Risk Factors for Autistic Disorder: A Case-Control Study

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Abstract

Background: Autistic disorder (AD) is one of the most serious psychiatric disorders in children and adolescents. Identification of relevant risk factors is a main step in disease management.

Objectives: The aim of this study was to determine probable risk factors for AD.

Methods: This case-control study was carried out in the Tabriz University of Medical Sciences. By convenience sampling method, 115 children with autism were selected from Rehabilitation Center of Autism Society in Tabriz, Iran. Moreover, 112 children were selected as control. AD was diagnosed based on DSM-IV-TR criteria by a child and adolescent psychiatrist.

Results: Asthma, epilepsy, microcephaly, hearing / vision impairments, allergy to milk/wheat, side effects of rubella vaccines, and language disorders in the immediate family members including siblings, parents' low education and lack of breastfeeding were more prevalent in AD children. Based on the logistic regression results, mothers' low education [Exp (B) = 4.59, CI = 2.13 - 9.87, P < 0.001] and lack of breastfeeding until the age of two [Exp (B) = 2.91, CI = 1.54 - 5.50, P < 0.01] were the predictors of AD.

Conclusions: Parents' education and lack of breastfeeding until the age of two could predict AD in children. Improving educational system and increasing families' awareness about benefits of breastfeeding will be valuable.

Keywords: Autism Disorder, Risk Factors, Case-Control Studies, Breast Feeding

1. Background

Autistic disorder (AD), according to the diagnostic and statistical manual of mental disorders (DSM-IV-TR) is associated with impaired social interaction, qualitative impairment in communications, significant restriction of activities and interests, and preoccupation with parts of objects (1). AD is now described as the diagnosis of autism spectrum disorder (ASD) in DSM5 (1). Estimated number of children with ASD varies from 8.5 to19.7 per 1000 in 4-year-olds (2) in different populations. This rate is reported to be 6.26 per 10000 in a sample of 5 years-old Iranian children (3). The burden is noteworthy and the life-time healthcare cost for each child with AD is estimated to be between 1.4 and 2.4 million dollars in the US (4).

Autistic spectrum disorders have a high economic burden (4), as well as individual, familial and social consequences (5) and therefore are considered as severe mental disorders (1). All of these indicate the importance of identifying the potential risk factors to explore possible preventive interventions. Since AD emerges early in life, evaluating possible risk factors occurring in the very first years might provide new insight in recognizing the etiologic factors. This issue has interested researchers in recent years.

There are several evidences for the role of both genetic and environmental factors. Mental disorders in general, are rated higher in family members of a child with AD. Schizophrenia spectrum disorders, affective and anxiety disorders, behavioral and emotional problems, language disorders and the broader autistic phenotype (6, 7) are reported to be more prevalent in parents of a child with AD compared to others. There are reports that consider alcohol use problem and advanced parental age (8, 9) as risk factors while the role of parents' educational level is controversial (10). Medical conditions are also reported to be common in children with AD, and being diagnosed early in life, like neurological problems, skull dysmorphism (11) and different types of allergy (12). There is disagreement about the role of breast feeding (13). The importance of nonheritable and perinatal risk factors for ASD is shown by studies about obstetric complications and exposure to chemicals and medications (14).

2. Objectives

To date, there is not a strong convergence in the results about risk factors of AD. Evidences to suggest that parental characteristics and obstetric conditions are associated with an increased risk of AD and ASD are accumulating but these variables should be examined in different populations. Environmental factors are highly influenced by the geographical and social conditions. In this regard, the current study was conducted to identify the perinatal, Familial and parental factors related to AD in a large sample of patients from Northwest Iran.

3. Methods

This case-control study was conducted in 2015. The study population included all children and adolescents younger than 18 years old with the diagnosis of autistic disorder who were registered at the Autism Society in Tabriz, Iran and selected from rehabilitation center of this society, using convenience sampling method. From a total of 130 registered children, 115 children and parents were enrolled in the study.

The other inclusion criterion was a minimum of high-school education for parents. Adoption was considered to be an exclusion criterion to ensure reliable source of information.

The diagnosis of AD for registered children in Autism Society in Tabriz is made by trained clinical psychologists using autism diagnostic interview (ADI). However, to ensure the diagnosis of autism, additional clinical interview based on DSM-IV-TR criteria by a child and adolescent psychiatrist was done.

Simultaneously, a mentally health control group was selected by convenience method from the children who attended the medical outpatient clinics affiliated to the Tabriz University of Medical Sciences. The parent version of the strengths and difficulties questionnaire (SDQ) was used to evaluate mental health status of children in the control group, and 112 children out of 140 were selected as controls. The reason for referral to medical outpatient clinics was infectious and gastrointestinal problems.

