CASE

At a 4-year-old health-supervision visit, J.B.’s mother expressed concern about his sluggishness and lack of energy during the past few months. Occasionally, he asked to be carried instead of walking. He showed less interest in play, although he continued to enjoy watching television. J.B.’s appetite was good, and he had not experienced a recent illness or physical trauma.

J.B. is a healthy child without significant illnesses, hospitalizations, or surgery. He was born at full term, of appropriate size for gestational age, and without prenatal or perinatal complications. His only medications were a multivitamin and fluoride. He has no known allergies, and his immunizations are up to date. He lives at home with his mother, father, and 6-year-old sister, who are all healthy. The parents are employed, and his mother denied any significant stress, marital conflicts, or recent change in the family’s pattern of living. J.B.’s family history is significant for myocardial infarction in 2 maternal uncles during their early thirties. A developmental history revealed that J.B. sat without support at 6 months of age and crawled at about the same time. His mother noted that he had difficulty pulling to a stand before his first birthday, and he did not walk until 2 years of age. Social, fine motor, and language development were achieved at appropriate times. He was toilet-trained a few months before the visit, and there were no recent changes in bowel or bladder habits.

A physical examination at the pediatrician’s office demonstrated normal vital signs and height and weight measurements between the 5th and 10th percentiles (head circumference was not measured). Throughout the history and examination, J.B. sat quietly in his mother’s lap. He appeared tired and did not make any significant effort to engage in spontaneous play activities. His head and neck examination were unremarkable. His thorax was barrel-shaped, and a grade 2–3/6 systolic murmur was auscultated at the apex; it was musical in quality and decreased when J.B. was placed in a sitting position. Peripheral pulses were normal. His abdomen was flat and non-tender, and normal bowel sounds were present. A soft, nontender liver edge was palpable 4 cm below the right costal margin; the spleen was 2 cm below the left costal margin. An abdominal mass was not palpated. In a standing position, his back appeared straight, with a mild lumbar lordosis, but without scoliosis. His extremities were thin with normal subcutaneous tissue; there was no joint tenderness, swelling, or erythema. There was no rash, jaundice, or scleral icterus. Neurological examination revealed normal tone and deep tendon reflexes. Although J.B. appeared to have symmetrically decreased muscle strength, he was not cooperative during the examination. His gait was broad-based without ataxia. Cranial nerve examination was normal.

Because of the hepatosplenomegaly, the pediatrician assessed J.B.’s liver function. The total and direct bilirubin and alkaline phosphatase were normal. The aspartate aminotransferase (AST) and alanine aminotransferase (ALT) enzyme levels were elevated; the AST was 557 units/mL, and the ALT was 360 units/mL. The hemoglobin was 12.5 mg/dL. A total white blood cell count and platelet count were normal. Hepatitis A, B, and C serologies were negative with the exception of the presence of hepatitis B surface antigen (HepBsAg) antibody (consistent with Hepatitis B vaccine-induced immunity).

At this point, J.B.’s pediatrician was uncertain about a diagnosis that would take into account lethargy, temper tantrums, delayed motor development, and hepatosplenomegaly associated with elevated serum transaminase levels. The abnormal gait and possible weakness on examination added further confusion to the diagnostic dilemma. Uncertain about the next step, the pediatrician referred JB to a pediatric gastroenterologist.

INDEX TERMS. hepatomegaly, muscular dystrophy, fatigue, motor developmental delay.

We need the whole physical for the whole patient. Plato

Dr Martin T. Stein

A delay in development or a persistent behavioral condition may, on examination, be associated with other physical symptoms or signs that may provide a clue to a diagnosis. At times, the finding on physical examination and a subsequent laboratory test are so striking that the next step is an immediate referral to a subspecialist. J.B. presented with a constellation of concerns, including fatigue (“sluggishness and lack of energy” for several months), diminished interest in play and spontaneous activities, and a delay in motor development. The finding on physical examination of mild hepatosplenomegaly and elevated serum transaminases led the primary pediatrician to consider an underlying liver disorder. A referral to a pediatric gastroenterologist followed these observations.

