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MEDICAL EDUCATION: LESSONS FROM PRACTICE OPEN ACCESS

When 'Liver Enzymes' Are Not Hepatic: Late-Onset Pompe Disease

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ABSTRACT

Elevated liver function tests are commonly attributed to hepatic disease but may reflect extrahepatic pathology. We describe the case of an 18-year-old athletic woman with a 2-year history of elevated aspartate aminotransferase (AST), alanine aminotransferase (ALT) and creatine kinase (CK) levels, initially investigated extensively for hepatic causes. Despite normal liver imaging and biopsy, ongoing abnormalities prompted metabolic evaluation, leading to the diagnosis of late-onset Pompe disease. This case highlights the diagnostic challenges of rare metabolic myopathies, the importance of recognising muscle-derived aminotransferase elevation and the need for broad diagnostic consideration when standard investigations are unrevealing.

JEL Classification: Anatomy and physiology, Diagnostic techniques and procedures, General medicine, Medical genetics

1 | Clinical Record

An 18-year-old woman was referred to hepatology for elevated serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) and lactate dehydrogenase levels noted on routine testing. These tests had been abnormal for 2 years before referral (Table 1). The remainder of liver function tests were normal. Creatine kinase (CK) was also elevated but this was attributed to the patient's triathlon training.

The patient was of athletic build, with no outward signs of liver disease. Her history was significant for allergic rhinitis, anxiety and depression. She reported minimal alcohol use, no illicit drugs or tobacco use and unremarkable sexual and travel histories. Medications included the oral contraceptive pill, mirtazapine (15 mg daily) and occasional paracetamol, but no other over-the-counter medications or supplements: medication-related causes of increased transaminases were considered unlikely.

Family history was significant for a dizygotic twin sister with unexplained elevation of transaminases, a third degree relative with possible Wilson's disease and a grandmother with chronic liver disease of unknown aetiology.

Investigations for viral and autoimmune causes of liver disease were unremarkable. Investigations for common genetic liver diseases are shown in Table 2. Ultrasound imaging of the liver showed patent vessels and normal parenchyma. A low caeruloplasmin level, coupled with possible family history of Wilson's disease, prompted a liver biopsy. The biopsy results showed no increase in copper-associated protein and no copper accumulation. There was also no steatosis, no increase in stainable iron and no features of autoimmune hepatitis. Focal lipofuscin pigment was identified in zone 3 hepatocytes.

Input from rheumatology and chemical pathology teams was sought: a myositis immunoblot and assessment of 3-hydroxy-3-methylglutaryl-coenzyme A reductase antibodies (an autoimmune

Lessons From Practice

- Elevated levels of aminotransferases are not specific for liver disease and may originate from skeletal muscle. If no hepatic cause for persistently elevated levels of aminotransferases is evident, creatine kinase should be measured and, if elevated, should prompt consideration of metabolic or inherited myopathies.
- Pompe disease can be treated with enzyme-replacement therapy to prevent or delay symptom progression. Late-onset Pompe disease can present insidiously without overt muscle or respiratory weakness, leading to diagnostic and treatment delays.
- Broad, multidisciplinary evaluation is essential when standard investigations do not explain biochemical abnormalities.

marker strongly associated with necrotising autoimmune myopathy) were negative, and macro-CK was not present. Dried blood spot (DBS) acylcarnitine and urine organic and amino acid profiles were within normal limits. The patient was referred to a metabolic medicine clinic, and next-generation sequencing of an adult-onset myopathy panel was performed, which showed that the patient was compound heterozygous for known pathogenic intronic (c.-32-13T>G) and missense (c.1222A>G) variants in the GAA gene, which encodes acid α-glucosidase. Reduced DBS acid α-glucosidase activity was seen (0.5 pmol/spot/h; reference interval [RI], 2.5–25.4 pmol/spot/h), consistent with a diagnosis of Pompe disease.

