

## ORIGINAL ARTICLE

# RHABDOMYOLYSIS - WHEN SHOULD ONE SUSPECT OF AN INHERITED METABOLIC DISORDER?

Joana Pires Borges, Maria João Gaia, Marta Vila Real, Helena Santos.  
Pediatrics Department, Vila Nova de Gaia/ Espinho Hospital Centre, Vila Nova de Gaia, Portugal.

### ABSTRACT

The present study aims to understand if there is a significant difference between the value of CK between children with and without an IMD; to compare the probability of recurrence between the two groups; to compare the main triggers of CK elevation and to establish a CK value as a cut-off for suspecting of an IMD.

We performed a cross-sectional study. We divide our sample in two groups: group 1 – the ones with an IMD; group 2 – the ones without an IMD. The following variables were studied: age, sex, trigger for CK increase, place of CK measurement, CK value and occurrence of recurrence.

A total of 138 patients were included, 7 with an IMD and 131 without. We found 198 cases of CK > 1000 IU/L, 55 in the first group and 143 in the second. The 7 patients in the first group had an IMD involving energy metabolism. In the group with an IMD, the CK presented a median of 11769 IU/L and in the second group of 2167 IU/L with a statistically significant difference ( $p < 0.001$ ). We conclude that there is an association between having an IMD and the recurrence of CK > 1000 IU/L ( $p < 0.001$ ). The optimal value of CK of 2709 IU/L was found to predict when one should suspect of an IMD.

### Introduction

Creatine kinase (CK) is an enzyme whose function is to catalyze the combination of creatine and adenosine triphosphate (ATP) to form phosphocreatine and adenosine diphosphate (ADP), an essential step for cellular energy generation and metabolism.<sup>1</sup>

It is well known that CK levels vary by age, race, and gender<sup>1,2</sup>, with differences in skeletal muscle mass, total body mass, and inherited differences between races being the most probable reasons for those differences.<sup>1</sup>

In a systematic review by Stahl et al<sup>3</sup> with the main goal of finding a definition of rhabdomyolysis, the authors concluded that the most consensual definition is a clinical syndrome of acute muscle weakness, myalgia, and swelling combined with a CK cut-off value of >1000 IU/L or >5x the upper limit of normal (ULN).

There are several possible causes for the occurrence of rhabdomyolysis, such as trauma, rigorous physical exercise, side effects of drugs such as statins, substances of abuse like ethanol and cocaine, and infections like viral myositis.<sup>1,2,3,4,5</sup>

The metabolic myopathies (MM) are a group of muscle disorders resulting from failed energy production related to defects in glycogen, lipid, or mitochondrial metabolism.<sup>6,7</sup> Patients with metabolic myopathies may present with indolent myopathic features, exercise intolerance or recurrent rhabdomyolysis.<sup>8,9</sup> MM belong to a group of heterogeneous genetically determined

conditions that are called inherited metabolic disorders (IMD).<sup>8,10</sup> IMD are the focus in the present work as a possible aetiology for CK elevation and are classically divided in three main groups: group 1 – disorders of intermediary metabolism affecting small molecules (symptoms by intoxication), group 2 - disorders involving primarily energy metabolism (the main responsible for metabolic myopathies) and group 3 - disorders involving complex molecules.<sup>10</sup>

The aim of the present study is: to understand if there is a statistically significant difference between the degree of CK elevation above >1000 IU/L between children with and without an IMD diagnosis in order to identify which patients should be further investigated; to compare the probability of recurrence between children with and without the diagnosis of IMD; to compare the main triggers of CK elevation >1000 IU/L in children with and without the diagnosis of IMD and to establish a CK value as a cut-off for suspecting of an IMD.

### Methods & Materials

We performed a cross-sectional study in the paediatrics department of a level II Portuguese hospital with a hospital catchment area serving 334 081 inhabitants, 61 225 of them in the paediatric age range.

We revised all clinical records of children (from birth to 18 years old) with at least one measurement of CK >1000 UI/L (data obtained from our hospital laboratory) between January 2009 and June 2020. After careful revision, we divide our sample in two distinct groups: group 1 – the ones with an inherited metabolic disorder diagnosis; group 2 – the ones without an established IMD diagnosis. We exclude all patients that had a known condition that increases CK levels,

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### ABBREVIATIONS

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**Address for Correspondance:** Joana Pires Borges, R. Conceição Fernandes S/N, 4434-502 Vila Nova de Gaia, Portugal.

**Email:** [joana.pires.borges@gmail.com](mailto:joana.pires.borges@gmail.com)

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besides IMD, specifically Duchenne muscular dystrophy, hypothyroidism, and dermatomyositis.

The following variables were studied: age, sex, trigger for CK increase, place of CK measurement (emergency department, medical appointment, or inpatient unit), CK value and occurrence of recurrence during the study period.

