A 4-year-old Hispanic boy was referred to our facility because of elevated levels of alanine transaminase (ALT) and aspartate transaminase (AST), which were detected during an evaluation of transient abdominal pain while the boy was in Puerto Rico. He was otherwise in perfect health; a review of systems was negative. His past medical history and birth history were noncontributory. Immunizations, including hepatitis B, were up-to-date. The family history was significant for tuberculosis and rheumatoid arthritis.

Physical examination revealed a well-nourished boy with growth at the 90th percentile and normal vital signs. There were no signs of liver disease, and the heart and lungs were normal. Abdominal examination revealed no organomegaly. Results of the neurological evaluation were unremarkable.

What is your differential diagnosis and how would you proceed?

The differential diagnosis of elevated levels of transaminase is vast and usually indicates liver dysfunction. Hepatitis can be of infectious, metabolic, toxic, or autoimmune etiology. Consequently, this patient underwent extensive laboratory tests to determine the cause of the hypertransaminasemia. Tests included a complete blood cell count; a coagulation profile; and measurements of blood urea nitrogen, creatinine, electrolytes, erythrocyte sedimentation rate, C-reactive protein, calcium, amylase, lipase, cholesterol, triglycerides, ferritin, g-glutamyl transpeptidase (GGT), α1-antitrypsin (to rule out α1-antitrypsin deficiency), copper, ceruloplasmin (to rule out Wilson disease), ammonia (urea cycle defects), serum amino acids (tyrosinemia, galactosemia, and other aminoacidopathies), urinary organic acids (organic acidemia), total protein, albumin, and bilirubin. All test results were within normal limits. Serological tests for hepatitis (types A, B, and C) and for Epstein-Barr virus, Cytomegalovirus, Bartonella henselae, Histoplasma, and HIV were negative.

Initial ALT and AST levels were 601 IU/L and 407 IU/L, respectively (normal, 7 to 40 IU/L and 9 to 80 IU/L, respectively). Test results for antinuclear antibodies (ANA) were positive (greater than 1:160); however, tests for anti-double-stranded DNA, antimitochondrial antibodies, liver kidney microsomal antibodies, antineutrophilic cytoplasmic antibodies (ANCA), and an extractable nuclear antibody (ENA) panel showed negative results. A tuberculin skin test was positive (greater than 14 mm), but chest films were normal.

Ultrasonograms of the liver were normal. The initial liver biopsy showed portal and lobular inflammation, "suggestive of autoimmune hepatitis." Liver tissue culture was negative for aerobic and anaerobic bacteria, acid-fast bacilli, and fungi.

Can this be autoimmune hepatitis?

With a presumptive diagnosis of autoimmune hepatitis, this young patient was treated with azathioprine and corticosteroids. Rifampicin was initiated for latent tuberculosis because of the potential for immunosuppression with immunomodulatory treatment. Despite 5 months of treatment, however, AST and ALT levels remained elevated. Levels were monitored weekly and ranged from 300 to 650 IU/L and 200 to 480 IU/L, respectively.

On review, the initial liver biopsy was thought to be inconclusive and all of the ancillary tests that help confirm autoimmune hepatitis were normal. Results of a second liver biopsy done later were...
also normal, despite persistent hypertransaminasemia. The diagnosis of autoimmune hepatitis was thus ruled out.

In view of persistent hypertransaminasemia without clinical or biochemical indicators of liver disease and a normal liver biopsy, hypertransaminasemia was thought to be of nonhepatic origin. Extrahepatic causes of hypertransaminasemia were then suspected, and additional blood tests led us to our final diagnosis.

**What additional blood tests would you order?**

Serum creatine kinase (CK) and aldolase levels were found to be elevated. These tests are not part of a routine metabolic panel in our institution and have to be specifically ordered.

**What might these results mean?**

Persistent asymptomatic elevation of AST and ALT levels may occur in patients with primary muscle disease.\(^1\)\(^,\)\(^2\) The CK level was 22,764 IU/L (normal, 32 to 250 IU/L) and aldolase was 264 IU/L (normal, 2 to 8 IU/L). These findings strongly pointed to primary muscle disease.

DNA analysis revealed a deletion at exon 45 of the dystrophin gene, which confirmed the diagnosis of Xp21 dystrophinopathy.

Over time, our patient demonstrated signs of muscle disease with proximal muscle weakness and pseudohypertrophy of calf muscles. He is currently being followed closely in the muscle clinic at our institute by a multidisciplinary team headed by a pediatric neurologist.

**What about the positive ANA?**

An ANA titer of 1:160 can be nonspecific and can even be found in healthy persons. A positive ANA with moderately high titers such as 1:160 when unsupported clinically has little or no significance.\(^3\)

Five percent of the general population may have a positive ANA titer; also, the false-positive rate for ANA is as high as 20\%.\(^4\)

We found no case reports of patients with Xp21 dystrophinopathy and positive ANA in literature. One case in an adult with limb-girdle muscular dystrophy and a positive ANA titer has been reported.\(^5\)

**What is an Xp21 dystrophinopathy?**

Xp21 dystrophinopathy includes Duchenne muscular dystrophy (DMD) and Becker muscular dystrophy. Some affected patients have cardiomyopathy as the only manifestation of the dystrophinopathy.

