SHORT ARTICLE

Association of autism spectrum disorder and gestational diabetes mellitus of mothers in Bangladesh

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Abstract

Background: Globally Approximately 1 in 110 children has Autism Spectrum Disorder (ASD) and the cumulative incidence of this disorder seems to be increasing. To date, the etiology of ASD is unknown. Gestational diabetes is a common pregnancy complication whose prevalence is increasing among women of reproductive age and results in both short-and long-term adverse outcomes for the offspring and may contribute to ASD risk. **Aims & Objectives:** The aim of the study was to determine the association of maternal gestational diabetes mellitus with autism spectrum disorder in children. **Material & Methods:** A case control study was conducted among the children 5-7 years old diagnosed with an autism spectrum disorder (n=99) in special need primary schools and a similar age control group of children (n= 198) without the disease at randomly selected primary schools. The groups of children were compared with the obstetric information regarding Gestational Diabetes Mellitus (GDM) of mothers during their index pregnancy. **Results**: Compared with the control subjects, cases had significantly older parents and were more likely to be high socioeconomic status. History of GDM during index pregnancy were higher in cases than controls [OR=2.30, CI= 1.36 – 3.91].Prenatal and perinatal risk factors were more prevalent among case mothers compared with controls. Collectively, these conditions were associated with a higher likelihood of ASD than controls. Among cases family history of DM were more common compared with controls [OR=23, CI= 10.84 – 48.94]. Case mothers had greater frequencies of threatened abortion [OR= 3.23, CI= 1.94-5.37], bleeding during pregnancy [OR=1.25, CI=0.20–7.61] and more likely to have experienced cesarean section. Male children were more affected by ASD [OR= 2.87, CI= 1.67 – 4.90] compared with controls. **Conclusions**: Maternal DM in pregnancy is responsible for at least a good proportion of cases of ASD which in turn has been proven as independent risk factors for autism.

Key Words

Autism spectrum disorder; GDM; Bangladesh

Introduction

Over the past decade, autism has emerged as a major public health concern globally. Although known for more than fifty years as one of the most severe childhood neuropsychiatric disorders, it was thought to be quite rare. Autism is defined as severe psychiatric disorder of childhood marked by severe difficulties in communication and forming relationships with other people, in developing language, repetitive, and limited patterns of behaviors and obsessive resistance to small changes in familiar surroundings (1). A low-functioning individual with autism might be non-verbal,

cognitively impaired, self-injurious, and virtually unable to connect with even the closest of family members. A very high-functioning individual with autism could be verbal, of above average cognitive ability, have idiosyncratic areas of interest with a tendency to gear social interaction around these, and may have formed strong bonds with family, teachers, and some peers. Recognizing this spectrum, many refer to the broad range of autistic-like conditions as Autism Spectrum Disorders (ASDs). Classic autism, the form with behavioral features closest to those described by Kanner (2) is called autistic disorder or nuclear autism. Once thought to be the predominant form, it may well account for less than half of the ASDs (3). Autism is a chronic disorder with an onset before the age of 3 years, characterized by the following three main sets of behavioral disturbances: social abnormalities, language abnormalities and stereotyped repetitive patterns of behavior (4). Diagnosis typically comes from a complete patient history, physical and neurological evaluation. The possible causes of autism include perinatal factors as neonatal anemia, high incidence of respiratory distress syndrome and high incidence of medication usage during pregnancy in the mothers of autistic children, also maternal bleeding after the first trimester and meconium in the amniotic fluid (5). Environmental factors such as mercury and radiation as possible causes of autism spectrum disorders (ASDs) (6). Approximately 1 in 110 children has ASD, and the cumulative incidence of this disorder seems to be increasing (7-8). Moreover, 1 in 83 children has other developmental delays (DDs) (9). An association between general developmental impairments and maternal diabetes previously observed. Studies involving women with diabetes found correlations between gestational measures of maternal lipid and glucose metabolism and poorer performance of the offspring on standardized IQ tests and motor development assessments Dionne et al (10) reported significant expressive language impairments in young children born to mothers with gestational diabetes (GDM) compared with children of women without diabetes. Insulin resistance and chronic inflammation in type 2 diabetes (T2D) and related conditions, including obesity and hypertension, have been well established (11-13). In addition, because sensitivity to insulin naturally decreases during gestation, women with impaired glucose tolerance before pregnancy may develop GDM when their insulin production becomes insufficient to maintain euglycemia (14-16).

