Marathoning with myotonic dystrophy type 2 (proximal myotonic myopathy) and leukopenia

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Abstract

Objectives: A mild, slowly progressive course of proximal myotonic myopathy, also known as myotonic dystrophy type 2, over years allowing the patient to continue with extreme sport activity, has been only rarely reported.

Methods: Case report.

Results: The patient is a 54-year-old female sport teacher who developed myotonia of the distal upper limbs at the age of 32 years. Over the following 22 years, myotonia spreaded to the entire musculature. Myotonia did not prevent her from doing her job and from marathoning and improved with continuous exercise. Additionally, she had developed hypothyroidism, ovarian cysts, incipient cataract, motor neuropathy, hepatopathy, leukopenia, and mild hyper-CK-emia. A heterozygous CCTG-repeat expansion of 500–9500 was found in the CNBP/ZNF9 gene. At the age of 54 years, she was still performing sport, without presenting with myotonia on clinical examination or having developed other typical manifestations of proximal myotonic myopathy.

Conclusions: This case shows that proximal myotonic myopathy may take a mild course over at least 22 years, that proximal myotonic myopathy with mild myotonia may allow a patient to continue strenuous sport activity, and that continuous physical activity may contribute to the mild course of the disease.

Keywords

Myotonic dystrophy, CCTG-expansion, ZNF9, CNBP gene, myotonia, physical exercise, sport

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Introduction

Myotonic dystrophy type 2, also known as proximal myotonic myopathy (PROMM), is an autosomal dominant, progressive multisystem disorder, affecting the muscle, peripheral nerves, central nervous system, eyes, ears, endocrine system, liver, blood (eosinophilia), and the myocardium.¹² PROMM is due to an unstable CCTG-repeat expansion in the CNBP/ZNF9 gene on chromosome 3q.³ Usually, the disorder starts with myotonia and weakness of the proximal muscles to progress within the skeletal muscles and to other systems later on.⁴ A mild, slowly progressive course allowing the patient to continue with extreme sport activity and leukopenia has been only rarely reported in PROMM.⁶

Case report

The patient is a 54-year-old Caucasian female, of height 170cm and of weight 63kg, who developed difficulties to open her feast at the age of 32 years. Until then she was working as a sport teacher and was performing high performance sport without problems. Since then she noted that particularly her explosive strength became impaired and she once fell when walking backward. Afterward, she recognized difficulties when climbing stairs and since age 48 years a feeling of muscle tension in the thighs was triggered by quick movements or voluntary contractions. She also noted that muscle stiffness improved during continuous exercise, being interpreted as warming-up phenomenon. Nonetheless,

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she was able to run marathons without major problems. Since age 51 years myotonia had affected the entire musculature, including the cervical and abdominal muscles, which she recognized only during sport as muscle burning without being handicapped. Cold or alcohol did not worsen myotonia. Her further history was noteworthy for right Achilles tendon rupture at the age of 20 years and ligament rupture of the left ankle also at the age of 20 years. Work-up for a paraneoplastic syndrome was negative. At the age of 45 years, struma uninodea with hypothyroidism was diagnosed. Her mother and three second cousins also presented with myotonia. She was regularly taking only l-thyroxin (50 µg/day). At the age of 50 years, myotonic dystrophy had been suspected for the first time.

