Brief Communication

Parental age. *Risk of autistic disorder*

Ahmed M. Al-Ansari, *MBCHB, FRCPc,*
Mohamed M. Ahmed, *BSc, MD.*

Advanced parental age at childbirth has previously been considered a possible risk factor of autism spectrum disorder.[1] Reported results on the relationship between advanced parental age at child birth and autistic disorder (AD) have been inconsistent. A recent review and meta-analysis revealed a significant association between advanced parental age and AD.[2,3] The accumulating data of the association does not indicate a direct causal effect, but it addresses an important public health concern. Bahrain, a developing country, showed a sharp decline in early marriage rates similar to other countries in the region. There are no epidemiological efforts locally, or regionally that address the importance of risk factors associated with AD, including advanced parental age. In this study, we aim is to examine the association of advancing parental age and childbirth order with AD.

A case control design study was planned to study the relationship between advanced parental age at childbirth and childbirth order with the incidence of AD. The study received approval from the ethical committee, Ministry of Health, Bahrain, and the parents gave their informed consent prior to inclusion in the study. The study was conducted between July and December 2010. Bahrain is an archipelago situated in the Arabian Gulf, East of the Kingdom of Saudi Arabia. It covers an area approximately 750 km^2, and has a population of 1.25 million, estimates for 2010. Health services are free and accessible to all residents. The country is characterized by a low infant mortality rate, 7.2 per 1,000, and high life expectancy rate of 74.8.

The study population was composed of cases evaluated at the Child & Adolescent Psychiatric Unit (CAPU) of the Psychiatric Hospital, Manama, Bahrain who received a diagnosis of AD in the period of 2000-2010 (n=100). The CAPU is the only referral clinic for the diagnosis of AD in Bahrain. The unit receives referrals for all types of psychiatric disorders from all kinds of sources including families. The diagnosis was made according to the: Modified Checklist for Autism in Toddlers (M-CHAT), the American Psychiatric Association Diagnostic and Statistical Manual of Mental Disorder (DSM IV TR), and the Childhood Autism Rating scale (CARS). A control group comprised an equal number of CAPU cases from the same time period. They were randomly selected from a pool of 350 cases, matched for age (5 years group), and gender within each group. The controls were cases of nocturnal enuresis (n=64), mild behavior disorder (n=10), and no psychopathology (n=26).

The medical records from CAPU were reviewed, and related data was extracted and entered in a specially designed form. Included in the form were items such as the child's age, gender, pregnancy, delivery, pre-natal, natal and post natal complications; stressful life events during childhood; early years of development, the child's sleeping history, eating pattern, language development, and birth order; the parents' age at child's birth; parents' education, employment, psychiatric and medical history; and the family history of AD, and consanguinity. Neither the cases nor their parents were interviewed. Parents of 9 cases and 21 controls were contacted by telephone, or home visit by the CAPU social worker to clarify missing data. Only one case from the study group was excluded due to doubtful diagnosis. The data were entered and analyzed using the Statistical Package for Social Sciences version 16.0. Chi-Square test of significance was used to assess differences when applicable. *P*-values ≤0.05 were considered significant. Age 30 years was chosen as arbitrary division between young and old parents' age by general consensus.

This report shows the results of an assessment of advanced parental age and birth order in relation to AD. The results of other examined factors are reported separately. Males outnumbered females by a ratio of 4:1. The mean age was 10.45±6.43 years, range 2-27 years. As shown in **Table 1**, there was a significant association of AD diagnosis with mean maternal age (p=0.004), and paternal age (p=0.003). Children of mothers in the oldest maternal age group (>30 years at child's birth), were 1.83 times more likely to develop AD (95% Confidence Interval [CI]: 1.02-3.28) in comparison with the reference group (mothers aged ≤30 years at child birth) in both cases and control. Children of fathers in the paternal age group (>30 years at child birth) were 2.08 times more likely to develop AD (95% CI: 1.15-3.7) in comparison with the reference group. More cases of individuals with AD were first in birth order in comparison with the control individuals, but this difference did not show any statistical significance (odds ratio 1.67, 95% CI: 0.91-3.06, p=0.095).

