Clinical Practice: Clinical Vignettes

Elevated Liver Enzymes Indicating a Diagnosis of Limb-Girdle Muscular Dystrophy

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A 27-year-old man presented to an internal medicine clinic to establish primary care. His past medical history was significant for elevated liver transaminases found during laboratory monitoring while taking isotretinoin for acne. He had an extensive workup spanning 7 years including serial hepatic function panels after withholding isotretinoin, viral serologies, and two liver biopsies, which eventually led to a diagnosis of an idiopathic elevation in serum transaminases. During his present evaluation, he endorsed complaints of significant muscle soreness with strenuous activity despite conditioning. Creatine kinase was found to be elevated at 11,778 U/l. Nerve conduction studies and electromyogram indicated a myopathy. DNA sequencing confirmed a diagnosis of limb-girdle muscular dystrophy. The aminotransferases are most notable for their association with liver pathology; however, they are also present in other tissues such as heart, kidney, and skeletal muscle. Muscle pathology, including the inherited muscular dystrophies, are often identified by elevations in creatine kinase, but can also be suggested by elevations of aminotransferases. This case illustrates that myopathies should be considered in patients with otherwise unexplained elevations in liver aminotransferases.

KEY WORDS: transaminases; creatine kinase; rhabdomyolysis; muscular dystrophy; limb-girdle muscular dystrophy.
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CASE PRESENTATION

A 27-year-old man presented to an internal medicine clinic to establish primary care. His medical history consisted of hypertension controlled with olmesartan and hydrochlorothiazide as well as a history of elevated liver enzymes. At the age of 16, the patient was found to have an alanine aminotransferase (ALT) of 117 U/l and aspartate aminotransferase (AST) of 106 U/l on routine labwork while taking isotretinoin for the treatment of acne. Bilirubin, alkaline phosphatase, PT/PTT, and albumin levels were all normal. Hemachromatosis, Wilsons's disease, and hepatitis A, B, and C screening were also unremarkable. A liver biopsy showed no signs of inflammation or fibrosis. The patient was diagnosed with a mild drug reaction. Several years after the isotretinoin was discontinued, a repeat ALT was 56 U/l and AST was 94 U/l. A second liver biopsy was again normal, and the patient was diagnosed with an idiopathic liver enzyme elevation.

At the current visit, the patient had no complaints except diffuse myalgias and mild nausea after strenuous aerobic activity despite conditioning. Vital signs showed a blood pressure 124/78 mmHg, pulse of 62 beats per minute, and BMI of 24 kg/m^2. Physical examination revealed a pleasant white male in no acute distress. His abdomen was soft, nontender, and without organomegaly or masses. Musculoskeletal examination showed no signs of muscle tenderness or atrophy. Strength was 5/5 in the upper and lower extremities. The remainder of the physical examination was unremarkable. Laboratory testing revealed an ALT of 100 U/l and AST of 295 U/l (the remainder of the comprehensive metabolic panel and complete blood count were normal and can be found in Table 1). Given the long-standing history of elevated liver transaminases and the patient's complaint of myalgias after exertion, a creatinine kinase (CK) level was obtained and returned elevated at 11,778 U/l. The patient's olmesartan/hydrocholorthiazide was held for potential drug-induced rhabdomyolysis[1], and after resting for 1 week, a repeat CK was 1,122 U/l. Upon exercise re-challenge, CK increased to 8,341 U/l. The thyroid-stimulating hormone, human immunodeficiency virus, antinuclear antibody, and erythrocyte sedimentation rate were all found to be normal. Subsequent nerve studies were normal, but an electromyogram showed patchy areas of abnormal signal consistent with a myopathy. A gene sequencing test for various muscular dystrophies revealed an autosomal dominant limb-girdle muscular dystrophy type 1C (CAV 3 mutation, caviolinopathy). Subsequently, the patient learned that his father had been found to have hyperCKemia in his early 40s. His father's CK level was "around 10,000," and he also took part in regular exercise. He had undergone an extensive workup including an

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Table 1. Laboratory Data

	Presentation	Withholding exercise	Exercise rechallenge
Na (mEq)	140	139	140
K (mEq)	4.2	4.8	3.9
Cl (mEq)	104	104	105
HCO3 (mEq)	30	30	31
BUN (mg/dl)	27	19	21
Cr (mg/dl)	1.1	1	1
Glucose (mg/dl)	95	96	140
Ca (mg/dl)	9.4	9.4	9.3
CK (U/l)	11,778	1,122	8,341
Prot (g/dl)	6.5	6.5	
Alb (g/dl)	4.1	4.2	
Tbili (mg/dl)	0.6	0.8	
AST (U/l)	295	48	
ALT (U/l)	100	62	
Alk Phos (U/l)	55	57	
WBC $\times 10^3$/cmm	6.8		
Hgb (g/dl)	14		
Hct (%)	40		
Plt $\times 10^3$/cmm	178		
TSH (mcIU/ml)			1.205
ESR (mm/h)			0
ANA			<1:80
RF			Neg
IgA (mg/dl)			230
IgG (mg/dl)			1,040
IgM (mg/dl)			88

ischemic forearm test (used to detect metabolic causes of muscle weakness by measuring lactic acid levels after a patient has completed 2 min of repetitive forearm exercises while a sphygmomanometer cuff occludes blood flow to the forearm[2]), nerve conduction study, electromyogram, and muscle biopsy, which did not end in a definitive diagnosis. Gene sequencing was not available at that time. The same diagnosis of limb-girdle muscular dystrophy is presumed given his history of hyperCKemia, current symptoms, and the heritability of the disease. His father is still living, and his only symptoms are soreness with strenuous exercise, chest atrophy, and symptoms consistent with rippling muscle disease (involuntary rolling contractions of muscles provoked by mechanical stimuli such as percussion and stretching the muscle).[3] He has not undergone any further testing since the patient's diagnosis.

