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Case report

HyperCKemia-MB due to macroCK type 1: Case report

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ABSTRACT

HyperCKemia is a rare condition characterized by a persistent increase in serum creatine kinase (CK) levels or some isoenzymes. Usually, there are no clinical, electromyography or histological manifestations, which involves a challenge at the time of diagnosis. The patient in question showed no characteristic signs or symptoms, apart from fatigue and post-exercise myalgia. Assessment was performed by rheumatology and endocrinology, determination of total CK and MB fraction in blood, and electromyography and protein electrophoresis were requested as part of the approach. This case report is considered as novel, interesting, and useful for clinical practice as few similar ones were found in the scientific literature. The difficult etiological diagnosis of this entity, and the algorithm used to arrive at it, are all presented. It is concluded that in those patients with hyperCKemia of unknown etiology, this diagnosis should be kept in mind, and be confirmed by performing a CK electrophoresis.

HiperCKemia-MB por macroCK tipo 1: reporte de caso

Palabras clave:
Creatina quinasa
Fracción MB
Macro CK
HiperCKemia

RESUMEN

La hiperCKemia es una condición poco frecuente caracterizada por un aumento persistente de los niveles de creatina quinasa (CK) sérica o de algunas isoenzimas, sin que suelan presentarse manifestaciones clínicas, electromiográficas o histológicas, lo cual implica un desafío a la hora del diagnóstico. El paciente cuyo caso se presenta aquí no mostró signos o síntomas característicos, únicamente fatiga y mialgias posteriores al ejercicio. Se llevó

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a cabo valoración por reumatología y endocrinología, determinación de CK total y fracción MB en sangre; además, se solicitó electromiografía y electroforesis de proteínas como parte del abordaje. Consideramos que este reporte de caso es novedoso, interesante y de utilidad para la práctica clínica pues se encuentran pocos similares en la literatura científica; adicionalmente, se pone en evidencia el difícil diagnóstico etiológico de esta entidad, así como el algoritmo utilizado para llegar a ella. Se concluye que este diagnóstico debe tenerse en mente en aquellos pacientes con hiperCKemia de etiología desconocida, y para confirmarlo es necesario hacer una electroforesis de CK.

Introduction

Creatine kinase (CK) is a dimeric enzyme of approximately 86 kDa whose function is to catalyze the combination of creatine and adenosine triphosphate (ATP) to form phosphocreatine and adenosine diphosphate (ADP), a crucial reaction for the generation of cellular energy and metabolism.[1]

It is a marker of the functional state of the muscle, whose level can be raised by tissue damage as a consequence of intense and prolonged training; this may be due to metabolic and mechanical causes. If after physical activity the levels remain high at rest, this may be a sign of muscle disease.[1,2]

There are 3 isoenzymes: CK-MM (skeletal muscle), CK-MB (heart muscle) and CK-BB (brain). The measurement of CK in serum reflects the sum of all 3. The asymptomatic elevation of serum CK is called hyperCKemia and the first logical step for its evaluation is to fractionate the 3 isoenzymes in order to identify the one responsible for the elevation of the total level.[1–3]

HyperCKemia is an infrequent condition, defined as a persistent elevation of serum CK levels, usually without clinical, electromyographic or histological manifestations, and with a benign course in the long-term. A little known cause of this is the presence of macrocreatine kinase (macroCK), a macroenzyme, that is, an enzymatic complex with a molecular mass higher than that which is usually found in serum, 250–350 kDa, compared with the 80 kDa that CK normally has.[2–4]

The two main causes that frequently interfere with the quantification of the CK-MB isoenzyme, specifically, are the existence of macroCK and the plasmatic elevation of the CK-BB isoenzyme. Both appear as elevated CK-MB isoenzyme values, but paradoxically with normal values of total CK[3–6].

There are some reports in the literature with this condition, one of them is the one conducted by Kleppe et al., in which it was found in 4 of 100 patients reported with hyperCKemia[7]. It has been described that it can affect people over 50 years of age, however, there are cases described in children, for which it has not been possible to determine the age of presentation nor the predominance of one gender.[8,9]

It is considered that this report is novel due to the scarce literature on the subject, and also interesting due to the approach presented, which highlights the diagnostic challenge that this clinical entity constitutes.