Further investigations showed no proximal muscle weakness and no evidence of respiratory muscle weakness or sleep-disordered breathing. Testing of the patient's twin sister also showed reduced DBS acid α-glucosidase activity as well as the presence of the same mutations in the GAA gene.

2 | Discussion

Pompe disease is an autosomal recessive disorder caused by mutations in the GAA gene and deficiency in lysosomal acid α-glucosidase, leading to the accumulation of glycogen in lysosomes. Pompe disease is a rare disease with an estimated prevalence of <1 in 50,000 people, and has infantile (<12 months) and late onset (infancy to late adulthood) forms, with complete or partial loss of enzyme activity, respectively [1, 2]. Clinical presentations of late-onset Pompe disease vary, may be insidious, and features such as proximal muscle weakness and respiratory deficiency have significant overlap with several other disorders, often leading to long delays in diagnosis [3]. In Australia, assessment of DBS acid α-glucosidase activity is considered the first-line screening test, followed by confirmation by genetic analysis; however, in cases such as this, in which clinical suspicion of Pompe disease was absent, genetic testing might precede biochemical testing [1].

In addition to clinical overlap, biochemical patterns may be misinterpreted, leading to an inappropriate focus for referral and further investigation. Although AST and ALT are referred to as 'liver enzymes', with ALT considered highly specific for liver, both enzymes are essential to intermediary metabolism and are expressed in all tissues, and at very high levels in highly metabolically active tissues such as muscle and kidney [4, 5]. The presence of elevated CK levels, when no hepatic cause for persistently elevated aminotransferases is evident, should lead to a change in focus to possible metabolic myopathy [6, 7].

Interestingly, identification of focal lipofuscin pigment in zone 3 hepatocytes in this patient's liver biopsy might reflect mild secondary lysosomal or metabolic stress rather than true age-related

TABLE 1 | Results of serum liver panel tests at first presentation to general practitioner, and 6 months later, including creatine kinase. All these enzymes remained elevated but stable over the course of her investigation.

Analyte	Initial	6 months	Reference interval
Albumin (g/L)	41	34	31–48
Protein (g/L)	71	70	57–80
Bilirubin (μmol/L)	11	4	<24
γ-glutamyl transferase (U/L)	14	16	<40
Alkaline phosphatase (U/L)	55	49	35–140
Alanine aminotransferase (U/L)	172	190	<35
Aspartate aminotransferase (U/L)	187	215	<40
Lactate dehydrogenase (U/L)	465	502	120–250
Creatine kinase (U/L)		1236	<150

TABLE 2 | Investigations for heritable causes of liver disease.

Analyte	Result	Reference interval	Comment
Ferritin (μg/L)	34	30–250	No indication to test for homeostatic iron regulator (HFE) gene mutations
α1 antitrypsin (g/L)	1.2	0.9–2.0	Within normal limits
α1 antitrypsin phenotype	MM		Normal phenotype: not associated with loss of function
Caeruloplasmin (g/L)	0.15	0.18–0.40	Mild decrease
Urine copper (μmol/24 h)	<0.24	<1.6	Within normal limits

lipofuscin, particularly in such a young patient. This finding is consistent with what is seen in muscle biopsies from patients with Pompe disease [8]; however, there are no published reports of lipofuscin deposition in the livers of patients with Pompe disease, which might reflect that liver biopsies are rarely performed in these patients. At the time of reporting the biopsy, the finding was regarded as incidental and non-diagnostic, although in retrospect, it might have been indicative of a lysosomal disorder.

This case illustrates the difficulties in diagnosing rare diseases, and the need for clinicians to think outside their specialty when confronted with a diagnostic conundrum, particularly as early diagnosis can be beneficial to long-term outcomes.

Author Contributions

Shauna Madigan: conceptualisation, investigation, writing – review and editing. **Georgina England:** conceptualisation, investigation, writing – review and editing. **Wayne Rankin:** conceptualisation, investigation, supervision, writing – original draft, writing – review and editing.

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Consent

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Conflicts of Interest

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Data Availability Statement

The authors have nothing to report.

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