RESEARCH PAPER

Intellectual Disability in Indian Children: Experience with a Stratified Approach for Etiological Diagnosis

SILKY JAIN, *VEENA CHOWDHURY, MONICA JUNEJA, #MADHULIKA KABRA, SANJEEV PANDEY, ANKUR SINGH, MALOBIKA BHATTACHARYA AND SEEMA KAPOOR

*From the Departments of Pediatrics and *Radio diagnosis, Maulana Azad Medical College, and #Department of Pediatrics, All India Institute of Medical Sciences; New Delhi, India.*

Correspondence to: Dr Seema Kapoor, Professor, Department of Pediatrics, Maulana Azad Medical College, New Delhi 110 002, India. drseemakapoor@gmail.com

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Objective: To study the clinico-etiological profile of children with intellectual disability using an algorithmic approach.

Design: Cross-sectional study.

Setting: Tertiary care centre in Northern India.

Participants: Consecutive children aged 3 months to 12 years, presenting with intellectual disability, confirmed by Developmental Assessment Scale for Indian Infants, Binet Kulshreshtha Test and Vineland Social Maturity Scale.

Method: All children were assessed on an internally validated structured proforma. A targeted approach included thyroid function tests, Brainstem evoked response audiometry, electroencephalogram, neuroimaging and metabolic screen done as a pre-decided schema. Genetic tests included karyotyping, molecular studies for Fragile X, Multiplex Ligation Dependent Probe Amplification and Array Comparative Genomic Hybridisation.

Results: Data of 101 children (median age 22 months) was analyzed. The etiological yield was 82.1% with genetic causes being the most common (61.4%) followed by perinatal acquired (20.4%), CNS malformations (12%), external prenatal (3.6%), and postnatal acquired (2.4%). Mild delay was seen in 11.7%, moderate in 21.7%, severe in 30.6% and profound in 35.6%.

Conclusion: It is possible to ascertain the diagnosis in most of the cases of intellectual disability using a judicious and sequential battery of tests.

Keywords: *Children, Etiology, India, Intellectual disability.*

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Intellectual disability (ID) is the presence of significant limitations both in intellectual functioning and adaptive behavior as expressed in conceptual, social and practical adaptive skills [1]. It occurs in 2-3% of the general population [2-4]. A careful search for the cause of child's observed delay has important implications with reference to the risk of recurrence, prognosis, follow-up and treatment [5]. The recent advances in fields of molecular biology, DNA technology and prenatal diagnostic techniques have opened up new avenues for detection and prevention of ID in families at risk. However, there is a paucity of vital data in this area from India.

