REVIEW ARTICLE

Research on autism spectrum disorders in India

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ABSTRACT

Autism spectrum disorders (ASD) are a complex group of neurodevelopmental disorders characterized by triad of impairments in communication skills, social skills and repetitive behaviour. Research on this category of developmental disorders is still in a nascent stage in India. This review article collates information on research done on ASD in India.

Keywords: autism, research, India

INTRODUCTION

Autistic spectrum disorders (ASD) are a group of neuropsychiatric disorders with specific delays and deviance in social, communicative and cognitive development. ASD includes autism, asperger's syndrome, and pervasive developmental disorder- not otherwise specified (PDD-NOS).

This review would discuss the following aspects of research done on ASD in India: clinical profile, rating scales, neurobiology, genetics, treatment and outcome. Databases such as PubMed, Google scholar, Indian databases such as INDMED, PsychINFO, and other sources were searched with relevant terms for preparing this review.

Clinical profile

Few cases of children with Autism were reported in the Indian scenario in the 60's and 70's. Sreedhar et al developed a questionnaire for the diagnosis of Autism. In a retrospective chart review of cases registered from 1981 to 1984 attending Child and Adolescent Psychiatry out-patient facility, Srinath et al reported that 31 cases met the ICD-9 criteria for autism. The cases ranged between 2.5 to 14 years of age. Male to Female ratio was 7.5:1. All developed symptoms by 30 months. Two patients had co-morbid seizure disorder.

Malhotra et al compared the socio-demographic and clinical profile of Pervasive developmental disorder (PDD) patients registered at CAP Clinic, PGIMER, Chandigarh between 1989 and 1999. Out of 2942 cases, 46 cases (1.6%) met ICD-10 criteria for different PDDs. 22 cases were of typical autism, 12 cases each were diagnosed as Childhood disintegrative disorder and other PDDs. 5 cases met criteria for atypical autism, 4 were of Asperger's syndrome and the rest were of Rett's syndrome (n=2) and PDD unspecified (n=1). Relatively high proportion (26%) of cases of CDD is notable as it has been suggested that CDD is only about one-tenth as common as autism. Seventy eight percent of the total sample was male, all exhibited classical symptoms, and temperamental variations were noted in the areas of activity, rhythmicity and attention span in most of the cases. Bharath et al reviewed in-patient data for a period of 1 year at NIMHANS and reported that 6 cases met ICD-9 criteria for Autism out of a total of 143 cases. Case reports and case series of Asperger's and Rett's syndrome have been reported in the published Indian literature.

Malhotra et al opined that Childhood disintegrative disorder (CDD) is a clinical syndrome characterized by disintegration of mental functions and regression of acquired language and intellectual functions after a period of normal development. In a case series from a tertiary care centre, 5 cases of CDD were diagnosed from 1980 to 1989. These cases constituted 0.22% of the total cases (2259) registered during this period. Age at first contact ranged between 5.5 to 12 years. Regression started at 74 years in one, while in all the other cases it started between 3 and 4.5 years of age. Unusually rapid onset (1 to 4 weeks) was a notable finding of this study. EEG showed seizure activity in one while nonspecific rhythm abnormalities were found in two cases. CT scan head was normal in all the cases.

In a study conducted at Paediatrics out-patient facility of a tertiary care hospital, 16 children (9 boys, 7 girls) with ASD were identified between 1997 and 1999 and the sex ratio was 1.3: 1. The mean age at referral was 42.8 months (range 34 to 56 months). All children had Childhood autism rating scale (CARS) scores in the autistic range. The mean score on CARS was 38.5 (range...
30.5 to 50) with 62.5% of the children scoring in the severely autistic range. A history of antenatal problems was present in 5 cases (31.3%). Twelve (75%) were normal deliveries, 3 (18.8%) were Caesarean and 1 (6.5%) was breech. Perinatal problems were reported in 4 cases (25%). The physical examination of all the children was essentially normal. Fifteen children had a normal head circumference. One child had a head circumference <2 SD of normal. None of the other children had any other recognizable neurologic problem.

