Developmental delay, regression and inherited metabolic disease

Caroline Griffith

HST Clinical Biochemist

Royal Manchester Children's Hospital

Initial presentation

- 1st child of these parents
- Parents second cousins
- Born a normal vaginal delivery at term, normal pregnancy and antenatal scans, no neonatal problems
- No family history of note, no history of problems in babies/children in the family
- Birth weight 2.595kg (9th centile)
- Presented to DGH with a history of poor feeding, poor weight gain, pain post feeds since birth
- Irritable, persistent crying
- Weight on admission 5.37kg (2nd centile)

Initial thoughts

- **Gastroesophageal reflux, ?cause**
- **Alternative feeds tried to exclude feed intolerance.**
- **Anti-reflux medication tried including a proton pump inhibitor, an anti-emetic and an antacid.**
- **All unsuccessful**

Initial investigations

- **Bloods**
  - **Normal renal function & liver function tests. Normal plasma lactate and ammonia**
- **A barium meal showed no aspiration or hiatus hernia**
- **Cranial Ultrasound Scan was performed because of the babies abnormal tone and showed abnormal thickening in ventricles ?Choroid cysts, ?heterotrophic (mislocated) grey matter ? Ependymal thickening, ? Tubular sclerosis**
- **MRI of the brain recommended**

Specialist Review

- **5/7 day history of neurological regression**
- **Loss of smile, no longer fixing and following**
- **Head control had been gained but was now lost**
- **Excessive crying, causing disturbed sleep**
- **Abnormal posturing, markedly increased tone, flexion at wrists and elbows**
- **Flexor spasms**
- **Impression ? Infantile spasms**

  ? Neurometabolic problem

Further Investigations

- **Full blood count, U&Es, LFTs, ammonia, lactate, blood gases, acylcarnitines, quantitative plasma amino acids – No significant abnormalities**
- **Urine organic acids, amino acids, mucopolysaccharides- No significant abnormalities**
- **MRI of the brain, EEG**
- **At a neurology review plasma very long chain fatty acids, white cell lysosomal enzymes, plasma biotinidase, copper, caeruloplasmin, transferrin isoelectric focussing and a TORCH screen were requested.**
- **CSF protein was elevated (1.7g/l Normal 0.05-0.45)**
- **CSF glucose & lactate were normal.**

Differential diagnoses

- **Initially, differential diagnosis**
  - **Gastroesophageal reflux disease ?cause**
  - **? Infantile spasms**
  - **? Neurometabolic problem**
  - **Cerebral malformation**
  - **??? Space occupying intracranial lesion**
- **The results of plasma very long chain fatty acids, plasma biotinidase, copper, caeruloplasmin, transferrin isoelectric focussing and the TORCH screen revealed no significant abnormalities.**
- **However white cell lysosomal enzyme assays revealed an abnormality!!!**

Diagnosis and Further Tests

- **A lysosomal enzyme screening panel using an artificial substrate showed a marked deficiency of leucocyte beta-galactocerebrosidase**

  0.17µmol/g protein/hr (Normal 0.8-4.0)

- **Confirmation by radioactive method using a natural substrate demonstrated a complete deficiency (0.01nmol/mg/hr, Normal 0.4-4.0)**

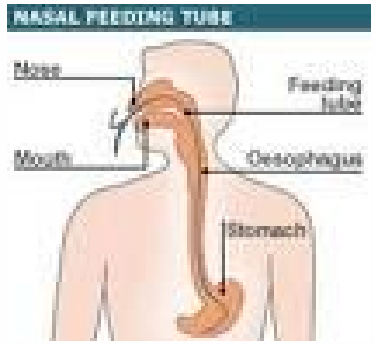
- **MRI of the brain showed considerably delayed myelination. Small areas of symmetrical high signal in the cerebellum and pons**

Diagnosis

- **Krabbe's Disease**
  - **Globoid cell leucodystrophy**

Treatment

- **Supportive**
  - **Nasogastric feeding required because of absent swallowing reflex**
  - **Baclofen (muscle relaxant to relief spasticity)**
  - **Chloral hydrate (sedative)**
  - **Domperidone (anti-emetic)**
  - **Lactulose (osmotic laxative)**
  - **Ranitidine (reduces gastric acid)**



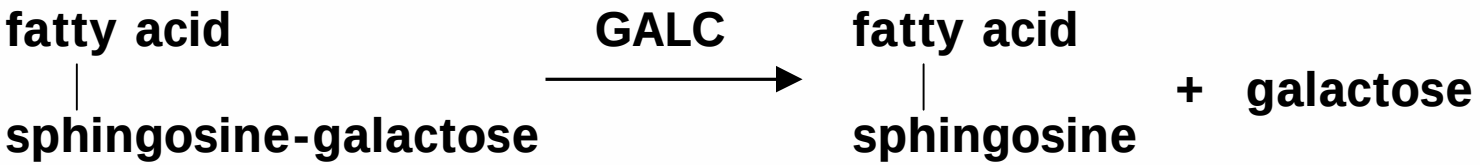
Krabbes Disease

What is Krabbes disease?

