CPK INCREASE AS AN OCCULT MARKER OF CEREBROVASCULAR DISEASE: A CASE REPORT

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[Aumento della CPK come marker occulto di malattia cerebrovascolare: descrizione di un caso]

ABSTRACT

Creatine phosphokinase (CPK), an enzyme belonging to the wide family of kinases, is a protein essential for cells energy metabolism, especially to high energy consumption ones, for its ability to produces ATP, starting from creatine phosphate and ADP. Reaction reversibility allows rapid production, use and release of energy. Three different diagnostically significant isoenzymes have been identified: CPK-MM (predominant localization in muscle), CK-BB (predominant localization in brain; this one cannot be identified in systemic circulation unless of blood-brain barrier injury) and CPK-MB (myocardial localization; useful to early diagnosis of myocardial infarction). An increase in serum CPK occurs in several pathological conditions; differential diagnosis of a hyper-CPKemia can, therefore, be extremely complex and expansive. Medical history collection as complete as possible is crucial, especially in situations that may be hidden due to poor patient cooperation. Here we report the clinical case of a 65 years old non-smoker woman, who had an isolated creatine kinase and lactate dehydrogenase increase, due to several syncopal episodes with consequential ground drop, by pre-existing impaired cerebral blood flow.

Key words: Creatine phosphokinase (CPK), hyper-CPKemia, chronic cerebrovascular disease.

Received *March 12, 2012;* ***Accepted*** *March 23, 2012*

Introduction

Creatine phosphokinase (CPK), also known as creatine kinase (CK), is an enzymatic protein, belonging to the wide family of kinases (or phosphotransferase), therefore able to transfer phosphate groups from high-energy donor molecules (e.g. adenosine triphosphate, ATP) to specific substrates (phosphorylation). Tissues, where this enzyme is most represented in, are the ones whose metabolism involves rapid energy consumption, such as myocardium, striated muscle, smooth muscle, retina photoreceptor cells, brain, and sperm. CPK serum concentration increase can be noticed in several diseases, including rhabdomyolysis, myodegenerative diseases, such as Duchenne muscular dystrophy, myocardial infarction, and acute renal failure[1-3].

According with the different localization (myocardium, striated muscle, and brain) and function, several CPK isoenzymes have been identified, some cytosolic, other mitochondrial. As a matter of fact, CPK is a dimer composed of two different subunits. There are at least three cytosolic localization of CK isoenzymes: CK-MM, CK-BB and CK-MB. Genes involved in subunits synthesis are, respectively, B and M, in 4q32 and 19q13 locus. In Table 1 are listed genes, their respective locations, and the expressed isoenzyme proteins[4-7].

Cytosolic CPK acts regenerating ATP from ADP and phosphocreatine, contrariwise mitochondrial isoenzymes is directly involved in ATP mitochondrial synthesis from phosphocreatine. MM isoform is localized in the sarcomeres, presenting, both in the myocardium and in the skeletal muscle, MB isoform presents, instead, single myocardial

expression, and BB isoform is, finally, expressed in smooth muscle and in several other tissues. Mitochondrial isoforms are ubiquitously expressed[1,8].

Gene	Locus	Protein	Isoenzyme	Tissue location
CKB	Chr. 14 q32.3	Creatine phosphokinase	BB, MB	Brain
CKBE	Chr. 14 q32.3	Creatine phosphokinase	None	Ectopic expression
CKM	Chr. 19 q13.2	Creatine phosphokinase	MM, MB	Muscle
CKMT1A CKMT1B	Chr. 15 q15 Chr. 15 q15	Mitochondrial creatine phosphokinase 1	mtCK, or umtCK	Ubiquitous
CKMT2	Chr. 5 q13.3	Mitochondrial creatine phosphokinase 2	mtCK, or smtCK	Sarcomeric

Table 1: CPK genes and isoenzymes expression.

CPK serum concentration is routinely required in many clinical conditions, especially in patients suffering from chest pain and acute renal failure. Nevertheless, its increase, especially MM isoenzyme, is a sensitive and specific muscle damage index, both traumatic and metabolic/inflammatory (crush syndrome, rhabdomyolysis, alcohol and/or drugs damage, and polymyositis)[1-8].

