Prenatal & Perinatal Risk Factors of Autism Spectrum Disorder

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Abstract:

Background: *Autism spectrum disorder (ASD) is lifelong neurodevelopmental disorder characterized by impairments in social function, communication, and certain behaviors. The etiology of ASD is unclear & it is believed to be multi-factorial, among those several prenatal & perinatal factors are found to be significant. So, the necessity of this study is to detect the presence of known risk factors of ASD which in turn may help in the early diagnosis and intervention for better long-term outcomes.*

Objective: *To find out prenatal and perinatal risk factors of ASD.*

Method: *A case control study was conducted with 112 cases of ASD and 201 controls of 2-6 years of age. The study was carried out in Center for Neurodevelopment and Autism in Children (CNAC), in the department of Paediatrics, Bangabandhu Sheikh Mujib Medical University and Autism Welfare Foundation (AWF). ASD was diagnosed by DSM-IV TR criteria. Mothers were interviewed and data were collected by semi-structured questionnaires.*

Results: *Total 5 risk factors were identified as the risk factors of ASD. They were: advanced paternal age (OR=2.84) and maternal age (OR=1.87); male baby (OR=2.01); environmental stress during pregnancy (OR=1.61) and preterm delivery (OR=1.80).*

Conclusions: *It is concluded that advanced paternal age, maternal age, male baby, environmental stress during pregnancy and preterm delivery are associated with increased risk of ASD.*

Keywords: *Autism Spectrum Disorder, risk factors.*

Introduction:

Autism spectrum disorder (ASD) is lifelong neurodevelopmental disorder with an onset before the age of 3 years characterized by impairments in social function, communication, and certain behaviors.[1,2] ASD include 3 different disorders of development, each with differing severities and patterns. The disorders are Autistic disorder (also called "classic" autism), Asperger syndrome, Pervasive developmental disorder-not otherwise specified (PDD-NOS).[1] Onset of unusual behavior often occurs in infancy or in the 2nd year of life and symptoms of ASD usually manifest by the age of 3 years and can last throughout a person's life.[3,4] It is estimated that worldwide about 1 in 100 children has autism.[5] The estimated prevalence of US children with ASD is 1 in forty.[6] According to a 2021 CDC report one in 54 children had been diagnosed with autism by age 8 in 2016, compared to 1 in 150 in 2000.[7] According to the survey conducted by Ministry of Health Family and Welfare of Peoples Republic of Bangladesh, overall mean prevalence for ASD was 1.55/1000 (n=7280). In Dhaka City the prevalence was 30/1000 and 0.68/1000 in rural populations.[8] Male-to-

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female ratio of ASD is 3:1.[9] The recurrence risk of autistic probands is 2 to 5 % .[10]

The exact etiology of ASD is unknown, but several genetic and non-genetic risk factors have been characterized that, alone or in combination.[11] Some studies showed environmental stress, threatened abortion, PET, diabetes, cardiac problem, systemic disease during pregnancy, multiple pregnancy, male child, prolonged labour, preterm birth, low birth weight , neonatal seizure, delayed cry, higher paternal and maternal age at birth as risk factors of ASD. [3,9,12-15]

Many factors make ASD difficult to understand and manage . Thus, recent research has focused on identifying specific biological abnormalities for diagnostic purposes as well as to measure changes resulting from treatment. The types of biomarkers identified include prenatal history, genetics, neurological including neuroimaging, neuro-physiologic, and visual attention, metabolic including abnormalities in mitochondrial, folate, trans-methylation, and trans-sulfuration pathways, immune including autoantibodies and cytokine dysregulation, autonomic nervous system, and nutritional.[16,17,18]

A correct and early diagnosis of ASD is so crucial because scientific research has demonstrated that children who receive intensive, sustained special education programs and behavior therapy by the age of 18-36 months can achieve better outcome in respect of self-care, social, and job skills, and often improve functioning and decrease symptom severity and maladaptive behaviors.[19,20] So if the risk factors could be identified earlier in a family and the diagnosis of ASD, early intervention is possible that ultimately reduce the subsequent sequele in children with ASD. A few studies have been done regarding the prenatal and perinatal risk factors of ASD in children but there is no published evidence in Bangladesh perspective. The present study was conducted to identify the prenatal & perinatal risk factors of ASD.

