Approach to Intellectual Disability

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Definition

Significant sub-average intellectual function existing concurrently with deficits in adaptive behaviour and manifested during the developmental period.

Intellectual disability/ mental retardation has 3 components:

i. Significantly abnormal intellectual performance (determined by a test of intelligence)

ii. Impairment of the ability to adapt to the environment

iii. Onset during development before the age of 18 years

Developmental delay is a term usually used for young children especially ≤5 years in whom formal IQ testing is not possible, refers to delay in attainment of milestones and implies deficit in learning and adaptation. When all spheres are involved (gross & fine motor, social & adaptive, language), referred to as global developmental delay.

Mental retardation/ intellectual disability includes:

- Static non - progressive disorders with onset of cognitive impairment from birth/ early childhood
- Progressive disorders with onset of cognitive impairment in childhood
- Hereditary neurodegenerative and metabolic disorders with neuro-regression beginning some time after a period of normal development

Mental retardation/ intellectual disability is said to be present when the intelligence quotient (IQ) is less than 70. Classification based on IQ:

- Mild: 50 -70
- Moderate: 35 – 50
- Severe: 20 – 35
- Profound: < 20

Etiology

- Known Genetic Causes:
    - Chromosomal 30 – 35%
        - Down syndrome
        - Other chromosomal anomalies
        - Microdeletion syndromes
    - Single gene disorders 8 – 10%
        - Multiple malformation syndromes 4 – 5%
        - Fragile X and other X linked MR 1 – 3%
        - Inborn errors of metabolism 4%
- Multiple malformation syndromes: (non – monogenic) 15%
    - Known sporadic syndromes
    - New or private syndromes
- Central nervous system malformations: 5 – 7%
    - Neural tube defects
    - Hydrocephalus
    - Neuronal migration disorders
    - Microencephaly
    - Other structural anomalies: holoprosencephaly, Dandy – Walker malformation etc.
- CNS dysfunction due to identified perinatal, prenatal & postnatal causes 15%
    - Infection – fetal infection, postnatal meningitis or encephalitis
    - Teratogenic exposures
    - Asphyxia
    - Hemorrhage or infarction
- Static insults presenting as cerebral palsy: without substantial evidence of an environmental cause 5 – 10%
- Unidentified: 40 – 60%

Down syndrome is the most common genetic cause of mental retardation. It affects 1 in 700 – 800 live born children and accounts for 20 - 30% of all cases of MR. Trisomy 21 is found in 95% cases of Down syndrome, translocation involving chromosome 21 occurs in 3 – 4% cases and mosaic trisomy 21 occurs in 1% of cases.

Fragile X syndrome is the most common monogenic disorder associated with MR and is the most common inherited cause for MR. It accounts for 1 – 2 % of all cases of MR and has an X – linked inheritance pattern.

Diagnostic Approach to Intellectual Disability

1. Detailed history
2. Physical examination
3. Baseline hematological and biochemical investigations
4. Thyroid function tests
5. Neuroimaging
6. Karyotyping
7. Fluorescence in situ hybridization (FISH)/ Multiplex probe ligation dependent amplification (MLPA) study for specific suspected microdeletion syndromes
8. Fragile X molecular genetic testing
9. Molecular genetic testing/ metabolic testing for suspected specific monogenic conditions
10. Cytogenetic microarray study

History

- Antenatal period (age at conception, teratogens [drugs and infection], other maternal illnesses, abnormal ultrasound)
- Perinatal period (prematurity, diificult labour, asphyxia, growth retardation, sepsis, hyperbilirubinemia)
- Postnatal period (seizures, history of meningitis /encephalitis, abnormal posturing, spasticity, visual and hearing problems, exposure to lead, behavioral changes, deterioration in school performance)
- Detailed developmental history (time of attainment of milestones; regression of milestones)

- History suggestive of metabolic disorders (failure to thrive, recurrent unexplained illness, seizures, ataxia, loss of psychomotor skills, recurrent somnolence/ coma, lethargy, abnormal body odour)

Family history

- Detailed family history including 3 generation pedigree
- Family history of MR, developmental delay, seizures and unexplained psychiatric disorders.
- Try to ascertain the pattern of inheritance
- History of congenital malformations, miscarriages, stillbirths, and early childhood deaths.

