Over the last half century, our country has witnessed enormous progress in medical practice. Prominent reasons for this include advancements in technology, pioneering research, and general awareness amongst practitioners. The same is true for the field of intellectual disability, which has come a long way, from being a relatively ignored field to rapidly becoming one of the more relevant ones in child health. We celebrate this welcome change by commemorating 50 years of publication of an article by Professor Sinclair on ‘Etiological diagnosis in mental retardation’ in the same journal [1]. The study, published in the summer of 1972, was remarkable at that time, as it showed a real world picture of the status of ‘mental retardation’ in India. Looking back, the assignment of a diagnosis of ‘mental retardation’ was largely clinical, based on history, examination and a few basic investigations [1]. A lot has changed since then, starting from the definition and terminology used for the medical condition. It is no longer ‘mental retardation’, removing the derogatory connotations, and replaced by a more apt term of ‘intellectual disability’ or ID [2].

The etiological diagnosis of global developmental delay or GDD (GDD/ID) is now more precise and it has changed the way these children are managed. Four major aspects of GDD/ID are being highlighted in this paper to depict the major transformation that has occurred over the last 50 years, in India and abroad. These are: definitions, the clinical spectrum, diagnostic modalities/facilities available, and the management component.

**Definitions**

*Intellectual disability:* ID is applied to children >5 years of age with significant deficits in intellectual and adaptive functioning and onset in early developmental period (<18 years). The intellectual functioning is assessed by measuring intellectual quotient (IQ) using age-appropriate standardized tests and includes individual’s ability to reason, judgement, problem solving, planning, abstract thinking, academic and experiential learning. The adaptive functioning includes person’s communication and social skills, and the ability to work independently [3,4].

*Global developmental delay:* GDD is applied to children <5 years of age with significant delay (>2 SD below the mean with age-appropriate standardized tests) in two or more developmental domains including gross/fine motor skills, cognition, speech/language, social/personal, and activities of daily living [3,4].

**Clinical Spectrum**

The advent of the new era of diagnostics has allowed for many more specific etiological diagnoses in patients with GDD/ID. The clinical spectrum of patients seeking diagnosis and management has also changed drastically, with reduction in incidence of birth-related adverse events (perinatal asphyxia, infections etc). Prominently, autistic spectrum disorders have risen multifold, even in the last decade. We looked at the spectrum of disorders in children presenting with GDD/ID at two clinics at our hospital – child development clinic and genetic clinic, and noted two different types of spectrums. The children attending child development clinic showed a varied spectrum – from pre and perinatal factors to genetically determined GDD/ID. The spectrum today is starkly different from what it was 50 years ago. Previously, etiological factors were divided simply into natal, post-natal and multiple factors. The
autistic spectrum disorders find no mention in 1972 data, but were seen in at least 28% of children in child developmental clinic presenting with GDD/ID. ASD is increasingly being recognized to occur, either alone or in associated with GDD today. Indian guidelines recommend that each child with GDD be screened for ASD at initial diagnosis and again at 3 years of age [5]. Other notable differences from the previous study [1] were the significant reduction in cases with congenital infections or teratogenicity [1]. Birth related events also seem to have reduced, but prematurity and low birth weight continue to be a significant part of GDD group. In a consecutive sample of 100 children with GDD presenting to our genetic clinic, 38% had no etiological diagnosis. Of the remaining 62, 18 had chromosomal disorders (Down syndrome in 10, other microdeletion syndromes), 11 had an inborn error of metabolism, 30 had other confirmed monogenic causes, and 4 were identified to have an imprinting disorder (PWS/Angelman syndrome). This shows the vast improvement in genetic diagnosis and refinement in diagnosis that is possible today. In the older study, Down syndrome and Turner syndrome were the only chromosomal disorders mentioned, with no microdeletions. The inborn errors of metabolism that were observed in the older study were homocystinuria and phenylketonuria, which were diagnosed non-specifically using basic urine chemical tests, whereas presently such cases are being genetically and biochemically proven, and may be a spectrum from MTHFR deficiency, glutaric acidemia type 1, phenylketonuria and arginase deficiency.

**Diagnosis of GDD/ID**

**Evaluation of a case of GDD/ID**

*Screening*: Recent guidelines give developmental surveillance and screening recommendations for pediatricians to assess children with GDD/ID. It is recommended to do developmental surveillance which includes detailed history and examination at routine immunization visits by primary pediatrician till two years of age [5]. The commonly used developmental screening tools include Denver developmental screening test (DDST-II), Developmental Profile (DP), and Ages and stages questionnaire (ASQ).

*Developmental assessment tests*: Significant advances have taken place in tools for developmental assessment. A formal developmental assessment is indicated after initial screening, and is performed using age-appropriate standardized tests. Various developmental assessment tools are now available e.g., Weschler intelligence scale for children (WISC) and its Indian adaption Malin’s intelligence scale for children (6-18 years), Binet Kamat Test of Intelligence (BKT) (>3 years), Development Assessment Scale for Indian Infants (DASII) (<30 months), and Vineland Social Maturity Scale (VSMS) (<15 years) [3,5]. The children with GDD/ID are classified into mild (IQ ≥ 50-69), moderate (IQ ≥35-49), severe (IQ>20-34) and profound (IQ < 20) (ICD-10) [6].