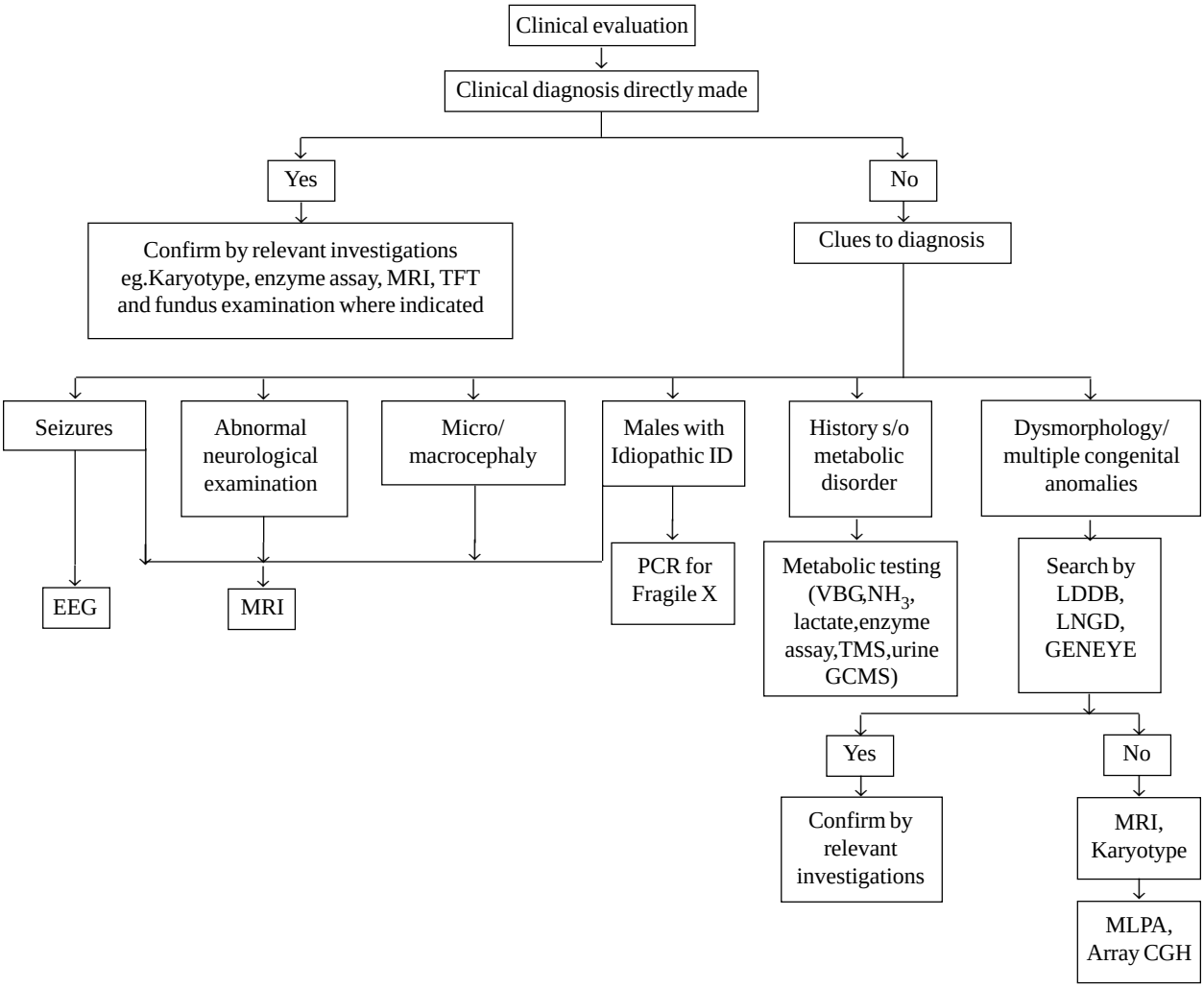
METHODS

This cross-sectional study was conducted at a tertiary care hospital in Northern India. Patients aged 3 months to 12 year who presented with ID over a period of 1 year from Feb 2010 to Feb 2011 were included. Patients were recruited consecutively from the Genetic clinic, Outpatient department, and Pediatric wards. Our genetic clinic is a weekly clinic. Only one or two consecutive patients who presented first to the clinic were included as detailed evaluation normally consumed 2-3 hours. Formal testing for developmental quotient (DQ), intelligence quotient (IQ) and social quotient (SQ) was done by a trained psychologist. DQ was done in children aged 3-30 months using Developmental Assessment Scale for Indian Infants. IQ was done in children aged 30 mo-12 yr using Binet Kulshreshtha Test. SQ was determined in all patients using Vineland Social Maturity Scale. Inclusion criteria used for the study were DQ/IQ <70 along with SQ <70. Patients presenting with neuroregression and autism were also included in the study. Previously diagnosed cases were not included. Inpatients, who were too sick to undergo detailed workup, and those whose attendants did not give consent were excluded. The severity of ID was graded into mild (IQ 50-69), moderate (IQ 35-49), severe (IQ 20-34) and profound (IQ under 20) using ICD-10 classification [6].

All children underwent detailed clinical evaluation as per a structured proforma that included perinatal events, regression of milestones, seizures, behavioural problems, symptoms suggestive of inborn errors of metabolism, hypothyroidism, three generation pedigree and social history. Examination included anthropometric,

dysmorphic, neurological and ophthalmologic assessment.

Targeted investigations were carried out on the basis of an algorithmic approach as depicted in ***Fig*. 1**. Magnetic resonance imaging (MRI) was done on an indicated basis in patients with seizures/microcephaly/abnormal neurologic examination/history of perinatal asphyxia. It was also done on a screening basis in patients with idiopathic ID where clinical evaluation did not give any clue to the diagnosis. Fundus examination and thyroid function tests (TFTs) were done in patients as indicated. Dysmorphology assessment was done using London Dysmorphology Database (LDDB) and Geneye Database. Conventional karyotyping with GTG banding at 500nm bandwidth was done in patients presenting with dysmorphism, multiple congenital anomalies or family history of ID. It was not done in some patients with dysmorphism, in whom alternative diagnosis was clinically evident (*e.g.*, mucopolysaccharidoses). Molecular studies for Fragile X (FRXA and FRXE) were done in patients with features suggestive of Fragile X syndrome and in all males with idiopathic ID [7]. Metabolic screen (venous blood gas, ammonia, lactate, Tandem mass spectrometry, gas chromatography) was done in patients with history or examination suggestive of a metabolic disorder (vomiting, seizure, abnormal odour, hypotonia/spasticity, cataract, ataxia, hepatosplenomegaly, psychomotor regression, history of recurrent abortions or neonatal deaths). Lysosomal enzyme assay was done on suspicion of lysosomal storage disorder. Electroencephalogram (EEG) was done in patients with seizures to identify the specific epileptic syndrome.



