Date Received : 12 APRIL 2024 | Accepted: 5 JUNE 2024
Indian Journal of Developmental & Behavioral Pediatrics
(Official Journal of IAP Chapter of Neurodevelopmental Pediatrics)
RESEARCH ARTICLE

Clinical profile of children with Autism spectrum disorder in a quaternary care hospital in south India

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Abstract:

Background: A multitude of presentations, co-morbid conditions, risk factors, and severity are associated with Autism Spectrum Disorders (ASD)

Aim: To describe the clinical profile of children affected with Autism spectrum disorder in a

quaternary care hospital in South India.

Methods: A cross-sectional descriptive study using a questionnaire method among children

aged 1.5-6 years was conducted. Demographics, risk factors, and developmental domains were assessed.

Results: The mean age of presentation was 34 months, male to female ratio was 7:1, 65% of patients were delivered by LSCS, most were firstborn, 88% had appropriate weight for gestational age, and 30% were preterm. The age of conception in 95% of mothers was < 30 yrs and 82% of fathers < 35 years. 80% were mild and the rest were moderate autism. 32 % of mothers had gestational diabetes mellitus and 30% had hypothyroidism. Respiratory distress and sepsis were the most common postnatal events noted. 70% of affected children had E-media exposure of more than 2 hours. Multiple regression analysis to determine the influence of various risk factors showed that all risk factors studied contributed 19% to the severity of autism. Multiple sensory domains were affected in 85%; mainly auditory, visual, and touch. Prevalence of developmental regression was 27%. Allergy and sleep disorders were the commonest comorbidities and were present in 67% of the study population.

Conclusion: Autism spectrum disorder has a variety of presentations and an onset within thefirst 2 to 3 years of life, making it imperative to facilitate early diagnosis and intervention. Appropriate awareness and use of severity scales and assessment systems can help inlocalizing the

Access this article online :
Quick Response Code:
Website :
https://ijdbp.in
DOI :
https://doi.org/10.5281/zenodo.13133837

main area of deficits in individual children and targeting treatment accordingly.

Keywords: Autism spectrum disorder, Indian Scale for Assessment of Autism, Developmental Profile 3, children, risk factors.

Introduction:

The prevalence of ASD in India seems to be steadily increasing, probably due to greater awareness and case identification. However, the scarcity of high-quality population-based epidemiological studies on ASD in India prevents accurate estimation of its prevalence [1].Despite the various symptoms of autism spectrum disorder appearing in early childhood, due to various reasons, there is a significant delay in diagnosis in India. [2] Early diagnosis and intervention have proven to cause significant improvements in cognitive, language, and social-emotional functioning in children with ASD. [3] The studies on the socio-demographic profiles of ASD are sparse inIndia. As the facilities for evidence-based intervention of children with ASD are becoming increasingly available in India, we must be better aware of the possible presentations, co-morbidities, risk factors, and the socio-demographic profile of these children. We attempt to study these aspects in children treated at our quaternary care referral center for children with ASD.

Materials & methods:

A hospital-basedcross-sectional observational descriptive study was conducted on all children between 1 and a half and 6 years of age who fulfilled the DSM 5 criteria for autism spectrum disorder and underwent detailed assessment and evaluation at our Integrated NeuroDevelopmentalCenter, from June 2020 to July 2021 after getting consent from the parents/caregivers.Institutional ethical and scientific committee clearances were obtained before commencing the study. The parents of all children studied were provided with the patient information sheet. Written informed consent from the parent/guardian was taken in a simple and easily understandable unambiguous language.

A detailed history (personal history, family history, socioeconomic history, birth history, risk factors, comorbidities, exposure to E-media and scholastic history), clinical examination (as described in proforma), Sensory profile (SSP 2), Autism severity (ISSA scale), development assessment (DP-3 scoring) were done. Developmental profile 3 (DP3) scoring was applied under 5 domains; physical, adaptive, social-emotional, cognitive, and communication; and a total standard score and composite General Development Standard (GDS) score was attained.

The revised Kuppuswamy socioeconomic status scale was used to assess the socioeconomic status (SES) of the family. [4]

The target sample size calculated by the formula $N = Z^2 (1-\alpha/2)p (1-p)/d^2$, where prevalence (p) was taken as 2.5/10000, was 37.

