Diagnosis and Management of Global Development Delay: Consensus Guidelines of Growth, Development and Behavioral Pediatrics Chapter, Neurology Chapter and Neurodevelopment Pediatrics Chapter of the Indian Academy of Pediatrics

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ABSTRACT:

Justification: Global developmental delay (GDD) is a relatively common neurodevelopmental disorder, however, paucity of published literature and absence of uniform guidelines increases the complexity of clinical management of this condition. Hence, there is a need of practical guidelines for the pediatrician on the diagnosis and management of GDD, summarizing the available evidence, and filling in the gaps in existing knowledge and practices. **Process:** Seven subcommittees of subject experts and members of Indian Academy of Pediatrics (IAP) chapter of neurodevelopmental Pediatrics and Neurology chapter, comprising of writing and expert group from among members of Indian Academy of Pediatrics and its chapters of Neurology, Neurodevelopment Pediatrics and Growth Development and Behavioral Pediatrics were constituted, who reviewed literature, developed key questions and prepared the first draft on guidelines after multiple rounds of discussion. The guidelines were then discussed by the whole group in an online meeting. The points of contention were discussed and a general consensus was arrived at, after which final guidelines were drafted by the writing group and approved by all contributors. The guidelines were then approved by the Executive Board of Indian Academy of Pediatrics (IAP). **Guidelines:** GDD is defined as significant delay (at least 2 standard deviations below the mean with standardized developmental tests) in at least two developmental domains in children under 5 years of age; however, children whose delay can be explained primarily by motor issues or severe uncorrected visual/hearing impairment are excluded. Severity of GDD can be classified as mild, moderate, severe and profound on adaptive functioning. For all children, in addition to routine surveillance, developmental screening using standardized tools should be done at 9-12 months,18-24 months, and at school entry; whereas, for high risk infants, it should be done 6-monthly till 24 months and yearly till 5 years of age; in addition to once at school entry. All children, especially those diagnosed with GDD, should be screened for ASD at 18-24 months, and if screen negative, again at 3 years of age. It is recommended that investigations should always follow a careful history and examination to plan targeted testing and, vision and hearing screening should be done in all cases prior to standardized tests of development. Neuroimaging, preferably magnetic resonance imaging of the brain, should be obtained when specific clinical indicators are present. Biochemical and metabolic investigations should be targeted towards identifying treatable conditions and genetic tests are recommended in presence of clinical suspicion of a genetic syndrome and/or in the absence of a clear etiology. Multidisciplinary intervention should be initiated soon after the delay is recognized even before a formal diagnosis is made, and early intervention for high risk infants should start in the nursery with developmentally supportive care. Detailed structured counselling of family regarding the diagnosis, etiology, comorbidities, investigations, management, prognosis and follow-up is recommended. Regular targeted follow-up should be done, preferably in consultation with a team of experts led by a developmental pediatrician/ pediatric neurologist.

Keywords: *Developmental assessment, Developmental screening, Early intervention, Intellectual disability.*

The global estimates of the prevalence of global developmental delay (GDD) range from 1-3% [1]. There are recent reports of much higher prevalence of 6.4% among children from Turkey and 8% from UAE [2,3]. In India, various studies report a prevalence ranging from 3-13%, depending upon the age group screened, tools used and geographical areas surveyed [4,5]; however, these estimates may not be a representative, as most of these studies were based only on developmental screening. GDD is reported to be 30% more common in boys as compared to girls, with the difference disappearing with increasing age [6].

The etiology of GDD is heterogeneous and can be divided into genetic and nongenetic causes, and categorized as prenatal, perinatal and postnatal according to the timing of exposure [7-9]. Genetic defects are the most common etiology occurring in nearly 30-50% of the cases, the proportion being similar in developed countries and India [10,11]. These can be classified into syndromic and non-syndromic GDD, wherein, syndromic delay clinically manifests as a typical phenotype (e.g. Down syndrome), dysmorphisms and congenital anomalies whereas, when the pathology is unknown and GDD is the only discernible feature, it is called as non-syndromic delay [12]. Potentially preventable causes like hypoxic ischemic encephalopathy (HIE) and hypothyroidism are more common causes in India as compared to developed countries [10,11,13-19] (**Table I**). As most Indian studies on GDD etiology are tertiary center based, they may be associated with a referral bias, and hence, not a true indicator of etiology in the community.

Children with GDD commonly have comorbidities, like epilepsy, visual problems, hearing impairment, sleep disturbances, motor impairment, autism, drooling, constipation and, behavioral and psychiatric problems [20-24] (**Box I**).

OBJECTIVE

These guidelines aim to provide pragmatic clinical guidelines for pediatricians on the diagnosis and management of GDD in the Indian settings.

PROCESS

The process of formulating the guidelines started in March, 2020. Subject experts and members of Indian Academy of Pediatrics (IAP) chapters of Neurology, Neurodevelopment Pediatrics, and Growth Development and Behavioral Pediatrics, were divided into seven subcommittees based on the expertise. Each group comprised of a writing team and a reviewing team. The seven subcommittees evaluated evidence on definition, etiology, clinical evaluation, investigations, management, neurological co-morbidities, and prognosis of children with GDD. Each subcommittee reviewed literature, developed key questions, analyzed published studies and prepared draft guidelines for their respective topic after multiple rounds of discussion. Subsequently, the guidelines and their evidence were discussed by the whole group in an online meeting held on 21 December, 2020. Points of contention were again discussed through multiple rounds of discussions via Google forms, online meetings and emails. Final guidelines were then formulated by consensus. These were approved by all experts and then approved by the Executive Board of Indian Academy of Pediatrics.

GUIDELINES

Definition

GDD is defined as a significant delay in two or more of the following developmental domains: gross/fine motor, speech/language, cognition, social/personal, and activities of daily living. Significant delay is defined as performance being two or more standard deviations lower than the mean, on age-appropriate, standardized norm-referenced testing [1,7]. However, strict adherence to this definition i.e., involvement of any two domains may allow children with developmental delays but intact cognition to be also labelled as GDD. Many guidelines, especially those on etiological workup, consider GDD to be a precursor of intellectual disability (ID). The term GDD has come into popular use as a surrogate label because of the difficulties in agreeing on the objective measurement of intelligence in a consistent, reliable, and valid fashion in the young child (<5 year). Typically, these children have delay across all domains.

The diagnostic category of GDD has been included for the first time as a subcategory under ID in the 5th edition of Diagnostic and Statistical Manual of Mental Disorders (DSM-5) and is to be diagnosed when an individual younger than five years of age fails to meet expected developmental milestones in several areas of intellectual functioning and is unable to undergo standardized testing for the same [25]. DSM-5 also recommends reassessment of these children after a period of time.

Although both GDD and ID share common features, and at their core, represent a disorder of cognition, it is important to understand that not all children who meet criteria for GDD go on to develop ID later. Reasons for this might include maturational effects, a change in developmental trajectory (due to an intervention), reclassification to a different disability category, or an imprecise use of the GDD diagnosis initially [26]. As lack of stimulation is a known key risk factor for poor child development and efficacy trials have shown structured psychosocial interventions to successfully mitigate developmental deficits, these children should be provided appropriate stimulation before being labelled as GDD [27,28]. **Web Table I** summarizes the differences between GDD and ID [1,8,9].

GDD has been earlier classified into three grades of severity based on developmental quotient (DQ) [19]; however, the Rights of Persons with Disability Act of India (RPwD Act) has classified it in line with ID as mild when social quotient (SQ) is 55-70, moderate: 36-54, severe: 21-35 and profound <20, respectively, based on adaptive functioning [29].

Guidelines

1A GDD is defined as significant delay (atleast 2 SD below the mean with standardized tests) in at least two developmental domains from the following: gross or fine motor, speech/language, cognition, social/personal and activities of daily living in children under 5 years of age. Even though cerebral palsy or other neuromotor impairments as well as visual impairment/hearing impairment are common comorbidities with GDD, children whose delay in two or more domains can be explained primarily by motor delay or severe uncorrected visual/ hearing impairment may need to be excluded from the diagnostic label of GDD.

1B Children with developmental delay and coexistent psychosocial deprivation should be provided stimulation and reassessed after 6-9 months, before being diagnosed as GDD.

1C Severity of GDD can be classified as mild, moderate, severe and profound based on adaptive functioning when social quotient (SQ) is 55-70, moderate: 36-54, severe: 21-35 and profound <20, respectively.

Developmental Surveillance and Screening

Developmental surveillance includes documenting the developmental history, eliciting parental concerns and performing developmental examination, whereas developmental screening refers to use of a brief standardized tool for identifying risk of developmental disorders [30]. For developmental surveillance, primary pediatrician can assess the age of attainment of milestones and presence of any developmental red flags [31]. Universal developmental screening can be done in community by non-specialists after undergoing training. For developmental screening, preference should be given to norm-referenced tests, which assess multiple domains. Psychometric properties and feasibility of use are other important parameters to consider while evaluating the suitability of the developmental screening tool for a given setting. For screening/surveillance of preterm babies, corrected gestational age is used till two years of chronological age. Developmental screening tools that are commonly used in India are listed in **Web Table II** [32-36].

