Asymptomatic hyperCKemia during a two-year monitoring period: A case report and literature overview

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Abstract. High creatine kinase (CK) levels can be associated with many disorders, including neuromuscular, cardiac, metabolic, endocrine and traumatic. Idiopathic hyperCKemia is a diagnostic dilemma for physicians even though its long-term prognosis is usually benign. We report a case of a Caucasian 61-year-old woman who presented as completely asymptomatic to her general practitioner with a serum CK (sCK) level at 6,122 IU/l. A complete diagnostic evaluation, including physical and laboratory examinations, electromyogram and muscle biopsy were negative for any neuromuscular or other disorder. Two years later the patient remains asymptomatic, active and overall healthy but sCK levels remain elevated, ≤6,591 IU/l (>50-fold higher than normal values).

Introduction

Creatine kinase (CK) is an enzyme which catalyzes the reaction of creatine and adenosine triphosphate to create phosphocreatine and adenosine diphosphate. The three isoenzymes involved are CK-MM, which is mainly present in skeletal muscle; CK-MB in cardiac muscle and CK-BB which is predominantly expressed in the brain. The sum of these three isoenzymes quantifies the total serum CK (sCK) levels (1,2). CK levels have been reported based on age, ethnicity and gender and can be stratified in a 'high CK' group among men of African descent with a mean CK value of 237.8 U/l, an 'intermediate CK' group comprising of non-African-American men and women with mean CK levels between 109.3 and 149.7 U/l and a 'low CK' group consisting of Caucasian women with mean CK levels between 64.6 and 79.8 U/l (3). Recent European Federation of Neurological Society (EFNS) guidelines recommended that hyperCKemia should be redefined as sCK >1.5 fold the upper limit of normal (4), according to a 97.5% threshold and normal values introduced by Brewster *et al* (5) for both genders of African and Caucasian descent.

CK measurement represents a usual laboratory parameter as a part of routine follow-up in the daily practice or to assess patients complaining of muscle-related symptoms. sCK (phospho) level elevation sometimes represents an incidental laboratory finding leading to a diagnostic enigma as it can be related to a variety of disorders such as those of neuromuscular, cardiac, metabolic, endocrine and traumatic origin (2,4,6). Other clinical situations that can lead to hyperCKemia include viral infections, toxin accumulation, heavy muscle exercise, surgery, pregnancy, obstructive sleep apnoea, neuroacanthocytosis syndromes, macro-CK, malignant hyperthermia syndrome and medications (4,6). However, elevated CK levels may be observed rarely among asymptomatic individuals.

We present a case of asymptomatic idiopathic hyperCKemia with such extremely high levels of CK as to be of the very few internationally reported and, to the best of our knowledge, the first case reported from a rural primary care setting in Greece. Thus, we carried out a literature overview by discussing this condition.

Case presentation

Informed consent was obtained from the patient for publication of this case report. A Caucasian 61-year-old woman with a previous history of arterial hypertension, diabetes mellitus and hyperlipidemia diagnosed 5 years ago and a transient ischemic attack at the age of 57, presented as completely asymptomatic to her general practitioner for a routine follow-up. She was under treatment with olmesartan/amlodipine (20+5 mg), vildagliptin/metformin (50+850 mg), atorvastatin 40 mg and aspirin 100 mg. Previous sCK levels after being started on statin were all within normal ranges. Routine serum chemistry revealed an elevated CK

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Table I. Biochemical result analysis (May 2014).

Laboratory parameters	Results	Normal ranges
Glucose	122 mg/dl	65-115
Urea	35.5 mg/dl	10.0-50.0
Uric acid	3.2 mg/dl	<5.7
Creatinine	0.44 mg/dl	0.50-1.00
Total cholesterol	192 mg/dl	70-200
Triglycerides	104 mg/dl	<200
HDL cholesterol	56 mg/dl	>35
Serum glutamic oxaloacetic transaminase	135.0 U/l	<31
Serum glutamic pyruvic transaminase	198.9 U/l	<31
Creatine phosphokinase	6,122 U/l	<142
Potassium (K)	4.1 mmol/l	3.5-5.1
Sodium (Na)	142.7 mmol/l	136.0-145.0

HDL, high-density lipoprotein.

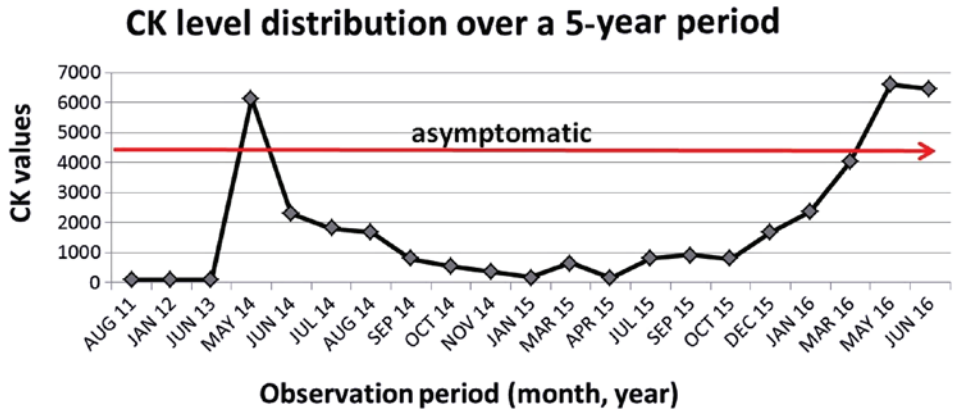

Figure 1. Creatine kinase (CK) level distribution over time.