The data was collected and entered into a Microsoft Excel sheet. Statistical analysis was performed by IBM SPSS Statistical software trial version 21. Categorical variables were described as frequency and percentage and continuous variables were described as Mean±S.D Yates corrected Chi-square/ Fisher Exact test was used to find the significance of study parameters on a categorical scale between two or more groups, non-parametric setting for qualitative data analysis. Fisher exact test was used when cell samples were very small. Multiple regression analysis was carried out to determine the influence of individual risk factors on the severity of autism (between mild and moderate autism groups).

Results:

The mean age of the 40 children recruited into

the study was 34 months; 35 (85%) were males. In 95% of cases,the maternal age at conception was less than or equal to 30 years and the paternal age was less than or equal to 35 years in 85.2%. Education qualification was graduation or more in 77.5% of fathers and 87.5% of mothers and 92.5% of the families were from upper and upper middle class.

Possible antenatal risk factors were noted in 65% of children [Table 1] and 30% and 12.5% of children had 2 and 3 or more risk factors, respectively. Gestational diabetes mellitus and hypothyroidism were the most common antenatally.The perinatal risk factors reported by caregiversare listed in Table 2. Sixty-five percent were delivered by LSCS and the rest were delivered vaginally. Eighty percent of the cohort were firstborn babies and the remainder were 2nd born; 88% had appropriate weight for gestational age, 1 baby had very low birth weight; and 30% were born preterm.

Table 1: Probable antenatal risk factors.

ANTENATAL RISK FACTORS	Number	Percentage
GESTATIONAL DIABETES MELLITUS	13	32.5%
HYPOTHYROIDISM	12	30.0%
URINARY TRACT INFECTION	6	15.0%
ANEMIA	5	12.5%
PREGNANCY-INDUCED HYPERTENSION	5	12.5%
ANTEPARTUM HEMORRHAGE	3	7.50%
HYPEREMESIS	2	5.00%
FEVER	2	5.00%

Table 2: Probable perinatal risk factors.

PERINATAL EVENTS	Number	Percentage
PREMATURITY	12	30%
RESPIRATORY DISTRESS	6	15%
SMALL FOR GESTATIONAL AGE	5	12.5%
SEPSIS	4	10%
HYPOGLYCEMIA	3	7.5%
PERINATAL ASPHYXIA	2	5%
CNS INFECTIONS	1	2.5%

Thirty children (75%) had a significant family history; out of which the most common was allergy (Table 3). Two of the cases had a family history of autoimmune arthritis.

Table 3: Significant Family History.

MEDICAL FAMILY HISTORY	Frequency	Percentage
ALLERGY	27	69.1%
SPEECH DELAY	5	12.5%
SEIZURE	4	10.3%
PSYCHIATRIC ILLNESS	3	7.5%
INTELLECTUAL DISABILITY	2	5.0%
AUTOIMMUNE ARTHRITIS	2	5.0%
SYNDROMIC	1	2.5%

A history of developmental regression was obtained in 11 (27.5%) of children. 70% of children were exposed to more than 2 hours (on an average 3-4 hours) daily to e-media.

Dysmorphic features were noted in 15%; neurocutaneous markers and macrocephaly in 10%, each (Table 4).

Table 4: Relevant examination findings in the cohort.

EXAMINATION FINDINGS	Frequency	Percentage
DYSMORPHIC FEATURES	6	15%
MACROCEPHALY	4	10%
NEUROCUTANEOUS MARKERS	4	10%
TONE ABNORMALITY	1	2.5%
NORMAL	25	63%

Autism severity assessed using ISAA scoring categorized 80 % as mild autism group, and the rest as moderately severe autism. The sensory domains affected in the cohort are given in Table 5 – most affected was auditory sensation (70%), followed by visual and touch. 87 % of moderate autism children had 3 or more sensory domains affected, while only 56 % of mild autism had 3 or more domain affection; 85 % of children had multi-domain affection.

Table 5: Profile of sensory domains affected.

