



Perinatal and Socio-Economic Risk Factors of Autism in Children attending a Tertiary Care Hospital in Bangladesh



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Abstract

Objective: Autism is a neurodevelopmental disorder where genetic factors play causal role. This case-control study explored the association between perinatal and socioeconomic status with risk of autism.

Method: It was a case control study among children who came from different areas of the country during the period of 2005 to 2015 for assessment in the outdoor facility of Bangabandhu Sheikh Mujib Medical University. One hundred children were diagnosed autism by Autism Diagnostic Observation Schedule (ADOS)-Generic. Among them 79 were boys and 21 were girls. Another one hundred children without autism were taken as control, 65 of them were boys and 35 were girls. Perinatal and socioeconomic risk factors were analyzed in these two groups, using medical records.

Result: Mean age of the ASD children was 3.51+1.58 year and control was 3.80+1.53. Male predominance was observed in ASD children. After univariate analysis three significant variables identified to pose as risk for autism. These were parental advanced level of education ($P<0.001$), urban residence ($P<0.001$) and neonatal jaundice ($P<0.001$). Variables like male sex, occupation as service holder and low birth weight at birth approached significance at the 0.05 level.

Conclusion: Results suggested that parental profile as well as perinatal environment are associated with risk of autism and this factor act independently.

Keywords: Autism; Perinatal; Socioeconomic; Risk factor

Abbreviations: ASD: Autism Spectrum Disorders; ADOS: Autism Diagnostic Observation Schedule; IPNA: Institute of Paediatric Neurodisorder and Autism; BSMMU: Bangabandhu Sheikh Mujib Medical University; BIND: Bilirubin-Induced Neurologic Dysfunction

Introduction

Autism spectrum disorders (ASD) are characterized by impaired social interactions, communication deviance and restricted stereotypical behavioral pattern. The prevalence of ASD ranges from 13.1 to 29.3 per 1,000 children aged 8 years in different communities throughout the United States [1] whereas prevalence in Bangladesh in rural community was found 0.75/1000 children. The study was done by screening tool MCHAT [2]. ASD is typically lifelong neuro-developmental disorder with onset before the age of 3 years [3,4]. The etiology of ASD is not fully understood, but twin and family studies suggest that genetic factors play substantial causal role. The recurrence risk of autistic probands is 2 to 5 % [5,6]. While genetic disorders

are commonly comorbid with autism, no genetic disorder is uniformly associated with autism. Similar cases of autism occur in children with and without genetic disorders. Given the variability in autism, even in groups of children who have the same genetic disorders, it seems likely that environmental factors play an important role in the development of these disorders and may influence severity [7,8].

It has been hypothesized that prenatal, natal and postnatal complications as well as social status of the parents may act through independent etiologic pathways to increase the risk of autism or may interact with a genetic deposition to increase the risk by interfering at critical times in the developmental process.

Several studies have focused on perinatal and socio-economic risk factors for autism. However, many of these studies have been done in small sample size. Even in some studies proper diagnostic tool has not been implemented. Further very few studies have taken place in developing country where the social burden is more. A number of studies examined several risk factors without mentioning the statistical significance [7,9,10]. Thus there is minimal consistent pattern of perinatal and social risk factors associated with autism. These variable results may be due to difference in the socioeconomic status, variation in the diagnostic criteria, health care facility and different types of control group along with the diagnostic tool variability. Other problems involved are differing study methodology and variability of the information source [11,12].

On the above background, this study has been done in a developing country like Bangladesh to analyze the risk factors of autism. The strength of the study is that we used Autism Diagnostic Observation Schedule (ADOS) -Generic for diagnosis of autism and we had a control group to make the study reliable.

Method and Material

Study setting

This study was carried out in the Institute of Paediatric Neurodisorder and Autism (IPNA), Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, a tertiary level teaching facility and Medical University in capital of Bangladesh.

Inclusion Criteria

- a. Children of 2- 6 year
- b. Diagnosed as autism by Autism Diagnostic Observation Schedule (ADOS) -Generic by a certified psychologist.

Exclusion Criteria

Who already diagnosed as other neurodevelopmental disorder or psychiatric disorder.

Study Design

It was a case control study; cases were taken as per inclusion criteria ranging from 2-16 years. 100 children met the inclusion criteria as Autism Spectrum Disorder (ASD). The control sample was comprised of 100 children in the same age group. The study was done from March 2005 to September 2015. Patient records

Parental Characteristics

Table 2: Distribution of the children by parent's information.

