Inborn errors of metabolism in the child with developmental delay

Dr. Maureen Cleary
Consultant Metabolic Paediatrician
Outline of talk

• Developmental delay

• Inborn errors of metabolism causing DD

• Clinical features suggest IEM

• Useful investigations
“Developmental delay”

• Definition
  - significant
    • two standard deviations below the mean of accepted developmental testing

• Incidence of developmental disabilities
  - 5-10% of childhood population
Definitions

• Global Dev delay in infants/young children
  - 1-3% of children < 5 years

• Mental retardation > five years (once IQ testing more reliable)
Paediatric assessment

• History

• Examination
  – Characterise the pattern of delay
    • Single domain
    • Multiple domains
  – Systematic examination

• Aetiology confirmed in almost 20%
<table>
<thead>
<tr>
<th>Cause</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosome abnormalities</td>
<td>4-28</td>
</tr>
<tr>
<td>Recognizable syndromes</td>
<td>3-7</td>
</tr>
<tr>
<td>Known monogenic conditions</td>
<td>3-9</td>
</tr>
<tr>
<td>Structural CNS abnormalities</td>
<td>7-17</td>
</tr>
<tr>
<td>Complications of prematurity</td>
<td>2-10</td>
</tr>
<tr>
<td>Environmental/teratogenic</td>
<td>5-13</td>
</tr>
<tr>
<td>'Cultural-familial' mental retardation</td>
<td>3-12</td>
</tr>
<tr>
<td>Provisional unique, monogenic syndromes</td>
<td>1-5</td>
</tr>
<tr>
<td>Metabolic/endocrine causes</td>
<td>1-5</td>
</tr>
<tr>
<td>Unknown</td>
<td>30-50</td>
</tr>
</tbody>
</table>
IEM as cause of dd

- **Not** common cause of ‘pure’ dd
  - 1%

- usually other features to suggest IEM

- however

  some IEM will present as pure dd
IEM as cause of delay

• **IMPORTANCE**
  
  - recurrence risk
  - prevention of metabolic crisis
  - there may be specific treatment
Which IEM’s can cause dd?

• Neurodegenerative disorders
  • lysosomal storage
  • peroxisomal storage
  • mitochondrial disease

• Toxic brain metabolites (acute)
  • organic acidurias
  • urea cycle defects
Which IEM’s can cause dd?

• Toxic brain metabolites (chronic)
  - non-ketotic hyperglycinaemia
  - phenylketonuria
  - galactosaemia

• Structurally abnormal brain
  - Smith-Lemli-Opitz
  - Disorder of carbohydrate glycoprotein
Developmental delay: establishing a cause

- HISTORY & EXAMINATION
  - 19%
- plus LABORATORY TESTS
  - 50%

  - cytogenetic/molecular 35%
  - EEG 8%
  - Neuroimaging 6%
Clinical features of IEM’s:

History

• Birth and prenatal
  - birth often normal in IEM

• family history
  • previous neonatal death
  • parental consanguinity
Clinical features: history

• past medical history
  • accompanying unusual episodes
    - hypoglycaemia
    - acute encephalopathy
    - very unwell with seemingly mild illness
  • unusual behaviour
    - protein aversion
    - ‘psychiatric’
Clinical features of IEM’s

- History of developmental delay
  - developmental regression*
  - single domain
    - motor
    - language
  - multiple domain
Developmental regression

• Strongly suggestive of IEM

  - lysosomal
  - peroxisomal
  - mitochondrial
Problems in interpretation clinical features

• early fatal disease before appreciable cerebral maturation has occurred

• extremely chronic disease where it is unclear if there is regression

• abrupt onset confused with infectious processes
Problems in interpretation clinical features

• intercurrent illness, seizures or drug therapies affect assessment

• manifestations of earlier nonprogressive lesions evolve
Lysosomal storage disorders

• Demyelination
  - infancy
  - early childhood
  - long-tract signs
  - clumsiness
  - MRI leucodystrophy
  - rapid progression

• KRABBE
• METACHROMATIC LEUCODYSTROPHY
Lysosomal storage disorders

• Direct storage
  - slower onset of neurology
  - developmental delay
  - leading to regression
  - hydrocephalus

• MUCOPOLYSACCHARIDOSIS
Peroxisomal Disorders

• **Group I**
  - failure of biogenesis of peroxisomes
  - **ZELLEWGER (CEREBRO-HEPATO-RENAL)**

• **Group II**
  - problems in biogenesis of peroxisomes but recognisable peroxisomes
  - **RHIZOMELIC CHONDRODYSPLASIA PUNCTATA**
  - **ZELLEWGER-LIKE SYNDROME**

• **Group III**
  - peroxisomes present
  - **X-LINKED ADRENOLEUCODYSTROPHY**
  - **CLASSICAL REFSUM**
Mitochondrial disorders

- any system
- any inheritance
- any age
Mitochondrial disorders

- Affect grey and white matter
- other suggestive signs
  - cardiomyopathy
  - eye signs (ret pig, cataract, ptosis)
  - muscle disease
  - haematological
  - liver disease
The A to Z of Mitochondrial Symptoms

