Clinical Approach To Intellectual Disability and Global Delay

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Intellectual Disability (ID)

- ID is a **neurodevelopmental disorder** with multiple etiologies
- It is characterized by deficits in **intellectual and adaptive functioning** of varying severity
- presenting **before 18 years** of age
- It is an **important public health issue** because of its prevalence
- Its management requires **early diagnosis and intervention**

Definitions

- ID **begins in childhood (<18)** and is characterized by limitations in both **intelligence and adaptive skills**, affecting at least one of three adaptive domains (conceptual, social, and practical), with varying severity. The **extent of adaptive impairment is key to defining ID and its severity**. The term ID replaces the older term of "**mental retardation".**

Adaptive skills used to define and determine severity of intellectual disability

Adaptive domain	Skills
Conceptual	These skills include language, reading, and writing (literacy); money, time, and number concepts (mathematics); reasoning; memory; self-direction; and judgment in novel situations.
Social	These skills include interpersonal social communication, empathy, ability to relate to peers as friends, social problem-solving, social responsibility, and self-esteem. Gullibility, the ability to follow rules, and avoiding victimization may also be included.
Practical	These skills include activities of personal care or daily living, such as eating, dressing, mobility, and toileting. Additional skills may include following a schedule or routine, using a telephone, managing money, preparing meals, occupational skills, and abilities in transportation/travel, health care, and safety.

- In the general population, the prevalence of **ID** is approximately 1 percent. (mild ID = %85)
- Prevalence of **Global Delay** is about 1 to 3 percent
- The prevalence of ID varies with age and gender. It is highest in **school-age and male** individuals

Syndromic versus nonsyndromic ID

- The term syndromic ID is applied when intellectual and adaptive impairment occurs with other **physical or comorbid symptoms** that may be recognizable as a syndrome
- When ID occurs **without features** of a possible recognizable syndrome, the term nonsyndromic ID is used

Global developmental delay (GDD)

- GDD is the preferred term to describe **intellectual and adaptive impairment in infants and young children <5 years old** who fail to meet expected developmental milestones in multiple areas of functioning
- **Not all children with GDD** will meet criteria for ID as they grow older. however, ID may also be applied to children <5 years who meet ID criteria as this can be important in obtaining supportive services

Key points in history and physical examination

- **History**

  Family history

  > Parental consanguinity, Family history of GDD/ID

  Antenatal history

  > IVF conception, Twinning, Maternal illness and/or drug intake, Maternal alcohol intake, Fetal scan findings

  Birth history

  > Prematurity, Growth parameters at birth, Birth injury, Birth asphyxia

  Neonatal history

  > Hypoxic-ischaemic injury/seizures, Prematurity-related complications, Jaundice Congenital abnormalities, Hypotonia

Postnatal history

> Developmental milestones, Seizures/epilepsy, Other neurological problems, Eye problems, Hearing problems, Behavioral concerns Progress at school Educational support (statement, education and health care plan), Skin problems, Feeding and eating problems, Postnatal growth, Bowel problems, Urinary problems
Sleeping pattern, Medications, Hospital admissions, Childhood immunizations

- **Physical examination**
  Growth parameters
  > Weight, Height, Head circumference, BMI
  Head-to-toe examination
  > Skull
  > Facial dysmorphism
  > Eyes
  > Ears
  > Teeth
  > Palate
  > Hands, fingers, nails and palmar creases
  > Pigmentary skin changes and hypertrichosis
  > Nipples
  > Sternum
  > Heart and femoral pulses
  > Abdomen (including umbilicus and inguinal areas)
  > External genitalia
  > Anal opening
  > Spine
  > Patellae
  > Feet, toes, nails and plantar creases
  > Joint hypermobility
  > Power, tone, deep-tendon reflexes, plantar reflexes, gait

Baseline investigations

Biochemistry

- **Blood:** calcium, phosphate, alkaline phosphatase; urate; CK; thyroid function tests; lactate; very long chain fatty acids; acylcarnitines; transferrin isoforms
- **Urine:** organic acids; amino acids; glycosaminoglycans and oligosachharides; sialic acid; sulphite; auccinylpurine; creatine and guanidinoacetate

Genetic

Chromosomal microarray

Molecular diagnostic test for Fragile X

Radiological

MRI brain (microcephaly, pigmentary skin anomalies, abnormal neurological examination)

