

Transaminitis in Duchenne's Muscular Dystrophy

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Abstract

Background: Persistently raised transaminase levels often prompt the clinician to investigate for liver pathology. Previously, some of our patients with Duchenne's muscular dystrophy have had investigations to look for liver disorders when the alanine transaminases (ALTs) were found incidentally to be high. **Aim:** The objective of the study was to ascertain the levels of the transaminases in patients with Duchenne's muscular dystrophy and to see if the levels of transaminases correlated with muscle enzymes such as creatine kinase (CK). **Materials and Methods:** This is a case series of 19 patients with Duchenne's muscular dystrophy. Alanine and aspartate transaminase (AST) levels and CK levels were measured in the serum of the patients. **Results:** In this series, ALT and AST levels were all found to be raised significantly in patients with biopsy-proven Duchenne's muscular dystrophy and Becker's muscular dystrophy. Alanine transaminase, in particular, was raised to a mean of 356 mmol/L, 9 times above the mean for normal. There was also good correlation between ALT and CK levels with a correlation coefficient of $r = 0.80$ and P value 0.01. Similar to CK, the transaminase levels were inversely proportional to mobility and to age. **Conclusion:** The presence of hypertransaminasemia in patients with muscular dystrophy should be attributed to muscle breakdown rather than to liver pathology and such patients should not be over-investigated for liver disease. In the absence of liver pathology, raised transaminases may be an early sign of occult muscular dystrophy and such patients should have CK levels checked to look for evidence of muscular dystrophy

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Introduction

Raised aminotransferase levels, especially that of alanine transaminase (ALT), have been traditionally attributed to liver pathology rather than to muscle disorders. However, raised alanine and aspartate transaminase (AST) levels have been found in patients with muscle diseases such as Duchenne's and Becker's muscular dystrophy, myotonic dystrophy and the inflammatory and endocrine myopathies.¹ Occasionally, the finding of raised transaminases has even allowed the early diagnosis of occult muscle disease.²⁻⁴ In our experience, and in some other case reports, some patients have actually been investigated for liver dysfunction. Because of the raised transaminase levels, hepatocellular damage was suspected rather than muscle pathology.

In this article, we report a series of 19 children with biopsy-proven Duchenne's muscular dystrophy who were all found to have raised transaminases, in particular, ALT. Our study attempts to correlate the level of creatine kinase (CK) with serum transaminase levels. Creatine kinase levels are used as a standard for muscle enzymes as CK is predominantly found in the muscle and is therefore one of

the enzymes known to be fairly specific for muscle disease. The distribution of total CK activity in various tissues (units/gram net weight) are: 3281 for muscle, 3.8 for liver, 402 for heart, 15 for kidney, 3 for pancreas and 13.4 for lung.⁵ Creatine kinase levels diminish with age with the duration of disease.⁶ We also wished to demonstrate that as the source of the transaminases was likely to be muscle, the levels of the transaminases would diminish with the duration of disease as a result of muscle decay and, similar to CK, would be lower in non-ambulant patients.

Materials and Methods

Nineteen children were seen in the Division of Paediatric Neurology in the Department of Paediatrics, National University Hospital from May 1996 to August 1999. They presented for evaluation at different stages of Duchenne's muscular dystrophy with typical features of limb weakness and calf pseudohypertrophy and underwent diagnostic investigations including CK levels, electromyography and muscle biopsy. Laboratory measurements of serum aminotransferase activities were measured in the serum of patients with an automated autoanalyser Vitros 950, Clinical

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Diagnostics, Rochester, USA with established reference values. Liver function tests including bilirubin levels were performed to ensure that there was no other indication of liver dysfunction with hyperbilirubinaemia or cholestasis.

Statistics

Data were analysed with bivariate correlation analysis and the relationship demonstrated with Pearson's correlation coefficient. A *P* value of <0.05 was considered statistically significant, and a *P* value of <0.01 as highly statistically significant.

