

Advanced Parental Age and Risk of Positive Autism Spectrum Disorders Screening

Abstract

Background: Autism Spectrum Disorder (ASD) is a life-long neurodevelopmental disorder and significantly influences the quality of life in children. The screening of ASD in children aged between 16-30 months to early detection and early intervention for better prognosis. **Methods:** This cross-sectional study was conducted in the southwest of Iran (Yasuj) with dominant Lore ethnicity in 2017. A total of 1504 mother-child pairs with children aged between 16-30 months were selected through simple random sampling from the integrated national health system as the framework. ASD screening was implemented using the Modified checklist for autism in toddlers- revised, with follow-up interview (M-CHAT-R/F). Demographic data such as sex of children, and parental age at their time of pregnancy were collected for all children. **Results:** Risk of ASD was low, moderate and high in 1447 (96.2%), 54 (3.6%) and 3 (0.2%) in screening, respectively. The estimated rate of ASD prevalence was 80 per 10000 (12 out of 1504) or 1 in 125. Mother's age ≥ 35 (P value = 0.002, OR = 11.65, CI_{95%}: 2.49-54.35) and father's age ≥ 40 (P value = 0.0001, OR = 19.64, CI_{95%}: 4.89-78.82) were predicting factors of ASD in toddlers aged 16-30 months. **Conclusions:** Given that, increasing the age of marriage in Iran and recent trend towards delayed childbearing; children born to older parents are at a higher risk for having ASD. So, increasing the public awareness is necessary.

Keywords: Autism spectrum disorder, mass screening, parent

Introduction

Autism spectrum disorder (ASD) is a set of heterogeneous and life-long neurodevelopmental disorder characterized by early-onset impairments in social interaction, verbal and non-verbal communication, unusually restricted, repetitive and stereotyped behaviours/interest. Also, ASD is often associated with sensitivity to sound, touch and light.^[1-5] ASD is a multifactorial disorder, from genetic to environmental factors.^[2-3] ASD affects male more than female and comorbidity (such as intellectual disability, epilepsy, depression, and obsessive-compulsive disorder) is common in more than 70% of individuals with ASD.^[2,4] Also, advanced maternal,^[6-12] or paternal,^[7-10,13,14] age in the offspring or both, is a consistent risk but its underlying biology is not clear yet. Gestational factors, and exposure to chemicals have been suggested to increase risk of ASD in some epidemiological studies, too.^[2]

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The prevalence of ASD has varied widely and increased in recent years.^[1,3,4,15] The worldwide prevalence is about 1 in 88 to 1 in 100.^[4,16] In a 2010 and 2012 systematic review of epidemiologic studies, the global prevalence of ASD was 7.6 per 1000 (1 in 132)^[16] and 62 per 10000, respectively.^[4] The overall prevalence of ASD in Europe, Asia, and the United States ranges from 2 to 25 per 1000, or approximately 1 in 40 to 1 in 500.^[16,17] The estimated rate of ASD prevalence is 157 per 10000 children in the United Kingdom.^[3] In 2010 and 2012, the estimated prevalence of ASD among eight years old children was 14.7 per 1000; 1 in 68 overall, 1 in 42 boys and 1 in 190 girls. In 2014, according to estimates from Centers' for Disease Control and Prevention (CDC)'s Autism and Developmental Disabilities Monitoring (ADDM) network, the prevalence has increased to 16.8 per 1000; 1 in 59 overall, 1 in 38 boys, and 1 in 151 girls.^[17] The National Health Interview Survey (NHIS) estimated the prevalence of in children age 3 to 17 years, 24.7 per 1000; approximately 1 in 40 children overall, 1

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in 28 boys, and 1 in 80 girls from 2014 to 2016.^[16,17] In South Asia, prevalence of ASD ranged from 0.09 in India to 1.07% in Sri Lanka that indicates approximately 1 in 93 children have ASD.^[18] In Iran, the result of Ghanizadeh's study revealed a prevalence rate of 19 per 1000 for probable autistic disorder in school children.^[3] The investigation of Samadi *et al.* indicated a rate of 6.26 per 10000 in 5 years old children.^[19]

