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RESEARCH ARTICLE

AUTISM SPECTRUM DISORDER: EVALUATION OF ETIOLOGICAL FACTORS AND SKILL DEVELOPMENT IN AFFECTED CHILDREN

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ABSTRACT

Autism spectrum disorders (ASDs) are rather complex conditions, which may exhibit milder social abnormalities and communication impairment and less rigid interest restrictions in affected children. In some cases of ASDs there is a genetic cause either at the chromosomal or gene level. However many non genetic factors may also play an important role. The present study was focused on evaluating the possible non genetic causes especially to understand the potential risk posed by prenatal and post natal environmental factors. We also attempted to assess the academic and social skill development of ASD children in special school and compared it with the skill development of ASD affected children in regular school. A total number of 184 individuals were studied. According to the present study the potential risk factors for autism are advanced maternal age, stress during pregnancy, supplements taken, gestation period, parity, age gap between children and birth weight. The risk of ASD in pregnancy was reduced when the expecting mothers consumed folic acid-calcium supplement regularly. We conclude that stress during pregnancy can be a major risk factor for ASD. Skill assessment in ASD children revealed that there was considerable progressive improvement of social, play skills and academic skills in children, attending special care section of regular school, rather than ASD children attending special school when their IQ was ≥ 40. We observed that the special care section helped to address their unique needs and cultivate their talents as compared to those studying in a special school. Based on our observations we suggest that necessary measures can be taken to reduce the risk of ASD pregnancy and further extend support to ASD children to enhance their skills at regular school rather than at special school especially in children with IQ ≥ 40.

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INTRODUCTION

Autismspectrumdisorders (ASDs) are developmental disabilities characterized by rote or repetitive behaviour, delayed language development, and hindered nonverbal communication, imagination, and social interactions. ASDs are neuro-developmental disorders also characterized by stereotypic behaviors. From the earlier research works, it is known that ASD is not caused by a single factor. Both genetic and environmental factors have the potential to increase the risk of ASD. Other factors may alter this underlying genetic liability such as sex, IQ, and prenatal and perinatal injury (Freitag *et al.,* 2007). The idea that preconception environmental exposures may be involved in ASD etiology arose in the 1970s from a retrospective case-control study of ASD that found a statistically significant difference in parental occupational exposure to chemicals during the preconception period. Over the past years, research into environmental risk factors for autism has grown dramatically, bringing evidence that an array of non-genetic factors acting during the prenatal period may influence neurodevelopment (Lyall *et al*., 2014). Therefore, the present study was undertaken with one of the objectives to evaluate the potential environmental risk factors for ASD. Early diagnosis of ASD is the key to managing the overall development of ASD-affected child. For early diagnosis early identification is needed. Since these children have poor skills, education should be focused on fostering these skills. Therefore, education has been defined as the fostering of acquisition of skills and knowledge to assist a child for developing independence and personal responsibility. The second objective of the present study was to identify the most conducive environment for these skill developments in the ASD children. Therefore, we assessed the social, motor, play, independent living skills and academic skills in children at regular school and special school by using a questionnaire for data collection form the parents and school teachers.

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MATERIALS AND METHODS

We adopted a cross-sectional study, to attain the objective of the study. A total number of 184 individuals were surveyed. The individuals surveyed were classified into two groups viz ASD group and control group. The sample population included ASD group consisting of 92 ASD subjects and control group constituted by 92 subjects of similar age group but with no h/o ASD. For achieving the first objective of this study, a Proforma was designed to collect information retrospectively from the mother. The prenatal history collected included data related to subjects mother during pregnancy period, like medication taken, stress, respiratory problems, maternal infection, fall during pregnancy, supplements taken, maternal diabetes, intake of sleeping pills during pregnancy and bleeding after first trimester, obstetric complications, type of delivery, drug induced labour, gestation, birth weight of subject, habit of chewing plastic in infants, ear infection and any other incidence during the infancy of the subject. For achieving the second objective of the study, a total number of 92 individuals were studied from special school and special section of regular school. Necessary information on the academic skills, motor skills, play skills, social skills and independent living skills of these childern was collected from the school teachers of the ASD subjects. Skills of the ASD children after joining regular and special school were studied using standard assessment tools for development. The information collected on etiological factors and skills was tabulated and analyzed. Mean and Standard deviation (SD) were computed for quantitative data. The statistical significance of associations between the various qualitative parameters was evaluated through Fisher's exact test (two tail) wherever necessary. Online calculators of statistics were used for standard deviation at *www.easycalculation.com* and fisher's test at *www.graphpad.com.*

RESULTS

The mean age of the ASD children studied was 9.02 ± 3.26 years. The mean age of detection of the ASD was 2.7 ±1.76 years with a variance of 3.11. The etiological factors assessed showed the following observations.