This case-control study was approved by the review board and Medical Ethics Committee of Tabriz University of medical sciences in 2015. A comprehensive explanation of the aim of the study was given to the parents of the participants and all gave written consent. Confidentiality of the information, and autonomy for leaving the research were complied.

3.1. Instruments

3.1.1. The Strengths and Difficulties Questionnaire

Strengths and difficulties questionnaire (SDQ)-parent version (15) includes 25 items and it is used to evaluate four category of signs and symptoms (emotional symptoms, behavioral problems, hyperactivity/inattention, and peer relationship problems) plus one ability scale, which reflects prosocial behavior. SDQ scoring is in a three-degree format (not true = 0, somewhat true = 1, certainly true = 2). The psychometric properties of the Persian version of SDQ on children aged 3 to 17 were confirmed by Ghanizadeh and Izadpanah (16) in Iran. The reliability is reported to be good (Cronbach's alpha coefficient = 0.73). SDQ was used for screening of children and selecting the control group.

3.2. Check List of Risk Factors

A checklist of probable risk factors was prepared according to results of available studies by authors. The medical profile, psychiatric interview and the detailed report provided by mothers were the source to fill out this check list. A negative answer was recorded if it was not possible to evaluate the study variables definitely.

Information was gathered in several levels. The medical history of children was investigated for current age, continuous breastfeeding until the age of two, caesarean section delivery, the length of pregnancy (earlier than 32 weeks and later than 42 weeks), asthma, epilepsy, macrocephaly, microcephaly, any degree of hearing loss, allergy to milk or wheat, jaundice, and the side effects of rubella vaccination (hospitalized or medical care).

The siblings' medical history was investigated for: macrocephaly/microcephaly, ASD, schizophrenia, intellectual disability, attention deficit/ hyperactivity disorder, and reason of death if deceased.

The histories of the aunts or uncles were investigated for macrocephaly/microcephaly, language disorders (with signs of slurred speech, speech impediment, or delayed speech development).

The same information was asked about parents, along with their living environment condition: Age, years spent in education, parents' kinship, parental psychiatric history (the use of psychiatric medication or psychiatric hospitalization), and living in small and restricted houses or apartments (area smaller than 50 m^2).

3.3. Statistical Analysis

SPSS software version 21 was used for analyses. Data are described as number (percentage) or mean $\pm$ standard deviation where appropriate. The independent *t*-test was used to compare the means and the Fisher's exact test was used to compare frequencies and determine the risk ratio

of autism. Odds ratios (OR) are also reported within 95% confidence interval to determine whether the variable is a risk. Moreover, the logistic regression was used to identify risk factors which could predict presence of AD from those factors which were reported to be significant. The significance level was considered to be less than 0.05.

4. Results

The study included 115 children with AD (59.1% boys) and 112 controls (62.5% boys, P > 0.05). Mean age of children with AD was 6.94 ± 3.55 years. The control group was selected to match them in terms of age to, with a men age of 7.63 ± 3.52 years (*t* value = 0.96, P > 0.05).

The mean age of mothers at birth was 27.79 ± 4.99 in AD group and 28.58 ± 4.70 in the control group (*t* value = 1.22, P > 0.05). The mean age of fathers at birth was also comparable between the two group and was 33.59 ± 6.46 in AD group and 34.45 ± 6.61 in the control group (*t* value = 0.98, P > 0.05).

Educational level of both mothers (OR = 5.28, CI = 2.87 - 9.71, P < 0.001) and fathers (OR = 1.80, CI = 1.05 - 3.06, P < 0.05) of children with AD was lower in comparison with the control group.

Breastfeeding until the age of two, asthma, epilepsy, macrocephaly, hearing/vision impairment, allergy to wheat and milk, problems arising while injecting rubella vaccines, small living area, language disorders in the immediate family members were significantly higher different in children with AD compared to controls. The rates, differences and odds ratios for health related conditions in the child and the families are described in Tables 1 and 2 in that order.

Significance variables recognized by the Fisher's exact test were included in the logistic regression model. Mother's low level of education [Exp (B) = 4.59, C.I. for EXP (B) = 2.13 - 9.87, P < 0.001] was introduced as predictors of AD where breastfeeding until the age of two [(Exp (B) = 2.91, C.I. for EXP (B) = 1.54 - 5.50, P < 0.01] was introduced as a protective factor.

5. Discussion

This case-control study was conducted to determine the parental, familial and perinatal factors related to AD in children and indicated mother's low level of education was associated with AD and breastfeeding until the age of two was a protective factor.

Results of this study were in line with previous reports where the importance of breast feeding as a probable etiological factor has been emphasized. It is reported that children who were not breastfed or were fed infant formula without docosahexaenoic acid/arachidonic acid supplementation were significantly more likely to have AD [17]. Breastfeeding might promote healthy cognitive development [18] and prevent autistic symptoms. Affecting the mother-child interactions, breastfeeding appears to influence the development of emotional and cognitive abilities of children. Moreover, breast milk contains oxytocin that is known to influence social bonding and social interaction [19].

