International Journal of Science and Research (IJSR)
ISSN (Online): 2319-7064
Impact Factor (2012): 3.358

Risk Factors of Autism: A Saudia Study

Dr. Adnan Amin Alsulaimani[1], Dr. Farihan Farouk Helmy[2], Dr. Moataza M. Abdel Wahab[3]

[1]Dean of Medical College, Taif University, KSA, Associate Prof. Consultant Pediatrician & Neonatologist
[2]Consultant Child Mental Health, Assistant Professor of Pediatrics, Medical College, Taif University, KSA
[3]Associate Professor of Biostatistics, High Institute of Public Health, University of Alexandria

1. Introduction

Autism was originally defined by Leo Kanner in 1943 as an innate inability to create normal, biologically determined, emotional contact with other [(1)]. It is a chronic disorder with an onset before the age of 3 years, characterized by the following three main sets of behavioral disturbances: social abnormalities, language abnormalities and stereotyped repetitive patterns of behavior [(2)].

Autistic spectrum disorders represent 3 of the pervasive developmental disorders defined in the Diagnostic and Statistical Manual of Mental disorders, fourth Edition (DSM-IV)[(3)], and in the Diagnostic and Statistical Manual of Mental disorders, fourth Edition, Text Revision (DSM-IV-TR)[(4)]: autistic disorder(AD), Asperger disorder, pervasive developmental disorder not otherwise specified.

Prevalence estimates for autism-spectrum conditions have shown a steady increase over the past four decades. In 1978, the consensus estimates for classic autism was 4 in 10000; today autism-spectrum conditions affect approximately 1% of the population[(5,6)]. Two population-based studies,[(7, 8)] conducted by the Centers for Disease Control and Prevention in the United States reported ASD prevalence of 3.4 and 6.7 per 1000 children. A recent study conducted by Zahrani 2013[(9)] found that the overall prevalence of autism in the primary school in Taif KSA whose age ranged from 7 to 12 years was 0.035 %.This massive increase is likely to reflect seven factors: improved recognition and detection, changes in study methodology, an increase in available diagnostic services, increase awareness among professionals and parents, growing acceptance that autism can coexist with a range of other conditions, and widening of the diagnostic criteria.[(10,11)] Boys are affected with ASD more frequently than are girls with an average male-to-female ratio 4.3:1[(12)], the cause for this difference is not well understood. Several theories have been proposed among which the involvement of sex chromosome in the etiology of ASD, and the role of hormonal influences in utero. However, none of these theories has been confirmed yet [(13)].

The diagnostic criteria require that symptoms become apparent before a child is three years old it is characterized by impaired social interaction and verbal and non-verbal communication, and by restricted, repetitive or stereotyped behavior [(4)]. Children with ASD also have higher rates of co morbidities including epilepsy, gastrointestinal problems, anxiety and depression, and respiratory, food and skin allergies [(14, 15)]. The outward appearance of autistic child may not indicate a disorder, diagnosis typically comes from a complete patient history, physical and neurological evaluation [(16)].

Results from twin and family studies provide evidence that autism has an important genetic component although how many genes may be involved remain unclear[(17,18)], however less than complete concordance in monozygotic twins reveals the necessary role of non-genetic factors in the etiology of autism [(19)]. Studies have shown an association between autism and obstetric complications, prenatal or intra-partum use of medications, and parental preconception chemical exposures [(20,21)]. Moreover, a study done by Brian et al [(22)] 2014 concluded that parental characteristics, such as age and level of education, may be associated with a risk of autism.

Studies focusing on single perinatal risk factor have reported a positive association for low birth weight (<2, 500 g), gestational age at birth of less than 37 weeks, and autism[(23,24)]. Despite significant research on prenatal, perinatal, neonatal, and other risk factors in autism, the causal nature of these associations is still disputed due to several current methodological limitation of studies[(25)]. Although environmental factors such as mercury and radiation have been proposed as possible causes of autism spectrum disorders (ASDs), multiple large epidemiological studies were undertaken[(20)]. Reviews of the evidence by the Centers for Disease Control and Prevention[(26)], the American Academy of Pediatrics, the Institute of Medicine of the US National Academy of Sciences[(27)] the UK National Health Service [(28)] all found no link between the vaccine and autism.

The aim of this work was to describe epidemiological, clinical and psychometric aspects of a group of Saudia autistic children in order to determine the possible risk factors of autism.

Patients and Methods

The present study was conducted through a case control study design. It enrolled 60 cases with autism diagnosed by DSM-IV-TR criteria (American psychiatric association, 1994 diagnostic and statistical manual of mental disorders, 4th edition criteria, text revised)[(29, 30)].

The patients were 46 males (76.7%) and 14 females (23.3%). Their age ranged from 19m to 96m (mean 37, SD ± 16 months). They were recruited from the mental health clinic integrated in Pediatric clinic, Prince Mansour

Military Hospital during period June 2011 to May 2013s.

One hundred and twenty healthy children comprised the control group. They were 92 males (76.7%) and 28 females (23.3%). Their ages ranged from 19m to 96m (mean 37, SD ± 16 months). They were recruited from different outpatient clinics. Two control subjects were matched for each case, in age, gender, environment and habitat.

All cases were subjected to the following:

1. Detailed history taking about age, sex of the patient, parental consanguinity, with special emphasis on; onset, course and duration of the disease.

- Antenatal or maternal history: age at patient's birth, history of threatened abortion, parity, chronic illness as Diabetes mellitus (DM), infections, smoking (active, passive), depression, medications (antidepressant drug), exposure to x rays, or chemical agents.
- Natal and postnatal history including, gestational age, complication during Labor or delivery, history of prematurity or intrauterine growth retardation, gestational age at birth, birth weight, perinatal problems and postnatal course especially occurrence of neonatal hypoxia, resuscitation, pallor and jaundice
- Developmental history (both mental and motor): age of sitting up without support, walking unassisted, first spoken word, combining words, accurate details of cognitive abilities, gross and fine motor functions, feeding disorders,
- Abnormal sleep patterns and history of vaccination.
- Past history including: major childhood illnesses, any previous therapies used to treat the child's condition.
- Family history for any similar conditions, any genetic diseases and other psychological or mental disorders in the family.

