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Research Paper

KNOWN CASE OF DUCHENNE MUSCULAR DYSTROPHY PRESENTING AS NON-ALCOHOLIC FATTY LIVER DISEASE

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Abstract

During a one-year period our frail six-year-old patient with weakness had been fully investigated and followed up for Nonalcoholic fatty liver disease (NAFLD) and other hepatic causes of his hypertransaminasemia, before a muscular origin of aminotransferases could be detected, because of a co-occurring diagnosis of histological and ultrasonographic liver steatosis. It should be stated, however, that even mild symptoms and signs, for example, asthenia, increased bulk of calves, and minor weakness associated with elevated transaminases, should have immediately prompted the search for DMD. DMD is a frequently unrecognized cause of increased serum muscular aminotransferases in the pediatric age group. Childhood obesity was not seen in our DMD case but a rare co-incidence of Ventricular septal defect was seen. Our frail patient well illustrates that DMD may be a special item of the ''NASH trash'' bin (nonalcoholic steatohepatitis) with isolated elevated transaminases and NAFLD confirmed on liver biopsy. The issue is of particular interest because a timely diagnosis, regular but low intensity exercise program and diet plan plays a key role in organizing management in DMD to avoid obesity related complication later.

Key words: Hypertransaminasemia, Non-alcoholic Fatty Liver Disease, Muscular dystrophies.

INTRODUCTION

Nonalcoholic fatty liver disease (NAFLD) encompasses a wide spectrum of conditions ranging from simple steatosis to steatohepatitis and liver cirrhosis with isolated elevated transaminasemia. It is the most common liver disorder in the pediatric age group, paralleling the epidemic of childhood obesity.[1-2] Duchenne muscular dystrophy (DMD) is often characterized in the early stage by central obesity unlike our case. We report a first case of biopsy-proven NAFLD in a non-obese, frail six-year-old patient with DMD to emphasize the relation between these two conditions as well as the peculiar management to avoid subsequent childhood obesity and related complications. Also our patient is first case in the world with co-incidence of ventricular septal defect, unlike the known cardiomyopathy complications in DMD.

CASE PRESENTATION

A six-year-old thin Indian boy with birth by normal per-vaginal delivery at 36 weeks of gestation and with normal developmental milestones till five years of age was brought by parents to our hospital with generalized weakness and loss of appetite (Fig. 1). On admission he was found to have difficulty in getting up from sitting condition and needed arms support to climb stairs. He underwent routine laboratory examinations. His hemoglobin level was 14 g/dl. Blood lipid profile was within normal limits.

The only reported abnormal laboratory tests were the increased serum levels of alanine aminotransferase (ALT) and aspartate aminotransferase (AST) (3 times upper normal values [unv] for both enzymes). He was then hospitalized because of the persistence of isolated hypertransaminasemia for approximately one year. Ultrasonography of the liver showed a bright pattern compatible with steatosis with diagnosis suggestive of a liver metabolic disorder, which was also confirmed at histology after needle liver biopsy (Fig. 2). During this one year, he was worked up for finding out the cause of isolated hypertransaminasemia. Both parents had normal serum aminotransferase levels and a recently performed abdominal ultrasonography without liver brightness.

The patient was in good general clinical condition, and his liver and spleen were not palpable even after one year, at present six years of age. Blood pressure was 120/64 mmHg. His chest auscultation showed a murmur and was accordingly referred to Echocardiography which showed a Ventricular septal defect (VSD). Repeated neurological examination revealed a cooperative patient with no cognitive, behavioral, or language delays. Gait was within normal limits, possible on heels and toes. The ability to climb upstairs and descend downstairs without support was reported by the mother. The bilateral mild increase in the consistency of the calf muscles along with a slightly abnormal Gower sign (the boy support to pull himself to an upright position) was compatible with DMD.

