Determinants of autism among children in Makkah Al-Mukarramah City, Saudi Arabia: A case-control study

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Abstract

Aim of Study: To identify risk factors associated with autism among autistic children in Makkah Al-Mukarramah City.

Subjects and Methods: Following a case-control study design, 100 autistic children 3-12 years old were selected from four rehabilitation centres in addition to 100 age-matched non-autistic children (control group) who were recruited from nearby kindergarten centers and primary schools. Based on relevant review of literature, an Arabic language questionnaire was designed by the researcher.

Results: There were significantly more male autistic children than non-autistic children (71% and 52%, respectively, p=0.006), with a female:male ratio of about 1:3. However, autistic and non-autistic children did not differ significantly according to their age groups, nationality or birth order. Most autistic children (74%) were diagnosed at the age of 4-8 years. The mean age at diagnosis was 6.1±2.4 years. The mean age of mothers of autistic children at their birth was significantly older than that of mothers of non-autistic children (35.1±5.9 years and 35.1±5.9 years, respectively, p=0.015), while mean age of fathers of autistic children at their birth was significantly older than that of fathers of non-autistic children (42.6±7.7 years and 39.7±8.8 years, respectively, p=0.016). Mothers of autistic children have been significantly more exposed to smoke than those of non-autistic children (15% and 6%, respectively, p=0.038). Autistic and non-autistic children did not differ significantly according to their family, prenatal and postnatal characteristics.

Conclusions: Most autistic children become diagnosed at 4-8 years old. The female:male ratio among autistic children is about 1:3. Advanced parental age is a significant risk factor for autism among their children. Exposure of mothers to smoke is a risk factor for autism among their children.

Recommendations: Screening of children, especially boys, for autism during their visits to the well-baby clinics and at school entry. Avoidance of exposure of pregnant mothers and children to smoke. Provision of health education to parents about autism and the importance of avoiding pregnancy at advanced parent ages.

Key words: Autism, Case Control, Risk factors, Saudi Arabia.

Introduction

Autism is a chronic neurodevelopmental disorder associated with an inability to communicate socially or to respond normally to some stimuli in the environment. A systematic review was done to estimate the global effect of autism in 188 countries and showed that autism affects about 21.7 million people as of 2013 (1).

According to the Center for Disease Control and Prevention, about 1 in 68 children has been estimated to have autism in U.S. It is five times more prevalent in boys than girls (2).

The etiology of autism is unknown, but several different factors that make a child more likely to have autism include biological and environmental factors. The genetic factors play a significant role in the disease. However, the presence of environmental risk factors can interact with these genetic factors and increase the possibility of occurrence of the disease (3-4).

Evidence suggests that the critical period for developing autism occurs before, during, and immediately after birth. A meta-analysis was done at the Department of Epidemiology, Harvard School of Public Health, and examined over 60 perinatal and neonatal factors and found an association with some of these factors (5).

Another systematic review summarized the pre, peri and neonatal risk factors that contribute to autism, and concluded that these factors may have a small risk for autism. However, the distinction was not possible if these risks should be considered purely environmental or relevant to genetic vulnerability (6).

A case–control study in Jamaica concluded that maternal and paternal age are associated with autism. Prematurity, low birth weight and small for gestational age are other risk factors for autism determined in research (7). These factors were found to be associated with autism in a case-control study conducted in Finland (8). Furthermore, a case-control study carried out in China, identified nine maternal risk factors that revealed a significant association with autism (9).

In addition, several maternal lifestyle factors such as nutrition and substance use can be related to many neurodevelopment diseases and therefore, may not be unique risk factors for autism (10).

A systematic review on epidemiology of autism concluded that there are limitations in research and no studies on identifying the burden and risk factors of autism in Gulf countries (11).

In Oman, a case-control study about the relation between breastfeeding and autism concluded that the risk of autism increases with delayed breastfeeding and no colostrum introduction, while exclusive breastfeeding and its continuation for two years significantly decreased the risk (12).