- ***Maternal Age:*** We observed that advanced maternal age was a potential risk factor for ASD. The frequency of ASD was higher in maternal age intervals of 31-35 and 36-40 years. The mean maternal age during pregnancy of the ASD subject's studied was 27.8 ± 5.36 years. The results indicate a significantly higher frequency of 26.09% ASDs in children born to mothers in age interval of 31 – 35 (*P = 0.0306*) as compared to the control.
- ***Oral Contraceptives*****:** The intake of oral contraceptives by the mother was also studied. The present study found no correlation between intake of oral contraceptives and ASD.
- ***Parity and ASD*****:** The frequency of ASD was higher in the first born and third born as compared to the control group. However the difference was found to be statistically insignificant (*P = 0.7804* for first born and *P = 1.000* for the third born).
- ***The age gap between the autistic children and other siblings:*** In the sample population, the age gap varied from 1-7 years. The mean age gap of the ASD subject's studied was 4.2 ± 1.47 years. The frequency of ASD was observed to be higher in those with a larger age gap of 4- 7 years as compared to the control. However the difference was found to be statistically insignificant *(P=0.3482 for 4 yrs* and *P=0.2756 for 6 &* 7years*).*
- ***Intake of medication during pregnancy and ASD:*** The present study showed an increase in the frequency of ASD in offspring of mothers who consumed medication during the first trimester of pregnancy. The study indicates that higher frequency of 39.13% of history of intake of medication in the mothers of ASD as compared to the control (28.57%). The difference was found to be statistically insignificant *(P=0.4312).*
- ***Stress during pregnancy and ASD:*** Stress on mothers during pregnancy was another factor studied. Mothers of the subjects were interrogated for physical and mental stress during their pregnancy, in both the control and ASD group. The frequency of stress during pregnancy was found to be higher in mothers of ASD group as compared to those in the control group. The difference was found to be statistically significant (*P=0.0257).*
- ***Respiratory problems during pregnancy and ASD:*** To evaluate the role of the hypoxic condition of a mother during pregnancy, we analyzed the sample population for respiratory problems during pregnancy. The present study found no correlation between respiratory problems during pregnancy and ASD.
- ***Maternal infection during pregnancy and ASD:*** Infection of the mother may be also a source of impeding the growth of the fetus, which can be a potential risk factor for ASD in offspring. The present study found no correlation between maternal infections during pregnancy and ASD (*P = 0.6887)*.
- ***Fall during pregnancy and ASD:*** This factor was studied to see if the physical impact of fall during pregnancy can be a potential risk factor. The frequency of ASD was higher in 13.04% of the mothers who had a fall during pregnancy as compared to the control. However, the difference was found to be statistically insignificant *(P=0.1226).*
- ***Intake of supplements during pregnancy and ASD*****:** Different types of supplements are necessary for growth and development of the fetus. The vital supplements include vitamins, folic acid, iron, and calcium. The present study tried to evaluate the effect of not consuming folic acid or calcium or both. Most of the mothers of ASD subjects had not consumed folic acid and calcium supplements (52%) as compared to the control (5.5%). The difference was found to be statistically highly significant *(P=0.0039).*
- ***Type of Delivery and ASD:*** This factor was studied to assess if stress on the child during normal delivery, use of forceps or suction during normal delivery could be a risk factor for ASD. The present study revealed increased frequency of ASD in those mothers who had normal delivery (73.91%) as compared to the control group. However, the difference is found to be statistically insignificant *(P=0.7937).*
- ***Labour Induced by Drugs and ASD:*** Labour inducing drugs may be a potential risk factor for ASD. Therefore, this factor was also studied. Labour was induced by drugs

in 40.91% of ASD group which was higher than that of the control group (31.71%). However, the difference was found to be statistically insignificant *(P=0.4444)*.