These study results are consistent with recently reported population-based, case-cohort design studies that found an association between advanced maternal and/or paternal age and the risk of AD.[4] However, our

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.

Table 1 - Distribution of cases and controls by maternal, paternal age at child birth and child birth order.

Item	Study group	Control group	Odds ratio	95% Confidence Interval	*P*-value
Maternal age at childbirth			1.83	1.02-3.28	0.041
Above 30	44	30			
30 and below	56	70			
Mean maternal age					0.004
At child birth	29.78	27.81			
Standard deviation	5.90	5.37			
Paternal age at child birth			2.08	1.15-3.76	0.016
Above 30	73	56			
30 and below	27	44			
Mean paternal age					0.003
At child birth	35.58	32.64			
Standard deviation	7.59	7.12			
Child birth order			1.67	0.91-3.06	0.095
First	37	26			
Second or more	63	74			

findings are in contrast to other studies that did not reach the same conclusion.[5] The study design was not optimal to achieve our objectives, in that clinical subjects were used as controls because a population based cohort was not available, and the control group was not a community based sample with wider representation. Other limitations of the study include the retrospective nature of data collection, and non-availability of national statistics relating to variables such as mean age at time of marriage for males and females. However, the use of one central case registry center (CAPU) and the control of social class added to the study validity. In a previous study,[6] using a similar method, the author could not find an association between maternal age (>35 years) and the risk of mild intellectual disability in the offspring.

Although the etiological mechanism explaining the relationship between advanced parental age at childbirth and the increased risk of AD remains unclear, it is possible that both genetic and epigenetic factors contribute to the etiology. In addition, older first time fathers had more assisted reproduction for example, which might have increased the risk for AD.[4] However, father's age as a risk factor for AD was not examined separately in the current study.

Studies that examined the association of advanced parental age and AD, but controlled for birth order found a negative association with the risk of AD,[2] and our finding regarding the role of birth order as a risk factor was not statistically significant. Since there were more AD study cases among first-born children than control group subjects, one should examine this in a larger population to assess accurately the association of childbirth and AD.

In conclusion, parental age, both maternal and paternal, above 30 years is associated with the risk of AD. First-born children were more prevalent in study cases than in the controls. The focus in the future should be directed to the identification of genetic and environmental factors associated with advanced parental age and first-born children, and the relationship with the development of AD.

Received 26th February 2012. Accepted 15th May 2012.

From the College of Medicine & Medical Sciences (Al-Ansari), Arabian Gulf University, Manama, and Department of ENT - Head and Neck (Ahmed), King Hamad University Hospital, Muharraq, Kingdom of Bahrain. Address correspondence and reprint requests to: Dr. Ahmed M. Al-Ansari, College of Medicine & Medical Sciences, Arabian Gulf University, PO Box 26671, Manama, Kingdom of Bahrain. Tel. +973 (1) 7279342. Fax. +973 (1) 7686003. E-mail: Aansari@health.gov.bh / Ahmedm.alansari@gmail.com

References

1. Koyama T, Kamio Y, Inada N, Inokuchi E. Maternal age at childbirth and social development in infancy. ***Research in Autism Spectrum Disorders*** 2011; 5: 450-454.
2. Durkin MS, Maenner MJ, Newschaffer CJ, Lee LC, Cunniff CM, Daniels JL, et al. Advanced parental age and the risk of autism spectrum disorder. ***Am J Epidemiol*** 2008; 168: 1268-1276.
3. Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. ***Br J Psychiatry*** 2009; 195: 7-14.
4. Cantor RM, Yoon JL, Furr J, Lajonchere CM. Paternal age and autism are associated in a family-based sample. ***Mol Psychiatry*** 2007; 12: 419-421.
5. Koyama T, Miyake Y, Kurita H. Parental ages at birth of children with pervasive developmental disorders are higher than those of children in the general population. ***Psychiatry Clin Neurosci*** 2007; 61: 200-202.
6. al-Ansari A. Etiology of mild mental retardation among Bahraini children: a community based case control study. ***Ment Retard*** 1993; 31: 140-143.