A repeated liver ultrasonography showed a mild residual liver brightness. To investigate a possible muscular origin of elevated aminotransferases, muscle-specific enzymes (eg, lactate dehydrogenase [LDH] and creatine kinase [CK]) were also evaluated. LDH was 500 IU/L (two times unv) and CK was 3445 IU/L (15 times unv). Finally for definite diagnosis, molecular testing for the dystrophin gene revealed absence of dystrophin gene on Western blot study. After definitive diagnosis of DMD, the patient was then referred to the pediatric cardiology unit where he has been adviced surgery for his VSD. The timely diagnosis of DMD is particularly important in light of the subsequent delay in starting corticosteroid treatment and potential lost opportunities for timely genetic counseling.

DISCUSSION

Becker muscular dystrophy (BMD) is also caused by mutations to the *dystrophin* gene. Together, DMD and BMD are collectively known as "dystrophinopathies," since they both arise as a consequence of *dystrophin* mutations. Mutations in a gene called *dystrophin* are responsible for the most common form of muscular dystrophy—Duchenne muscular dystrophy.[3] The dystrophin protein is responsible for maintaining muscle strength, so when the *dystrophin* gene is mutated in a way that prevents the dystrophin protein from being produced or functioning normally, muscles become weak.[4]

While similar to DMD, BMD has significantly milder symptoms (Mayo Clinic 2012). These differences are attributed to the type of mutation that arises in the *dystrophin* gene. If the *dystrophin* gene is mutated in a way that leads to very little or no dystrophin protein, then the patient has more severe symptoms and is diagnosed with DMD. However, if the gene is mutated in a way that simply lowers the production of dystrophin protein, then the effect is less severe and those people are diagnosed with BMD.[4] The incidence of BMD is approximately one-tenth that of DMD.[4] In BMD, unlike DMD cardiac involvement usually starts later, in the third decade of life.

DMD occurs more frequently in young males, and accounts for approximately half of all muscular dystrophies.[4] In DMD, muscle weakness typically starts in the pelvis and legs, but can also occur in the arms, neck, and other regions of the body, while muscles of the face are

normally spared. Calf muscles are also enlarged due to an accumulation of fatty tissue. Our case showed similar finding with gradual increase in severity.

People with DMD usually lose their ability to walk sometime between 7 and 13 years of age (CDC 2012),[4] and they often die of respiratory failure before reaching age 40 as a result of damage to muscles that control breathing. About two-thirds of DMD cases run in families and one-third are caused by spontaneous mutations. In our case, family tracing for the disease showed no findings, thus implying that DMD in our case was due to sporadic genetic mutations.

Females who carry the mutation usually do not display any symptoms, but about 8–10% of them will show some manifestation of the disease. When these symptoms do occur, they are typically more minor than the severe muscle weakness seen in males (Bushby 2005)[5]. The child's mother had no such similar complaints in our case.

Signs and symptoms usually become evident when the child starts walking and may include clumsiness and falling more often than other children of the same age, delay in walking difficulty getting up from the sitting or lying position, difficulty running and jumping, walking on tip toes, large calf muscles, waddling gait, delay in using language and learning disabilities. Our patient had majority of the above mentioned symptoms which progressively increased in severity.

Approximately 90% of patients with DMD die from cardiomyopathy or muscular respiratory failure (Finsterer 2006)[6]. Endocrine (hormonal) problems also appear in DMD and the glucocorticoid medications frequently used for treatment can have additional adverse effects on the hormonal system (Ashizawa 2011)[7]. Furthermore, some studies have reported that DMD patients have problems with blood clotting, which can complicate surgery (Morrison 2011)[8]. So, in our current case, a rare finding of VSD was noted with DMD rather than cardiomyopathy.

To our knowledge, only two child obesity cases have been reported with association of NAFLD, isolated hypertransaminasemia and DMD/BMD till date.[9-10] In our case, only difference was that the child was not obese, but thin. We think that deranged metabolic pathways lead to isolated elevated transaminasemia and later NAFLD and childhood obesity. We conclude that deranged metabolic pathways lead to isolated hypertransaminasemia and later NAFLD and childhood obesity which needs planned management and follow ups.

Figure 1 inset: A six-year-old frail child with weakness in lower limbs. Figure 1 arrow shows hypertrophy of calf muscles and dystrophic thigh muscles.