- ***Gestation Period and ASD:*** Gestation period was evaluated to see if there is significance with pre and post-term births. The frequency of post-term births was found to be higher in the ASD group (13.04%) as compared to the control (4.76%). However, the difference was found to be statistically insignificant *(P=0.1226)*.
- ***Birth Weight and ASD:*** The birth weight of ASD babies was either higher or had low birth weight as compared to the normal. The mean of birth weight of the ASD subject's studied was 3.03± 0.85 kg as compared to the control where mean birth weight was 2.95± 0.48 kg. Significantly higher frequency (*P=0.0018)* of low birth weight of 1-1.9kg in the ASD group as compared to the control. Higher frequency of high birth weight of 4 – 4.9 kg observed in the ASD group was found to be statistically insignificant *(P=0.229)*.
- ***Chewed Plastic Toys in Infancy*****: Lead poisoning is the leading health risk associated with chewing on plastic. Therefore, this** factor was studied to assess if ingestion of toxic components from plastic toys during infancy can act as a risk factor. We recorded a high frequency of positive history of chewing of plastic toys in infancy, in the ASD group (30.43%) as compared to the control. However, the difference was found to be statistically insignificant *(P=0.1077)*.
- ***Day Care and Risk of ASD*****:** We analyzed this factor as ASD children may be subjected to emotional insecurity if sent to Day care centres at early. The present study found no correlation between day care and risk of ASD.
- ***Insufficient Attention Received By Child*****:** The study revealed that 13.04% subjects of that of ASD group received insufficient attention as compared to 9.52% subjects in control(Fig:3.34). However, the difference is considered to be statistically insignificant *(P=0.4869)*.
- ***Breast feeding Duration:*** The mean breast-feeding duration in the ASD subject's studied was 1.45 yrs with standard deviation of ± 1.13 and variance 1.27. The present study revealed higher frequency of mothers who breast fed their child for a shorter duration of 0 – 0.5 yrs in the ASD group (40.91%) as compared to the control. However the difference was found to be statistically insignificant *(P=0.2046)*. We also noted higher frequency of mothers who breast fed their child for a longer duration of 3.5 -4 yrs in the ASD group (9.10%) as compared to the control. However the difference was also found to be statistically insignificant *(P=0.0581)*.

Therefore, the study concludes that the factors with the strongest evidence for an association with autism risk include advanced maternal age and stress during pregnancy while folic acid-calcium supplement intake was found to be reducing the risk of ASD *(Table-1)*. The factors having no risk of ASD are intake of medications, fall, respiratory problems and bleeding during pregnancy. For assessing the skill development in ASD children in regular and special school, the 92 subjects with autism spectrum disorder (ASD) were grouped into two based on the type of school attended. Most of the ASD cases were diagnosed at the age of 2.6 – 3.0yrs of age. The mean age of detection of ASD was 2.69 ± 1.77 yrs. The mean average IQ of the subjects studied was 43.57 ± 12.96. Group 'A' constituted 45.22% of the ASD children, who went to regular school. Group 'B' consisted of 54.78% of ASD subjects who studied at special school. These students were assessed for Social skills, Play skills, Motor skills, Academic skills and Independent Living skills. The results were noted on five-point–Lickert-scale *(Table-2)*. Studying at regular school enabled the ASD subjects to attain good social skills, play skills and academic skills. Education at special school, enabled enhancement of motor skills and independent learning skills. We observed that early schooling enables ASD children to develop social skills, and academic skills better. ASD subjects who joined special school at later age, showed slow development of all skills.

