
بسم الله الرحمن الرحیم

Approach to developmental delay

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Developmental delay

To understand developmental delay and intellectual disability

To develop an approach to screening for developmental delay using the most current guidelines.

To review preliminary steps to be taken when a child with developmental delay is identified

GDD v/s ID

Global Developmental Delay(GDD): A disturbance in an individual child (<5y) across two or more developmental domains

Defined operationally as a significant delay (2 or more SDs) lower than the mean on objective norm-referenced age-appropriate testing in two or more developmental domains.

Typically there is delay across all domains look for this!

Mental Retardation(MR): A disability characterized by significant limitation both in intellectual functioning and in adaptive behavior as expressed in conceptual , social and practical adaptive skills.

The term intellectual disability(ID) has replaced mental retardation.

GDD

Global developmental delay (GDD) is defined as a delay in two or more developmental domains of

Communication,

motor (gross/fine),

speech/language ,

Problem solving,

social/ personal

affecting children under the age of 5 years.

DIFFERENT DEVLOPMENTAL TESTS

Bayley scales for infant development,2th edition(BAYLEY2)

16 days to 3years 6 months15 days

Bayley infant neurodevelopmental screening(BINS)

3-24 months

Denver developmental screening test2(DENVER2)

Birth – 6 years

Ages and Stages Questionnaire (ASQ).

1 month to 60 months

DIFFERENT INTELLIGENCE OR COGNITIVE TESTS

Wechsler intelligence scale for children 4 edition(WISC-4)

6years to 16 years 11months 30 days

Comprehensive test of nonverbal intelligence (CTONI)

6 years to 90 years old

Different INTELLIGENCE OR COGNITIVE TESETS

Stanford- binet intelligence scales 5th edition(SB5)

2 years to 85 years

Letter international performance scale, revised (LETTER 5)

2 years to 20years 11 months

Differential ability scales

2years6 months to 17 years 11 months

GDD CLASSIFICATION

The degree of developmental delay is further subclassified as:

mild(functional age <33% below chronological age),

moderate (functional age 34%–66% of chronological age) and

severe (functional age <66% of chronological age).

GDD PREVALENCE

With a prevalence of 1%–3%, GDD is one of the most common conditions encountered in pediatrics

GDD DIAGNOSIS

Establishing a diagnosis enables clinicians to define treatment options and conduct surveillance for known complications as well as provide prognosis and condition-specific family support (including family planning choices).

This ensures the best overall outcomes for the child and their families/careers.

A diagnosis may also provide an explanation, a source of closure or acceptance to parents and stops clinicians advancing to potentially more expensive and invasive tests.

First-line assessment and investigations

History and physical examination

The diagnosis of exogenous causes includes teratogenic agents (alcohol and drugs); prenatal, perinatal causes (prematurity, infections); and social causes often best assessed by history but must not be assumed.

Categories and Causes of Mental Retardation

CATEGORIES	CAUSES
Prenatal	Genetic
	Chromosomal (e.g., trisomy 21, Prader-Willi syndrome, Williams' syndrome, translocations)
	Syndromic single gene (e.g., fragile X, Rubinstein-Taybi, Coffin-Lowry syndromes)
	Nonsyndromic single gene (e.g., oligophrenin [*OPHN1*], *FMR2* mutation)
	Metabolic (e.g., phenylketonuria, galactosemia, Smith-Lemli-Opitz syndrome)
	Acquired
	Fetal alcohol syndrome
	Other maternal substance abuse
	Nutritional (e.g., maternal phenylketonuria, iodine deficiency)
	Infection (e.g., rubella, toxoplasmosis, cytomegalovirus, human immunodeficiency virus)
	Stroke
	Unknown causes (most likely genetic but can be acquired)
	Clinical syndromes without genetic diagnoses (e.g., Schinzel-Giedion, Marinesco-Sjögren, Marden-Walker syndromes)
	Multiple congenital anomaly and mental retardation
Perinatal	Birth asphyxia
	Infection (herpes simplex virus encephalitis or group B *Streptococcus* meningitis)
	Stroke (embolic or hemorrhagic)
	Very low birth weight, extreme prematurity
	Metabolic (e.g. hypoglycemia, hyperbilirubinemia)
Postnatal-environmental	Toxins (e.g., lead)
	Infection (e.g., *Haemophilus influenza* b meningitis, arbovirus encephalitis)
	Stroke
	Trauma (consider nonaccidental source)
	Poor nutrition
	Poverty
Undetermined	Familial
	Nonfamilial

First-line assessment and investigations

Investigation following a thorough clinical history (including a family pedigree, pregnancy and birth history) and a detailed physical examination by a trained specialist lead to a higher diagnostic yield.

Hepatosplenomegaly and GDD

Argininosuccinic aciduria
Gaucher's disease
GM_1 gangliosidosis (generalized)
Glycogen storage disease types I and III
Hydroxykynureninuria
Hyperpipecolatemia
Mucopolysaccharidoses
Neuronal ceroid lipofuscinosis
Niemann-Pick disease

Vomiting and metabolic acidosis and GDD

Box 32-6 Vomiting

Hyperammonemia (all types)
Hyperglycinemia
Hyperlysinemia
Hypervalinemia
Increased intracranial pressure
Lactic acidosis
Maple syrup urine disease
MELAS syndrome (i.e., mitochondrial myopathy, encephalopathy, lactacidosis, and stroke)

Box 32-9 Metabolic Acidosis

Ketotic hypoglycemia
Lactic acidosis
Maple syrup urine disease
Methionine malabsorption syndrome
Methylmalonic acidemia
Mitochondrial encephalomyopathy
5-Oxoprolinuria (pyroglutamic aciduria)
Propionic acidemia

First-line assessment and investigations

Identification and correction of sensory deficits are essential, while evaluating these children and may provide pointers to the underlying etiology.

Eye abnormalities and GDD

- Cataracts
  - Cerebrotendinous xanthomatosis
  - Cockayne's syndrome
  - Cretinism
  - Down syndrome
  - Galactosemia
  - Lowe's syndrome
  - Marinesco-Sjögren syndrome
  - Myotonic dystrophy
  - Pseudohypoparathyroidism
  - Rubella (gestational)
  - Trichothiodystrophy
- Cherry-red spot in macular area
  - GM_1 gangliosidosis (generalized)
  - Neuraminidase deficiency
  - Niemann-Pick disease type A
  - Tay-Sachs disease
- Chorioretinitis
  - Clouding of cornea
  - Congenital lues
  - Cytomegalic inclusion body disease
  - Hunter's syndrome
  - Hurler syndrome
- Corneal ulcers
  - Familial dysautonomia
- Dislocated lenses
  - Homocystinuria
  - Sulfite oxidase deficiency
- Glaucoma
  - Lowe's syndrome
  - Rubinstein-Taybi syndrome
  - Sturge-Weber syndrome
- Nystagmus
  - Hyperpipecolatemia
  - Hypervalinemia
  - Joubert's syndrome
- Photophobia
  - Cockayne's syndrome
  - Hartnup's disease
  - Homocystinuria

hearing abnormalities and GDD

Conduction deafness
- Hunter's syndrome
- Hurler syndrome

Hyperacusis
- GM_1 gangliosidosis (generalized)
- Krabbe's disease
- Subacute sclerosing panencephalitis
- Sulfite oxidase deficiency
- Tay-Sachs disease

Sensorineural deafness
- CHARGE syndrome (i.e., coloboma, heart defects, atresia choanae, retardation of growth and development, genitourinary problems, and ear anomalies) [Menenzes and Coker, 1990]
- Kearns-Sayre syndrome
- MELAS syndrome (i.e., mitochondrial myopathy, encephalopathy, lactacidosis, and stroke)
- MERRF syndrome (i.e., myoclonus epilepsy associated with ragged-red fibers)
- Refsum's disease

First-line assessment and investigations

An examination of the child's developmental status in all domains (gross motor, fine motor, language, socioemotional and cognitive skills) using a recognized tool to provide a normative comparison should also be conducted.