Autism screening: Autism spectrum disorder (ASD) and GDD are not only common comorbid conditions but children with isolated ASD without involvement of cognition may even get a diagnosis of GDD, in view of delay in ≥2 domains (personal-social and language). Autism screening and early diagnosis is important for instituting specific interventions that have been documented to improve the long-term prognosis of ASD.

Guidelines

2A For all children, routine developmental surveillance should be done till two years of age during every immunization visit using questions specifically related to current age-appropriate milestones.

2B In addition, developmental screening using standardized screening tools should be done at 9-12 months, 18-24 months of age, and at school entry.

2C For high risk infants, in addition to surveillance, developmental screening should be done at 4-6 months, 9-12 months, 18-24 months and yearly till 5 years of age; and once at school entry.

2D Children diagnosed as GDD should be screened for ASD at 18- 24 months (as per the routine ASD screening guidelines for all children), and if screen negative, again at 3 years of age.

Clinical Evaluation

Comprehensive clinical evaluation remains the cornerstone for identification of etiology, associated co-morbidities, and assessment of developmental status as well as for planning intervention in children with GDD (**Fig.1**). The assessment of developmental status in various domains by a pediatrician can be used to provisionally diagnose GDD- as a delay in ≥ 2 domains (DQ < 70), for initiating timely management. The child should; however, be referred to the experts at the slightest suspicion, even if clinical assessment is not possible.

The definitive diagnosis of GDD requires norm-referenced standardized tests of development which are to be administered by trained personnel. The choice of tests in the Indian context is limited because most of the tests are norm-referenced for the Western population, and the norms for available Indian tests have not

been revised for more than 20 years. The severity of the GDD is assessed by using standardized tools for adaptive behaviors. The adaptive behaviors are social, communication and motor skills used for day-to-day functioning of an individual. The commonly used developmental and adaptive behavior tests are given in **Web Table III** [37-44]. The ones most commonly in use in India are Developmental Assessment Scale for Indian Infants (DASII), Bayley Scale of Infant Development (BSID), and Vineland Social Maturity Scale (VSMS).

Guidelines

3A A detailed history and clinical examination for assessment of developmental delay, etiological risk factors and comorbidities should be recorded as accurately as possible.

3B Definitive diagnosis of GDD should be based on the results of standardized tests of development.

Investigations

The aim of investigations is to establish the etiology, especially the treatable conditions, understand the recurrence risk, and identify the co-morbid conditions. Investigations are prioritized for the identification of treatable conditions, keeping in mind the clinical clues, essentiality of the investigation, and availability of resources.

Vision and hearing: Severe visual and hearing impairment can manifest as delay in multiple domains, as well as exacerbate the existing developmental problems and impact results of developmental testing. Visual assessment includes a comprehensive ophthalmologic examination including visual acuity, fundoscopy and extra-ocular movements. Visual evoked potential (VEP) is indicated in suspected cases of cerebral visual impairment (CVI). The choice of hearing screen is based on the type of hearing loss anticipated and available resources. Otoacoustic emissions (OAE)/brainstem evoked response audiometry (BERA) screener being objective and feasible methods are considered optimal screening tools [45]. Full diagnostic evaluation with auditory steady state response (ASSR)/BERA and/or behavioral audiometry is considered, if the child fails screening tests [46].

Blood investigations: These should be targeted towards identifying treatable conditions causing GDD, amongst which hypothyroidism is the most important. Congenital hypothyroidism accounts for around 1-3% cases of cognitive delay and due to limited reach of newborn screening programs in India, may be missed easily. In addition, many associated chromosomal abnormalities e.g. trisomy 21, 45X and 22q11 deletion, have an increased risk of hypothyroidism. Early identification of hypothyroidism and its timely treatment may markedly impact the prognosis and hence is an essential investigation in all cases of GDD [1,18]. Nutritional deficiency of vitamin B12, inborn errors of cobalamin metabolism, and iron deficiency may also be associated, especially in children having a restricted diet or pica [47,48]. Apart from these, around 20-30% of children with neuromuscular disorders such as Duchenne muscular dystrophy (DMD) have associated cognitive delay, which may present with GDD before other neurological deficits becomes obvious. Measurement of serum creatinine kinase (CPK) may aid in screening for these disorders [49]. Serum lead levels should be done in cases where specific history of environmental exposure is present

[1,49]. Studies have shown biotinidase deficiency as an important treatable cause of developmental delay and therefore, should be considered in these children even without characteristic clinical markers, more so in the absence of widespread routine newborn screening in India [50].

Neuroimaging: Abnormalities in neuroimaging may be seen in 30-70% cases with GDD [49]; however, its contribution towards an etiological diagnosis range from 10-40% [51]. Yield of neuroimaging increases two- to five-fold when neurological abnormalities like abnormal head size, seizures and abnormal neurological findings are present. For children with mild GDD without any motor abnormalities or specific clinical features, neuroimaging may be deferred. Plain magnetic resonance imaging (MRI) or computed tomography (CT) is usually sufficient for evaluation of GDD. MRI has been found to have a higher sensitivity than CT in detecting abnormalities and is the preferred modality. However, sequential use of CT followed by MRI should be discouraged. Mitochondrial disorders and cerebral creatine deficiency syndromes are additional treatable condition, which may be picked on proton magnetic resonance spectroscopy (MRS) [49,51–53].

Electroencephalogram (EEG): It is indicated in patients where history or examination is suggestive of epilepsy or an epileptic syndrome. Although, the evidence is limited, children with CVI are at higher risk of underlying epileptic encephalopathy and may warrant an early EEG.

Metabolic testing: It is amongst the second line investigations and is considered in cases of GDD where neonatal screening has not been done, there is history of consanguinity, family history of a similar illness or unexplained miscarriages, developmental regression, episodic decompensation or examination findings suggestive of a specific etiology [54,55].

Genetic testing: Studies show that genetic etiology may be identified in 30-50% of cases of GDD based on the patient selection and techniques utilized [50]. Due to the presence of large number of tests in the armamentarium to identify a genetic etiology, often it is a challenge to choose an appropriate test and patients may undergo several tests before a conclusive diagnosis is reached [52]. The family needs to be counselled that despite undergoing all possible tests, etiology may still not be established. This is important as many of these tests are expensive and may reveal inconclusive or uncertain findings [53,54]. These guidelines focus on choosing an appropriate test based on the history and clinical phenotype of the patients but with a caveat that there is a considerable overlap at times and clinical classification may be difficult in many scenarios.

It is important that the treating clinicians identify common genetic disorders early, based on the clues (**Web Box I**) and advise the parents regarding the need for genetic testing, which may be done locally, if available, and/or do timely referrals to experts who can interpret the results and provide information about variant interpretations and secondary findings. Some of these disorders may require early therapeutic intervention and majority may benefit by early intervention and management of co-morbidities. Moreover, in a significant proportion of cases, recurrence can be prevented by counselling and prenatal testing if a specific genetic etiology is identified.

Web Table IV summarizes various techniques, indications of their use, yield and important advantages and pitfalls [51,52,55-58]. A simplified approach for genetic testing in GDD/ID is depicted in **Fig. 2** and approach towards genetic evaluation of GDD according to the level of care, is shown in **Fig. 3**.

Guidelines

4A Investigations should always follow a careful history and detailed examination to plan targeted testing, wherever required.

4B Vision and hearing screening are recommended in all cases especially before subjecting the child to standardized tests of development.

4C Neuroimaging is recommended when specific clinical indicators are present. If available, MRI/MRS should be obtained in preference to CT scan.

4D EEG is recommended only in children with clinical suspicion of epilepsy or epileptic syndromes.

4E Biochemical and metabolic investigations should be primarily targeted towards identifying treatable conditions causing/associated with GDD.

4E.1 Evaluation of thyroid function should be considered in all children with GDD, especially in the absence of documented newborn screening results. The tests may need to be repeated at regular intervals in children who are at high risk (e.g. Down syndrome) or have symptoms suggestive of hypothyroidism.

4E.2 Biotinidase deficiency should be ruled out, especially in absence of newborn screening.

4E.3 Iron and B12 deficiency should be considered, even in the absence of other pointers.

4E.4 Lead levels are recommended in cases with risk of environmental exposure.

4E.5 Creatinine phosphokinase (CPK) is recommended in young boys with unexplained GDD.

4F Appropriate genetic tests are recommended in presence of clinical suspicion of a genetic disorder and/or in the absence of a clear etiology.

Management

Early intervention for high-risk newborns

In all cases, the mainstay of treatment is early detection and early intervention. Evidence suggests that developmentally supportive care in neonatal intensive care unit (NICU) setting could have significant effect on mental and motor development of preterm infants, at 12 and 24 months of age [59]. The core measures of developmentally supportive care include protected and maintained sleep rhythms, pain and stress assessment and management, positioning and handling, protecting the skin, provision of a healing environment, and family-centered care [60].

Management of treatable causes

In addition to common treatable causes like congenital hypothyroidism and nutritional deficiencies, around 116 treatable inherited metabolic disorders (IMDs) causing GDD/ID have been identified, and the number is increasing with the advent of new technologies [61]. Even though these IMDs are rare, identification and early implementation of specific therapy can improve developmental outcome, halt progression of an

ongoing developmental delay and lead to improvement in associated comorbidities like seizures [62]. An app is available for the clinicians for more information on treatable IMDs (*https://treatable-id.org/about.html).*

Healthcare interventions

Infants and young children with developmental difficulties need access to primary health care just like other children of same age including components of early childhood development (ECD), which are good health (immunization, dental care and treatment during illness), optimal nutrition, opportunities for early learning, responsive parenting, and safety and security [63]. Growth monitoring is done using the usual growth charts; however, special growth charts are to be used in those with syndromes like Down syndrome and Prader-Willi syndrome [64-66]. **Table II** briefly outlines the health care interventions for children with GDD.