Table 1. Association of etiological factors with frequency of ASD

Factors	Frequency		Significance(fishers exact test)
	Control Group	ASD Group	
Intake of Medication during pregnancy	28.57%	39.13%	P=0.4312
Stress during pregnancy	11.90%	30.43%	*P=0.0257
Respiratory Problems During Pregnancy	14.29%	8.70%	P = 0.4168
maternal infection during pregnancy	7.32%	4.35%	P = 0.6887
fall during pregnancy	4.76%	13.04%	P=0.1226
Bleeding during pregnancy	19.05%	14.28%	P = 0.4898
Not taken Folic acid and calcium	5.50%	52.00%	**P = 0.0039
Maternal age:			*P = 0.0306
31-35 yrs	9.52%	26.09%	
36-40 yrs	0%	4.35%	
Normal Delivery	66.67%	73.91%	P=0.7937
Obstetric complications	21.95%	13.04%	P=0.1226
post term births	4.76%	13.04%	P=0.1226
low birth weight(less than 1.9kg)	1.30%	16.65%	***P=0.0018
Labour inducing drugs	31.71%	40.91%	P=0.4444
Chewed Plastic Toys in Infancy	15.79%	30.43%	P=0.1077
Insufficient Attention Received By Child	9.52%	13.04%	P=0.4869

* Significant , ** and *** highly Significant

Table 2. Skill improvement in ASD subjects at regular and special school

Skill Assessed	Group A (Regular school)	Group B (Special school)
Social Skill (SS)	4.65	2.03
Play skills (PS)	3.8	1.99
Motor Skills(MS)	2.93	3.65
Academic Skills (AS)	2.85	2.41
Independent Living skills(ILS)	1.7	2.3

Another notable observation was that, the overall development of the child with mild autism. Children with mild autism having IQ ≥ 40 showed remarkable improvement of most skills in special section of regular school than at the special school.

DISCUSSION

Etiological factors indicating a potential risk for increasing frequency of ASD were maternal age, stress during pregnancy, supplements taken, gestation period, parity, age gap between children and birth weight. Factors that showed no association with ASD included family history of seizures, oral contraceptive taken, and medication during pregnancy, respiratory problem during pregnancy, maternal infection, and fall during pregnancy and bleeding during pregnancy. This study revealed that maternal age during pregnancy is very crucial factor in determining the neurological development of the fetus. Our findings are consistent with the findings of Croen *et al.,* 2007*;* Kolevzon *et al.,* 2007 and Gardener H, 2009, which state that older parents may be statistically more likely to have children with autism. The frequency of ASD was higher in the first born and third born as compared to the control group. However the difference was found to be statistically insignificant. Our findings are contrary to study of *Chaste P* and Leboyer (2012), which showed that risk of ASD was high for first born children. According to study of Gardener H (2009), maternal medication use was associated with a 46% increased risk. The present study however, does not agree with the outcome of his result, because though we observed higher frequency of ASD in mothers who had taken medication during pregnancy as compared to the control, the difference was found to be statistically insignificant.

The important revelation of this study was the association of maternal stress during pregnancy and increased the risk of ASD. The frequency of stress during pregnancy was found to be significantly higher in mothers of ASD group as compared to those in the control group. Strongest evidence of maternal hypertension and ASD risk is indicated in the studies of Gardener *et al.* (2009). Studies of Rai *et al.* (2012), also revealed that exposure to stressful life events during the prenatal period is associated with an increased risk of offspring ASD. Whether this association is causal or reflects the risk of autism with severe depression during pregnancy requires further research. The nutritional supplements taken were found to be having a positive influence in decreasing the ASD risk, as per the present study. Most of the mothers of ASD subjects had not consumed all supplements as compared to the control. This study reinforces the findings of Schmidt *et al.* (2012), which indicated that women who consume the recommended daily dosage of folic acid, the synthetic form of folate or vitamin B-9, during the first month of pregnancy may have a reduced risk of having a child with autism. Studies of Lyall *et al.* (2014) also support that higher maternal intake of certain nutrients and supplements like folic acid has been associated with reduction in ASD risk. Vitamin D deficiency – either during pregnancy or early childhood – may be an environmental trigger for ASD in individuals genetically predisposed for the broad phenotype of autism (Kočovská *et al.,* 2012). On the basis of these results, we argue that though the high frequency of ASD shows no statistical significance, possibly the important role of vitamin D and folic acid cannot be overlooked.