2. Psychiatric Evaluation

- Confirmation of diagnosis using DSM-IV-TR criteria of autism (29, 30)., i.e., impairments of language, social skills, and restricted stereotyped interest or activity.
- Assessment of severity of autistic symptoms using childhood autism rating scale (CARS) (31) which rates the child on a scale from one to four in each of fifteen areas (relating to people, emotional response, imitation, body use, object use, listening response, fear or nervousness, verbal communication, non-verbal communication, activity level, and consistency of intellectual response, adaptation to change, visual response, taste, smell, touch response and general impression).
- Assessment of mental age using Stanford-Binet intelligence scale (1986) (32), to calculate the intelligence quotient (IQ). This test is used to measure the child cognitive abilities. It is suitable for children aging from 2 to 16 years. The test has two items, the verbal and the performance and the test item is chosen according to the child abilities. IQ was calculated by dividing the mental age by the chronological age multiplied by 100. Subnormal intellectual function is diagnosed when IQ is below 70.

2. Statistics Analysis

By using SPSS version 16.0, the differences in categorical variables between cases and control were compared with X^2 test.
Logistic regression was used to study the risk factors associated with the occurrence of autism. An informed written consent was obtained. The study protocol was approved by the hospital's ethical committee.

3. Results Could Be Summarized In the Following Points

1. Sociodemographic Factors

Table 1: shows that 35% of mothers of autistic patients were university graduated, in comparison to only 7.5% of control group, this difference was statistically significant (X^2= 29.19, p=0.0001). Moreover, as regards mother's work, 18.3% of mothers of autistic children were professionals and 81.7% were housewives, versus 6.7% and 93.3% of control group respectively, and this was also statistically significant (X^2 =5.76, p=0.016).

Table 1: Distribution of the study sample according to sociodemographic factors

		Group						X^2 p
		Control		Cases		Total		
		No.	%	No.	%	No.	%	
Sex	Male	92	76.7%	46	76.7%	138	76.7%	0.00 1.000
	Female	28	23.3%	14	23.3%	42	23.3%	
Father level of education	Primary	18	15.0%	11	18.3%	29	16.1%	1.77 0.770
	Preparatory	32	26.7%	13	21.7%	45	25.0%	
	Secondary	56	46.7%	26	43.3%	82	45.6%	
	University	11	9.2%	7	11.7%	18	10.0%	
	Post graduate	3	2.5%	3	5.0%	6	3.3%	
Father job	Professional	12	10.0%	7	11.7%	19	10.6%	2.61 0.457
	Military	96	80.0%	48	80.0%	144	80.0%	
	Clerck	12	10.0%	4	6.7%	16	8.9%	
	Manual	0	.0%	1	1.7%	1	.6%	
Mother level of education	Illeterate	1	.8%	1	1.7%	2	1.1%	29.19 0.0001
	Primary	24	20.0%	15	25.0%	39	21.7%	
	Prepreatory	46	38.3%	13	21.7%	59	32.8%	
	Secondary	40	33.3%	9	15.0%	49	27.2%	
	University	9	7.5%	21	35.0%	30	16.7%	
	Post-graduate	0	.0%	1	1.7%	1	.6%	
Mother job	Working	8	6.7%	11	18.3%	19	10.6%	5.76 0.016
	Housewife	112	93.3%	49	81.7%	161	89.4%	

Table 2: shows no statistically significant difference between cases and controls as regards their age, weight, height, birth order, age of mother at time of delivery, While father's age at the time of delivery was higher in cases (median 38y) than in controls (median 33y) and this was statistically significant (Mannwhitney z=2.143, p=0.016).

Table 2: Distribution of study sample according to some child and parental characteristics

	Group															Mann-Whitney Z, p	
	Control					Cases					Total						
	Mean	SD	Min	Max	Median	Mean	SD	Min	Max	Median	Mean	SD	Min	Max	Median		
Age	37	16	19	96	32	37	16	19	96	32	37	16	19	96	32	0.219	0.826
Weight	14	4	1	40	14	15	5	10	42	13	14	4	1	42	14	0.627	0.531
Height	96	10	79	136	93	95	10	80	136	94	96	10	79	136	93	0.237	0.812
Birth order	3	2	1	9	3	3	2	1	8	3	3	2	1	9	3	0.090	0.929
Age of mother at delivery of child	31	8	18	49	30	32	6	17	42	32	31	7	17	49	31	1.200	0.23
Age of father at delivery of child	34	9	20	55	33	37	8	22	52	38	35	8	20	55	34	2.413	0.016

Fig 1: showing the classification of patients according to CARS scores, 15 of patients (25%) mild, 25 of patients (41.6%) moderate, while 20 of patients(33.3%) severe.

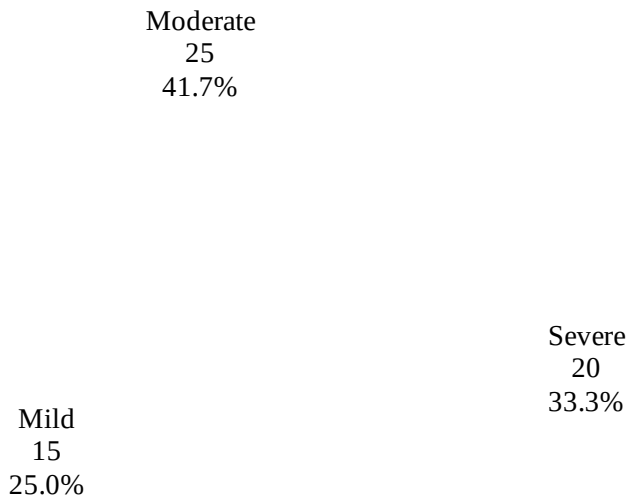

Figure 1: Classifications of autistic patients according to CARS Scores

Figure 2: The distribution of autistic patients according to degree of IQ, while 33 autistic patients (55%) had mild to severe retardation, and 22 patients (35.7%) had below average mentality, only5 autistic patients (8.3%) had normal mentality.