MPS, Mucopolysaccharidosis; TFT, Thyroid function test; MR, Mental retardation; EEG, Electroencephalograph; LDDB, London Dysmorphology Database, MLPA, Multiplex Ligation Dependent Probe Amplification.

FIG. 1 *Algorithm for etiological diagnosis of intellectual disability.*

Brainstem evoked response audiometry (BERA) was done in patients with hearing or language abnormality. If BERA could not be done, hearing impairment was assessed by Otoacoustic Emission (OAE). Multiplex Ligation-Dependent Probe Amplification (MLPA) was done in patients with dysmorphism and/or multiple congenital anomalies who demonstrated a normal karyotype. Array Comparative Genomic Hybridisation (array CGH) was done in patients in whom MLPA was also non-contributory but was affordable.

Following the above approach, etiologically diagnosed patients were categorized into six broad groups using the Finnish classification [8] which is based on the timing and type of injury to the central nervous system. Six broad groups were as follows: genetic causes, CNS malformations, external prenatal factors, perinatally acquired disorders (1 week before and 4 weeks after delivery), postnatally acquired disorders and unclassified/ idiopathic causes. Genetic causes were further classified into chromosomal abnormalities, single gene defects, contiguous gene syndromes, and recognizable syndromes. The recognizable syndrome category included those syndromes for which diagnosis was strongly suggested by LDDB search, but the exact locus of genetic defect is not known. When diagnosis was ambiguous, consultation was done with an independent trained clinical geneticist (expert review). An etiological diagnosis was considered established only if clinical features were supported by investigations.

Evaluation of the association between clinical features and etiological diagnosis was made. Following clinical features were evaluated: severity of delay, gender, neuroregression, behavioural problems, seizures, consanguinity, family history of ID, microcephaly, facial dysmorphism, non facial dysmorphism (skeletal/hair/ cardiovascular/gastrointestinal/urogenital anomalies) and abnormal neurological examination (spasticity/hypotonia). Contribution to diagnosis by history/examination/ investigations was studied. Diagnostic yield of various investigations was also determined. Written informed consent from the primary caregivers was obtained and the study was approved by the Institutional ethics committee.

Descriptive statistics of the study population was generated on the basis of etiological classification used. Chi square test or Fisher-exact test was applied to explore the bivariate association between presence of clinical markers and determination of etiology. For each of them, odds ratio, likelihood ratio and 95% confidence interval were calculated and a *P* value of <0.05 was taken as significant.

RESULTS

A total of 142 consecutive children were identified with ID over a period of 1 year. Out of the same, 13 did not give consent, 11 did not come in follow-up, 12 inpatients were sick and 6 were found to have DQ >70 on formal evaluation. Therefore, above patients were excluded, leaving 101 patients for final analysis. The median age at presentation was 22 months (3months-12yr) and 65 (64.3%) were males. Twelve (11.8%) had mild, 22 (21.7%) had moderate, 31(30.6%) had severe and 36 (35.6%) had profound ID.

An etiological diagnosis for ID could be made in 83 patients, giving an etiological yield of 82.1%. Genetic causes constituted the most common category accounting for 51/83 (61.4%) of the cases followed by perinatal acquired 17 (20.4%), CNS malformations 10 (12%), external prenatal 3 (3.6%) and postnatal acquired causes 2 (2.4%) (***Table* I** and **II**). Down syndrome was the most common cause accounting for 14.8% of all cases. Chromosomal disorders constituted 36.5% (19/52) of genetic causes single gene 48% and recognizable syndromes 11.5%.

Regression of milestones was present in 12 (11.9%) of the total number of cases, behavioral problems in 15 (14.9%), seizures in 39 (38.6%), consanguinity in 14 (13.9%), facial dysmorphism in 45 (44.6%), microcephaly in 30 (29.7%), family history in 16 (15.8%), non-facial dysmorphism in 41 (40.6%) and neurological deficit in 48 (47.5%). There were 28 children with cerebral palsy. Four children had autism. Etiological yield did not differ across gender and categories of ID. Regression of milestones (*P*=0.007) and behavioral problems (*P*=0.025) were significant negative predictors of etiology (***Web Table* I**).

