CASE REPORT

Cardiac involvement in proximal myotonic myopathy

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Abstract

Proximal myotonic myopathy (PROMM) is a recently described autosomal dominantly inherited disorder resulting in proximal muscle weakness, myotonia, and cataracts. A few patients with cardiac involvement (sinus bradycardia, supraventricular bigeminy, conduction abnormalities) have been reported. The cases of three relatives with PROMM (weakness of neck flexors and proximal extremity muscles, calf hypertrophy, myotonia, cataracts) are reported: a 54 year old man, his 73 year old mother, and 66 year old aunt. All three presented with conduction abnormalities and one had repeated, life threatening, sustained monomorphic ventricular tachycardia. This illustrates that severe cardiac involvement may occur in PROMM.

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A familial disorder of proximal muscle weakness, myotonia, and cataracts (proximal myotonic myopathy (PROMM)) has recently been described.[1 2] PROMM can be distinguished from myotonic dystrophy clinically and genetically. In both diseases, patients are afflicted to varying degrees by myotonia and muscle weakness. The pathophysiological mechanisms are not understood. Suppression of the homeodomain encoding (DMAHP) gene, located adjacent to the CTG repeat expansions in the 3' untranslated region of the DMPK protein kinase gene on chromosome 19q13.3, may play a role in the pathogenesis of myotonic dystrophy.[3] Anticipation is common in myotonic dystrophy, but has hitherto not been reported in PROMM. Thus, there are no hints for abnormal repeat expansions of trinucleotides in PROMM.

Cardiac conduction abnormalities are frequent in myotonic dystrophy, but only a few individuals with PROMM and cardiac arrhythmias have been reported in the literature: one patient with intermittent supraventricular bigeminy,[4] one with a non-fatal cardiac arrest, unspecified arrhythmias, and right bundle branch block,[5] and one with a cardiac conduction abnormality that was treated with a permanent pacemaker.[1]

We describe three related patients with findings consistent with PROMM who also have cardiac abnormalities. In one case, symptomatic sustained monomorphic ventricular tachycardia occurred repeatedly. A myocardial biopsy specimen was consistent with cardiomyopathy in this subject. All three patients have cardiac conduction abnormalities, but no signs or symptoms of congestive heart failure.

Case reports

PATIENT 1

Patient 1, a 54 year old man, was first seen at the age of 18, when he complained of left sided chest pain. At the age of 35, cataracta coronaria et pulverulenta et corticalis posterior were removed from both eyes. Raised creatine kinase (CK) was first documented when he was 37 years old. Signs and symptoms of muscle weakness and myotonia were first described when he was 41. The examining neurologists suggested the diagnosis of myotonic dystrophy. A comprehensive neurological evaluation six years later revealed thigh muscle atrophy with some bilateral calf hypertrophy and percussion myotonia. The electromyogram was consistent with myotonia.

At the age of 51, he reported lower back pain, myalgia of the thighs, and a feeling of heaviness in both legs without cramping when climbing stairs. He had mild weight loss, fatigue, and tremor after exertion. A bicycle ergonometry examination was limited by lancing pains in both legs after 4.5 minutes.

A delay of the PQ interval was first documented at the age of 40 and was progressively pronounced in subsequent years. At the age of 53, electrocardiography revealed complete right bundle branch block and a PQ interval of 0.3 seconds. Holter monitoring (24 hour) showed intermittent second degree AV block, Wenckebach-type. He had not had any episodes of syncope but complained of occasional dizziness.

Two months later he became dizzy during work. As he works at our hospital, he received immediate medical attention. Monomorphic ventricular tachycardia was observed and terminated with lidocaine. The physical examination was notable for lean stature, absent pedal pulses, and small testes.