- **Deficiency of the lysosomal hydrolase beta-galactocerebrosidase (0-5% activity)**
  - **Also known as galactosylceramide beta-galactosidase**

Pathophysiology

- **Galactosylceramide abundant and located exclusively in the myelin sheath. Synthesised by oligodendroglia and Schwann cells**
- **Galactosylceramidase is necessary to break down galactosylceramide to ceramide + galactose**



- **Accumulation of psychosine (deacylated sphingosine-galactose) which is toxic and causes destruction of oligodendroglia and Schwann cells**

Genetics and Inheritance

- **Estimated incidence 1 in 100,000 births**
- **Inheritance pattern – Autosomal Recessive**
- **Pan-ethnic**
  - **But increased in consanguineous groups**
- **Four clinical forms; infantile, late infantile, juvenile, adult**
  - **A wide spectrum of clinical severity**

Disease progression (infantile form)

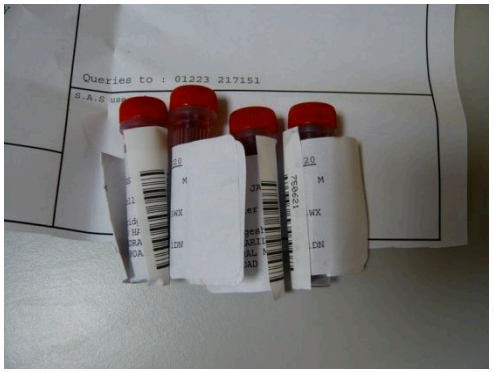
- **Stage 1 – irritability, arrest of psychomotor development, feeding difficulties**
- **Stage 2 – psychomotor regression, hypertonia, abnormal reflexes, optic atrophy. Seizures**
- **Stage 3 – severe neurologic impairment, loss of voluntary movements. Blindness, deafness and loss of awareness of external stimuli.**

- **Outcome: Infection and respiratory failure are the usual causes of death**

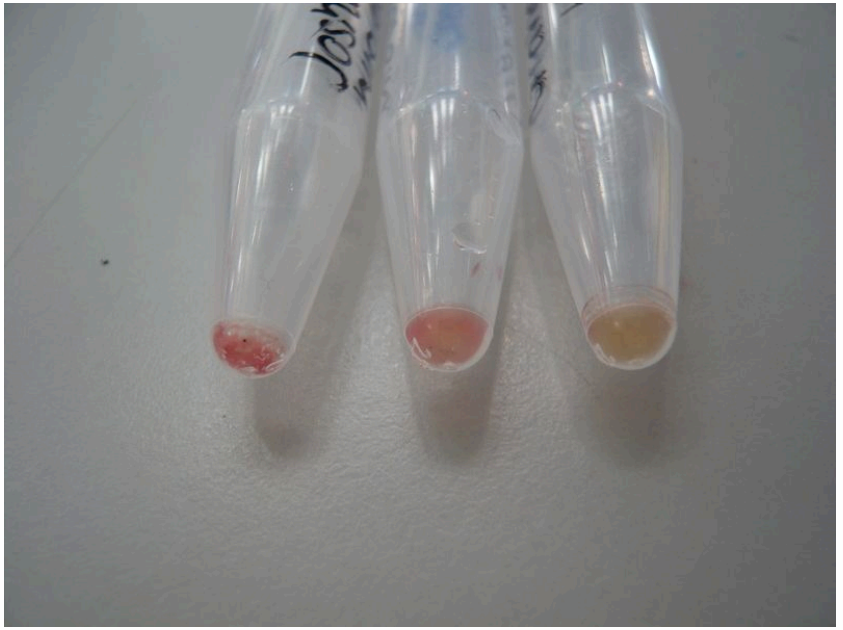
Diagnosis

- **Carried out by assaying beta-galactocerebrosidase enzyme activity in leucocytes**
- **Willink laboratory method**
  - **Two stage for potentially affected individuals**
    - **White Cell Enzyme screen using a fluorimetric artificial substrate**
    - **Confirmation of low results with a specific test using the radioactively labelled natural substrate**