Clinical features suggestive of ASD were reported in children with a diagnosis of Tuberous Sclerosis. [15] Studies in children with Mental retardation have reported ASD co-morbidity in the range of 47% to 96%. [16, 17] Girimaji et al reported 46% co-morbidity in children with ASD. Most common co-morbid disorders were ADHD, anxiety disorders including obsessive compulsive disorder, bipolar affective disorder and circadian rhythm disturbance of sleep. [18]

Rating scales

A cut-off score of > or = 33 was suggested in a study of Childhood Autism Rating Scale in Indian children and adolescents suspected of having autism. The inter-rater reliability (ICC=0.74) and test-retest reliability (ICC=0.81) for CARS were good. Besides the adequate face and content validity, CARS demonstrated good internal consistency (Cronbach’s alpha=0.79) and item-total correlation. [19] An evaluation of sensitivity of Autism behaviour checklist (ABC) was done by Juneja et al. [20] Fifty-one children were enrolled in the study. The mean age was 3.28 +/-1.89 years. The ratio of boys to girls was 2.2:1. The mean Childhood Autism Rating Scale score was 447 +/- 6.22, with all children having scores in the autistic range. The mean ABC score was 724, with a standard deviation of 14.2. By using the originally suggested cut-off score of 67, only 40 children in this study were diagnosed with autism. When lower cut-offs were used, the sensitivity increased, with a sensitivity of 98% and a cut-off of 45. ABC cut-off needs to be lowered to increase its sensitivity for diagnosis of autistic disorder.

Neurobiology

Narayan et al measured Cerebrospinal fluid (CSF) concentrations of the serotonin and dopamine metabolites, 5-hydroxyindoleacetic acid (5HIAA) and Homovanillic acid (HVA), respectively, in a group of 17 children with Autistic Disorder (DSM-III-R). [21] The group means observed for 5HIAA (135 +/- 91 nmol/L) and HVA (502 +/- 324 nmol/L) in the autistic children were not significantly different from those seen in the control group of 15 non-neurologically impaired children (5HIAA, 122 +/- 120 nmol/L; HVA 401 +/- 378 nmol/L). In a study of Brainstem Auditory Evoked Responses (BERA), it was noted that 42.8% of children with a diagnosis of Autism had pathological BERA suggesting a possible dysfunction at brainstem level. The authors hypothesized that faulty modulation of the auditory input leads to failure in the development of complex cognitive skills. [22]

Studies of trace elements in hair and nail samples of children with Autism revealed significant elevation in the concentration of Copper, Lead, and Mercury and significant decrease in the concentration of Magnesium and Selenium. This could be well correlated with their degrees of severity. [23] There have been reports of lower protein content and higher percentage of nitration in hair and nail of autistic children. [24] Increase urinary levels of oxidative stress markers like thiobarbituric acid-reacting substances, lipid hydroperoxides, 4-hydroxy nonenal, protein carbonyls, etc have been reported in children with Autism compared to healthy controls. [25] Naik et al reported significant increase in nuclear transcription factor-kB DNA binding activity in peripheral blood samples of children with Autism. [26] Gupta et al studied cerebral perfusion using SPECT in children with autism, mental retardation and matched controls. [27] Frontal and prefrontal areas showed marked hypo perfusion in cases of autism and mental retardation compared to controls.

Genetics

Manjunatha et al did a crypto genetic investigation in autistic children with the aims of finding the association and prevalence of fragile X syndrome in autistic children. [28] Though none of the six cases studied had fragile X chromosome, fragile sites were noted in autosomes 1, 2, 3, 5 and 6.

Engrailed 2 (EN2) is a homebox transcription factor involved in the patterning of cerebellum during brain development. Linkage analysis and studies on knockout mice support EN2, located on chromosome 7q36.3, as a potential risk locus for Autism. Candidate gene approach also suggested association of EN2 with autism spectrum disorder (ASD) in various populations. Sen et al suggest positive genetic correlation of EN2 with autism in the Indian population. [29]