Early developmental interventions

Studies have shown that early intervention in children with developmental disabilities improves their developmental potential and functioning, and also benefits caregivers and families [67,68]. This requires a multi-disciplinary team consisting of developmental pediatrician/pediatric neurologists, clinical psychologists, occupational therapists, physiotherapists, special educators and speech therapists. The goals and specific treatment modalities should be individualized, depending on the cause and severity of GDD. In case of non-availability of a multidisciplinary team, the primary pediatrician can advise parents about simple stimulation activities, till the child is seen by domain experts [69]. General principles of developmental intervention are outlined in **Box II**, and the activities for developmental intervention and stimulation in various domains have been described in the Mother and Child Protection (MCP) guidebook of Government of India (*https://nhm.gov.in/New_Updates_2018/NHM_Components/Immunization/Guildelines_for_immunization/MCP_Guide_Book.pdf).*

Management of problem behaviors

Studies indicate that young children with developmental delays are 3-4 times more likely to exhibit behavioral problems as compared to their typically developing peers [70,71]. Common behavioral problems observed in these children include severe tantrums, aggression, non-compliance and hyperactivity [72]. These behavioral problems impede the child's learning, and add to the stress of the family [73]. A flowchart for managing behavioral problems is given in **Fig. 4**.

MANAGEMENT OF CO-MORBIDITIES

The common comorbidities of GDD are discussed here briefly and guidance on management is provided in **Web Table V**. For detailed information on each condition, specific guidelines should be followed or expert opinion solicited.

Epilepsy: Around 15 – 30% of children with GDD have a risk of developing epilepsy as compared to 4% in general population and the prevalence increases with increasing severity of GDD. Refractory epilepsy and some epileptic encephalopathies can themselves contribute to developmental delay as well as impair the gain in milestones in those with manifest GDD. The diagnosis of seizure in a child with GDD may at times be

difficult. Some seizure manifestations such as staring spells, myoclonic seizures and astatic seizures may be subtle and can be missed. On the other hand, dystonic posturing may be misdiagnosed as a seizure. Important associated epileptic encephalopathies include epileptic spasms (West syndrome) and Lennox-Gestaut syndrome. Early diagnosis of epileptic spasms is important as the time-lag from onset of symptoms to treatment significantly impacts developmental outcomes and response to treatment. Broad principles of treating epilepsy in children with developmental delay are the same as any child with epilepsy. The choice of antiepileptic medications depends on the ease of availability and safety profile of the drug. Usually, cognitive and behavioral abnormalities in these children are attributed to the effect of antiepileptic medications. Though, there is a lack of robust data on these effects, drugs with better neurocognitive profile may be preferred in these children.

Febrile seizures: Children with GDD are at a greater risk of having recurrent febrile seizures, febrile status epilepticus and progression to future epilepsy [74]. The risk of future epilepsy increases when there is presence of complex febrile seizures and/or family history of epilepsy**,** and in such cases, abnormal EEG may be helpful in establishing prognosis for development of later epilepsy [75,76]. Factors responsible for the increased risk of recurrence of febrile seizures are similar in these children when compared with their typically developing peers [77,78]. As for any other child, intermittent prophylaxis is considered when the risk of recurrence of febrile convulsion is high [79].

Visual deficits: The prevalence of visual problems in children with developmental delay has been reported to range from 15-75% [82]. Refractive errors are the commonest and seen in approximately 50% of cases [80]. Other common deficits include strabismus, optic atrophy, nystagmus and CVI [22,80,81]. As vision is central to early learning, social interaction and motor development; early identification and treatment of visual impairment is crucial. Studies have documented improvements in motor skills and social behaviors after correction of refractive errors in children [82]. At present, there is no standard treatment for CVI, and data regarding functional visual outcomes is limited; however, children with CVI and other low vision conditions may benefit from environmental modifications to promote visual functioning [46]. These include a simple visual environment to avoid overcrowding and utilizing objects with color, high contrast and motion to facilitate visual recognition [83].

Hearing impairment: Prevalence of hearing impairment in GDD ranges from 10-17% [20]. Few studies have shown that the children having mild to moderate GDD with comorbid hearing impairment may also have some improvement after timely cochlear implant, even though they may not achieve their full language potential [84].

Sleep disturbances: these are common and predispose children to behavioral and cognitive impairments. Causes for disturbed sleep include regulation problems, alteration of sleep-wake cycle due to anti-seizure and sedative medications; and obstructive sleep apnea due to co-morbid conditions like Down syndrome, obesity, pseudobulbar dysfunction or hypotonia. The first line of management is promotion of improved

sleep habits or sleep hygiene [85]. When these are not effective, melatonin administered around 3-4 hours before tentative bed time may be considered.

Cerebral palsy: It is a common co-morbidity occurring in 8-30% of children with GDD and should be managed as per standard treatment [20,86].

Learning issues: The underlying condition, subnormal DQ, and the comorbidities may hinder learning and delay schooling for children with GDD to a varying level. The Right to Education Act (RTE) stipulates that children with disabilities receive their educational services appropriate to address their educational needs in the least restrictive environment possible. The extent of inclusion may depend on the level of delay, the severity of associated comorbid conditions, and maladaptive behaviors like aggression and self-injurious behaviors. The services of special education teachers may be helpful for individualized intervention.

Guidelines

5A Early intervention for infants at risk of developmental delay should start in the Neonatal Intensive Care Unit (NICU) with neurodevelopmentally supportive care.

5B Potentially treatable causes of GDD should be identified and specific treatment started as early as possible.

5C Children with developmental delay should receive routine health care interventions at par with the typically growing peers, at all levels of care.

5D Early intervention should be initiated soon after the delay is recognized, instead of waiting for a formal diagnosis.

5E Screening for co-morbidities like behavioral problems, epilepsy, cerebral palsy, visual and hearing impairment, and sleep disturbances with appropriate referrals should be done to ensure timely intervention.

5F For co-morbid febrile seizures, EEG is indicated when associated with family history of epilepsy and/or complex febrile seizures. Intermittent prophylaxis is recommended in the presence of any one additional risk factor for recurrence of febrile seizure.

5G Children with GDD should receive preschool education services in the least restrictive environment that is possible and appropriate to address their needs.

Counselling

Counselling the family regarding the diagnosis, etiology, anticipated comorbidities, investigations, management, prognosis and follow-up is an important aspect of GDD management. In addition, parents should also be made aware of social support and legal provisions available.

Disclosing the diagnosis: Various studies have suggested that the parent's adaptation to their child's condition may be modulated by the way in which the diagnosis is conveyed to them. It is important to communicate the diagnosis to the family clearly and directly, in a compassionate manner, emphasizing equally the child's strengths as well as deficits [71,87,88]. Also, possibility of improvement with consistent intervention, even in severely delayed children, must be reiterated while setting reasonable expectations.

Counselling regarding investigations: As etiology of GDD is complex, patients may need to undergo several tests before a conclusive diagnosis is reached. The family needs to be counselled that despite undergoing all possible tests, which may be expensive, etiology may still not be established.

Pretest counselling: This should always be done before ordering genetic tests, which should not only include information about the various tests available but also about the possibility of unrelated genetic condition being unveiled. Many a times, a genetic variant of uncertain significance may be found necessitating review of the findings few years later in light of new information available.

Guidelines

6A It is strongly recommended that the family should be counselled regarding the diagnosis, etiology, anticipated comorbidities, investigations, management, prognosis and follow-up; once at the time of initial diagnosis, and again whenever more etiological information is available/etiology is established.

Prognosis and Follow-up

There is a scarcity of published studies which have looked at long term prognosis of GDD and this limits the ability to predict developmental outcomes precisely in these children. Based on the available literature, several factors have been found to affect the prognosis including severity of GDD, its etiology, presence of comorbidities, family's socio-economic status, age at diagnosis and initiation of intervention, availability of specific treatment for underlying etiology, and compliance to therapy. The degree of delay is the most consistent predictor of long-term prognosis with mild cases doing well in comparison to moderate-severe cases of GDD. Early intervention has been documented to minimize developmental delays with gains in adaptive, academic and social functioning. However, nearly two-thirds children will get the diagnosis of ID later in life and another 20%; even though functioning well in society, may get an alternative neurodevelopmental diagnosis.

Follow-up: it includes tracking the child's development in all domains, screening for comorbidities on a continued basis, planning additional investigations and interventions, whenever needed, parental training, and ensuring compliance. Documentation of the assessments, targets as well as therapy plan by all members of a multidisciplinary team is a must. Follow-up plan for those with manifest GDD should be customized as per the individual child's needs, as many children with GDD, especially those with moderate to severe GDD or multiple comorbidities, require frequent monitoring. Review of diagnosis should be carried out annually, at least in the initial years, to pick up possibly missed comorbid neurodevelopmental disorders. **Box III** enlists the key points to be assessed on follow-up.