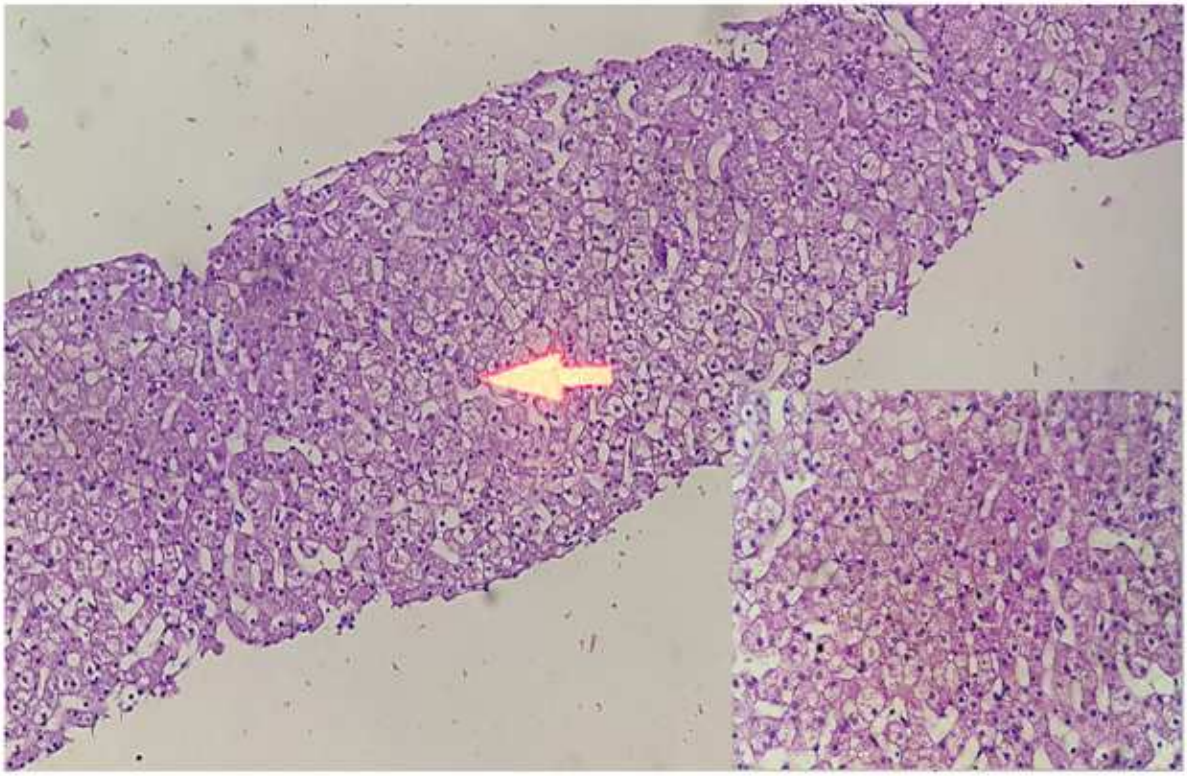

Figure 2: Needle liver biopsy showing mild micro/macrovacuolar simple steatosis without inflammation and fibrosis (H&E, x100). Figure 2 inset shows the same (H&E, x400)

CONCLUSION

During a one-year period our non-obese It should be stated, however, that even mild symptoms and signs, for example, asthenia, increased bulk of calves, and minor weakness associated with isolated elevated transaminases, should have immediately prompted the search for DMD. DMD is a frequently unrecognized cause of increased serum muscular aminotranferases in the pediatric age group. NAFLD has hitherto been reported in patients with DMD in obese children twice but not in frial children like in our case. We conclude that in DMD, the metabolic derangement may occur earlier causing isolated hypertransaminasemia that gets involved in causing NAFLD development and complicate later in childhood obesity. Thus we believe that health care providers should be aware that early DBMD is a condition predisposing to overweight and consequently also to fatty liver disease (NAFLD). Poor responsiveness of hypertransaminasemia to diet and lifestyle changes is a sign for underlying conditions other than NAFLD alone. Including CK measurements in the initial diagnostic workup would be an easy and inexpensive way to shorten the time to establishing the diagnosis of DMD in any child with elevated transaminases. Also one must look for other cardiac related complications with DMD like VSD in our case.

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