Results

Data on the 19 patients are shown on Table I. None of the patients had any clinical signs and symptoms of liver dysfunction, in particular any jaundice or hepatomegaly, and liver function tests showed normal bilirubin, alkaline phosphatase and gamma glutamyl transferase levels. In all the patients, ALTs were consistently above the appropriate range for the age group, with a mean of 356 mmol/L, ranging from 81 to 1057 mmol/L with a standard deviation of 237 mmol/L. The mean ALT level was 9 times above the mean for normal patients in the age group. In comparison, the AST levels were 8 times above the expected mean for age. The mean AST level was 240 mmol/L with a standard deviation of 167 mmol/L and range of 48 to 703 mmol/L. As expected, these patients also had high CK levels, and in the few (4) patients who had their aldolase levels measured, this parameter was also markedly raised. Creatine kinase levels could not be measured above 32,000 U/L. Taking

32,000 U/L as the maximum level, the mean of CK was 15,790 U/L and was raised 83 times above the mean for the sex and age group.

In 5 patients, prednisolone had been started to maintain muscle function, but in 2 patients, the transaminase and CK levels had been done prior to the start of therapy.

Figure 1 shows the correlation between ALT levels and CK levels including all the patients regardless of whether they were on prednisolone therapy or had had myoblast therapy. The highest level that could be measured for CK was 32,000 U/L, above which no discriminatory value could be obtained. The correlation coefficient (*r*) was 0.8, which was highly statistically significant (*P* = 0.01). When patients with prednisolone therapy and previous myoblast therapy were excluded, there was a marginally stronger relationship demonstrated as the correlation coefficient *r* was 0.84 with significance at *P* value of 0.01. This is likely to be due to the fact that prednisolone may decrease CK levels in patients with muscular dystrophy.⁷ With regards to the other enzymes, AST was also found to have significant correlation of 0.80 with CK (Fig. 2).

There was an inverse relationship between the duration of disease and ALT levels, and this same relationship was also seen when comparing CK levels with disease duration. Using the Pearson's correlation for ALT level versus the duration of symptoms, the correlation coefficient was *r* = -0.68 with significance at *P* = 0.01. For CK and the duration of symptoms, the correlation coefficient was *r* = -0.72 with significance at *P* = 0.01.

TABLE I: CLINICAL DATA ON PATIENTS WITH DUCHENNE'S AND BECKER'S MUSCULAR DYSTROPHY

Patient	Age at time of tests (y)	Duration of symptoms (y)	Race	ALT mmol/L	AST mmol/L	LDH mmol/L	CK U/L	Current treatment
1	8	5	Chinese	357	146	2302	13,620	Nil
2	14	11	Nepalese	99	633	822	1760	Nil
3	14	10	Chinese	159	133	1622	8365	Nil
4	6	3	Chinese	670	320	5941	25,472	Nil
5	10	7	Chinese	264	248	3571	20,053	Prednisolone
6	9	6	Chinese	277	114	1852	9619	Nil
7	6	3	Chinese	1057	461	4665	>32,000	Myoblast transfer
8	10	7	Chinese	334	233	2126	8855	Prednisolone
9	7	4	Malay	600	475	4351	>32,000	Nil
10	10	7	Chinese	347	206	3132	>32,000	Nil
11	7	4	Chinese	260	134	1850	9370	Nil
12	2	1	Indian	543	703	8065	>32,000	Nil
13	8	5	Malay	223	207	2378	9456	Nil
14	11	8	Chinese	245	181	1650	6094	Prednisolone
15	16	13	Malay	189	151	1142	5895	Prednisolone
16	11	9	Malay	453	370	3323	17,591	Prednisolone
17	6	3	Chinese	451	290	4312	30,369	Nil
18	17	14	Chinese	149	73	692	3629	Nil
19	13	10	Chinese	81	48	726	1868	Nil

ALT: alanine transaminase; AST: aspartate transaminase; CK: creatine kinase; LDH: lactate dehydrogenase

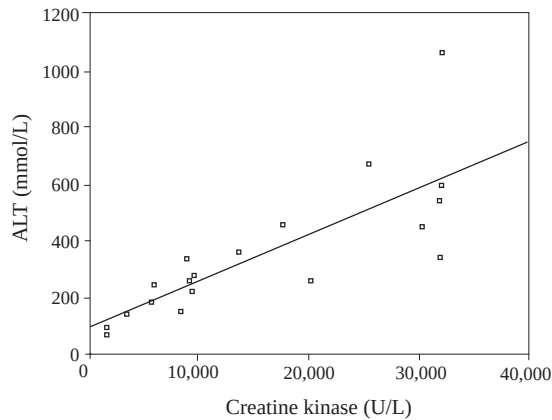


Fig. 1. Correlation between alanine transaminase (ALT) and creatine kinase (CK).