Guidelines

7A Regular follow-up targeting all the developmental domains and associated comorbidities should be done. Consultation with a team of experts led by a developmental pediatrician/ pediatric neurologist may be considered, if possible. Apart from this, primary pediatrician may also play an important role in supporting the family and ensuring the compliance to therapies**.**

Rights of Persons with Disabilities Act 2016 and Disability Certification

The Rights of Persons with Disabilities Act, 2016 empowers persons with disabilities with certain rights and entitlements, legal provisions and provides a framework for assessment and certification [28]. GDD as a disability is included under the gambit of 'ID'. The Act defines ID as a condition characterized by significant limitation both in intellectual functioning and in adaptive behavior. Persons above the age of 5 years are given a diagnosis of ID, while children between the ages of 1-5 years are given a diagnosis of GDD. The minimum age for certification is one completed year. Children below the age of 5 years are issued a temporary certificate wherein a reassessment is required after a period of 3 years or at 5 years of age (whichever is earlier). Intellectual functioning is to be assessed by testing IQ on Binet Kamat test (BKT) and adaptive functioning through Vineland Social Maturity Scale (VSMS). Certification is done by the medical board headed by the medical superintendent/chief medical officer/other equivalent authority as notified by the state government and comprises of a *i)* pediatrician or pediatric neurologist, *ii)* clinical or rehabilitation psychologist, and *iii)* psychiatrist.

Role of referring pediatrician in disability certification: The pediatrician should identify GDD as well as screen for associated comorbidities (hearing/ vision/ locomotor impairments/ epilepsy) and refer accordingly for detailed disability assessment.

CONCLUSION

Preventable causes of GDD should be addressed by providing adequate perinatal care including prenatal testing for genetic disorders, care during pregnancy and postnatal care in subsequent pregnancy, preventing infections and nutritional deficiencies in children, ensuring good health, providing opportunities for early learning and, focusing on child safety measures.

Pediatricians are often the first point of contact for all children, including those with developmental delay. Early identification of the developmental delay, its management, and multidisciplinary intervention are of paramount importance, as are establishing an etiological diagnosis, identifying and treating comorbidities, and guiding the prognosis. The role of pediatrician is central in collaborating with parents and multidisciplinary teams to provide seamless coordinated care to children and their families, so as to improve their medical outcomes and social functioning.

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Table I. Etiology of Global Developmental Delay

Timing of exposure	Possible causes	Proportion of diagnostic yield	
		India	*Other countries*
Prenatal Genetic Environmental	Chromosomal aberrations (e.g. Trisomy 21)	19-20%	5 - 10%
	Monogenic (including Fragile X syndrome)	1 - 25%	3 -10%
	Multiple malformations or clinically recognizable syndromes	6 - 14%	3-10%
	Metabolic/ Inborn error of metabolism	3 - 4%	1 - 8%
	Cerebral dysgenesis / CNS malformations	10-11%	2 - 18%
	Intrauterine infection	3 - 4%	0.4 - 2%
	Toxins/ teratogens (e.g. alcohol, valproate, cocaine)	1 %	2 - 9%
Perinatal Acquired Environmental	Hypoxic ischemic encephalopathy (HIE)	14-31%	9-10%
	Neonatal complications: Bilirubin	1%	-
	encephalopathy/Meningitis/ encephalitis sequelae	2%	-
	Prematurity/ birth trauma		
Postnatal Acquired Environmental	Hypothyroidism[a]	3-11%	-
	Brain tumor	1%	1%
	Infantile tremor syndrome	1%	-
	Severe psychosocial deprivation/neglect	-	3-4%
	Nutritional deficiencies (e.g. iodine, vitamin B12, thiamine)	-	-
	Toxins (e.g. lead)	-	-
	Post Traumatic	-	-

[a] *Hypothyroidism may be found overlapping with other causes such as Down syndrome, other genetic syndromes, some inborn errors of metabolism, and secondary to maternal antithyroid antibodies*

Table II: Suggested Minimal Standard of Healthcare and Developmental Interventions for Different Levels of Facilities

Levels	*Level 1 (Pediatrician with/ without access to one therapist)*	*Level 2 (District level hospitals/DEIC/ developmental pediatrician with access to multiple therapists)*	*Level 3 (Tertiary centre with multidisciplinary team including developmental pediatrician/ pediatric neurologist and access to geneticist)*
Health Care Interventions (Routine pediatric medical and dental care)	Routine pediatric healthcare. Ensure compliance and provide follow-up care for children referred back from higher centres	Routine pediatric healthcare Ensure compliance and provide follow-up care for children	Routine pediatric healthcare Ensure compliance and provide follow-up care for children
Management of treatable causes of GDD/IEM (inborn errors of metabolism)	Management of nutritional deficiency including iron and B12 deficiency. Screening and treatment for hypothyroidism	Screening and treatment for hypothyroidism, suspect and investigate for IEMs associated with GDD	Diagnosis/ Medical management/ Specialized diets for IEMs
Identification and treatment of common dysmorphic and genetic syndromes	Identification, management and follow- up of Down syndrome	Identification, management and follow-up of common easily identifiable syndromes associated with GDD (e.g. Cornelia De Lange syndrome, neurocutaneous syndromes)	Identification, management and follow- up of all syndromic GDD
Developmental interventions	Mild GDD with no red flags. Advise appropriate stimulation activities [a] and follow-up Refer to higher level if no improvement	Management of mild to moderate GDD Multi-domain intervention	Detailed evaluation and Intervention planning for all levels of severity by multidisciplinary team [b]

[a] *Activities for developmental intervention and stimulation in various domains have been described in MCP card*

[b] *Child can be followed by referring pediatrician, and compliance with therapies and medications ensured. Children with severe problems may require continued follow-up at higher centres*

DEIC- district early intervention centre, GDD- global developmental delay, IEM- inborn error of metabolism, MCP card- mother and child protection card

Box I. Comorbidities of Global Developmental Delay

Medical Comorbidities
Neurological • Visual deficits (15-75%) • Hearing impairment (9 -17%) • Epilepsy (5-30%) • Cerebral palsy (8-30%) • Pseudobulbar dysfunction (feeding issues) (20-47%) • Sleep issues (40-80%) Non-neurological • Recurrent infections • Protein energy malnutrition (40-70%) • Drooling (45%) • Constipation (30-60%) • Nutritional anemia (5.5%)
Psychiatric/ Behavioural Comorbidities
Attention deficit hyperactivity disorder (35-40%), Autism spectrum disorder (15-20%), stereotypic movement disorders (with/ without self-injurious behaviours), mood disorder, anxiety disorder, aggression and disruptive behaviours (26%)

Box II: General Principles of Developmental Intervention

- The cardinal principle should be early intervention using multiple modalities.
- Functional skills to be taught or addressed will depend on core deficits, needs of the child and family, and associated co-morbidities. Intervention plan should be individualized, keeping in mind the child's functional level in different domains. The next immediate milestone should the target for intervention.
- As children gain skills in different areas simultaneously, congruent skills should be chosen from multiple domains at a time, therefore multidisciplinary intervention[a] is preferred. Pediatrician should ensure that all domains are being targeted during intervention
- Toys and activities should be appropriate to child's developmental age. Play should be used to teach target skills, as this helps the child learn better. The activities should be chosen such that they are difficult enough to be interesting, but easy enough to be accomplished.
- Parents and other family members should be actively involved in the process, and implement the strategies at home during daily activities.

[a]*Multidisciplinary intervention requires involvement of multiple healthcare disciplines like developmental pediatrics/ pediatric neurology, special education, clinical psychology, occupational therapy/ physiotherapy and speech therapy*

Box III Key Points to be Assessed During Follow-up

Documentation of new milestones achieved.
Improvement/ no change/ regression in the developmental domains involved in the child: involvement of a previously uninvolved developmental domain or any regression in milestones should prompt referral to secondary or tertiary level for detailed evaluation.
Screening and monitoring for anticipated comorbidities (epilepsy, feeding problems, vision impairment, hearing problems, sleep problems, autism, behavioural issues, neurological problems etc.)
Compliance with therapies and medications, and monitor for side effects, if any.
New parental concerns
Growth parameters and head circumference
Routine pediatric management including nutrition, immunization, etc. Counselling
Guide and advice regarding preschool education and disability certification and government benefits
Guide families regarding parent/ sibling training program, Non- government organizations, self-help groups
Schedule next follow-up

