Increased Serum Creatine Kinase

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CASE DESCRIPTION

A 38-year-old white male taxi driver was referred to a lipid clinic by his general practitioner for management of combined hyperlipidemia. He was a smoker with a 20 pack-year history. His father had died of myocardial infarction at age 55 years. Examination of this patient revealed a blood pressure of 136/99 mmHg and a body mass index of 29 kg/m², with no clinical signs of hyperlipidemia. Cholesterol testing revealed a total serum cholesterol value of 251 mg/dL (6.5 mmol/L; reference interval, 3.7–7.0 mmol/L), an HDL concentration of 30.9 mg/dL (0.8 mmol/L; reference interval, 0.7–1.8 mmol/L), and triglycerides of 539 mg/dL (6.1 mmol/L; reference interval, <1.7 mmol/L), results consistent with metabolic syndrome. The patient’s calculated 10-year cardiovascular risk was >20%, indicative for primary prevention of hyperlipidemia with a statin, after changes in lifestyle (1). Baseline biochemical investigations before starting the statin showed a serum creatine kinase (CK)4 activity of 889 U/L (reference interval, 24–195 U/L) and alanine aminotransferase activity of 61 U/L (reference interval, <50 U/L). The results of other tests were within their respective reference intervals: total bilirubin, 0.8 mg/dL (13 μmol/L; reference interval, <14 μmol/L); alkaline phosphatase, 95 U/L (reference interval, <150 U/L); and γ-glutamyl transferase, 49 U/L (reference interval, <50 U/L). The results of other laboratory investigations (including renal function, blood count, serum vitamin B₁₂, folate, serum protein electrophoresis, antinuclear antibodies, C-reactive protein, and thyroid function) were normal. At 30 years of age, the patient’s mother had been diagnosed with lower limb muscle weakness, which made her unable to dorsiflex her feet. His 48-year-old brother and 38-year-old maternal half-brother were both fine.

On questioning, the patient admitted to a weekend of heavy physical activity before the test but had no other major complaints.

PATIENT FOLLOW-UP

At this point, the most likely cause of the increased serum CK activity was heavy exercise; however, after a week of lower physical activity, the patient’s serum CK activity was still increased at 737 U/L.

Owing to the persistently increased serum CK, the patient was referred for metabolic investigations, including the ischemic forearm test, plasma and urinary amino acids, and a plasma carnitine profile. The test results for amino acids and the carnitine profile were all normal.

The ischemic forearm test showed a borderline increase in ammonia that was lower than expected, with a normal increase in lactate concentration. These results suggested the possibility of heterozygous myoadenylate deaminase (MADA) deficiency.

During his visit for the ischemic forearm test, a steppage gait was observed. On questioning, the patient admitted that he had been aware of slightly weak legs all his life. He was referred for electromyography (EMG) testing, nerve conduction velocity (NCV) studies, and neurology and genetics services, with a working diagnosis of hereditary sensory motor neuropathy of the Charcot–Marie–Tooth (CMT) type. An examination by a neurologist confirmed high arched feet and champagne bottle-shaped legs, weakness in ankle dorsiflexion and evertor muscles. Several reflexes were absent with no gross sensory loss detectable upon light touch, pinprick, vibration, and proprioception in the upper and lower limbs. EMG and NCV evaluations showed severe demyelinating, with lower limb motor conduction in the demyelinating range. The patient had sensory potentials for the left upper limb of very low amplitude, and an
absent sural sensory potential. The EMG results showed widespread evidence of chronic partial denervation. The findings were suggestive of an inherited polyneuropathy. A review by a clinical geneticist also suggested a hereditary sensory motor neuropathy; however, a mutation analysis revealed no mutations in the common disease-causing genes PMP22\(^5\) (peripheral myelin protein 22) and MPZ (myelin protein zero).

**DISCUSSION**

This previously unreported case of CMT, with its subclinical neuromuscular symptoms diagnosed during investigation for increased serum CK, highlights the need for a rational diagnostic approach to patients with increased CK activity. In a systematic review of increased CK activity, Kyriakides et al. recommended important steps in the diagnosis (2). These steps consist of excluding nonneuromuscular causes (such as statin drugs) and nonmyopathic causes, including macro CK. Documenting a family history of neuromuscular disease and a CK activity >1.5 times the upper reference limit was recommended, as well as repeating the test and excluding the possibility of an exercise-induced increase. EMG and NCV evaluations were recommended as the next line of investigation.

