Gasping for breath – diagnostic dilemmas in infantile apnoea

James Nurse, Sarah Williams, Mark Beattie, Gary Connett, Andrea Whitney
Southampton General Hospital

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Clinical presentation and diagnostic journey

-3 — Admission to DGH
5-month-old with a history of desaturation, back arching, and cyanosis. Initially managed as bronchiolitis.

Cries just prior to going rigid, appears unable to breath and floppy after. Rigid episodes since 5 weeks of age.

-3 — CT head
No acute intracranial abnormality

-3 — MRI head
No abnormality seen to account for clinical presentation

0 — Transfer to SGH
On-going episodes, no clear cause identified. Transfer to Southampton for neurology (& other speciality) input.

1 — Neurology review
First child of unrelated parents, increasing frequency of apnoeic episodes and stiffening seen from 5 weeks. No history of infection or birth trauma with normal development.

Unlikely infantile onset dystonia, manage as **Sandifers**. Not consistent with seizures, requires gastro input.

2 — Gastro review
Infant mixed feeding with good growth and no vomiting. Normal examintion aside from mild laryngomalacia.

Likely **GORD**, add Gaviscon to PPI and consider weaning.

5 — Fibreoptic bronchoscopy
Marked broadening of the membranous trachea in the subglottis. Consistent with significant **tracheomalacia**.

Suggest trial of non-invasive ventilation and regular Azithromycin

6 — Sleep study
3% ODI elevated ++ with prolonged period with saturations < 90%.

10 — CT neck & chest
Mild narrowing of the subglottic trachea without evidence of a compressive neck mass or vascular ring.

10 — Sleep study (CPAP)
Study has improved over baseline but 4% ODI still elevated for age.

10 — USS abdomen
Enlarged liver with diffusely increased reflectivity. The spleen is enlarged with otherwise normal appearance.

12 — Laryngotracheobronchoscopy & flexible bronchoscopy (ENT)
Laryngomalacia evident in certain positions. Trachealis noted to be prominent in mid tracheal position.

Impression: **Laryngomalacia** but unclear if this is the cause of the current symptoms.

16 — White cell enzymes
Sent in view of squint, organomegaly, low platelets, and unexplained apnoeas.

18 — Prolonged EEG
Apnoeic episode captured. No epileptiform activity but bradyarrhythmia during episode.

24 — Diagnosis
White Cell Enzymes expedited by Willink Lab.

Chitotriosidase: **14,278.2** nmol/ml/hr (4-120)
(Non-specific biomarker of storage disorders)
Beta-glucocerebrosidase: **0.34** nmol/mg/hr (L)
Consistent with **Gaucher Disease**

Subsequently confirmed to have bi-allelic variants in *GBA1* gene, segregated in parents.

37 — Parents
AM's parents were strong advocates for their child throughout.

Once a storage disease was considered **they** identified Gaucher Disease as a likely differential.

37 — Denouement
Following diagnosis the palliative care team became actively involved. AM was discharged to a hospice after 6 weeks in hospital and passed away in the loving care of his parents at 7 months of age.

This case presented significant diagnostic challenges requiring the input of neurology, respiratory, gastroenterology, ENT, radiology, haematology, ophthalmology, PICU and, ultimately, palliative care. Despite a number of diagnoses being proposed, no-one wanted to discharge this child until a satisfactory formulation was found.

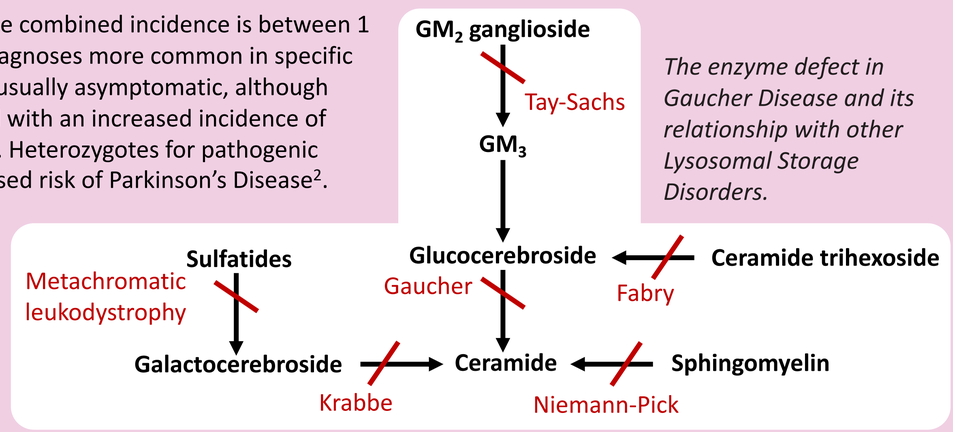
Lysosomal Storage Disorders

Lysosomes are membrane-bound cell organelles with a vital role in antigen presentation, inflammatory regulation and autoimmunity. The majority of the lysosomal storage diseases (LSDs) are caused by mutations in the genes encoding a lysosomal enzyme; over 70 specific LSDs have been described to date[1].