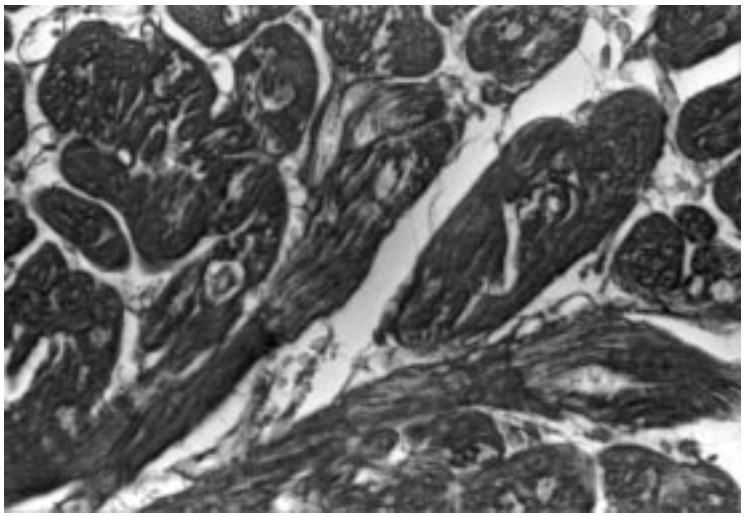

Figure 1 Myocardial biopsy specimen showing considerable variation in diameters of the myocytes and slight, focal rarefication of myofibrils (trichrome staining; original magnification ×40).

Neurological examination revealed slight weakness of neck and hip flexors and elbow extensors, mild thigh muscle atrophy, and comparatively prominent calves. Action and percussion myotonia were missed. Reduced tendon reflexes and impaired pallesthesia indicated a peripheral neuropathy.

Electrocardiography showed sinus rhythm at 62 beats/min with frequent monomorphic extrasystoles, first degree AV block (PQ interval 0.24 seconds), and right bundle branch block. Left sided cardiac catheterisation excluded major coronary artery stenosis. The left ventricle was of normal size; contractility was slightly reduced, although quantitative assessment was impaired by frequent extrasystoles. Myocardial biopsy showed distinct myocyte hypertrophy and some endocardial fibrosis. There was no sign of inflammation. The average myocyte diameter was 28 μm (normal range up to 15–18 μm), the largest myocytes reaching diameters of more than 40 μm. The nuclei were enlarged, and nucleoli prominent (fig 1).

An electrophysiological study of the heart revealed prolonged AV conduction (atrial to His interval 179 ms, His to ventricle interval 62 ms). Wenckebach conduction was reached at a stimulation frequency of 92 beats/min, 2:1 conduction at a frequency of 110 beats/min. During programmed ventricular stimulation at the right ventricular apex, a monomorphic ventricular tachycardia with a frequency of 250 beats/min was repeatedly induced. Ventricular tachycardia terminated spontaneously within 25 seconds.

Neurophysiological assessment confirmed a moderate demyelinating motor and sensory polyneuropathy. The electromyogram showed myotonic discharges. There were no clear signs of myopathy, but slightly neuropathic (high amplitude and prolonged) motor unit potentials.

A skeletal muscle biopsy showed distinct but unspecific signs of myopathy, including a wide spectrum of fibre diameters and some evidence of fibre necrosis.

As well as a CK of 205 U/l (normal range, up to 90 U/l) his γ glutamyl transferase was raised (121 U/l; normal range, up to 28 U/l). Analysis of the (CTG)n repeat polymorphism in the 3' untranslated region of the myotonic dystrophy gene DMPK by polymerase chain reaction[6] revealed 11 CTG repeats on each chromosome (normal range, 5–37).

Over the next weeks, the sustained monomorphic ventricular tachycardia recurred spontaneously during treatment with various antiarrhythmic regimens including continuous intravenous lidocaine, sotalol, and amiodarone. The patient was eventually treated with an implantable cardioverter-defibrillator. He has since had several episodes with multiple discharges due to fast ventricular tachycardia (240–260 beats/min). Amiodarone was resumed with the hope of reducing the frequency or preventing the ventricular tachycardia. He is currently free from symptoms and working full time.

PATIENT 2

The 73 year old mother of patient 1 was surgically treated for bilateral cataracts at the age of 67. She reported difficulties climbing stairs and getting up from a squatting position as well as occasional dizziness.

Neurological examination showed slight bilateral ptosis, unilateral hypacusis, a slight unilateral winging scapula, moderate bilateral weakness of the neck and hip flexors as well as elbow, foot, and toe extensors. Her calves appeared hypertrophic. She presented with a severe, irregular finger tremor and slow extension of the fourth and fifth fingers after opening her fist.

Electrocardiography showed sinus rhythm of 71 beats/min with first degree AV block (PQ interval, 0.33 seconds) and left anterior bundle branch block. Echocardiography was normal.

