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Surveillance Highlights

Muscle problems in juvenile-onset acid maltase deficiency (Pompe disease)

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A 13-year-old male presents with a 3-month history of progressive fatigue and muscle pain, exacerbated by exercise. He is the second child of healthy, nonconsanguineous parents. The parents note normal early motor and speech development. Their only concern relates to his fatigue, noting that he tires before his peers while playing hockey. On review of systems and past medical history, he reports morning headaches and chronic diarrhea, which is treated with occasional loperamide. His physical examination was significant for generalized low muscle bulk, scapular winging, thoracolumbar scoliosis, and mild weakness of the hip flexors. Four months after his initial clinic visit he developed pneumonia. During his hospital stay, it was noted that he had progression of weakness on a Limb-Girdle pattern with a positive Gowers' sign. An electromyography (EMG) was ordered, that revealed a myopathic pattern in the paraspinal muscles. Serum creatine kinase (CK) was elevated on two occasions (986 and 1,037 U/L; normal < 175 U/L). Whole-body muscle MRI T1 images demonstrated high signal in the tongue and quadriceps with sparing of the rectus femoris and gracilis. A muscle biopsy demonstrated vacuoles inside the fibres containing increased glycogen (periodic acid -Schiff [PAS] stain) and increased lysosomal activity on acid phosphatase reaction. A dry blood spot (DBS) test showed reduced acid alpha-glucosidase (GAA) activity (0.4 μmol/L/h of protein; normal value: > 3 μmol/L/h). Sanger sequencing of GAA demonstrated a homozygous mutation (c.1364A>T, p.Tyr455Phe) confirming late-onset Pompe disease of the juvenile-onset form. After genetic counselling with the family, enzyme replacement therapy was initiated.

Learning points

- Pompe disease, also known as glycogen storage disease type II (GSD-II), is an inherited, autosomal recessive disease that results from abnormal lysosomal storage of glycogen in body tissues. Children with Pompe disease have a deficiency of the lysosomal enzyme acid alpha-glucosidase. Alpha-1,4-glucosidase is a lysosomal enzyme involved in the degradation of glycogen within cellular vacuoles (1,2).
- The clinical spectrum of Pompe disease ranges from the severe, infantile-onset form to the milder juvenile phenotype that develops later in childhood. The variability in disease severity relates to the amount of residual GAA enzyme activity in the muscle (1,2).
- Infantile Pompe disease is characterized by profound hypotonia and muscle weakness, cardiac manifestations (left ventricular hypertrophy, cardiomyopathy), respiratory distress, hepatomegaly, feeding difficulties (facial hypotonia, macroglossia, tongue weakness, and/or poor motor skills),

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failure to thrive, and normal cognition. Without treatment, patients develop a left ventricular outflow obstruction. Death commonly occurs in the first 2 years due to cardiopulmonary insufficiency (1,3).

- Later-onset presentation can present any time in childhood or adulthood. Most patients will present with muscle weakness predominantly in a proximal or limb-girdle pattern, without cardiac involvement. Children are found to have high serum CK levels and/or exercise intolerance due to respiratory insufficiency. The natural history of patients with juvenile-onset Pompe disease is not well defined, involving a spectrum of different clinical manifestations including scoliosis, gastrointestinal involvement (hepatomegaly and irritable bowel-like symptoms), chronic pain, and joint contractures (1,3).
- The diagnosis is based on clinical manifestations together with measured GAA enzyme activity (in the DBS test) and/or Sanger sequencing of the GAA gene. Other studies that can be helpful include an EMG, which classically demonstrates a myopathic pattern (involving rarely seen pseudomyotonic paroxysmal discharges) and total body muscle MRI, which typically shows the early involvement of the tongue, paraspinal, abdominal, and thigh muscles, with sparing of the sartorius, rectus, and gracilis. Muscle biopsies demonstrate glycogen accumulation in membrane-bound vesicles, and PAS staining reveals an abundance of glycogen (1,4).
- Differential diagnosis during the infantile period includes other forms of glycogen storage disease (type III and IV due the cardiomegaly and Hypotonia) and Spinal Muscular Atrophy; later-onset differential diagnosis with Limb-Girdle Muscular Dystrophies, dystrophinopathies and GSD V and VI due the weakness pattern and hyperCKemia (1).
- Importantly, 20 to 30% of the patients with later-onset Pompe may not show classical changes on the muscle biopsy. Many patients with late-onset Pompe disease experience long delays until diagnosis, with a mean delay of 4.1 years from symptom onset until diagnosis. A protracted diagnostic odyssey is costly, stressful for the patient and family, and delays the possibility of enzyme replacement therapy (1,3).
- Enzyme replacement therapy can improve cardiomyopathy, respiratory function, and prolong survival in patients with infantile Pompe, as well as improve muscle strength, pulmonary function, and survival in patients with late-onset Pompe disease (1,3).
- A Canadian Paediatric Surveillance Program (CPSP) study on infantile and later-onset paediatric Pompe disease is underway to better understand the presenting symptoms and clinical characteristics of paediatric Pompe disease (2).

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