- Aminoglycoside deafness
- Bone marrow dysfunction
- Cardiomyopathy
- Diabetes
- **Episodic** vomiting
- Fever
- Gastrointestinal Motility
- Hepatomegaly
- **Idiopathic** dystonia
- Jaundice
- Kidney dysfunction
- Lipomas
- Malformations

- Neuropathy
- Optic atrophy
- **Progressive** organ involvement
- Questionable diagnosis
- Retinitis pigmentosa
- Seizures
- Tachypnea
- Unexplained assoc symptoms
- Vascular abnormalities
- Wasting
- Xertional myoglobinuria
- Yucky outlook
- Zestless
Mitochondrial disease

- **LEIGH DISEASE** or **LEIGH-LIKE SYNDROME**
  - can be slow onset regression
  - episodic hyperventilation
  - basal ganglia changes
Clinical features associated with IEM

• Examination
  - Growth
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings
Clinical features associated with IEM

• GROWTH

  - failure to thrive common
  - head circumference
    • microcephaly
    • macrocephaly
Clinical features associated with IEM

• Examination
  - Growth
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings
Clinical features of IEM: Examination findings

• Appearance
  - eyes
  - hair
  - skin
  - dysmorphic
Clinical features of IEM: Exam

• Eyes
  - cataract
    - peroxisomal disorders
    - homocystinuria
    - gyrate atrophy of choroid and retina
    - (galactosaemia)
  - corneal clouding
    - mucopolysaccharidosis
  - cherry red spot
    - neurolipidoses
Clinical features of IEM: Exam

- Hair
  - coarse
    - mucopolysaccharidosis
  - kinky
    - Menkes disease
Clinical features of IEM: Exam

• Skin
  - thickened, coarse
    • MPS
    • Refsum’s disease
Clinical features of IEM: Exam

- Dysmorphism
  - Smith-Lemli-Opitz
  - Carbohydrate deficient glycoprotein disorders
  - MPS
  - Menkes
  - Peroxisomal
Clinical features of IEM: Examination findings

• Examination
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings
Clinical features of IEM: organomegaly

- Hepatomegaly/splenomegaly
  - Gauchers
  - Niemann-Pick
  - other storage disorders
Clinical features of IEM: Examination findings

- Examination
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings
Clinical features of IEM: exam

- Smell
  - sweaty feet
    - isovaleric aciduria
  - maple syrup urine
    - maple syrup urine disease
Clinical features of IEM: Examination findings

- Examination
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings
Clinical examination: neurological findings

- Hypotonia
- Hypertonia
- Dystonia
- Macrocephaly
- Microcephaly
Clinical examination: neurological findings

• Hypotonia
  - muscle disorders
  - initial phase of neurological regression

• Hypertonia
  - neurodegenerative disorders
Clinical examination: neurological findings

• Dystonia
  - neurotransmitter defects
  - mitochondrial disorders
  - glutaric aciduria type I
  - Wilson’s disease
Clinical examination: neurological findings

• Macrocephaly
  - CANAVAN
  - L-2 HYDROXYGLUTARIC ACIDURIA
  - GLUTARIC ACIDURIA TYPE I
  - TAY-SACHS
Clinical examination: neurological findings

- Microcephaly
  - SULFITE OXIDASE DEFICIENCY
  - MATERNAL PKU
  - AS RESULT OF NON-SPECIFIC DAMAGE
Developmental delay

- No historic clues
- No regression
- No examination abnormalities (apart from dd)

- Which disorders may cause this picture?
Developmental delay

- Propionic/methylmalonic acidaemia
- D-2 or L-2 hydroxyglutaric aciduria
- 4-hydroxybutyric aciduria
- Urea cycle disorders
- Homocystinuria
- Creatine deficiency
- Sanfilippo Disease
Developmental delay

• Which investigations should be carried out in dd without other specific features?

• No consensus
Investigations global delay; no clues

- **Blood**
  - CK
  - FBC
  - U/Es
  - LFTs
  - TFT
  - Lactate
  - Ammonia
  - Urate
  - Amino acids

- **Urine**
  - Amino acids
  - Organic acids
  - glycosaminoglycans
Interpretation of results

• **CK**
  - Fatty acid oxidation disorders, muscle disease

• **Lactate**
  - Erroneous
  - Gluconeogenetic disorders
  - Pyruvate metabolism
  - Mitochondrial disorders

• **Ammonia**
  - Urea cycle
  - Liver dysfunction
  - Erroroneous

• **Urate**
  - Glycogen storage
  - Purine disorders
  - Molybdenum cofactor deficiency
Developmental delay without clues

• Importance of serial evaluation

• Diagnoses increase 5-20% with return visits
  - two visits in first year of life
  - yearly until early school years
  - re-evaluation during puberty
Summary

• Several IEM’s are associated with dd

• Neurological regression makes IEM very likely

• If no specific features IEM unlikely

• Laboratory tests necessary for diagnosis