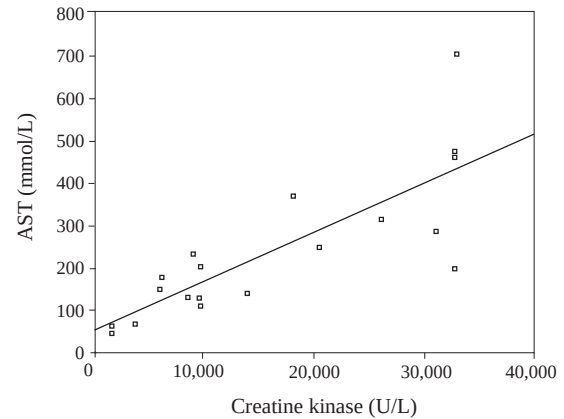


Fig. 2. Correlation between aspartate transaminase (AST) and creatine kinase (CK).

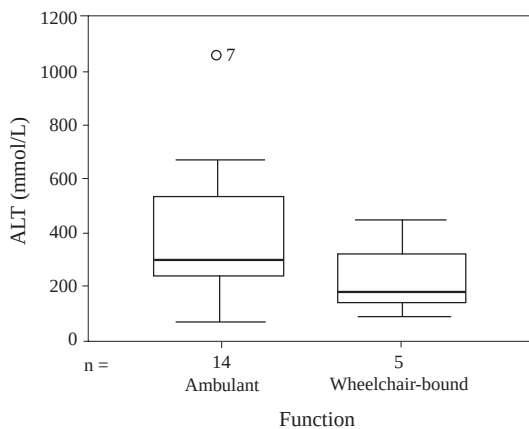


Fig. 3. Comparison between alanine transaminase (ALT) levels in ambulant and wheelchair-bound patients.

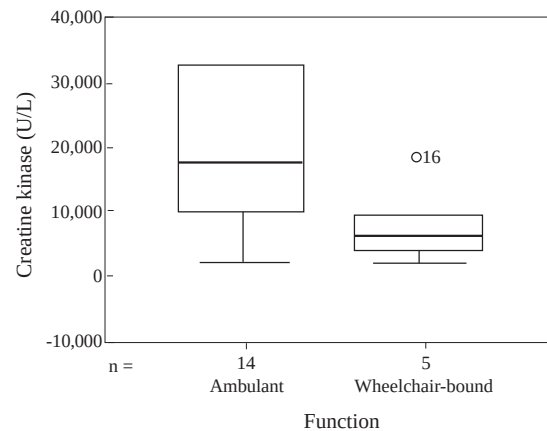


Fig. 4. Comparison between creatine kinase (CK) levels in ambulant and wheelchair-bound patients.

The ALT and CK levels were also compared against function of the patients. Fourteen patients were still ambulant, but 5 patients were wheelchair-bound. None of the patients were bed bound. The median values of ALT and CK were lower in the wheelchair-bound group compared to the ambulant group (Figs. 3 and 4). The median ALT in the wheelchair-bound group was 245 mmol/L and in the ambulant group was 395 mmol/L. The median CK in the wheelchair-bound group was 7456 U/L and in the ambulant group was 18,735 U/L. This difference was less marked when AST levels were compared in both groups.

Discussion

Although there has been significant advances made in the area of molecular diagnosis of Duchenne's muscular dystrophy, it has been found that there is usually a delay in diagnosis still, similar to that in the early 1980s.⁸ Besides neonatal screening of CK levels which increases the cost of health care, doctors should be aware of the other markers suggestive of Duchenne's muscular dystrophy so as to allow for earlier diagnosis.

