بسم الله الرحمن الرحیم

Evidence For Evaluations Of The Child With Global Developmental Delay

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انتظار می رود فراگیر در پایان این درس بتواند :

- تاخیر تکاملی گلوبال را تعریف و درجه بندی کند.
- موارد برررسی های تشخیصی (متابولیک) مبتنی بر شواهد در کودک با تاخیر تکاملی گلوبال را نام ببرد.
- موارد برررسی های تشخیصی (تصویر برداری عصبی) مبتنی بر شواهد در کودک با تاخیر تکاملی گلوبال را فهرست کند
- موارد برررسی های تشخیصی (ژنتیک) مبتنی بر شواهد در کودک با تاخیر تکاملی گلوبال را توضیح دهد.
- موارد برررسی های تشخیصی (شنوایی و بینایی) مبتنی بر شواهد در کودک با تاخیر تکاملی گلوبال توضیح دهد.

Global developmental delay (GDD) and intellectual disability (ID) affect up to three per cent of the pediatric population .The diagnosis of GDD is limited to children younger than 5 years old, but these children often evolve to meet diagnostic criteria for ID and probably represent the same population

Developmental Quotient

DQ = Developmental Age/ Chronologic age X 100

DQ <70	**(More than -2 SD)**	**Delay**
DQ 70-85	**(-1 to -2SD)**	**Monitor**
DQ >85	**(Less than -1 SD)**	**Typical range**

***Perform for each stream of development**

"Global developmental delay"(GDD) defined as:

Significant delay in 2 or more developmental domains, including :1. gross or fine motor, 2.speech/language,3. cognitive, 4.social/personal, and 5.activities of daily living and is thought to predict a future diagnosis of ID

- **GDD is not a diagnosis**

GDD vs ID

- The term GDD is usually reserved for younger children (i.e., typically less than 5 years of age),
- whereas

The term ID is usually applied to older children when IQ testing is more valid and reliable.

The more severe the ID/ DD, the more likely to find etiology.

Etiology is found in 40% to 60% of all cases;

however, in mild ID/DD cases is 24%, which is significantly lower.

Definition of "etiology" proposed by Schaefer and Bodensteiner: "a specific diagnosis [is]

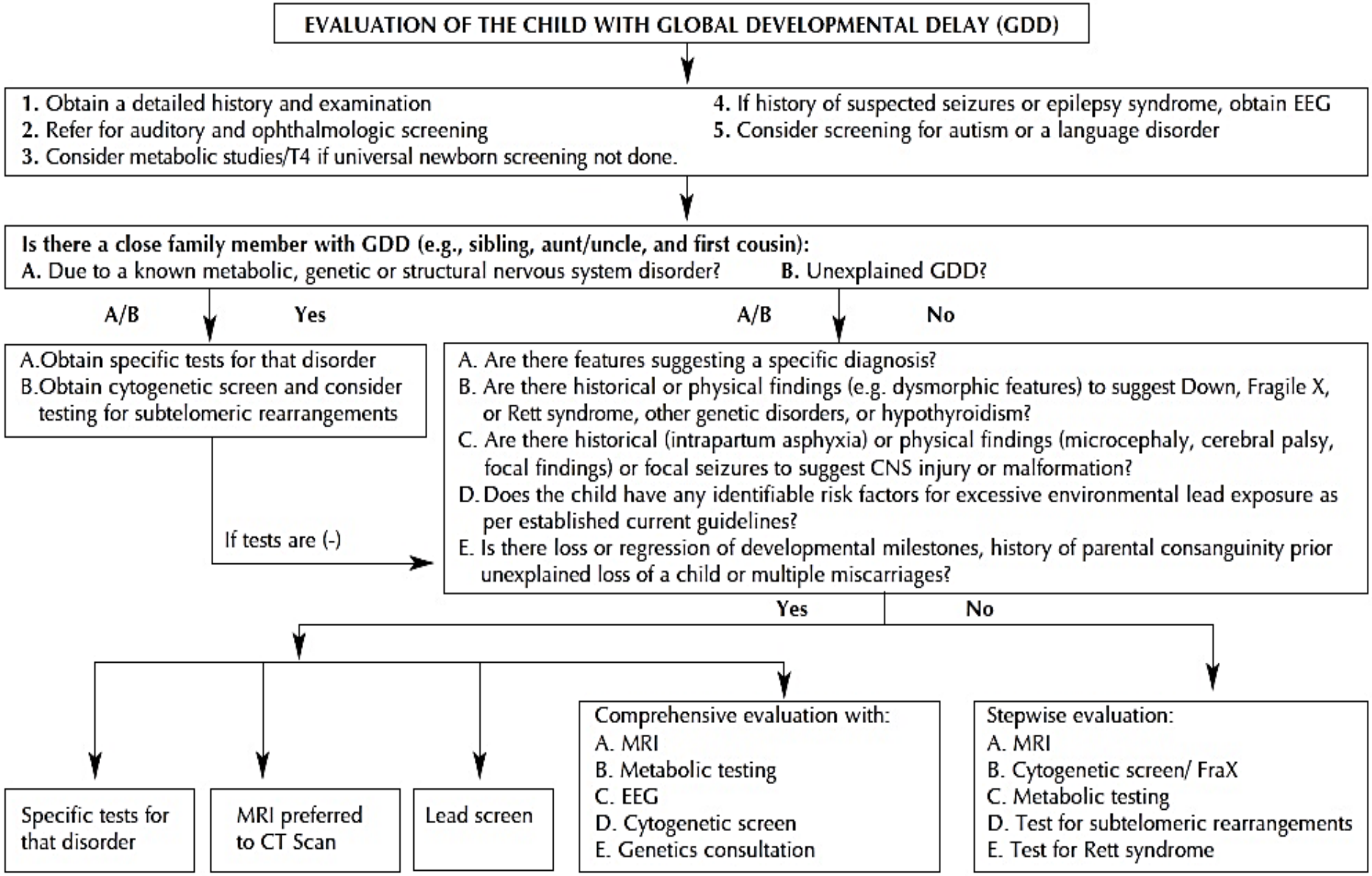
- Can be translated into useful clinical information for the family, including providing information about prognosis, recurrence risks, and preferred modes of available therapy.
- For example, agenesis of the corpus callosum is a finding or sign and not a diagnosis,
- whereas Down syndrome is a clinical diagnosis, and when confirmed by a routine chromosome study.

