Elevated aminotransferase activity as an indication of muscular dystrophy: Case reports and review of the literature

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S ZAMORA, C ADAMS, JD BUTZNER, H MACHIDA, RB SCOTT. Elevated aminotransferase activity as an indication of muscular dystrophy: Case reports and review of the literature. Can J Gastroenterol 1996;10(6):389-393. Five male children are reported in whom incidental recognition of elevated serum alanine aminotransferase (ALT) activity initiated investigation to identify the cause of suspected hepatocellular injury. All five were later diagnosed with X chromosome-linked muscular dystrophy. The serum level of ALT, generally considered to be specific for hepatocellular injury, was increased two to 25 times above normal in all the reported cases. Paradoxically, the increase in ALT activity was greater than that of serum aspartate aminotransferase (three to 16 times normal), an enzyme whose elevation is generally recognized as being less specific and indicative of muscle, cardiac, kidney, pancreatic, red blood cell or hepatic injury. At presentation to the gastrointestinal service, one case, age 2.5 months, had no symptoms or signs of neuromuscular dysfunction, while the other four had previously unrecognized hypertrophy of the calves, proximal limb weakness, positive Gower's sign or delayed gross motor skills. All five patients had marked elevation of serum creatine kinase activity and histopathologically confirmed muscular dystrophy. The practical clinical implication of this report is that children with elevated serum ALT, in the absence of other signs and symptoms of hepatic injury, may have occult muscular disease – most frequently muscular dystrophy. Although the clinical signs of muscular dystrophy may be subtle or absent, early determination of creatine kinase will suggest the correct diagnosis and minimize extensive and invasive investigation focusing on hepatic injury.

Key Words: *Aminotransferase activity, Liver function tests, Muscular dystrophy*

Activité élevée de l'aminotransférase comme indicateur de la dystrophie musculaire : rapport de cas et survol de la littérature

RÉSUMÉ : Les cas de cinq enfants de sexe masculin sont présentés ici. On a identifié fortuitement chez eux une élévation de l'activité de l'alanine aminotransférase sérique (ALT) qui a poussé les médecins à tenter d'identifier la cause d'une lésion hépato-cellulaire soupçonnée. Les cinq ont reçu par la suite un diagnostic de dystrophie musculaire liée au chromosome X. Les taux sériques d'ALT en général considérés spécifiques à la lésion hépatocellulaire atteignaient de 2 à 25 fois la limite normale dans tous les cas. Paradoxalement, l'augmentation de l'ALT était plus marquée que celle de l'aspartate aminotransférase (3 à 16 fois la normale), une enzyme dont l'élévation est en général reconnue comme moins spécifique et indicatrice d'une lésion musculaire, cardiaque, rénale, pancréatique, érythrocytaire ou hépatique. À l'admission au service de gastro-entérologie, l'un des cas âgé de 2,5 mois ne présentait ni symptômes, ni signes de dysfonction neuromusculaire, alors que les quatre autres présentaient déjà une hypertrophie des mollets, une faiblesse des membres proximaux, un signe de Gower positif et un retard de la motricité grossière. Les cinq patients présentaient une élévation marquée de l'activité de la créatine kinase sérique et une dystrophie musculaire histopathologiquement confirmée. Les implications cliniques pratiques de ce rapport font que les enfants qui présentent une ALT sérique élevée en l'absence d'autres signes et symptômes de lésions hépatiques peuvent souffrir d'une maladie musculaire occulte, le plus fréquemment de dystrophie musculaire. Bien que les signes cliniques de la dystrophie musculaire soient subtils ou inexistants, le dosage précoce de la créatine kinase indiquera le diagnostic correct et réduira le recours à des investigations extensives et effractives comme le dépistage d'une atteinte hépatique.

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In the pediatric population, prolonged elevation of the serum aminotransferases (alanine aminotransferase [ALT] and aspartate aminotransferase [AST]) is often attributed to liver disease (1). This happens especially if the ALT level is elevated because this enzyme is known to be selectively concentrated in the liver and is a more specific index of liver damage than AST level (2-5). However, failure to recognize that the aminotransferases, and ALT in particular, are not exclusively present in the liver may lead to extensive investigation for liver disease and a delay in diagnosis for children with muscular diseases who present with prolonged elevation of the aminotransferases and only subtle neuromuscular signs (6-11).

Muscular dystrophies are accompanied by a well recognized pattern of enzyme disturbances (12,13). Creatine kinase (CK) shows the most striking elevation and is the most sensitive and specific enzyme for diagnosis (13,14). Aldolase, lactic dehydrogenase and aminotransferases are also frequently elevated, although to a lesser extent. Elevation of aminotransferase activity is found in up to 90% of patients with muscular dystrophy (13,15) and is particularly evident in children during the early stages of the disease (16,17).