CK is the most diagnostically sensitive test for muscle injury. The enzyme is located on the inner mitochondrial membrane, on myofibrils, and in the muscle cytoplasm. The enzyme catalyzes the production of high-energy ATP via transfer of a phosphate from creatine phosphate, which is the major storage reservoir of energy during muscle rest, to ADP. CK participates in the transfer of high-energy phosphate from the mitochondria into the cytoplasm, where it is used during muscle contraction (3). CK is a dimer and has 3 distinct forms (MM, MB, and BB). Skeletal muscle has the highest amount of CK of any tissue, which is >99% MM with small amounts of MB (4). Serum activities of CK-MM may be increased in a number of conditions, including after strenuous exercise, inflammatory myopathies, infectious myopathies, dystrophinopathies, rhabdomyolysis, medications, metabolic myopathies, malignant hyperthermia, endocrine myopathies, and channelopathies. CK may also be increased in patients who have no primary muscular disease but drink excessive amounts of alcohol, take drugs like statins, or have macro CK. There also may be secondary involvement of muscle, as in such neurogenic disorders as amyotrophic lateral sclerosis, hereditary spinal muscular atrophy, postpolio syndrome, and some neuropathies, including hereditary polyneuropathy (reported above). Because of additional features observed in the examination and the medical history, there are generally no diagnostic difficulties with these conditions (2). As in our case, however, many patients with only subtle symptoms may not volunteer the symptoms to their clinicians, or the disorder may not be suspected and therefore not be referred to the relevant specialists.

One of the screening investigations used for the differential diagnosis of muscle disorders is the ischemic forearm test. It involves measuring the lactate and ammonia in the plasma produced by forearm exercise under ischemic conditions in a fasting individual. The test involves obtaining venous plasma for baseline measurements of lactate and ammonia, inflating a sphygmomanometer cuff around the upper arm to occlude arterial supply to the forearm, and then exercising the forearm anaerobically. The cuff is retained for 2 minutes and then released, and samples are collected for the measurement of lactate and ammonia at intervals of 1, 2, 3, 5, and 7 min after deflating the cuff. A normal response is a maximum increase in both plasma lactate >19.8 mg/dL (>2.2 mmol/L) and plasma ammonia >119 μg/dL (>70 μmol/L). Responses below these values are considered abnormal. The most important clinical use is in screening for a possible disorder of carbohydrate metabolism, in particular McArdle disease (glycogen storage disease type 5, a deficiency of glycogen phosphorylase). It is also useful in screening for glycogen storage disease type III (debrancher enzyme deficiency) and MADA deficiency; however, some healthy individuals and some patients with metabolic myopathies may fail to show an increase in plasma ammonia to the maximal concentrations achievable, particularly when the exercise has been submaximal owing to poor effort during the test (5). We believe poor effort was the case for our patient, rather than heterozygous MADA, because it explains the clinical findings best.

CMT is a heterogeneous group of genetic disorders that present with a chronic progressive neuromuscular disease affecting both the motor and sensory nerves. More than 40 underlying gene mutations have been identified. These genes encode proteins with different locations (myelin, Schwann cells, and axons) and different functions, but they share the common final pathway of axonal degeneration. CMT is the most common inherited neurologic disorder, affecting 40 in 100 000 individuals. In most patients, duplication of the PMP22 gene produces the “classic” phenotype, which is characterized by an onset in the first 2 decades of life, distal weakness, sensory loss, foot deformities (such as a high arched foot and contracted toes), and absent ankle reflexes. Many patients develop severe disability in infancy or early childhood, whereas others develop few, if any, symptoms until adulthood (6). CMT historically was classified into 2 different types on clinical, electrophysio-

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\(^5\) Human genes: PMP22, peripheral myelin protein 22; MPZ, myelin protein zero.
logical, and genetic grounds. CMTX is the X-linked type, which is clinically and neuropathologically similar to CMT type 1 (CMT1); however, male patients with CMTX are more severely affected than female patients. Autosomal recessive forms are very rare and are classified as CMT4 (7). A simplified classification of CMT is presented in Table 1, along with the mode of inheritance and the number of involved genes (6–8).

There is no specific biochemical test for CMT; however, 3%–30% of a subset of CMT patients in a Japanese cohort were reported to have increased CK activity (9). Genetic testing is used in CMT classification, which should be guided by the clinical phenotype, inheritance pattern, and electrophysiological features. One of several recent recommendations for helping diagnose CMT is shown in Fig. 1 (10). The basis of this recommendation is classifying CMT according to the NCV findings into CMT1, CMT2, or intermediate between CMT1 and CMT2. As Fig. 1 shows, once the mode of inheritance was taken under consideration, searching for the relevant mutations covered most of the mutations in the studied population (10).

There is still no effective drug therapy for CMT. Supportive treatment is limited to rehabilitative therapy and surgical treatment of skeletal deformities and soft-tissue abnormalities. Management requires a multidisciplinary approach, with close collaboration between the neurologist and other professionals. Most commonly, the onset of symptoms occurs in the first 2 decades, and the disease has a slowly progressive course. The age of onset, disease course, rate of progression, and overall severity vary, however, depending on the specific type of CMT.