There is growing evidence that ASD can often be diagnosed during the second year of life, usually at 12-15 months,^[4] before the child's third birthday.^[1,20] Early detection of developmental disorder is essential for early intervention, because early comprehensive behavioral interventions can improve social communication,^[2] and provide the better chance for better outcome.^[21,22] The American Academy of Pediatrics recommends ASD-specific screening of all children between 18 and 24 months of age because there are critical times for early social and language development.^[4,16] On the other hand, there is significant economic burden (direct and indirect costs) from medical care to special education for families with autistic children. In the United States, it is estimated that \$11.5-60.9 billion is imposed to the government per year for children with ASD and it is 4-6 times greater than those without ASD. Also, intensive behavioral interventions for children with ASD cost \$ 40000-60000 per child per year.^[17] Generally, autistic disorders has accounted for more than 58 Disability Adjusted Life Years (DALYs) per 100000 populations.^[23]

As noted above, the ASD prevalence rate varies widely across the world and these differences can be related to some factors such as age, diagnostic criteria, geographic location and culture. On the other hand, symptoms of ASD usually become apparent between 12-15 months,^[4] and there is limited and inadequate information about ASD in developing countries such as Iran especially in toddlers.^[3] In addition, several evidences suggest that early detection, and early intervention can lead to better prognosis which increases the chance of being more independent and successful entrance in public education.^[11] Therefore, this study was conducted to screen children aged 16-30 months, attending primary health care services in Southwest Iran (Yasuj) in 2017 to estimate the prevalence rate for probable ASD and its probable risk factors to build capacity to pay more attention to developmental disabilities at policy making and implementation levels. This age group was chosen due to the development of standard questionnaire for screening ASD of infants with at least 16 months of age.

Methods

It was a cross-sectional study undertaken in Yasuj (the centre of Kohgiluyeh va Boyer-Ahmad province) located in Southwest of Iran with dominant Lore ethnicity. In Yasuj, there are five urban health centers and the electronic health file of all children is available from integrated national

health system as the framework. Out of 3041 children aged between 16-30 months, a total of 1504 mother-child pairs with children aged between 16-30 months were selected through simple random sampling and recruited the study. After explaining the purpose of the study a written informed consent was taken from all 1504 mothers for their participation in each step. Out of 54 children, 13 screened positive in follow up interview and were referred to pediatric psychiatrist. ASD screening was implemented at routine pediatric appointment for periodic health care in urban health centers using the Modified checklist for autism in toddlers- revised, with follow-up interview (M-CHAT-R/F). The M-CHAT-R/F is a 2- step screen tool, which is free for clinical, research and educational use and requires little or no training for health care provider. In the first step, mothers completed a 20-item paper- and- pencil based questionnaire using a yes/no format to indicate the child's current skill and behavior which took less than 5 minutes. If 0-2 items were failed, children were classified as low risk without need to further assessment unless parent's concern about delay in development. If 3-7 items were failed, children were classified as moderate risk and the mothers received a follow-up interview designed to collect more specific information about the failed items. All of the 54 mothers of their children need to be followed -up, completed step two, too. Children, who continue to fail two or more questions in one-to-one interview by psychiatrist, were referred to pediatric psychiatrist for further diagnostic evaluation and early intervention as needed. Children, who failed 8 or more items in first step, were classified as high risk and directly were referred to pediatric psychiatrist for further diagnostic investigation. In this study, follow-up interviews were conducted by the psychiatrist immediately after M-CHAT-R and diagnostic evaluation was done by one pediatric psychiatrist. With closer follow-up, all of the children based on their risk of ASD, completed the study. M-CHAT-R/F has been translated to Persian and validated for Iranian children by Akbarzadeh. This tool has 85% sensitivity and 99% specificity for screening ASD.^[16,24,25] Inclusion criteria were:(1) chronological age between 16 and 30 months at the time of screening, (2) absence of known genetic or neurological disorders, (3) absence of sensory/motor disorders or visual/hearing impairment and (4) acute medical illness to preclude testing. Exclusion criteria were incomplete filling the questionnaire at the first step. Demographic data such as sex of children and parental age at time of pregnancy were collected for all children.

A representative sample size of 1504 children was calculated at the 95% confidence level, prevalence of ASD = 0.06 (6 in 10000) in Iran,^[3] and $d = 0.2$ P.