Table 2. Causes of global developmental delay/intellectual disability

Broad category	Possible causes	Proportion of diagnostic yield*
Prenatal intrinsic	Genetic	Up to 47%
	Central nervous system malformations	Up to 28%
	Metabolic	
Prenatal extrinsic	Teratogens/toxins (drugs of abuse, medications, etc.)	Up to 21%
	Infections	
Perinatal	Asphyxia	Up to 55%
	Prematurity	
	Neonatal complications	
Postnatal	Neglect/psychosocial environment	Up to 11%
	Infections	
	Trauma	
	Toxins	

Expected Benefits of Evaluation for DD/ID

1. Clarification of etiology
2. Provision of prognosis or expected clinical course
3. Discussion of genetic mechanism(s) and recurrence risks
4. Refined treatment options
5. Avoidance of unnecessary or redundant diagnostic tests
6. Information regarding treatment, symptom management, or surveillance for known complications
7. Provision of condition-specific family support
8. Access to research treatment protocols
9. Opportunity for comanagement of appropriate patients in the context of a medical home to ensure the best health, social, and health care services satisfaction outcomes for the child and family


EVALUATION OF THE CHILD WITH GLOBAL DEVELOPMENTAL DELAY (GDD)
1. Obtain a detailed history and examination
2. Refer for auditory and ophthalmologic screening
3. Consider metabolic studies/T4 if universal newborn screening not done.
4. If history of suspected seizures or epilepsy syndrome, obtain EEG
5. Consider screening for autism or a language disorder
Is there a close family member with GDD (e.g., sibling, aunt/uncle, and first cousin):
A. Due to a known metabolic, genetic or structural nervous system disorder?
B. Unexplained GDD?
A/B
Yes
A/B
No
A. Obtain specific tests for that disorder
B. Obtain cytogenetic screen and consider testing for subtelomeric rearrangements
If tests are (-)
A. Are there features suggesting a specific diagnosis?
B. Are there historical or physical findings (e.g. dysmorphic features) to suggest Down, Fragile X, or Rett syndrome, other genetic disorders, or hypothyroidism?
C. Are there historical (intrapartum asphyxia) or physical findings (microcephaly, cerebral palsy, focal findings) or focal seizures to suggest CNS injury or malformation?
D. Does the child have any identifiable risk factors for excessive environmental lead exposure as per established current guidelines?
E. Is there loss or regression of developmental milestones, history of parental consanguinity prior unexplained loss of a child or multiple miscarriages?
Yes
No
Specific tests for that disorder
MRI preferred to CT Scan
Lead screen
Comprehensive evaluation with:
A. MRI
B. Metabolic testing
C. EEG
D. Cytogenetic screen
E. Genetics consultation
Stepwise evaluation:
A. MRI
B. Cytogenetic screen/ FraX
C. Metabolic testing
D. Test for subtelomeric rearrangements
E. Test for Rett syndrome

