Study of prenatal, natal, and neonatal risk factors associated with autism

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ABSTRACT

Introduction: Autism spectrum disorder is one of the common developmental disabilities. Underlying autism etiology is most likely polygenic but environmental factors may also contribute. Obstetrical and neonatal risk factors have been considered for the development of autism. **Objectives:** The objectives of the study were to know the presence of antenatal, perinatal and neonatal complications in autistic children. **Materials and Methods:** Children who were diagnosed with autism were included in the study. Visits were made to the special school for the collection of data with prior consent, and birth details were collected from the parents**. Results:** A total of 54 children were included in the study. Age of the children ranged from 3 years to 17 years with the mean age of 10.93 years. 39 (72.2%) were boys and 15 (27.8 %) were girls. Advanced maternal age at delivery was noted in 24% of the cases. Antenatal risk factors were seen in 24% of cases and natal risk factors in 20% of the cases. 17% had birth asphyxia. Neonatal intensive care unit admission was noted in 20% of cases, neonatal seizures in 5.6%, respiratory distress in 9.3%, and low birth weight in 17% of cases. 60% of them were first born. Overall, the presence of antenatal, natal, and postnatal risk factors were noted in 57% autism cases. **Conclusion:** In children with autism, there is increased prevalence of obstetric and neonatal risk factors. These variables should be examined in future for precise assessments of exposures.

Key words: *Antenatal, Autism, Natal, Postnatal, Risk factors*

Autism spectrum disorder (ASD) is one of the common developmental disabilities. It begins in early childhood and persists throughout adulthood, affects three crucial areas of development, namely, communication, social interaction, and creative or imaginative play. According to the WHO report 2017, 1 in 160 children have an ASD, and to prevalence appears to be increasing globally [1]. In India, rising trend was observed in the recent study showing the prevalence of 0.15 % [2]. The etiology of autism is largely unknown. ASDs are influenced by a variety of genetic, environmental and immunological factors that alter the key developmental processes. It is now believed that the mechanism underlying autism etiology is most likely polygenic and that environmental factors may interact with genetic factors [3]. Brain of the autistic child shows the various macroscopic, microscopic, and functional abnormalities suggesting that the etiologically relevant period may be in utero or possibly in early infancy [4]. Some brain abnormalities observed in individuals with autism may reflect a potential role of oxygen deprivation during development [5].

Obstetrical and delivery factors, as well as neonatal exposures, have been the focus of a significant amount of research as possible risk factors for autism. Perinatal insults with genetically mediated immunological activation may increase the risk of autism in the child. Hence, this study was undertaken with the purpose of knowing the presence of antenatal, natal, and neonatal complications in autistic children.

MATERIALS AND METHODS

This retrospective study was conducted in special schools in Dakshina Kannada district between March 2016 and March 2017. Prior Ethical Clearance was obtained from the Institutional Ethical Committee. Children who were diagnosed with autism by a psychiatrist using International Classification of Diseases -10 criteria were included in the study. Autism was mainly a clinical diagnosis based on the history and behavioral observation of the child. All ASD coming under F.84 category were included in the study. To aid in the diagnosis and rate the level of severity Childhood Autism Rating Scale (CARS) was used for all children. It is a behavior rating scale intended to help diagnose autism. It evaluates the severity of autistic behaviors in 15 functional areas by assigning a score from 1 to 4. An overall score is calculated by adding all the grades and to stratify patients into three levels as “severely autistic” (score between 37 and 60), “mildly to moderately autistic” (score between 30 and 36.5), and “absence of ASD” (score <30). Flowchart is given to show the work pattern.

Visits were made for the collection of data with prior consent and parents were informed to bring the birth records. Birth details were noted down from birth records whenever available and also from the mother. Data collection was done using a predesigned questionnaire. Details included were birth order, maternal age at delivery, spacing between the pregnancies, and

season during birth. Antenatal risk factors included were fever, pregnancy-induced hypertension (PIH), antepartum hemorrhage, fetal distress, gestational diabetes, and drug intake. Natal risk factors such as birth asphyxia, instrumental delivery, abnormal presentation, umbilical cord complications, multiple births, and birth injury were noted down. Details of the postnatal factors noted were birth weight, jaundice, respiratory distress, neonatal seizures, meconium aspiration, gestational age, and neonatal sepsis.