Table 1 – Follow-up of total CK and MB fraction.

Date	CK total (U/l)	CK-MB (ng/ml)
15/10/2019	153	185.2[a]
10/10/2019	190	210.8[a]
22/02/2018	182	161
26/01/2018	201	212[a]
14/11/2017	157	124
09/08/2017	161[b]	164[a]
12/07/2017	165[b]	181[a]
05/01/2017	247	201
24/10/2016	262	224
18/08/2016	5.301	220
15/08/2015	420	237
30/06/2015	235	268[a]

CK: creatine kinase.
Normal reference values CK: men, 30–200 U/l; women, 29–168 U/l.
Normal reference values MB fraction: less than 25 U/l.
[a] CK-MB fraction above the total CK.
[b] Control values of total CK close to the upper limit of normality.

Case presentation

A male patient in the third decade of life, with a history of primary nephrotic syndrome, with histopathological diagnosis of focal and segmental hyalinosis since he was 2 years old; in addition, he had multiple associated comorbidities such as low bone mass, depression and several surgical interventions, among which a L5-S1 fixation due to spondylolisthesis and corrections in both feet due to bilateral serpentine foot stand out. He has been receiving treatment with deflazacort 12 mg/day, mycophenolate 1.5 g/day, cyclosporine 100 mg/day, enalapril 5 mg/day, vitamin D 2000 IU/day and escitalopram 10 mg/day.

At the beginning of 2015, the patient suffered a relapse of his underlying kidney disease, with massive proteinuria, quantified at this time above 14 g in 24 h urine, hypoalbuminemia and the presence of anasarca. Finally, during hospitalization, complete remission was achieved; however, there was persistent elevation of CK, specifically of the MB fraction, without any apparent cardiac or organic cause (Table 1).

In the middle of the year 2016, after starting physical activity of moderate-vigorous intensity consisting in aerobic

exercise and weight-bearing strength workout, there was a marked elevation in CK levels (Table 1) without any secondary renal alteration. The patient initially consulted the rheumatology unit, which, together with endocrinology and sports medicine, indicated the cessation of exercise, which had not really been directed or prescribed by a professional, as well as close monitoring of CK and MB fraction levels.

In addition, an electromyography was requested ([08/23/2016]: normal study, no inflammatory or non-inflammatory alteration of the muscle fiber was demonstrated. No evidence of polyneuropathy), whose result was completely normal, thus ruling out the possibility of an ongoing myositis.

Subsequently, in controls carried out in 2017, specifically on August 9 and July 12, an improvement and a significant decrease in total CKemia were observed, with values close to the upper limits of normality, but drew the attention the persistence over time of increased levels of the CK-MB isoenzyme, as can be observed in the follow-up shown in Table 1.

Due to that was described previously, the medical team suspected the possible presence of macroCK, and for this reason a CK electrophoresis was requested, which was performed on July 5, 2017, and finally demonstrated the presence of a macroCK type 1 (creatine kinase with separation of isoenzymes: total CK:186; CK-MM: 32.7%; CK-MM: presence of a macro CK type 1 [67.3%]; CK-MB: 0%; CK-BB: 0%).

A brief flowchart to illustrate the diagnostic pathway that is proposed to be followed in the presence of hyperCKemia is presented in Fig. 1.

Discussion

In this report, a case of macroCK is presented in the context of a hyperCKemia associated with a laboratory artifact, which consisted in the elevation of CK-MB levels above the value of total CK. Two types of macroCK are described in the literature: type 1, which is the case of the patient presented, is a complex of IgG-CK antibody, formed by any CK isoenzyme (MM, MB or BB) but, it is usually the complex of IgG together with CK-BB; its prevalence ranges between 0.43% and 1.2%, and it is often associated with underlying autoimmune diseases, particularly with myositis. However, it is worth highlighting in this specific case, with a history of glomerulopathy, that the presence of macroCK was not associated with it, nor did it have a negative impact on the renal function of the patient, as can be observed in the rabdomyolysis that could indeed have a “malignant” behavior and generate a possible kidney injury in a previous nephropathy. The type 2, in contrast, has been described due to an oligomeric mitochondrial CK and is often seen in patients with malignancy or liver disease, with a prevalence ranging from 0.5% to 3.7%.[10–12]

