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ASSOCIATION OF PERINATAL RISK FACTORS WITH AUTISM SPECTRUM DISORDER: A RETROSPECTIVE STUDY AT TERTIARY CARE CENTRE, MUMBAI

Pediatrics

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ABSTRACT

Background: Autism spectrum disorder (ASD) is a complex neurodevelopmental condition, which is characterized by cognitive, behavioral, and social dysfunction. Their onset occurs in early childhood and during this period, there are various factors associated with autism risk. Hence,the present study was undertaken to determine the prevalence of various perinatal risk factors and its association with ASD in children. **Methods:** This was a retrospective study, included 200 cases of ASD over 5 years registered in pediatric neurodevelopment clinic at TN Medical College and BYL Nair Hospital, Mumbai. Study population divided in two groups- cases of ASD with perinatal risk factor and cases of ASD without perinatal risk factor. The prevalence of various perinatal risk factors in children with different grades of ASD calculated. **Results:** Based on ISAA score 149(74.5%) cases had mild autism and 51(25.5%) cases had moderate autism. The prevalence of various perinatal risk factors in children with different grades of ASD was found to be 79.5%(159/200). Pregnancy induced hypertension, bad obstetric history in mother were significant risk factor for ASD. Lower segment caesarian section as mode of delivery was risk factor found to be associated more with mild form of autism, but statistically significant association was found with vacuum delivery. We observed prematurity, low birth weight (LBW) and neonatal seizures as significant risk factor, which may have contribution towards pathogenesis of ASD. **Conclusion:** The awareness between pediatrician and obstetrician about association of perinatal risk factors and ASD will definitely add to prevention and timely intervention of high risk patients.

KEYWORDS

Autism, Neurodevelopmental, Perinatal, Risk factor, Pathogenesis, Prematurity

INTRODUCTION

Autism is a neuro-developmental disorder that is defined by deficit in social reciprocity, communication and by unusual restricted behavior beginning in infancy and toddler years. The prevalence of autism has been estimated at 13/10,000 and is believed to be rising [1] The etiology of autism is heterogeneous and has neurobiological in origin and this being a focus of epidemiologic research for over 40 years. Various etiologies have been proposed in occurrence of autism such as heritability, as there is high recurrence risk (2-19%) for autism among siblings as well as higher concordance (37-90%) in twin studies [2].Advance maternal and paternal age pose an additional risk factor for development of autism [3]. Boys are at four times greater risk of being autistic than girls and internationally gender distribution was found to be similar [4].With widespread use of vaccines like measles, mumps and rubella has also been proposed in implication of autism [5]. The association between congenital rubella infection and autism was initially reported in as early as 1971. However, recent data revealed that congenital rubella infection is associated with psychiatric disorder and incidence of 4.12-7.03% accounts for autistic population [6]. Fetal exposure to valproic acid, ethanol, thalidomide and misoprostol has been linked with increased risk of autism [7].

Antenatal and perinatal factors have been the focus of a significant amount of research on the possible risk factors for autism. Very few retrospective studies are conducted in India to determine the role of various perinatal risk factors like pregnancy induced hypertension (PIH), bad obstetric history, mode of delivery, low birth weight (LBW), prematurity, neonatal seizures in the development of autism. Hence, the present study was undertaken to determine whether these perinatal risk factors are associated with increased risk of ASD, so that measures can be taken to prevent the development of ASD.

MATERIALS AND METHOD

It is aretrospective cross sectional descriptive study conducted in pediatric neurodevelopment clinic at TN Medical College and BYL Nair Hospital, Mumbai.The study was planned to determine the prevalence of various perinatal risk factors in children with different grades(mild/moderate/severe) of ASD enrolled between January 2011 to December 2015. Various perinatal risk factors assessed were - PIH, bad obstetric history, mode of delivery, LBW, prematurity, neonatal seizures.This study was approved by ethics and scientific committee of TN Medical College and BYL Nair Hospital.Total 200 cases of ASD including classical autism, aspergers and atypical autism of different clinical severity (graded by ISAA score) aged between 18 months to 12 years diagnosed by DSM IV criteria were included.Patients with other co-morbid medical or genetic conditions as primary diagnosis and which can have autism as co-morbidities such as Tuberous sclerosis, Homocystinuria, Phenylketonuria, Angelman syndrome, Prader-willi syndrome, Williams's syndrome; children with congenital or acquired sensory deficit like deaf, mutism or blindness and structural anomalies; case whose data was not completely available were excluded from the study.