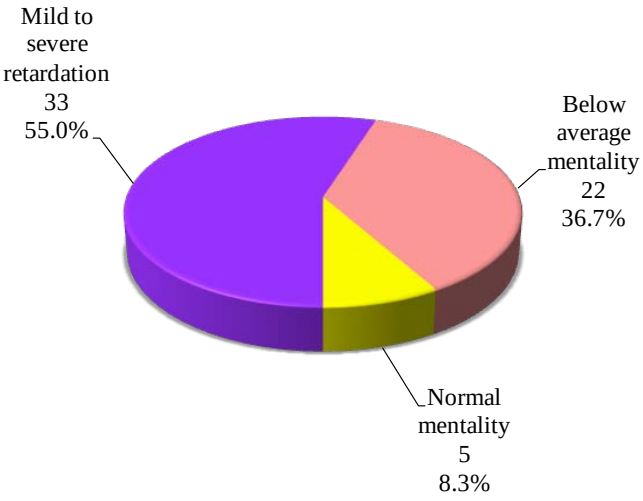

Figure 2: The degree of IQ of autistic group

Table 3: Shows that 55% of parents of autistic children were first degree consanguineous versus only 36.7% of controls, this was statistically significant (X^2=5.492, p=0.019). Moreover, 39% of autistic children had positive family history of psychiatric disease compared to only 18.3% of controls and this was statistically significant (X^2= 8.96, p=.003), 36.9% versus only 11.7% of families of cases of autistic patients and controls respectively had a positive family history of autism and this difference was statistically significant (X^2 = 15.62, p=.0001).

Table 3: Distribution of the study sample according to consanguinity and psychiatric hereditary disorders

	Group						X^2 *p*
	Control		*Cases*		*Total*		
	No.	*%*	*No.*	*%*	*No.*	*%*	
Parents Consanguinity	44	36.7%	33	55.0%	77	42.8%	
Degree of consanguinity							1.654 0.0198
First degree	21	48.8%	21	63.6%	42	55.3%	
Second degree	22	51.2%	12	36.4%	34	44.7%	
History of psychiatric disorder in family	22	18.3%	23	39.0%	45	25.1%	
Degree of relation							5.492 0.003
First degree	2	40.0%	7	30.4%	9	32.1%	
Second degree	3	60.0%	12	52.2%	15	53.6%	
Other family members	0	.0%	4	17.4%	4	14.3%	
History of autism among family members	14	11.7%	22	36.7%	36	20.0%	
Degree of relation							15.62 0.0001
First degree	1	7.7%	5	22.7%	6	17.1%	
Second degree	5	38.5%	5	22.7%	10	28.6%	
Other family members	7	53.8%	12	54.5%	19	54.3%	

Table 4: shows that 30% of mothers of autistic children compared to only 12.5% of mothers of control group were diabetics, this difference was statistically significant (X^2= 8.182, p=0.004), it is worth mentioning that 48.3% of mothers of autistic patients versus only 11.7% of controls were exposed to psychic trauma during pregnancy, this difference was also significant (X^2=29.57, p=0.0001). As regards smoking, 33.3% of mothers of autistic children were exposed to passive smoking during pregnancy compared to only 20.8% of controls and this was statistically significant (X^2=3.333,p=0.0001).

Table 4: Distribution of the study sample according to Pre natal factors

	Group						X^2 p
	Control		Cases		Total		
	No.	%	No.	%	No.	%	
Diabetes mellitus	15	12.5%	18	30.0%	33	18.3%	8.182 0.004
Viral infection	5	4.2%	3	5.0%	8	4.4%	0.065 0.798
Psychological stress during pregnancy	14	11.7%	29	48.3%	43	23.9%	29.57 0.0001
Received any antidepressive drugs	1	.8%	2	3.3%	3	1.7%	1.525 0.217
Had antipartum hge	8	6.7%	5	8.3%	13	7.2%	0.166 0.684
Smoked cigarettes	4	3.3%	1	1.7%	5	2.8%	0.411 0.521
Exposed passive smoking	25	20.8%	20	33.3%	45	25.0%	3.333 0.0001
Exposed irradiation	8	6.7%	4	6.7%	12	6.7%	0.1
Exposed to toxic materials	0	0	0	0	0	0	0

Table 5: Regarding prenatal, natal and postnatal factors, the study shows that 26.7% of cases compared to 18.3% of controls were delivered by cesarean section, yet this difference was not statistically significant. Meanwhile, 25% of cases versus 10% of controls had abnormal presentation, and 35% of cases compared to 20% of controls had low birth weight the difference were statistically significant (X^2=7.059,p=0.008*, and X^2=4.8,p=0.028*, respectively), Although there was no significant difference between cases and controls in relation to preterm and neo-natal jaundice, 41.7% of cases compared to only 26.7% of controls were admitted to nursery and this difference was statistically significant (X^2=4.159, p=0.041*).

Table 5: Distribution of the study sample according to natal factors

	Group						X^2 p
	Control		Cases		Total		
	No.	%	No.	%	No.	%	
Caesarine delivery	22	18.3%	16	26.73%	142	78.9%	1.668 0.197
Abnormal foetal presentation	12	10.0%	15	25%	153	85.0%	7.059 0.008*
Low birth weight	24	20.0%	21	35.0%	135	75.0%	4.800 0.028
Exposure to hypoxia	5	4.2%	3	5.0%	8	4.4%	.065 0.798
Pre-term delivery	21	17.5%	16	26.7%	37	20.6%	2.058 0.151
Hyperbilurubenimia	33	27.5%	17	28.3%	50	27.8%	.014 0.906
Nursery admission	32	26.7%	25	41.7%	57	31.7%	4.159 0.041

Table 6: Regarding their physical condition during the first two years of life, there was no significant difference between cases and controls in relation to congenital anomalies, chronic illnesses, intake of antibiotics during first two years, 25% of cases versus 12.5% of controls had repeated gastro-enteritis, this difference was statistically significant (X^2=4.5, p=0.034*).