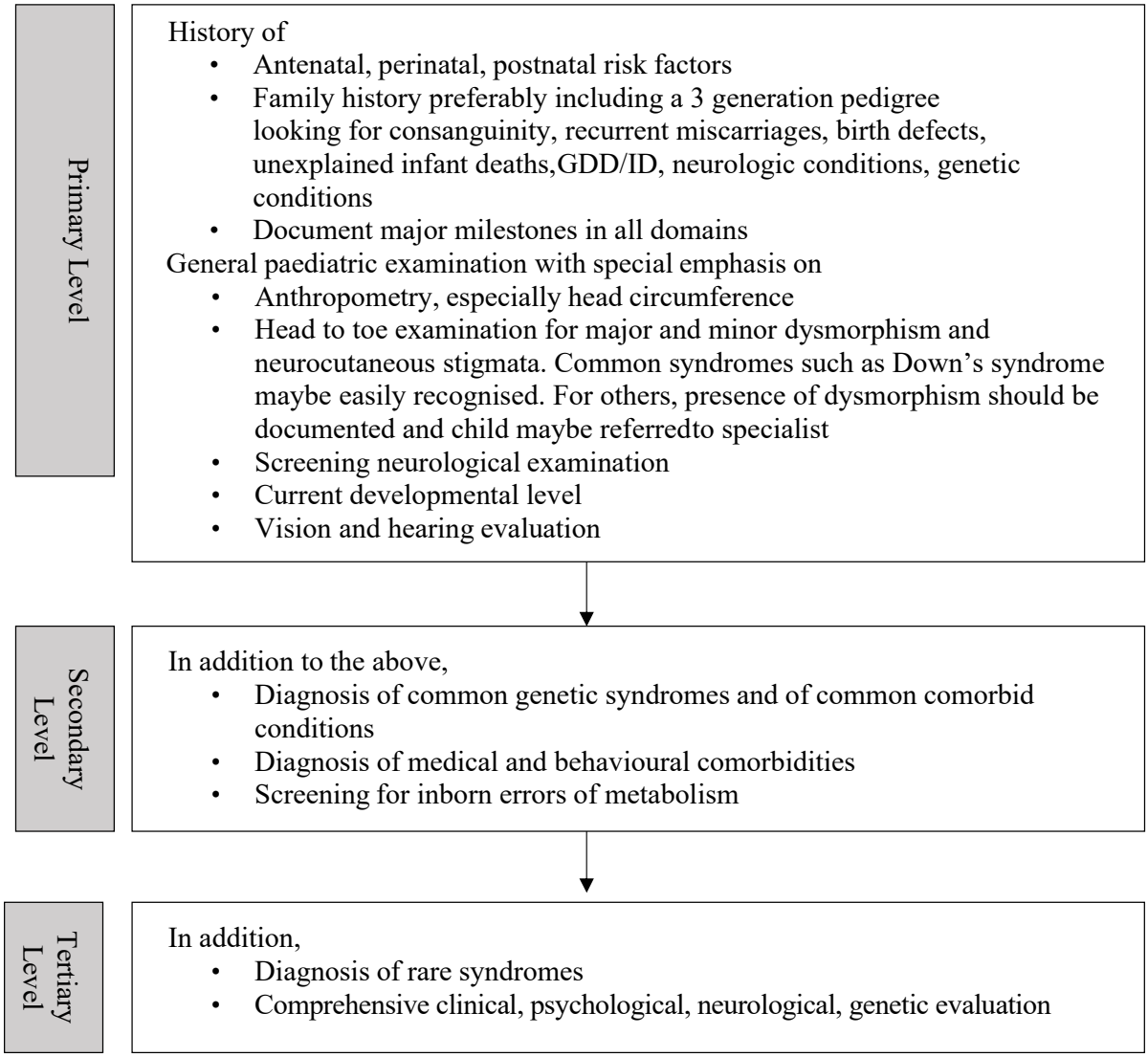
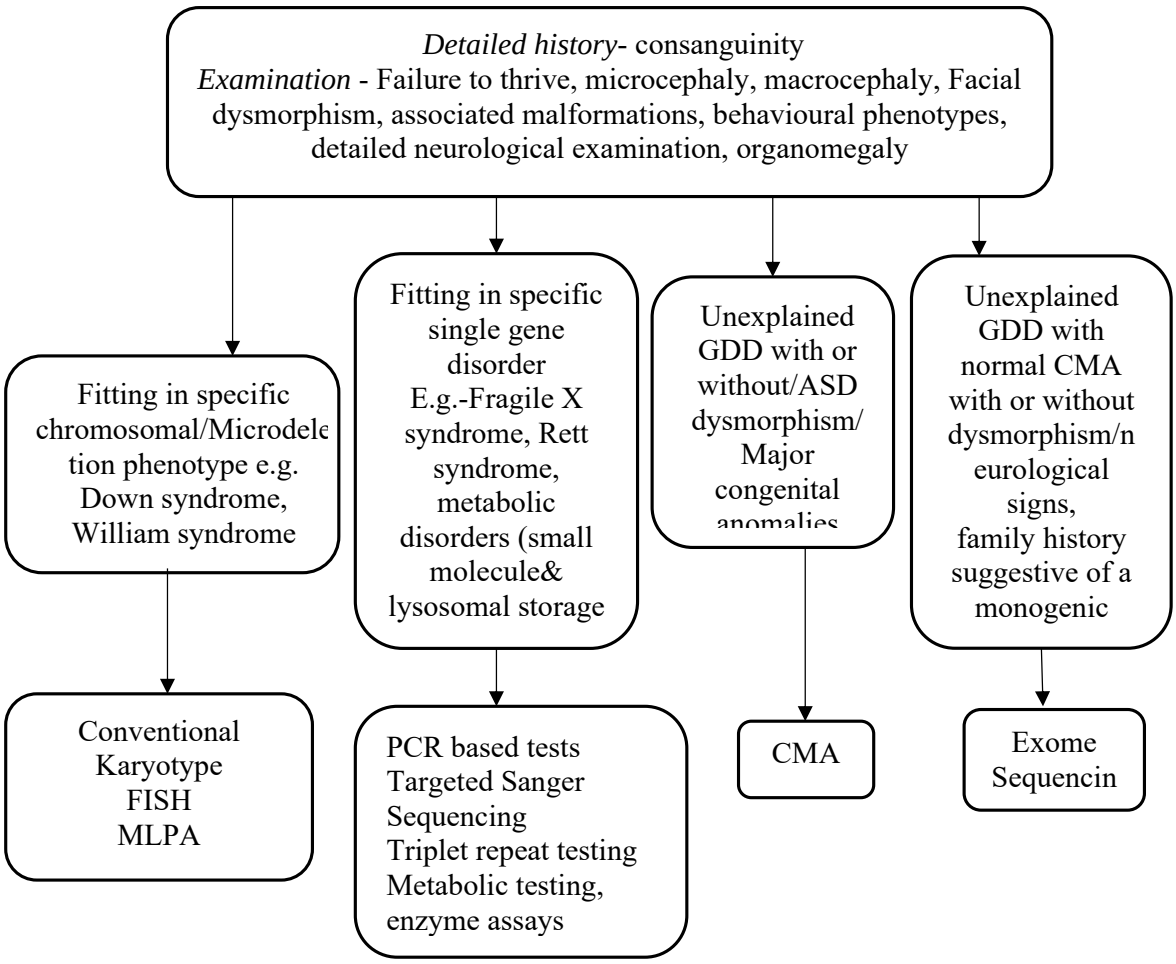
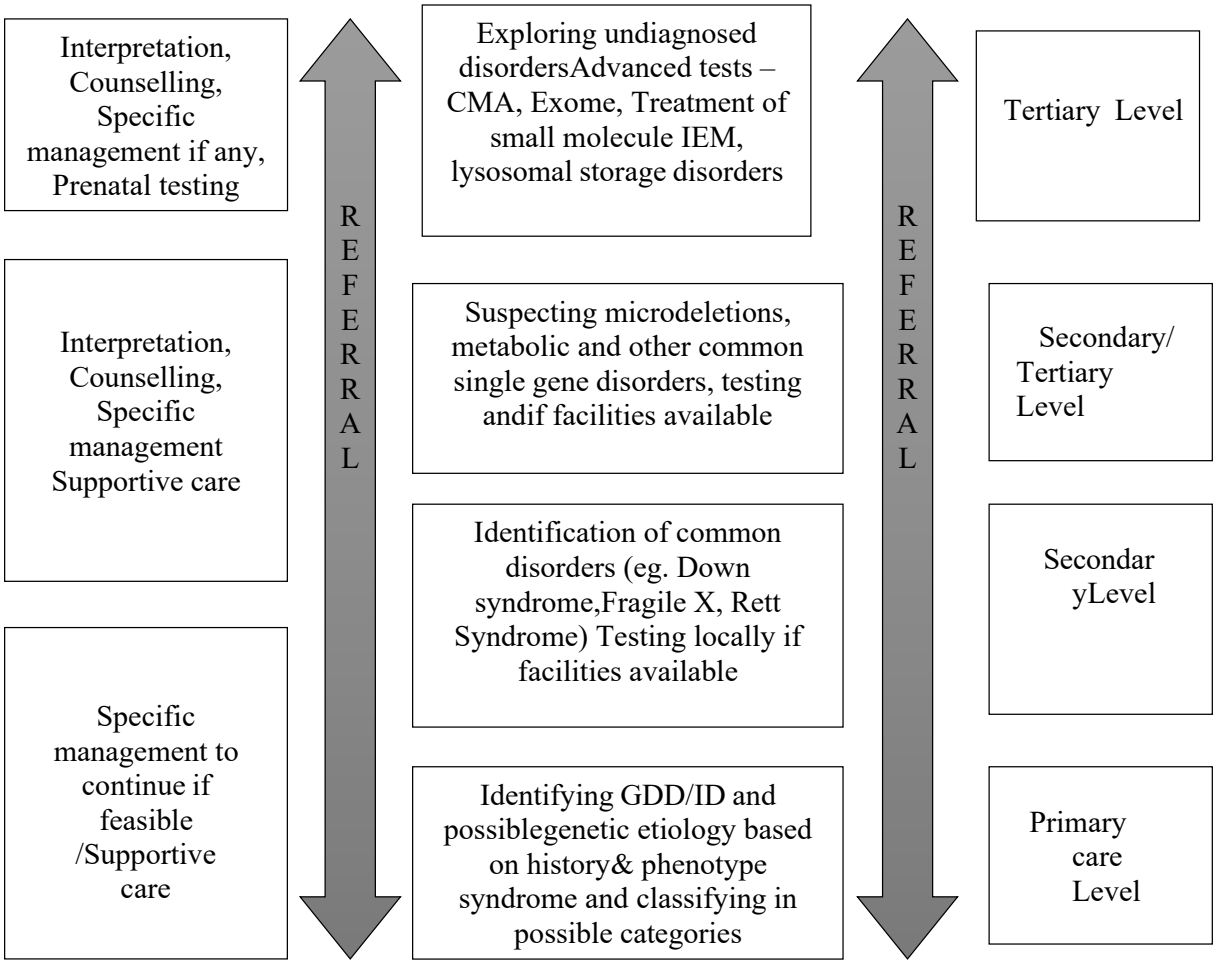