Most studies in Saudi Arabia on autism focused on biomarker studies as risk factors. A cross-sectional study done on 49 autistic children found that the communication problem is the most characteristic of an autistic patient with the presence of consanguineous marriages in approximately 29% (13).

Several diagnostic tests make an early diagnosis of autism by the age of 2 years very reliable. However, many cases do not reach final diagnosis until an age of 3 years. Currently, there is no cure for autism but research shows that early intervention treatment services up to 3 years can improve and increase the quality of life and functional independence (2).

The early diagnosis and early intensive treatment have the potential to affect the outcome (14). The diagnosis of autism can be made clinically, based on the history, examination, and observation of behavior. The establishment of appropriate management strategies in the early years can help to minimize or even avoid subsequent behavioral problems (15).

However, despite the increasing prevalence of autism worldwide, there is lack of research about its nature, determinants, diagnosis, and management. Therefore, this study aimed to identify risk factors associated with autism among autistic children in Makkah Al-Mukarramah City.

Subjects and Methods

Following a case-control research design, this study was conducted during 2018 in Makkah Al-Mukarramah City. By simple random sampling, four rehabilitation centers were selected. All autistic children aged 3-12 years old registered in the selected study rehabilitative centers were included. Children with associated other diseases (e.g., ADHD or epilepsy) were excluded.

The minimum sample size for this study was decided according to Dahiru et al. (16), to be 196. Therefore, to fulfill the required sample size, the researchers included 200 children, 100 autistic children and 100 age-matched non-autistic children (control group) who were recruited from nearby kindergarten centers and primary schools.

Based on relevant review of literature, an Arabic language questionnaire was designed by the researcher. The questionnaire was validated by academic professors of epidemiology and family medicine. The questionnaire included demographic data of parents and subjects, as well as pre, peri and neonatal risk factors that may be associated with autism.

A pilot study was conducted on 20 children (10 autistic children and 10 healthy controls) to test the clarity of the study questionnaire. Moreover, the questionnaire's internal consistency was tested by applying Cronbach's alpha coefficient. The data of participants in the pilot study were not included in the main study.

Collected data were coded before computerized data entry. The Statistical Package for Social Sciences (SPSS version 23) was used for data entry and statistical analysis. Descriptive statistics (e.g. number, percentage, mean, and standard deviation) were calculated and tests of significance, (i.e., X^2 and unpaired t-test) were applied. P-values < 0.05 were considered as statistically significant.

Results

Table 1 shows that there were significantly more male autistic children than non autistic children (71% and 52%, respectively, p=0.006), with a female:male ratio of about 1:3. However, autistic and non-autistic children did not differ significantly according to their age groups, nationality or birth order.

Figure 1 shows that 74% of autistic children were diagnosed at the age of 4-8 years, while 12% were diagnosed before their fourth year of age and 14% were diagnosed after their 8th year of age. The mean age at diagnosis was 6.1±2.4 years.

Table 2 shows that autistic and non-autistic children did not differ significantly according to their family characteristics, i.e., number of siblings, parents' educational status, parents' consanguinity, family monthly income or family history of autism.

Table 3 shows that mean age of mothers of autistic children at their birth was significantly older than that of mothers of non-autistic children (35.1±5.9 years and 35.1±5.9 years, respectively, p=0.015). Similarly, mean age of fathers of autistic children at their birth was significantly older than that of fathers of non-autistic children (42.6±7.7 years and 39.7±8.8 years, respectively, p=0.016). Mothers of autistic children have been significantly more exposed to smoke than those of non-autistic children (15% and 6%, respectively, p=0.038). However, other prenatal characteristics of autistic children did not differ significantly from those of non-autistic children, regarding maternal diseases during their pregnancy, intake of non-prescribed drugs during pregnancy, fetal problems or duration of pregnancy.