It is a credit to the pediatric gastroenterologist that...
J.B.’s evaluation was comprehensive. As described in detail in the first commentary, the child’s abnormal liver-function studies were integrated with other important observations, including a delay in motor development, a family history that suggested a genetic disorder, and a more detailed evaluation of weakness during the physical examination. A careful synthesis of the facts available to the primary care clinician led to a suspicion of a diagnosis outside of the gastrointestinal system. This kind of medical practice, where the patient is seen as a whole person and not in terms of individual organs and systems, was described several years ago by the British pediatrician, John Apley.¹ Using cardiology as an example, he wrote: “The cardiologist, however expert in physiology and cardiac function, is incomplete as a diagnostician and doctor if he fails to look beyond the functioning of the heart to the functioning of the patient as a person. On the whole, good diagnosticians are good listeners. History-taking can be crucial, and further questions to highlight the developmental history, which can be added to see if anything suspicious emerges, should not be omitted with any one child…”

I asked Dr Neelesh Tipnis to provide the initial commentary. Dr Tipnis is a Fellow in Pediatric Gastroenterology at Children’s Hospital San Diego, University of California, where J.B. was evaluated. Dr Paul Schultz, a senior pediatric neurologist at the same institution, wrote the second commentary. The discussion on the Developmental-Behavioral Pediatric Web site yielded important additional comments from Dr Richard Jacobson.

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J.B. has 4 major problems: elevated serum aminotransferase levels, hepatomegaly with mild splenomegaly, muscle weakness, and isolated gross motor delay. Elevated serum aspartate aminotransferase (AST, SGOT) and alanine aminotransferase (ALT, SGPT) enzymes are a frequent cause of referral to a pediatric gastroenterologist. AST and ALT are intracellular enzymes used to catalyze the conversion of aspartate and alanine, respectively, to glutamine and acetyl-coenzyme A (CoA), which serves as an important link to the citric acid cycle for energy production. When compared with serum, AST is found in highest concentrations in myocardial tissues (7800:1), followed by skeletal muscle (7000:1), liver (5000:1), kidney (4500:1), pancreas (1400:1), lungs (500:1), and red blood cells (15:1).¹ In comparison, the ALT tissue-to-serum ratio reveals higher concentration in liver tissue (2850:1) and kidney (1200:1), with smaller levels in skeletal muscle and myocardium (300–400:1). Cell injury results in the liberation of these intracellular enzymes and raises serum aminotransferase levels. Therefore, the differential diagnosis of elevated aminotransferase enzymes is broad.

Investigating hepatic causes of chronic elevated aminotransferase enzymes is a reasonable place to start in J.B. because of the hepatosplenomegaly discovered on physical examination. Chronic liver infection, passive congestion, cholestatic liver disease, hepatobiliary tumors, and inappropriate storage of fat, glycogen, and metals are possible etiologies. Cardiac disorders such as acute myocardial infarction, myocarditis, pericarditis, and cardiomyopathy often cause elevations of aminotransferase enzymes. Active skeletal muscle injury from disorders such as rhabdomyolysis, viral or pyomyositis, muscular dystrophy, or rheumatic myositis causes elevations in serum aminotransferase enzymes. Other disorders including renal infarcts, intestinal infarcts, shock, pancreatitis, cholecystitis, endocrinopathies, and heparin therapy may also lead to elevations of aminotransferases.

The additional findings of muscle weakness and isolated gross motor delay with hepatomegaly help narrow the potential etiologies in J.B. For example, liver storage diseases typically present in this fashion.² Glycogen storage disease, particularly type II (Pompe’s disease) and type III (Cori-Fabry), presents with progressive hepatosplenomegaly, fasting hypoglycemia, and variable degrees of muscle weakness. Niemann-Pick disease is the result of a defect in sphingomyelinase. Four variants of Niemann-Pick are associated with hepatosplenomegaly during infancy, often with prolonged jaundice. Types A and B present during early infancy with failure to thrive and progressive muscle weakness and global developmental delay. Types C and D Niemann-Pick present during the toddler years with predominant gaze disturbances and extrapyramidal signs, followed by muscle weakness and gross motor delay. Gaucher’s disease results in characteristic radiographic long-bone findings (Erlenmeyer flask) and massive hepatosplenomegaly as the result of abnormal sphingolipid accumulation because of a deficiency in β-glucosidase. The infantile, neuronopathic form includes ataxia, peripheral neuropathy, and seizures. The more common nonneuronopathic form of Gaucher’s disease (type 1) is characterized by bone marrow infiltration and hypersplenism. The diagnosis is made by the finding of the Gaucher cell on bone marrow biopsy and polymerase chain reaction testing. Enzyme replacement therapy is available.

Hepatobiliary disease is the presenting sign of cystic fibrosis in 1% of patients.³ Eighty percent of patients with cystic fibrosis have fat accumulation in the liver on autopsy. Many will have focal biliary cirrhosis and progress to end-stage liver disease. Chronic malnutrition from pancreatic insufficiency can lead to muscle weakness, atrophy, and loss of developmental milestones.