The described finding of an elevated CK-MB above the total CK value is important because when quantitative serological assays (immunoinhibition techniques) are performed to identify CK, the presence of a macroCK is indistinguishable and falsely elevates the true CK level. This occurs more frequently when there is the presence of macroCK type 1, while when there is macroCK type 2, the serum levels of CK are lower,[13] this is explained by immunoinhibition techniques, which are based on the use of anti-M monoclonal antibodies that block the M monomers of the CK-MM and CK-MB isoenzymes; and only the monomer B remains free. This system considers the non-existence of the BB fraction in serum, which usually occurs in healthy subjects. Thus, the residual activity of the sample (treated with anti-M serum) is interpreted as coming exclusively from the monomer B of the isoenzyme; this value (50% of the MB activity) is automatically doubled and in this manner the total values of said isoenzyme are obtained. The presence of macroCK or CK-BB isoenzyme alters these results, since their enzymatic activities are not inhibited by the anti-M serum and are erroneously considered as coming from the monomer B of the MB fraction. Finally, when these values are doubled, they reach figures that can exceed those of the total CK.[3]

Every form of macroCK can be differentiated by electrophoresis; therefore, it is a test that should be considered in hyperCKemia not explained by other causes, particularly in those who are affected by immune or malignant diseases. Electrophoresis is useful for differentiating between types 1 and 2, since the first would be located between the MM and MB bands, structurally formed by immune complexes, and the second between the MM band and the cathode, because they are mitochondrial CK polymers. In the cases of disproportionate increases in CK-MB isoenzyme, the electrophoresis, in addition to confirming the actual values of the MB fractions, helps to differentiate possible causes that may interfere with the results, such as macro-CK-1, macro-CK-2, CK-BB, actual elevations of the CK-MB isoenzyme of non-cardiogenic origin, or other situations that are much less frequent.[3]

Serum CK can increase physiologically after exercise or other muscular changes that do not represent disease, however, since the hyperCKemia was described, it has been taken into consideration whether the persistence of elevated levels necessarily indicates the development of muscle pathology. In the review conducted by Brancaccio et al.[2] is outlined that isolated hyperCKemia, with normal muscle biopsy and electromyography, does not represent a real risk of developing a myopathy, and even though the increase in this enzyme may be a warning of the beginning of a muscular dystrophy, only in 55% of the patients studied with persistently elevated CK was there any finding of muscle disease.

By the year 2006, Coral Alvarado et al.[4] reported 2 cases of hyperCKemia in previously healthy patients which were no related with neuromuscular diseases, nor did they have a related family history, as in the case presented, in which there is no report of related comorbidities in the family. Unfortunately, there was no in-depth study that allowed them to assess what type of CK was the responsible for the global elevation, unlike our patient in whom finally was determined as macroCKemia type 1.

Galarraga et al.[11] described 2 cases in patients aged 59 and 79 years, respectively, who started with chest pain, in whom the only value that was found to be elevated at the beginning was CK. In both cases, the lack of suspicion led to a delay of months or years to find the diagnosis and a large investment in paraclinical tests throughout that time.

The first case concluded with a diagnosis of macroCKemia type 2, as a consequence of an IgG-producing non-Hodgkin’s lymphoma. As mentioned before, type 2 is usually related to