Repeated clinical/dysmorphology and developmental assessments over time are more informative than one-off assessments in planning investigations and management.

First-line assessment and investigations

Some studies have demonstrated that we can identify the cause of developmental or cognitive delay in a one-third of cases by history and examination alone.

With clinical evaluation prompting investigations, we can identify another one-third.

It is only the latter one-third that are identified by investigations only.

The presence of abnormal neurology, microcephaly, female gender, dysmorphism, abnormal prenatal or perinatal history and absence of autistic features are linked with higher etiological yield of investigations. Investigations following comprehensive clinical evaluation are also cost effective.

Genetic study(karyotype)

- Genetic investigation by means of standard karyotyping was recommended as a first-line investigation for many years.
- The most common genetic etiology for GDD is DOWN syndrome

Genetic study(CMA)

The implementation of ‘molecular karyotyping’ or chromosome microarray (array-based comparative genomic hybridization (aCGH)) has changed the state of play.

Recent evidence-based international guidelines promote the use of aCGH as a first-tier investigation for GDD if no etiological indicators from history and examination are found.

The higher sensitivity that it has for identifying submicroscopic deletions and duplications (than standard karyotyping methods) and better definition of the breakpoints and size of imbalances all make microarray a suitable first-line test.

Genetic study(CMA)

Chromosome microarray(CMA) has been described to be the ‘single most efficient diagnostic test’ for GDD after history and examination.

Genetic study

A literature search of 33 studies that used this technique in nearly 22 000 patients has demonstrated that the diagnostic yield of CMA is between 15% and 20%, while karyotyping is 3%.

Miller DT, Adam MP, Aradhya S, et al. Consensus statement: chromosomal microarray is a first-tier clinical diagnostic test for individuals with developmental disabilities or congenital anomalies. Am J Hum Genet 2010;86:749–64.

Genetic study(CMA)

The diagnostic yield of microarray is supported by a health economics report, which showed cost saving when comparing a National Health Service (NHS) clinical genetics service use of CMA as a first-tier test while evaluating learning disability, compared with CMA as second line after negative karyotyping

Genetic study

DOES WE NEED STANDARD KARYOTYPE WITH CGH ARRAY?

Genetic study(CMA limitation)

Molecular karyotyping will not detect conditions where structural changes in the chromosomes result in no loss or gain of genetic material such as balanced translocations or inversions, ring chromosomes and low-level mosaicism.

A standard karyotype is still required if such a disorder is suspected (eg,refractory epilepsy, if a family is known to have a balanced translocation associated with a phenotype, a history of multiple miscarriages or clinical features to suggest mosaicism).

Syndromes caused by methylation defects (eg, Beckwith-Wiedemann, Angelman syndrome) or mutations in single genes will also go undetected unless specifically tested.

GENETIC STUDY FOR GGD

In a genetic based GDD do we need another test if CMA and standard karyotype were normal?

Genetic study(FMR test)

Fragile x syndrome affects approximately 1/5000 births, typically causing moderate ID in boys and a variable phenotype in girls (unaffected to significant).

Some people with FXS have physical abnormalities. These may include:

a large forehead or ears, with a prominent jaw

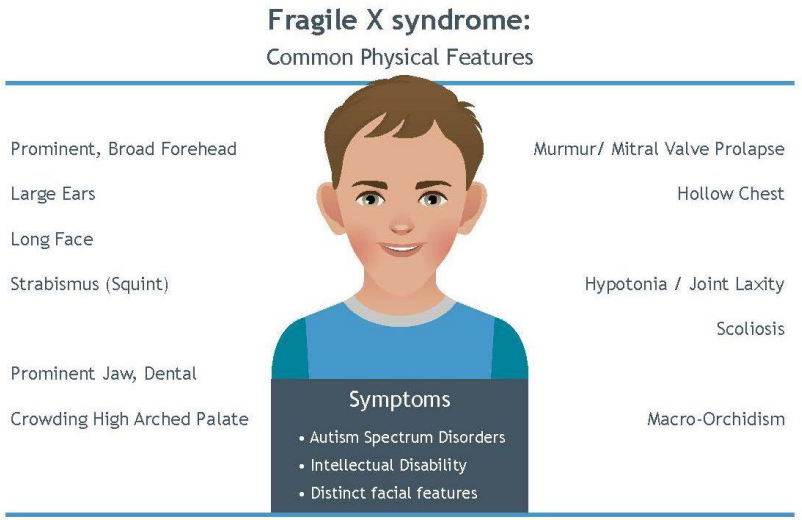
an elongated face

protruding ears, forehead, and chin

loose or flexible joints

flat feet

Fragile X Phenotypic features evolve and are not as apparent in younger children



Genetic study(FMR test)

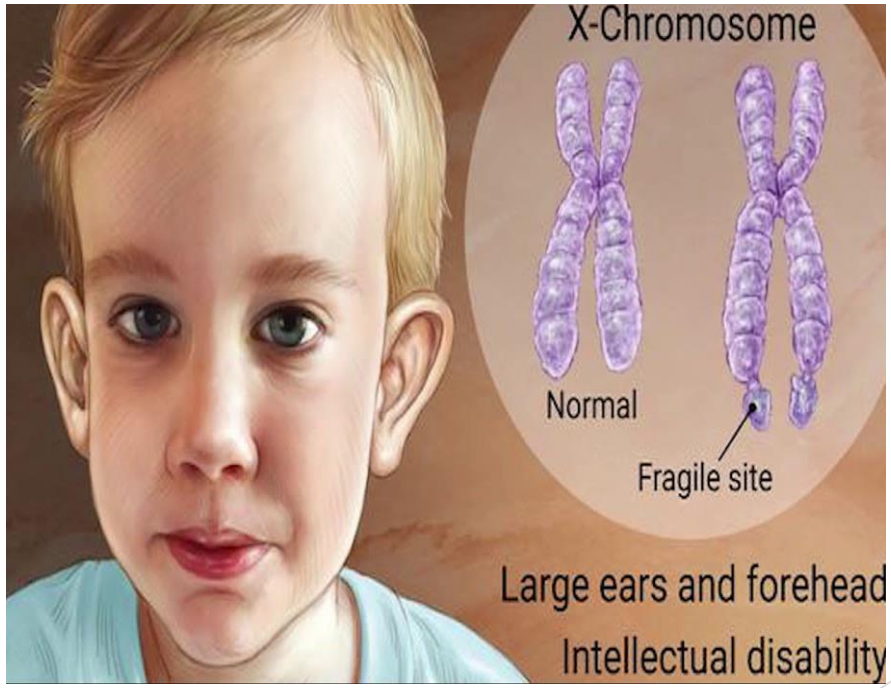
Fragile X is the most inherited cause of familial GDD/ID.

most guidelines recommended FMR testing fragile X for children(either gender) with GDD, without profound physical disability, as an additional first-tier genetic investigation.

