MALIGNANT hyperthermia (MH) is a life-threatening anesthesia-related complication characterized by a hypermetabolic response of skeletal muscle which can be triggered by anesthetic drugs such as halothane and succinyllcholine. Although some genes have been identified to be involved in MH (such as the ryanodine receptor gene [RYR1] and the dihydropyridine receptor [DHPR] gene) the underlying molecular defect remains unclear in the majority of MH-cases. However, apart from central core disease, which is regularly associated with MH-susceptibility, the association of other neuromuscular diseases with MH has been reported anecdotaly.

Here we report a 41-yr-old man with a long history of progressive muscle weakness, myalgia, and recurrent myoglobinuria due to two unrelated metabolic defects, i.e., mitochondrial myopathy in combination with myoadenylate deaminase (MAD) deficiency. The patient tested positive for malignant hyperthermia susceptibility (MHS) by the halothane caffeine in vitro contracture testing (IVCT) procedure.

Case Report

A 41-yr-old man, who had been under medical observation for 27 yr because of severe exercise intolerance with longstanding myalgia, muscle cramps, recurrent myoglobinuria, and progressive muscle weakness, was admitted to our unit for MH testing prior to umbilical hernia surgery. The relief of the proximal limb muscles was slightly reduced and signs of muscle weakness were apparent (difficulties in climbing stairs and in elevating his arms). Serum creatine kinase and lactate dehydrogenase levels at rest were strikingly elevated, CK 3,700 U/l (normal 80 U/l); LDH 395 U/l (normal 240 U/l), but a previous muscle biopsy from the rectus femoris muscle was reported as unremarkable. Because clinical symptoms progressively deteriorated, an extensive clinical reassessment was undertaken at age 35, but no additional clues establishing a definite diagnosis could be deduced. At the age of 41 yr a myosonographic examination of the quadriceps femoris muscle was suggestive of a myopathic lesion. The patient had not, nor had any member of his family, ever experienced an anesthetic complication. Remarkably, his mother was reported as having suffered from progressive muscle weakness. She died at the age of 65 yr suffering cognitive impairment (progressive presenile dementia), generalized stiffness of the musculature with slowness and awkwardness of movements, resembling combined Parkinson and Alzheimer disease. The maternal brother, as well as the patient’s brother, were both described as normal. The patient had no children.

To assess the patient’s MH status we performed IVCT testing according to the protocol of the European MH Group. Muscle bundles from the vastus lateralis were excised under regional anesthesia, and halothane and caffeine were administered to viable muscle fascicles of 16–25 mm resting length.

The IVCT test with caffeine and halothane (contracture at 1.5 mm caffeine: 4.5 mN and at 0.11 mm halothane: 2.5 mN, respectively) established the diagnosis MHS (contracture thresholds: more than 2 mN at ≤2 mm caffeine and ≤0.44 mm halothane) in this patient (Fig. 1).

To screen for a possible genetic defect related to MHS, molecular genetic analysis of the patient’s ryanodine-receptor 1 (RYR1) gene ruled out any of the five most common RYR1-mutations related to MH, which are found in approximately 25% of MH-patients in central Europe: G1021A = Gly341Arg, C1840T = Arg614Cys, C6487T = Arg2163Cys, G6502A = Val2168Met, G7300A = Gly2434Arg.

Subsequent histologic examination of a separately excised muscle sample revealed myopathic changes such as increased variability of fiber diameters, mildly proliferated endomysial connective tissue, single necrotic muscle fibers, as well as internally nucleated fibers (Fig. 2A). However, immunohistochemical and Western-blot investigation with respect to the expression of muscular-dystrophy-related proteins such as dystrophin, sarcoglycans (α, β, γ, δ), dystroglycans, merosin, caveolin-3, calpain-3, and dysferlin yielded normal results.

Though no typical ragged red fibers were observed in the Gomori-trichrome stain, the sarcoplasm of many fibers had a coarse appearance (Fig. 2A, asterisk). By enzyme histochemistry, almost complete lack of MAD-activity was disclosed (Fig. 2B). This finding was corroborated on the molecular level when we identified a homozygous C34T mutation according to Fishbein et al.® in the patient’s AMPD 1 gene.

By oxidative enzyme histochemistry (reduced nicotinamide adenine dinucleotide-tetrazolium reductase (NADH-TR), succinate dehydrogenase (SDH), cytochrome-c-oxidase (CCO)), subsarcolemmal mitochondrial aggregates became visible. Approximately 10% of the muscle fibers showed a marked decreased reactivity of CCO in the respective stain (Fig. 2C). At the ultrastructural level, the mitochondria showed multiple structural abnormalities, such as paracrystalline inclusions (Fig. 2D).