DISCUSSION

The aminotransferases (AST and ALT) catalyze reactions that convert alanine and aspartate into alpha-ketoglutarate, which provides a source of nitrogen for the urea cycle. Their highest concentrations are found in hepatocytes, making them valuable markers of liver pathology. They are typically used in conjunction with alkaline phosphatase, gamma glutamyl transpeptidase, bilirubin, albumin, and prothrombin time to determine the pattern (cholestatic or hepatic) and severity of liver dysfunction.[4,5] These patterns along with a thorough history and physical examination can narrow a very broad differential for liver pathology to more specific causes. The aminotransferases, however, are not confined to the liver. Their production outside of the liver has been observed as far back as the 1950s,[6] and they are found in the heart, kidneys, erythrocytes, and skeletal muscle, among other places. This gives them the potential to suggest pathology related to any cell that contains them (see Table 2). Elevated transaminases have been observed in various myopathies, hyperthyroidism, and celiac disease and even used as a marker for myocardial infarction.[7–10] In fact, due to the larger proportion of skeletal muscle, adult males have four times more ALT and 26 times more AST on average in their muscle than in their liver.[11]

The association of AST and ALT release during muscle damage is well known. In an emergency room study of 215 patients presenting with rhabdomyolysis and no liver injury, the incidence of elevated AST was 93.1 % (95 % CI, 88.7 % to 95.8 %) and elevated ALT was 75.0 % (95 % CI, 68.7 % to 80.2 %) in patients with a CK of ≥1,000 U/l ($p<0.0001$).[12] The AST was found to fall in parallel with CK, suggesting a direct relationship with muscle damage. The ALT was found to fall at a lower rate given its longer half-life (the half-life of AST is 17±5 h, while that of ALT is 47±10 h).[7,13] No significant elevations were found in INR, suggesting that the elevations in AST and ALT were likely from muscle damage alone. Another study looked at liver function testing in patients known to have myotonic dystrophy and showed significant elevations in patients who had a normal liver, were free of medications, and not pregnant.[14] It has even been shown that significant levels of AST and ALT have persisted for up to a week in normal, healthy men after exercise.[15] With initial muscle injury, AST

Table 2. Extrahepatic Causes of Elevated Transaminases

Rhabdomyolysis
Aquired disorders of muscle
Inflammatory myopathy
Vasculitis
Etc.
Congenital disorders of muscle
Muscular dystrophy
Inborn errors of metabolism
Etc.
Exercise
Heat stroke
Seizure
Sepsis
Renal failure
Thyroid disorders
Diabetes
Hemolysis
Myocardial infarction
Adrenal insufficiency
Anorexia nervosa
Celiac disease

values are typically higher than ALT, which is consistent with the larger amount of AST in muscle tissue. In a study of patients presenting with rhabdomyolysis due to extreme exercise, seizures, and myositis, the average AST/ALT ratio was >3 initially, but then approached 1 a few days later, which was believed to be due to the shorter half-life of AST. This trend was seen in our patient.

Muscular dystrophy (MD) is an inherited group of disorders resulting from defects in genes required for the normal function of skeletal muscle. Clinical manifestations of MD can range from asymptomatic hyperCKemia to severe debilitation and death early in life. Most autosomal recessive forms produce symptoms early in life and are severe. Autosomal dominant forms have slower, less debilitating courses, which may not manifest clinically until early or late adulthood. The CAV 3 caviolinopathy, which our patient has, is an autosomal dominant mutation that usually presents later in life with elevation of CK and mild muscle weakness. The long-term prognosis is generally good.

As both the lead author and patient of this clinical vignette, I have learned a considerable amount not only about muscular dystrophy, but also about the art and evolution of a diagnosis. My new internist was able to elicit a key piece of history—muscle soreness after exercise. This history, combined with the knowledge that the aminotransferases could be elevated in the setting of muscle damage, allowed him to make the diagnosis that had gone unrecognized by specialists during a previous 7-year workup. Technological and scientific advances have provided a multitude of tests that aid physicians in making diagnoses. However, if one is not careful, these tests can become a hindrance by shifting our focus away from the history and physical exam. Our case also illustrates that it is important to remember the difference between what a laboratory test typically indicates (AST and ALT usually indicate liver pathology) and what a laboratory test actually measures (AST and ALT are objective measures of the amount of two enzymes). The entire previous workup focused completely on a single organ system instead of evaluating for an extra-hepatic cause of the elevated transaminases. Tinsley Harrison, the author of Harrison's Principles of Internal Medicine, once said, "There are five routes to the medical diagnosis-history, history, history, history, and the physical exam." In our case, a single piece of history changed the course of a workup from one organ system to another.

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