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Contiguous Xp21 deletion involving Duchenne muscular dystrophy and McLeod neuroacanthocytosis syndrome results in rapidly progressive and fatal cardiomyopathy

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Abstract

Dilated cardiomyopathy is an expected manifestation and common cause of death in patients with Duchenne muscular dystrophy. We present an unusually rapid progression of cardiomyopathy in a boy with Duchenne muscular dystrophy. Expanded genetic testing revealed a contiguous Xp21 deletion involving dystrophin and XK genes, responsible for Duchenne muscular dystrophy and McLeod neuroacanthocytosis syndrome, respectively, resulting in a more severe cardiac phenotype.

Case report

Duchenne muscular dystrophy was diagnosed at two years of age due to gross motor delays, family history, and creatine kinase elevation. Targeted genetic testing revealed a deletion of the entire dystrophin gene, the boundaries of which were unknown. He was on prednisone from four to seven years of age followed by deflazacort until his death at 12 years old. He was non-ambulatory by eight years old.

His cardiac function was monitored serially with echocardiograms. At eight years old, enalapril was started prophylactically. Shortly thereafter, metoprolol was started for sinus tachycardia. Left ventricular systolic function remained normal through nine years old. Over the next two years, left ventricular ejection fraction fell from 55 to 50%, with escalation in heart failure medications. At 11 years old, ejection fraction was 30%. Six months later, ejection fraction was 12%. He was admitted to optimise heart failure medications and initiate nocturnal positive pressure ventilatory support. His heart failure regimen included sacubitril/valsartan, metoprolol, spironolactone, dapagliflozin, and furosemide. He remained asymptomatic. Ambulatory electrocardiogram monitoring revealed short runs of ventricular tachycardia. He did not meet criteria for implantable cardioverter-defibrillator due to low arrhythmia burden and risk of implant.

Due to the aggressive cardiac decline, further genetic testing including chromosomal microarray showed a 6.8 Mb pathogenic deletion of Xp21.2p21.1, involving dystrophin and XK genes, consistent with Duchenne muscular dystrophy and McLeod neuroanthocytosis syndrome (McLeod syndrome). A duplication involving chromosome 18q12.2 was considered a variant of unknown significance.

In the next several months, he developed symptomatic hypotension, requiring dose reduction and withdrawal of medications. Because of the hemocompatibility issues presented by McLeod syndrome, which limited his ability to receive emergent blood transfusions, he was not a candidate for ventricular assist device. At 12 years of age, he died suddenly at home due to suspected cardiac arrest.

The patient's medical history was also notable for obesity, obstructive sleep apnoea, expressive language delay, and autism spectrum disorder. There was an extensive maternal history of muscular dystrophy and cardiac death among females, including a maternal aunt who died at 31 years of age due to an unspecified heart condition, and a maternal grandmother who died at 39 years of age due to an enlarged heart (Fig. 1). Parental consanguinity was denied.

Discussion

Duchenne muscular dystrophy is an X-linked recessive disorder due to dystrophin gene mutation. In a state of reduced dystrophin, muscle fibre integrity is lost, leading to degeneration and functional impairment. Gross motor delays manifest in children around 2.5 years old.[1]