Asthma and allergy to milk/wheat are reported to be associated with autism. Angelidou et al. [12] proposed mast cell activation to be one of the possible causes of higher rate of allergy in children with AD. Mast cell activation by allergic, infectious, environmental and stress-related triggers, especially prior to birth, would release pro-inflammatory and neurotoxic molecules. This result was not replicated in our study, and the factors which are associated with immune system (asthma and allergy) were not a risk factor in our study sample. This is in line with other reports like Lyall et al. [20] who reported no difference in the prevalence of asthma and allergies in general, between autistic and healthy children; however, food allergy was reported to be related to ASD in the study sample.

Our findings also indicated that epilepsy, macrocephaly, and hearing/vision impairments were associated with AD. Previous reports have considered macrocephaly [11, 21], epilepsy and neurological problems [22] to be common problems in AD. However, the research in the community-based study shows that there is no evidence to support a strong link between a large head size and ASD [23]. A large-scale study reported high rate of macrocephaly but also a wide distribution of head circumference in children with ASD [21], while there is not much data from Iranian population. Same results exist about the association between congenital sensory impairment and ASD [24]. Higher incidence of epilepsy, macrocephaly, and hearing/vision impairments might indicate shared genetic and neurological problems with AD [21]. Therefore, these findings emphasize the neural-biological deficits in autism.

In our study sample, complications after rubella vaccination were reported more prevalent by parents of children with AD, but it was not a predicative factor. There is scarce evidence showing that males receiving the measles-mumps-rubella (MMR) vaccine prior to 24 or 36 months of age are more likely to receive an AD diagnosis [25]. In contrast, several studied report that exposure to the MMR vaccine is unlikely to be associated with ASD [26]. Higher rate of complication might reflect a general and non-specific vulnerability.

Our results showed no relationship between AD and delivery by C-section, premature or delayed delivery. In the

Table 1. Health Related Conditions in the Child as Risk Factors for AD; as Number (Percentage) and Comparison Between Children with AD and Controls

Variables	AD (N = 115)	Control (N = 112)	Fisher's Exact Test		Odds Ratio
			χ^2	P	OR (95% CI)
Breastfeeding until two years	40 (34.8)	73 (65.2)	20.97	< 0.001	3.80 (2.18 - 6.61)
Asthma	30 (26.1)	10 (8.9)	11.50	0.001	3.60 (1.66 - 7.78)
Epilepsy	8 (7)	1 (0.9)	5.47	0.03	8.29 (1.02 - 67.48)
Microcephaly	8 (7)	0	8.07	0.007	17.79 (1.01 - 312.03)
Hearing/vision impairment	29 (25.2)	12 (10.7)	8.06	0.006	2.81 (1.35 - 5.84)
Allergy to wheat/milk	16 (13.9)	6 (5.4)	4.74	0.04	2.85 (1.07 - 7.58)
Rubella vaccination side effect	15 (13)	2 (1.8)	10.38	0.002	8.25 (1.84 - 36.97)
C-section delivery	41 (35.7)	42 (37.5)	0.08	0.78	0.92 (0.53 - 1.58)
Birth before 32 weeks	14 (12.2)	14 (12.6)	0.01	0.99	0.96 (0.43 - 2.11)
Birth after 42 weeks	0	1 (1)	1.03	0.49	0.32 (0.01 - 7.95)
Jaundice at birth	12 (10.4)	11 (9.8)	0.02	0.99	1.06 (0.45 - 2.53)

Table 2. Health Related Conditions in the Family as Risk Factors for AD; as Number (Percentage) and Comparison Between Children with AD and Controls