History and physical examination

- an etiological diagnosis based on history and physical examination was found in 12.5% to 38.6% of cases.
- A three-generation family history, a psychosocial history, detailed prenatal and birth histories and the timing of major milestones should be recorded as accurately as possible ;
- A neurodevelopmental assessment;
- When a specific etiology is suspected at that point or when a family history of disorder associated with GDD/ID has been established, specific testing for this disorder should be ordered first

Table 3. History and physical and neurodevelopmental exams

History	Physical and neurodevelopmental exams
Family history Three-generations review, looking for: • Recurrent miscarriages • Birth defects • Infant deaths • GDD/ID • Neurologic conditions • Genetic conditions • Ethnic background • Consanguinity **Psychosocial history** • Parent language, education, employment • Parental drug/alcohol abuse • Child care arrangements • History of abuse or neglect and involvement of child protective services **Prenatal history** • Prenatal ultrasound • Screening for fetal aneuploidy • Maternal diabetes or hypertension • Infections • Exposure to medications or toxins **Birth history** • Weight and height • Head circumference • Apgar score • Length of hospitalization **Red flags suggestive of inborn errors of metabolism** • Table 4 **Developmental milestones** • Regression or lack of milestones • Timing of parents' first concern	**Physical exam** • Growth parameters • Head shape • Fontanelle • Cutaneous stigmata • Spine • Heart abnormalities • Abdomen check for organomegaly • Limb abnormalities • Genital abnormalities **Neurodevelopmental exam** • Neurological exam • Congenital abnormalities • Dysmorphic features • Current developmental level

Sensory evaluation

According to the AAN and other reviews ,children with GDD/ID should be referred for a formal assessment of their vision (optometry or ophthalmology) and hearing.

Identifying a sight or hearing deficit can alter management course and guide further investigation.

Genetic testing

- Chromosome microarray referred to as comparative genomic hybridization or CGH) as a first-line investigation in children with GDD/ID.
- It is the single test with the best diagnostic yield (at 8% to 20%), exceeded in efficacy only by clinical evaluation from an experienced clinician specializing in GDD/ID .
- The variation in yield reported in different studies can be explained by the absence of stratification for severity and the presence of other anomalies. Therefore, it remains uncertain whether CMA is useful in mild (according to DSM-5) familial ID.

Karyotype

- The use of standard karyotyping is not recommended as a first line test, because its sensitivity is less than one-half that of CMA in children diagnosed with GDD/ID.
- However, karyotyping is recommended instead of CMA for clinically suspected aneuploidy (e.g., Turner syndrome, trisomy 21) or a family history of chromosomal rearrangements or multiple spontaneous abortions .For the latter scenario, parental chromosome karyotyping should be ordered first.

Fragile X DNA testing

- Fragile X is the most common genetic cause, representing 2% to 6% of affected boys and 1% to 4% of affected girls. Because the clinical phenotype is often nonspecific in infants and young children with Fragile X, AAP and AAN guidelines both recommend that Fragile X DNA (FMR1) testing be considered as part of first-line investigation for boys and girls with GDD/ID as defined in the DSM-5 .

Rett syndrome testing

- Rett syndrome is found in 1.5% of girls with moderate-to-severe ID According to the AAP and the AAN, MECP2 molecular analysis should be ordered when:
- Characteristic symptomatology is present
- Moderately-to-severely affected girls .

Whole-exome or -genome sequencing

- Whole-exome sequencing permits analysis of coding regions for known genes and the identification of causal mutations in up to 40% of patients with severe ID .
- Variations of unknown significance are still a challenge and need to be interpreted with caution. Given these limitations, exome or genome sequencing is not actually recommended for primary care physicians but may become a first line investigation in the near future.