We analyzed pre-recorded case history forms of all patients satisfying the inclusion criteria to collect information regarding demographic data, multiaxialdiagnosis, perinatal history and clinical parameters. All relevant data recorded on separate case record form. Available data analyzed and prevalence of various risk factors such as mode of delivery, prematurity, bad obstetric history, PIH, LBW, neonatal seizures etc. was assessed individually. Comprehensive data prepared and association of various factors was studied with respect to the clinical severity of ASD as detected by ISAA score (Indian scale for assessment of autism)score.Two groups were made, one with association of perinatal risk factors and development of various grades of autism like mild, moderate and severe and other group, which had ASDbut not associated with significant perinatal risk factor. Inference drawn accordingly by which factors those were strongly associated with various severity of autism was taken into account and P value was calculated.

Statistical analysis

Statistical analysis was done using PSPP version 0.8.5 software. Association between qualitative variables was assessed by Chi-Square test, with continuity correction for all 2 X 2 tables and by Fisher's Exact test for all 2 X 2 tables where Chi-Square test was not valid due to small counts. To assess predictors of degree/grade of autism Binary Logistic Regression was applied with classification of autism as dependent variable and a set of independent (predictor) variables including PIH, bad obstetric history, LBW, neonatal seizure, preterm and mode of delivery.

RESULTS

Out of 200 patients analyzed, 139 (69.5%) were male and 61(30.5%) were female. Males outnumbered the females by ratio of 2.27:1 suggesting that ASD is more prevalent in males as compared to females. Based on ISAA score 149 (74.5%) cases had mild autism and

51 (25.5%) cases had moderate autism. We observed lowest prevalence of ASD in age group 2-3 years (10.5%) and highest in age group 10-12 years (36%), (Figure 1) as most of the patient coming to OPD came for certification and as a part of evaluation of poor academic performance. Those diagnosed early were brought to medical attention due to speech delay and poor eye contact.

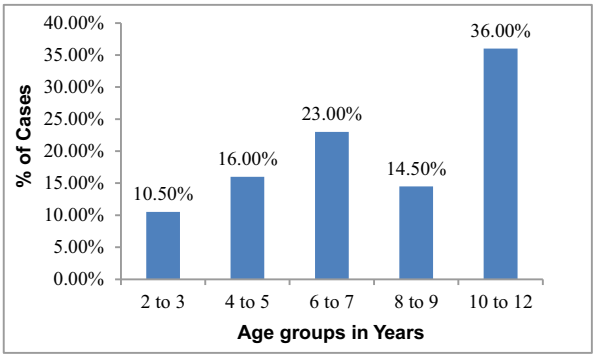

Figure 1: Age distribution among the cases

Perinatal risk factors included in the study were significantly associated with development of ASD as compared to those who did not have perinatal risk factors but still had autism, calculated by using Pearson chi square test with p value<0.05, (Table 1).

The prevalence of various perinatal risk factors in children with different grades of ASD was found to be 79.5% (159/200). The prevalence of perinatal risk factors in children with moderate and mild autism was 30.2% (48/159) and 69.8% (111/159) respectively, (p=0.0027).