Ethical consideration

This study was approved by ethics committee of Yasuj University of Medical Sciences (ethic code

yums.REC.1396.123). Mothers were assured of their confidentiality. After explaining the purpose of the study a written informed consent was taken from all 1504 mothers for their participation in each step.

Statistical analysis

Data analyses were performed by using SPSS₁₆ (SPSS, Chicago, IL, USA) software. Continuous variables with normal distribution were presented as mean ± standard deviation. Nominal variables were taken as counts (or frequencies) and were compared by Chi-square test. Multivariate logistic regression was used to determine predicting factors of ASD. All statistical tests were based on two-tailed probability. *P* value <0.05 was considered statistically significant.

Results

The demographic characteristics of children and their parents are shown in Table 1.

Risk of ASD was classified as low, moderate and high in 1447 (96.2%), 54 (3.6%) and 3 (0.2%) in screening, respectively.

Follow-up evaluation was conducted for 54 children with moderate risk. Out of 54 children, 13 (24%) screened positive in follow-up interview and were referred to pediatric psychiatrist. Diagnosis of ASD was confirmed for 10 of 13 (77%) children. In high risk group, 2 of 3 (66%) children, ASD diagnosis was confirmed by pediatric psychiatrist. In all, 12 children (75% of those

assessed clinically) had met the criteria for ASD in the received feedback from pediatric psychiatrist. Generally, the estimated rate of ASD prevalence among toddlers aged 16-30 months was 80 per 10000 (12 out of 1504) or 1 in 125.

Comparison the demographic characteristics between screened positive and negative toddlers are shown in Table 2.

Based on logistic regression, mother's age ≥35 (*P* value = 0.002, OR = 11.65, CI_{95%}: 2.49-54.35) and father's age ≥40 (*P* value = 0.0001, OR = 19.64, CI_{95%}: 4.89-78.82) were predicting factors of ASD in toddlers aged 16-30 months.

Discussion

To our knowledge, this is the first epidemiological research on the prevalence of ASD in toddlers aged between 16-30 months in Lore ethnicity of Yasuj city in Iran. In our study nearly 4% of toddlers had screened positive for ASD on M-CHAT-R/F. This is lower and approximately half of (9.4%) screened positive toddlers compared to Indian study (80.2%: low risk, 10.28% moderate risk and 9.24%: high risk).^[26] The estimate prevalence of ASD in toddlers was 80 per 10000 (1 in 125) that is lower than the worldwide estimated prevalence of ASD.^[17] In our study, the estimated prevalence of ASD was lower than reported prevalence of ASD in United Kingdom (157 per 10000), England (98 per 10000), United States (90 per 10000),^[3] and South Asia (1 in 93),^[18] and higher than reported prevalence of ASD in Japan (13 per 10000), China (9.8 per 10000),^[27] and previous study in Iran (190 per 10000).^[3] Several factors may explain the lower prevalence of study in Iran compared to developed countries. In Iranian culture, individuals with disability are not well accepted in community and don't receive adequate environmental and social support. So, parents tend to hide their children's problem and avoid them to attend in the community. This matter can lead to under recognition of ASD unlike developed countries that parent to obtain a diagnosis for their children's disability as this enables them to access additional services, which

Table 1: The demographic characteristics of children and their parents

Variables	Mean±SD/ frequency
Children's age (months) (mean±SD) [†]	20.26±3.74 (16-30)
Sex: Number (percentage)	
Girl	749 (49.8)
Boy	755 (50.2)
Maternal age (years) (mean±SD) [†]	28.01±1.37 (17-44)
Paternal age (years) (mean±SD) [†]	32.3±1.59 (19-50)

SD=Standard deviation

Table 2: Comparison the demographic characteristics between screened positive and negative toddlers

Variables	Screened positive (moderate and high risk)	Screened negative (low risk)	<i>P</i>	Odd's Ratio	95% confidence interval odd's ratio
Sex [‡]					
Girl	26 (3.5%)	723 (96.5%)	0.51	0.84	0.49-1.42
Boy	31 (4.1%)	724 (95.9%)			
Maternal age [‡]					
Age <35	50 (3.4%)	1442 (96.6%)	0.0001*	40.37	14.86-149.16
Age ≥35	7 (58.3%)	5 (41.7%)			
Paternal age [‡]					
Age <40	49 (3.3%)	1442 (96.7%)	0.0001*	47.08	12.38-131.63
Age ≥40	8 (61.5%)	5 (38.5%)			