The following case report is representative of asymptomatic hyper-CPKemia in an women, aged 65 years, secondary to recurrent syncopal episodes, by altered cerebral blood flow, with consequential, repeated, ground falls, initially undiagnosed, due to patient lack of cooperation in history collection.

Case report

A 65 years old, non smoker, woman was admitted to our Department, as outpatient, due to the onset, for almost a month, of persistent legs weakness and right shoulder pain. The patient did not report anything significant, except for essential hypertension, treated with angiotensin II receptor blockers, since 2005.

Clinical examination showed no abnormalities, except for pain during active and passive movements of the right shoulder; similarly, routine hematochemical blood tests (complete blood count, liver and renal function test, glycaemia, natraemia, kalaemia, calcaemia, magnesaemia, iron metabolism, electrophoresis of proteins) were all in the normal range.

Electrocardiogram showed left ventricular overload nonspecific signs (ST segment depression in inferior and lateral leads), and 24-hour ambulatory blood pressure monitoring ("arterial hypertension well controlled by the therapy") and echocardiography (ejection fraction 60%, mild mitral regurgitation, with mildly dilated left atrium) were performed. Patient underwent a venous lower limbs Doppler ultrasound, also within the limits, except for left tibial veins slight ectasia and incontinence, with evidence of some perforating vein that feeds small superficial veins of the leg.

Patient was then revaluated ten days after first admission, reporting persistence of the above-mentioned symptoms. Physical examination was unchanged, as well as blood tests, except for a CPK (245 IU/L, r.r. female 26-192 IU/L) and lactate dehydrogenase (LDH) (527 IU/L, r.r. 240-480 IU/L) isolated increase.

Patient underwent carotid Doppler ultrasound ("tortuosity of left vertebral artery, V2 segment"), thyroid ultrasound ("bilateral subcentimeter hypo/anechoic nodules"), upper and lower abdomen ultrasound ("presence of three cysts in the liver, one in S2 and S3 of 0.8 cm maximum diameter, the others, subcapsular, in correspondence of S4, the maximum diameter of, respectively, 0.7 and 0.3 cm), and ultrasonography of right shoulder joint ("nonspecific right shoulder periarthritis").

Subsequent outpatient visit demonstrated persistence of elevated CPK and LDH values, without any change in physical findings and chemistry parameters. Dual-emission X-ray absorptiometry, pointing out a "senile osteoporosis framework" (lumbar T-score: -2.6 SD; left femoral T-score: -1.9 SD), and a whole spine x-ray, showing "radiological signs of cervical, dorsal and lumbar spondylarthrosis, D11, D12 and L1 vertebral bodies minor wedge fracture, interbody space shrinkage from C4 to C7 and L5-S1", were also performed.

Due to the persisting rise of CPK and LDH, thyroid and parathyroid hormones (all within normal limits), and non organ-specific autoantibodies (anti-dsDNA, ANA, anti-Jo-I, anti-nRNP, anti-Scl-70, anti-Sm, anti-Ro, anti-La and anti-ENA, all negative) assays were performed, as well as adenoviruses, coxsackievirus, herpes viruses, human immunodeficiency virus, Salmonella, Brucella,

Legionella and Listeria serology and celiac disease antibodies test (anti-gliadin, anti-tissue transglutaminase, anti-endomysial), all resulting within reference range.

During a subsequent control, considering the persistence of CPK and LDK increase, medical history was revaluated, paying particular attention to pharmacological history, without encountering intake of drugs and/or food able to determine isolated CPK increase. A new physical examination was performed, highlighting upper and lower limbs bruises; appropriately questioned, patient reported something that she wilfully neglected, cause it 'seemed unimportant'. She referred that, for about 3 months, had suffered from repeated lipothymia episodes, which led to several ground falls, during daily routine duties, which only recently begun to emerge as superficial hematoma. For this reason, 24h ambulatory ECG monitoring (within limits), carotid Doppler ultrasound re-evaluation ("left vertebral artery flow rate reduction", and brain CT scan with intravenous contrast ("chronic cerebrovascular disease framework") were performed. The patient was dismissed with final diagnosis of 'syncopal-like episodes, with multiple ground falls and increasing of CPK serum levels, in patients affected with left vertebrobasilar insufficiency, essential hypertension, senile osteoporosis, complicated by vertebral fractures (D11-D12-L1), right shoulder not specific periarthritis, mild to moderate peripheral venous insufficiency, and non-toxic multinodular goitre'. Therefore, patients started treatment with ASA (300mg/die), strontium ranelate (2g/die) and cholecalciferol (2,500IU/die).