Table 4 shows that natal characteristics among autistic children did not differ significantly with those of non-autistic children.

Table 5 shows that characteristics of autistic children after labor did not differ significantly from those of non-autistic children, regarding their admission to pediatric intensive care unit, incidence of neonatal jaundice or type of feeding during the first 6 months.

Table 1: Personal characteristics of participant autistic compared with non-autistic children

Characteristics	Non-autistic		Autistic		P Value
	No.	%	No.	%	
Age groups					
• ≤5 years	11	11.0	9	9.0	
• 6-10 years	78	78.0	77	77.0	
• >10 years	11	11.0	14	14.0	0.753
Gender					
• Male	52	52.0	71	71.0	
• Female	48	48.0	29	29.0	0.006
Nationality					
• Saudi	81	81.0	88	88.0	
• Non-Saudi	19	19.0	12	12.0	0.171
Birth order					
• 1st	27	27.0	23	23.0	
• 2nd-3rd	29	29.0	39	39.0	
• 4th +	44	44.0	38	38.0	0.328

Figure 1: Age at diagnosis of autism

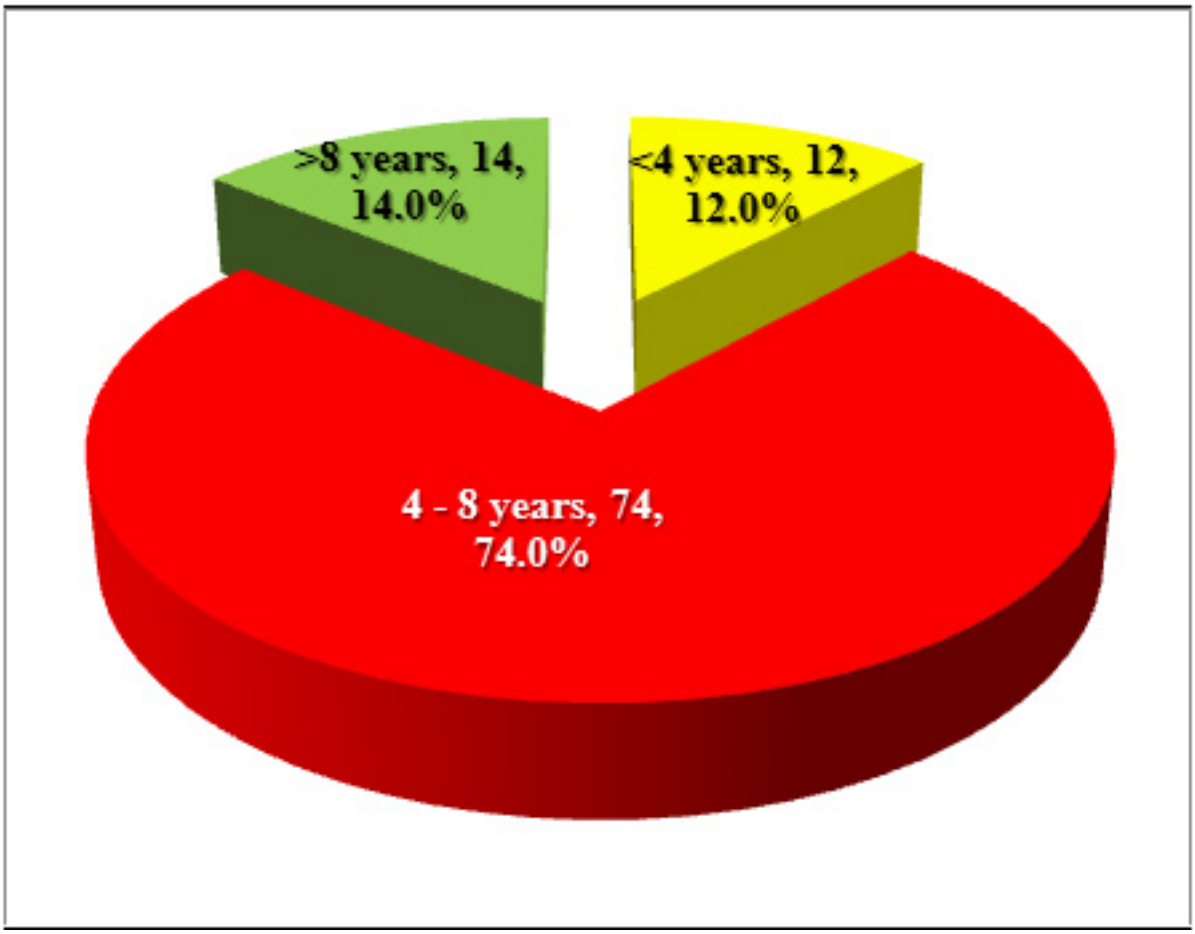

Table 2: Family characteristics of participant autistic compared with non-autistic children

Characteristics`	Non-autistic		Autistic		P Value
	No.	%	No.	%	
No. of siblings					
• 0	1	1.2	4	4.7	
• 1-4	68	80.0	60	69.8	
• 5+	16	18.8	22	25.6	0.198
Mother's educational status					
• Illiterate	9	9.0	13	13.0	
• Primary	9	9.0	10	10.0	
• Intermediate	9	9.0	11	11.0	
• Secondary	43	43.0	34	34.0	
• University	30	30.0	32	32.0	0.718
Father's educational status					
• Illiterate	8	8.0	7	7.0	
• Primary	10	10.0	11	11.0	
• Intermediate	10	10.0	24	24.0	
• Secondary	33	33.0	26	26.0	
• University	39	39.0	32	32.0	0.116
