Evaluation of Children With Global Developmental Delay/Intellectual Disability

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Objectives

- Define and discuss Global Developmental Delay and Intellectual Disability.
- Discuss the screening options and etiologies for both Global Developmental Delays and Intellectual Disability.
- Discuss the importance of identifying a specific etiology for children with Global Developmental Delays.
Definitions

- **Global Developmental Delay (GDD)**
  - Term typically for children < 6 years of age
  - 1-3% of children in this age group
  - Significant Delay (> 2 SD) in 2 or more of the following domains
    - Gross/Fine Motor
    - Speech/Language
    - Cognition
    - Social/Personal
    - Activities of daily living
  - Many, but not all, may later manifest intellectual disability
Definitions

- Intellectual Disability
  - Usually applied to children > 6 years of age
  - IQ testing in children > 6 years is more valid
  - Mild Intellectual Disability
    - IQ 50-70
  - Moderate to severe Intellectual Disability
    - IQ < 50
Identification

- Developmental Surveillance
  - Formal screening, parental reports
- Identification of biological and social risk factors
- Identification of environmental influences – culture, parental skills, neglect, opportunity
- Attempt to differentiate between GDD, speech-language delay and autism
- Early intervention
  - May improve outcome
- Diverse etiologies
Investigation of Etiology

- History and Physical – may yield an etiology in 30-40% of cases
- Hearing and visual assessments
- EEG – particularly useful with concomitant history of seizures
- CT/MRI scan of the brain, MR spectroscopy
- Blood tests – lead level, thyroid function
- Cytogenetic studies – karyotype, subteleomeric FISH, Chromosomal microarray, whole exome sequencing
- Testing for inborn errors of metabolism
History and Physical

- **History**
  - Prenatal and Birth History
  - Developmental History
  - Family History, consanguinity, history of fetal/infant demise
  - Past history of acute events, episodes of decompensation, seizures

- **Physical examination**
  - Dysmorphic features
  - Cutaneous abnormalities
  - Organomegaly
  - Cardiac examination
  - Neurological examination
  - Congenital abnormalities
Cutaneous Examination
Cutaneous Examination
Seizures and Developmental Delay

- Children with developmental delay have a significantly higher incidence of epilepsy (10-20%).

- Epileptic Encephalopathies
  - Conditions in which the epilepsy and the associated EEG abnormalities contribute, at least in part, to the developmental delay
  - Often show evidence for developmental regression or slowing/arrest of development
  - Seen most often with onset of epilepsy in infancy
EEG in Developmental Delay

- Has confirmatory value if there is a history indicative or suggestive of seizures, encephalopathy or a particular epileptic syndrome
- Important to recognize subtle seizures
  - Infantile spasms
  - Drop attacks, head drops, atonic seizures
  - Myoclonic seizures
  - Staring spells
- Of considerable value if there is a history of regression in speech-language or regression in milestones
  - Epilepsy aphasia syndromes – Landau Kleffner syndrome
  - Epileptic encephalopathies – Dravet syndrome etc.
- EEG yield in developmental delay without definite seizures is low and may reveal non-specific epileptiform abnormalities
Neuroimaging in Developmental Delay

- Screening with CT/MRI is quite useful in determining an etiology of developmental delay
- MRI is superior to CT
  - CT abnormalities – 30%
  - MRI abnormalities – 48-65%
- Presence of physical findings such as focal deficits, microcephaly increase the likelihood of abnormalities on neuroimaging
Neuroimaging in Developmental Delay

- MRI abnormalities
  - CNS malformations – lissencephaly, polymicrogyria, pachygyria, heterotopias, cortical dysplasias, schizencephaly
  - Cerebral atrophy
  - White matter disease/abnormalities
  - Post-ischemic lesions
  - Phakomatosis – Neurofibromatosis, Tuberous Sclerosis
  - Specific malformations – Dandy Walker, Joubert syndrome
Lissencephaly

Pachygyria

4-month old female with developmental delay. Developed infantile spasms at 6 months of age.
Subcortical Band Heterotopias
Hemispheric Malformations of Cortical Development

- T2 weighted sagittal image
  - Predominantly posterior involvement
  - Posterior dysplastic and pachygyric cortex
  - Moderately increased volume on the right with midline shift in the occipital area
  - Ex vacuo effect anteriorly

Focal Cortical Dysplasia

Presented at age 8 months with infantile spasms. Currently 7-years old with seizures well controlled.
7-Year old child with intractable seizures, starting at age 2 months.
Multifocal Cortical Dysplasia In Tuberous Sclerosis
X-Linked Periventricular Heterotopias

12-year old girl presented with new onset complex partial seizures.
Schizencephaly

Polymicrogyria/Cortical Dysplasia

Presented at age 8 months with partial secondarily GTC seizures; Subsequently developed infantile spasms.
Polymicrogyria/Cortical Dysplasia
Inborn Errors of Metabolism