Table 1:Classification of ASD based on perinatal risk factors

Classification of autism	Perinatal risk factors		Total
	Yes	No	
Moderate autism	48 (30.2%)	03 (7.3%)	51 (25.5%)
Mild autism	111 (69.8%)	38 (92.7%)	149 (74.5%)
Total	159 (100%)	41 (100%)	200 (100%)

Pregnancy induced hypertension (PIH) and bad obstetric history in mother were significant risk factor for ASD. The association of mild autism with a background of PIH and bad obstetric history in mother was significantly greater when compared to the case with moderate autism (p value<0.05). Lower segment caesarian section (LSCS) as mode of delivery was risk factor found to be associated more with mild form of autism, but statistically significant association was found with vacuum delivery. Even the number of babies born preterm was in small amount i.e. total of 23 out of 200, but it had statistically significant association with ASD (P value <0.05) We observed prematurity, low birth weight (LBW) and neonatal seizures as significant risk factor, which may have contribution towards pathogenesis of ASD, (Table 2).

Table 2: Association of perinatal risk factors with autism spectrum disorder

Perinatal risk factors		Classification of autism			P value
		Moderate	Mild	Total	
PIH	Yes	35 (40.7%)	51 (59.3%)	86 (100%)	0.0000
	No	16 (14.0%)	98 (86%)	114 (100%)	184
Maternal Bad Obstetric History	Yes	10 (62.5%)	6 (37.5%)	16 (100%)	0.0004
	No	41 (22.3%)	143 (77.7%)	184 (100%)	
Mode of delivery	LSCS	42 (29.4%)	101 (70.6%)	143 (100%)	0.0703
	FORCEP	01 (14.3%)	06 (85.7%)	07 (100%)	
	VACUUM	05 (71.4%)	02 (28.6%)	07 (100%)	
	Normal vaginal	03 (7.0%)	40 (93.0%)	43 (100%)	
Low birth weight	Yes	10 (58.8%)	07 (41.2%)	17 (100%)	0.0023
	No	41 (22.4%)	142 (77.6%)	183 (100%)	7
Neonatal seizures	Yes	28 (84.8%)	05 (15.2%)	33 (100%)	<0.05
	No	23 (13.8%)	144 (86.2%)	167 (100%)	
Preterm	Yes	16 (69.6%)	07 (30.4%)	23 (100%)	<0.05
	No	35 (19.8%)	142 (80.2%)	177 (100%)	

The study found significantly high prevalence of co morbidities in children with mild grade of autism (P<0.05). There was statistically significant association of ADHD with mild autism (p<0.05) as shown in Table 3.

Table 3: Various co morbidities in different grade of autism

Co morbidities	Classification of autism		Total
	Mild	Moderate	
ADHD	27 (57.4%)	20 (42.6%)	47 (100%)
Epilepsy	7 (87.5%)	1 (12.5%)	8 (100%)
Mild MR	2 (50%)	2 (50%)	4 (100%)
Congenital hypothyroidism	1 (50%)	1 (50%)	2 (100%)
Congenital heart disease	1 (100%)	0 (0.0%)	1 (100%)
Global developmental delay	1 (100%)	0 (0.0%)	1 (100%)
Total Co morbidities present	39 (61.9%)	24 (38.1%)	63 (100%)
No co morbidity	110 (80.3%)	27 (19.7%)	137 (100%)
Total	149 (74.5%)	51 (25.5%)	200 (100%)

DISCUSSION

In literature relevant to ASD there are multiple theories regarding etiology are proposed such as perinatal, neurobiological, environmental and genetic etc. Our study was an attempt to review selected perinatal risk factors and their prevalence in a group of children in autism in a retrospective manner. Various perinatal risk factors and their association with differential grades of autism were compared in this study.

