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Elevated Creatinine Kinase in a 6-Year-Old Boy

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Paucisymptomatic or asymptomatic but persistently elevated serum creatine kinase is not an uncommon pediatric neurology referral question. The challenge is in promptly identifying etiologies with specific treatments, even if they are rare. The presenting features for a child or adolescent with juvenile-onset Pompe disease (JOPD) can be nonspecific and heterogeneous. Clinical manifestations can appear at any age after 2 years and before adulthood, with insidious onset of symptoms related to slowly progressive skeletal or respiratory muscle weakness. This reported case highlights the importance of screening for JOPD in children with "hyper-CK-emia." Dried blood spot measuring acid α-glucosidase enzyme activity is reliable, rapid, noninvasive, and inexpensive, allowing early diagnosis. Diagnosis of JOPD is important as enzyme replacement therapy with alglucosidase alpha, an intravenous recombinant α-glucosidase, is available, and early treatment improves muscle function, quality of life, and long-term survival.

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Case

A 6-year-old boy was referred for an outpatient pediatric neurology evaluation following detection of mildly elevated serum creatine kinase (sCK) at 908 and 667 IU/L (normal reference range: 40-240 IU/L) on 2 occasions, with elevated alanine and aspartate transaminases, in the absence of identifiable liver disease. Investigations had been performed for nonspecific intermittent abdominal pain over the previous 2 years.

At presentation, a history of intermittent activity intolerance and myalgia following light activity was elicited. Exertional myalgia and fatigue in comparison to peers were reported. However, he continued to participate in football and cricket without overt difficulties. There was no history of pigmenturia or myalgia precipitated by fasting or illness.

This is on a background of being born at term following an uncomplicated pregnancy and delivery. Neonatal progress was uneventful, without feeding difficulties or respiratory illnesses. Uncomplicated orchidopexy was performed at 11 months. Independent walking was achieved at 18 months, late in comparison to his 2 brothers who achieved it at approximately 14 months of age. There are no cognitive or schooling concerns. The boy is the middle of 3 children to healthy, unrelated parents. There is no known family history of muscle or neurologic problems; only insulin-dependent diabetes mellitus in a maternal aunt and thyroid disease in the maternal grandmother.

Examination revealed a slim, nondysmorphic young man with weight and height tracking along the 25-50th centile. He had mild pectus excavatum. There was no scoliosis. Initial neurologic examination was unremarkable; however, proximal weakness with a subtle waddling gait became evident over the following 6 months. There was no Gowers sign. There was no facial weakness, ptosis, or ophthalmoparesis. Neck flexor weakness was mild. There were no contractures. Funduscopy and cardiac and abdominal examinations were unremarkable. Specifically, there was no displaced apex beat, and no organomegaly.

Further investigations demonstrated persistently elevated sCK in the upper hundreds (746 IU/L) without preceding illness or physical exertion. Serum alanine aminotransferase, aspartate aminotransferase, and lactate dehydrogenase were elevated 2-5 times the upper limit of normal. All other investigations were normal including full blood examination, thyroid and renal function, vitamin D, fasting glucose, lactate,

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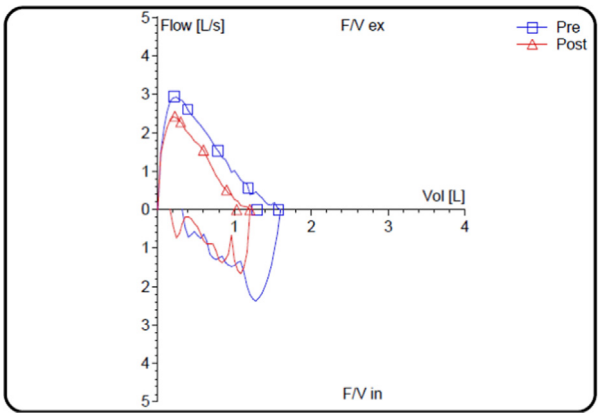
ammonia, acylcarnitine, urine organic and amino acids, and urine myoglobulin. Fasting free fatty acids to ketone ratio was high at 2.8. Nonischemic forearm exercise test was nondiagnostic. A dried blood spot (DBS) screening test for acid α-glucosidase (GAA) enzyme activity demonstrated below normal levels. Repeat testing was similarly abnormal, and urinary tetrasaccharides were elevated at 120 (normal reference range: <20). Molecular genetic testing for *GAA* gene on skin fibroblasts demonstrated 2 heterozygous pathogenic mutations (c.−32–13T > G and c.258dup), and Western blot testing documented presence of cross-reactive immunological material (CRIM). The suspected diagnosis of juvenile-onset Pompe disease (JOPD) was confirmed.