Genetic study(FMR test)

Triplet expansion more than 200 CGG in chromosome x is the cause of Fragile x

50-200 CGG expansion is premutation and is associated with fragile X tremor-ataxia syndrome (FXTAS) and primary ovarian insufficiency (POI).



X-LINKED MENTAL RETARDATION

GENE	FUNCTION	LOCUS	STUDY
Genes Primarily Implicated in Nonsyndromic Mental Retardation			
PAK3	P21 (CDKN1A)-activated kinase 3	Xq23	Allen et al., 1998
GDI1	GTP dissociation inhibitor 1	Xq28	D'Adamo et al., 1998
IL1RAPL1	Interleukin 1 receptor accessory protein-like 1	Xp21.3	Jin et al., 2000
ARHGEF6	Rac/Cdc42 guanine nucleotide exchange factor 6	Xq26.3	Kutsche et al., 2000
SLC6A8	Creatine transporter 8	Xq28	van der Knaap et al., 2000
FACL4	Long-chain fatty acid–coenzyme A ligase 4	Xq23	Meloni et al., 2002
AGTR2	Angiotensin II receptor, type 2	Xq23	Vervoort et al., 2002
FTSJ1	*S*-adenosylmethionine-binding protein	Xp11.23	Freude et al., 2004
DLG3	Synapse-associated protein 102 (anchoring protein)	Xq13.1	Tarpey et al., 2004
NLGN3	Neuroligin 3 (postsynaptic receptor)	Xq13.1	Jamain et al., 2003
NLGN4	Neuroligin 4 (binds Neurexin)	Xp22.32	Laumonnier et al., 2004
PQBP1	Polyglutamine binding protein 1	Xp11.23	Kalscheuer et al., 2003
RPS6KA3	Serine/threonine kinase	Xp22.12	Chechlacz and Gleeson, 2003
ZNF41	Zinc-finger protein involved in chromatin activation	Xp11.3	Shoichet et al., 2003
Genes Implicated in Syndromic and Nonsyndromic Mental Retardation			
OPHN	Rho-GTPase activating protein (cerebellar hypoplasia)	Xq12	Billuart et al., 1998
ARX	Aristaless-related homeobox (X-linked lissencephaly with ambiguous genitalia [XLAG])	Xp22.11	Sherr, 2003
MECP2	Methyl-CpG binding protein 2 (Rett syndrome)	Xq28	Gomot et al., 2003

Genetic study(MeCP2 test)

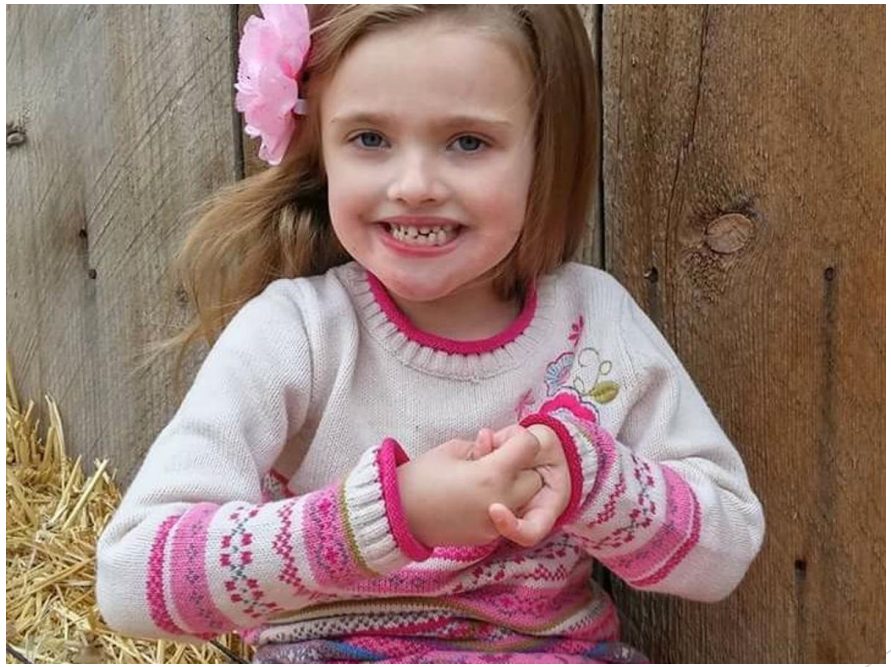
Moderate to severe GDD/ID and female MeCP2 testing

There are more than 900 different mutations found on the MECP2 gene.

Rett syn occurs worldwide in 1 of every 10,000 female births, and is even rarer in boys.

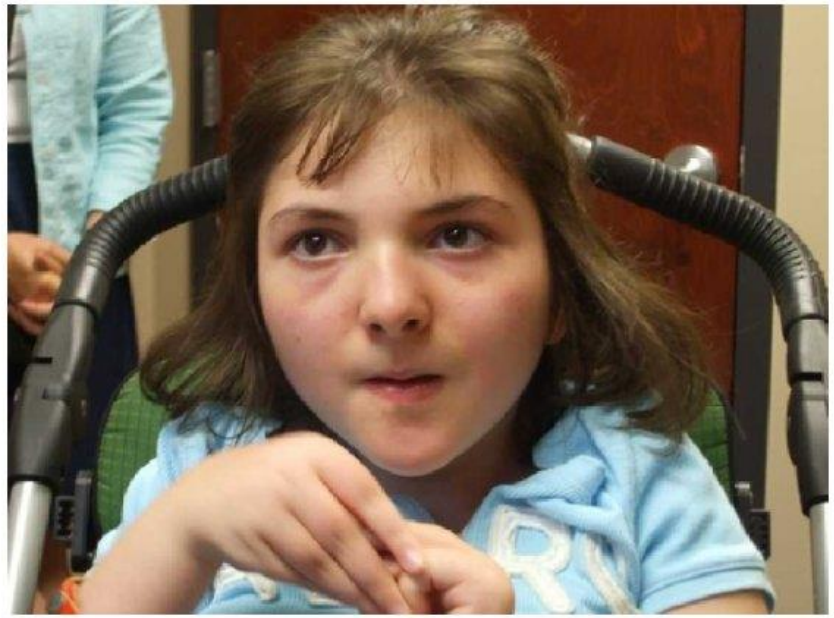
The hallmark of Rett syndrome is near constant repetitive hand movements.

Rett syndrome is usually recognized in children between 6 to 18 months as they begin to miss developmental milestones or lose abilities they had gained.