Table 6: Distribution of the study sample according to Post natal factors

	Group						Chi square test
	Control		X^2		Total		X^2, p
	No.	P	No.	p	No.	%	
Genetic disease	14	11.7%	5	8.3%	19	10.6%	.471 0.493
Chronic illnesses	10	8.3%	4	6.7%	14	7.8%	.155 0.694
Recurrent gastro-intestinal problems	15	12.5%	15	25.0%	30	16.7%	4.5 0.034
Recieved more than three coarses of antibiotics during first Two years	18	15.0%	10	16.7%	28	15.6%	.085 0.771

Table 7: Regarding developmental mile-stones, there was no significant difference between cases and controls as regards motor mil-stones (sitting, and walking). Meanwhile, delay among autistic children than control group was detected for language development (saying first word (in 90% vs 9.2%), two word sentences (in 100% vs 4.2%), complete sentences (in 100% vs 3.3%)) and recognition of mother (in 90% vs 2.5%), The differences were statistically significant.

Table 7: Distribution of the study sample according to developmental mil stones

	Group						*Chi square test*
	Control		*X^2*		*Total*		*X^2*
	No.	*P*	*No.*	*p*	*No.*	*%*	*p*
Delayed sitting	17	14.2%	9	15.0%	26	14.4%	.022 0.881
Delayed walking	17	14.2%	10	16.7%	27	15.0%	.196 0.658
Delayed saying words	11	9.2%	54	90.0%	65	36.1%	113.28 0.001
Delayed two words sentences	5	4.2%	60	100.0%	65	36.1%	159.23 0.0001
Dealyed saying complete sentences	4	3.3%	60	100.0%	64	35.6%	163.1 0.0001
Delyed in recognition of mother	3	2.5%	54	90.0%	57	31.7%	141.5 0.0005

In figure (3) Shows that First noted symptoms among autistic children by their mothers was delayed speech in 28% of cases, followed by stereotyped movements in 23%, absent of eye contact in 18%, not recognizing the mother in 13%, and 10% playing alone. Moreover 5% of autistic patients were not responding to their names and 3% had convulsions.

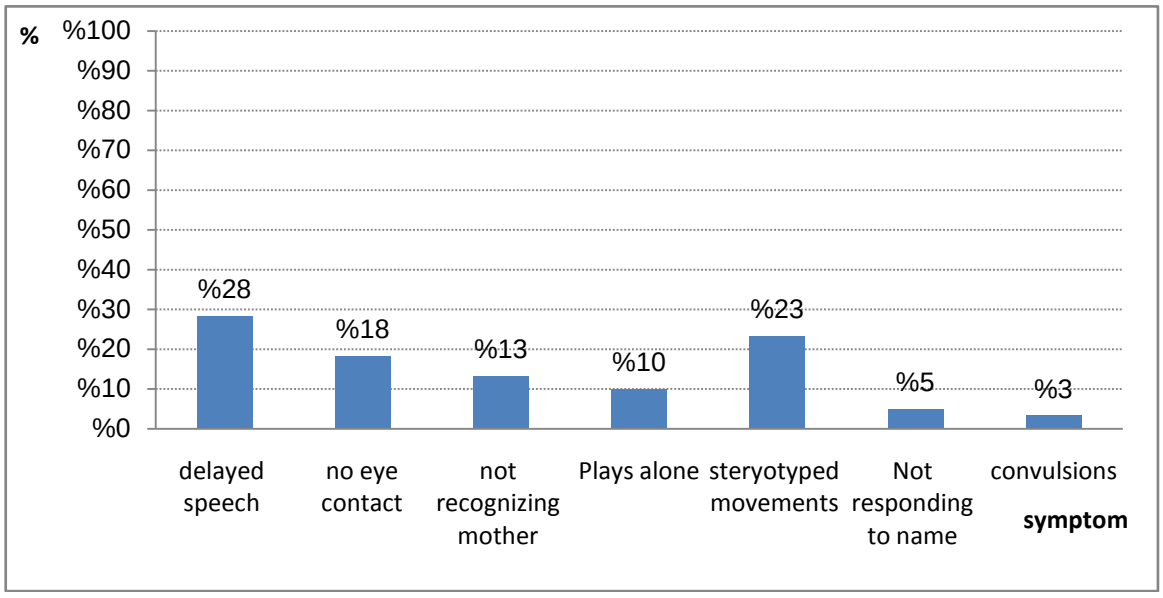

Figure 3: First Noticed Symptom

Table 8: Shows that regarding children social interaction there was statistical significant difference between cases and controls in following aspects, preferring to be alone, playing with others, starting conversation with others, sharing play with other children, cannot understand body language (X^2=180, p = .0001- X^2 = 171, p =.0001, (X^2 = 167, p=.0001, X^2=163,p=.0001, X^2=167,p=.0001) respectively.

Table 8: Distribution of the study sample according to child social interaction

	Group						X2 p
	Control		Cases		Total		
	No.	%	No.	%	No.	%	
Prefer to be alone	0	.0%	60	100.0%	60	33.3%	180 0.0001
Playing with others	118	98.3%	0	.0%	118	65.6%	171.3 0.0001
Can start conversation with others	3	2.5%	60	100.0%	63	35.0%	167.1 0.0001
Have any social relationship	116	96.7%	0	.0%	116	64.4%	163.1 0.0001
Cannot understand body language	3	2.5%	60	100.0%	63	35.0%	167.1 0.0001

Table 9: By using logistic regression model, high paternal age, positive family history of psychiatric disease, and autism, history of maternal diabetes mellitus, and exposure of the mother to stress during pregnancy were associated with a statistically significantly increased risk of autism **Hosmer and Lemeshow X^2=10.288 P=.245**

Table 9: Significant risk factors of autism by using logistic regression model

	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I. for EXP(B)	
							Lower	Upper
Father's age	.069	.024	7.994	1	.005	1.071	1.021	1.124
Family history of psychiatric disease	1.049	.452	5.380	1	.020	2.855	1.177	6.926
Family history of autism	1.954	.501	15.193	1	.000	7.059	2.642	18.859
DM of mother during pregnancy	1.566	.512	9.341	1	.002	4.787	1.754	13.067
Stress of mothers during pregnancy	2.272	.459	24.474	1	.000	9.702	3.943	23.868
Constant	-4.847-	1.027	22.269	1	.000	.008		

Hosmer and Lemeshow X^2=10.288 P=.245

4. Discussion

There is agreement amongst all professionals that autism is one of the most puzzling diseases. It is characterized by a triad of (social impairment, repetitive behavior, communication difficulties), so a kid who has autism has trouble in linking words to their meaning, doesn't like changes in routines, and acts in unusual ways[33]. Its prevalence has surged in recent years [34].