In a population-based retrospective study from Australia identified an almost 3-fold increased risk for having a child with autism for mothers who had pre-gestational diabetes or GDM, comparing mothers of 119 autistic children with an intellectual disability to 236,964 controls born between 1983 and 1992.17 Many developing countries are with lack of study on ASD children, Bangladesh is one of them where data on GDM and ASD is still inadequate.

Epidemiologic studies on the association of maternal diabetes in pregnancy and risk of ASD in the offspring are sparse. A meta-analysis of prenatal risk factors for ASD estimated the combined risks from studies conducted through March 2007.(18) This meta-analysis included (4) studies on maternal pre-gestational diabetes or GDM and autism; (19, 20-26) in total 2,764 study participants and 685 autism cases. Among the prenatal risk factors, GDM was one of the strongest risk factors for autism with a 2-fold risk for autism across studies. In addition, a population-based retrospective study from Australia identified an almost 3-fold increased risk for having a child with autism for mothers who had pre-gestational diabetes or GDM, comparing mothers of 119 autistic children with an intellectual disability to 236,964 controls born between 1983 and 1992 [OR=2.89 (95% CI: 1.28, 6.51] (27). Autism is most likely a "multifactorial" disorder. It is estimated that based on worldwide epidemiologic studies autism appears to be increasing at a rate of 3.8% per year.(28)

Therefore, it is urgent to conduct a case control study on autism spectrum disorder to considering the concurrent rise in obesity and diabetes in pregnancy, as well as the modifiable nature of these disorders, their associations with ASD may shed light on the prevention of ASD.

Aims & Objectives

The objective of the study was to determine the association of autism spectrum disorder and gestational diabetes mellitus

Material and Methods

It was a case control study conducted among the ASD children studied in special need schools and non ASD children studied in primary and kindergarten schools in Dhaka city.

Seven special need schools in the shamoli and Mohammadpur area of Dhaka city were selected for the study. As well some primary and kindergarten schools of same area of Dhaka city were selected as control for the study after matching age, area of residence. The study period was from July, 2011 to Dec, 2012. By 50% relative precision, 95% CI and 50% exposure rate, 99 number of case and about double number (198) of control participants were taken as per calculation. However, 13 controls were excluded because of giving incomplete data. So, 185 controls were found for analysis. This study included in each groups after matching with age (5 -7 yrs) and area of residence.

The ASD children for case and general children for control group were selected randomly according to the fulfillment of the selection criterion. A semi structured questionnaire with check list was used to collect the data.

The data were analyzed in SPSS 17 software and Microsoft excel. The t-test, chi-square test, logistic regressions were done according to application.

Ethical consideration: The ethical committee of the Diabetic Association of Bangladesh approved the protocol. All the respondents willingly participate in this study and singed an informed consent. They were informed about their right to withdraw from the study at any time without showing any cause. The participants were reassured about the confidentiality of data and the use of this data only for this research purpose. The questionnaires were kept securely. All the procedures were done with giving respect and dignity to the participants

Results

The study reveals that among case group male and female children were 74.70% and 25.30% respectively. On the other hand, in control group, 50.80% and 49.20% were male and female children respectively (Table-1). It was found that there is significant relationship between ASD and sex distribution of the study subjects. Higher proportions of male children were affected by ASD than female children. It is found that most of the children (64.6%) in case group were in 7years age group. Followed by 6 years age group (30.3%) and 5years age group (5.1%). In control group (44.9%) were in 7 years age group followed by 5 years age group (30.8%) and 6 years age group (24.3%). The study reveals that among the cases 2% of the mother completed up to primary level education, 27.30% completed up to SSC, 30.30% completed HSC, and 40.40% completed university education (Table-1). However, among the control 68.60% mother completed up to primary level education, 13%completed up to SSC, 9.20% completed up to HSC and 9.20% completed their university education.

Association of gestational diabetes mellitus (GDM) and ASD.