To ascertain the frequency with which elevated serum aminotransferases have initiated investigation for liver disease in patients with previously unrecognized muscular dystrophy, we reviewed the past 10 years of case records at the Alberta Children's Hospital, Calgary, Alberta for all patients younger than 18 years registered with a diagnosis of muscular dystrophy. To raise awareness of the need to consider muscular dystrophy as a potential cause of elevated aminotransferases we present the clinical histories of five patients with previously undiagnosed X chromosome-linked muscular dystrophy who were referred to the gastroenterology clinic for evaluation of elevated 'liver enzymes'. The literature is reviewed and similar previously published cases are summarized.

CASE PRESENTATIONS

Over the past 10 years there were 68 patients younger than 18 years diagnosed with muscular dystrophy at the Alberta Children's Hospital: Duchenne muscular dystrophy (26 cases), myotonic muscular dystrophy (20), Becker muscular dystrophy (seven), limb girdle muscular dystrophy (five), congenital muscular dystrophy (two), fascio-scapulohumeral muscular dystrophy (one) and unclassified muscular dystrophy (seven). The presenting clinical findings that led to a diagnosis of muscular dystrophy were neuromuscular signs (44 cases, 65%), screening against a background of a positive family history of muscular dystrophy (19, 28%) and unexplained elevation of serum aminotransferase activity (five, 7%). The children in the last group are the subjects of this report. Aminotransferase activity was measured using standard, previously published methodology (18,19).

Case 1: A 10-week-old male was referred for an eight-week history of elevated hepatocellular enzymes. The patient was born at term after an uncomplicated pregnancy. At three weeks of age, while on a soy-based formula, he presented with blood-flecked stools which were investigated and attributed to soy protein-induced allergic colitis. Mild elevation of the aminotransferases (ALT 74 U/L, AST 162 U/L) with normal serum bilirubin and alkaline phosphatase were noted incidentally and attributed to an *Escherichia coli* urinary tract infection. At nine months of age growth velocity was normal (along the 25th percentile for weight and height), and physical examination was unremarkable. However, the serum aminotransferases remained modestly elevated over the preceding months. The following investigations were performed without identifying an etiology: serology for toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis, Epstein-Barr virus, hepatitis A, B and C, urine for reducing substances, urinary amino acids and organic acids, plasma for amino acids, serum for alpha-1-antitrypsin level and protease inhibitor (PI) typing, and abdominal ultrasound. Percutaneous liver biopsy demonstrated no abnormality by light or electron microscopy. One month later, in addition to persistently elevated aminotransferases (ALT 396 U/L, AST 569 U/L), CK was found to be markedly elevated (25,602 U/L). Growth and development remained normal, and evaluation in the neuromuscular clinic disclosed no clinical sign or symptom of muscular disease. However, a muscle biopsy at age 11 months demonstrated a degenerative myopathy consistent with muscular dystrophy. Dystrophin staining was not performed on the muscle and DNA deletion analysis did not reveal a deletion of the dystrophin gene. At five years of age he has proximal limb weakness, calf hypertrophy, present deep tendon reflexes and toe walking consistent with Duchenne muscular dystrophy.

Case 2: A male infant presented at age six weeks with group B streptococcus meningitis complicated by a small right parietal infarct and seizures, which were treated with phenobarbitone. The pregnancy and delivery were normal. His gross motor development was slightly delayed. He walked without support at age 17 months, which was thought to be a sequelae of the meningitis. At 18 months of age serum aminotransferases obtained as part of routine monitoring for long term phenobarbitone therapy were found to be elevated (ALT 363 U/L, AST 303 U/L), with no evidence of cholestasis. He was referred to the gastrointestinal service for further investigation. Physical examination demonstrated no sign of liver, muscle or neurological disease. The following studies were normal or negative: serology for toxoplasmosis, rubella, cytomegalovirus, herpes, syphilis, Epstein-Barr virus, hepatitis A, B and C, urine for reducing substances, urinary amino acids and organic acids, plasma for amino acids, serum for alpha-1-antitrypsin level and PI typing, antinuclear antibodies, quantitative immunoglobulins, serum ceruloplasmin, urinary copper excretion on penicillamine, sweat chloride and abdominal ultrasound. A liver biopsy disclosed no abnormality on light microscopy and only a mild increase of smooth endoplasmic reticulum on electron microscopy. A neurological examination at age 2.5 years was normal, the phenobarbital was discontinued and there was no further seizure activity.