Fig.1 Clinical evaluation of a child with global developmental delay



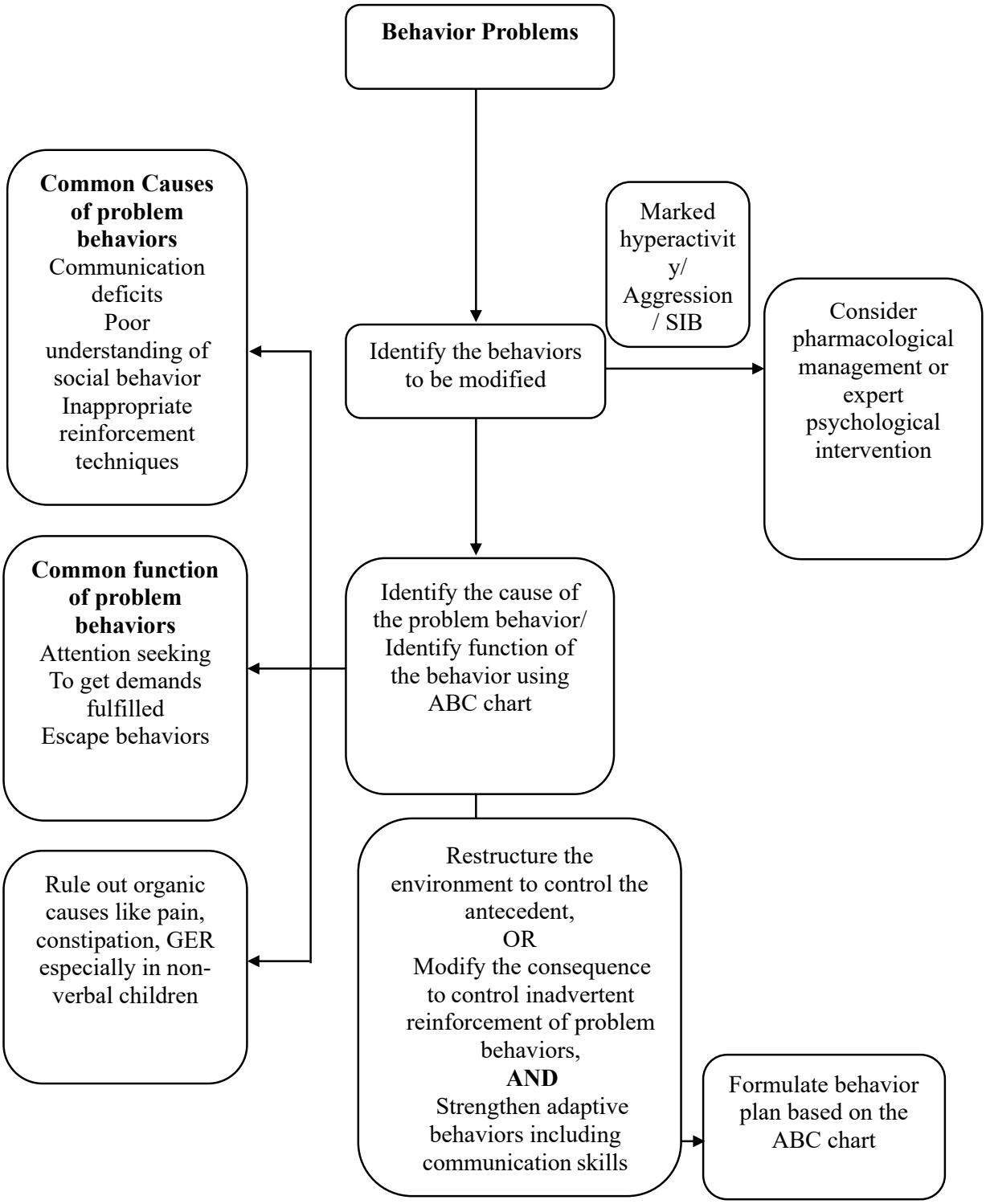
ASD- autism spectrum disorder, CMA- chromosomal microarray, GDD- global developmental delay, FISH-fluorescent in situ hybridization, MLPA-multiplex ligation probe assay

Fig.2 Approach to Genetic testing in global developmental delay



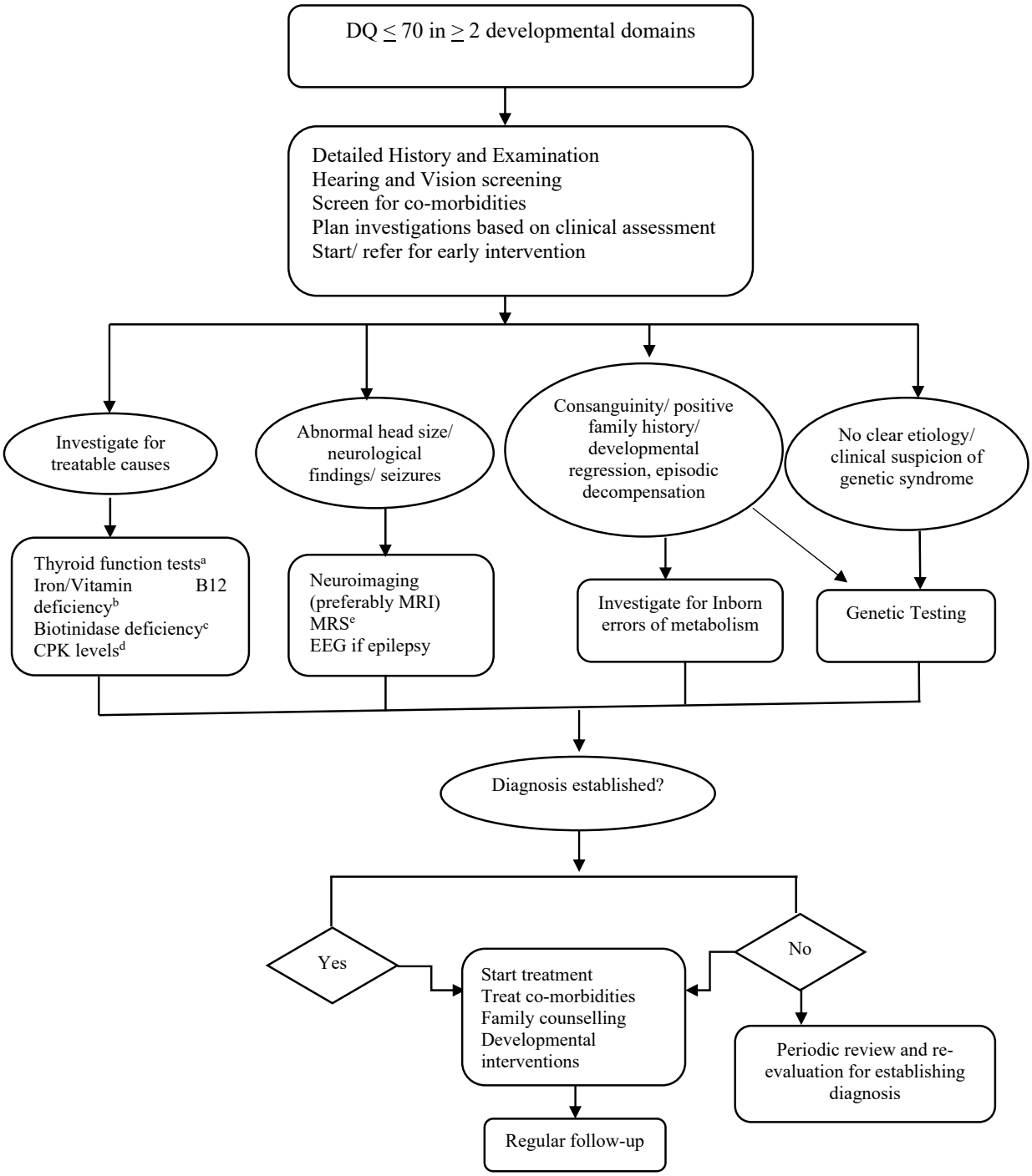
CMA – Chromosomal microarray, GDD- global developmental delay, IEM – Inborn error of metabolism, ID- intellectual; disability

Fig. 3 Genetic testing of global developmental delay at different health care levels