SENSORY DOMAINS AFFECTED	Frequency	Percentage
AUDITORY	28	70.0%
VISUAL	19	47.5%
UNDER RESPONSIVENESS / SEEKING	18	45.0%
TOUCH	17	42.5%
ORAL SENSORY	15	37.5%
BODY POSITION PROPRIOCEPTION	15	37.5%
MOVEMENT	11	27.5%

Evaluation of developmental domains using DP3 showed that in our cohort the social, emotional, and cognitive domains were slightly more affected than the communicative domain (Table 6), The mean global developmental score was 49.2, indicating delay.

Table 6: DP3 scores of different domains.

DEVELOPMENT PROFILE DP3	MEAN	SD
PHYSICAL	79.7	12.4
ADAPTIVE	66.5	11.2
SOCIAL-EMOTIONAL	55.3	10.1
COGNITIVE	54.9	10.6
COMMUNICATIVE	57.4	11.4
GENERAL D SCORE	49.2	11.1

Multiple regression analysis was done on various risk factors (Table 7); none of them showed any significant influence on the severity of autism. The main 10 risk factors studied together accounted for around 19% of the variation in the explained variable (severity of autism).

Table 7: Multiple regression analysis of risk factors influencing the severity of Autism.

PREDICTORS	R-value	P value	Partial regression coefficient
GDM/DM (antenatal)	0.2	0.2	-0.01
Anemia (antenatal)	-0.2	0.2	-0.23
UTI (antenatal)	-0.03	0.8	-0.06
Mode of delivery	-0.02	0.8	-0.19
Respiratory distress (neonatal)	0.1	0.4	0.03
Sepsis(neonatal)	0.04	0.8	-0.16
Allergy(neonatal)	0.2	0.2	0.28
Speech delay (family history)	-0.2	0.24	-0.21
Seizure (family history)	0.06	0.7	0.14
Time spent on electronic media	-0.1	0.6	-0.13
Total R of all predictors	0.43		
Total R^2 of all predictors	0.19		

Total R-value between 0 to 0.3 shows negligible correlation and between 0.3 to 0.5 low positive correlation

The total R^2 value is 0.19 implies that the 10 main factors studied together account for 19% of the variation in the explained variable (severity of autism)

Discussion:

The mean age of presentation in our study was 34 months, with reported mean ages in literature ranging from 38-120 months. [5] This may be due to the relatively early suspicion, and consultation by the educated parents, from the upper to upper-middle socioeconomic status in our study cohort. The male predominance [87.5% males] in our study correlated with existing data in Indian and Western literature. [6,7]The known risk factors for autism spectrum disorders include advanced parental and maternal age, a sibling with ASD, prematurity, a history of ART, maternal diabetes, and maternal obesity, as well as the use of antiepileptic or antidepressant drugs. [8] No significant correlation with parent's age at conception was noted in our study with only 17 % of parents having an age above 35 years at conception. The firstborn child was affected in 80 % of our cases, as in theexisting meta-analysis. [9] One possible reason for this pattern could be that parents may be worried about having a second child with ASD - a phenomenon described as the "stoppage rule". [10]

One-fourth of our children had some form of family medical history, the most prevalent being allergies, speech delay, and seizures. A positive family history of mental and neurological disorders including ASD has been associated with higher odds of ASD in index persons. [11]

Our study had hypothyroidism in 30% of mothers - a known association reported not due to direct effects of thyroid hormones. It is postulated that pathways that influence maternal thyroid function may have etiologic roles in ASD. [12] Maternal diabetes isassociated with ASD in a meta-analysis. [13] Children with ASD in our study had 32.5% mothers with GDM. The pathway through which hyperglycemia may impact neurodevelopment may be mediated by oxidative stress. Further, GDM is associated with a greater risk of adverse obstetric outcomes. Anemia was documented in 12% of mothers in our study and when diagnosed during the first 30 weeks of pregnancy, but not later, was associated with an increased risk of diagnosis of ASD and lower IQ. [14,15] Iron deficiency affects fetal myelination, dendrite arborization, and synthesis of monoamine neurotransmitters, which are implicated in the etiology of ASD and ADHD. Maternal hyperemesis [16], and to some extent, pregnancy-induced hypertension,[17]cesarean delivery,[18]and preterm delivery [19,20] are risk factors for ASD in the offspring as noted in this study.