Genetic study(MeCP2 test)

- Loss of speech
- Loss of purposeful use of hands
- Involuntary hand movements such as handwashing
- Loss of mobility or gait disturbances
- Loss of muscle tone
- Seizures or Rett “episodes”
- Scoliosis
- Breathing issues
- Sleep disturbances
- Slowed rate of growth for head, feet and hands



Genetic study(MeCP2 test)

Rett syndrome is

most often misdiagnosed as autism,

cerebral palsy,

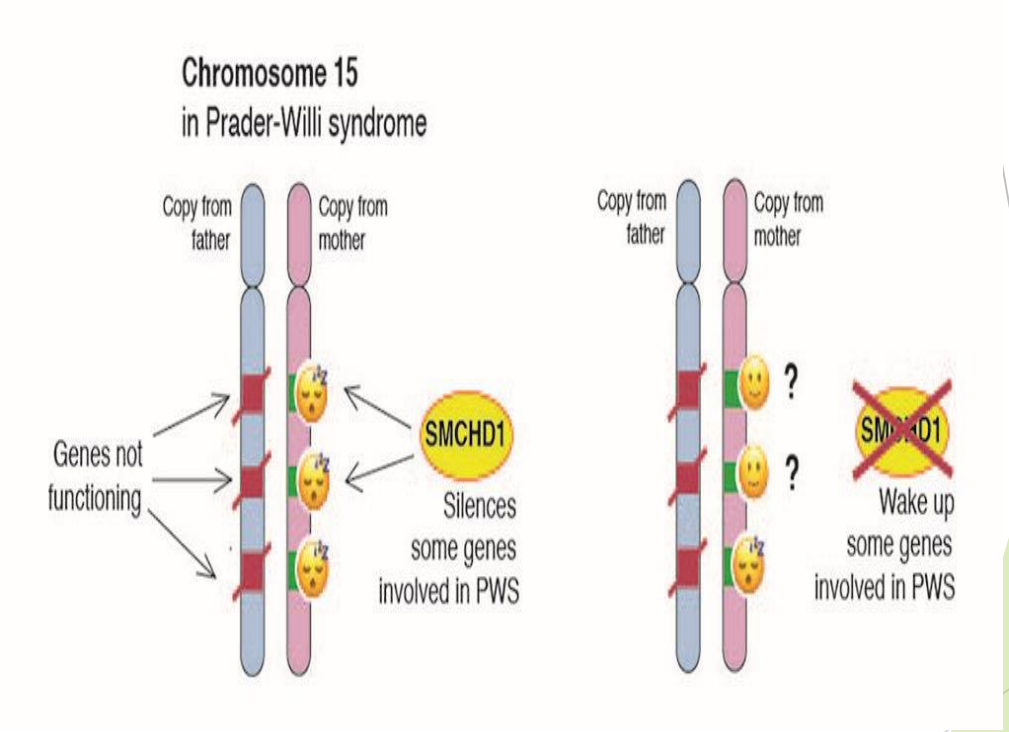
or developmental delay

PWS/AS

This region of chromosome 15 is located at 15q11.2-q13 and has been designated the Prader-Will syndrome/Angelman syndrome region (PWS/AS).

In individuals with PWS, the nonfunctioning PWS/AS region is always located on the number 15 chromosome inherited from the father.

Microarray testing will detect ~70% of PWS or AS, ie. all cases caused by chromosome 15 deletion and some cases caused by UPD

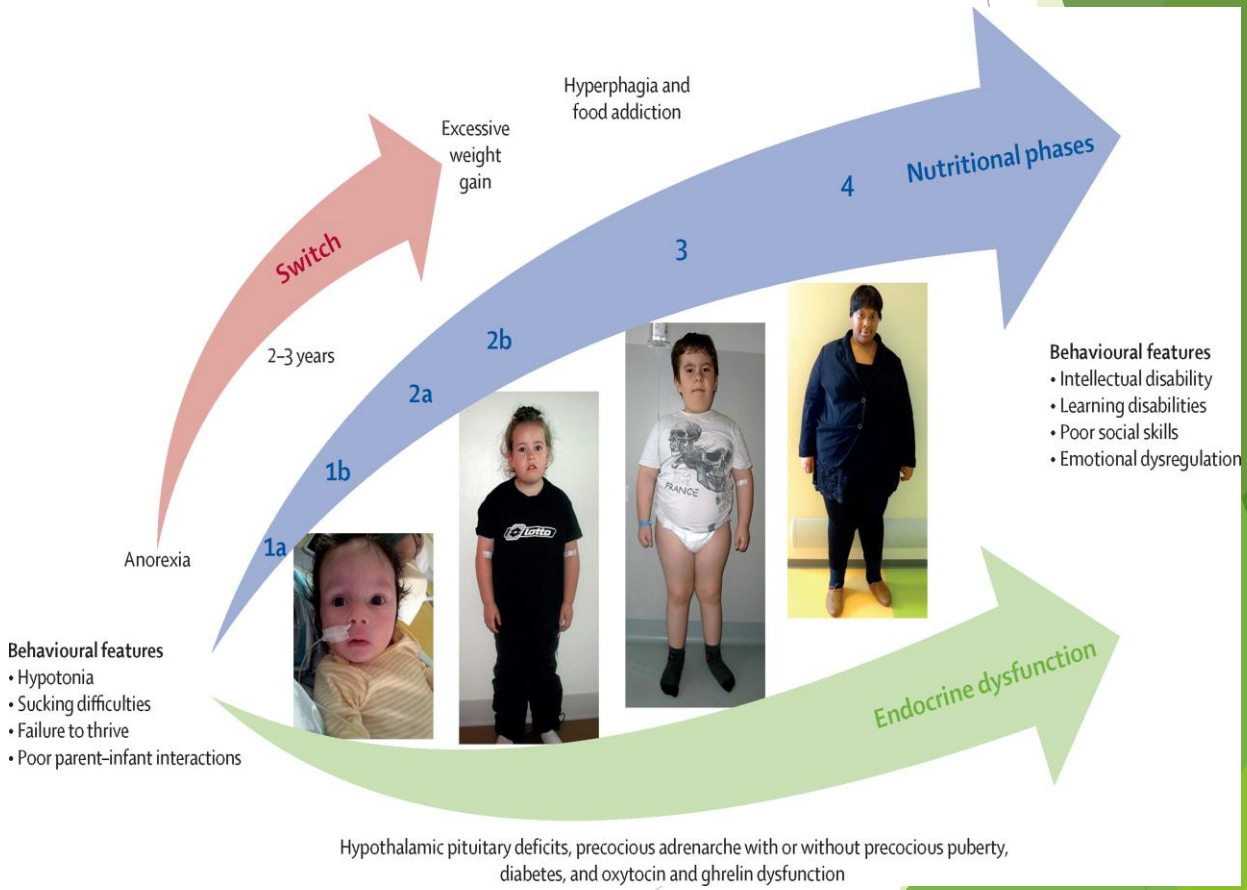


prader willi syndrome(PWS)

PWS is **a rare non-inherited genetic disorder**,

approximately one out of every 15,000 births. PWS affects males and females with equal frequency and affects all races and ethnicities

PWS is the first disorder confirmed to be due to imprinting errors



prader willi syndrome(PWS)

Infancy:

Poor muscle tone.