At 4.5 years of age he was referred to the gastroenterology clinic for evaluation of constipation. He had difficulty climbing stairs and Gower's sign on physical examination. Aminotransferases were again noted to be abnormal (ALT 526 U/L,

AST 307 U/L) and CK was elevated (10,950 U/L). Because of the abnormalities found on the previous liver biopsy and concern that the significant elevation of the serum ALT (more than 10 times the upper limit of normal) indicated a coexistent hepatic disorder, a second liver biopsy was performed along with a muscle biopsy. The liver biopsy was normal. The muscle biopsy showed a degenerative myopathy consistent with Duchenne muscular dystrophy. Neither dystrophin staining of the muscle nor DNA analysis for the dystrophin gene were performed.

Case 3: A 5.5-year-old male had been previously well except for an episode of pyelonephritis at age 16 months. Following a 'flu-like illness at age five years, he developed abdominal pain, fatigue and weakness. Growth velocity had been normal (height and weight between the fifth and 10th percentiles). He was slow in motor development, walking at 18 months. Aminotransferases were elevated (ALT 690 U/L, AST 620 U/L), without evidence of cholestasis, and he was referred to the gastrointestinal service for evaluation.

Physical examination revealed mild calf hypertrophy, proximal limb weakness and a positive Gower's sign. CK was markedly elevated (25,400 U/L), as were repeat aminotransferase levels (ALT 1000 U/L, AST 785 U/L). There were no other clinical or biochemical features of underlying liver disease (normal bilirubin, albumin and prothrombin time). A muscle biopsy showed a degenerative myopathy. Dystrophin staining with monoclonal antibodies showed absent immunoreactivity in more than 90% of fibres, consistent with Duchenne muscular dystrophy. DNA deletion analysis did not reveal a deletion for the dystrophin gene.

Case 4: A seven-year-old male presented who had been born prematurely at 29 weeks of gestational age. The postnatal period was complicated by hyaline membrane disease and apnea of prematurity. His motor skills were mildly delayed (sat at 10 months and walked without support at 15 months corrected gestational age) and he exhibited mild attention and behavioural problems which were attributed to his prematurity. During an investigation for abdominal pain at age seven years, elevated aminotransferases were found (ALT 761 U/L, AST 494 U/L, no cholestasis) and he was referred for evaluation to the gastrointestinal service.

Physical examination revealed normal strength, deep tendon reflexes and mild calf hypertrophy. There were no clinical features and no other biochemical abnormalities suggestive of underlying liver disease. CK was markedly elevated (19,141 U/L) and a muscle biopsy showed a degenerative myopathy consistent with muscular dystrophy. Dystrophin staining of the muscle was not performed; however, DNA deletion analysis showed a deletion of the dystrophin gene. The diagnosis was Becker muscular dystrophy.

Case 5: The mother of a 14-month-old male discovered a 'cloud' over his left pupil; it was shown to be a cataract and was treated by left lens aspiration and anterior vitrectomy. The pregnancy had been uncomplicated and the child had been otherwise well. Extensive investigation to exclude a metabolic disorder causative of cataracts was unremarkable except for elevated aminotransferases (ALT 541 U/L, AST 855 U/L). He was referred to the gastrointestinal service for evaluation of a suspected hepatic disorder. At initial assessment at age 18 months, examination revealed no clinical or other biochemical features of underlying liver disease, mild motor delay and proximal weakness, which the parents had attributed to impaired visual acuity. CK was significantly elevated (24,420 U/L). Muscle biopsy showed a degenerative myopathy. Dystrophin staining with monoclonal antibodies showed many fibres with absent dystrophin immunoreactivity. There was no deletion of the dystrophin gene on DNA analysis. The findings were consistent with Duchenne muscular dystrophy.

DISCUSSION

The measurement of serum aminotransferase activity is most useful clinically in the evaluation of hepatobiliary disorders (1,20). Elevation of the aminotransferases is generally interpreted as reflecting hepatocellular necrosis, as opposed to elevation of alkaline phosphatase or gamma-glutamyl transpeptidase activity, which principally reflects cholestasis. However, marked overlap exits between these two categories of liver dysfunction (21). The clinician must also remember that aminotransferases are present in other organs. The heart, skeletal muscle, kidney and pancreas are rich in both AST and ALT compared with serum (2), and these extrahepatic sources should always be considered in the differential diagnosis of hypertransaminosemia. For example, in myocardial infarction, significant elevations of both AST and ALT have been described (22) and are widely recognized. Although less marked than the increase in serum CK, elevations of aminotransferases are the rule in the necrotizing and destructive myopathies (dystrophinopathies, limb girdle muscular dystrophy and inflammatory myopathies), versus the usually normal levels of serum aminotransferase activity in the congenital structural myopathies, myotonic dystrophy and spinal muscular atrophy (12,14,23). The most significant elevations of aminotransferase activity occur in the X chromosome-linked dystrophinopathies: Duchenne muscular dystrophy and Becker muscular dystrophy. In these patients, elevated levels are easily detected in the early asymptomatic stages when there is a greater bulk of degenerating muscle, and the levels generally decline as the disease progresses and muscle bulk decreases (13).