Despite some small studies suggesting the association of some perinatal insults as risk factors for ASD, it is not clear whether they are risk factors for ASD by themselves or play a secondary role in children with a genetic predisposition. It is possible many events that are known to produce neonatal morbidity could together increase the risk.[21,22] We have noted some perinatal insults in our children of which respiratory distress and sepsis were prominent. Seventy percent of patients had a screen time of more than 2 hours in our study, though there was no statistically significant correlation noted. Higher screen exposure in young children interferes with cognitive development (23) and is associated with altered brain processing.[24] In siblings of children with ASD who go on to develop ASD, overgrowth of the visually related brain areas at 6 to 12 months of age is one of the earliest findings. [25] However, children predisposed to ASD may have a preference for screens, or parents of children already displaying ASD symptoms may be more reliant on screens to soothe a child with self-regulation issues. Children with ASD process sensory information in a different manner such that they may tend to seek out media content that is more visually intense or calming.

Multiple regression analysis was done on various risk factors included in this study. The 10 risk factors for autism studied together accounted for around 19% of the variation in the explained variable and after controlling the variables, none of the risk factors by themselves showed a significant influence on the severity of autism. This could be because a synergistic influence of many risk factors may lead to the development of autism; no single risk factor can be implicated. [26]

The spectrum of autism in the community varies from 26% mild, 41.6% moderate, and 33.3% severe in a group of 2–5-year-old children in Bihar [27] to 46% mild, 47% moderate and 7% severe in a Spanish school cohort. [28] Autism severity assessed in our study using ISAA scoring recorded 80 % to mild autism group, and the rest to moderate severity. No case of severe autism was noted in our study group. The data suggests that the bulk of the increase in autism prevalence the world over may be attributed to the increasing number of children on the mild

end of the spectrum being diagnosed. This also implies that many children in the spectrum may be able to live a life on their own if appropriate interventions, at the right time, are instituted.

In 70 % of our patients, the auditory domain was affected followed by visual and touch. Three or more sensory domains were affected in 56% and 87% of mild and moderate autism, respectively and multi-domain affection was noted in 85% of children in our study. An increasing number of domains affected and the presence of multiple co-morbidities are the feature of higher severity of autism. [29]Developmental regression was noted to be 27 % in our study, which is comparable to other studies[30] and the age when regression was reported was around 2 years as in our study. The reasons for regression and the presence of developmental deviances before the time when regression was noted, were not studied.The domains affected according to DP3 scales and co-morbidity profile were different in our study in comparison to textbook cases. The social, emotional, and cognitive domains were mostly affected, though classically communication and social interaction are more detailed in the literature. Allergy and sleep disorders constitute about 67% of co-morbid conditions in our cohort, as compared to the higher prevalence of ADHD and anxiety disorders.

Limitations of the study:

The small sample size and the predominantly upper and upper-middle-income group in our cohort cannot be extrapolated to the ground statistics in Kerala. Only children up to 6 years old were studied without follow-up; hence the effect of age of diagnosis on outcome could not be assessed.

Conclusion:

Autism spectrum disorders are one of the commonest, yet most delayed-diagnosed cognitive impairment disorders of childhood. The earlier mean age at diagnosis in our study can be attributed to greater awareness and education status of the caregivers, and more cases will likely be diagnosed earlier owing to the increased availability of specialist services. The risk factors previously described in literature such as male gender, maternal co-morbidities, and screen time were present but no correlation with the severity of the disorder could be established. Increasing awareness could be the reason for the large number of mild cases being detected; suggesting the contribution of these cases to the increasing incidence of autism reported in recent times. No risk factor singly could be identified as the cause of ASD suggesting a synergistic influence of multiple factors. With the increasing availability of specialists and advanced interventions in the country, coupled with the proven benefits of early management, it is imperative to spread awareness about the clinical profile of autism to facilitate early diagnosis and early intervention.