Materials and methods:
A case-control study was carried out in the Center for Neurodevelopment and Autism in Children (CNAC) in the department of Pediatrics, Bangabandhu Sheikh Mujib Medical University (BSMMU) and Autism Welfare Foundation (AWF), Mohammadpur, Dhaka, Bangladesh from March 2014 to June 2015 (16 months). Cases were collected from BSMMU (CNAC) and AWF. Controls were collected from BSMMU outpatient department and from other discipline of Pediatrics (children without ASD). They were recruited randomly on consecutive days matching their age 2-6 years and having no identifiable criteria for ASD. A total of 400 children were enrolled into the study, among them 313 cases and controls of same age and sex were selected who met the inclusion criteria.

Inclusion Criteria: Case-112 autistic children of 2-6 years of age diagnosed by DSM (Diagnostic and Statistical Manual)-IV-TR criteria. Control- 201 healthy children of same age and sex with age appropriate developmental status.

Children with mental disorder due to other cause and children without any birth record were excluded from the study. Ethical clearance was obtained from the institutional review board of BSMMU and authority of AWF. Informed written consent was taken from the parents. Confidentiality of the respondents were maintained properly. They were also given the right to withdraw their participation at any time during study period and if they would have been withdrawn from the study, the treatment of their children would be continued.

Mothers were interviewed according to data collecting form. A preformed semi structured data collecting form were used for data collection. It included particulars of the patients, socio economic status and education of the parents, prenatal conditions, perinatal and neonatal history, paternal and maternal age at birth of the patient. Hospital records and medical records were also collected.

Data analysis
Data were entered and analyzed using the software "Statistical Package for Social Science" (IBM SPSS version 20.0 for Windows). After entering the data, exploratory data analysis (EDA) was done to reveal possible errors in the data. Following statistical analysis were done-Chi square test, Student's t-Test, Odds ratio, binary logistic regression. Significance level á was set at 5% so p value <0.05 was considered as significant.

Result:

Table I

Association between demographic characteristics and ASD

Demographic characteristics		Group		p-value
		Case(n = 112)	Control(n = 201)	
Age of the children# (yrs)		4.02 ± 1.1	4.1 ± 1.05	0.758
Maternal age at birth# (yrs)		27.5 ± 5.0	24.3 ± 5.3	< 0.001
Paternal age at birth# (yrs)		34.3 ± 4.7	30.7 ± 6.8	< 0.001
Gender*	Male	85 (76)	121 (60)	0.005
	Female	27 (24)	80 (40)	
Income* (Taka)	<6000	09 (8.0)	28 (13.9)	
	6000 – 12000	21 (18.8)	88 (43.8)	< 0.001
	>12000	82 (73.2)	85 (42.3)	
Residence*	Rural	16 (14.3)	59 (29.4)	0.003
	Urban	96 (85.7)	142 (70.6)	

\# Data were analyzed using Student's t-Test and presented as mean ± SD.

* Data were analyzed using Chi-square (χ^2) Test.

Table I demonstrates the comparison of demographic characteristics between case and control groups. There was no significant difference between case and control groups with respect to age of the children . The average maternal and paternal ages of the autistic children at birth were significantly higher than their control counterpart (p < 0.001 and p < 0.001 respectively). Male children were more prone to develop ASD than the female ones (p = 0.005). ASD was observed to be significantly higher in children with family income Taka >12000 (p <0.001). Urban children tend to develop ASD more often than their rural counterparts do (p = 0.003).

Table II highlights the association of genetic, environmental and behavioral factors with ASD. Consanguinity was not found to be associated with ASD (p= 0.051). Environmental stress was significantly higher in case group than that in control group (p < 0.001). While mothers' behavioral problem was not associated with ASD, torture on mothers by fathers was considerably higher in the case group than that in the control group (p = 0.167).

Table II

Association between genetic, environmental, behavioral factors and ASD

Genetic, environmental and behavioral factors*	Group		p-value
	Case(n = 112)	Control(n = 201)	
Consanguinity	14(12.5)	43(21.4)	0.051
Environmental stress	43(38.4)	40(19.9)	< 0.001
Behavioral problem in mother	11(9.8)	17(8.5)	0.685
Torture by father	15(13.4)	17(8.5)	0.167

* Data were analyzed using Chi-square (χ^2) Test. Figures in the parentheses indicate corresponding percentage