Variables	AD (N = 115)	Control (N = 112)	Fisher's Exact Test		Odds Ratio
			χ^2	P	OR (95% CI)
Small home	48 (41.7)	29 (25.9)	6.35	0.01	2.05 (1.16 - 3.59)
Parents					
Parents' kinship	23 (20)	15 (13.4)	1.77	0.21	1.61 (0.79 - 3.28)
Father's mental disorder	1 (0.9)	2 (1.8)	0.36	0.61	0.48 (0.04 - 5.39)
Mother's mental disorder	8 (7)	3 (2.7)	2.25	0.21	2.71 (0.70 - 10.51)
Siblings					
Death in childhood	5 (4.3)	2 (1.8)	1.24	0.44	2.5 (0.47 - 13.16
Language disorders	10 (8.7)	2 (1.8)	5.41	0.03	5.23 (1.12 - 24.47)
Autism spectrum disorders	0	0	< 0.001	1	0.97 (0.19 - 49.51)
Schizophrenia	0	0	< 0.001	1	0.97 (0.19 - 49.51)
Mental retardation	2 (1.7)	0	1.96	0.49	4.95 (0.23 - 104.39)
Hyperactivity/inattention	3 (2.6)	1 (0.9)	0.96	0.62	2.97 (0.30 - 29.02)
Autism	1 (0.9)	0	0.97	0.99	2.94 (0.11 - 73.12)
Mother's education*	20 (17.4)	59 (52.7)	31.13	< 0.001	5.28 (2.87 - 9.71)
Father's education*	42 (36.5)	57 (50.9)	4.76	< 0.03	1.80 (1.05 - 3.06)
Macrocephaly/microcephaly	3 (2.6)	0	2.96	0.24	7 (0.35 - 137.09)
Immediate family					
Macrocephaly/microcephaly	1 (0.9)	1 (0.9)	< 0.001	1	0.97 (0.06 - 15.76)
Language disorders	14 (12.2)	3 (2.7)	7.38	0.01	5.03 (1.40 - 18.04)

previous reports (27, 28), a C-section delivery was detected to be a risk factor causing autism. The general anesthesia for a C-section is also suggested as probable main factor (28). Further studies are needed to consider confounding factors by specifying type and time of anesthesia, the difficulty and type of delivery. Given the high frequency of C-section in Iran, this report has a unique value about the role of a C-section in AD, showing no association.

Neonate jaundice and other obstetric complications were not related to AD in our study. It is now well known

that AD is unlikely to be caused by a single obstetric factor. The increased prevalence of obstetric complications is most likely due to the underlying genetic factors or an interaction of these factors with the environment influencing nervous system (28). Results also indicated that parents' kinship, their history of psychiatric disorders, skull dimorphism in the immediate members of family, deaths of a sibling due to a disease, AD, schizophrenia, intellectual disability, hyperactivity/inattention, and AD in siblings were not related to AD. These findings did not fully comply with the findings of previous studies (10, 29). However most of the studies indicate a complicated relationship between family history of disorders and AD and there is no conclusion.

Problems in language are characteristic of AD. Consistent with previous reports, language disorders were more in the families of autistic children (30). This finding emphasizes a genetic connection between language disorders and AD. On the contrary, Pilowsky et al. (31) reported that language skills in the siblings of children with AD are not much different from the others. Methodological difference and age of participants might explain this difference and should be examined in further studies.

Small and restricted living area was another issue of this study. Smaller living space reflect lower socioeconomical level, where several disorders are more common and at the same time can facilitate contagion of viral infections. Smaller living space was associated with higher odds of AD, but it was not a predictive factor. It is obvious that this factor might be correlated with level of education and mental and medical conditions of parents.

Inconsistent with previous studies, parents of AD children had lower educational degrees (11, 32). This could be explained by cultural and geographical differences. Basically, parents' low level of education can be one of the barriers for giving a better care to children (33). This factor, which is introduced as a predictive factor in our study, can be attenuated and families can benefit from different kinds of training courses.

This study has some limitations. Even if all of the children registered with autism community were eligible for this study, not all of children with AD are diagnosed or registered. So this study was not population based and this will limit the results. Although only educated mothers were included to ensure better data collection, recall bias might be a serious limitation. While low education of mother is introduced as an independent risk factor, excluding illiterate parent might influence the result in part. Moreover, the severity of AD was not controlled. A good example is that all of children with AD, who were at school age, were attending especial schools and this implies that out sample could not include high function AD. Although this study might not have sufficient statistical power to detect differences in rates of AD between those exposed to the risk factors and those unexposed, we believe results will still add evidence to available data because there are not much reports from Iranian population .The abovementioned limitations and the questions arose in the discussion indicate the importance of complementary studies that use large, population-based birth cohorts with precise assessments of exposures and potential confounders.

5.1. Conclusions

Results of this study indicated that several health-related conditions are more prevalent in children with AD. Our results introduced mothers' low educational levels and lack of breastfeeding until the age of two as predictors of AD. Improving the educational level of mothers and increasing their awareness about benefits of breastfeeding may be considered as important protective interventions. Although not verified as independent risk factors for AD, these should be examined in future studies.

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Footnotes

Authors' Contribution: Shahrokh Amiri And Ayyoub Malek designed the research. Shahrokh Amiri, Ayyoub Malek, Mahan Asadian and Afshin Razzaghi Rezaih collected the clinical data. Salman Abdi performed statistical analysis and interpreted the data. Shahrokh Amiri and Ayyoub Malek drafted the manuscript. Sara Farhang revised it critically for important intellectual content. All authors have read and approved the final manuscript.

Conflict of Interests: The authors declare that they have no competing interests.

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