Wilson’s disease is a progressive disorder caused by a defect in copper transport. Copper and lipid accumulation occurs in hepatocytes and neuronal cells and within joint, renal, and endocrine tissues.
Age of presentation is variable but occurs most often during adolescence. Accumulation of hepatic copper results in pathologic changes in the liver such as micro- and macrovesicular lipid deposition leading to progressive hepatic fibrosis with mild elevations in serum aminotransferases. Occasionally, fulminant hepatic failure with a hemolytic anemia occurs. Motor symptoms generally occur late in the disease and include dystonia, weakness, choreiform movements, dysarthria, and gait disturbances. Dystonia may produce a “frozen face” appearance. Psychiatric manifestations are a result of copper accumulation in the cerebral cortex and basal ganglion. Inattentiveness, diminished social functioning, deterioration in school performance, and psychosis may occur.

Searching for a hepatic cause of elevated aminotransferases in this case is a logical first step in the presence of hepatosplenomegaly. However, elevated AST and/or ALT have been reported in children with muscular dystrophy. Duchenne muscular dystrophy (DD) is an X-linked disorder that is the most common hereditary neuromuscular disease, occurring in all races, with an incidence of 1:3600 male live births. Elevations of aminotransferase enzymes are found during the early asymptomatic period when the greatest amount of muscular degeneration occurs. Hepatomegaly was a feature in 8 of 24 patients with muscular dystrophy referred to a gastroenterologist for evaluation of elevated AST. In these cases, no clinical evidence of hepatic disease was found. All children had a history of delayed walking and signs of muscular dystrophy, including calf pseudohypertrophy and proximal muscle weakness. Creatine kinase (CK) is principally found in skeletal muscle and only in small amounts in the liver. The presence of an elevated CK often >240 times normal values with the appropriate history and physical findings should raise suspicion for the diagnosis of muscular dystrophy. The diagnosis of DD can be confirmed by gene testing for the characteristic dystrophin gene deletions and histopathologic changes on muscle biopsy. Affected children should be screened for cardiac, pulmonary, and cognitive sequelae of muscular dystrophy.

My evaluation of J.B. would begin with a careful review of the history, paying careful attention to the onset of weakness, a developmental history for clues of more global developmental delay, a family history of other affected males, and the ascertainment of the height of immediate relatives to evaluate his short stature. A neurological examination should include an assessment of upper and lower motor neuron function; the determination of muscle strength, tone, bulk, and reflexes are very important in a child with delayed motor development. Cardiac murmurs or extra heart sounds might be indicative of a cardiomyopathy associated with a global myopathic process. The abdominal examination should delineate liver and spleen size and texture. Laboratory testing should include studies to assess the presence of infection (hepatitis B and C and Epstein-Barr viral titers), serum α1 antitrypsin levels, serum copper and ceruloplasmin levels for Wilson’s disease, an antinuclear antibody titer and anti-liver/kidney microsomal antibody titer to assess for rheumatologic processes, a sweat chloride test, and a serum CK. Radiographic studies would include an ultrasound of the abdomen to assess the liver parenchyma for evidence of abnormal storage, fibrosis, or congestion and a chest radiograph to evaluate the lungs and heart for evidence of pulmonary disease and cardiomegaly. An echocardiogram would be beneficial in screening the child for a cardiomyopathy.

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J.B. presented with reduced motor function, interpreted as “lethargy.” At 4 years of age, he was recently toilet-trained. His inability to walk independently until 2 years of age should have been an alarming symptom in a child with a normal birth history. Hepatosplenomegaly led to an evaluation of liver function, which revealed elevations of AST and ALT. A subsequent examiner noted pseudohypertrophy of the calf muscles and ordered a serum CK level, which was markedly elevated. The constellation of gross motor developmental delay, proximal weakness, subsequently apparent pseudohypertrophy of the calf muscles, and elevation of the CK led to the diagnosis of DD. The diagnosis was confirmed by a molecular genetic test that demonstrated a characteristic deletion of the DD locus. The most common initial signs or symptoms of DD are delayed gait development, expressive language delay, and abnormal liver-function tests performed during an evaluation of other conditions such as gastrointestinal symptoms or hepatosplenomegaly. For years we have advocated the performance of a CK determination on any boy with a normal birth history who is not walking independently by 18 months of age and the determination of proximal leg strength in any boy with delayed speech development. The latter is performed by asking the child to stand up from a seated position on the floor while observing the use of his arms (Gower’s sign) to assist his weak legs by pushing on his thighs. Early diagnosis before 4 to 5 years of age does not necessarily lead to an improved outcome, but it does allow for carrier detection for the mother, who has a 60% to 70% chance of being a carrier of this X-linked...
recessive disorder. If she is a carrier, future pregnancies can be evaluated by amniocentesis to detect the presence of DD.