Parent's information	Autism Group (n=100) No. (%)	Control Group (n=100) No. (%)	P value
Father			
Age			0.102
< 35 years	29	40	
> 35 years	71	60	
Education			<0.001*

were reviewed and data was collected on structured proforma especially prepared for this purpose. The controls were recruited randomly on consecutive days matching their age 2-16 years and having no features of autism. Detailed history regarding age, sex, environment, parental educational, social status, and habitat was taken. Antenatal history was taken including age of parent at birth, history of threatened abortion, any fetal loss, parity, chronic illness like hypertension, diabetes, infection in pregnancy , medication during pregnancy. Natal and postnatal history including gestational age, perinatal insult like asphyxia, prematurity, sepsis, birth weight, mode of birth etc. was taken. Developmental history, family history and vaccination history was taken.

Data Management and Statistical Analysis

The data was coded, entered and analyzed using Windows SPSS version 21.0. In descriptive analysis, the mean and standard deviations of the continuous variables and percentages of categorical variables were computed. A p-value of < 0.05 was considered statistically significant.

Ethical Considerations

Ethical clearance was taken from the Ethical Review Committee (ERC) of the Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka.

Results

Baseline Characteristics

Table 1: Age and sex of the studied children.

	Autism Group (n=100) Mean±SD	Control Group (n=100) Mean±SD	P value
Age	3.51±1.58	3.80±1.53	0.752
Male	79	65	0.027*
Female	21	35	

No significant difference of age was seen between children with Autism and Control group in respect of age (p = 0.752) but male predominance was found in ASD group (p= 0.027).

The age and sex of our children are presented in Table 1. Mean age of children with autism was 3.51+1.58 year and control was 3.80+1.53. The majority of the children with autism (79%) were male which was statistically significant comparing the from control group.

Illiterate	0	2	
< Graduate	28	57	
Graduate	28	14	
> Graduate	44	27	
Occupation			0.007*
Service	66	51	
Business	27	25	
Unemployed	2	3	
Others	5	21	
Income			0.985
<10000	19	19	
10000-30000	59	58	
> 30000	22	23	
Mother			
Age			0.212
< 35 years	77	84	
> 35 years	23	16	
Education			<0.001*
Illiterate	3	1	
< Graduate	41	75	
Graduate	27	7	
> Graduate	29	17	
Occupation			0.032*
Service	34	24	
Business	4	0	
Housewife	62	74	
Others	0	2	
Income			0.052
<10000	83	93	
10000-30000	14	7	
> 30000	3	0	
Resident			<0.001*
Rural	18	45	
Urban	82	55	
Consanguinity			0.205
Yes	6	11	
No	94	89	
Any behavioral problem in father	0	0	-
Yes	100	100	
No			
Any behavioral problem in other	1	0	0.316
Yes	99	100	
No			

Table 3: It 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 multivariate analyses were all entered directly into the model. Of the variables, higher education, urban area and neonatal jaundice were emerged as independent predictors of ASD ($p = 0.01$, $p = 0.01$ and $p < 0.001$ respectively).

	B	S.E.	df	P value	OR	95% C.I. for EXP(B)	
						Lower	Upper
Education	1.21	0.48	1.00	0.01	3.34	1.30	8.63
Occupation	-0.66	0.68	1.00	0.33	0.52	0.14	1.95
Income	-1.06	0.60	1.00	0.08	0.35	0.11	1.13
Urban	1.00	0.40	1.00	0.01	2.72	1.24	5.97
Consanguinity	1.17	0.83	1.00	0.16	3.21	0.64	16.21
Diabetes mellitus	-19.52	24003.50	1.00	1.00	0.00	0.00	-

Hypertension	-0.83	0.67	1.00	0.22	0.44	0.12	1.62
Maternal stress during pregnancy	-21.11	22506.10	1.00	1.00	0.00	0.00	-
Neonatal jaundice	-4.09	1.33	1.00	<0.001	0.02	0.00	0.23
Neonatal seizure	-0.52	1.21	1.00	0.67	0.59	0.06	6.38
Delayed crying	1.21	0.63	1.00	0.06	3.37	0.97	11.65

Age of the parents and their income had no significant impact on autism. However, level of education seemed to have effect on autism. Parents of children with autism, both mother and father, who had done graduation and above had significantly increased autistic children (p value significant, Table 2). Moreover, profession of the parents also showed significant impact on autism. In this study, mother and fathers who were service holder had more children with autism (P value 0.032 and

0.007 respectively). Moreover, place of habitat also had significant relation with autism; urban children had more frequency of autism than rural (P value <0.001). However, in multivariate analysis higher education, residing in an urban area emerged as independent predictor for ASD (P value 0.01, 0.01, OR 3.34, 2.72 respectively) (Table 3). Behavioral problems in parents and consanguinity did not seem to pose any risk in autism.