Further discussion will be limited to DMD—the most common of the Xp21 dystrophinopathies. It was also the diagnosis in our patient.

**DUCHENNE MUSCULAR DYSTROPHY**

The disease carries the name of French neurologist Duchenne, who described some of the clinical and muscle biopsy features. The disorder occurs in about 1 of 3000 male births. Because its inheritance is X-linked recessive, females are rarely affected.

**Pathogenesis.** A genetically determined deficiency of dystrophin (a sarcolemmal membrane protein) adversely affects other membrane proteins leading to muscle fiber breakdown.

**Clinical features.** Clinical manifestations are uncommon at birth. Some boys may exhibit delayed motor milestones, especially in walking, running, jumping, climbing stairs, etc. A wide-based waddling gait with exaggerated lumbar lordosis is characteristic. Gower sign is positive and the affected muscles feel firm and rubbery.

Muscle weakness follows a stereotypical pattern. Weakness first appears in the muscles of the pelvic girdle and proximal muscles of the lower extremity; this is followed by weakness of other skeletal muscle groups. Muscles innervated by cranial nerves remain relatively unaffected. Usually by age 8, patients lose their ability to walk and climb stairs; by age 10, they are dependent on long leg braces; by age 12, they are wheelchair-bound.

Once a patient is wheelchair-bound, scoliosis sets in and progresses over time, which leads to respiratory insufficiency. Unless patients receive respiratory support, death ensues in the third decade of life—most commonly from respiratory insufficiency and pneumonia.

Ninety percent of patients with DMD have ECG abnormalities. Tall R waves in right precordial leads with an increase in R/S amplitude ratio in V\(_1\), and deep narrow Q waves in left precordial leads are common. Congestive heart failure and arrhythmias may occur.

Acute gastric dilatation or intestinal pseudo-obstruction consists of sudden episodes of emesis and abdominal pain and distention, which may lead to death.

The average IQ of patients with DMD is 1 standard deviation below the mean. This impairment is not progressive; verbal ability is mainly affected.

**Key lab features.** CK is the most important enzyme in the diagnosis of DMD and other myopathies. Elevated CK levels at birth precede obvious clinical manifestations.

Besides CK, levels of aldolase, AST, and ALT also tend to be elevated and follow the same course as CK levels.\(^6\)

Early recruited, short duration, low amplitude, polyphasic motor unit potentials are...
characteristic on electromyography. Muscle biopsy typically shows variability of fiber type distribution, consisting of type 1 fiber predominance and type 2 fiber deficiency followed by the eventual replacement of muscle by fibrofatty connective tissue. The definitive diagnosis of DMD can be made by demonstrating abnormalities in dystrophin. DNA analysis identifies deletions and duplications in approximately 56% of patients with DMD, and full sequencing of the gene identifies 97% of affected patients.

**GENETICS OF X-LINKED DYSTROPHINOPATHIES**

Although the inheritance is X-linked recessive, 33% of all DMD cases represent new mutations. A DMD phenotype can be observed in females in the following scenarios:

- If the female has an XO genotype (Turner syndrome).
- If she has a structurally abnormal X chromosome.
- If there is X-autosome translocation.

A DMD phenotype can also be observed in a female if a patient with Xp21 dystrophinopathy fathers a child with a carrier female.

Carrier detection can be done by pedigree analysis, CK determination, and DNA analysis. DNA analysis is the gold standard for diagnosis if the mutation is known. Carrier detection and prenatal diagnosis are important for genetic counseling. Such counseling should be offered to all families with X-linked dystrophinopathies.

**MANAGEMENT**

Patients with muscular dystrophy need the care of a multidisciplinary team at a tertiary care center; physical therapy, occupational therapy, and bracing are extremely important. Surgical release of heel cords may be necessary along with tendon transfer surgeries. A proper fitting wheelchair that promotes extensor posture can delay the onset of scoliosis. Surgical stabilization of the spine should be considered in patients with curves of 35 to 45 degrees.

Trials have shown that prednisone can improve muscle strength, pulmonary function, and functional ability in patients with DMD. Maximal improvement occurs within 3 months at a dosage of 0.75 mg/kg every day or on alternate days. Prednisone increases strength by increasing muscle mass and decreasing muscle breakdown. Corticosteroids are associated with several adverse effects and must be carefully considered before their use is initiated.  

Gene therapy for muscular dystrophy is still experimental and clinical trials are under way.

**THE TAKE-HOME MESSAGE**

There is a need to be aware of the possibility of occult muscle disease when evaluating patients with persistent unexplained mild to moderate elevation in AST and ALT. Extrahepatic sources of ALT and AST include muscle, heart, pancreas, lung, erythrocytes, and kidney. In the absence of a definitive hepatic cause, simple tests that measure CK and aldolase early in the workup may redirect the diagnostic workup and help avoid invasive tests, such as liver biopsy.

**References:**


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