Parents' consanguinity	41	41.0	45	45.0	0.568
Family monthly income					
• <5000 SR	31	31.0	33	33.0	
• 5000-10000 SR	50	50.0	41	41.0	
• >10000 SR	19	19.0	26	26.0	0.360
Family history of autism	7	7.0	7	7.0	1.000

Table 3: Prenatal and natal characteristics of participant autistic compared with non-autistic children

Prenatal Characteristics	Non-autistic		Autistic		P Value
	No.	%	No.	%	
Mother's age at start of pregnancy (Mean±SD)	33.1±5.7		35.1±5.9		0.015
Father's age at start of pregnancy (Mean±SD)	39.7±8.8		42.6±7.7		0.016
Maternal diseases during pregnancy					
• Gestational diabetes	4	4.0	6	6.0	0.506
• Preeclampsia	0	0.0	1	1.0	1.000
• Psychiatric problems	1	1.0	1	1.0	1.000
• Hypothyroidism	5	5.0	4	4.0	1.000
• Anemia	17	17.0	12	12.0	0.359
Mother's intake of unprescribed drugs	5	5.0	4	4.0	1.000
Mother's exposure to smoke	6	6.0	15	15.0	0.038
Fetal problems					
• Breech presentation	2	2.0	4	4.0	0.683
• Meconium staining	5	5.0	4	4.0	1.000
• Fetal hypoxia	6	6.0	5	5.0	1.000
Duration of pregnancy					
• <37 weeks	11	11.0	7	7.0	
• 37-40 weeks	85	85.0	87	87.0	
• >40 weeks	4	4.0	6	6.0	0.519

Table 4: Natal characteristics of participant autistic compared with non-autistic children

Natal Characteristics	Non-autistic		Autistic		P Value
	No.	%	No.	%	
Type of labor					
• Spontaneous vaginal	68	68.0	71	71.0	
• Assisted vaginal	5	5.0	2	2.0	
• Caesarian section (CS)	27	27.0	27	27.0	0.509
- Type of anesthesia for CS:					
- Spinal	9	33.3	4	14.8	
- General	18	66.7	23	85.2	0.111
Child's birth weight					
• <2500 gm	13	13.0	20	20.0	
• 2500-3500 gm	81	81.0	76	76.0	
• >3500 gm	6	6.0	4	4.0	0.360

