Infantile Pompe disease; comorbidities, challenges, and treatments.

DALKEITH Troy 1, 2; PALMER Julie 1; SPARGO Merran 3; WATERS Karen 6; LU Mimi 6; DALBY-PAYNE Jacqueline 5; THACKER Kunal 7; BIGGIN Andrew 4; ELLAWAY Carolyn 2, 3

Pompe disease (Glycogen storage disease type 2 – GSD2 – OMIM 232300), is an autosomal recessive disorder characterised by homozygous or compound heterozygous variants of the GAA gene, located on chromosome 17q25. The GAA gene is responsible for encoding the enzyme, α-glucosidase (acid maltase), to enable breakdown of lysosomal glycogen. Deficiency of alpha-glucosidase results in glycogen accumulation within the lysosomes, which are responsible for breakdown and recycling of cellular waste products.

At 5mths of age
- Initial presentation
- Well up to 2 months of life, slow weight gain ~100g/week
- Presented at 2 months of age with bronchiolitis requiring paediatric intensive care unit admission, with subsequent readmission with bronchiolitis at 3 months of age
- Silent aspiration on barium swallow, commenced NG feeding
- Sleep study showed respiratory failure, nocturnal non invasive ventilation initiated
- Vitamin D deficient
- Hypotonia

From 5mths of age
- Admitted for chest infection
- Significant central hypotonia and head lag, good spontaneous antigravity movements of arms and legs
- Infantile Pompe diagnosed during admission (alpha-glucosidase <0.1umol/h/l (range 0.3-10.0))
- Hypertrophic cardiomyopathy

From 2yrs of age
- Five protracted paediatric intensive care unit admissions related to respiratory insufficiency and infections
- Chronic respiratory failure
- Home chest physiotherapy, cough assist and nebulised hypertonic saline
- Wheelchair assistance required for mobility

Build up of cellular glycogen, particularly in muscle cells and fibres leads to impaired function. Infantile onset Pompe disease (IOPD) usually manifests shortly after birth and before 4-5 months of age, with severe occurrences having almost complete deficiency of the α-glucosidase.

We describe the journey of an 8-year-old female with cross-reactive immunological material (CRIM) positive IOPD, homogygous for the p.G607D mutation, diagnosed at 5 months, compounded by comorbidities; including inflammatory bowel disease (IBD), precocious puberty and hypertension.

Acknowledgement to Australian Society of Inborn Errors of Metabolism (ASiEM) for financially supporting conference attendance.

Sydney Children’s Hospitals Network Human Research Ethics Committee (HREC) approval CCR2021/17
Progressive skeletal and respiratory muscle weakness
Increase in duration of Non Invasive Ventilation (NIV) support
No significant rise in Alglucosidase alfa antibody levels were observed
Low bone mineral density (BMD) and precocious puberty (pubic hair, breast bud development, facial acne and sweating) were also observed
Bilateral hip dysplasia

Subsequent reduction in respiratory and skeletal muscle weakness and two ICU admissions.
5-week history of frequent stooling and haematochetauria, infection excluded.
Histology demonstrated chronic colitis with mild architectural changes throughout the colon suggestive of IBD. Terminal ileum biopsies were normal
Commenced Infliximab induction with improvement in bowel symptoms band IBD biochemical markers. Steroids contraindicated due to existing low BMD and myopathy

Hypertension (systolic >130mmHg) was observed on regular admissions
Worsening IBD symptoms post Infliximab induction
Attempts at dose reduction or frequency of Infliximab infusions proved unsuccessful with patient either developing symptoms of a flare or Infliximab drug levels dropping into the sub-therapeutic range
Repeat VFSS confirmed ongoing oropharyngeal dysphagia with no aspiration.
Bilateral varus derotation osteotomies of proximal femurs
Consideration of scoliosis surgery, currently delayed
Dose escalation of Alglucosidase alfa to weekly treatment

Outcome:
- Alglucosidase alfa frequency increased to 20mg/kg weekly from 6.8yrs, which led to some improvement in skeletal muscle strength. Since then only two paediatric intensive care unit admissions
- Increasing dependency on day time Non invasive Ventilation (NIV) support despite weekly enzyme replacement therapy
- Since 5yrs of age there has been a 50% increase in daily use of Non invasive Ventilation (NIV)
- Progressive development of upper and lower limbs contractures
- Bilateral varus derotation osteotomies of proximal femurs performed, and anaesthetic well tolerated
- Low BMD and precocious puberty were managed conservatively
- Increasing hypernasal speech
- Ambulatory blood pressure monitoring revealed 60% of systolic readings above 95th centile for age. Renal and cardiac causes of hypertension were excluded. This was managed with lisinopril 2.5mg daily
- Infliximab induction commenced with initial improvement of symptoms and biochemical markers. Dose escalation up to 10mg/kg 4-weekly was required due to worsening IBD symptoms and low Infliximab trough levels. Oral Methotrexate was added
- Infliximab drug levels subsequently improved. Attempts at Infliximab dose or frequency reduction or proved unsuccessful with patient either developing symptoms of a flare or drug levels becoming sub-therapeutic. Commenced Mesalazine enemas due to ongoing IBD flare up
- Alglucosidase alfa continues to be tolerated well. Infliximab is administered subsequent to, but on same day as ERT without issue

Conclusion:
This case highlights the long-term challenges of managing patients with IOPD and evolving co-morbidities. Treatment options for IOPD are limited, and this case required compassionate access dose escalation of Alglucosidase alfa with effect.

References