Pregnancy and Delivery Complications

Table 4: Low birth weight babies were significantly associated with autism. (p value <0.001).

Natal problems	Autism Group (n=100) No. (%)	Control Group (n=100) No. (%)	P value
Gestational age			0.081
Preterm Term	3 97	1 99	
Mode of delivery			0.113
LUCS NVD	65 35	54 46	
Birth weight			<0.001*
Normal LBW VLBW	75 21 4	87 12 1	
Prolong labour			0.155
Yes No	0 100	2 98	
Any other problem during delivery			0.155
Yes No	2 98	0 100	

Among maternal pregnancy complications threaten abortion, pre-eclamptic toxemia, diabetes mellitus, cardiac disorder, hypertension, environmental stress, maternal stress, multiple pregnancy did not occur significantly higher rate than those of normal. Among the perinatal factors, significant higher incidence of low birth weight and very low birth weight babies were found in autistic group (p value <0.001). While, gestational age, mode of delivery, prolong labour were not significantly associated with either of the groups. In the postnatal complications neonatal jaundice was present in higher number in autistic group while perinatal asphyxia was more common in control group. No significant relation with neonatal seizure was found. (Tables 4 & 5). After univariable logistic regression neonatal jaundice emerged as independent predictor of ASD (p<0.001).

Discussion

This is a case control study nested in children of 2-16 year in a tertiary care centre to address the possible association of

perinatal and socio-economic risk factors in developing autism. The sample size allows reliable estimates of risk factors in univariate analyses. We have done ADOS for autism diagnosis which is generally considered having high validity and reliability [13]. We studied children attending outdoor facility of the hospital.

The study suggests role of perinatal and social risk factors in ASD population. After analyzing univariate analysis three significant variables were identified which were parental graduate level of education, urban residence and neonatal jaundice. Variables like male sex, occupation as service holder and low birth weight at birth approached significance at the 0.05 level

We found a significant link between autism and neonatal jaundice. Similar association has been found by Luis E Lozada et al in their study [14]. They found that children who develops ASD are more likely to have an admission with a diagnosis of

jaundice in the neonatal period (odds ratio = 1.18; P =.001) and more likely to require treatment for this jaundice (odds ratio = 1.33; P = .008). We did not studied the requirement of treatment of jaundice as variable. It is already known that bilirubin is a neurotoxin. The globus pallidus, cerebellum, hippocampus, and subthalamic nuclear bodies have been identified as areas

in the brain vulnerable to bilirubin toxicity [15,16]. There is evidence of lower gray matter volumes in the putamen and cerebellar hypoplasia in individuals with autism, creating a degree of overlap that may indicate shared mechanisms [17-19]. Additionally, there is overlap in the clinical features of bilirubin-induced neurologic dysfunction (BIND) and ASD [15] (Table 6).

Table 5: In the post-natal condition of the study children, neonatal jaundice was significantly associated with children with autism (p<0.05) and delayed cry with control group (p 0.038).

Post-natal condition	Autism Group (n=100) No. (%)	Control Group (n=100) No. (%)	P value
Neonatal jaundice			<0.001*
Yes	19	1	
No	81	99	
Neonatal seizure			0.651
Yes	2	3	
No	98	97	
Delayed crying			0.038*
Yes	6	15	
No	94	85	
Any other problem during postnatal period			0.174
Yes	4	1	
No	96	99	

Table 6: None of the prenatal factors could be associated with increased number of autism.

Prenatal condition	Autism Group (n=100) No. (%)	Control Group (n=100) No. (%)	P value
Threaten abortion			0.756
Yes	5	6	
No	95	94	
Pre Eclamtic Toxaemia			0.316
Yes	0	1	
No	100	99	
Diabetes Mellitus			0.155
Yes	2	0	
No	98	100	
Cardiac cause			-
Yes	0	0	
No	100	100	
Hypertension			0.138
Yes	12	6	
No	88	94	
Maternal stress during pregnancy			0.081
Yes	3	0	
No	97	100	
Multiple pregnancy			0.651
Yes	2	3	
No	98	97	
Any other problem during prenatal period			0.017
Yes	2	10	
No	98	90	

Birth weight has long been studied as a risk factor for developing autism. Our study result had similarity with study done by Burd et al. [7] and Larsson HJ et al. [8] who found low

birth weight was significantly associated with ASD. Other factors found to be significant were Apgar score at one and five minutes, father’s age, the trimester prenatal care started, termination

of prior pregnancy, gestation less than 36 weeks [7,8]. This factors were not analyzed in our study. It is noteworthy that birth weight is the net result of at least 3 factors: genetic, growth potential, duration of pregnancy and rate of fetal growth. The genetic growth potential is unknown, making it difficult to disentangle the effect of these factors [20]. Birth weight also found to be important risk factor in autism in a large, register based study from Sweden [21]. It is here to mention that birth weight, birth length, pattern of intrauterine growth, mode of delivery, complications during pregnancy have frequently been studied in link with autism. Hultman et al. in their study found three fold increases in risk of autism among children with a low 5 minute Apgar score [21]. Congenital malformation is also well documented in autism which is not studied in our work [6].