Autism is a complex disorder that doesn't have a single cause but it has distinct causes that often co-occur [35]. Although its etiology is unknown , it is estimated that the concordance rate in monozygotic twins is 60% to 92% compared with the 0% to 10% in dizygotic twins[36]. The incomplete concordance in monozygotic twins indicates a role of environmental factors, **which include certain foods, infectious diseases [37], heavy metals, solvents, diesel exhaust, and phenols used in plastic products, pesticides, alcohol, smoking, and vaccines [38].** Moreover, increased prevalence would suggest directing more attention towards changing environmental factors instead of continuing to focus on genetics-environmental factors that have been claimed to contribute to autism or exacerbate its symptoms[39,40]. However it is now believed that the mechanism underlying autism etiology is most likely polygenic and potentially epistatic and those environmental factors may interact with genetic factors to increase risk[41].

Our result pointed to the higher risk of autism among boys (76.7%) than girls (23.3%). This finding was consistent with that reported by El Bas et al [42] and Itzchak et al [43] who found that the percentage of autism was (82%, 81%) among males compared to (18%, 19%) among females respectively. Moreover Shu et al. [44] said that autism is more than twice as common in boys as girls, and this ratio increases to 5:1 at the high-ability end of the autism spectrum. This could be because of genetic differences between the sexes, or that the criteria used to diagnose autism are based on the characteristics of male behavior. However, our understanding is far from complete, and this will remain the case until we know more about the causes of autism.

King and Bear man [45] studied the relationship between socioeconomic status and prevalence of autism, their results showed that higher levels of parental education and parental economic resources were consistently associated with an increase in the likelihood of diagnosis. In relation to our study while parental economic resources cannot be a measured variable as both cases and control were military patients and having same eligibility to free services, there was statistically significant difference between mothers of autistic children and control group in relation to university graduation (35%, 7.6%) respectively. Moreover, as regards mother's work, 18.3% of mothers of autistic children were professionals and 81.7% were housewives, versus 6.7% and 93.3% of control group, respectively, making maternal education important factor for diagnosis.

While Paul et al [46] reported that the median age of identification of autistic cases was 5.7 years, according to our result it was 2.8 years. This difference can be explained in the light of that there is often a wide variation in the age which children present for diagnosis or to obtain necessary therapy, in different socioeconomic groups. Katarzyna et al [47] reported that the earliest symptoms of autism often appear before a child's second birthday, but most children with autism are not diagnosed until they are in preschool or elementary school. Parametric survival models revealed that several factors were associated with a younger age of identification: being male, having an IQ of 70 or lower [46].

The possibility that autism is more common in offspring of older parents has generated considerable interest[48], our study showed that although there was no difference between mother age of autistic children and mothers of control group at time of delivery, father's age at the time of delivery was higher in cases (median 38) than in controls (median 33) and this was statistically significant. Our result is consistent with Reichenberg et al [49] illustrated that there was an association between advancing paternal age and risk of ASD. They concluded that offspring of 40 years men or older were 5.75 times more likely to have ASD compared with offspring of men younger than30 years, while advancing maternal age showed no association with ASD after adjusting for paternal age. Confirmation of such an association could have important public health implications in light of increasing trends in recent decades regarding paternal age among KSA community.

According to Cars score [31] 33% of our cases had sever degree of autism, 41% had moderate degree, and 25% had mild degree. In relation to IQ 55% of our patients presented with mild to severe mental retardation, 35.8% with below average mentality and 8.3% with normal mentality. This is in accordance with Baron-Cohen et al[50]. who reported that autistic children have spectrum of IQ ranged from 0 to 60.

Although many authors [42,51] had reported that most of parents of autistic children are non-consanguineous, our study showed that the majority of autistic parents (55%) was first degree consanguineous. Moreover, this study showed a statistically significant difference between cases and controls concerning family history of psychiatric disorders, as 39% of autistic children had positive family history of psychiatric disease compared to only 18.3% of controls. This is concordant with researchers[51,52] that discovered that parents of autistic children are twice as likely to have had psychiatric illness, and that rates of autism rose substantially if parents had suffered schizophrenia, depression or a range of other personality and psychiatric disorders.

Concordant to AL-Baz et al [42]results that reported family history of autism in 16% of cases versus 1% of control, our results revealed that 36.9% versus only 11.7% of families of cases of autistic patients and controls respectively had a positive family history of autism and this difference was statistically significant.

An association between general developmental impairments and maternal diabetes has been previously observed[53], more over a population-based study [54]in young children provided evidence that maternal metabolic conditions are a risk factor for autism, developmental delay without autistic symptoms, and impairments in several domains of development, particularly expressive language, after adjusting for sociodemographic and other characteristics. This current study showed that 30% of mothers of autistic children compared to only 12.5% of mothers of control group were diabetics, this difference was statistically significant.

A study conducted by Ronald[55] et al found associations between autism and factors such as tropical storms, family discord and women's self-reports of stress during pregnancy. Although our result is in concordant with this as 48.3% of mothers of autistic patients versus only 11.7% of controls were exposed to psychic trauma during pregnancy, it contradict the result of a recent epidemiological study[56] which found that experiencing a stressful event, such as the death of a family member or a severe illness, during pregnancy does not increase the risk of having a child with autism. In relation to smoking during pregnancy, it has been linked to numerous pregnancy complications and birth defects, such as low birth weight, preterm labor, congenital heart defects, and placental problems[57], no studies showed direct correlation between maternal smoking during pregnancy and autism. Researchers involved with the Center for Disease Control and Prevention's United States[58] autism surveillance program found that children with high-functioning autism, such as those with Asperger's Disorder, were more likely to be born to women who smoked during pregnancy. Our results revealed that 33.3% of mothers of autistic children were exposed to negative smoking during pregnancy compared to only 12.8% of controls and this was statistically significant, it is worth mentioning that due to cultural basis we cannot be sure whether mothers of autistic children were smokers or were really exposed to negative smoking as they stated.