Lead poisoning is the leading health risk associated with chewing on plastic. Plastic toys contain many toxic components including lead. In the present study, we recorded a high frequency of positive history of chewing of plastic toys in infancy, in the ASD group as compared to the control. Toxicants, such as heavy metals, pesticides and chemicals, can damage cells by converging on similar biochemical pathways to produce adverse effects, such as increasing oxidative stress, depleting glutathione and impairing cellular signaling (Li *et al.,* 2007). Exposures to environmental toxicants, such as mercury, lead, arsenic, polychlorinated biphenyls and toluene, are known to cause neuro developmental disorders (Grandjean *et al.,* 2006). Exposures to environmental toxicants have also been implicated in ASD (Palmer RF, *et al.,* 2009*;* Windham GC *et al.,* 2006*;* Roberts EM *et al.,* 2007*).* The present study found no correlation of family h/o seizures, intake of oral contraceptives, Respiratory problems during pregnancy or maternal infections during pregnancy. However, studies of Atladottir *et al.* (2010) supports the hypothesis that maternal infection triggers a vulnerability to develop autistic disorder in the fetus who supported by the evidence from results with rodent models. It seems that gestational viral infections trigger a maternal immune response, which can perturb foetal brain development, at least in part through interleukin-6 (Bradstreet *et al.,* 2007). Association of maternal gestational diabetes, maternal bleeding during pregnancy and maternal medication with ASD is suggested in the study of Bouvard *et al.* (1995). The present study revealed higher frequency of mothers who breast fed their child for a shorter duration of 0 – 0.5 yrs in the ASD group as compared to the control. We also noted higher frequency of mothers who breast fed their child for a longer duration of 3.5 -4 yrs in the ASD group as compared to the control.

This difference was also found to be statistically insignificant. Breastfeeding may also be beneficial to the emotional development of the autistic child since it provides a special opportunity for autistic children to experience close physical and emotional contact. Prolonged duration of sucking may be attributed to the emotional security which the ASD child may be seeking from the mother. Heterogeneity in some studies may be on account of methodological limitations that have impaired the precision and validity of results as most studies include small sample size, non-normal control groups, broad disease definition, and retrospective parental recall of exposures which may result in the high possibility of recall bias. Thus, the rising prevalence of ASD, coupled with the severe emotional and financial impact on the families, underscores the need for large, prospective, population-based studies with the goal of elucidating the modifiable risk factors, particularly those during the prenatal period. Assessment of skill development indicates that ASD children studying at regular school attain good social skills, play skills and academic skills while those at special school develop their motor skills and independent learning skills. This is because the ASD children interact with unaffected children at regular school and show behavioral changes as those seen in these unaffected children. So their development of skills is at a faster pace as compared to a homogenous classroom of ASD children. Secondly, the special attention required for progress of the skills is specific to each child based on the IQ of the affected child. Therefore, we

suggest that children with IQ ≥ 40 showed be admitted in special section of regular school rather than a special school. Also, attempts should be made to detect ASD earlier with the joint efforts of the parents, pediatrician and teachers, so that ASD children can be sent to school at early age. However, we recommend that selection of the school should be based on the IQ of the child. Children with more severe ASD often face difficulties in regular educational settings because of their very distinct learning needs. Such students benefit from education in special school. However those with mild autism, show enhanced skill development in regular school provided they have trained teachers to give extra attention in special care section to address their unique needs.

Conclusion

ASD is a complex disorder resulting from the combination of genetic and environmental factor. Many factors may have a potential for increasing the risk of ASD. Those having genetic susceptibility may be more vulnerable to develop ASD when exposed to the environmental risk factors. In the present study, the factors with the strongest evidence for an association with autism risk included advanced maternal age and stress during pregnancy while folic acid-calcium supplement intake was found to be reducing the risk of ASD. The factors with evidence against a role in autism risk included were intake of medications, fall, respiratory problems and bleeding during pregnancy. To enhance skill development in ASD children, the decision of where a child should be educated has to be based on the skills and needs of the individual student, as well as the needs of the parent. Some children can work effectively and benefit from regular education programs, while others will need special classrooms for part or all of the day where the physical environment, curriculum, and personnel can be organized and manipulated to reflect individual needs. For a child to be mainstreamed in a regular school, the deciding factor must be the environment of the school and the severity of ASD. The child with autism will benefit from an environment that is inclusive and that which makes accommodations for his/her particular needs.

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