Approximately 10% of those boys with similar presentations have a milder form of the disease, referred to as Becker dystrophy (BD). Prognosis depends on accurately differentiating DD from BD, which can often be done by molecular genetic testing. In the 30% of cases that have no demonstrable deletion, a muscle biopsy is needed to histologically analyze the dystrophin level, which is diminished in BD and absent in DD.

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REFERENCES

Web Site Discussion
The case summary for the Challenging Case was posted on the Developmental and Behavioral Pediatrics Web site‡ (www.dbpeds.org.list) and the Journal’s Web site (www.lww.com/DBP). Comments were solicited.

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Weakness, elevated transaminases, and a history of maternal uncles with heart disease (perhaps a cardiomyopathy rather than the reported ischemic heart disease) suggests an X-linked genetic disorder, in particular a dystrophinopathy. The elevated AST and ALT could come from muscle, and so an astute gastroenterologist would check a CK even in a patient without other features pointing to liver disease. This is an occasional reason for referral to our neuromuscular clinic. The uncles are not said to be weak, which would suggest that the phenotype would be the milder Becker variety of muscular dystrophy. If this is the correct diagnosis, then the child’s apparent fatigue could simply reflect progressive proximal weakness.

However, an enlarged liver and spleen is not a typical feature of dystrophinopathy, so something else might be going on. There is an X-linked glycogen storage disease (type VIII) that affects the liver and is associated with hypercholesterolemia (which might be associated with ischemic heart disease in the uncles), but this disorder is not associated with myopathy.

So I come back to BD as the most likely explanation. The diagnosis can be made with serum CK, which should be in the thousands, and DNA testing for a deletion of the dystrophin gene. If a deletion is not found, a muscle biopsy, with histochemistry for glycogen and immunostaining for dystrophin, would be the next step. An electromyogram is not necessary unless there is doubt about the weakness or if the CK is normal.

Dr Martin T. Stein

New information is slow to work its way into clinical practice. When I heard this case at our Grand Rounds Conference, I was certain that I knew the origin of the elevated serum transaminase levels; it must represent liver disease in J.B. A medical school memory from more than 3 decades ago reminded me that, of the 2 enzymes, the serum ALT (formally known as SGPT) was specific for the hepatocyte, whereas the serum AST (formally known as SGOT) was derived from muscle, hepatocyte, and a variety of other cells. The case discussion by Dr Tipnis makes it clear that both enzymes may be increased in muscle injury. Knowledge of that fact may have redirected my attention away from chronic liver disease associated with developmental delay and chronic fatigue—the wrong path to be sure!

Pattern recognition is the most frequent cognitive mechanism used by physicians when establishing a clinical diagnosis. It serves our use well, in that symptoms and signs of a particular condition are often clustered in recognizable patterns. To make the most out of this diagnostic process requires both the acquisition of sufficient clinical information, the ability to use as much of the information as possible (rather than discard critical data), and the courage to include as much of the information as possible in a unifying diagnosis. John Apley had this in mind when he wrote about the “one child” noted in my introductory comments.

This case also illustrates the importance of including specific information on development in all medical histories. Knowledge of a developmental delay apparently limited to the motor domain was a critical piece of information. It was not given the proper attention when the primary care clinician discovered abnormal liver-function tests. Presumably, an unspecified hepatic disorder was the clinician’s reason for referring J.B. to a gastroenterologist. Had J.B.’s “sluggishness and lack of energy” been evaluated more carefully, a proximal pattern of weakness in the lower extremities might have been demonstrated during the examination by the primary care clinician. In my office, I have a higher-than-usual examination table that allows a child to walk up 3 steps to reach the top. Children with proximal muscle weakness, a hallmark of DD and BD, have difficulty with this...
task. The Gower sign, the hallmark of a proximal muscle weakness, is described by Dr Schultz. In addition, Dr Schultz pointed out another reason to pay attention to developmental delay in this case when he suggested that, in any boy with delayed walking beyond 18 months without an explanation, a serum CK determination is an appropriate screening test for muscular dystrophy. In fact, the CK in children with DD is elevated before the onset of weakness.4

REFERENCES

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