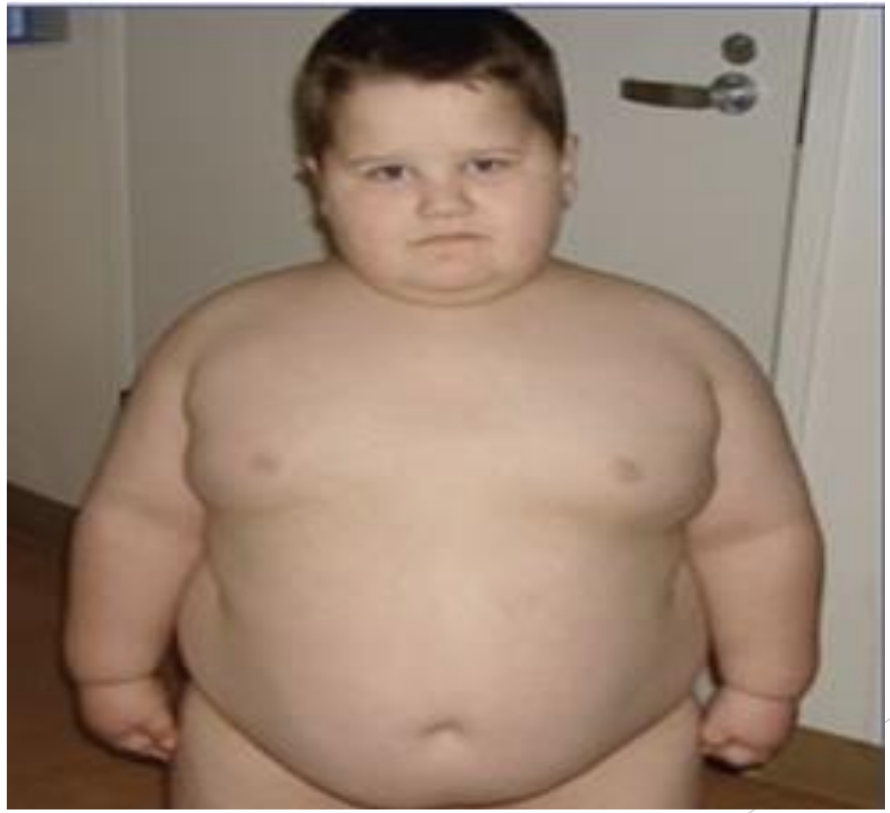
Distinct facial features. almond-shaped eyes

Poor sucking reflex.

Generally poor responsiveness.
Underdeveloped genitals. .

prader willi syndrome(PWS)

Early childhood to adulthood
•Food craving and weight gain
•Underdeveloped sex organs .
•Poor growth and physical development
•Cognitive impairment
•Delayed motor development
•Speech problems .
•Behavioral problems.
•Sleep disorders.
•Other signs and symptoms
• PWS is the most common genetic cause of life-threatening childhood obesity.



ANGELMAN syndrome (AS)

one child in every 10,000 to 20,000

Rare genetic disorder

UBE3A gene on chromosome 15 is missing or mutated.

Most diagnoses are made between the ages of two and five years of age.

ANGELMAN syndrome (AS)

Angelman syndrome (AS) is characterized by severe developmental delay or intellectual disability,

severe speech impairment,

gait ataxia and/or tremulousness of the limbs,

and unique behavior with an apparent happy demeanor that includes frequent laughing, smiling, and excitability.

ANGELMAN syndrome (AS)

molecular genetic testing (methylation analysis and *UBE3A* sequence analysis) identifies alterations in approximately 90%

next generation sequencing and GDD

A systematic clinical approach can help to identify a genetic cause for global developmental delay (GDD) and ID

Chromosomal microarray (CMA) is the first line diagnostic genetic test for individuals with GDD/ID

Second-line genetic tests include next-generation sequencing of GDD/ID gene panels or trio clinical exome or whole exome sequencing (CES/WES)

Use of genomic tests such as CMA, CES and WES can reveal incidental findings unrelated to the diagnosis of GDD/ID

Inborn error of metabolism(IEOM) study

Recent work emphasized 90 treatable metabolic disorder and GDD/ID.

IEOM study is controversial in different regions world, depended on:

Family history,

Parental consanguinity,

Documented developmental regression,

Suggestive dysmorphology,

Involvement of nonectodermal organ system , and

possible white matter involvement observed on imaging or

peripheral electrophysiologic studies

Phenylketonuria

PKU is the most common IEOM

a musty odor in the breath, skin or urine

neurological problems that may include seizures

skin rashes (eczema)

fair skin and blue eyes, because phenylalanine can't transform into melanin

abnormally small head (microcephaly)

hyperactivity

intellectual disability

delayed development

behavioral, emotional and social problems

psychiatric disorders

Other tests

There are also some conditions where early diagnosis can be made from simple and cheap biochemical screening tests.

This includes creatine kinase and thyroid function tests as well as ferritin, vitamin B12 and lead on a selective basis when Pica, dietary restrictions (vegan diet in child/mother) or environmental exposure risk is possible.

While these tests seldom lead to a diagnosis, they also may add to a diagnosis (eg, macrocytic anemia in organic acidemias, abnormal triiodothyronine in Allan-Herndon-Dudley syndrome).

Allan-Herndon-Dudley syndrome

MCT8 (monocarboxylate transporter 8) = *SLC16A2* is highly expressed in liver and brain.

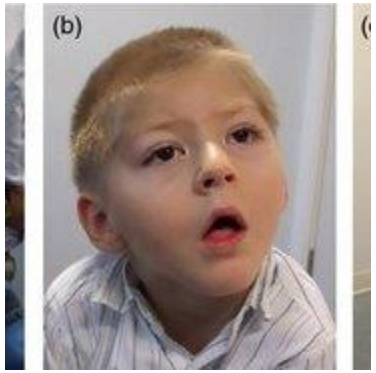
rare x-linked disorder

Increased free T3

T4 level low level of normal

TSH level normal

Free T_3/T_4 ratio >0.75 (expressed as mmol/mmol)



Allan-Herndon-Dudley syndrome

Onset before age two years often with hypotonia and feeding difficulties

Developmental delay / intellectual disability ranging from mild to profound intellectual disability

Extrapyramidal findings: dystonia, choreoathetosis, paroxysmal movement disorder, hypokinesia, hypomimia (masked facies)

Pyramidal signs

Late-onset seizures, often with drug resistance

Allan-Herndon-Dudley syndrome

This constellation of measurements of thyroid function enables quick screening for AHDS in males presenting with

mental retardation,

congenital hypotonia,

Gait problems

and generalized muscle weakness

Neuroimaging

MRI of the brain has been used selectively and non-selectively in evaluating patients with GDD.