Table III

Maternal conditions during pregnancy among the mothers of the studied children

Maternal status during pregnancy	Group		p-value
	Case(n = 112)	Control(n = 201)	
Threatened abortion	30(26.8)	40(18.9)	0.105
Pre-ecclamptic toxemia	6(5.4)	6(3.0)	0.295
Diabetes mellitus	13(11.6)	30(14.9)	0.414
Cardiac problem	3(2.7)	3(1.5)	0.368
Systemic disease during pregnancy	17(15.2)	28(13.9)	0.763
Multiple pregnancy	6(5.4)	5(2.5)	0.317

*Data were analyzed using Chi-square (χ^2) Test. Figures in the parentheses denote corresponding percentage

Table IV
Perinatal factors associated with ASD

Perinatal factors/conditions	Group		p-value
	Case (n = 112)	Control (n = 201)	
Mode of delivery (LUCS)	65(58.0)	66(32.8)	< 0.001
Prolonged labour	23(20.5)	42(20.9)	0.940
Preterm birth	20(17.9)	14(7.0)	0.003
Low birth weight (kg)	25(22.3)	32(15.9)	0.160
Neonatal hyperbilirubinaemia	53(47.3)	73(36.3)	0.057
Neonatal seizure	5(4.5)	4(2.0)	0.209
Delayed cry	26(23.2)	19(9.5)	0.001

*Data were analyzed using Chi-square (χ^2) Test. Figures in the parentheses denote corresponding percentage

Table V
Predictors of ASD among the studied children with unadjusted and adjusted ORs

Variables of interest		Univariate analysis		Multivariate analysis		β value	Intercept value
		Unadjusted Odds Ratio (95% CI of OR)	p-value	Adjusted Odds Ratio(95% CI of OR)	p-value		
Fathers' age at birth	>34 years	2.4(1.4-4.4)	0.001	2.84(1.24-5.10)	<0.001	2.601	
Mothers' age at birth	>30 years	2.1(1.5-4.2)	<0.001	1.87(1.17-3.85)	0.042	1.706	
Sex (male child)		2.1(1.2-3.4)	0.005	2.01(1.30 – 2.95)	0.021	2.234	
Environmental stress		2.5(1.5- 4.2)	< 0.001	1.61(1.10 – 2.61)	< 0.001	2.003	-4.088
Preterm delivery		2.9(1.4-6.0)	0.003	1.80(1.02 – 2.72)	0.014	1.802	
Delivery by LUCS		2.8(1.7- 4.5)	< 0.001	0.54(0.07 – 4.15)	0.301	0.591	
Delayed cry		2.9(1.5 - 5.5)	0.001	0.28(0.13 – 0.61)	0.541	0.089	

Table III shows association of ASD with maternal conditions and diseases. Threatened abortion was considerably higher in the case group (26.8%) than that in the control group (19.9%), although the difference did not reach the level of significance (*p* = 0.105). All other variables were almost identically distributed between the groups.

Nearly 58% of the autistic children were delivered by lower uterine caesarean section as opposed to 32.8% in the control group (p < 0.001). The incidence of prolonged labour was not different between case and control groups (20.5% vs. 20.9%, p = 0.940).The frequency of preterm birth was much higher in the case group (17.9%) than that in the control (7%) (p = 0.003). Nearly one-quarter (23.2%) of the autistic children had delayed cry compared to 9.5% of the control group (p = 0.001). Neonatal hyperbilirubinaemia was nearly (marginally) significant in case group than that in control group (p = 0.057). However, birth weight and neonatal seizure was not observed to be associated with ASD (p = 0.160 and p = 0.209) (Table IV).

Table V demonstrates the binary logistic regression analysis of Odds Ratios for characteristics of the children likely to develop ASD. The variables revealed to be significantly associated with ASD in univariate analyses were all entered directly into the model of the 7 variables, higher paternal and maternal age, male sex, environmental stress and preterm delivery were emerged as independent predictors of ASD (p < 0.001, p = 0.042, p = 0.021, p < 0.001 and p = 0.014 respectively).