Table 5: Characteristics of participant autistic compared with non-autistic children after labor

Characteristics	Non-autistic		Autistic		P Value
	No.	%	No.	%	
Admission to PICU	13	13.0	7	7.0	0.157
Incidence of neonatal jaundice	23	23.0	25	25.0	0.741
Feeding during the first 6 months					
• Breastfeeding	29	29.0	27	27.0	
• Artificial feeding	12	12.0	20	20.0	
• Mixed feeding	59	59.0	53	53.0	0.302

Discussion

Autism constitutes a group of neurodevelopmental disorders, which are manifested by persistent impairment in social communication and interaction and restricted and repetitive patterns of behavior, interests, or activities (17). It is the leading mental cause of disability among children aged under five years, and accounts for about 8 million disability adjusted life years (18).

Most cases of autism remain of unknown etiology (5). Nevertheless, new technologies and large population-based epidemiological studies could shed some light on the possible risk factors for its etiology (19).

The present study followed a case control research design aiming at identifying risk factors associated with autism among autistic children in Makkah Al-Mukarramah City.

Regarding the personal characteristics associated with autism, the current study revealed that the mean age for diagnosis of autism was 6.1±2.4 years. Autism was diagnosed among participant autistic children mainly before their eighth year of age.

Daniels and Mandell (20) noted that there is a considerable variation in the age at diagnosis of autism. Hrdlicka et al. (21) reported a mean age at diagnosis of 6.2±2.7 years, while Kurasawa et al. (22) reported a mean age of 7.2±4.2 years. In the National Survey of Children's Health, USA, Rydzewska et al. (23) reviewed that 24.6% of autistic children were diagnosed before their third year of age, while 44.5% were diagnosed at 3–5 years and 30.9% were diagnosed after the age of five years. Therefore, it is important to screen children, especially boys, for autism by the primary care physicians, during their visits to the well-baby clinics, as well as at school entry by the school health physician.

This study showed a female:male ratio of about 1:3. However, autistic and non-autistic children did not differ significantly according to their age groups, nationality, birth order, or according to their family characteristics (i.e., number of siblings, parents' educational status, consanguinity, monthly income or family history of autism).

These findings are in accordance with that reported by Kurasawa et al. (22), who found a female-to-male ratio of 1:3 among autistic children, while Honda et al. (24) reported a female-to-male ratio of 1:2.5.

Halladay et al. (25) noted a wide variability in this female-to-male ratio from 1:2 to 1:7. However, the most commonly reported ratio in literature is 1:4. This 1:4 ratio seems to represent a consistent finding in almost all epidemiological studies conducted in different countries, at different times, and using different diagnostic criteria (14).

Several genetics studies have displayed patterns of risk variations consistent with a protective effect against the autism phenotype in females (26-29). However, the neuro-developmental, cellular and molecular aspects by which these factors determine the risk for autism are still not fully understood (30).

Maternal educational level higher than secondary school was a significant risk factor for autism (31). Moreover, socioeconomic status was reported by some to be a significant risk factor for autism (32). However, this association has been denied by Delobel Ayoub et al. (33), who attributed difference in incidence of autism according to socioeconomic status to the accompanied healthcare disparity, as children in families with higher socioeconomic status are more likely to receive health care and subsequently more likely to be diagnosed.

Regarding prenatal characteristics of children, the current study revealed that mothers of autistic children were significantly more exposed to smoke than those of non-autistic children.

Several researchers reported significant associations between autism and exposure of pregnant mothers to smoke or tobacco use (30; 34-35).

However, it is to be noted that the exposure to smoke by children who developed autism cannot be decided whether being prenatal or after birth. It is difficult to distinguish active smoking by pregnant mothers, or their passive exposure to smoke and exposure of children to smoke after birth (36).