[†]Chi-square test was used for analysis, [‡]Fisher's Exact test was used for analysis, *Significant *P*

are not sufficient and available in Iran. An additional explanation for lower prevalence of ASD in current study may be low age of target population, because it's difficult to detect ASD in very young (non-verbal) children and differentiate it from some behavior's in normally developed children and intellectual disability.^[23] On the other hand, higher prevalence of ASD compared to the countries in Asia regions, may be due to increased awareness in recent years as ASD are frequently discussed in the mass media,^[15] that has led to earlier referring children to clinicians and earlier diagnosis. Robins *et al.* that used the same tool as our study (M-CHAT-R/F) indicated a prevalence 1 in 127,^[15] which is in agreement with our results. Globally, it must be mentioned that changing in diagnostic criteria in last decade, can be another explanation for increasing the prevalence of ASD since recent years.

In our study, there was no significant sex difference. Contrary to most studies with dominant prevalence in male,^[3,4,6,16,17] but was in agreement with Ravi *et al.*,^[26] that has done investigation in the same age group with the same screening tool in India. Detecting no difference in sex may be related to cultural background in Iran especially in Lore ethnicity that prefer to have boy child. So, it may influence reporting the impairment/disability in boy children by parents till they reach school age and teacher notice difficulties with peer interactional inability to make friends.^[28] It should be mentioned that in first step of ASD screening, children's mother complete the questionnaire and may avoid reporting their children developmental delay.

The result of this study was consistent with the findings of most studies that revealed advanced maternal,^[6-12,29] and paternal,^[7-10,13,14] age in the offspring, have significant relation with increased risk of ASD. Also, it has been shown that each 10-year increase in maternal and paternal age is associated with a 20% and 30% increase in ASD, respectively.^[8,10] Inter pregnancy interval ≥ 60 months, was associated to increased risk of ASD, too.^[7] It can be due to increased maternal and paternal age. So, marriage in appropriate age and taking appropriate childbearing space must be mentioned by individuals in reproductive age. Possible explanations for relationship between advanced parental age and risk of developing ASD can be as below:

- 1) Increasing occurrence of genomic alteration and chromosomal^[11,14]
- 2) Epigenetic dysfunction (heritable, but reversible regulation gene expression^[11,30]
- 3) Accumulated exposure to different environmental toxins over the life course that can result in genomic and/or epigenetic alterations in the germ cells and induction DNA damage, germ line mutations, and global hyper methylation in germ cell, and have long term developmental consequences in offspring^[11]
- 4) Endocrine and hormonal changes with advanced maternal age^[11]

- 5) Increased incidence of infertility conditions and use of infertility treatments that may influence on the maternal hormonal profiles^[9,11]
- 6) Older parent might be more aware and conscious and seek health services for children with developmental delays earlier than younger parent^[9]
- 7) Increased risk of de novo genetic mutations in the germ line of older fathers^[24,31,32]
- 8) Trinucleotide repetition instability as the on probable mechanism for the risk of ASD with advanced maternal age.^[12]

Limitations

Suggestions: 1-Based on the cultural influences on parental perception of children's disability, we recommend to researcher to conduct further comprehensive epidemiological studies in toddlers in different regions of Iran that the results can be comparable. 2-Given that, there was an association between advanced parental age and risk of ASD in cross sectional study, conducting further epidemiological studies such as case control and cohort studies is recommended for assessing cause and effect relationship.

Conclusions

In summary, in 75% of screened positive toddlers in M-CHAT-R/F, ASD diagnosis was confirmed. So, health care providers and physicians can be confident that the most screen positive children need further diagnostic investigation. Given that, ASD significantly interfere with quality of life, and early initiation of remedial interventions can improve the prognosis, wide spread implementation of screening is recommended to reduce the age of ASD diagnosis. Also, the results of this study indicated a significant association between advanced maternal and paternal age in offspring and the risk of ASD in Iranian toddlers similarly to most studies. On the other hand, due to the increases age of marriage in Iran and tendency to delay childbearing, reproductive health specialists should inform individuals in reproductive age about the probability increase of having a child with ASD in future.

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Conflicts of interest

There are no conflicts of interest.

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