Considering PIH during antenatal period it was found that PIH in mother had significant risk factor in moderate grade of autism than mild form with significant association with p value<0.05. This finding is comparable with the study done by Mann et al [8],Kantola et al [9] and Walker et al [10]. However, most of the studies conducted across the world were prospective case control in which children born with above mention risk factors were followed in their course of life and association of these risk factors and development of autism were studied. In the current study, there was significant association between bad obstetric history and autism with p value<0.05. Study conducted by Warren et al shown that mother who experienced recurrent abortion or still birth had antibodies against the antigens processed on paternal lymphocytes such antibodies reacts with fetal tissue and result into fetal death,eleven such mothers of autistic children were examined, six mothers had antibodies that reacted with lymphocytes of the autistic child. Five of these six mothers had bad obstetric history, as these antigens, which are expressed on lymphocytes, are found on cells of the central nervous system and, other tissues of the developing embryo, suggesting that maternal immunity may be associated with the development infantile autism [11]. Also the present study found significant association of mode of delivery through vacuum with moderate grade of autism (P<0.05). LSCS as a mode of delivery though was associated more with milder form of autism but no statistically significant association as p value= 0.07. Similar study conducted by Curran et al reported that emergency CS was significantly associated with ASD in partially adjusted analysis, but this effect disappeared in the fully adjusted model and concluded that children born by LSCS are approximately 20% more likely to be diagnosed as having ASD. However, the association did not persist when using sibling controls, implying that this association is due to familial confounding by genetic and/or environmental factors [12]. Curran et al conducted meta-analysis, they found thirteen studies reported an adjusted estimate for LSCS-ASD, producing a pooled odds ratio (OR) of 1.23 (95% CI: 1.07, 1.40). They concluded that delivery by LSCS is associated with modest increased odds of ASD when compared to vaginal delivery. Although the effect may be due to residual confounding, the current and accelerating rate of LSCS [13]. Langridge et al found that forceps and vacuum extraction during delivery were no longer associated with an increased risk of ASD, while elective CS was associated with ASD [14].

There was significant association found between low birth weight and moderate grade of autism children (p value <0.05) which is correlated with the previous studies [8, 15]. Preterm as a risk factor, 16(69.6%) children diagnosed as moderate and seven (30.4%) mild grade of autism were born preterm. Remaining 35(19.8%) who were not associated with above risk factor were moderate autism and 142(80.2%) were belonging to mild autism. Even the numbers of babies born preterm were in small amount i.e. total of 23 out of 200. However, it had significant association with autism spectrum disorder with p value<0.05. These results are in accordance with the study

conducted by Mackay et al [16] and Kuzniewicz et al [17]. Neonatal seizure as a risk factor had significant association with autism as 28(84.4%) with history of seizure during neonatal period had moderate autism and five (15.2%) with above risk factor had mild autism, indicating significant association with p value<0.05. As very few studies are conducted using above risk factor and finding their association with autism, Experimental studies on animal models conducted by Talos et al and found that strong association of seizures in early part of life and development of autism with significant p value 0.00001 [18]. Study conducted by Paul et al by inducing seizures in rat by 15 fluro-ethyls shown behavioral changes in rat which include impaired socialization deviant behavior similar to ASD [19]. With above experiences from animal model we can conclude that changes occurring in various part of developing brain during seizures lead to development of autism. Various literature reviews also supported that effect of seizures on developing brain may results in behavior issues in further life due to underlying immaturity of developing brain, incomplete myelination, and poorly developed synapses.

Strength of study

Large sample size, good clinical spectrum as study was performed at Tertiary Care Centre and we could get large sample size and good spectrum of study subjects. There are very few Indian studies available, which reported the association of perinatal risk factor and ASD. This study definitely will give valuable contribution to existent research in this topic among the Indian subgroup of patients.

Limitation of the study

1) Type of study being retrospective and descriptive in nature, there are limitation to predict the association between risk factors and established causal relationship, prospective case control study is required to study causal relationship between risk factor and autism.
2) Data available from prefilled proforma was variable in quality, as it was dependent on the skill of history taking; ability of relatives to recall the details, few of the histories did not have the accurate details.
3) Some risk factors assessed in our study did not have standard definitions or diagnostic criteria that may have created a bias.
4) We could not include other prevalent risk factors like birth asphyxia, neonatal jaundice, gestational diabetes mellitus, and gestational hypothyroidism, as there were no definite defining criteria.

CONCLUSION:

As the present study had shown significant association between some perinatal risk factors with ASD, this association should not be overlooked, as most of these risk factors are preventable by adequate perinatal care of mother and baby.However, there is no direct causal, relationship established between these perinatal risk factors and autism but it definitely has contribution to multi-factorial etiological origin of autism.

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