Khalil et al. (31) stated that although prenatal exposure to tobacco smoke is associated with behavioral problems, exposure to smoke during infancy and early childhood can be more hazardous to the child's developing brain than prenatal exposure. Furthermore, exposure of children to smoke is common and usually continues for longer periods than the nine months' exposure during pregnancy.

Park et al. (37) added that home environment tends to be similar prenatally and postnatally. Eskenazi and Castorina (38) reported adverse neurocognitive development among children who were passively exposed to smoke after birth compared to those who were only passively exposed to smoke in utero. Moreover, exposure of the fetus to smoke passes through the protective placental barrier; while postnatal exposure of the child to smoke occurs through direct inhalation (39).

Gardener et al. (5) stated that prenatal risk factors have been assessed by many epidemiologic studies for the association with autism. Some studies supported the hypothesis that obstetrical complications may potentiate the risk for developing autism. However, the specific complications, magnitude of effect, and the overall conclusions of these studies were mostly inconsistent, possibly due to methodological variations (40).

Advanced parents' age at birth of their children in the present study were significantly associated with autism.

These findings are in accordance with those reported by some other studies, which showed increased maternal age as being associated with autism, and also being associated with chromosomal abnormalities and obstetric complications (41-43).

Research provided a growing evidence for the hypothesis that mutations contribute to the association between advanced paternal age and autism (44). On the other hand, older maternal age has been associated with chromosomal changes (45-46); and genomic modifications (47).

Reichenberg et al. (48) suggested that the association between older fathers' age and autism among their children can be due to imprinted genes, de novo spontaneous mutations that accumulate with advancing age in spermatagonia.

However, since both mother's age and father's age are positively and strongly correlated, it has been suggested that it is possible to consider that advanced maternal age only or paternal age only is the one that is etiologically relevant. Therefore, to counterbalance any possible confounding, controlling for maternal age, showed that significant associations for paternal age at birth with autism were still observed (48; 32), while controlling for paternal age, the relative risk for older maternal age with autism was not statistically significant (odds ratio = 1.06, p=0.08 (5). Therefore, Sandin et al. (49) suggested that fathers' older age may be more associated with the risk of development of autism among their children than advancing maternal age.

Finally, Khalil et al. (31) stressed that the exact etiology for autism remains not clear. Both environment and genes possibly play an important role. Autism is most probably a heritable disorder. However, in monozygotic twins, there is almost 70% concordance. This suggests that nongenetic factors, e.g., environmental (prenatal and perinatal) factors (prenatal and perinatal) also play a significant role (4). Several sociodemographic factors that have been reported by some studies to be associated with autism include advanced parents' age, family socioeconomic status, prematurity, low birth weight. Some of these risk factors have been previously studied. Only a few risk factors were consistently associated with autism (4; 9; 33; 41-43).

It is currently believed that the mechanism underlying autism etiology is most likely polygenic and potentially epistatic, and that environmental factors may interact with genetic factors to increase risk (50-51).

Study limitations

This study was conducted in a limited local area, i.e., Makkah Al-Mukarramah City. Therefore, the generalization of its results should be cautiously considered. Moreover, it followed a case-control research design, with its main drawbacks of being prone to selection and recall bias (52).

This study concluded that most autistic children become diagnosed at 4-8 years old. The female:male ratio among autistic children is about 1:3. Advanced parental age is a significant risk factor for autism among their children. Exposure of mothers to smoke is a risk factor for autism among her children. Therefore, it is recommended to screen children, especially boys, for autism during their visits to the well-baby clinics and at school entry. Avoidance of exposure of pregnant mothers and children to smoke. Provision of health education to parents about autism and the importance of avoiding pregnancy at advanced parent ages. The conduction of further, nationwide studies on risk factors for autism, with prospective study design with larger sample sizes.

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