Statistical analysis was performed using SPSS software 22 and proportions were compared using the Z test. To associate between different risk factors and autism, Chi-square test was done, and $p<0.05$ was taken as significant.

RESULTS

A total 54 children with autism were included in the study. The mean CARS score was 39.31 (range - 30–54.5). Age of the children ranged from 3 years to 17 years with the mean age of 10.93 years. The mean maternal age at delivery was 26 years (range - 19–37 years). Although advanced maternal age was a risk factor for autism, mothers age 30 or above was noted in 24% of cases. 64% belonged to lower middle classification according to Kuppuswamy socioeconomic scale. 39 (72.2%) of them were boys and 15 (27.8%) were girls. 73% were delivered vaginally, and 27% were delivered by cesarian section, and 60% were first born. The next common group of birth order was 3rd or higher (24%). 36% of them had birth spacing of 2 years, and 24% of then had 1 year. 42% of them were born during summer month (between mid-February and May).

Fig. 1 shows the distribution of antenatal, natal, and postnatal risk factors in children with Autism. Antenatal risk factors noted were PIH (14%) including eclampsia in one mother, fever, antepartum hemorrhage, and hyperemesis gravidarum. Natal risk factors noted were instrumental delivery, meconium aspiration, birth asphyxia (17%), and abnormal presentation. Description of the postnatal risk factors is given in Figs. 2 and 3. Z test done for comparison of proportions for antenatal risk factors for autism was found to be significant ($p<0.001$). Similarly, comparison for proportions of combined natal and neonatal risk factors was also significant ($p<0.001$). However, the association between antenatal and natal risk factors with autism (by Chi-square test) was statistically significant ($p=0.063$). Overall, the presence of antenatal, natal, and postnatal risk factors was noted in 57 % autism cases.

DISCUSSION

For the development of ASD, the most significant factors may be genetic and other environmental exposures during the prenatal, pregnancy, and newborn period. In the present study, we have analyzed the proportion of autistic children having the significant antenatal, natal, and neonatal risk factors. Hallmayer *et al*. had concluded that even in twins, environmental factors common to twins explain about 55% of the liability to autism rather than the common genetic pool [6]. Sandin *et al*. had found that the

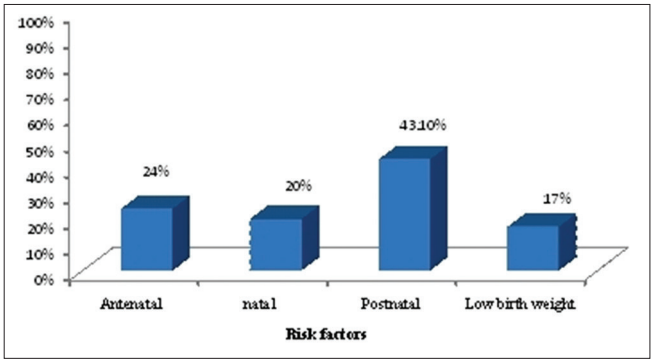

Figure 1: Graph showing the distribution of antenatal, natal, and postnatal risk factors in children with autism

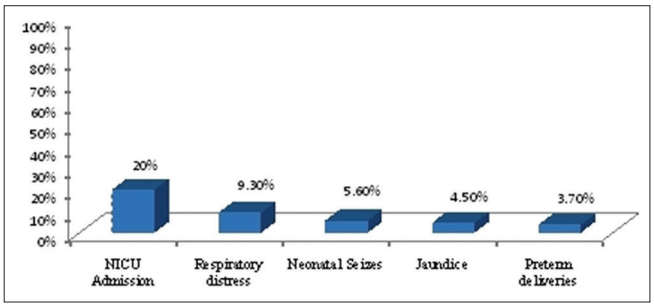

Figure 2: Showing the distribution of postnatal risk factors

crude relative risk of autism interval increased monotonically with increasing maternal age after ruling out other potential confounding factors but in our study advanced maternal age, more than 30 was noticed in 24% of the cases [7]. In a study conducted by Leonard *et al*., it was found that autism risk increases with increasing socioeconomic advantage. In contrast, we found that the majority are from the lower middle socioeconomic status [8]. Male gender remained strongly associated with autism as observed in many studies [9]. A similar finding is observed in our study where 72% of them are males. Glasson *et al.* noted in their study that the majority were firstborn [10]. A similar finding is noticed in our study where 60% of them are first born.