The study reveals (Table-2) that among cases, 40.4% respondents had history of GDM during their index pregnancy and 60% respondents had no diabetes during index pregnancy. On the other hand, 22.7% respondents had history of GDM during their index pregnancy in the control group.

It was found that there is a statistical significant association of gestational diabetes mellitus and ASD.

Distribution of children according to co morbid symptoms of ASD.

According to the co morbid symptoms of autism spectrum disorder (ASD), 34.3% children had intellectual disability, 18.2% had attention deficit and 20.2% had hyperactivity disorder,

2.0 % had learning disability and 25.3% had behavioral problem among the case group. (figure 1)

Age at onset of ASD symptoms: ASD symptoms were first recognized by mothers of the ASD child. Age at onset of ASD symptoms widely varied in different socioeconomic condition. In our study we found 43.3% children had age at onset of ASD symptoms were 15 -18 months, 17% were age of 19 22 months and 39.4% at the age of 23- 26 months. We found higher proportion of mothers could recognize ASD symptoms in between 15 to 18 month children.

The study reveals that 4.04% and 5.94% mothers had pregnancy-induced hypertension in their index pregnancy in cases and controls respectively. This difference found statistically significant. As regards to GDM, 40.4% of case had GDM in the index pregnancy in comparison to 22.7% respondents of control. This difference found statistically significant. About 3.30% case participants had Eclampsia with comparison to 3.78% control participants. This difference found statistically significant. Among case group 2.02% respondents had history of bleeding during index pregnancy compared to 1.62% controls. Regarding mode of delivery in index pregnancy, 28.28% of cases did deliver their baby through normal vaginal delivery and 71.7% through cesarean section. In control group 72.8% participants delivered their baby through normal vaginal delivery

and 27.2% through cesarean section. This difference found statistically significant in our study (Table-3)

As regards of family history of DM, 90(61.6%) and 56(38.4%) had positive family history of DM in case and control respectively. We found family history of DM higher among case families than control families. This difference found significant in this study. Positive family history of ASD in mother's family were 39(52%) and 36(48%) in case and control respectively. This difference found significant in this study. Positive family history of ASD in father's family were 39(54.2%) and 33(45.8%) in cases and controls respectively. We found positive family history of ASD were higher in case families than controls. In our study, we found this difference significant.(Table-4)

Discussion

In our study, GDM reported in 40.4% of cases versus 22.7% of controls. This difference is statistically significant (p= <0.05). There was statistical association between GDM and risk of ASD (OR = 2.30, CI=1.36 -3.91). A population-based retrospective study from Australia identified an almost 3-fold increased risk for having a child with autism for mothers who had pre-gestational diabetes or GDM, comparing mothers of autistic children with an intellectual disability to controls born between 1983 and 1992 (OR=2.89 , 95% CI: 1.28, 6.51) (29) .Evaluating pregnancy complications and obstetric sub optimality as risk factors among women in the Nurses' Health Study II, GDM was significantly associated with having a child with any of the ASD (OR=1.76 (95% CI 1.34, 2.32), p <0.0001) (29). These findings are consistent with Gardener et al. (20) that gestational diabetes has been associated with various adverse pregnancy outcomes.

Age of onset of autism reported by mothers was found to be 43.3% child at age of 15 to 18 months, 17% of children at age of 19 to 22 months and 39.4% of children at age of 23 to 26 months. These findings are consistent with Gray and Tonge (30) who found that parents become concerned about autistic behaviour of their children at the age of 12–30 months. On the other hand, Mandell *et al*. (31) found that there is often wide variation in the age in which children present for diagnosis or to obtain necessary therapy, in different socioeconomic groups .

The study revealed that 54% cases of autistic children were of high social class. Mean monthly family income were in taka 22667.77 among cases in compared to 12054.05 taka in controls. About 40% mothers of case had higher education in comparison to 17% in control group. We found maternal higher education and maternal advanced age at pregnancy were related. Maternal higher education influence the family income. Therefore, these two factors were related with socioeconomic status of the family and indirectly related with risk of ASD. These difference are statistically significant (p= <.001). This finding was consistent with a recent study by Durkin and colleagues (32) using area-based measures of socioeconomic status found that prevalence of autism increased with socio-economic status in a dose-response manner express that higher education level of mothers had more age and consequence is advanced age at child birth.