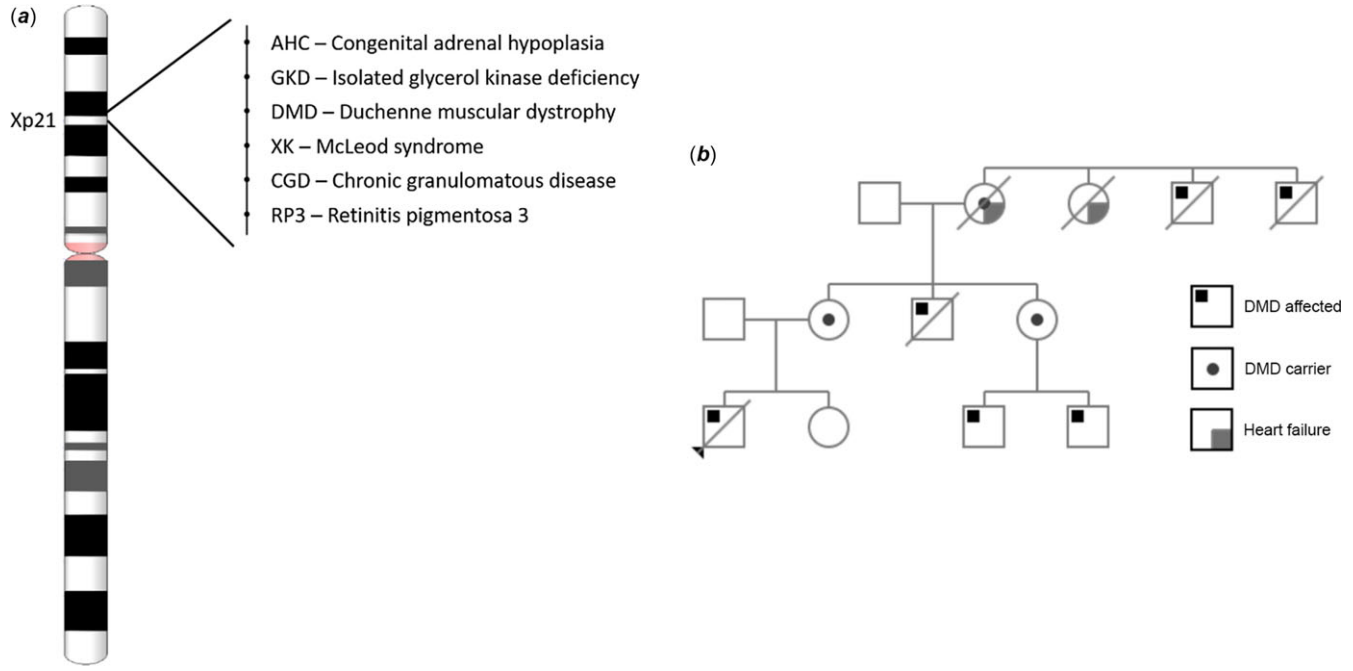

Figure 1. (***a***) Depiction of the X-chromosome, highlighting the Xp21 region and the included genetic syndromes. (***b***) Patient's family pedigree.

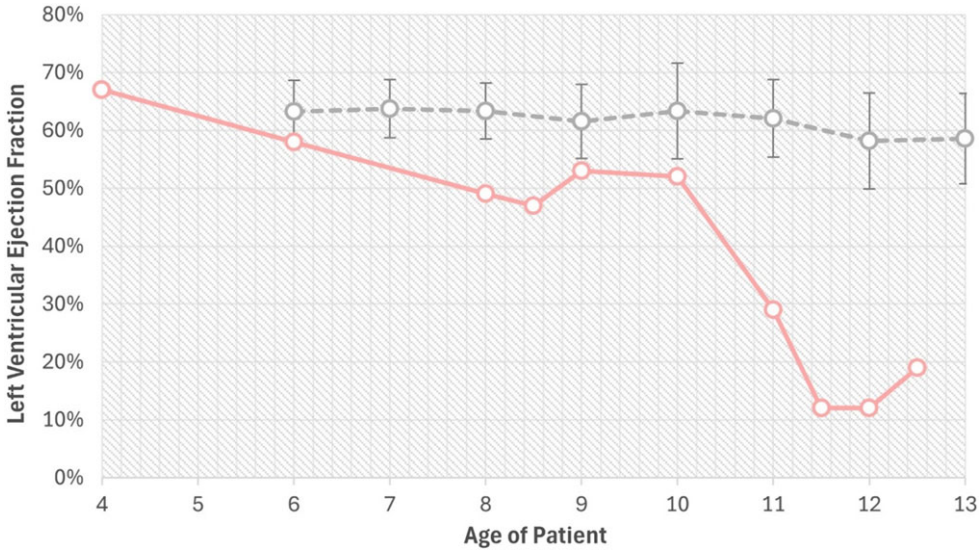

Figure 2. Left ventricular ejection fraction of our patient (red, solid line) plotted against expected ejection fraction of patients with Duchenne muscular dystrophy (black, dashed line), adapted from Lao et al, *Circulation*, *144*(1) [10].

