Case Report

An Indian family with an Emery-Dreifuss myopathy and familial dilated cardiomyopathy due to a novel LMNA mutation

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Abstract

Emery-Dreifuss myopathy can be associated with a cardiomyopathy and cardiac dysrhythmias. The inheritance pattern of Emery-Dreifuss muscular dystrophy (EDMD) is X linked, whereas EDMD2 is autosomal dominant. EDMD2 is caused by lamin A/C gene (LMNA) mutations that produce alterations in the lamin proteins that are integral to nuclear and cell integrity. A 53-year-old man was brought to us with a right internal carotid artery dissection. Detailed work-up of the patient and family members revealed some unusual features, and genetic sequencing of the LMNA gene was undertaken. A novel mutation was identified in two of the samples sent for analysis. We present the first Indian family of EDMD2 with familial dilated cardiomyopathy and cardiac dysrhythmias in whom LMNA gene sequencing was performed. A novel mutation was identified and additional unusual clinical features were described.

Key Words

Calculated AV node, cardiac conduction system calcification, cardiomyopathy, EDMD, familial DCM, LMNA mutation, myopathy

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Introduction

Emery-Dreifuss muscular dystrophy (EDMD) and limb-girdle muscular dystrophy type 1B (LGMD1B) are similar muscular dystrophies associated with cardiac arrhythmias and cardiomyopathy. Inheritance is X-linked recessive when the emerin gene is mutated, resulting in EDMD or autosomal dominant when the lamin A/C gene (LMNA) mutation is mutated, resulting in EDMD2 or LGMD1B. LMNA mutation carriers present at an early age with features of skeletal myopathy, cardiac dysrhythmias or cardiomyopathy. The clinical course can also be punctuated by ventricular tachycardia or sudden cardiac death. Numerous mutations have been identified in the LMNA gene. Until now, genetic sequencing of LMNA mutations in Indian families has not been described. We describe the first large Indian family with a combination of Emery-Dreifuss myopathy, familial dilated cardiomyopathy (FDCM) and cardiac conduction abnormalities due to a novel LMNA mutation.

Case Report

A 53-year-old man was admitted to the neurology intensive care unit with an acute ischemic stroke of 2 h duration. On examination, he had a dense right hemiplegia and global aphasia. Computed tomography (CT) brain was normal. He was started on IV thrombolysis with 20 mg of Recombinant Tissue Plasminogen Activator (rtPA) and taken up for intra-arterial thrombolysis. Four-vessel digital subtraction angiography (DSA) revealed a left internal carotid artery dissection with flame-shaped occlusion at the carotid bifurcation. Despite multiple attempts, the artery could not be recanalized and the procedure was abandoned. He remained densely hemiplegic and aphasic after the procedure. On detailed questioning, his brother revealed that 10 members of his extended family had undergone cardiac permanent pacemaker implantations (PPI) in the past 15 years. The youngest brother of the proband had developed difficulty in walking and had been diagnosed with a possible myopathy or spinal muscular atrophy 5 years earlier. He had undergone a PPI 2 years earlier. Another cousin reported a stiff back and had restricted spinal flexion as well as a mild myopathy and a PPI. The possibility of a familial cardiac conduction defect with skeletal myopathy was considered and further detailed evaluation was undertaken. Additional evaluation of the proband revealed wasting of the shoulder girdle, enlarged forearms (Popeye forearms), wasting of the peroneal muscles and high arched feet. Examination of his sibling with...
the myopathy and the cousin with a stiff back showed the same muscular phenotype. Echocardiogram showed a dilated left ventricle with an ejection fraction of 39%, suggesting a dilated cardiomyopathy (DCM). A CT chest revealed calcification of the A-V node as well as the proximal bundle of His [Figure 3]. Ultrasound abdomen revealed small liver (8 cm) with coarse echotexture, portal vein dilatation and mild splenomegaly (suggestive of cirrhosis). Three weeks after admission, the patient developed massive hematemesis and expired. After discussion with the family and obtaining informed consent, blood was sampled from the patient as well as from a first cousin and dispatched to Diagenos Lab (Germany) for genetic sequencing. The entire coding region of the LMNA gene was sequenced by polymerase chain reaction (PCR). PCR products were analyzed by direct sequencing. This revealed a heretofore undescribed heterozygous mutation in the LMNA gene: c.1059_1060 delGC insCT (p.[Gln353His];[Gln354Term]). This mutation resulted in two amino acid changes. The amino acid change p.Gln354Termin resulted in a premature termination signal.