### Table 1. Classification and genetics of CMT.

<table>
<thead>
<tr>
<th>Disease name</th>
<th>Pathology</th>
<th>Inheritance mode</th>
<th>Genes/chromosomal loci associated with disease, n</th>
<th>Proportion of all CMT, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMT1</td>
<td>Abnormal myelin</td>
<td>AD</td>
<td>9</td>
<td>40–50</td>
</tr>
<tr>
<td>CMT2</td>
<td>Axonopathy</td>
<td>AD</td>
<td>19</td>
<td>10–15</td>
</tr>
<tr>
<td>CMT4</td>
<td>Either myelinopathy or axonopathy</td>
<td>AR</td>
<td>10</td>
<td>Rare</td>
</tr>
<tr>
<td>CMTX</td>
<td>Axonopathy with secondary myelin changes</td>
<td>XLG</td>
<td>2</td>
<td>10–15</td>
</tr>
</tbody>
</table>

a Intermediate dominant (dominant inheritance with NCV between demyelinating and axonopathic) and other rare forms are not included.

b AD, autosomal dominant; AR, autosomal recessive; XLG, X-linked disease.

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**Fig. 1. Diagram of genetic mutations in CMT.**

AD, autosomal dominant; CMT1, demyelinating CMT; ICMT, intermediate CMT (NCV findings between demyelinating and axonopathic); CMT2, axonal CMT; F, female; M, male; GJB1, gap junction protein, beta 1, 32kDa; MFN2, mitofusin 2.
on the CMT form, the causative gene, and the type of mutation. Moreover, substantial phenotypic variabil-
ity occurs, even within the same CMT type (6).

The likely mode of inheritance in our patient was autosomal dominant. The neuropathy occurred in 2
generations, so it is unlikely to be autosomal recessive. The patient’s brother and half-brother were unaf-
fected, so it is unlikely to be X-linked. Although the common disease-causing genes PMP22 and MPZ were not mutated in this case, the diagnosis is probably CMT1, because of the clinical and neurophysiological findings of demyelinating sensorimotor neuropathy in the patient and his mother. This is not surprising, because some reports identified no specific mutation in up to one-third of CMT patients (6). In view of the normal results in liver-related tests, including for γ-glutamyltransferase, the increased alanine amino-
transferase in our patient was probably secondary to muscle, rather than hepatocellular, damage.

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Commentary
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The authors describe a case of Charcot–Marie–Tooth disease (CMT) referred to a lipid clinic for manage-
ment of combined hyperlipidemia. An increased creatine kinase concentration led to a more thorough workup, including physical, electrophysiology, and

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family history evaluations, the results of which were consistent with a diagnosis of CMT.

The patient was tested for 2 of the most common causes of CMT: duplication of the PMP22 (peripheral myelin protein 22) gene (which accounts for approximately 67% of demyelinating CMT cases) and mutations in the MPZ (myelin protein zero) gene (approximately 10% of demyelinating CMT cases) (1). The most likely mutated gene for this patient is GJB1 (gap junction protein, beta 1, 32kDa). Mutations in this gene cause CMT1X and affect about 10% of all people with CMT and 18% of those with demyelinating CMT. CMT1X is inherited in an X-linked manner. The authors correctly determined that the inheritance is dominant in the family, with multiple generations affected, but it is not clear that it is an autosomal condition, rather than X-linked. A pedigree excludes an X-linked inheritance only if there is male-to-male transmission, which the authors do not report. The 2 brothers of the patient could have inherited the mother’s X chromosome that did not have the mutated GJB1 gene.

The list of genes that cause CMT is rapidly expanding, and the most recent count is over 70 genes (http://www.molgen.ua.ac.be/CMTMutations/; accessed July 2013). Although the majority of people will have a mutation in one of 4 genes [PMP22, MPZ, GJB1, or MFN2 (mitofusin 2)], it can be difficult determine the genetic cause if the test results for mutations in these genes are negative. Involving a specialty center to help determine the genetic cause of a person’s CMT may be helpful. The authors did a very good job of finding a genetic condition in a person who presented with unrelated symptoms. This case highlights that people with CMT are not immune to other conditions and that a full workup can be valuable.

Commentary

Christina M. Lockwood1*

This case illustrates the extensive clinical and genetic heterogeneity in the hereditary motor and sensory neuropathies. There is no simple means for detecting these inherited neuromuscular disorders. An increased creatine kinase value should prompt further investigation, including repeat measurement after a period of rest. If creatine kinase remains increased and other causes are excluded, a thorough family history, a physical examination, and a neurologic evaluation are essential for establishing a clinical diagnosis of Charcot–Marie–Tooth disease (CMT). Molecular genetic testing provides a definitive diagnosis if a mutation is detected.

The algorithmic approaches that have been proposed for molecular CMT testing use a sequential, rather than a parallel, strategy. If the family history is not consistent with male-to-male transmission, testing for PMP22 (peripheral myelin protein 22) gene duplication should be initially performed, because it is by far the most common type of CMT1 (CMT type 1) (approximately 70% of patients). Sequence analysis of the 2 most frequently mutated genes, MPZ (myelin protein zero) and PMP22, identifies an additional 15% of CMT1 cases (1).

Reference


1 Human genes: PMP22, peripheral myelin protein 22; MPZ, myelin protein zero; GJB1, gap junction protein, beta 1, 32kDa; MFN2, mitofusin 2.

2 Human genes: PMP22, peripheral myelin protein 22; MPZ, myelin protein zero.