Apart from the fetal factors, we also studied parental behavior. Parental behavioral disorder did not seem to be associated with autism in our study but some studies done in abroad found strong association between them [8]. Historically genetic links have been found between schizoid personality traits and autism [22]. In some studies advanced parental age and maternal age were significantly related to autism [23-25]. However, our results showed no increased risk of autism associated with parental age.

We studied the information about the socioeconomic status of the parents. In unadjusted analyses urban population and graduate level of education emerged as independent predictor of autism. Burd L et al. in their case control study in USA have also found that maternal education was significantly associated with autism but in a reverse way. For each year of difference in parents education between the cases and controls (lower education was the risk factor for autism), the risk of autism increased. After logistic regression the odds ratio was 1.24 [7]. On the other hand, Larsson et al did not find any statistically significant association between autism and maternal education, rather they have mentioned that socioeconomic factors play little or no role in the etiology of their country Denmark where access to health care system is equally available for all and free of charge [8]. In a very recent study by For-Wey Lung, although more children of mothers with lower-than-average education were positive on screening, more children of mothers with higher-than-average education were also diagnosed with ASD. Thus here, maternal educational disparity was found between ASD clinical diagnosis and community screening [26].

In our study we did not find any significance of occupation and income of parents after logistic regression. But in some studies, association of occupation has been related to autism. Aisha et al. have found that certain paternal occupations, including engineering, healthcare, and accounting/financial analysis are in a higher likelihood of having a child with an ASD diagnosis. Furthermore, they have observed more severe autistic symptomology (as indicated with higher ADI-R scores) in children of parents who both had highly technical occupations as

well as in those for whom only the father had a highly technical occupation [27].

Geographic variation in ASD occurrence has been observed, and urban residence has been suggested to serve as a proxy for etiologic and identification factors in ASD. We examined the association between urbanicity level and ASD. After logistic regression children who belonged to urban areas had a significantly increased diagnosis of autism. The urban-rural geographic gradient has also been detected for other psychiatric disorders than ASD, e.g. schizophrenia, bipolar affective disorder, and depression [28-30]. The high risk found in our study for children born in the capital and capital suburb could support the hypothesis of environmental agents acting during pregnancy or early in life of the child affecting the risk for ASD, such as infections or air pollutants containing neurotoxic or immunotoxin properties, a hypothesis that has been investigated by Kalkbrenner et al. [31] To date, however, there is little evidence for the influence of such environmental pollutants including specific agents on the development of ASD. Our finding of an increased risk of ASD in urban areas compared to rural areas is in accordance with findings from studies of geographically and ethnically diverse areas such as Japan, Taiwan and the United States [32-34].

We studied the association of perinatal factors like threaten abortion, pre-eclamptic toxemia, diabetes mellitus, cardiac disorder, hypertension, environmental stress, maternal stress, multiple pregnancy, mode of delivery, gestational age, prolong labour causing autism. None of these seemed significantly related to autism. But some studies have found perinatal factors like breech presentation, primary caesarian section to be significantly causing autism ($P < 0.05$) [35]. This relationship is difficult to explain. The over presentation of first-born children in ASD may be explained by the parents' reluctance to have more children after 1 child has been diagnosed with autism [36]. It is here to mention that currently the field of ASD genetics is expanding rapidly, and it is likely that genetic subsets will be identified in the near future [35]. However, the risk factors which we have identified may provide clue to an etiology of autism in developing country perspective like Bangladesh.

Conclusion

The finding of this study suggests that parental educational status, urban localization and neonatal jaundice are independently associated with ASD risk. So while reviewing a case of autism these factors should be taken into consideration. Moreover, additional investigations should be targeted to find out the environmental and genetic impact on autism. The strength of this study is that ADOS has been used by a pediatric psychologist to detect autism.

Ethical Consideration

Informed written consent has been taken from the parent/legal guardian of the patients. Ethical clearance has been taken

from the institutional review board of the university.

Conflict of Interest

No funding has been taken in this research work.

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