BRIEF REPORT

Consider Muscle Disease in Children with Elevated Transaminase

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The transaminases alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are markers of hepatocellular injury but are highly concentrated in muscle cells. Consequently, muscular dystrophies such as Duchenne muscular dystrophy, lead to hypertransaminasemia. Elevation in ALT and AST is most striking during the early stages of disease, before onset of or when only subtle signs of muscle disease are present. Thus, the incidental finding of elevated ALT/AST may be the presenting sign of muscle disease in many children and provides an opportunity for early diagnosis. Many physicians, however, pursue extensive workup for liver disease in children who present with the incidental finding of elevated ALT/AST. This results in delayed diagnosis and initiation of treatment and increased expense and may lead to unnecessary invasive procedures. We report 12 patients with muscle disease who presented with a variety of symptoms and were found to have an incidental finding of elevated ALT/AST. We propose a rapid screening process for evaluating children with the incidental finding of elevated ALT/AST to shorten the time to diagnosis of muscle disease. (J Am Board Fam Med 2012;25:536–540.)

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Serum creatinine kinase (CK) is markedly elevated with breakdown of muscle and is considered a diagnostic marker of muscular dystrophies.[1–5] However, it also has long been recognized that alanine aminotransferase (ALT) and aspartate aminotransferase (AST) are present in high concentrations in muscle; elevation of ALT and AST can signal disruption of the muscle membrane.[1,4,6] ALT and AST also are found, to a lesser extent, in cardiac muscle, the pancreas, and the kidneys.[7,8] Nevertheless, these transaminases frequently are considered to be specific indicators of liver injury and are included in the complete metabolic panel routinely used to screen patients for evidence of liver disease.

Although the majority of patients with chronic hypertransaminasemia ultimately will demonstrate evidence of liver disease, the finding of elevated AST/ALT in the absence of other laboratory abnormalities typically associated with liver disease can pose a diagnostic challenge. Several case reports demonstrate isolated hypertransaminasemia as an initial finding of muscle disease in children.[9–12] Despite this, many children with muscle disorders continue to undergo costly and invasive workups for liver disease in the face of the incidental finding of elevated ALT and AST. Here, we report 12 patients with muscle disorders who presented to our muscle clinic only after extensive investigation for liver disease. We propose a rapid screening process for evaluating children with elevated ALT/AST.

Results

Twelve patients ultimately diagnosed with muscle disorders first presented with a variety of clinical symptoms. Initial blood work showed that they had elevated transaminase levels (ALT/AST). Patients ranged in age from 7 months to 16 years at initial presentation (Table 1). A wide variety of com-

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Table 1. Patient Characteristics at Presentation and Follow-up

Age, years	ALT, IU/L	AST, IU/L	Reason for Metabolic Panel	Symptoms	Initial CK, IU/L	Muscle and Neurologic Symptoms at Presentation	Muscle and Neurologic Symptoms at Follow-up	Final Diagnosis
2	273	50	Tonsillitis	None	4,867	Calf hypertrophy	N/A	DMD/BMD
								Exon 45–47 deletion
<1	341	451	Failure to thrive	Failure to thrive	19,874	Calf hypertrophy	Wide-based gait, decreased reflexes	DMD/BMD
						Shoulder weakness		Exon 3–44 deletion
<1	246	497	Splenomegaly seen during routine physical	None	12,587	Hyperextensibility	N/A	DMD/BMD
						Head lag		Exon 3–29 deletion
6	477	324	Poor growth	Dark urine	12,121	None	Toe walking	Undiagnosed
5	>50	>40	Gastroenteritis	Short stature	14,752	Calf hypertrophy	Weakness	DMD
							Gower sign	Exon 49–54 deletion
11	140	94	Abdominal pain	Abdominal pain	5,833	Headaches	Headaches	BMD
								Exon 45–47 deletion
1	118	196	Feeding intolerance, failure to thrive	Failure to thrive, feeding intolerance	17,919	Developmental delay	Hearing loss	DMD/BMD
						Hypotonia, head lag, speech delay	Sleep apnea, head lag, Gower sign	Exon 8–11 deletion
3	497	318	Upper respiratory tract infection	None	22,009	Weakness,	Calf hypertrophy, weakness	DMD
						Decreased reflexes, hypotonia, Gower sign		Exon 20–25 deletion
2	300–400	300–400	Prolonged diarrhea	Chronic constipation, anemia	12,000	Calf hypertrophy	Fatigue, hypotonia, calf hypertrophy, Gower's sign	BMD/DMD
						Weakness		Exon 48–52 deletion
4	186	235	Leg pain, failure to thrive	Failure to thrive, abdominal pain, dark urine	9,932	Decreased mobility, limp	Fatigue, muscle cramping	Dystroglycanopathy
2	99	80	Urinary tract infection		917	None	Hyperextensibility	DMD/BMD carrier
								Heterozygous for exon 48–50 deletion
16	195	147	Unknown	None	12,131	None	None	Undiagnosed

Reference ranges: ALT, 0–50; AST, 0–40; γ-glutamyl transpeptidase, 5–55.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMD, Becker muscular dystrophy; CK, creatinine kinase; DMD, Duchenne muscular dystrophy; IU/L, international units per liter.

plaints prompted evaluation of a complete metabolic panel in these children, including infection in 4, failure to thrive/poor growth in 4, prolonged diarrhea in one, abdominal pain in one, and splenomegaly in one. ALT levels ranged from 99 to 477 IU/L and averaged 266 IU/L, whereas AST levels ranged from 50 to 497 IU/L and averaged 249 IU/L (Table 1). Serum gamma-glutamyl transferase (GGT) was only checked in 4 patients, but was found to be normal in all (data not shown).

