Inborn errors of metabolism in the child with developmental delay

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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%

CAUSE OF MENTAL RETARDATION IN LITERATURE SURVEY (%)

Chromosome abnormalities	4-28
Recognizable syndromes	3-7
Known monogenic conditions	3-9
Structural CNS abnormalities	7-17
Complications of prematurity	2-10
Environmental/teratogenic	5-13
'Cultural-familial' mental retardation	3-12
Provisional unique, monogenic syndromes	1-5
Metabolic/endocrine causes	1-5
Unknown	30-50

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
  - ZELLWEGER (CEREBRO-HEPATO-RENAL)
- Group II
  - problems in biogenesis of peroxisomes but recognisable peroxisomes
  - RHIZOMELIC CHONDRODYSPLASIA PUNCTATA
  - ZELLWEGER-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

L12

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

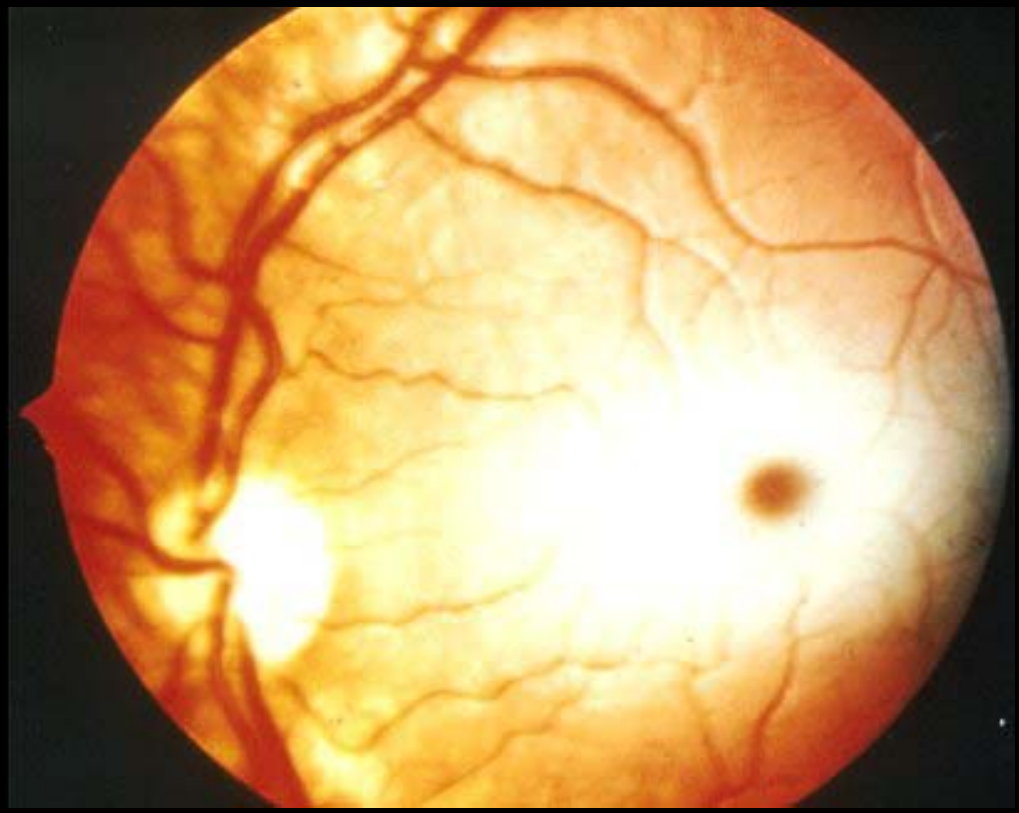
- Examination
  - Growth
  - Appearance
  - Organomegaly
  - Smell
  - Neurological findings

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