Financial Support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References:

1. Chauhan A, Sahu JK, Jaiswal N, Kumar K, Agarwal A, Kaur J, Singh S, Singh M. Prevalence of autism spectrum disorder in Indian children: A systematic review and meta-Analysis. Neurology India 2019; 67: 100. 10.4103/0028-3886.253970.
2. Bhavnani S, Lockwood Estrin G, Arora R, Kumar D, Kakra M, Vajaratkar V, Juneja M, Gulati S, Patel V, Green J, Divan G. "I was Confused … and Still am" Barriers Impacting the Help-Seeking Pathway for an Autism Diagnosis in Urban North India: A Mixed Methods Study. J Autism Dev Disord 2022; 52(4): 1778-1788.
3. Okoye C, Obialo-Ibeawuchi CM, Obajeun OA, Sarwar S, Tawfik C, Waleed MS, Wasim AU, Mohamoud I, Afolayan AY, Mbaezue RN. Early Diagnosis of Autism Spectrum Disorder: A Review and Analysis of the Risks and Benefits. Cureus 2023; 15(8): e43226. doi: 10.7759/cureus.43226.
4. Saleem SM, Jan SS, Modified Kuppuswamy socioeconomic scale updated for the year 2021. Indian J Forensic Community Med 2021; 8(1): 1-3.
5. van 't Hof M, Tisseur C, van Berckelear-Onnes I, et al. Age at autism spectrum disorder diagnosis: A systematic review and meta-analysis from 2012 to 2019. Autism 2021; 25(4): 862-873.
6. Bhat BA, Hussain A, Qadir W, Dar SA. Sociodemographic and clinical profile of children with autism spectrum disorders – An observational study from a tertiary care hospital. BLDE University Journal of Health Sciences 2019; 4(2): 72-77.
7. Raina SK, Chander V, Bhardwaj AK, Kumar D, Sharma S, Kashyap V, Singh M, Bhardwaj A. Prevalence of Autism Spectrum Disorder among Rural, Urban, and Tribal Children (1-10 Years of Age). J Neurosci Rural Pract 2017; 8(3): 368-374.
8. EmbertiGialloreti L, Mazzone L, Benvenuto A, Fasano A, Alcon AG, Kraneveld A, Moavero R, Raz R, Riccio MP, Siracusano M, Zachor DA, Marini M, Curatolo P. Risk and Protective Environmental Factors Associated with Autism Spectrum Disorder: Evidence-Based Principles and Recommendations. J Clin Med. 2019; 8(2): 217. doi: 10.3390/jcm8020217.
9. Gardener H, Spiegelman D, Buka SL. Prenatal risk factors for autism: comprehensive meta-analysis. Br J Psychiatry 2009;195(1): 7-14. doi: 10.1192/bjp.bp.108.051672.
10. Lord C., Mulloy C., Wendelboe M., Schopler E. Pre- and perinatal factors in high-functioning females and males with autism. J Autism Dev Disord 1991; 21(2): 197–209.
11. Xie S, Karlsson H, Dalman C, Widman L, Rai D, Gardner RM, Magnusson C, Schendel DE, Newschaffer CJ, Lee BK.Family History of Mental and Neurological Disorders and Risk of Autism. JAMA Netw Open. 2019;2(3):e190154. doi: 10.1001/jamanetworkopen.2019.0154.
12. Rotem RS, Chodick G, Shalev V, Davidovitch M, Koren G, Hauser R, Coull BA, Seely EW, Nguyen VT, Weisskopf MG. Maternal Thyroid Disorders and Risk of Autism Spectrum Disorder in Progeny. Epidemiology 2020; 31(3): 409-417.
13. Rowland J, Wilson CA. The association between gestational diabetes and ASD and ADHD: a systematic review and meta-analysis. Sci Rep 2021; 11(1): 5136. doi: 10.1038/s41598-021-84573-3.