The serum transaminase levels are often measured as part of liver function tests that may be done for a variety of reasons in childhood. Classical teaching indicates that serum aspartate aminotransferase activity is the least organ-specific, ALT is more liver-specific and CK is the most muscle-specific. In our group of patients, 2 had actually undergone further investigations to assess for liver pathology when both the alanine and AST levels were found to be high during routine liver function tests for unrelated reasons. Stenhammar et al⁹ reported a case of a child with coeliac disease who was mistakenly diagnosed to have hepatic disease because of elevated transaminases, but was subsequently found to have muscular dystrophy. The knowledge about organ specificity of various enzymes such as the transaminases is therefore important if patients are not to be over-investigated for various pathologies. Transaminases may be found in various different tissues. The activity of ALT¹⁰ in tissues relative to the serum is 300 for muscle, 2850 for the liver, 1200 for kidneys, 130 for the pancreas, 45 for the lung and 7 for erythrocytes. Serum AST levels are the least specific. AST is widely distributed in various tissues, with elevation of 5000 for muscle, 7100

for the liver, 7800 for the heart, 4500 for the kidney, 1400 for the pancreas, 500 for the lung and 15 for erythrocytes. Creatine kinase is more specific for the muscle as the distribution in tissue was highest in skeletal and cardiac muscle compared with other tissues.⁵

Konagaya et al¹ biopsied a series of 40 patients with various neuromuscular disorders, and ALT was found on assay of biopsied muscle to be increased in patients with Duchenne's muscular dystrophy, Fukuyama muscular dystrophy, myotonic dystrophy, inflammatory and endocrinological myopathy and amyotrophic lateral sclerosis. Alanine transaminase catalyses the synthesis of alanine from amino acids derived from the breakdown of muscle proteins.

In this study, a significant increase of ALT was demonstrated to be a consistent finding in all the patients with Duchenne's muscular dystrophy regardless of stage of disease, although the levels decreased with the duration of disease, presumably because of decrease in residual muscle mass available for breakdown. The levels of ALT seem to follow a similar course with the levels of serum CK with duration of symptoms as described on Figures 3 and 4. There was a good correlation with CK levels, indicating that the level of ALT is related to the muscle pathology rather than liver disease. Similarly, AST was also raised in these patients. In all these patients, the ALT and the AST levels correlated with the level of CK (Figs. 1 and 2). As such, the raised "liver enzymes", namely alanine and AST and in these patients is likely to be due to muscle breakdown.

Therefore, the finding of raised transaminases in a routine set of liver function tests should always raise the possibility in the clinician's mind that other than liver dysfunction, muscle pathology must be considered. In fact, occult muscular dystrophy should be considered in patients who have unexplainable abnormalities of serum transaminase levels. Morse and Rosman³ reported 4 children, including a girl in whom Duchenne's muscular disease was diagnosed after persistently raised transaminases were found on routine screening. Other primary muscle diseases also need to be considered, as a series of patients with myopathy¹¹ was previously described to have presented with persistent hypertransaminasemia. Rutledge et al⁴ also described raised transaminases in patients with other muscular dystrophies such as scapuloperoneal muscular dystrophy. Finally, as mentioned earlier, Konagaya et al described increased transaminases in the muscle biopsies of patients with muscular dystrophies, myotonic dystrophy, amyotrophic lateral sclerosis and inflammatory myopathies.

Analysis of the serum transaminases and CK is therefore useful in the work-up of patients in whom a primary muscle disease is suspected. In this series of 19 patients, it is characteristic for the transaminases to be raised in Duchenne's muscular dystrophy. Creatine kinase levels were raised 80 times above the mean, compared with either ALT or AST, both of which were raised about 10 times above the mean for the age group. This is of course likely to be related to the specificity of CK to the muscle.¹² Should the transaminases be raised persistently in patients with no clinical features of liver disease, CK should be considered as it is the most useful and specific marker of muscle disease. It is a good screening test before going on to muscle biopsy or even other extensive work-up for liver pathology such as hepatitis serologies and even liver biopsies.

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