Regarding natal and post-natal factors, a recent study[59] noted that pregnant women who have their labor started or sped up artificially are slightly more likely to have autistic children, putting an explanation that "infants destined to develop autism are less likely to send out the correct biochemical signals for normal progression of labor. Concerning our result although 26.7% of cases compared to 18.3% of controls were delivered by cesarean section, yet this difference was not statistically significant. In relation to birth weight and autism, 35% of cases compared to 20% of controls had low birth weight the difference were statistically significant. Birth weight is the net result of at least three factors: genetic growth potential, duration of the pregnancy, and rate of fetal growth[60]. As the genetic growth potential is unknown, and our study showed no significant difference between cases and controls in relation to length of gestation, therefore this indicates that our study shows a relation between being small for gestational age due to intrauterine growth retardation and not to preterm birth is associated with an increased risk of autism. These findings are consistent with

results of a recent population-based case-control study conducted in Finland 2013 [61] which concluded that low birth weight, is strongly related to childhood autism.

A meta-analysis review published in 2010[62] that examined Over 60 perinatal and neonatal factors showed association between abnormal presentation, in general specially breech presentation, fetal distress and an increased risk of autism and this is consistent with our result as 25% of cases versus 10% of controls had abnormal presentation, and 41.7% of cases compared to only 26.7% of controls were admitted to nursery due to fetal distress and this difference was statistically significant. It is worth mentioning that our study showed statistically significant difference between number of cases and controls admitted to nursery and as we know that preterm, small for gestational age, hyper bilurbinemia, and fetal distress are common causes of nursery admission, plus that there was no statistical difference between cases and controls in relation to preterm and hyper-bilirubinemia, so we can conclude that according to our result fetal distress, small for gestational age are two important risk factor for autism.

Regarding physical condition during first two years of life, there was no significant difference between cases and controls in relation to congenital anomalies, chronic illnesses, intake of antibiotics during first two years. Regarding the relation between children gastrointestinal disorders to autism: nested case-control study [63] using data from the UK General Practice Research Database found no evidence that children with autism were more likely than children without autism to have had defined gastrointestinal disorders at any time before their diagnosis of autism, this is inconsistent with our result that concluded that 25% of cases versus 12.5% of control had repeated gastro-enteritis, this difference was statistically significant.

Although there was no statistical significant difference between cases and controls in relation to motor mile stones, there was significant difference in relation to language development. This is inconsistent with an Egyptian study [42] that was conducted to determine possible risk factors of autism; they found statistically significant difference in all studied developmental milestones between autistic children and control group. Moreover McPartland [64] found that children with autism may be delayed in acquiring motor activity, such as bicycle riding. They may be poorly coordinated or have an abnormal gait or posture, poor hand writing.

In 28.3% of our patients the specific presenting symptom of autism was delayed speech, in 18.3% started with loss of eye contact, 13.3% the condition presented with inattention to mother in 10% symptoms started with preferring to play alone. In concordance with our results Noens et al[65], reported that about a third to a half of individuals with autism do not develop enough natural speech to meet their daily communication needs. Also Volkmar and klin[66] concluded that social impairments were recognizable in ASDs diagnosed children as poor eye contact, inability to utilize nonverbal gestures, and inability to play the same way as typically developing children. Other studies [42, 67] reported that children with autism presented a series of abnormal behaviors, including no social smile, no eye contact, no respond to own name and delay in language.

To conclude autism is one of five disorders that falls under the umbrella of Pervasive Developmental Disorders (PDD), a category of neurological disorders characterized by ‘‘severe and pervasive impairment in several areas of development.’[2,3,4]’ Despite a growing body of research, the etiology of autism remains unknown and highly uncertain[35]. According to our logestic regression they were consistent to results of recent studies that showed that high paternal and not maternal age[50], positive family history of psychiatric disorder[51,52] and autism among family members[42], maternal diabetes mellitus[54], exposure of mothers to stress [55] were associated with high risk of autism. Other risk factors male children, high maternal education consanguinity, abnormal presentation, low birth weight due to small for gestational age, nursery admission and repeated gastrointestinal disorders although not proven as independent risk factors for autism , these variables should be examined in future studies that use large population based birth cohorts with precise assessments of exposures and potential confounders.

Autism is a devastating condition with no known cure. The rising prevalence, coupled with the severe emotional and financial impact on the families, underscores the need for large, prospective, population-based studies with the goal of elucidating the early-life modifiable risk factors.

5. Recommendations

- Early detection of cases of autism through: National screening program (CHAT) for preschoolers and increase the awareness of populations and families by the early symptoms and signs of autism as delayed speech and loss of eye to eye contact.
- All children should be screened with standardized developmental tools at specific intervals (at the 9–18–24–30 months) for early detection of ASDs.
- Proper management of autistic children including behavior, educational, cognitive and pharmacotherapy through expanding and fortifying the autism specialized rehabilitation centers.

Acknowledgments

The authors are most grateful to Administration and staff of Prince Mansour Military Hospital and Al-Hada research Center (Taif, KSA) for their great help. We also thank all who participated in the study.