We report five male children with X chromosome-linked muscular dystrophy (four with Duchenne muscular dystrophy and one with Becker muscular dystrophy) in whom elevated serum aminotransferase activity was first recognized incidental to investigations that were initiated to exclude the possibility of hepatic dysfunction associated with the following presenting complaints or conditions: rectal bleeding, anticonvulsant therapy, abdominal pain and cataracts. In each patient the biochemical abnormality initiated investigation, sometimes extensive and invasive (two children had liver biopsies), to identify the cause of suspected hepatocellular injury. At presentation to the gastrointestinal service, the first case had no symptoms or signs of neuromuscular dysfunction and the other four had previously unrecognized calf

TABLE 1
Reported cases of muscular disorders with elevated aminotransferase activity

Case	Diagnosis	Age (years)	Liver biopsy	Elevation (months)	Neuromuscular clinical findings	Enzymes					
						CK	ALT	Times norm*	AST	Times norm	Reference
1	DMD	0.8	Normal	9	No	25,602	396	9.9	569	11.4	Present study
2	DMD	4.5	Normal	32	Yes	10,950	526	13.2	307	6.1	Present study
3	DMD	5.5	–	6	Yes	25,400	1000	25	785	15.7	Present study
4	BMD	7.3	–	3	Yes	19,141	966	24.2	546	10.9	Present study
5	DMD	1.6	–	4	Yes	24,420	447	11.2	317	6.3	Present study
6	DMD, Turner	3	–	1	Yes	10,000	460	18.4	437	12.5	6
7	DMD	2.5	–	?	Yes	16,640	41	1.6	275	7.9	6
8	DMD	0.75	–	?	Yes	15,980	260	10.4	388	11.1	6
9	BMD	10	–	?	No	3000	63	2.5	55	1.6	6
10	PMD	2.7	–	1	Yes	17,000	362	NA	408	NA	7
11	PMD	10	Abnormal	24	Yes	4323	289	NA	88	NA	7
12	PMD	14	Abnormal	24	Yes	5210	208	NA	114	NA	7
13	PMD	6	–	1	Yes	12,130	227	NA	129	NA	7
14	PMD	9	Abnormal	24	Yes	4120	215	NA	132	NA	7
15	MG	15	–	12	No	11,370	132	2.9	253	6.3	8
16	LGMD	9	Normal	46	Yes	396	110	4.4	84	4.2	9
17	Polymyositis	13	–	6	Yes	6930	120	NA	112	NA	10
18	DMD	8	–	24	Yes	20,000	188	NA	284	NA	10
19	SCPMD	12	–	13	Yes	5203	93	NA	109	NA	10
20	NM	3	–	4	Yes	14,000	380	NA	263	NA	10
21	DMD	1	Abnormal	12	No	24,640	440	14.7	347	11.6	11
22	DMD	6	–	8	Yes	10,000	267	8.9	356	11.9	11
23	BMD	6.5	Normal	24	Yes	5000	158	5.3	170	5.7	11
24	KWS	14.5	–	2	Yes	612	118	3.9	118	3.9	11

*All cases were male except 6 and 19. *Upper limits of normal (IU/L) – cases 1-5: creatine kinase (CK) 105, alanine aminotransferase (ALT) 40, aspartate aminotransferase (AST) 50; cases 6-9: CK 170, ALT 25, AST 35; cases 10-14: not reported; case 15: CK 180, ALT 45, AST 40; case 16: CK 80, ALT 25, AST 20; cases 17-20: not reported; cases 21-24: CK 50, ALT 30, AST 30. BMD Becker muscular dystrophy; DMD Duchenne muscular dystrophy; KWS Kugelberg-Welander syndrome; LGMD Limb girdle muscular dystrophy; MG Muscle glycogenosis; NA Not available; NM Necrotizing myopathy; PMD Progressive muscular dystrophy (DMD or BMD); SCPMD Scapuloperoneal muscular dystrophy; Times norm Times the upper limit of normal*

hypertrophy, proximal limb weakness, positive Gower's sign or delayed gross motor skills. All five patients had marked CK elevation and histopathologically confirmed muscular dystrophy. In three patients a diagnosis of muscular dystrophy was not initially entertained. Delay in acquisition of gross motor skills was attributed to a previous neurological insult: meningitis (case 2), prematurity (case 4) and impaired visual acuity (case 5).