White cell enzyme assay preparation

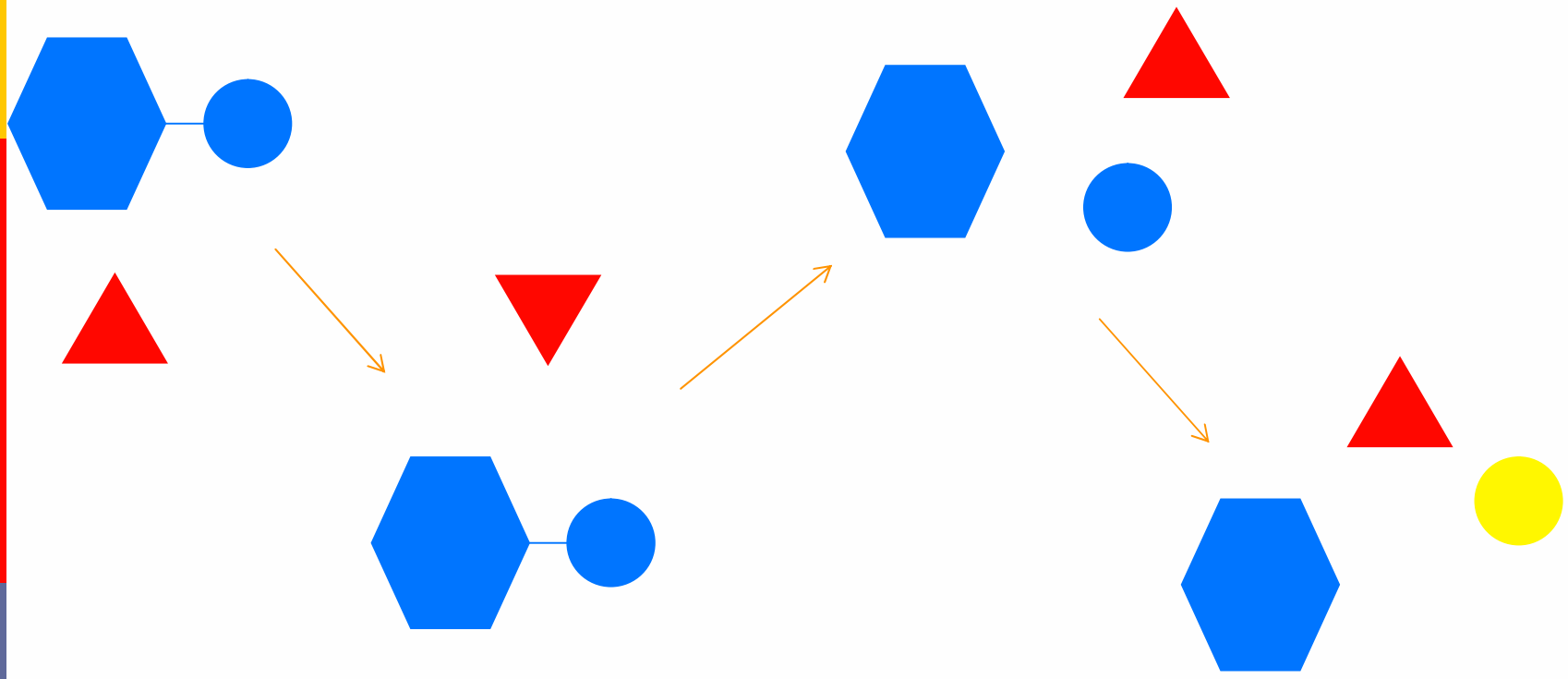


EDTA blood



White cell pellets and plasma

Fluorimetric white cell enzyme assay principles



Substrate

4-methylumbelliferone

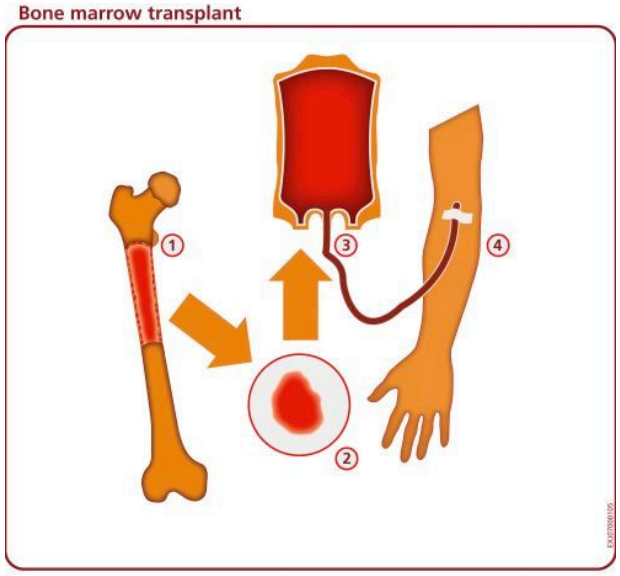
Enzyme

Treatment and monitoring

- **No curative treatment**
- **Palliative care**
  - **Drugs to control reflux**
  - **Drugs to reduce hypertonicity**
  - **Drugs to relieve pain – morphine if necessary**

Treatment (cont.)

- **Bone marrow transplant**
  - **Reported to have some limited success**
  - **Must be initiated early (before signs of neurological impairment)**



Prognosis/Prevention

- **Poor**
- **Almost all infantile Krabbes patients die before 2 years of age**
- **Carrier testing – not reliable by enzyme assay but can be done by DNA analysis if the primary mutation is defined**
- **Prenatal diagnosis is possible by enzyme analysis however a rare pseudodeficiency state exists which has to be excluded by assays on parental samples.**

Summary

- **The patient followed the typical course for an infantile onset Krabbes disease case with early onset reflux, abnormalities of tone, rapid loss of gained skills (neuroregression) and abnormal brain scans.**
- **Krabbes disease has no specific somatic manifestations**
- **CSF protein is often elevated.**
- **Diagnosis is by assay of the affected lysosomal enzyme, beta-galactocerebrosidase**
- **There is no curative treatment, only palliative support, but counselling can be provided for the parents**