The patient was then readmitted to our outpatient, to perform clinical and hematochemical follow-up, at three, six and twelve months, with syncopal episodes disappearance and progressive and complete CPK and LDH values normalization.

Discussion

CPK is an essential enzyme in cell energy metabolism, since it has the property of forming ATP, starting from creatine phosphate and ADP. Reaction reversibility allows rapid production, use and release of energy. CPK may be found in high amounts in myocardium, skeletal muscle, retina photosensitive cells, brain and sperm, in minor amounts, in smooth muscle, thyroid, kidney and liver. Three different isoenzymes, diagnostically significant, have been proved: CPK-MM, or muscular type, which represents about 95% of total CPK, CPK-MB, or heart type, which represents about 5%, and CPK-BB, or brain type, which usually is never found in healthy subjects, as blood-brain barrier prevents its passage into general blood circulation. These isoenzymes are exclusively cytoplasmic, although, more recently, has been identified mitochondrial isoforms, placed on the inner surface of the mitochondrial outer membrane[1].

Due to the variability of normal ranges established by different assessment methods, CPK increase may be defined, in relation to the maximum normal value, as: "mild" (equal or less than to 2 times normal value), "moderate" (greater than two and less than 4 times normal value), "marked" (greater than 4 and less than 10 times normal value), "severe" (greater than 10 times normal value). Usually, values in women are about half those observed in men[9]. Infants physiologically present total CPK high value up to 10 times normal, probably due to physiological stress of childbirth, which generally falls within the limits already at day 4, but sometimes may remain elevated for up to 6-10 weeks[10].

CPK increase can occur under 'paraphysiological' conditions such as: increase in outside temperature, with values greater than 37° C; subjects coming from equatorial countries or at least most exposed to sunlight; physical exercise, even in trained people or athletes; intense or unusual sporting activity[11-15].

Causes of pathological CPK serum increase are listed in Table 2[16,17].

In neuromuscular diseases, CPK value can rise up to 50 to 100 times normal range, as seen in several kind of muscular dystrophy, the most serious and widespread of which is surely Duchenne progressive muscular dystrophy, associated with typical muscle symptoms, which could guide to diagnosis[18-20]. Acute myocardial infarction is associated with CPK-MB early increase, whose serum pathological values can be found just after 4-6 hours from chest pain onset, its peaks just between 16 and 20 hours, and its fall, usually, within 48 hours, unless there is infarction area expansion[21-23]. Particular attention should be given to drugs assumption: statins treatments in patients with high cholesterol levels can lead to mild to moderate levels serum CPK increase, sometimes associated with mild muscle symptoms, which usually regress after drugs discontinuation[24-26]. Other drugs that can produce an increase in serum CPK are anticoagulants,