Visual and hearing deficit were found in 29 (28.7%) and 23 (22.7%) patients, respectively. Fundus was abnormal in 18 patients (17.8%). Hypothyroidism was detected in 11(10.8%) including 2 patients with isolated hypothyroidism (one with congenital hypothyroidism and another due to mother's thyroid peroxidase antibodies), 6 with Down syndrome, 1 with Albright hereditary osteodystrophy, 1 with 18q subtelomeric deletion and 1 in a child with birth asphyxia.

Diagnostic yield of investigations: Karyotype yielded diagnosis in 15 out of 33, metabolic screen 14/34, LDDB search 8/26, Fragile X 1/4, MLPA 1/10, array CGH 3/ 5.MRI was done in 73 patients. It was abnormal in 52/ 73(71.2%), but findings consistent with a specific etiology were found in 29/73(39.7%) patients. When done on a screening basis, diagnostic yield was 8% (2/25) and when done on an indicated basis yield significantly increased to 56.2% (27/48).Diagnosis was made on the basis of investigations alone in 21/83 (25.3%) patients and it helped in confirming the clinically suspected

TABLE I SPECIFIC ETIOLOGICAL DIAGNOSIS IN GENETIC DISORDERS CATEGORY

Chromosomal	19
Down syndrome	15
Subtelomeric deletions	1
Chromosomal aberrations by Array CGH	3
Contiguous gene syndromes: Williams syndrome	1
Single gene syndromes	**25**
FragileX	1
Albrights hereditary osteodystrophy	1
Fukuyama congenital muscular dystrophy	2
Rett syndrome	1
Tuberous sclerosis	1
Epileptic syndromes	3
Congenital hypothyroid	1
Baller gerold syndrome	1
Metabolic	**14**
Small molecule	**4**
Pyruvate dehydrogenase deficiency	1
Malonic aciduria	1
Homocystinuria	1
Free carnitine deficiency	1
Large molecule	**10**
Mucopolysaccharidoses	7
Gaucher disease	2
Canavan disease	1
Recognizable syndromes	**6**
Trigonocephaly C	1
Cardiofaciocutaneous syndrome	1
Goldenhar syndrome	1
Kabuki syndrome	1
Hypomelanosis of Ito	1
Pai syndrome	1

diagnosis in 41/83 (49.3%). Overall, it contributed to diagnosis in 62/83 (74.6%). History gave a clue to diagnosis in 25/83 (31%), examination in 43/83 (51.8%).

DISCUSSION

We report a study from a tertiary care-setup in Northern India with the aim of establishing an etiological diagnosis using relevant investigations in an algorithmic manner. An etiological diagnosis could be assigned to 83 of 101 patients which accounts for a high yield of 82.1%. History and examination alone contributed to approximately 25% of the diagnosis. In another 50%, they gave important clues for further investigation and in the remaining 25%; diagnosis was established solely by investigations.

TABLE II ETIOLOGICAL PROFILE OF OTHER CATEGORIES

CNS malformations	10
Lissencephaly	4
Closed lip schizencephaly	1
Giant open lip schizencephaly	1
Polymicrogyria	1
Corpus callosum agenesis	1
Dandy Walker malformation with lissencephaly	1
Congenital hydrocephalus	1
Perinatal acquired	17
Perinatal asphyxia	14
Meningitis with hydrocephalus	2
Hypothyroid due to Mother's TPO Ab	1
External prenatal	2
Fetal valproate	1
Antenatal asphyxia	1
Postnatal acquired	2
Brain tumor (Glioma)	1
Infantile tremor syndrome	1

Although the etiologic yield has varied widely in studies [9-22] from 20 to 86% depending on the definition used for ID, the population studied (whether from a developmental neurology unit or a genetic unit), the extent of diagnostic workup and the technological advances over time, a yield as high as 80% has not yet been reported in Indian literature except in a study by Balasubramanian, *et al.* [19]. They reported a yield of 86% in a cohort of patients with ID without autism. This may be due to an overall lack of comprehensive Indian studies on the concerned topic and probably also due to the lack of resources essential for establishing the diagnosis in some genetic disorders. The most recent study by Jauhari, *et al.* [22] with an etiologic yield of 54.1% in 122 patients has been reported from a pediatric neurology setting with a different cohort and diagnostic armamentarium. A study done recently by Tikaria, *et al.* [21] has reported a diagnostic yield of 73%, but they restricted their population to less than 5 year olds. Therefore, the results from the above studies may not be generalizable in contrast to our study where we enrolled children of all ages from both pediatric inpatient and outpatient department (including the genetic clinic), with/without autism. Moreover, our study used wider range of genetic investigations like array CGH and MLPA, which have not been used in previous studies.

With the use of sophisticated tests, we found that genetic causes represented the most common cause of ID. Our etiological spectrum resembles that in most of the Western studies and also the study by Tikaria, *et al*. [21]

WHAT IS ALREADY KNOWN?