In addition to the five patients reported here we found 19 other cases of muscular disorders with similar presentations recorded in the literature (6-11). Almost all were males with the X chromosome-linked dystrophinopathy; however, other muscular disorders such as myositis and muscle glycogenesis have been responsible for 'unexplained' (nonhepatic) and incidentally demonstrated persistent hypertransaminosemia (Table 1). The biochemical abnormalities documented in 24 patients (five from this study and the 19 previously reported cases) are remarkable not only for the impressive elevation of CK (up to 240 times the upper limit of normal), but also for the mild to moderate elevation of ALT (up to 25 times the upper limit of normal). The degree of ALT elevation in these patients is much higher than some authors (13) have indicated as being consistent with muscular dystrophy. Elevated aminotransferase activity in many of these patients was demonstrated incidentally during the investigation of abdominal pain or trauma, transitory febrile illness, screening before elective surgery or drug therapy monitoring. Subsequently, as occurred with our patients, some of these children were extensively investigated in an effort to document liver disease, although the majority of them lacked hepatomegaly or other clinical signs of hepatocellular damage.

CK is principally an enzyme of skeletal muscle origin. It is present only in minimal amounts in the liver, with a concentration ratio in skeletal muscle:liver of 863:1 (24). Thus, significant CK elevation is almost exclusively attributable to muscular damage, such as that occurring in muscular dystrophy. The organ of origin for the elevated serum aminotransferases in muscular dystrophy patients is controversial. Compared with the serum, skeletal muscle is rich in aminotransferase activity, although to a lesser extent than the liver (2). A rise in the serum activities of both AST and ALT can easily be explained by the muscle degeneration observed in patients with muscular dystrophy. However, a few authors have suggested a hepatic origin. Morrell (25) reported elevated hepatocellular enzymes and previous episodes of unexplained jaundice in patients with muscular dystrophies, and suggested that this was indicative of liver involvement in these disorders. Kleine (26) found a marked elevation of sorbitol dehydrogenase and glutamate dehydrogenase in children with Duchenne muscular dystrophy, and suggested a hepatic origin for the elevated serum aminotransferases.

Aminotransferase isoenzymes from human liver have been partially characterized and both cytosolic and mitochondrial isoenzymes have been identified (27,28). However, specific isoenzymes for various organs – which could settle this controversy – have, to our knowledge, not been described. Canine X chromosome-linked muscular dystrophy is a model of Duchenne muscular dystrophy (29). Enzymatic analysis and histological examination of the liver in animals with both this disease and elevated ALT favour a solely muscular origin for the elevated aminotransferase (30). Furthermore, liver biopsies performed in patients with muscular dystrophy and elevated serum aminotransferases do not consistently demonstrate abnormality; only four of eight such patients who were biopsied showed pathological changes (Table 1). While no conclusion can be drawn from such a small sample, it should be noted that the four children with abnormal liver biopsies also presented with hepatomegaly and are probably not representative of the majority of patients with muscular dystrophy who lack clinical findings of liver disease.

While we aim to raise awareness of the need to consider muscular dystrophy as a cause of elevated serum aminotransferase activity, we must remember that patients with muscular dystrophy may also develop liver disease (7,11). In the context of an appropriate history, with symptoms and signs suggestive of liver dysfunction and a rise in serum aminotransferase activity, investigations for specific hepatic disorders and a liver biopsy may be appropriate in muscular dystrophy patients.

CONCLUSIONS

Although a muscular site of origin for the elevated serum aminotransferases in muscular dystrophy remains unproven, the practical clinical implication illustrated by the cases summarized above is that children with elevated serum aminotransferases, in the absence of other signs and symptoms of hepatic disease, may have occult muscular disease. In our hospital, 7% of patients registered with the diagnosis of muscular dystrophy were diagnosed after referral to the gastroenterology service for evaluation of unexplained elevation of the serum ALT. Although considered to be specific for hepatocellular injury, serum ALT was often more elevated than AST in our patients with muscular dystrophy. Contrary to some pediatric reference texts (3,4), an elevated ALT should not automatically point towards hepatic injury. Careful history and physical examination will often suggest unrecognized muscle disease. However, clinical signs of muscular dystrophy may be subtle or absent, especially in infants, and early CK determination will provide a clue to the diagnosis and minimize extensive and invasive investigations focusing on hepatic injury.

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