CK = creatine kinase; MRI = magnetic resonance imaging

Additional biochemical investigations in specific cases

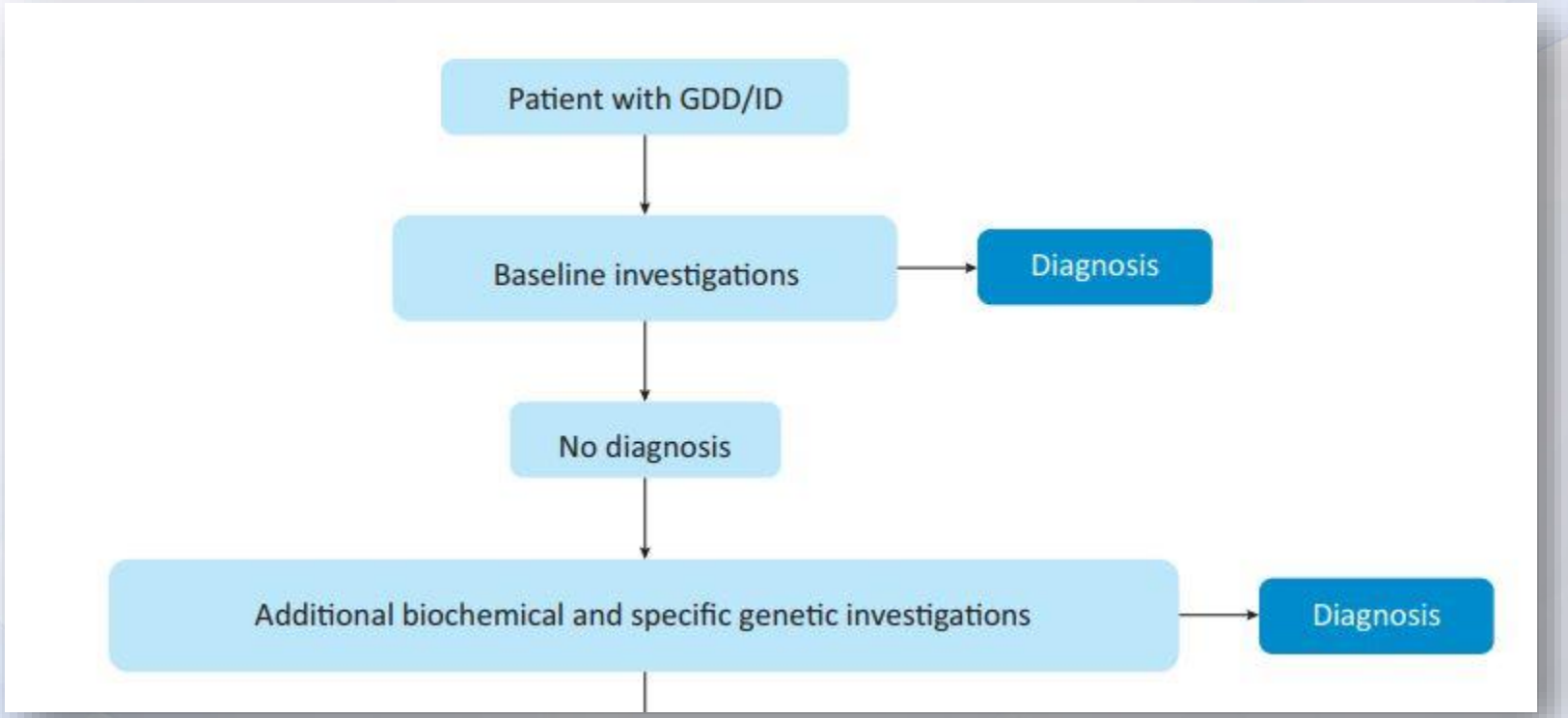
- **Urine:** purines and pyrimidines
- **Blood:** ammonia; copper and caeruloplasmin; cholesterol and 7-dehydrocholesterol; biotinidase; white cell lysosomal enzymes; plasmalogens, pipecolic acid and phytanic acid; cholestanol; prolidase
- **Cerebrospinal fluid (CSF):** glucose (including CSF to plasma glucose ratio); glycine (including CSF glycine to plasma glycine ratio); lactate; pyruvate; neurotransmitters
- **Muscle:** respiratory complexes
- **Hair:** amino acid analysis