Regarding family history of diabetes mellitus, 61.6% of case versus 38.4% of controls had positive family history of DM. This difference found statistically significant (OR=23.06, CI= 10.84 – 48.94, (p=0.001)). Family history of DM is one of established risk factors for GDM. Our study reveals that positive family history of DM is strongly associated with ASD in children as this risk factor play a causal role for GDM which in turn increased the risk of ASD.

Our study reveals that GDM and advanced maternal age at child birth and family history of DM is significantly associated with risk of ASD .Family history of DM, obesity, lack of physical activity and advanced maternal age at birth is the major risk factors of GDM among the women of reproductive age. On the other hand, GDM, advanced maternal age at child birth and family history of DM were collectively increased the risk of ASD

Conclusion

Global trend of gestational diabetes mellitus has been rising as well as the ASD among children. Overall ASD prevalence estimates varied widely across all sites was 11.3 per 1,000 (one in 88) children. Our study found there is an association between ASD and gestational diabetes mellitus.

In our study we found GDM, advanced parental age, positive family history of DM as a predictor of ASD and these findings suggest that same underlying factors plays the causal role for developing both these adverse health outcomes. From this findings it is reasonable to conclude and hypothesized that maternal DM in pregnancy which is termed as GDM, is responsible for a certain proportion of cases of ASD which in turn has been proven as independent risk factors for autism.

Authors Contribution

All authors have contribute equally.

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Tables

TABLE 1 SOCIO DEMOGRAPHIC CHARACTERISTICS OF THE STUDY SUBJECTS

Variables		Cases(99)		Controls(185)	
		Number	Percentage	Number	Percentage
Sex	Male	74	74.7	94	50.8
	Female	25	25.3	91	49.2
Age	5 years	5	5.1	56	30.8
	6 years	30	30.3	46	24.3
	7 years	64	64.6	83	44.9
Mother's education	Up to primary	2	2.0	127	68.6
	SSC	27	27.3	24	13.0
	HSC	30	30.3	17	9.2
	Graduation and above	40	40.4	17	9.2

TABLE 2 GDM DURING INDEX PREGNANCY AMONG MOTHERS

Gestational diabetes mellitus (GDM)	ASD n (%)	Non-ASD n (%)	p-value	OR	95% CI of OR
Yes	40(40.4)	42(22.7)	<0.05	2.30	1.36 – 3.91
No	59(59.6)	143(77.2)			

TABLE 3 DISTRIBUTION OF RESPONDENTS ACCORDING TO PERINATAL RISK FACTORS

Risk factors	Cases (99) , n(%)	Controls (185), n (%)	p-value
Pregnancy induced hypertension(PIH)			
Yes	4(4.04)	11(5.94)	<0.001
No	95(95.9)	174(94.0)	
Gestational Diabetes mellitus(GDM)			
Yes	40(40.4)	42(22.7)	<0.05
No	59(59.59)	143(77.27)	
Eclampsia			
Yes	3(3.03)	7(3.78)	<0.001
No	96(96.9)	178(96.21)	
Bleeding during pregnancy			
Yes	2(2.02)	3(1.62)	<0.001
No	97(97.7)	182(98.3)	
Mode of delivery			
Normal vaginal delivery	28(28.28)	135(72.9)	

Cesarean section	71(71.7)	50(27.02)	<0.001

n = number of participants, Comparison done by chi-square test.

TABLE 4 DISTRIBUTION OF RESPONDENTS ACCORDING TO FAMILY HISTORY RELATED RISK FACTORS

Risk factors	Cases n (%)	Controls n (%)	P- value
Family history of DM			
Yes	90(61.6)	56(38.4)	
No	9(6.5)	129(93.5)	<0.001
Maternal family history of ASD			
Yes	39(52.0)	36(48.0)	
No	60(28.7)	149(71.3)	<0.009
Paternal family history of ASD			
Yes	39(34.4)	33(45.8)	<0.003
No	60(28.7)	152(71.7)	

Figures

FIGURE 1 DISTRIBUTION OF CHILDREN (CASES) ACCORDING TO THE CO MORBID SYMPTOMS OF ASD