Eight of the 12 children already had exhibited signs or symptoms of muscle disease (eg, calf hypertrophy, toe walking, and muscle weakness) at initial presentation to the neuromuscular clinic. Despite these early signs and symptoms, the average time from identification of elevated ALT/AST to discovery of elevated CK levels was 7 months. The majority of patients had undergone extensive workup for liver disease before a serum CK was checked. In addition to an abundance of serum testing, abdominal ultrasound was performed on 10 of the12 patients and an abdominal MRI was performed on 2 (Table 2). Of particular concern, 4 patients underwent liver biopsies, and only one yielded abnormal pathology. Serum CK testing was ultimately ordered by specialized gastroenterology clinics for 11 patients and an inpatient pediatrics team for the 12th patient.

When these patients first presented to the muscle clinic, serum CK levels averaged 12,078 IU/L (range, 4867–22,009) (Table 1). The majority (8 of 12) displayed subtle signs of muscle disease, including calf hypertrophy, mild weakness, and hypotonia. Two more patients became symptomatic within 1 year of presenting to muscle clinic. Subsequently, 8 patients were diagnosed with Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy by genetic testing, one of whom was identified as a manifesting (symptomatic) female carrier of a dystrophin mutation and one of whom was diagnosed with a dystroglycanopathy. Two patients remain undiagnosed on a genetic basis but carry a clinical diagnosis of muscular dystrophy (Table 1).

Discussion

DMD is estimated to affect one in 3500 live male births.[13] A recent multistate study indicates that signs and symptoms of DMD appear, on average, at age 2.5 years.[14] However, because the initial signs and symptoms are mild, there is an average delay of 1 year before children receive medical attention. An additional year-long delay occurs before serum CK levels are measured or children are sent to a neurologist for formal evaluation and treatment.[14] Furthermore, although the majority of children first present to their family physician or pediatrician, the primary care provider was the first to check a serum CK in only one third of cases.[14]

In the past, life expectancy was poor; however, because of improved respiratory therapy, physical therapy, and supportive measures, life expectancy now has improved greatly and boys are living well

Table 2. Clinical Evaluation for Elevated AST/ALT and Time to Diagnosis of Muscle Disease

Liver Imaging	Liver Biopsy	Time to CK Measurement (months)	Time to Neurology Consultation (months)	Time to Diagnosis (months)
US	No	3.5	16	17
US	No	0.5	3	1
US	No	2	4	4
None	No	2	2	Undiagnosed
US	No	1	2	3
MRI, MRCP, HIDA	Laparoscopic biopsy	9	9	11
None	No	0.75	1	2.5
US	Needle biopsy	14	14	15
MRI, MRV	Needle biopsy	15	16	18
US	Laparoscopic biopsy	24	25	31
US	No	4	5.5	4
US	No	8	10	Undiagnosed
N/A	N/A	7.0 (average)	9.0 (average)	10.7 (average)

AST/ALT, aspartate aminotransferase/alanine aminotransferase; HIDA, Hepatobiliary Iminodiacetic acid scan; MRCP, magnetic resonance cholangiopancreatography; MRI, magnetic resonance imaging; MRV, magnetic resonance venography; US, ultrasound.

into their mid-20s. Because of newer clinical and pharmaceutical interventions, early diagnosis has become even more important. Corticosteroids have been shown to slow disease progression and are emerging as a standard treatment for DMD.[15–19] Some authors suggest that initiation of steroid treatment as early in the disease process as possible may prolong functionality during later treatment.[17] Interestingly, in our study and others, elevated ALT/AST may be seen in early stages of the disease before symptoms of muscle weakness are noted by the family.[10,11,20] Further molecular and pharmaceutical advances are on the horizon, and true disease-modifying agents are in early trials.[21,22]

Many children with muscle disease remain undiagnosed for extended periods after the finding of elevated transaminases. In our study, a primary muscle etiology for elevated ALT/AST was not considered for more than a year in a quarter of the patients, and one patient waited 2 years before evaluation of serum CK. In addition, testing for liver disease involved invasive liver biopsy in one third of patients. To prevent delays in diagnosis, as well as unnecessary invasive testing, it is important to maintain a high index of suspicion for extrahepatic sources of ALT and AST.

We propose a simplified process for rapid screening in patients with elevated ALT/AST on the basis of the recommendations of the DMD Care Considerations Working Group.[16] Children with elevated ALT/AST who also have elevated bilirubin or alkaline phosphatase on the metabolic panel should be evaluated for gastrointestinal disease. Elevated serum GGT can be used to identify patients with liver disease.[9] A CK level should be obtained in patients with elevated ALT/AST without clear gastrointestinal disease and could be done at the same time as serum GGT. The patient also should be evaluated for symptoms of gait disturbance, falls, or muscle pain and be examined for calf hypertrophy or muscle weakness. A quick developmental screen should be performed and questions regarding gross motor milestones (onset of independent walking) should be asked. Gower sign is common in children with proximal muscle weakness; because of poor hip and thigh strength, it is characterized by using hands and arms to push on thighs to raise the body from a supine position to a standing position. Family history regarding the presence of muscle disease should be obtained. If signs or symptoms are positive, the patient should be evaluated by a neurologist for muscle disease. In the absence of findings suggestive of either liver or muscle disease, other causes of elevated transaminases, such as those with a renal, pancreatic, or cardiac origin, must be addressed.

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