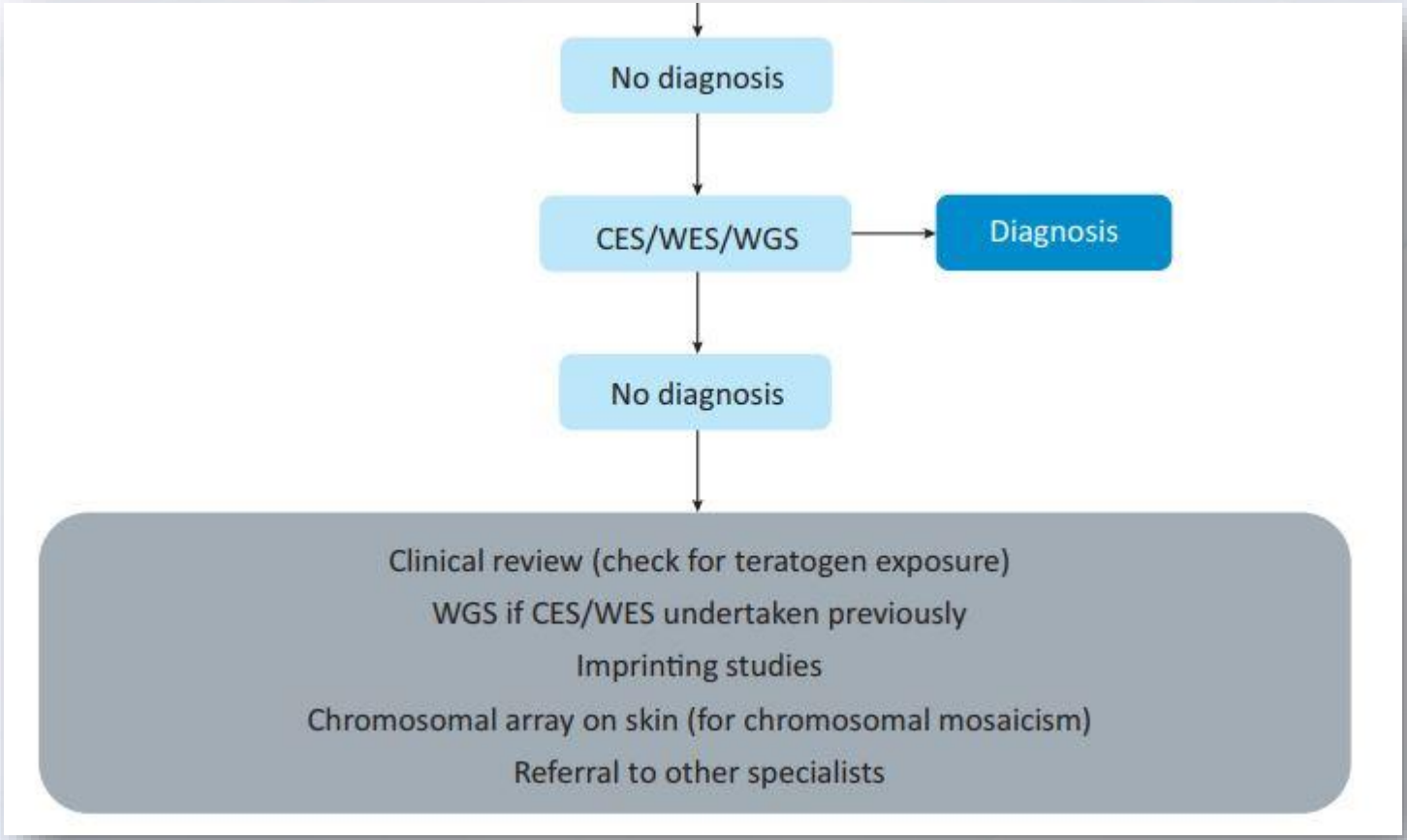
Genetic investigations in specific cases

- Specific genetic test (Sanger sequencing and copy number analysis) for suspected monogenic disorder
- Next-generation sequencing (and copy number analysis) of panel of genes (eg suspected X-linked disorder or based on phenotype, eg epilepsy or neuro-imaging abnormality)
- Chromosomal microarray and/or standard karyotype in cultured skin fibroblasts
- Methylation tests at imprinted chromosomal loci, including methylation-specific MLPA test for Prader-Willi and Angelman syndromes
- Triplet-primed PCR for myotonic dystrophy
- Clinical exome sequencing or whole exome sequencing
- Whole genome sequencing

MLPA = multiplex ligation-dependent probe amplification; PCR = polymerase chain reaction

A suggested diagnostic pathway for GDD/ID




No diagnosis
CES/WES/WGS
Diagnosis
No diagnosis
Clinical review (check for teratogen exposure)
WGS if CES/WES undertaken previously
Imprinting studies
Chromosomal array on skin (for chromosomal mosaicism)
Referral to other specialists