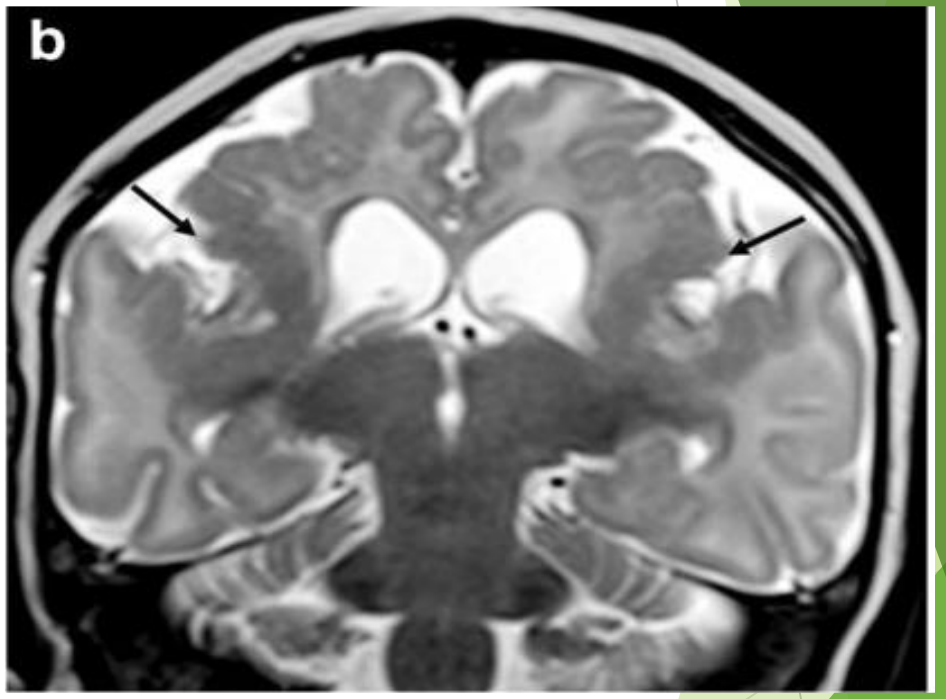
The diagnostic yield of MRI is higher when used in patients where GDD is associated with clinical signs such as abnormal head circumference (microcephaly, non-familial macrocephaly, rapid change in head circumference), focal neurological signs or epilepsy.

Neuroimaging

Targeted imaging was hence advocated by previous guidelines. Previous studies have demonstrated abnormal results in targeted imaging in about 41% compared with 14% with non-selective screening.

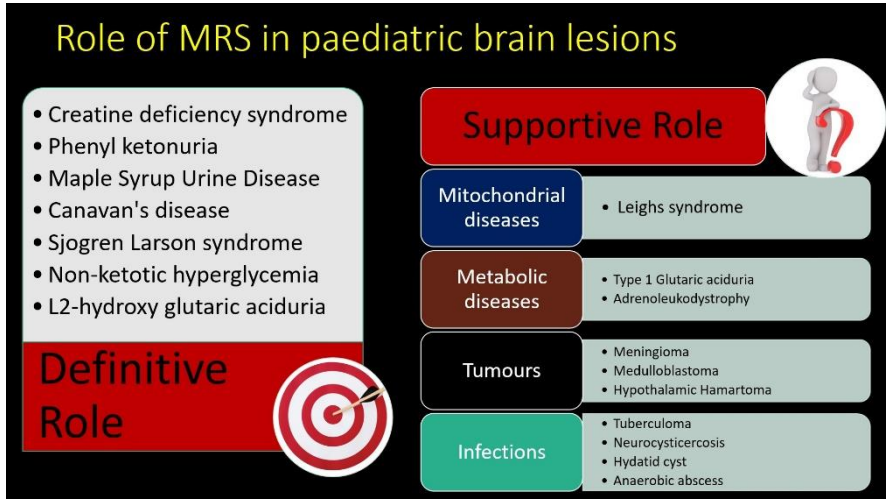
Ex.4 months old F and GDD and microcephaly

bilateral perisylvian malformation of cortical development (polymicrogyria) with thickening and disorganization of the cortex extending into the parietal lobes (arrows)



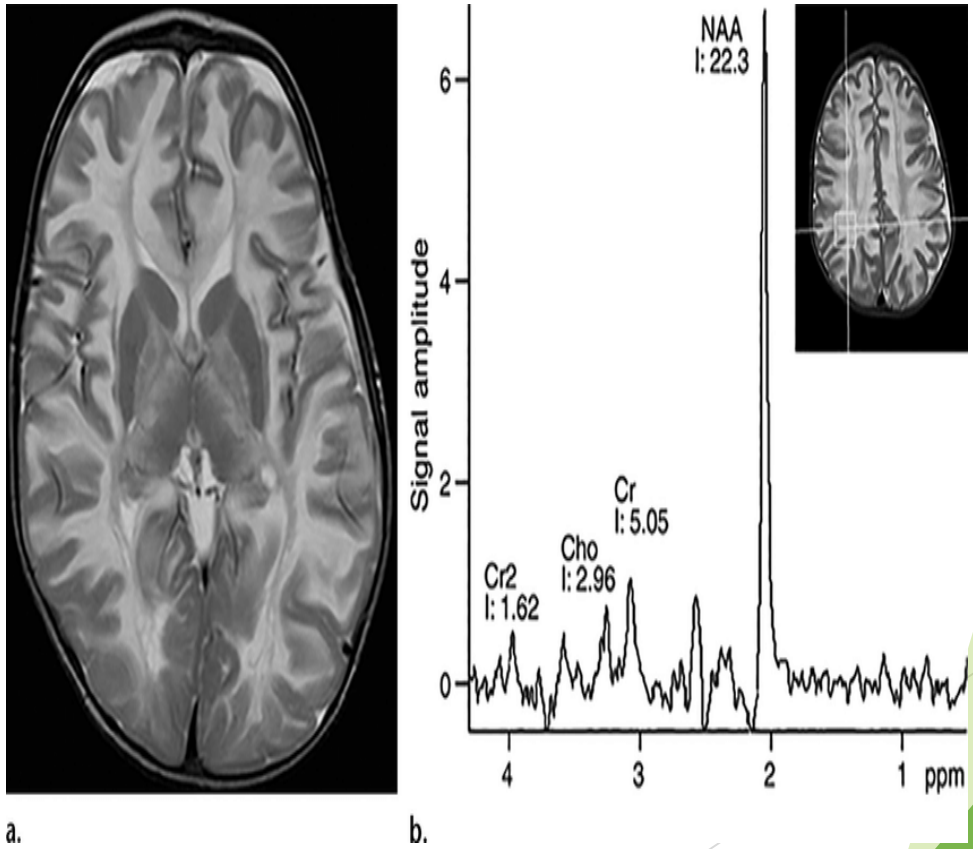
Neuroimaging

More complex MRI protocols (eg, proton magnetic resonance spectroscopy, (MRS) are promising tools to investigate GDD and enable a non-invasive measure of brain metabolites such as lactate or white matter choline, but studies have so far failed to show an increased diagnostic yield, and hence these are best used as second line in selected patients.