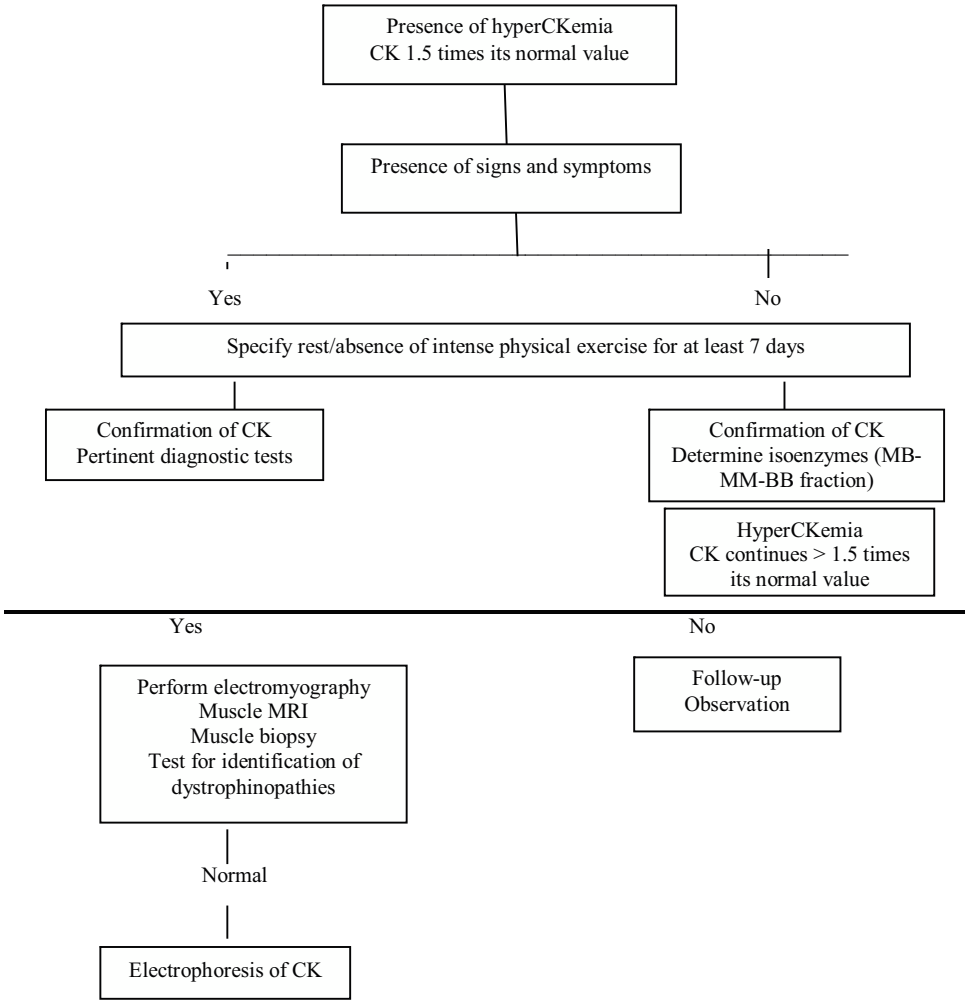

Fig. 1 – Flow chart, hyperCKemia diagnostic pathway.

diseases with a worse prognosis. The second patient was diagnosed with macroCKemia type 1 after electrophoresis, but at the time of publication, the case was still under study. Unlike our patient, the 2 previous patients were older, although without relevant antecedents, but it is worth mentioning the difficulty and the time required for the diagnosis, similarly to our case.

Through this report, we seek to illustrate the diagnostic challenge that macroCKemia constitutes. It is considered that it is a complete presentation of the case since there was access to the clinical and paraclinical information necessary to build the follow-up that finally led to the diagnosis by means of CK electrophoresis. In addition, during the approach and management, the patient did not present any type of complication, nor were there significant limitations at the time of the construction of this report.

Conclusions

MacroCK is a very infrequent condition, but it is considered to be a cause of hyperCKemia that should be taken into account in those patients in whom no other organic etiology can be determined; the method to diagnose it in those in whom it is suspected is the electrophoresis of CK. Once the presence of macroCK and its type have been determined, it is recommended to search for associated conditions such as autoimmunity or malignancy in those who still do not have any of these diagnoses.

Ethical Considerations

The research ethics committee of the School of Health Sciences, *Universidad Pontificia Bolivariana* approved the research. The authors have complied with the relevant ethical standards for publication and have the informed consent of the patients.

Conflict of interest

The authors do not report any conflict of interest for the preparation of this article.

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