- Screening for inborn errors of metabolism has a yield of 0.2-4.6% depending on clinical features and extent of testing performed
- Higher yield if newborn screening was not done
- Factors suggestive of inborn error
  - Positive family history, consanguinity, history of fetal demise or unexplained deaths in childhood
  - Episodic decompensation, episodic seizures, episodes of encephalopathy
  - Developmental regression
  - Organomegaly, multiple organ dysfunction
  - Dietary selectivity, unusual odors
  - Hearing loss
  - Coarsening of facial features
  - MRI findings of abnormal myelination and/or basal ganglia signal abnormalities
Inborn Errors of Metabolism

- Screening tests for inborn errors of metabolism
  - Plasma amino acids, ammonia, acylcarnitine profile, serum uric acid
  - Urine organic acids
  - Urine and plasma creatine and guanidinoacetate
  - Serum transferring electrofocusing (carbohydrate deficient glycoprotein)
  - Plasma Very Long Chain Fatty Acids (VLCFAs), phytanic acid
  - Serum 7-dehydrocholesterol (Smith-Lemli-Opitz)
  - Urine mucopolysaccharides and sialic acid
  - Blood for lysosomal enzyme deficiencies
  - CSF glucose, lactate, pyruvate, glycine, organic acids, folate, and neurotransmitter metabolites
  - CPK, TSH and free T4
Inborn Errors of Metabolism

- Testing for congenital disorders of glycosylation
  - Yield up to 1.4%
- Testing for creatine synthesis and transport disorders
  - Yield up to 2.8%
  - Potentially treatable
Cytogenetic testing

- Genomic-wide testing for DNA rearrangements
  - G-Band Karyotyping
    - Detects chromosomal structural changes with a resolution of 3-5 million base pairs (3-5 Mb)
  - Subteleomeric FISH testing
    - Detect copy number changes (deletions or duplications) for which specific probes are constructed
    - Resolution of 1 Mb
- Microarray tests
  - Oligonucleotide probes
  - Resolution of 30,000 – 35,000 base pairs (kb)
Cytogenetic Studies

- Chromosomal microarray testing is abnormal on average in 7.8% of subjects with GDD/ID and in 10.6% of those with syndromic features.

- Interpretation
  - Diagnostic – previously causative
  - Possibly diagnostic – absent in unaffected parents
  - Uncertain significance – inherited from an unaffected parent

- Results are often complex and require help of a medical geneticist.
Cytogenetic Studies

- Chromosomal Microarray has limitations. It can identify only unbalanced copy number changes. Not sensitive for:
  - Inversions
  - Balanced insertions
  - Reciprocal translocations
  - Polyploidy
  - Low level mosaicism (<20-25%)
  - Rearrangements in repeat sequences
  - Point mutations
  - Duplications/deletions undetectable test’s resolution
Cytogenetic studies

- Karyotype studies are abnormal in > 4% of subjects with GDD/ID and in 18.6% of those with syndromic features

- Subtelemomic FISH testing is abnormal in
  - 3.5% of subjects with GDD/ID
  - 4.2% of those with syndromic features
  - 0.5% of those with mild impairment
  - 7.4% of those with moderate/severe impairment
Fragile X-syndrome

- Most common inherited disorder causing global developmental delay
- CGG Trinucleotide repeats
  - 5-40 repeats – Normal
  - 41-55 repeats – Intermediate
  - 56-200 repeats – Premutation
  - > 200 repeats – Full mutation
- Prevalence of full mutation 1:3700 to 1:8900
- Prevalence of premutation 1:1000
- FMRI testing has a yield of at least 2% in males and females with mild GDD/ID
X-Linked Genetic Testing

- X-Linked intellectual disability (XLID) accounts for 10% of cases of ID
- > 70 cloned genes cause XLID
- Family history often definitely points to or is suggestive of an X-Linked mutation
- Common X-Linked genes
  - FMRI – Fragile X syndrome
  - ARX
  - JAR1D1C
  - SLC6A8
- Testing for XLID genes positive in 42% males from definite X-Linked families, 17% males from possible X-Linked families
Whole Exome Sequencing

Sequencing
- Standard
- Next gen
- Exome
- Genome

Karyotype
- ArrayCGH
- MLPA
ArrayCGH vs Next Gen Sequencing
Benefits of identifying a specific etiology

- Relieves anxiety/uncertainty
- Limits further costly and invasive diagnostic tests
- Improves understanding of treatment and prognosis
- Helps to anticipate and manage associated medical and behavioral comorbidities
- Empowers caregivers to become involved in support and research networks
- Counseling for recurrence risk
- Prevent recurrence – screening for carriers, prenatal screening
Conclusions

- Global developmental is seen in 1-3% of children below the age of 6 years
- History and Physical may give important clues to the underlying diagnosis
- While blood tests and testing for inborn errors of metabolism may be helpful, MRI scan of the brain and cytogenetic studies provide the most information
- There are significant benefits to the identification of a specific etiology including improving understanding of treatment and prognosis