Physical examination

- Complete anthropometric assessment (height, weight, head circumference, upper segment: lower segment ratio)
- Detailed dysmorphologic evaluation from head to toe and comparison of findings with available literature, OMIM and dysmorphology databases (such as London Dysmorphology DataBase, POSSUM)
- Detailed neurological evaluation:
    - higher mental functions,
    - cranial nerve deficits,
    - motor and sensory system examination,
    - cerebellar signs,
    - involuntary/ abnormal movements,
    - persistence of neonatal reflexes
- Ophthalmological examination should be done in all cases to look for corneal, lenticular and retinal abnormalities – can provide an important clue to the diagnosis
    - Retinal changes/ pigmentary degeneration: specific syndromes (Norrie disease, Bardet Biedl syndrome, mitochondrial disorders, NCL)
    - Chorioretinitis: congenital intrauterine infections
    - Cherry red spot: specific storage disorders (gangliosidosis, mucolipidosis, Niemann Pick disease)
    - Corneal clouding: mucopolysaccharidosis, oligosaccharidosis, mucolipidosis

- Cataract: galactosemia, congenital rubella syndrome, Lowe syndrome, congenital myotonic dystrophy, Cockayne syndrome
- Lens dislocation: homocystinuria, sulfite oxidase deficiency

- Assessment of the behavioural phenotype (e.g. self mutilation in Lesch Nyhan syndrome, self mutilation, aggression and sleep disturbances in Smith Magenis syndrome, autistic features in Fragile X and duplication 15q, hyperphagia and sleep disturbances in Prader Willi syndrome, typical hand movement stereotypes and breathing abnormalities in Rett patients)
- Complete general and systemic examination

Baseline Investigations:

- Complete hemogram including RBC indices (may provide clue to diagnosis eg. alpha thalassemia – mental retardation syndrome, macrocytosis in abnormalities of vitamin B12 metabolism etc.)
- SGPT: gross liver function assessment
- Serum creatinine: gross renal function assessment
- Serum creatine phosphokinase: young male patients with DMD may initially present with developmental delay

Serum T4 & TSH:

- Hypothyroidism must be excluded in all cases of developmental delay especially when clinical features of hypothyroidism are seen and in younger children (< 2 years) where no specific cause is identifiable
- Hypothyroidism may be associated with some genetic syndromes e.g. Down syndrome
- Very important to exclude because it is a treatable cause.

Neuroimaging:

- Recommended when :
  - abnormal head size: microcephaly/ macrocephaly
  - seizures
  - focal motor/ neurological findings on neurological examination
  - associated malformations esp. facial malformations

- Preferable to do if no other aetiology is obvious; in conditions like neuronal migration anomalies and some cases of pre/ perinatal insult there may be no other clinical diagnostic clue
- MRI is preferable to CT Scan for neuro-imaging and is much more informative
- Neuroimaging helps to identify hypoxic ischemic sequelae, vascular insults, neuroectodermal syndromes, intracranial structural defects and neuronal migration abnormalities.
- CT Scan head is better for documentation of intracranial calcifications associated with old hemorrhage, tuberous sclerosis complex and congenital CMV or toxoplasmosis infection, and for craniosynostosis

Specific tests based on the clinical features in each individual case:

Examples:

- Electrophysiological studies: EEG/ Audiometry/ EMG/ NCV
- TORCH serology: for suspected congenital intrauterine infections in infants
- Ultrasonography to look for renal malformations
- Echocardiography to look for cardiac malformations

Genetic Evaluation:

Should be done in all cases of intellectual disability without a definitely proven environmental cause. The label of 'cerebral palsy due to adverse perinatal events should not be given until there is definite evidence in neuroimaging.

Karyotyping:

- Should be done in all cases with intellectual disability, where a specific monogenic cause has not been clinically identified
- Conventional karyotyping (up to 550 band-level) yields a diagnosis in 2.5 – 3% of unexplained/ idiopathic MR cases

FISH/ MLPA study:

- To confirm the diagnosis of clinically identified microdeletion syndromes such as Prader-Willi syndrome, Angelman syndrome, Di George syndrome, Williams syndrome etc.
- MLPA panels to test for multiple common microdeletions in one test are available commercially

Testing for Fragile X syndrome:

- Fragile X screening can be done through PCR- based tests but confirmation requires Southern Blot testing.
- If fragile X molecular genetic testing is done using a phenotypic checklist of 7 features (proposed by de Vries et al, *J Med Genet* 1999) the diagnostic yield is ~7 – 8 % (long jaw, high forehead, large and/or protuberant ears, hyper extensible joints, soft and velvety palmar skin with redundancy on the dorsum of the hands, testicular enlargement, and behavior of initial shyness and lack of eye contact followed by friendliness and verbosity).
- Younger children have subtle dysmorphism which may be missed; therefore fragile X testing is recommended in all children especially males with idiopathic MR even in the absence of a family history.