14. Wiegersma AM, Dalman C, Lee BK, Karlsson H, Gardner RM. Association of Prenatal Maternal AnemiaWith Neurodevelopmental Disorders. JAMA Psychiatry 2019; 76(12): 1294-1304.
15. Drassinower D, Lavery JA, Friedman AM, Levin HI, Običan SG, Ananth CV. The effect of maternal haematocrit on offspring IQ at 4 and 7 years of age: a secondary analysis. BJOG 2016; 123(13): 2087-2093.
16. Fejzo MS, Mullin P. Neurodevelopmental delays and in utero exposure to hyperemesis gravidarum. Martin CR, Preedy VR, Rajendram R (Eds.), Diagnosis, management and modeling of neurodevelopmental disorders, Academic Press, Cambridge (2021), pp. 229-240
17. Xu RT, Chang QX, Wang QQ, Zhang J, Xia LX, Zhong N, Yu YH, Zhong M, Huang QT. Association between hypertensive disorders of pregnancy and risk of autism in offspring: a systematic review and meta-analysis of observational studies. Oncotarget 2017; 9(1): 1291-1301. doi: 10.18632/oncotarget.23030
18. Zhang T, Sidorchuk A, Sevilla-Cermeño L, Vilaplana-Pérez A, Chang Z, Larsson H, Mataix-Cols D, Fernández de la Cruz L. Association of Cesarean Delivery With Risk of Neurodevelopmental and Psychiatric Disorders in the Offspring: A Systematic Review and Meta-analysis.JAMANetw Open 2019; 2(8): e1910236. doi:10.1001/jamanetworkopen.2019.10236.
19. Agrawal S, Rao SC, Bulsara MK, Patole SK. Prevalence of Autism Spectrum Disorder in Preterm Infants: A Meta-analysis. Pediatrics 2018; 142(3). doi:10.1542/peds.2018-0134.
20. Schieve LA, Tian LH, Rankin K, Kogan MD, Yeargin-Allsopp M, Visser S, Rosenberg D. Population impact of preterm birth and low birth weight on developmental disabilities in US children. Ann Epidemiol 2016; 26(4): 267-274.
21. Gardener H, Spiegelman D, Buka SL. Perinatal and neonatal risk factors for autism: a comprehensive meta-analysis. Pediatrics 2011; 128(2): 344-355.
22. Guinchat V, Thorsen P, Laurent C, Cans C, Bodeau N, Cohen D. Pre-peri- and neonatal risk factors for autism.ActaObstetGynecolScand 2012; 91(3) :287-300.
23. Guellai B, Somogyi E, Esseily R, Chopin A. Effects of screen exposure on young children's cognitive development: A review. Front Psychol. 2022 Aug 17;13:923370. doi: 10.3389/fpsyg.2022.923370. eCollection 2022.
24. Hutton JS, Dudley J, DeWitt T, Horowitz-Kraus T. Associations between digital media use and brain surface structural measures in preschool-aged children. Sci Rep 2022; 12: 19095. https://doi.org/10.1038/s41598-022-20922-0.
25. Heffler KF, Sienko DM, Subedi K, McCann KA, Bennett DS. Association of Early-Life Social and Digital Media Experiences With Development of Autism Spectrum Disorder-Like Symptoms. JAMA Pediatr 2020; 174(7): 690-696.
26. Nadeem MS, Al-Abbasi FA, Kazmi I, Murtaza BN, Zamzami MA, Kamal MA, Arif A, Afzal M, Anwar F. Multiple Risk Factors: A Challenge in the Management of Autism.Curr Pharm Des 2020; 26(7): 743-754. doi: 10.2174/1381612826666200226101218.

27. Kumar S, Mahanta P, Galstaun K, Kumar A, Kumar H, Shekhar A. Prevalence of Symptoms of Autism among 2-5 Year-Old Children in Bihar, India. The International Journal of Indian Psychology 2023; 11: 404-411.
28. Hidalgo MP, Moreso VN, Sans JC. Autism spectrum disorder prevalence and associated sociodemographic factors in the school population: EPINED study. Autism 2021; 25(7): 1999-2011. https://doi.org/10.1177/13623613211007717.
29. Waizbard-Bartov E, Fein D, Lord C, Amaral DG. Autism severity and its relationship to disability. Autism Res 2023; 16(4): 685-696. doi: 10.1002/aur.2898.
30. Tan C, Frewer V, Cox G, Williams K, Ure A. Prevalence and Age of Onset of Regression in Children with Autism Spectrum Disorder: A Systematic Review and Meta-analytical Update. Autism Res 202; 14(3): 582-598. doi: 10.1002/aur.2463.