SIB – Self injurious behaviors
ABC – Antecedent- Behavior-Consequence (where, Antecedent is the event or situation that occurred before the behavior was shown, Behavior refers to details of the behavior exhibited and Consequence to the sequence of events immediately after the behavior)

Fig.4 Management of behavioral problems in a child with GDD



[a] *especially in absence of documented newborn screening results*

[b] *especially in children having a restricted diet or pica*

[c] *especially in the absence of newborn screening*

[d] *boys with history or findings suggestive of conditions like Duchenne muscular dystrophy*

[e] *where mitochondrial disorder is suspected or for diagnosis of cerebral creatine deficiency syndrome in children with unexplained GDD and normal MRI*

MRI- magnetic resonance imaging, MRS-magnetic resonance spectroscopy, EEG- electroencephalogram, DQ- developmental quotient

Fig.5 Approach to a child with global developmental delay

Web Table I Difference Between Global Developmental Delay (GDD) and Intellectual Disability (ID) [1,8,9]

	Global developmental delay	*Intellectual deficit*
Definition	DSM-5 reserves the term GDD for an individual who fails to meet expected developmental milestones in several areas of intellectual functioning and applies to those who are unable to undergo systematic assessments of intellectual functioning, including children who are too young to participate in standardized testing. AAN defines GDD as subset of developmental disabilities defined as significant delay in two or more of the following developmental domains: gross/fine motor, speech/language, cognition, social/personal and activities of daily living.	DSM-5 defines ID as a neurodevelopmental disorder with onset during the developmental period that includes both intellectual and adaptive functioning deficits in conceptual, social and practical domains.
Age group	Children <5 years	Applies to older children when testing of intellectual functioning is valid and reliable (usually after 5 years of age). [a]The onset is usually before 18 years of age.
Diagnosis	Based on clinical assessment and standardized testing of a child in major domains of development requires diagnostic reassessment after a period of time.	Based on clinical assessment and standardized testing of intellectual and adaptive functioning. Stable diagnosis.
Natural course	Even though most children will have cognitive impairment subsequently, not all children go onto develop ID later.	It is a permanent disability requiring supportthroughout life.

[a]*Intellectual functioning can be tested from as early as 2 years using tests like Leiters, Wechsler Preschool and Primary Scale of Intelligence (WPPSI). However, data for validity and reliability is limited below 5 years of age.*

Web Table II Brief Description of Development Screening Tests for Pediatric Office Setting [32-36]

Development Screen test	*Domains tested*	*Age range*	*Time taken*	*Administration*	*Interpretation*	*Psychometric properties*	*Ease of use and feasibility*
Domain wise screening tools							
Ages and Stages Questionnaire (ASQ)	Gross motor, fine motor, communication, problem – solving, personal – social	1-66 months; 21 age-specific forms with 30 questions	10-15 mins	Parent reported questionnaire. Can be completed by parents/ caregivers independently or with the assistance of professionals.	Risk categorization: typical/ needs monitoring/needs further assessment	Moderate sensitivity and specificity	Includes intervention activities. Training required for interpretation. Indian studies available.
Denver Development Screening Test-II (DDST)	Gross motor, fine motor-adaptive, personal-social, language. Includes 5 "Test Behavior" items	0-72 months	10-15 mins	Directly administered by a professional in a standardized manner.	Item wise pass/fail/ caution Interpreted as normal/suspect or untestable	Low to moderate sensitivity and specificity	Low sensitivity limits applicability as a screening tool.
Developmental Profile (DP)	Physical, adaptive, behaviour, communication, cognitive, social-emotional	0-12 yrs 11 months (DP 3) 0-21 years (DP- 4)	25-30 mins	Can be completed by parents themselves-checklist or by parental interview including direct observation by professional.	Provides age equivalent and norm based standard scores in each domain and a general developmental score. Risk categorization: delayed/ below average/ average / above average / well above average.	Moderate to high; correlation with Vineland-II	Gives DQ. Includes intervention activities. Training required. Expensive.
RBSK screening tool	Vision, hearing, speech, motor, cognition, social	0-6 years		Directly administered by history and examination.	Domain wise pass/ fail	Not available	Not validated. Not norm referenced.
General Screening tools which do not screen domain wise							
Trivandrum Developmental Screening Chart (TDSC)	Gross motor, fine motor/adaptive, personal-social, language	0-6 years	10-15 mins	Directly administered by history and examination.	Pass/ fail for each item. Developmental delay considered if ≥ 1 fail obtained.	Moderate sensitivity and specificity	Minimal training required. Can be used as a community screening tool.
Baroda Development Screening Tool (BDST)	Motor and mental	0-30 months	15-20 mins	Directly administered by history and examination.	Pass/ fail for each item. Developmental age as per 50% and 97% pass placement each item.	Low sensitivity, high specificity	Can be used as a community screening tool.

Web Table III Developmental Assessment Tests [37-44]

Test	*Age*	*Description*	*Advantages*
Binet-Kamat Test of Intelligence (BKT)	3 years to adulthood	Includes both verbal and performance tests	Simple to score and administer available in Hindi, Marathi and Kannada
Vineland Social Maturity Scale (VSMS)	Birth to 15 years	Assessment of social and adaptive functions or social competency	Culturally appropriate and can be used in nonverbal children; Easy and quick to administer
Development Assessment Scale for Indian Infants (DASII)	Birth to 30 months	Gives mental and motor DQ	Uses indigenous material Norms have been developed for Indian population
Bayley Scales of Infant Development – IV (BSID-IV)	16 days to 42 months	Cognitive, language, motor, social emotional, adaptive behaviour	Internationally validated tool
Mullen Scales of Early Learning	Birth to 68 months	Five scales: Gross motor, visual reception, fine motor, expressive language, and receptive language	Helps in assessing visual and auditory learning thereby enabling the assessment of cognition
Griffiths Scales of Child Development – III (Griffith's III)	Birth to 6 years	Measures six areas of development including foundations of learning, language and communication, eye- hand coordination, personal-social-emotional, gross motor	Assessment is in line with latest research, new norms address Flynn-effect
Gesell Developmental Assessment (GDA)	2 year 6 months to 9 years	Direct observation to evaluate a child's cognitive, language, motor and social-emotional responses in five components (developmental, letter/numbers, language/comprehension, visual/spatial and social/emotional/adaptive)	The overall performance level (age appropriate, emerging or concern) can be used as a guide to customize curricula and/or identify need for additional diagnostic evaluation.
Vineland Adaptive Behaviour Scale (VABS)	Birth to 90 years	Correspond scales to the three broad domains of adaptive functioning- communication, daily living skills, and socialization	Helps in measuring the capabilities in dealing with everyday life; Identifies maladaptive behaviours which may be useful for planning the behaviour intervention

DQ - Developmental quotient

Web Table IV Genetic Testing in Children with Global Developmental Delay [51,52,55-58]

Test	*Yield*	*Indications*	*Remark*
Karyotype	3-5% excluding Down syndrome	GDD/ID with specific phenotype e.g. Down syndrome, Trisomy 13, 18. Dysmorphism, Multiple congenital anomalies	Detects abnormalities more than 5-10 kb in size, operator dependent Still used in resource poor settings as first line due to relatively easy availability and less cost. Can detect balanced chromosomal rearrangements. Chromosome analysis is also indicated when there is a family history of chromosome rearrangement or multiple miscarriages because it can detect balanced chromosomal abnormalities, which CMA does not detect.
Targeted Fluorescent in situ Hybridization (FISH)	Will depend on the phenotypic accuracy for identifying the disorder	Should be offered in situations with specific phenotypes indicating a known microdeletion syndrome e.g. William syndrome, velocardiofacial syndrome, 1 p36 del., etc.	FISH probes assess a specific copy number variant (CNV) associated with a specific syndrome. When there is a strong suspicion of a specific syndrome, FISH can be done; however, if the suspected diagnosis is not cot confirmed by FISH, it must be followed by CMA to establish the diagnosis. Metaphase FISH shows whether a duplicated region is at its normal location. Thus, FISH metaphase analysis is often used to assess the relatives of the affected patient for balanced rearrangements.
Testing for Fragile X syndrome	Yield will depend on case selection criteria, higher if scoring criteria are applied. Nonspecific testing yield is approximately 7%	Recommended as first line test in males with severe to moderate GDD, behavioural problems and autistic features with specific dysmorphic features described or with no obvious dysmorphology but with a normal or large head	Fragile X testing is responsible for significant proportion of cases with ID in males and mild to moderate delay in carrier females. This requires specific tests to pick up triplet repeats which are not picked up by routine sequencing or next generation sequencing (NGS) based tests
Testing for Rett Syndrome Gene sequencing & MLPA	With fulfilling RTT criteria nearly 100%. About 2% without a suggestive phenotype	Recommended in females fulfilling clinical criteria for Rett syndrome. MECP2 sequencing is also recommended if no etiology is found for GDD/ID with ASD in all females, and males with suggestive phenotypes.	Second-tier testing for GDD/ID includes MECP2 full gene analysis in females. Several guidelines suggest MECP2 testing along with sequencing and MLPA in girls with severe GDD.
Multiplex Ligation dependent Probe Assay (MLPA)	Depend on patient selection and disorders being tested e.g. microdeletion/duplications Rett syndrome	Assess a specific copy number variant (CNV) associated with a specific syndrome. Should be offered in situations with specific phenotypes indicating a known microdeletion syndrome e.g. William syndrome, Velocardiofacial syndrome, 1 p36 del, etc. Is at times used to evaluate for	Reliable and relatively low-cost method for specific phenotypes including common and rare microdeletion/microduplication syndromes. Specific MLPA kits are available for GDD patients suspected to have microdeletions/duplications which include many known syndromes Rapid turnaround time