Clinical neurologic examination at the age of 51 years revealed mild atrophy of the temporalis muscles, mild myotonia and warming up after forced lid closure, and percussion myotonia of the thenar and the gastrocnemius muscles. Creatine kinase (CK) was mildly elevated to values between 300 and 600 U/L since at least age 32 years (Table 1). There was mild, constant leukopenia. Liver enzymes were mildly elevated since age 22 years (Table 1). Ophthalmologic investigations revealed an incipient cataract bilaterally. Nerve conduction studies revealed an increased latency and a reduced amplitude of the peroneal nerves bilaterally and a reduced amplitude of the right median nerve. Needle electromyography (EMG) of the right deltoid and right anterior tibial muscle was normal. EMG of the vastus lateralis muscle bilaterally revealed abnormal spontaneous activity in the form of positive sharp waves but normal muscle architecture. Magnetic resonance imaging (MRI) of the thighs revealed a T2-hyperintensity of the semimembranosus and semitendinosus muscles bilaterally, being interpreted as edema. Cardiologic examination was normal. Ultrasonography of the abdomen revealed ovarian cysts bilaterally. Gastroscopy revealed gastritis and reflux. Genetic investigations disclosed no CTG-repeat expansion on the DMPK (Dystrophia Myotonica Protein Kinase) locus. Investigation of the CNBP/ZNF9 locus revealed a heterozygous CCTG-repeat expansion of 500–9500 repeats, why PROMM was diagnosed. Clinical neurologic examination at the age of 54 years was completely normal, particularly no clinical myotonia could be detected this time. The trapezius percussion sign was negative, there was no tremor, no calf hypertrophy, and she reported no restless-leg-syndrome or myalgias. She denied hypersomnia, cognitive deficits, or previous complications during general anesthesia. There was no autonomic involvement (normal heart rate response to Valsalva or change of posture, normal heart rate variability in time and frequency domain, no increased QT-variability). She reported recurrent infections.

**Discussion**

The presented patient is interesting for several aspects. First, clinical manifestations of PROMM were mild. She had non-disabling myotonia, an incipient cataract, polyneuropathy, hypothyroidism, hepatopathy, leukopenia, ovarian cysts, and mild hyper-CK-emia. In the majority of the cases, patients present with more severe clinical manifestations, such as disabling myotonia, painful myalgias, proximal muscle weakness, calf hypertrophy, tremor, hypersomnia, cardiomyopathy, or arrhythmias. Only occasionally may PROMM manifest with mild clinical manifestations, such as hyper-CK-emia or weakness of a single muscle. Second, the patient was able to continue with her previous sport activity. Despite the occurrence of myotonia, she continued with marathoning without being severely handicapped. In the presented case, it appears that sport had rather a beneficial than a worsening effect. Arguments for this speculation are that long-distance running did not deteriorate her condition and did not prevent her from continuing with regular sport activity. It is even conceivable that her extensive exercise before onset of PROMM delayed the onset of muscular manifestations and resulted in a better muscle performance than without previous physical exercise. Possibly, physical exercise stabilized mitotic instability of the CCTG-repeat expansion in somatic, particularly muscle cells. Third, PROMM in the presented patient hardly progressed over a long period of time. This is not only the case for the skeletal muscles, which did not show weakness, wasting, myalgias, or calf hypertrophy even at the age of 54 years, but also for all other types of organ involvement. There was no rapid progression of endocrinological involvement, hepatopathy, neuropathy, or cataract. Leukopenia has not been described together with PROMM and could explain her propensity for recurrent infections. However, leukopenia and leukocyte dysfunction is known from myotonic dystrophy type 1.
Whether the severity of the phenotype correlates positively with the CCTG-repeat length in PROMM is largely unknown since no reliable studies on this matter have been carried out. However, with regard to myotonic dystrophy type 1, it can be speculated that the correlation between CCTG-repeat length and severity of the phenotype is positive. A mild phenotype with a CCTG-repeat length of 100 has been only rarely reported. Whether the mild phenotype in the presented patient was due to reduced somatic variability of the CCTG-repeat expansion remains speculative since only DNA from blood lymphocytes but no other tissues had been investigated. Mitotic instability of the CCTG-repeat expansion is a typical genetic feature of PROMM and could be explained by the formation of mini-dumbbell structures and mini-loop intermediates by slippage in the nascent strand during DNA replication.

In conclusion, this case shows that PROMM may take a mild course over at least 22 years, that PROMM with mild myotonia may allow a patient to continue strenuous sport activity, and that continuous physical activity may contribute to the mild course of PROMM. The genotype/phenotype correlation between the CCTG-expansion and the mild phenotype is weak.

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