Direct muscle injuries:
• bruises
• sprains
• tears
• crush syndrome
Indirect muscle injuries:
• high fever with chills
• seizures or severe dystonia
• diagnostic procedures (electromyography)
• *intramuscular therapies:* by needle direct action on striated muscles effect of injected drugs: nonsteroidal anti- inflammatory drugs (diclofenac), antibiotics (ceftriaxone)
• surgery
• spine abnormalities
Neuromuscular disorders:
• muscular dystrophies (Duchenne progressive muscular dystrophy, etc..)
• spinal amyotrophy (amyotrophic lateral sclerosis, etc.)
Metabolic myopathies
• glycogenolysis abnormalities (myophosphorylase kinase deficiency, phosphorylase kinase deficiency)
• glycolysis abnormalities (phosphofructokinase deficiency, phosphoglycerate kinase deficiency, phosphoglycerate mutase deficiency, lactate dehydrogenase deficiency)
• lipid metabolism abnormalities (carnitine deficiency, carnitine palmitoyltransferase II deficiency, short-chain acyl-CoA dehydrogenase deficiency, very long chain acyl-CoA dehydrogenase deficiency)
• purine metabolism abnormalities (monoadenenylate deaminase deficiency)
• other (Ca2+-ATPase deficiency)
Drugs:
• statins
• anticoagulants
• morphine
• alcohol
• salicylates high doses
• amphotericin B
• fibrates
• antiretroviral drugs
• beta-blockers
• immunosuppressive drugs
• hydroxychloroquine
• general anesthetics
Other disease (infections, organ and endocrine diseases):
• viral infections (influenza and parainfluenza virus, adenovirus, coxsackievirus, echovirus, herpes virus)
• bacterial infection (streptococcus, staphylococcus, salmonella, legionella, listeria,)
• cardiologic disease (acute myocardial infarction, myocarditis, etc. [CPK-MB isoenzyme increase]
• kidney disease (acute renal failure, chronic renal failure)
• connective tissue disease (polymyositis, dermatomyositis, systemic lupus erythematous)
• celiac disease
• endocrine disorders (hypothyroidism, thyrotoxicosis, hypoparathyroidism, hyperparathyroidism, diabetic ketoacidosis, non ketoacidosic hyperosmolar diabetic coma)
• acute electrolyte disturbances (hyponatraemia, hypernatraemia, hypokalaemia, hyperkalaemia, hypocalcaemia, hypercalcaemia, hypomagnesaemia, hypermagnesaemia)
Idiopathic benign hyper-CPK-emia

Table 2: CPK increase aetiology.

morphine, alcohol, high doses of salicylates, amphotericin B, fibrates, antiretroviral drugs, beta-blockers, immunosuppressive drugs, hydroxychloroquine and some general anesthetics (individuals who have a predisposition to malignant hyperthermia may present hyper-CPKemia before surgery, in absence of other clinical symptoms, which must induce physicians to use safe anesthetic protocol)[27-35].

Finally, in literature, it is reported a condition, known as 'Idiopathic benign hyper-CPK-emia', in which it can be observed a persistent elevation of CPK in an asymptomatic patient, with normal neurological and laboratory findings. It can be a familial condition in up to 46% of the cases. Familial IH is a benign genetically heterogeneous condition that is autosomal-dominant in at least 60% of cases, with a higher penetrance in men[17,36,37].

Our patient showed recent onset of mild-to-moderate hyper-CPKemia, associated with increased serum LDH, in absence of associated muscle or cardiac symptoms/signs, so, after exclusion of neuromuscular disease family history and presence of acute or chronic muscle/heart damage, we accounted all others possible secondary hyper-CPKemia causes. Patient denied she had undergone, in the recent past, to unusual physical exertion, or to have been engaged in sports activity, or have suffered from muscular trauma of any kind. Medical history was silent for fever, muscle tremors, seizures, dystonia, intramuscular injections, surgery or other invasive procedures. Drug history was negative about assumption of statins and/or other drugs able to cause muscle damage. Normality of all the other blood tests allowed also to exclude kidney and liver failure or electrolyte imbalances, as well as the negativity of serological infective, autoimmune, endocrine and inflammatory markers permitted the exclusion of infections, connective tissue diseases and endocrine disorders.

Finally, after a more careful and mastered clinical history interview, patient reported the late onset of syncopal episode during the course of normal daily tasks, moreover associated with physician's detection of lower limbs hematoma. These data, combined with the report of carotid Doppler ultrasound and brain CT scan with intravenous contrast, induced us to make final diagnosis of hyper-CPKemia; secondary to recurrent syncopal episodes, with repeated ground falls, in patients with impaired cerebral blood flow.

Conclusions

Serum CPK increased levels may be epiphenomenon of several diseases, which produce, either directly or indirectly, myocardium or skeletal/smooth muscle damage. Accounting type and abundance of possible etiologic agents to be investigated, and consequently the amount of blood chemistry and instrumental tests, a through medical history can help to solve this clinical question. Among all possible causes, direct muscle trauma is undoubtedly the most frequent, especially in the elderly population. The clinical case we reported shows that multiple syncopal episodes, and consequent falls to the ground, may be the correct and 'trivial' explanation of a pathological increase in CPK serum levels. For this, an accurate patient history investigation, 'urging' also those information that may be silenced by the patient, as well as carotid Doppler ultrasound and possibly, if risk/benefit ratio would make it appropriate, brain CT scan, should be included in CPK pathologic increase diagnostic work-up.

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