Discussion

The family that we have described had an autosomal-dominant familial cardiac dysrhythmia appearing in the 4th–5th decades of life and skeletal myopathy with humero-peroneal preponderance and stiff back with reduced spinal flexion. Other unusual features included cardiac conduction system calcification, cirrhosis. A stiff back can be associated with rigid spine syndrome (SEPN1 mutations), Bethlem myopathy and Ullrich congenital muscular dystrophy, which are allelic disorders caused by collagen VI gene mutations, EDMD 2 (LMNA mutations) or calpain-deficient LGMD (CAPN3 mutations).[3] Two patients in this family also had a DCM. This last feature helped classify the disorder as a FDCM.[4] EDMD is usually characterized by elbow/ankle contractures, muscular dystrophy and cardiomyopathy. Clinically, the combination of autosomal-dominant inheritance, humero-peroneal predominant skeletal myopathy, stiff back with limited spinal flexion and a familial DCM suggested the diagnosis of EDMD2. Hence, we proceeded with genetic sequencing of the LMNA gene.

The LMNA gene or the LMNA gene is located on chromosome 1q 21-22. It encodes the lamin proteins that form part of the
nuclear lamina. The lamin proteins (isoforms A and C) are important in chromatin structure and nuclear stability, and are composed of intermediate filament proteins, which provide scaffolding to the nuclear envelope and are located in the nuclear lamina, a layer that is attached to the inner membrane of the nuclear envelope. The lamin proteins interact with a variety of proteins, including lamin B receptors, lamin-associated polypeptides and emerin. However, the process by which these mutations result in different phenotypes is unknown, although it is postulated that apoptosis in the cardiac conduction system may lead to the conduction abnormalities.[5] Mutations in the LMNA gene are associated with several diseases, including EDMD, LGMD type I B, dilated cardiomyopathy with conduction abnormalities, autosomal-recessive Charcot-Marie-Tooth disease type 2 (CMT2B1), familial partial lipodystrophy of the Dunnigan-type (FPLD), mandibuloacral dysplasia (MAD) and Progeria syndrome.

Cardiac dysrhythmias in familial DCM tend to occur along a continuum. Sinus bradycardia as a result of SA nodal dysfunction is seen in the early stages, followed by atrial arrhythmias and atrial myopathy. Subsequently, A-V nodal dysfunction sets in, followed by LV dysfunction (ventricular myopathy). Sudden cardiac death can occur at any time, as was seen in our family also. Hence, the importance of identification of an LMNA mutation is that it should trigger consideration of a pacemaker with an implantable cardioverter-defibrillator (ICD) rather than an ordinary pacemaker as all our patients were subjected to.

Calcification of the cardiac conduction system is unusual and is seen only in a few conditions such as Lev’s disease, calcific aortic stenosis, mitral annular calcification or, rarely, in chronic hemodialysis patients with metastatic calcification.[6] Familial DCM has not yet been reported with AV node or bundle of His calcification.

Steatosis has been described in one case of lipoatrophy due to LMNA mutations, but cirrhosis is hitherto undescribed.[7] Our family is the first reported association of cirrhosis with LMNA mutation. Unfortunately, the type and cause of cirrhosis in this family could not be elucidated further as liver biopsy could not be performed.

In conclusion, this is the first documented Indian family with an Emery-Dreifuss myopathy, familial DCM, calcification of the cardiac conduction system and cirrhosis due to a novel LMNA mutation.

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