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Discussion:

In the present study it has been found that paternal age (OR=2.84; CI=1.2-5.1) and also maternal age at birth (OR=1.87; CI=1.1-3.8) have significant association with ASD.There are some studies that support these findings. A cohort study comprising 30,902 cases of ASD born between 1985–2004 showed that paternal and maternal age were associated with increased RR of ASD after adjusting for confounding and the other parent's age (mothers 40–49 years vs 20–29 years, RR = 1.15 (95% confidence interval (CI): 1.06–1.24), P-value <0.001; fathers~* 50 years vs 20–29 years, RR = 1.66 (95% CI: 1.49–1.85), P-value <0.001).[12] A cohort study was done in Northern California, where 593 children were diagnosed as ASD and 1,32,251 children without ASD were included as control. In their study they found the maternal age (RR= 1.31; CI= 1.07-1.62) and paternal age (RR= 1.28; CI= 1.09-1.51) older than 34 years at birth was significantly associated with increased risk of ASD.[21]A report in the medical journal "Nature" says it is the age of the father at the time of conception, not the age of the mother that can raise the risk of autism in a child. New mutations are frequent enough as fathers aging alone can explain the increase for the risk of autism.[22]

Present study results pointed to the higher risk of ASD in boys than girls (OR=2.01; CI=1.30-2.95). This finding was consistent with the study done by Itzchak who found 461 children (81%) out of 564 participants were male autistic patients.[23] El-Baz also stated that ASD was more than twice as common in boys as girls.[24] Loomes did a review and meta-Analysis where it shows male female ratio in ASD is 3:1.[9]

In this study it has been found that environmental stress during pregnancy was a significant risk factor for ASD, (OR=1.61; CI=1.10-2.61). Alamoudi conducted a study with 459 mothers of children with autism (aged 2–14 years). Environmental factors, consanguinity, and ASD family history were assessed. Result showed that the moderate severity in prenatal life events was associated with ASD than history of no stress(p = .031; OR: 3.82).[13] Similar findings were found in a case control study done by Zhang et al. in China. In their study 95 children were taken as case and 95 children as control. They found maternal unhappy mood during pregnancy (OR=6.22;

CI= 3.12-12.41) as the probable risk factors of autism.[3] It has been reported that prenatal stress or exposure to environmental or social stressors including family problems is associated with increased risk of autism.[25,26] It has been hypothesized that maternal unhappy mood during pregnancy may increase the level of hormones such as adrenalin in a mother's body, causing placental vasoconstriction which may affect fetal cerebral blood flow, or directly affect fetal hormone levels, with a negative impact on fetal development.[3]

In the present study it has been found that preterm infants have significant risk of developing ASD (OR=1.80; CI=1.02-2.72). There are some studies that support these findings. Gadassi did a study to examine the long-term risk for ASD in 110 preterm children (born at a gestational age of ≤34 weeks) and 39 full-term children assessed at ages 18, 24, and 36 months. At 18 and 24 months, a higher long-term risk for ASD was found for preterm children compared to full-term children.[14] Kolevzon et al. had done a cohort study at New York. They found prematurity are the major risk factors for autism.[26] El-Baz et al. did a case control study in Egypt also mentioned gestational age at birth of less than 37 weeks as the risk factors of autism.[24]

In this study, delayed cry was found to be the risk factor of ASD in univariate analysis (OR=2.9; CI=1.5-5.5). Similar findings were found in different studies done by Hisle-Gorman, Gardener et al. and Guinchat et al.[15,28,29] While, low birth weight has been found to be the risk factor of ASD by some authors.[29,30,31] But the present study did not identify low birth weight as the risk factor.

The present study found family income >12000 taka group (p <0.001) and children from urban area (p = 0.003) have significant association with ASD. No study has been found in abroad to support these findings. This might be hypothesized that there is lack of awareness in poor family and in rural areas, so the child with ASD remain undiagnosed.

In univariate analysis, advanced paternal and maternal age, male child, environmental stress, delivery by LUCS, preterm delivery, and delayed cry were found to be significantly associated with ASD, but when these 7 variables were entered directly into binary logistic regression model, advanced paternal and maternal age, male child, environmental stress during pregnancy and preterm delivery were emerged as

independent predictors of ASD with risk ratios being 2.84, 1.87, 2.01, 1.61 and 1.80 respectively.

Conclusion:

This study found that advanced paternal and maternal age, male children, environmental stress during pregnancy, preterm delivery were associated with an increased risk of ASD. These variables should be examined in future studies that use large, population-based birth cohorts with precise assessments of exposures and potential confounders to confirm this study. This may help in early identification as well as possible preventive measures.

Recommendations:

1. Early screening for diagnosis of ASD should be done where the risk factors of ASD are present in the family.

2. Further study may be done with larger sample size and long follow-up period.

Limitations of the study:

1. Information of the data was based on maternal recall memory.

2. Controls were taken from different setups.

Conflict of Interest

Dr. Mohsina Akter Lucky declares that she has no conflict of interest.

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