References

[1] Kanner L. Autistic disturbances of affective contact. Nerv Child. 1943; 2: 217-250.
[2] F.R.Volkmar,A.Klin .Issues in the classification of autism and related conditions.F Volkmar, R Paul, A. Klin,D. Cohen, Handbook of autism and pervasive

developmental, neurobiology, and behavior, 3rded, 2005, Wiley, Hoboken,NJ,pp. 5-41
[3] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition(DSM-IV). Washington, DC: American Psychiatric Publishing; 1994
[4] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, text Revision(DSM-IV-TR). Washington, DC: American Psychiatric Publishing; 2000
[5] Rutter M. Diagnosis and definition of childhood autism. J Autism Child Schizophr 1978;8:139-61
[6] Barid G, Simonoff E, Pickles S, Meldrum D, etal. Prevalence of disorders of the autism spectrum in a population cohort of children in South Thames: the special needs and Autism Project(SNAP). Lancet 2006;368:210-5
[7] CDC. Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network, United States,2006. MMWR 2009:58(SS-10)
[8] CDC. Prevalence of autism spectrum disorders-Autism and Developmental Disabilities Monitoring Network,14 sites, United States,2008. MMWR 2012:61(No.SS-3
[9] Al-Zahrani A. Prevalence and clinical characteristics of autism spectrum disorders in school-age children in Taif-KSA. Int J Med SCI Public Health 2013; 2(3); 578-582
[10] Charman T. The prevalence of autism spectrum disorders. Recent evidence and future challenges. Eur Child Adolesc Psychiatry 2002; 11:249-56
[11] Wing L, Potter D. The epidemiological of autistic spectrum disorders: is the prevalence rising? Ment Retard Dev Disabil Res Rev 2002; 8:151-61
[12] Fombonne E. 2005. Epidemiological studies of pervasive Developmental disorders. In Handbook of Autism and Pervasive Developmental Disorders, ed. FVolkmar, R Paul, A Klin, D Cohen, pp. 42-69. Hoboken,NJ: Wiley
[13] Rutter M. Incidence of autism spectrum disorder: changes over time and their meaning. Acta Paediatr.2005;94:2-15
[14] Gurney JG, McPheeters ML, Davis MM. Parental report of health conditions and health care use among children with and without autism . Arch Pediatr Adolesc Med.2006;160(8):825-30
[15] Ghaziuddin M, Ghaziuddin N, GredenJ. Depression in persons with autism: implications for research and clinical area. J Autism Dev Disorders.2002;32(4):299-306
[16] Nazeer N, Ghaziuddin M. Autism Spectrum Disorders: Clinical Features and Diagnosis. Pediatric Clinics of North America:2012;59(1):19-25
[17] Risch N, Spiker D, Lotspeich L, etal A genomic screen of autism : evidence for a multilocus etiology. Am J Hum Genet. 1995;65:493-507
[18] Pickles A, Bolton P, Macdonald H, etal.. Latent-class analysis of recurrence risks for complex phenotypes with selection and measurement error: a twin and family history study of autism. Am J Genet. 1995;57:717-726
[19] Richler J, Luyster R, Risi S, et al Is there a regressive phenotype of autism spectrum disorder associated with the measles-mumps rubella vaccine? A CPEA study. J Autism Dev Disorder. 2006;36(3):299-316
[20] Gardener H, Spiegelman D, Buka S. Perinatal and Neonatal Risk factors for Autism: A comprehensive Meta-analysis. Pediatrics. 2011;128(2):344-355
[21] Gardener H, Spiegelman D, Buka S. Prenatal risk factors for autism: a comprehensive meta-analysis. Br J Psychiatry. 2009;195(1):7-14
[22] Brian M. D'Onofrio, Martin E. Rickert, Emma Frans, Ralf Kuja-Halkola, Catarina Almqvist, Arvid Sjölander, Henrik Larsson, Paul Lichtenstein (2014). "Paternal Age at Childbearing and Offspring Psychiatric and Academic Morbidity". JAMA Psychiatry 71 (4): 432–438.
[23] Abel K, Dalman C, Svesson A, et al. Deviance in Fetal Growth and Risk of Autism Spectrum Disorder. Am J Psychiatry 2013; 170:391–398
[24] Liperopoulous C, Bassan H, Sullivan N. Positive screening for autism in Ex-preterm Infants: Prevalence and Risk Factors. Pediatrics Vol. 121 No 4 Aprail 1, 2008 pp. 758-765
[25] Bolton P, Pickles A, Harrington R. Season of birth : issues, approaches and findings for autism. J Child Psychol Psychiatry 1992, Vol 33,: 509-530
[26] Measles, mumps, and rubella (MMR) vaccine". Centers for Disease Control and Prevention. 22 August 2008. Archived from the original on 7 April 2008. Retrieved 2008-12-21.
[27] Institute of Medicine (US) Immunization Safety Review Committee (17 May 2004). Immunization Safety Review: Vaccines and Autism. Institute of Medicine of the National Academy of Sciences. PMID 20669467. Retrieved 13 June 2007.
[28] 28 – MMR The facts. NHS Immunisation Information. 2004. Retrieved 2007-09-19
[29] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Washington, DC: American Psychiatric Association; 1994.
[30] American Psychiatric Association. Diagnostic and statistical manual of mental disorders. 4th ed. Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Publishing; 2000
[31] E. Schopler, R.J. Reichler, B.R. Renner The childhood autism rating scale (CARS): for diagnostic screening and classification of autism Irvington, New York (1986)
[32] Stanford-Binet International Scale. 4th ed. 2 years to adult, useful for handicapped children; 1986
[33] Kidd P. Autism, an extreme challenge to integrative medicine. Part I: the knowledge base Altern Med Rev, 7 (2002), pp. 292–316
[34] 34- Caronna E,, Milunsky J, Tager-Flusberg H. Autism spectrum disorders: clinical and research frontiers. Arch Dis Child 2008;93:518-523 doi:10.1136/adc.2006.115337
[35] 35- Freitag C M. The genetics of autistic disorders and its clinical relevance: a review of the literature. Mol Psychiatry, 12 (1) (2007), pp. 2–22
[36] 36- Bailey A, Le Couteur A, Gottesman I, Bolton P, Simonoff E, et al. 1995. Autism as a strongly genetic disorder: evidence from a British twin study. Psychol.