		multiple microdeletion syndromes as kits are available and also to screen the CNVs in subtelomeric regions which are frequently associated with GDD/ID syndromes	
Chromosomal Microarray (CMA)	~15-20% (~10% higher than the detection rate by karyotype analysis in the GDD/ID/ASD population).	Unexplained GDD, ASD, and multiple congenital anomalies (MCAs).	Able to identify submicroscopic deletions and duplications (less than ~ 5-10 Mb, the size of many of the deletions which cannot be detected by karyotype It also identifies regions of homozygosity, which can be scrutinized for autosomal recessive conditions and imprinting disorders Does not detect balanced rearrangements Counselling regarding getting inconclusive results as variants of unknown significance (VOUS) can be identified. TAT -2-3 weeks Cost high
Sanger Sequencing	Depending on patient selection	When a specific phenotype is identified	Expensive if the gene is big or caused by multiple disease-causing genes (genetic heterogeneity). In that situation NGS based tests are preferable.
Exome Sequencing	30-50% depending on patient selection	Developmental delay/intellectual disability, or multiple congenital anomalies not specific to a particular genetic syndrome. More useful if pedigree indicates a mendelian inheritance. There are uniformly followed guidelines for exome sequencing in general, which also apply to ID/GDD, but it needs to be kept in mind that at times there may be difficulty in clearly defining an indication which are as below: The phenotype or family history data strongly implicate a genetic etiology, but the phenotype does not correspond with a specific disorder for which a genetic test targeting a specific gene is available on a clinical basis A patient presents with a defined genetic disorder that demonstrates a high degree of genetic heterogeneity, making WES analysis of multiple genes simultaneously a more practical approach A patient presents with a likely genetic disorder, but specific genetic tests available for that phenotype have failed to arrive at a diagnosis	Exome sequencing detects variations in the coding regions of all known genes; WES or morbid genes which means genes with a known human phenotype; CES. Targeted panels can be used for a specific group of disorders (e.g. lysosomal storage disorders). Does not detect triplet repeat disorders, changes in intronic regions, large deletions & duplications Counselling regarding getting inconclusive results as variants of VOUS can be identified. Cost still prohibitive TAT 4-6 weeks WGS can detect variations in the intronic regions also but interpretation is more difficult and is not used routinely in clinical practice

Metabolic testing	Poor yield for small molecule diseases if isolated GDD/ID For large molecule diseases likely high if careful patient selection	GDD/ID in isolation (not common) but metabolic testing should be considered if it is in combination with autism, neurodegeneration, failure to thrive, lethargy, episodic symptoms such as epilepsy and encephalopathy, multiple organ dysfunction, dietary selectivity, unusual odours etc. Large molecule diseases present with GDD/ID coarse facial features, joint contracture, neuroregression etc.	Poor yield if cases with isolated GDD tested. Diagnosis may need confirmation by molecular studies. Selection of tests would depend on clinical suspicion. E.g. for small molecule diseases HPLC, TMS, GCMS, for large molecule diseases like storage disorders-enzyme assays

CES- clinical exome sequencing, TAT-Trans-activator of transcription, HPLC-high pressure liquid chromatography, TMS-tandem mass spectrometer, GCMS-gas chromatography mass spectrometry, VOUS-variants of unknown significance WES-whole exome sequencing, WGS-Whole Genome Sequencing

Web Table V Management of Comorbidities in a Child With Global Developmental Delay

Comorbidity	*Primary Level*	*Secondary Level*	*Tertiary Level*
Behavioral problems	Parental counselling regarding responsive caregiving, consistent discipline, avoiding inadvertent reinforcement of problem behaviors	Antecedent-behaviour-consequence (ABC) charting Behavioral modification of common behavioral problems	Severe behavioral problems-Behavior modification by psychologist
Hyperactivity	Recognition of age inappropriate level of activity and timely referral Monitoring for side effects of medications if any	Behavioral management and pharmacotherapy Monitoring for side effects of medications if any	Behavioral management and pharmacotherapy, especially for poorly controlled cases Monitoring for side effects of medications if any
Irritability, aggression and self-injurious behavior (SIB)	Recognition and early referral Monitoring for side effects of medications if any	Behavioral management and pharmacotherapy Monitoring for side effects of medications if any	Behavioral management and pharmacotherapy, especially for difficult to control cases Monitoring for side effects of medications if any
Epilepsy	Neuroimaging if clinically indicated. Explain home management of seizure. Starting 1st line antiepileptic drug and dose titration as required. Ensuring early clinical recognition of epileptic spasm and ensuring appropriate timely management Referral to higher level if poor seizure control	EEG/ Neuroimaging as indicated Combination ASM if required Referral to higher level of care if complex epilepsy, refractory epilepsy or developmental regression	Review diagnosis, ancillary testing as indicated, rational polytherapy, precision epilepsy medicine, epilepsy surgery evaluation, ketogenic diet. Referral back with clear instructions for dose titration, liaising with pediatrician at primary/ secondary level for monitoring and follow-up.
Motor impairment	Guidance and supervision of Intervention for mild motor problems other than cerebral palsy (as per RBSK manual)	Occupational/ Physiotherapy for motor delay/ impairment	Occupational/ Physiotherapy for motor delay/impairment/ aids and appliances if needed
Significant speech delay	Rule out hearing impairment/ manage impacted wax and otitis media	BERA screening, speech therapy	Speech therapy/ augmentative speech devices
Hearing impairment	Refer to ENT	Hearing aids	Hearing aid/ cochlear implant where indicated
Drooling	Advice regarding oral hygiene	Oro-motor exercises/ Glycopyrrolate	Oro-motor exercises/ Glycopyrrolate
Sleep problems	Advise sleep hygiene, rule out modifiable factors	Sleep hygiene, rule out modifiable medical causes like OSA Melatonin, if needed	Investigations for sleep problems Specific management of predisposing condition Pharmacotherapy if indicated
Squint	Refer to ophthalmologist and ensure compliance with ophthalmological management	Eye exercises, patching, management of refractive errors, if any	Surgical management

Cerebral visual impairment (CVI)	Suspect CVI and refer for evaluation Simple visual stimulation	Active visual stimulation	Detailed assessment and individualized management
Autism spectrum disorder (ASD)	Screen for ASD at 18-24 months Refer for detailed evaluation if suspected ASD Monitor compliance with therapies	Diagnosis and individualized intervention plan	Diagnosis and individualized intervention plan

EEG-Electroencephalogram, ASM-antiseizure medication, BERA- brain evoked response audiometry, OSA-obstructive sleep apnea

Web Box I Common Genetic Disorders Associated With GDD/ID

Condition	Distinctive Feature
Down syndrome	Flat facies, upward slant of eyes, epicanthal folds, small low set ears, clinodactyly, sandal gap, congenital cardiac defects, GI tract abnormalities, hypothyroidism, hypotonia, simian crease
Prader-Willi syndrome	Narrow forehead, 'up slanting'' palpebral fissures, almond eyes, small hands and feet, truncal obesity, short stature
Cornelia de Lange syndrome	Growth retardation, arched eyebrows, synoophrys, anteverted nares, maxillary prognathism, long philtrum, thin lips, and 'carp' mouth, in association with prenatal and postnatal growth retardation, mental retardation and, in many cases, upper limb anomalies.
Angelman syndrome	Severe speech impairment, gait ataxia, a unique behavior with an inappropriate happy demeanour including frequent laughing, smiling, and excitability. Microcephaly, large mouth, prominent jaw, seizures are common.
Williams syndrome	Periorbital puffiness, anteverted nares, full lips, stellate pattern in iris, cardiovascular disease (elastin arteriopathy, peripheral pulmonary stenosis, supravalvar aortic stenosis, hypertension), connective tissue abnormalities, unique personality characteristics (cocktail party syndrome) and endocrine abnormalities (hypercalcemia, hypercalciuria, hypothyroidism, and early puberty). Feeding difficulties, hypotonia and hyperextensible joints.
22q11.2 deletion syndrome	Short palpebral fissures; broad midnose (pear-shaped); long, tapered fingers, heart disease (particularly conotruncal malformations), palatal abnormalities (velopharyngeal incompetence, submucosal cleft palate, bifid uvula, and cleft palate), immune deficiency. Hearing loss can be sensorineural and/or conductive.
Neurocutaneous syndromes	Involvement of brain along with distinctive cutaneous features E.g. Tuberous Sclerosis, Von Hippel Lindau syndrome, Sturge weber syndrome
Fragile-X syndrome	Elongated face, large ears, high arched palate, macroorchidism, (postpubertal) joint hypermobility. Congenital cardiac defect, connective tissue disorder and hypotonia. 1/3rd of individuals have features of autism and seizures occur in about 15% of males and 5% of females.
Rett syndrome	Early neurological regression that severely affects motor, cognitive and communication skills leading to microcephaly, speech delay, stereotyped hand movements, autistic features. Motor abnormalities including abnormal muscle tone, ataxia and apraxia, and often seizure disorder.