Balasubramanian et al compared children with intellectual disability and autism and those with intellectual disability alone and found that 50.6% cases with fragile X syndrome and 11.6% cases with other chromosomal anomalies in the group with intellectual disability and autism and 23.3% cases with Fragile X syndrome and 30.5% cases with other chromosomal anomalies in those with intellectual disability alone. [30] Fragile X syndrome (FXS) is the most commonly inherited form of autism. Suvarthan et al describe recent findings from mouse models of FXS that have identified synaptic defects in the basolateral amygdala that are in many respects distinct from those reported earlier in the hippocampus. [31] Guhathakurta et al, [32] failed to establish
any association or linkage of 5-HTTLPR with autism in the Indian population by case-control studies and family-based approaches; however, when a meta-analysis of all the available data, inclusive of the present study, was carried out, a highly significant preferential transmission of the S allele from parents to the affected offspring was observed. Mohammed et al studied genetic polymorphisms in children with Autism and matched controls.\textsuperscript{33} The five polymorphisms which were studied include cytosolic serine hydroxyl methyl transferase (SHMT1 C1420T), methylene tetrahydrofolate reductase (MTHFR C677T and MTHFR A1298C), methionine synthase reductase (MTRR A66G), methionine synthase (MS A2756G). MTHFR 677T-allele frequency was found to be higher in autistic children compared with non-autistic children. The frequencies of MTRR 66A allele and SHMT1 1420T allele were lower in autistic group compared with non-autistic group. The authors concluded that MTHFR C677T is a risk factor, whereas MTRR A66G and SHMT1 C1420T polymorphisms reduce risk for autism. MTHFR A1298C acts additively in increasing the risk for autism.

**Treatment**

In a study conducted 30 subjects diagnosed with ASD in the Communication DEALL (Com DEALL) units in Bangalore, statistically significant increase in all eight developmental domains and statistically significant decrease in symptoms as measured by the CARS, were seen.\textsuperscript{34} Malhotra et al studied the efficacy of Picture Exchange Communication System (PECS) as an adjunct treatment to behavioural management.\textsuperscript{35} In a 16-week open-label study on 40 children with autism divided into two groups, risperidone group showed significant improvement in areas like irritability and hyperactivity, while the fluoxetine group showed significant improvement in speech deviance, social withdrawal and stereotypy. When the two drugs were compared, fluoxetine showed greater improvement in stereotypy, while both drugs showed improvement on the general autism scale; and on anger, hyperactivity and irritability scales.\textsuperscript{36} Malhotra et al reported experience with psychological intervention with parents of autistic children.\textsuperscript{37} Treatment methods were drawn from Treatment and Education of Autistic and related Communication handicapped Children (TEACCH) protocol. Emphasis was given on behavioural strategies aimed at enhancing eye to eye contact, reduction of maladaptive behaviour, structuring time, activities and physical environment. Considerable time was given to parents to teach them these techniques, to educate them about the nature of the disorder and its management, and a supportive mode of counselling to help them deal with emotional fallout of the diagnosis. These were used on 5 children with autism in 3-6 sessions of 45-60 minutes each. Results showed that the parents found this brief contact helpful. They found emotional aspects of the support to be the most helpful.

Studies have explored complementary and alternative medicine (CAM) treatment approaches like Yog therapy. In a study using Integrated Approach to Yoga Therapy (IAYT) for two years, it was observed that there were significant improvements in imitation and other skills, and in behaviour at home and family relationships. The putative role of mirror neuron activation has been hypothesized for this effect.\textsuperscript{38}

**Outcome**

Sitholey et al reported a case of autistic disorder who recovered spontaneously without any intervention in 13 days.\textsuperscript{39} Nizamie et al reported improvement in autistic regression symptoms with comprehensive multi-modal treatment approach in motor, language, and social domains, and also in the activities and skills of daily living.\textsuperscript{40} In a follow-up study conducted at a tertiary care hospital, Malhi et al recruited 77 (64 boys,13 girls) children in whom a diagnosis of Autistic Disorder (AD) and Pervasive Developmental Disorder-Not Otherwise Specified (PDD-NOS) was made at age 3 years or less as per the DSM IV criteria.\textsuperscript{41} Diagnosis of Autistic disorder was stable for 33 out of 37 (89.18%) children and the PDD-NOS were stable for only 1 out of 6 (16.67%) children.

**Conclusion**

The current scenario of research in ASD is limited to largely clinic-based case reports, case series, retrospective chart reviews, few attempts to study neurobiological, genetic substrates and effectiveness of available treatment approaches. There is a need to focus future research initiatives in the area of ASD on the following areas:

- Large multi-centre community prevalence studies
- Outcome studies of well-defined cohort of subjects with ASD;
- Exploration of neurobiological substrates using assessments like neuroimaging, neuropsychological profile, eye movement recording etc.
- Setting up of clinic-based registry at different Child Guidance Clinics across the country.
- Development and validation of effective screening and early intervention modules.
- Development and validation of psycho education and treatment manuals for parents of children with ASD.

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References

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