**Assessment of Comorbidities**

Increased knowledge and awareness in care and management of GDD/ID has made it mandatory to assess for comorbidities today. The common associated comorbidities include seizures, ASD, vision impairment, and hearing impairment. A comprehensive evaluation for these associated comorbidities needs to be done in every child with ID/GDD. Neuroimaging is often indicated, based on history and physical examination e.g., abnormal head size, neurocutaneous stigmata, and seizures. Magnetic resonance imaging (MRI) with MRS (magnetic resonance spectroscopy) is preferred over computerized tomography (CT) scan [4,5]. None in the older study had any MRI or CT scan done, and the only radiological investigation performed in almost all cases was X-ray of the skull [1].

**Diagnostic Tests**

The field of diagnostics has evolved significantly in the last half century. The diagnostic tests mentioned in the 1972 study were limited to basic urine metabolic tests (e.g., ferric chloride), X-rays, serological tests for congenital infections, and karyotyping, which was only performed wherever indicated [1].

The etiology of ID/GDD is now understood to be quite heterogeneous with nearly equal contribution acquired and genetic causes, a thorough investigation is mandated. Genetic causes contribute up to 50% cases of GDD/ID. Sometimes an early postnatal injury can mask an underlying genetic cause [4,5]. The genetic etiology of ID is highly diverse, including cytogenetic abnormalities affecting the entire chromosomal to sub-microscopic copy number variants and single nucleotide variants in single genes. The genetic tests utilized are as follows:

*Conventional genetic tests*: The genetic testing can be approached in two ways. It may be phenotype driven or performed upfront as a blanket testing with use of molecular and cytogenetic tests. It is phenotype driven when history and examination is highly suggestive for a recognizable syndrome e.g., Down syndrome. In such a scenario, targeted testing can be offered such as conventional genetic tests like karyotyping for Down syndrome, fluorescent in situ hybridization (FISH)/ Multiplex ligation probe amplification (MLPA) for as targeted copy number variants e.g., 7q11.23 del, 22q11.2 del and PWS/Angelman syndrome. Karyotyping has a diagnostic yield of 3% excluding Down syndrome. Fragile
X syndrome accounts for 2-7% cases of ID based on patient selection and can be tested by methylation studies/triplet-primed PCR [5].

**Chromosomal microarray (CMA):** In 2010, American college of Medical Genetics and Genomics (ACMG) recommended chromosomal microarray (CMA) as a first-tier test in children with unexplained ID/GDD and congenital anomalies [7]. The diagnostic yield of chromosomal microarray is between 14-20% in different studies and similar yield of 14.2% is reported from India [8].

**Next generation sequencing (NGS):** Over the past two decades, massive parallel sequencing based next generation sequencing (NGS) technology has entered as the newer diagnostic frontier for ID. The reported yield for large gene panels and exome/genome sequencing is between 8-20% [9,10] and 25 to >50% [11-13] in different studies. In 2021, ACMG expert panel recom-mended exome sequencing/genome sequencing (ES/GS) can be considered as a first or second tier test for pediatric patients with ID/GDD/congenital anomalies [13].

However, there remain many challenges with genetic testing in India, including cost of testing and un-availability of tests at many centers.

**Testing for inherited metabolic causes:** Testing for metabolic disorders is indicated based on neonatal screen, family history, consanguinity, neuroregression, episodic decompensation, physical examination (coarse facies, rash, peculiar odor), and neuroimaging. Biotinidase deficiency is a common treatable cause of ID and should always be ruled out. The other metabolic tests are ammonia, plasma amino acids, urine organic acids etc.

**Treatable GDD/ID**

The recognition of ‘treatable’ ID now forms major part of the management of GDD/ID, as there is more focus on treatment as compared to before. Treatable ID App is a digital tool launched in 2012, and recently updated in 2021, which provides information to clinicians on inherited metabolic causes of ID which are amenable to treatment [14]. The App provides information on 116 inherited metabolic disorders causing ID which have treatment available in form of nutritional therapy, pharmacological therapy, supplementation of vitamins/trace elements, hematopoietic/stem cell transplant, enzyme replacement therapy and gene-based therapy [14].

In conclusion, after a long and hard journey over the last 50 years, we are now in a good position. There is far greater understanding about intellectual disability and global developmental delay. We have many more resources to dig deep and determine the etiology which then enables us to provide a more accurate and meaningful treatment. With vast expansion of the ‘treatable ID’, we can look forward to an era of newborn screening in our country, where at least the common and easily treatable disorders would be screened for, to give a better disease-free life to our future children. In the developed world, newborn screening has expanded in recent decades to >50 disorders and is already preventing deaths and disabilities in millions of children worldwide. With this note, we look forward to the next 50 years!

**Acknowledgment:** Dr Ashima Mehta helped in compiling the data from the child development clinic.

**Contributors:** SBM: writing the manuscript, collecting data from genetic clinic; SS: writing the manuscript, literature search; PS: collection of data from child development clinic, and assistance in writing. All authors read the manuscript and provided critical comments and suggestions to modify content.

**Funding:** None; **Competing interests:** None stated.

**REFERENCES**