MRS AND GDD

Canavan disease and increased NAA peak



Neuroimaging

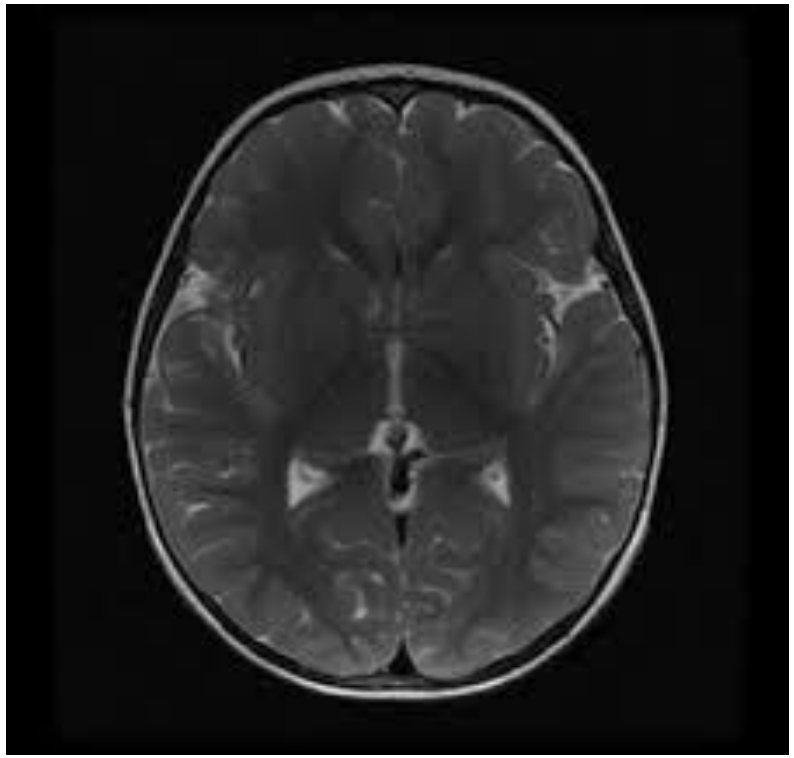
MRI is a more sensitive test and has no radiation exposure,

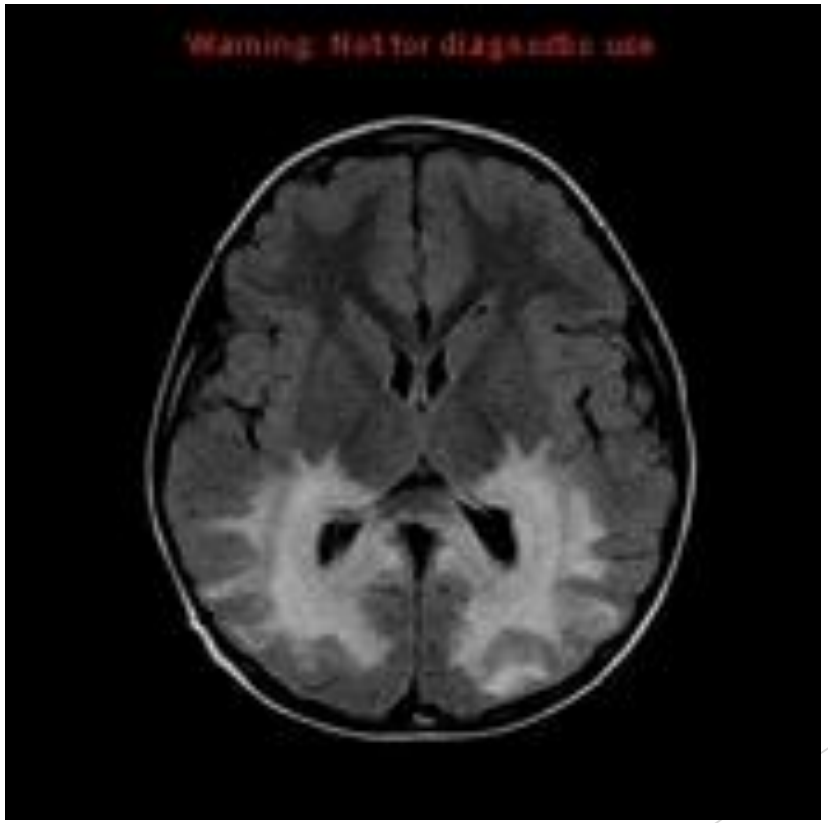
making it a preferred choice over CT.

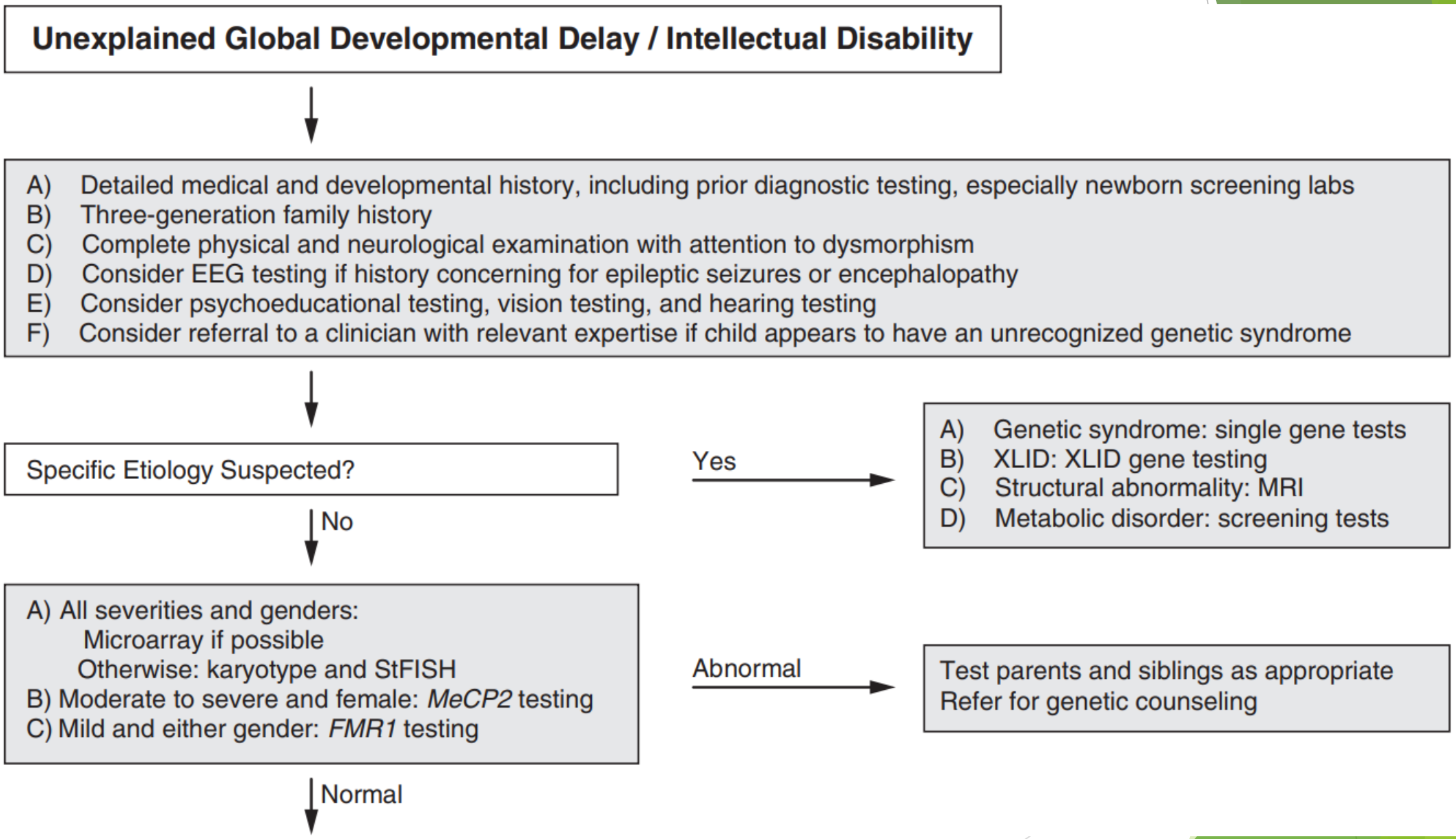
However, all children under 5 years will need sedation or a general anesthetic, which has a slim risk attached, and some children will need further investigations including a lumbar puncture.