Molecular genetic testing:

- If a specific monogenic disorder is suspected clinically, mutation analysis of the relevant gene to be done for confirmation

Metabolic testing:

- If a specific inborn error of metabolism (IEM) is suspected clinically, the relevant biochemical assay such as enzyme assay/ plasma amino acid HPLC/ urine GCMS for organic acids etc. is to be done for confirmation. Most IEMs present with neuroregression and have a progressive course
- Routine metabolic evaluation in unexplained MR has an average diagnostic yield of only around 1%.

Cytogenetic microarray:

- Has a diagnostic yield of around 12 – 15% in idiopathic MR.
- Has been recommended as the first line diagnostic test for idiopathic MR by the American College of Medical Genetics.
- Detects genome-wide copy number variations (CNVs- deletions/ duplications).
- Algorithm has to be followed to determine the pathogenicity of a detected CNV.

Management:

- For most cases of MR, treatment is mainly symptomatic and supportive.
- Mainstay of therapy: early stimulation/ physiotherapy/ vocational training/ special schooling/ speech therapy
- Institutionalization is to be discouraged and integration into society is encouraged.
- Multidisciplinary approach: for appropriate management

Genetic counseling

Depends on the aetiology:

A. Chromosomal causes of MR:

- usually not familial except when one of the parents is a carrier of a balanced chromosomal rearrangement.
- risk of recurrence in de novo chromosomal disorders is low (usually < 1%)
- In translocation Down syndrome, when one of the parents is a balanced translocation carrier the recurrence risk is variable:
  - 2 - 5% if the father is a carrier
  - 10 – 15 % if the mother is a carrier
  - 100% if either parent is a carrier of 21; 21 translocation

B. Single gene disorders:

- Risk of recurrence depends on the mode of inheritance:
- Autosomal recessive disorder: the risk of recurrence is 25% in the next sibling
- Autosomal dominant disorder: the risk of recurrence for the sibling is 50% if one of the parents is affected; in a sporadic case (de novo mutation), the risk of recurrence in the sibling is very low but gonadal mosaicism cannot be ruled out.
- X-linked recessive disorders: the risk of recurrence for boys is 50%, whereas females usually do not manifest the disorder.

C. Environmental causes:

- Recurrence is unlikely but can occur if the causative agent persists in the environment of the other child e.g. lead exposure, intrauterine exposure to teratogens like alcohol or specific drugs

D. When no etiology is identified:

- Empiric risks of recurrence can be predicted when no specific etiology is identified (but prenatal diagnosis is not possible)

Accompanying feature	Approx. risk of recurrence
Microcephaly alone	1 in 6 to 1 in 8 (10 – 15%)
Microcephaly with other features	1 in 30 (3%)
Infantile spasms	1 in 30 to 1 in 100 (1 – 3%)

Non – specific dysmorphic features	1 in 25 to 1 in 30 (3 – 4%)
Malformation	1 in 50 (2%)
No specific features; male proband	1 in 13 (8%)
No specific features; female proband	1 in 20 (5%)
Holoprosencephaly with normal karyotype & no forme fruste in parents	1 in 20 (5%)
Lissencephaly type 1	Very low (<1%)
Lissencephaly type 2	1 in 4 (25%)
Cerebellar hypoplasia	1 in 8 (12.5%)
Schizencephaly/ asymmetric porencephaly	Very low
Cerebral palsy (diplegia/ hemiplegia)	1 in 200 to 1 in 400
Symmetrical spasticity	1 in 8 to 1 in 9 (10 – 12%)
Asymmetric neurological signs	1 in 50 to 1 in 100 (1 – 2%)
Ataxic diplegia	1 in 24 (4%)
Congenital ataxia	1 in 8 (12.5%)

Prenatal Diagnosis:

- Fetal karyotyping (preferably amniotic fluid): if proband has an identified chromosomal anomaly
- Fetal sample FISH/ MLPA/ cytogenetic microarray analysis: if proband identified to have microdeletion/ CNV detected by FISH, MLPA or microarray
- Fetal (CVS/ cultured amniocytes) targeted mutation analysis/ linkage analysis: if proband has monogenic disorder with identified/ unidentified mutation
- Fetal tissue (CVS/ cultured amniocytes/ amniotic fluid) enzyme assay/ metabolite assay: if proband identified to have a specific metabolic disorder
- Fetal targeted anomaly scan at 16 – 18 weeks and/ or serial USG monitoring for multiple malformation syndromes/ microcephaly/ CNS malformation syndromes (fetal MRI may also be done)