Metabolic work up

Although the prevalence of inherited metabolic conditions is relatively low (0% to 5% in these studies), the potential for improved outcomes after diagnosis and treatment is high

Treatability of metabolic conditions is important in the workup

Selected Clinical Findings or Laboratory Abnormalities Suggesting a Metabolic Disorder

- Failure of appropriate growth
- Recurrent unexplained illness
- Seizures
- Ataxia
- Loss of psychomotor skills
- “Coarse” appearance
- Eye abnormalities (cataracts, ophthalmoplegia, corneal clouding, abnormal retina)
- Recurrent somnolence/coma
- Hepatosplenomegaly
- Metabolic/lactic acidosis
- Hyperuricemia
- Hyperammonemia
- Low cholesterol
- Structural hair abnormalities

Table 5. Tier-1 laboratory investigations for unexplained GDD/ID

Blood*	Urine*
• Complete blood count • Glucose • Blood gas • Urea, creatinine • Electrolytes (to calculate anion gap) • AST, ALT • TSH • Creatine kinase • Ammonia • Lactate • Amino acids • Acylcarnitine profile, carnitine (free and total) • Homocysteine • Copper, ceruloplasmin** • Biotinidase*** • Ferritin, vitamin B12 when dietary restriction or pica are present • Lead level when risk factors for exposure are present	• Organic acids • Creatine metabolites • Purines, pyrimidines • Glycosaminoglycans

ALT Alanine aminotransferase; AST Aspartate aminotransferase; GDD Global developmental delay; ID Intellectual disability; TSH Thyroid-stimulating hormone.

*Perform testing after 4 h to 8 h of fasting. **Recommended tier-1 test in the TIDE protocol, but not by AAP, AAN. Consider as a first-line investigation when hepatomegaly, dystonia, abnormal liver function findings are present. ***Clinical expert recommendation only. Consider biotinidase testing when severe hypotonia, seizures are present.

Thyroid screening

In the setting of existing newborn screening programs for congenital hypothyroidism, screening of children with developmental delay with thyroid function studies is not indicated unless there are systemic features suggestive of thyroid dysfunction.

Lead

Lead poisoning can affect mental and physical development severely, especially in children younger than 5 years of age, leading to conditions such as autism spectrum disorder, loss of milestones (particularly related to language) and encephalopathy (18). The AAN is the only association to recommend lead level dosing in children with risk factors for exposure

Neuroimaging

Neuroimaging studies, including computed tomography or magnetic resonance imaging (MRI) reveal nonspecific abnormalities in approximately 30% of children with GDD/ID, anywhere between 2% and 80%, depending on the study, but neuroimaging contributes to understanding the etiology underlying GDD/ID in only 0.2% to 2.2% of cases .