Screening electrocardiogram and echocardiogram were normal. Six-minute walk test (6MWT) on a 20-m track was completed easily and was within normal limits at 571 m (normal reference range: 516 m ± 61.8). Quick motor function tests were normal. However, respiratory function testing demonstrated a significant 23% drop in forced vital capacity (FVC) in supine compared to upright posture (Fig. 1). A whole-body magnetic resonance imaging scan showed fat infiltration in the proximal lower limb muscles (Fig. 2). Paraspinal muscles appeared normal.

This boy has shown subtle deterioration throughout the 10 months from presentation to diagnosis. He experiences mild fatigue and intermittent myalgia. Although his motor function is relatively preserved, he has emerging respiratory muscle involvement with impaired lung function testing. Interestingly, his initial symptoms of intermittent abdominal pain have now resolved. The child is under close surveillance and will commence lifelong fortnightly enzyme replacement therapy (ERT) with alglucosidase alpha when the natural expected improvement on serial 6MWT with age is no longer observed.



	Predicted	Upright (Pre)	Supine (Post)	Change
FEV1	1.14-1.44	1.29	1.03	-20.3%
FVC	1.29-1.63	1.57	1.20	-23.8%
FEV1/FVC (%)	77.55-89.21	82.26	86.06	4.5%

Figure 1 Respiratory function test showing mild restrictive lung function in supine position. FEV1, forced expiratory volume in 1 second.

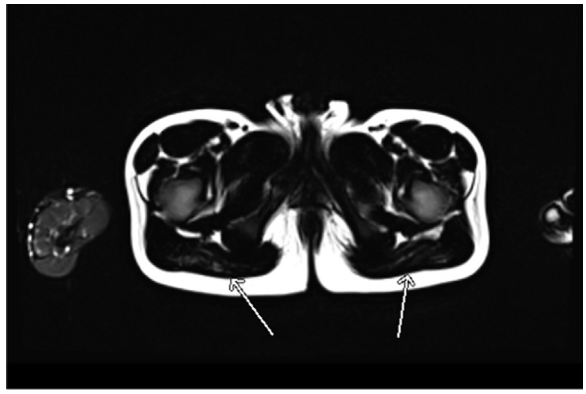


Figure 2 Axial T2 image showing patchy increased signal in the gluteus maximus (arrows) consistent with fat infiltration.

Discussion

CK is a muscle enzyme involved in converting phosphocreatine and adenosine diphosphate to creatine and adenosine triphosphate to generate energy crucial for muscle function. When there is muscle injury and sarcolemmal disruption, leakage of CK into the blood stream can occur, resulting in an elevation of sCK.

An elevation in sCK greater than 1.5 times normal is considered abnormal[1,2] and can be associated with no symptoms or minor symptoms such as nonspecific cramps, myalgia, or fatigue. There are a number of possible causes for chronic or recurrent elevation of sCK,[3,4] with many being self-limiting and associated with spontaneous normalization of sCK over time (Table 1). After exclusion of systemic causes, more persistent and repeated elevation of sCK in childhood is suspicious for an underlying inherited neuromuscular cause (Table 2).

There is a strong argument for extended investigations in children with persistently elevated sCK.[5] In 1 study, up to 85% of children less than 15 years old with sCK > 500 IU/L on 2 occasions, normal examination and minimal symptoms were subsequently diagnosed with a muscular dystrophy or a metabolic myopathy.[6] A diagnosis is particularly important for long-term management and prognosis, given the increased risk of malignant hyperthermia with anesthesia and the potential requirement for multidisciplinary care and cardiac surveillance.

A rare but important myopathy to consider in all children with chronically elevated sCK is acid maltase deficiency, or Pompe disease. Pompe disease is an autosomal recessive disorder with partial or complete deficiency of the GAA enzyme, a lysosomal enzyme involved in the breakdown of

Table 1 Acquired Causes of Elevated Serum Creatine Kinase

Exercise/activity related
Drugs/toxins
Metabolic
Nutritional deficiencies
Trauma
Infections/inflammation including autoimmune
Critical illness

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