Severe muscle weakness typically presents between 7 and 12 years of age with many becoming non-ambulatory around 13 years old.[2] Cardiac involvement, predominately dilated cardiomyopathy, presents around 14 years old.[2]

With advances in respiratory and other therapies, cardiovascular disease has become the most common cause of death, with a median survival of 28 years in the most recent era.[3] Congestive heart failure, arrhythmias, and sudden cardiac death are all commonly encountered. Our patient's ventricular function declined rapidly compared to the general Duchenne muscular dystrophy population (Fig. 2). In a cohort of >650 patients with Duchenne muscular dystrophy, left ventricular ejection fraction declined at a rate of 1.6% per year.[4] Our patient also showed earlier onset of loss of ambulation at age of eight years. The aggressive nature of his cardiac disease prompted expanded genetic testing revealing a large pathogenic deletion of Xp21.2p21.1 that included both dystrophin and XK genes, consistent with Duchenne muscular dystrophy and McLeod syndrome.

McLeod syndrome has multiorgan system involvement with heterogeneous clinical features.[5] Central nervous system manifestations include movement disorders such as chorea, cognitive disorders, and psychiatric symptoms. Neuromuscular manifestations develop late and include absent deep tendon reflexes and muscle weakness. Creatine kinase levels are elevated but dystrophin content is normal. Cardiac manifestations include dilated cardiomyopathy and tachyarrhythmias. Among 17 patients with McLeod syndrome, two-thirds showed signs of cardiac disease, which presented at ages >40 years.[6]

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The cardinal feature of McLeod syndrome is red blood cell acanthocytosis, which results in typically asymptomatic and compensated haemolysis. Without the XK protein, which attaches the Kell antigen to the red blood cell, these cells are more likely to form acanthocytes and hemolyze. Our patient was not anaemic and did not have markers of significant haemolysis; however, acanthocytes were noted on peripheral smear. Alloantibodies in the Kell and Kx blood group system can also cause strong reactions to transfusions of incompatible blood. Therefore, male patients must avoid blood transfusions with Kx antigens. This requires Kx-negative blood, which is extremely rare or, if possible, banked autologous blood. The child was not an appropriate candidate for ventricular assist device due to these hemocompatibility issues.

Xp21 contiguous deletion syndromes result from partial deletions of the Xp21 region of the X-chromosome. Genes within this region include those responsible for congenital adrenal hypoplasia, glycerol kinase deficiency, Duchenne muscular dystrophy, McLeod syndrome, chronic granulomatous disease, and retinitis pigmentosa (Fig. 1). The most commonly reported combination of syndromes involves Duchenne muscular dystrophy, glycerol kinase deficiency, and congenital adrenal hypoplasia.[7] The co-occurrence of Duchenne muscular dystrophy and McLeod syndrome has been rarely reported. In 1985, Francke et al described a male patient who suffered from chronic granulomatous disease, McLeod syndrome, Duchenne muscular dystrophy, and retinitis pigmentosa.[8] Patients with chronic granulomatous disease and Duchenne muscular dystrophy have been more frequently reported.[9] The gene deletion causing these two disorders also spans the XK gene, so it is likely that McLeod syndrome, being less clinically severe, may have been present but unrecognised until discovered by chromosomal microarray. Other contributory but unrecognised mutations may have been discovered through whole exome sequencing, which was not performed. Nonetheless, because of the cardiac manifestations of both Duchenne muscular dystrophy and McLeod syndrome, this combination likely contributed to our patient's aggressive cardiomyopathy. It may also explain the maternal family history of early cardiac death, which is rare in female carriers of Duchenne muscular dystrophy.

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Competing of interest. None.

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