These defects lead to the accumulation of macromolecules within the lysosomes, with multisystem consequences, although organ involvement varies by disease. Most are autosomal recessive and the severity of disease is also impacted by the degree of residual enzyme activity.

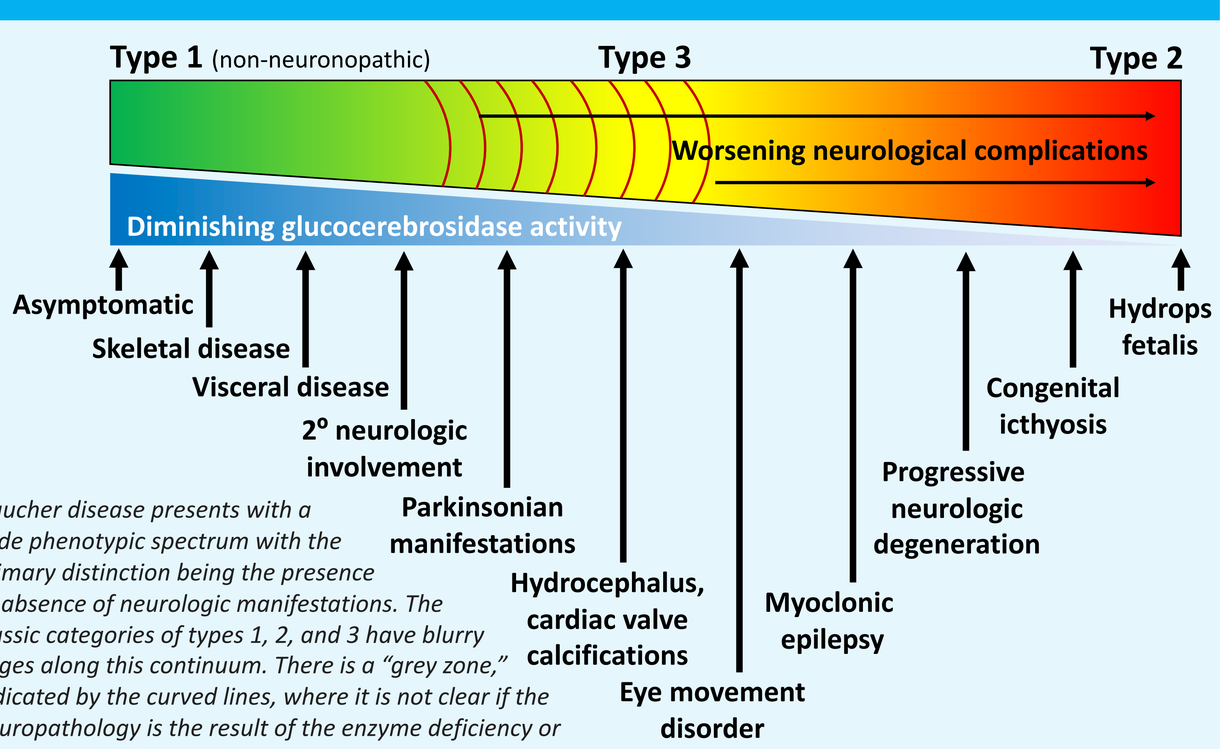
Though individually rare, the combined incidence is between 1 in 5000-8000, with some diagnoses more common in specific ethnic groups. Carriers are usually asymptomatic, although carrier status may be linked with an increased incidence of neurodegenerative disease. Heterozygotes for pathogenic *GBA1* variants are at increased risk of Parkinson's Disease[2].

In Gaucher disease (GD) biallelic variants in *GBA1* cause glucocerebrosidase deficiency. It is classically divided into 3 types based on neurologic progression.



The enzyme defect in Gaucher Disease and its relationship with other Lysosomal Storage Disorders.