Med. 25:63–77
[37] 37- Libbey JE, Sweeten TL, McMahon WM, Fujinami RS. 2005. Autistic disorder and viral infections. J. Neurovirol. 11:1–10
[38] 38- Chakrabarti, E. Fombonne Pervasive developmental disorders in preschool children JAMA, 285 (24) (2001), pp. 3093–3099
[39] 39- Newschaffer CJ, Croen LA, Daniels J et al.. The epidemiology of autism spectrum disorders . Annu Rev Public Health. 2007 [Retrieved 2009-10-10];28:235–58. doi:10.1146/annurev.publhealth.28.021406.144007. PMID 17367287.
[40] 40- T.L. Arndt, C.J. Stodgel, P.M. Rodier. The tetralogy of autism. Int J Dev Neurosci, 23 (2–3) (2005), pp. 189–199
[41] 41- Epigenetics of autism spectrum disorders. Hum. Mol. Genet. (2006) 15 (suppl 2): R138-R150. doi: 10.1093/hmg/ddl213
[42] 42- El-Baz F, Ismael N, Nour El-Din S. Risk factors for autism: An Egyptian study. Egyptian Journal of Medical Human Genetics Volume 12, Issue 1, May 2011, Pages 31–38
[43] 43- Itzchak EB, Zachor DA, Assaf Harofeh. Male: female ratio is related to autism spectrum disorder in the family and to maternal age. Harofeh Medical Center, Zerifin, Israe. Franklin Hall B Level 4 (Philadelphia Marriott Downtown l); 2010.
[44] 44- Shu, F B, Lung, Y. Change The mental health in mothers with autistic children: a case –control study in Southern Taiwan kasohsing J Med Sci (6) (2000), pp. 308–314
[45] 45- King M, Bearman P. Socioeconomic Status and the Increased Prevalence of Autism in California. Am Sociol Rev. Apr 1, 2011; 76(2): 320–346.
[46] 46- Paul T, Maureen D, Matthew M, Craig N, S.M.etal.Timing of identification among children with an autism spectrum disorder: findings from a population-based surveillance study. J Am Acad Child Adolesc Psychiatry, 48 (5) (2009), pp. 474–483
[47] 47- Katarzyna K, Rhea A, Fred V. Autism spectrum disorder in the second year: stability and change in syndrome expression J Child Psychol Psychiatry (2006)
[48] 48- Maureen S. Durkin, Matthew J. Maenner, Craig J. Newschaffer. Advanced Parental Age and the Risk of Autism Spectrum Disorder. Am J Epidemiol. 2008;168(11):1268-1276
[49] 49- Reichenberg A, Gross R, Weise M, et al. Advancing paternal age and autism. Arch Gen Psychiatry, 63 (9) (2006), pp. 1026–1032
[50] 50- Baron-Cohen S, Hoekstra R,, Knickmeyer R et al. The autism-spectrum quotient (AQ): adolescent version J Autism Dev Disord, 36 (2006), pp. 343–350
[51] 51- Al-Hifthy E, Ghaziuddin M Autism in Saudi Arabia: Presentation, Clinical Correlates and Comorbidity Transcultural Psychiatry June 2009 vol.
[52] 52- Daniels J, Forssen, U , Hultman C. Parental Psychiatric Disorders Associated With Autism Spectrum Disorders in the Offspring. Pediatrics Vol. 121 No. 5 May 1, 2008 pp. e1357 -e1362 oi:10.1542/peds.2007-2296
[53] 53- Rizzo TA, Dooley SL, Metzger BE, etal. Prenatal and perinatal influences on long-term psychomotor development in offspring of diabetic mothers. Am J Obstet Gynecol. 1995;173(6):1753–1758
[54] 54- Krakowiak P, Walker C, Bremer A, Maternal Metabolic Conditions and Risk for Autism and Other Neurodevelopmental Disorders Pediatrics 2012;129;e1121;
[55] 55- Ronald A, Pennell CA, Whithouse A J. Prenatal Maternal stress associated with ADHD and Autistic traits in early childhood. Front Psychology 2010(6) DOI: 10.1371
[56] 56- Rai D, Golding J, Magnusson C et al. Prenatal and Early Life Exposure to Stressful Life Events and Risk of Autism Spectrum Disorders: Population-Based Studies in Sweden and England. PLOS ONE 2012
[57] 57- Ness RB, Grisso JA, Hirschinger N, et al. (February 1999). "Cocaine and tobacco use and the risk of spontaneous abortion". N. Engl. J. Med. **340** (5): 333–9
[58] 58- Centers for Disease Control and Prevention. 2007. Preventing Smoking and Exposure to -Secondhand Smoke Before, During, and After Pregnancy.
[59] 59- Gregay SG, Anthopolos R, Grotegut CA. Association of autism with increased or augmented childbirth in north Carolina birth record (1990-1998) and education research (1997-2007) daraisase. Jana Pediatrics 2013; 167(10): 959-66.
[60] 60- Larson HJ, Eaton WW, Madsen KM, et al. Risk factors for autism: parental factors, parental psychiatric history, and socioeconomic status. American Journal of Epidemiology 2005; 161:916-25.
[61] 61- Lampi KM, Lehtonen L, Swominen A, et al. Risk of autism spectrum disorders in low birth weight and small for gestational age infant. The Journal of Pediatric 2012; 161(5): 830-836.
[62] 62- Garderer H, Spicgelman D, Buka SL. Perinatal and nconaral risk factor for autism: a comprehensive meter-analysis. Pediatrics 2011; 128(2): 344-355.
[63] 63- Black C. Relation of childhood gastrointestinal disorders to autism: nested cases-worked study using data from UK general practice research database. BMJ 2002; 325: 419.
[64] 64- McParland JP. Asperger syndrome. Adolecs Med Clinic 2006; 17(3): 771-788.
[65] 65- Noens I, Berchelacer-Onnes V, Verporten R, et al. The com for: an instrument for the indication of augmuitive communication in people with autism and intellectual disability. J intellec disabl Res. 2006; 50(9): 261-632.
[66] 66- Volkmar FR, Klin A, Rubin E, et al. Autism and the pervasive developmental disorders. J Child Psychology and Psyctratry 35(5): 861-876.
[67] 67- Xicy, Ma HW, Hua TY, et al. Behavioral patterns of artistic children during infancy. Chunases J Contemy Pedar 2006: 6: 470-472