To further delineate a suspected mitochondrial myopathy, we screened the mitochondrial DNA extracted from the patient’s muscle for all known pathogenic point mutations according to Raffelsberger et

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We identified a nucleotide exchange C-T at nucleotide position 10084 within the ND3 gene, which encodes a subunit of the complex I of the mitochondrial respiratory chain. This base pair substitution replaces the amino acid isoleucine by a threonine in the transcribed polypeptide. The substitution was detected at an almost 100% level in the mtDNA isolated from skeletal muscle. This base pair exchange has not been reported to be pathogenic so far. No other alterations of the mtDNA were detected such as deletions or duplications using Southern-blotting (not shown).

As the results of all morphologic investigations of the muscle biopsy were consistent with the diagnosis of a mitochondrial myopathy, the patient was further clinically tested by bicycle ergometry (30 watt for 15 min). Indeed, already before the patient underwent this test pathologic lactate values were detected: (before exercise: 3.7 mM; normal: ≤2 mM). After 15 min bicycle riding at 30 watts, lactate levels increased up to 4.0 mM whereas in normal probands lactate remains within the normal range. Even 30 min after ergometry, lactate was still elevated (2.4 mM). These test results were reproducible in a second setting performed 1 week later.

Discussion

This case report describes the combination of a slowly progressive muscle disorder caused by two distinct metabolic defects and malignant hyperthermia susceptibility (MHS). The relevance of the pathogenic role of the metabolic defects detected is strengthened by the fact that the most common mutations in the RYR1 gene were excluded as a possible cause of MHS in this patient. Both metabolic defects which we disclosed in the patient’s skeletal muscle are related to the energy-metabolism of the muscle.

The muscle-specific enzyme myoadenylate deaminase is involved in the energy metabolism of the skeletal muscle by conversion of adenosine monophosphate to ammonia and inosine monophosphate and thereby facilitating the regeneration of ATP from ADP. MAD deficiency represents a frequent defect of skeletal muscle caused by mutations in the AMPD1-gene, characterized by symptoms like myalgia and cramps, exercise intolerance, elevated CK levels and rhabdomyolysis.5,6 The patient reported here showed all these clinical symptoms as well as increased CK-values.

The second defect affecting the energy metabolism in muscle was a mitochondrial dysfunction leading to severe, slowly deteriorating muscle-related symptoms such as weakness, myalgia and cramps, and recurrent myoglobinuria. On the one hand, this diagnosis was strongly supported by the specific findings in the muscle biopsy. On the other hand, pathologically increased levels of lactate in the serum at rest as well as an abnormal increase of serum lactate levels during bicycle exercise were found.

Mitochondrial diseases represent disorders caused by functional impairment of mitochondrial energy metabolism affecting primarily tissues and organs with a high-energy demand like skeletal and cardiac muscle and the central nervous system. Clinical manifestations of mitochondrial disorders are variable, ranging from isolated myopathy to complex multisystem syndromes.7 More than 40 years ago, the combination of myopathy and severe hypermetabolic symptoms resembling a hyperthyroidism syndrome were assigned to the defective
respiratory control of mitochondria. Meanwhile, a huge variety of well-defined syndromes due to mitochondrial dysfunctions have been identified.

In the mitochondrial DNA from our patient, we excluded all pathogenic point mutations known to date by sequencing all regions of the mitochondrial genome where these point mutations are located (‘hot spots’). Moreover, any gross rearrangements of the mitochondrial DNA such as duplications or deletions were ruled out by Southern blotting. However, we detected a base pair substitution T→C at nucleotide-position 10084 in the mitochondrial DNA within the ND3 gene. This substitution was detected in a high proportion (more than 75%) of mitochondrial genomes in muscle. Although this base-pair substitution is not highly conserved among several species, it might represent a mitochondrial “at-risk haplotype” for MH-susceptibility. The ND3 gene encodes a polypeptide which is assembled to the multi-protein-complex-I of the mitochondrial respiratory chain and thus is directly involved in the mitochondrial-based energy metabolism by conferring ATP to the cells.

Concerns about MH susceptibility in patients suffering from mitochondrial disorders are based on a possible mitochondrial involvement in the pathogenesis of MH. Defects in the mitochondrial function seem to play a major role in the development of a MH crisis and mitochondrial Ca\(^{2+}\) efflux is known to be involved in the perpetuation of MH. Guidelines for the anesthetic management of these patients are lacking and clinical case reports are contradictory: Ohtani et al. reported on a MH crisis in a mitochondrial myopathic patient after induction with succinylcholine. The patient was treated promptly and successfully, but whether a subsequent IVCT confirmed or ruled out MH susceptibility remains unreported. It is noteworthy that other patients suffering from mitochondrial myopathies seem to have received MH triggering substances (halothane, succinylcholine) not leading to any complications.

Our data do not yet confirm an association between MHS and combined metabolic defects in skeletal muscle such as MAD deficiency and mitochondrial myopathy, both affecting the energy metabolism. However, this case report extends the spectrum of metabolic defects of the skeletal muscle as a possible cause of MHS and may warrant the consideration of MH susceptibility in patients with metabolic muscle disorders.

References