Gaucher disease – a phenotypic continuum[3]



Gaucher disease presents with a wide phenotypic spectrum with the primary distinction being the presence or absence of neurologic manifestations. The classic categories of types 1, 2, and 3 have blurry edges along this continuum. There is a "grey zone," indicated by the curved lines, where it is not clear if the neuropathology is the result of the enzyme deficiency or due to a secondary cause.

Ataxia

Non-immune fetal hydrops
LSDs found in 10% of cases

Hepatosplenomegaly

Eye signs
visual loss, corneal clouding, cherry red spots

Symptoms suggestive of LSDs typically develop over time[4]

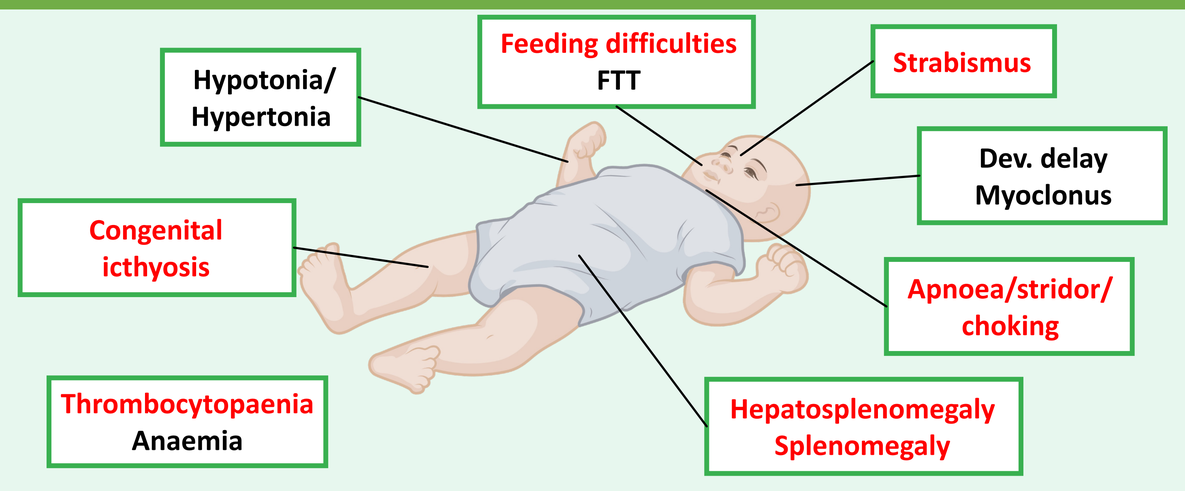
Coarse facial features

Increasing weakness

Dev. regression

Bone disease
e.g. dysostosis multiplex

Clinical features in Type 2 Gaucher Disease[5]

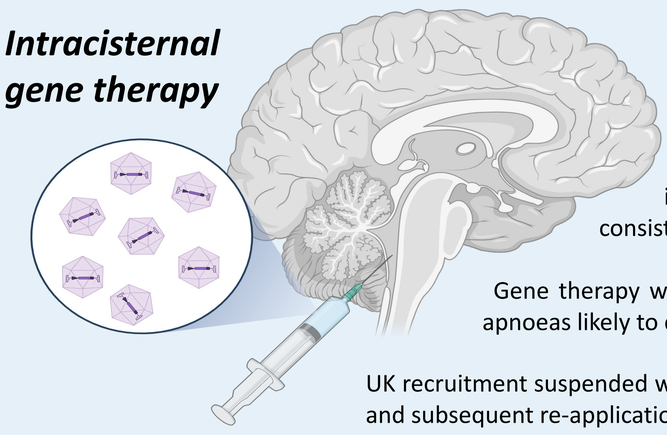


Time to diagnosis from first symptoms: 1 week - 11 months (mean: 5m)[5]

Findings in red, typically seen at presentation

A new hope – could gene therapy be the answer?

Intracisternal gene therapy



There is a phase 1/2 study to evaluate the safety efficacy of an AAV-mediated gene therapy in infants with Type 2 Gaucher Disease (GD2).

Recruiting in the USA and Manchester, including patients with bi-allelic *GBA1* mutations consistent with GD2 and a clincal diagnosis of GD2.

Gene therapy will not rescue existing damage, therefore profound apnoeas likely to continue irrespective of treatment success.

UK recruitment suspended when AM was diagnosed due to a change in protocol and subsequent re-application to MHRA; therefore not an option for AM.

References:

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