Among the antenatal factors, we noticed PIH (14%) to be the predominant factor while as in a study conducted by EI-Baz *et al*., only threatened abortion (11%) in a mothers had statistical significance compared to controls [11]. Conde-Agudelo *et al*., systematically evaluated the studies conducted on the relationship between birth spacing and the risk of ASD and concluded that children born to women with IPIs of <12 months and long interval of 60–84 months had a significantly increased risk of ASD [12]. In our study, birth spacing <12 months was seen in 24%. In a study by Zerbo *et al*., the season of conception and the risk of autism was analyzed and found out that autism risk is higher in patients with winter conception [13] but limited studies are conducted in tropical countries with relation to the season of the birth. In our study, it was found that the majority were born during the summer month. In a review done on assessment of prenatal and perinatal risk factors for autism by Kolevzon *et al*., the significant obstetric

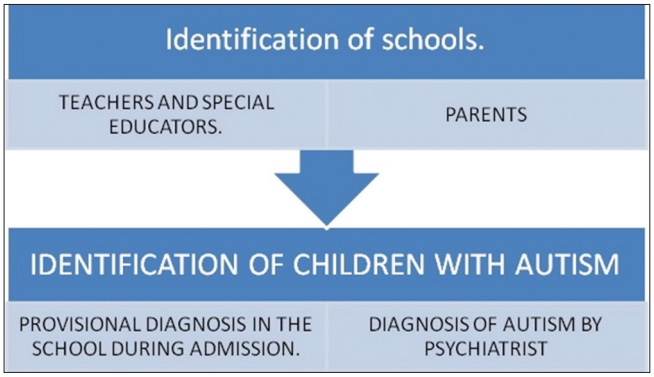

Figure 3: The work pattern

conditions birth weight, duration of gestation and intrapartum hypoxia [14]. A similar finding was observed in our study where low birth weight (LBW) was noted in 17% of the cases.

Bilder *et al*. found an association between breech presentation and autism and no significant association with neonatal factors [15], which is contradicting to our study where the neonatal factors were noticed in >50% of cases, and abnormal presentation was seen less frequently. As birth asphyxia and abnormal presentation are all interlinked, multivariate analysis would have been better to tell exact picture. Larsson *et al*. showed that low Apgar score at 5 min and gestational age <35 weeks were associated with increased risk of autism; however, in our study, birth asphyxia was found in 85%, but preterm deliveries were seen only in 3.7% of the cases [16].

Mohammed *et al*. found that the incidence of autism was 4.7% over 2 years period among the babies requiring neonatal intensive care unit (NICU) admission who were later followed at High-Risk Neonatal Follow-up Program [17]. In our study also, NICU admission was seen 20% of the cases. Increased incidence of epilepsy in autistic children is known fact, but neonatal seizures as a risk factor for the development of autism by altering the synaptic development is recently being hypothesized and is being evaluated [18]. Our study showed the neonatal seizures were present in 5.6% cases. In a study conducted by Hadjkacem *et al*., postnatal respiratory infections were identified as main factor associated with autism [19]. In our study, 9.3% children had respiratory distress. In a study conducted by Lozada *et al*., history of admission with a diagnosis of neonatal jaundice was present in (21.9%) of children with ASD and the percentage of children receiving procedure treatment was high in autistic children compared to controls [20]. However, in our study, only 4.5% cases had significant Jaundice.

In a recent study conducted by Mamidala *et al.*, on a large population of patients in India, 25 risk factors were evaluated, and advanced maternal age, preterm birth, neonatal jaundice, and birth asphyxia were found to be significantly associated with the risk of ASD [21]. In our study also, antenatal, natal, and postnatal factors were present in 57% of cases with a history of NICU admission in majority of them which was mainly due to birth asphyxia and LBW. In our study, we have not taken controls, which is a major limiting factor. Risk factors such as jaundice and preterms are more common in general population compared to the study group which will be difficult to explain without controls. Paternal age was not taken into consideration, which is another limiting factor. Furthermore, chances are there that mothers would not have been able to recollect all the events during birth very precisely.

CONCLUSION

In children with autism, there is an increased presence of obstetric and neonatal risk factors. These may be related to autism risk that is genetically vulnerable. These variables should be examined in future for precise assessments of exposures by doing prospective studies of high-risk newborns.

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