- Etiological yield in cases with ID is low and perinatal causes predominate in developing countries.

WHAT THIS STUDY ADDS?

- The etiological spectrum of ID in a tertiary care centre from India resembles that in the Western countries with genetic causes being common.
- A judicious use of a battery of targeted investigations can significantly improve the yield in ID.

with a similar design unlike the study by Jauhari, *et al* [22] where perinatal causes constituted the most common category. This may be explained by the population characteristics as children were enrolled from a neurology clinic.

Features like microcephaly, dysmorphism and focal neurological deficit have been shown to be predictors of etiological yield in most of the studies [13,16, 20,22]. This is in contrast to our study where none of the above features were found to be significant. The reasons for this disparity are not clear. It might be explained by the characteristics of our undiagnosed group which was very small compared to the diagnosed group (18 *versus* 83); therefore the two groups were not comparable. Of the undiagnosed group, 44% children were dysmorphic and did not identify with any known syndrome. They could have represented the new genetic disorders resulting from high prevalence of consanguinity in our patient population. However, array CGH, which might have given a clue to diagnosis, could not be carried out in these patients due to financial reasons.

MRI when done on a screening basis, was abnormal in 44% but yielded a specific diagnosis in only 8% of those who were screened. This is in accordance with AAP recommendations [23] that although MRI is often useful in the evaluation of a child with ID, it is not a mandatory study and has a higher diagnostic yield when indications exist. In almost all the investigations, yield was high except MLPA and EEG. EEG was done in all patients with seizures but it helped in making a specific diagnosis of epileptic syndromes in only 3/39(7.6%). MLPA detects subtelomeric rearrangements, too small to be detected by conventional cytogenetic analysis. It is based on PCR amplification of ligated probes hybridized to chromosome ends. It was done in ten patients with dysmorphism in whom karyotype was normal. It revealed 18q subtelomeric deletion in 1 patient. In a recent study carried out by Mandal, *et al* . [24], MLPA was found to be abnormal in only 3 (4.6%) out of 65 cases of idiopathic ID, thus confirming the lower diagnostic yield of MLPA in unexplained ID.

Array CGH scans the genome with a high resolution, for small chromosomal aberrations (gains/losses) or copy number variants (CNV), which are not detected on conventional karyotyping [25]. In a recent study by Shoukier, *et al.* [26], pathogenic CNVs were found in 13.2% of 342 children with idiopathic ID. Due to financial issues, array CGH could be done in only five patients with dysmorphism who had inconclusive LDDB search, normal karyotype and normal MLPA. It revealed causal diagnosis in three of them. If we had evaluated the entire undiagnosed group, our estimates on the true yield of array would have been more realistic. In the last few years, array CGH has emerged as a first tier test in the context of a child with unexplained ID and multiple congenital anomalies. It is also important for the continued discovery of new genetic syndromes.

The strength of our study was a stepwise approach for making a diagnosis using a wide array of advanced genetic investigations in a representative population of children with ID. We admit that we report a higher number of metabolic cases due to increased referrals to the unit. Also, the sample size was small as the work was done over limited period of one year. Diagnosis of uncommon syndromes like Baller Gerold, Trigonocephaly C syndrome and Pai syndrome was made on the basis of LDDB search only. They could not be confirmed by investigations as they do not have a definite known genetic locus. Due to non-availability of high resolution banding, karyotype could not pick up chromosomal anomalies other than trisomy 21.

Hypothyroidism in (10.8%) patients with one patient detected at 12 years of age with isolated hypothyroidism reinforces the importance of diagnosing hypothyroidism early in life and also the need of a country wide newborn screening program for diagnosing congenital hypothyroidism.

It can be concluded that a stepwise approach should be carried out for establishing the diagnosis of ID, using technological advances over time. Further such studies are required using MLPA and array CGH in India, to elucidate the real etiological spectrum of ID in Indian children.

Contributors: SJ: conducted the study and prepared the manuscript; SK: critically reviewed the manuscript and will act as a guarantor for the study; VC: interpreted and analysed

radiological findings, was involved in planning and final evaluation of the manuscript. MJ: helped in quantification of intellectual disability, helped in diagnosing autism and in planning of the study; MK: helped in MLPA analysis and also acted as external expert for dysmorphic review and in planning and conduct of the study.; SP: did the biochemical enzymatic testing, helped in manuscript preparation; MB: did statistical analysis and in reappraisal of the manuscript; AS: contributed to the clinical workup of the cases and drafting the manuscript. All authors approved of the final manuscript.

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