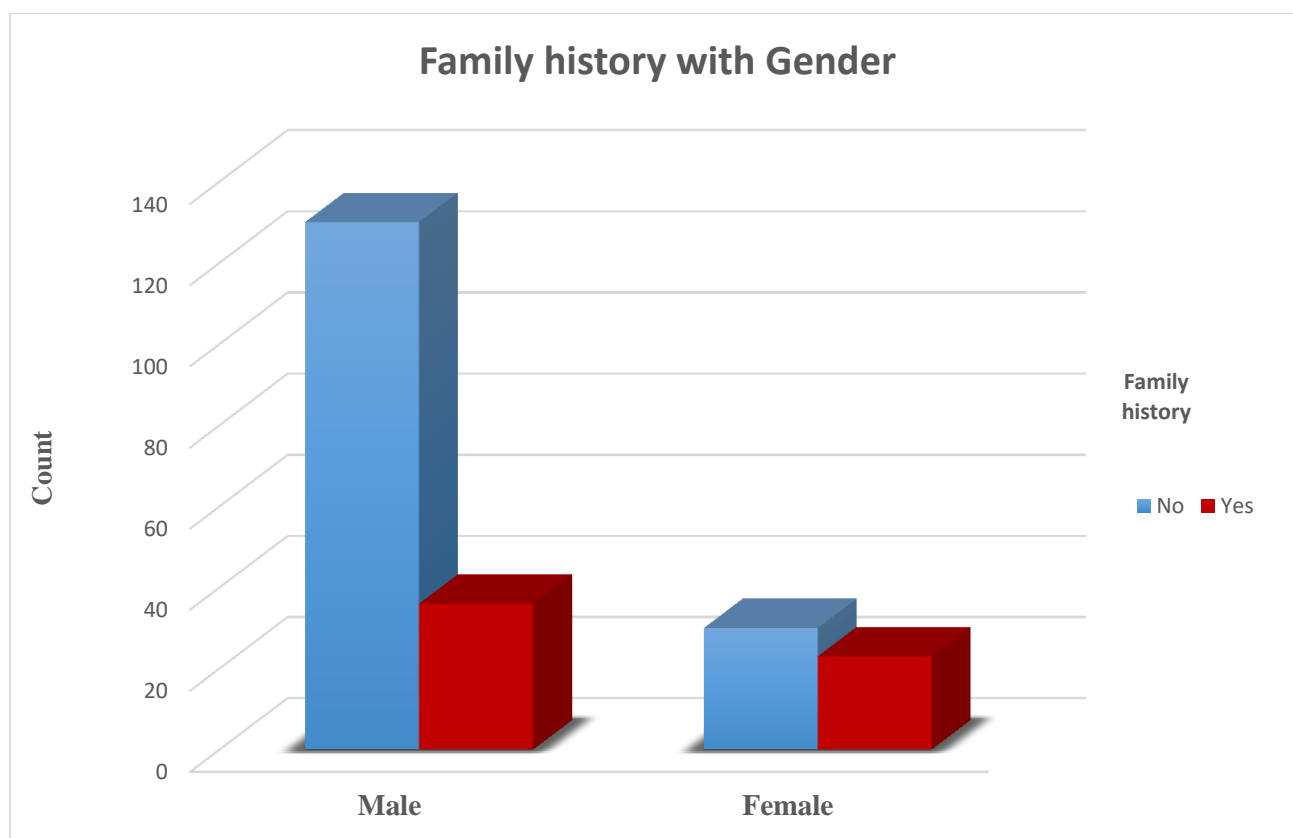


Figure 1: Bar chart show the results of cross tabulation between Gender and family history.

4.DISCUSSION

This is the first study in Kurdistan which investigated the correlation between sex differences and family history as intervening variables on ASD. Result on the table 3 and Figure 1 showed an association between Sex differences and family history and ASD. That most of the autistics are male about 166 (75.8%), while female about 53 (25.2%), which means the ratio is 3:1 and at the same time if someone be autistic in the family in future will be mostly male and this is highly significant in our study. The recent study is similar to this review that analyzed fifty-four studies, about 53,712 diagnosed with autism in the total 13,784,284 members, were 43,972 male and 9,740 female, so results of the studies carried out that true the ratio of male to female is 3:1 (Loomes et al., 2017). as well as in total 219 (100.0) autistics about 59 (26.9%) have family history. Our results agree with a large study in Sweden, they found that in 567 436 index persons about 6895 autistics had family history of neurological and mental disorder that association to ASD (Xie et al., 2019). However, our study related to this study that showed children with ASD were significantly more likely than their cohort comparisons to be male, an example of a potential confounder that is possibly more important in Middle Eastern populations is consanguinity (Sasanfar et al., 2010). We believe that this differences between autistic male and female is return to some factors like genetic factor, Environmental, physiological like some hormones, cell brain developmental problem during embryonic developmental. As well as the study of Ferri and his colleagues support our words that showed studies on the basic of biology for male predominance in autism and other neurological disorders include a higher genetic burden in women and sex-specific genetic variants that expose men to different risks or protect them or includes a discussion of epigenetic changes. Specially, testosterone of fetal is involved in many characteristics of development and may interact with neurotransmitters, neuropeptides or immune pathways to contribute to male susceptibility (Ferri et al., 2018). As well as further studies have reported trends, with siblings with (autism, attention deficit hyperactivity disorder (ADHD), or intellectual disability, or schizophrenia, depression, bipolar disorder, or anxiety), it has been reported that children with autistic parents

are more likely to have autism (Hansen et al., 2019, Jokiranta-Olkonieni et al., 2016, Jokiranta et al., 2013), these result agree with our results that in total 219 (100.0) autistics about 59 (26.9%) have family history with ASD or intellectual disability, and ADHD.

5.CONCLUSIONS

The aim of the recent study was to assess the family history and sex differences among Kurdish autistic children in Erbil city, so we have been found significant associations between Autism Spectrum Disorder, Sex Differences, and Family History, as a genetic Factors in among group of Kurdish children was at higher risk of ASD.

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Conflict of Interest (1)

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