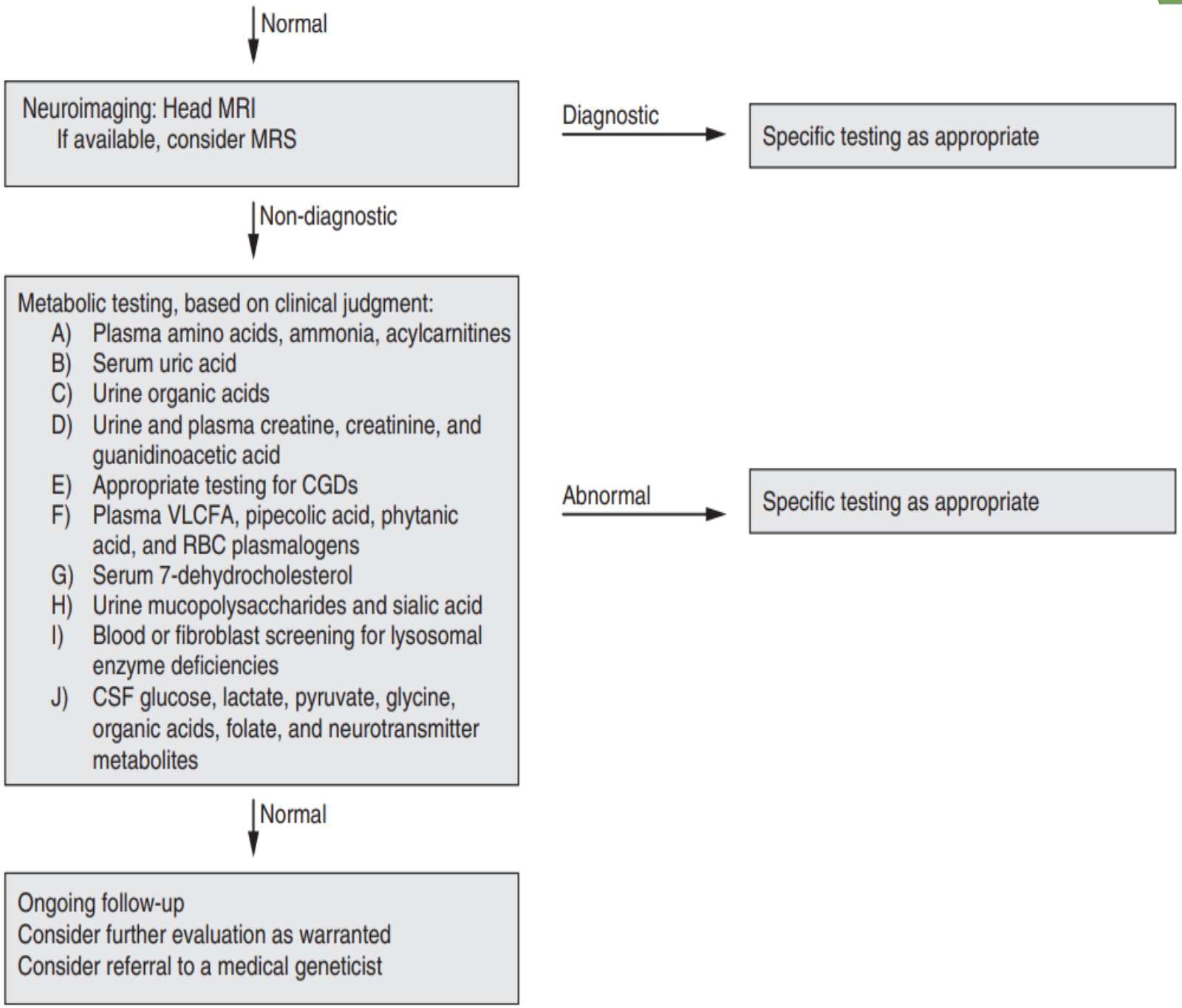
There is an argument, therefore, that children requiring brain imaging should see a specialist prior to imaging, if an anesthetic is required

Neuroimaging






Unexplained Global Developmental Delay / Intellectual Disability
A) Detailed medical and developmental history, including prior diagnostic testing, especially newborn screening labs
B) Three-generation family history
C) Complete physical and neurological examination with attention to dysmorphism
D) Consider EEG testing if history concerning for epileptic seizures or encephalopathy
E) Consider psychoeducational testing, vision testing, and hearing testing
F) Consider referral to a clinician with relevant expertise if child appears to have an unrecognized genetic syndrome
Specific Etiology Suspected?
Yes
A) Genetic syndrome: single gene tests
B) XLID: XLID gene testing
C) Structural abnormality: MRI
D) Metabolic disorder: screening tests
No
A) All severities and genders:
Microarray if possible
Otherwise: karyotype and StFISH
B) Moderate to severe and female: MeCP2 testing
C) Mild and either gender: FMR1 testing
Abnormal
Test parents and siblings as appropriate
Refer for genetic counseling
Normal


Normal
Neuroimaging: Head MRI
If available, consider MRS
Diagnostic
Specific testing as appropriate
Non-diagnostic
Metabolic testing, based on clinical judgment:
A) Plasma amino acids, ammonia, acylcarnitines
B) Serum uric acid
C) Urine organic acids
D) Urine and plasma creatine, creatinine, and guanidinoacetic acid
E) Appropriate testing for CGDs
F) Plasma VLCFA, pipecolic acid, phytanic acid, and RBC plasmalogens
G) Serum 7-dehydrocholesterol
H) Urine mucopolysaccharides and sialic acid
I) Blood or fibroblast screening for lysosomal enzyme deficiencies
J) CSF glucose, lactate, pyruvate, glycine, organic acids, folate, and neurotransmitter metabolites
Abnormal
Specific testing as appropriate
Normal
Ongoing follow-up
Consider further evaluation as warranted
Consider referral to a medical geneticist

Thanks for your attention