EEG

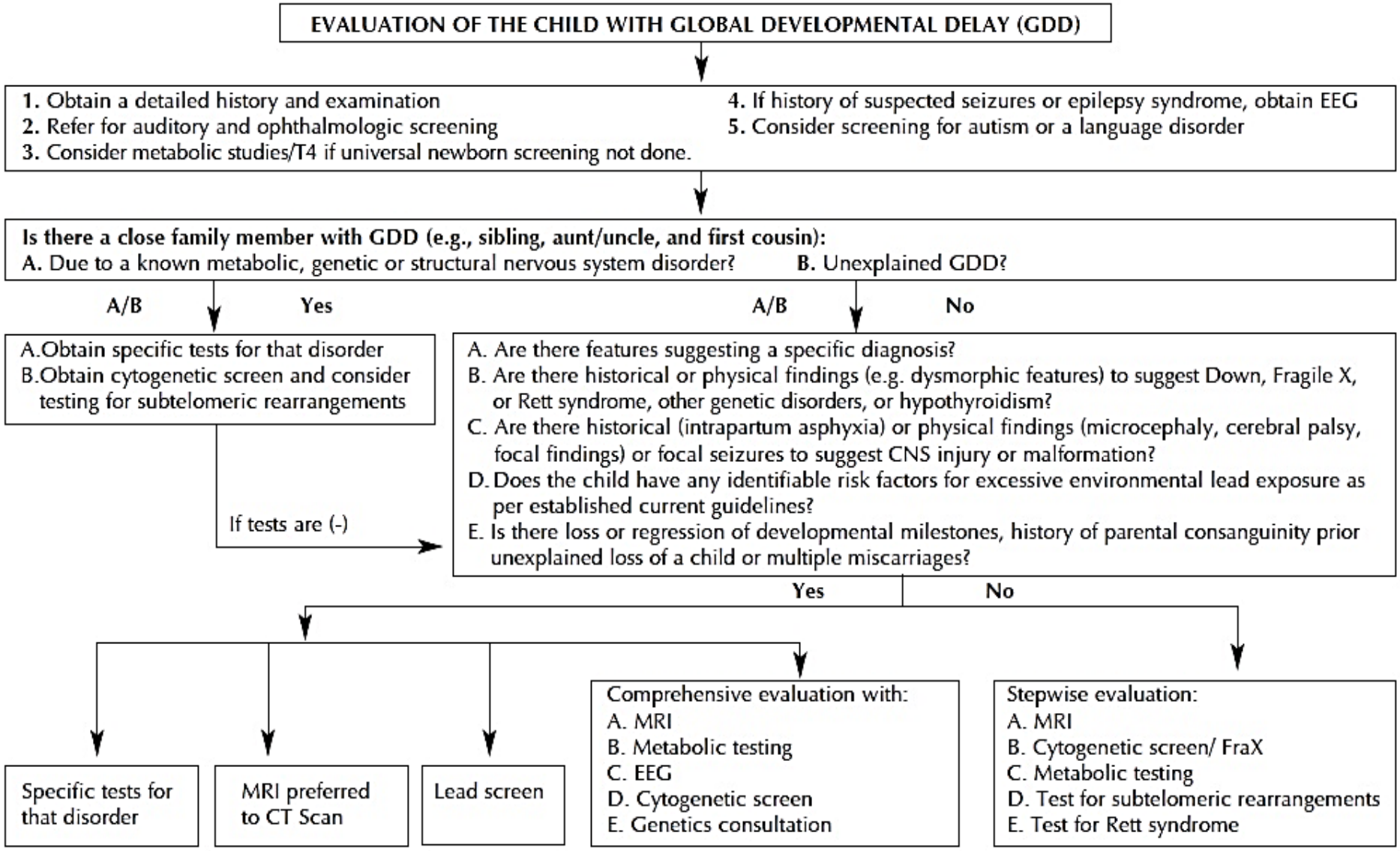
- An EEG can be obtained when a child with global developmental delay has a history or examination features suggesting the presence of epilepsy or a specific epileptic syndrome
- Data are insufficient to permit making a recommendation regarding the role of EEG in a child with global developmental delay in whom there is no clinical evidence of epilepsy.

RECOMMENDATIONS

- History and physical examination are still the best first steps for establishing a diagnosis and should be systematically conducted for each child with suspected global developmental delay (GDD) and intellectual disability (ID).
- When a specific diagnosis is not suspected following clinical evaluation, consider a stepwise approach to investigation.
- To promote an evidence-based approach to evaluating children with GDD/ID, coordinating physician efforts with testing at provincial/territorial or regional referring centers is essential.
- Formal vision and hearing testing is critical for all patients with suspected GDD/ID.
- When no etiological diagnosis has been identified following history and physical examination, Fragile X, chromosomal microarray, Tier-1 metabolic testing, +/- brain imaging is recommended.

- Chromosomal microarray and Fragile X DNA testing are first line investigations for children with unexplained GDD/ID.
- Evidence supports Tier-1 (Table 5) testing for treatable inborn errors of metabolism (IEMs) in children with unexplained GDD/ID, even when clinical red flags are absent and a normal newborn screen has been obtained.
- Brain imaging is recommended as a first-line investigation for patients with microcephaly, macrocephaly, seizures or abnormal neurological findings. Order lead level and iron studies for children at risk.
- Whole-exome or -genome sequencing may be indicated in the clinical setting in future, when these tests are more readily available.

If no further studies appear warranted, develop a plan with the family and medical home for needed services for child and family; also develop a plan for diagnostic reevaluation.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D. Test for subtelomeric rearrangements
E. Test for Rett syndrome

- There was no uniform consensus regarding the ‘right’ or ‘wrong’ approach.
- No unifying or single algorithm was found appropriate for every patient or every situation.
- A large number of variables currently affect the physician’s evaluation process.”