The sensory nerve conduction velocities of the sural and superficial peroneal nerves were slightly reduced, whereas the sensory nerve compound potentials were normal. Electromyography revealed myotonic discharges, one high frequency discharge of 170 Hz, some myokymia-like grouped series, and slightly prolonged motor unit potentials indicating a neuropathy.

CK (105 U/l) and γ glutamyl transferase (44 U/l) were raised. The numbers of CTG repeats were 11 and 26.

PATIENT 3

The 66 year old aunt of patient 1 was first noted to have myalgia and abnormal sensitivity to pressure in her thighs. Weakness of the proximal leg musculature and cardiac arrhythmias became evident at the age of 60. Three years later a cataract was removed. At the age of 65 she noticed some myotonic blocking of the fingers.

Physical examination revealed slight bilateral temporal atrophy, slight calf hypertrophy, and pronounced weakness of neck and elbow flexors. There was also considerable asymmetric paresis of the hip flexors. She could not get up from a squatting position. After exertion

she exhibited a coarse tremor of the hands. Electromyography detected occasionally myotonic discharges. A muscle biopsy showed an increase in central nuclei consistent with an early stage of a myopathy.

Electrocardiography showed sinus rhythm of 84 beats/min with a bifascicular block. Echocardiography was normal.

CK (255 U/l) and γ glutamyl transferase (25 U/l) were raised. Genetic examination was not performed.

Detailed questioning gave no hint of other affected relatives.

Discussion

The family described is remarkable for having both symptoms and signs consistent with PROMM and cardiac abnormalities. It is well known that cardiomyopathy and cardiac arrhythmias may accompany some forms of myopathy, such as the dystrophinopathies, Emery-Dreifuss myopathy, mitochondrial myopathies, and myotonic dystrophy. Cardiac abnormalities have been described in some people with PROMM but not in detail.[1 4] To our knowledge, this is the first report of a family with PROMM in which more than one individual had cardiac abnormalities. In all three subjects, detailed documentation facilitated the retrospective assessment of their cardiac abnormalities. Skeletal muscle biopsies were performed in two of the three patients showing mild unspecific myopathic abnormalities consistent with PROMM.[5 7] Typical features of myotonic dystrophy such as ring binds and sarcoplasmic masses were not shown.

The diagnosis of PROMM appears highly probable in all three subjects according to the results of clinical examination and electrophysiological testing. Genetic analysis was performed in patients 1 and 2 showing no increase of the myotonic dystrophy associated (CTG)n repeat number, ruling out myotonic dystrophy as a diagnosis.[4 5 7–10]

All three subjects had cardiac conduction abnormalities. Patients 1 and 2 had first degree AV block, patients 1 and 3 had complete right bundle branch block, and patients 2 and 3 had left anterior hemiblock pattern on electrocardiography. First degree heart block is the most common cardiac abnormality in myotonic dystrophy, but more severe heart blocks also occur, occasionally resulting in sudden death.[10 11] Thus, the cardiac abnormalities found in PROMM resemble those in myotonic dystrophy.

All three patients reported occasional dizziness, which was most pronounced in patient 3. Dizzy spells may be related to cardiac conduction abnormalities. They had no signs of heart failure.

Patient 1 had life threatening cardiac arrhythmias in the form of recurrent fast ventricular tachycardias. These tachycardias were fairly resistant to antiarrhythmic drugs. They could be induced during programmed ventricular stimulation, although they terminated spontaneously in that setting. AV conduction appeared significantly impaired on electrophysiological study, indicating that this patient was at risk for both bradycardic and tachycardic events. Since implantation of a cardioverter-defibrillator, fast ventricular tachycardias have been terminated many times by the device.

The myocardial biopsy of patient 1 exhibited slight, unspecific changes consistent with cardiomyopathy. It seems reasonable to conclude that the cardiac rhythm abnormalities were related to myopathic changes. It appears equally plausible that the cardiac conduction abnormalities in all three subjects were to some extent familial; the conduction abnormalities in patients 2 and 3 may also have been caused by cardiac myopathic changes. Therefore, the cardiomyopathy could be related to the familial myopathy in all three subjects—that is, it is possible that cardiomyopathy is one manifestation of PROMM.

These cases indicate that severe cardiac abnormalities, especially conduction abnormalities and ventricular arrhythmias, occur in PROMM. Patients with PROMM should therefore be carefully examined for cardiac abnormalities, especially if they have dizziness or syncope.

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