level at 6,122 IU/l [normal CK values of the manufacturer of the CK assay (HITACHI-ROCHE, COBAS 6000; Roche Diagnostics GmbH, Manheim, Germany) was <167 IU/l) without CK-MB fraction elevation. Levels of SGOT 135 IU/l, SGPT 199 IU/l and HGB 10.9 g/dl were detected (Table I). Electrolytes and kidney function parameters were all within normal ranges. No myalgias, cramps, fatigue or other neurological symptoms were described, while family history was negative for any neuromuscular disease and non-informative for any sCK elevations. Physical examination including neurologic evaluation, showed no evidence of neuropathy while vital signs measures and ECG findings were all normal. Further laboratory investigations including thyroid and parathyroid hormone levels, abdominal ultrasonography, computed tomography of the thorax and abdomen revealed no pathological findings. Electromyogram of left and right tibialis anterior and gastrocnemius muscles was negative for any type of myopathy. Muscle biopsy did not reveal any significant alterations. Striated muscle fibers with normal size and without hypertrophy, atrophy, necrosis, inflammation or malignant lesions of neoplasia were identified microscopically. Discontinuation of statin therapy and abstinence from any physical exercise were strongly suggested for a 7-day period of observation (4). After a period of 2 years the patient remains asymptomatic but sCK levels remain elevated, ranging between 180 and 2,372 U/l with sporadic peaks rising to 6,591 IU/l (>50-fold higher than normal values) and without any obvious reason for such laboratory deviations.

Discussion

The currently reported case, after 2 years of patient follow-up, shows that extremely abnormal CK levels are not necessarily associated with neuromuscular exhaustion and physical demolition. This finding of CK elevation was noted and repeatedly confirmed in routine blood check procedures (Fig. 1) with a patient being active and self-describing a 'healthy' overall condition. Additionally, it was shown that there was a total divergence between laboratory levels, medication intake and biopsy findings. The most negative effect of CK abnormality was related to the great stress provoked on both patient and physician by an extremely abnormal laboratory result. Discontinuation of statin therapy was assessed to be risky due to a previous cardiovascular event that occurred in

our patient. As there are reports suggesting that this condition is under-recognized by primary care physicians (7), it is crucial to identify case-finding approaches to better detect and report similar cases for primary care settings.

The term 'idiopathic hyperCKemia' was first introduced by Rowland *et al*, defining an uncommon condition characterized by persistent elevation of the serum concentration of CK without any clinical, neurophysiological or histopathological evidence of neuromuscular disease, using the available laboratory procedures (8). In a number of cases this benign condition could be inherited as an autosomal dominant trait, known as Familial Idiopathic HyperCKemia (9).

Brewster and de Visser (10) added criteria for exclusion such as hypothyroidism, medication side effects and family history of neuromuscular disorder, while Prelle *et al* suggested that a non-diagnostic muscle biopsy is required for a real case of idiopathic hyperCKemia (6). Despite the fact that in some cases CPK concentration levels may be extremely high, long-term follow-up has no clinical impact since the prognosis of this condition is benign (11,12). A follow-up study identified persistent hyperCKemia in 78% of asymptomatic patients after a 6-year period as well as an association between CK normalization and a normal muscle biopsy in 22% (12).

Some researchers have correlated the high level of hyperCKemia (CK levels >5- to 10-fold normal) and early age with an increased possibility to reach a specific diagnosis after a muscle biopsy (6,13). In our case, despite the extremely high levels of CK, after all the recommended diagnostic procedures, a specific diagnosis was not established. According to Dabby *et al*, even though muscle biopsy is often non-normal in patients with persistent hyperCKemia, the majority of the abnormalities are non-specific, rendering the confirmation of a definite diagnosis relatively low (14). On the other hand, based on a diagnostic approach to pauci- or asymptomatic hyperCKemia guidelines, a normal electromyogram increases the probability of a normal biopsy to ≤74-80% (4,6,15).

Weglinski *et al* associated malignant hyperthermia susceptibility, an autosomal dominant disease, to almost half of patients with idiopathic hyperCKemia and suggested that caffeine-halothane contracture testing be used in patients with persistent elevated CK levels who undergo a muscle biopsy procedure (16). Another important cause of increased CK levels is Duchenne dystrophy (17). Guidelines suggest DNA analysis for Duchenne/Becker mutation in case of women of <3-fold CK elevation to exclude a carrier status (4). However, our patient had a 50-fold CK level elevation. Her son and daughter, adults of late thirties, are healthy without any sign of neuromuscular disorder. No family history of similar laboratory findings was reported.

Another cause of idiopathic hyperCKemia may be the caveolin-3 gene mutations. Three elements of the Caveolin gene family have been recognized, *Cav-1*, *Cav-2* and *Cav-3* (18). The latter one, *Cav-3*, is expressed mainly in muscle cells such as smooth, skeletal and cardiac cells (19). *Cav-3* gene deficiency leads to four skeletal muscle phenotypes, including the isolated hyperCKemia (20). Persistent isolated sporadic hyperCKemia was the only manifestation in two children with a novel sporadic Cav-3 p.R26Q mutant (21,22). Additionally, in a case of familial hyperCKemia the Cav-3p. P28L substitution was identified (23).

Even though genetic testing was strongly suggested to our patient and her family members, mainly for research reasons, the patient refused to undergo any other type of examination, based on her asymptomatic clinical situation and the negative family history for any neuromuscular or other inherited disorder. The patient remains under close follow-up.

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