Statistical analysis was performed using IBM SPSS Statistics version 23. Categorical variables are presented as frequencies and percentages and continuous variables as medians and interquartile ranges as they were non-normally distributed. Normal distribution was evaluated using Kolmogorov Smirnov test or through analysis of skewness and kurtosis. Mann-Whitney test were used to compare the CK value between the group with an IMD diagnosis and the one without. To assess the association between the presence of an IMD diagnosis and the occurrence of recurrence of elevation of CK >1000 IU/L, we used the Fisher's exact test. To find a CK value that can be used as cut-off for when one should suspect of the presence of an IMD, a receiver operating characteristic (ROC) curve was drawn. All reported p values are two-tailed, with a p-value of <0.05 indicating statistical significance.

## Results

A total of 138 patients were included, 7 with IMD diagnosis (group 1) and 131 without IMD diagnosis (group 2). During the study period we found 198 cases of CK >1000 IU/L, being 55 of them in the first group and 143 in the second group. All the 7 patients in the first group had an inherited metabolic disorder involving primarily energy metabolism. Table 1 shows the main characteristics of the studied population and table 2 shows detailed information about the different IMD diagnosis.

Median age was 5 years in group 1 versus 8 years in group 2 and 90.9% of patients in group 1 were males versus 77.6% in group 2. In the first group, the occurrence of an infection was the most common trigger to an elevation of CK >1000 UI/L, occurring in 41.5% of the cases, with acute gastroenteritis being the most common diagnosis (13.8% of the total of cases). In this context, the specific symptoms of each type of infection were preponderant. In the remaining aetiologies, like excessive physical exercise and dehydration, myalgia and muscle weakness were the most common symptoms along CK elevation. In group two, the most common cause of increase of CK >1000 I/L was, by far, viral myositis representing 82.8% of the cases, and with identification of Influenzavirus B in 47.4% of them. Table 3 shows detailed information about the different triggers for CK elevation.

In the first group, CK was measured in emergency department in 84.6% of the cases, in a medical appointment in 12.3% of the cases and in the inpatient unit in 3.1% of them. In the second group, 94.8% of the measurements were in emergency department, 1.5% in a medical appointment, and 3.7% in the inpatient unit.

When analysing the CK median value between the two groups, we found that in the first group (group with an IMD diagnosis), the CK had a median value of 11769 IU/L (interquartile range of 16392 IU/L, minimum of

1368 IU/L, maximum of 101637 IU/L) and in the second group (without an IMD diagnosis) the CK value had a median of 2167 IU/L (interquartile range of 2717 IU/L, minimum of 1024 IU/L, maximum of 26398 IU/L). There is a statistically significant difference between the CK median between children with an IMD diagnosis and the ones without ( $p < 0.001$ ).

In the first group, 57.1% of the patients had at least one episode of recurrence of CK value >1000 IU/L. In the second group the percentage of recurrence was 5.3%. We conclude that there is a statistically significant association between having an inherited metabolic disorder and the recurrence of CK >1000 IU/L ( $p < 0.001$ ; OR = 23.619 [IC 95:4.404-126.662]).

In the attempt of finding a CK value that can be used in the clinical setting to predict when one should suspect of a hidden inherited metabolic disorder, we draw a ROC curve finding the optimal value of CK of 2709 IU/L (sensitivity of 90.9%, specificity of 60.8% and area under the curve of 0.853).

**Table 1.** Main characteristics of the studied population.

	<b>Group 1 – IMD diagnosis</b>	<b>Group 2 - without IMD diagnosis</b>
Patients, n (total=138)	7	131
CK measurement > 1000 UI/L, n (total=198)	55	143
Age in years, median	5	8
Males, %	90.9	77.6
Place of CK measurement, %	84.6	94.8
- Emergency Department	12.3	1.5
- Medical Appointment	3.1	3.7
- Inpatient Unit		
CK in IU/L, median	11769	2167
CK in IU/L, maximum	101637	26398
CK in IU/L, minimum	1368	1024
Recurrence, n(%)	4(57.1)	7(5.3)

**Table 2.** Type of inherited metabolic disorder (group 1 patients)

Very long-chain acyl-CoA dehydrogenase deficiency
Long-chain 3-hydroxyacyl-CoA dehydrogenase deficiency
Medium-chain acyl-CoA dehydrogenase deficiency
Multiple acyl-CoA dehydrogenase deficiency
Partial deficiency of complex IV of the mitochondrial respiratory chain
Glycogen storage disease type IX
Glycogen storage disease type V

**Table 3.** Etiologies for CK elevation; A – group 1 (IMD diagnosis); B – group 2 (without IMD diagnosis).

Group 1 – IMD diagnosis		Group 2 – without IMD diagnosis	
Infectious disease	41.5%	Infectious disease	85.7%
More common acute gastroenteritis	13.8%	More common acute myositis	82.8%
Physical exercise	13.8%	Physical exercise	2.2%
Dehydration	4.6%	Trauma	1.5%
Postoperative	3.1%	Convulsion	1.5%
Trauma	1.5%	Postoperative	1.5%
Consumption of illicit substances	1.5%	Consumption of illicit substances	0.7%
No identifiable factor	33.8%	No identifiable factor	6.5%

### Discussion

Creatine kinase is a muscular enzyme whose serum values increase, among other aetiologies, in the presence of metabolic myopathies.<sup>1,8,10</sup> Although occasionally we can find chronic CK elevation in patients with those kind of myopathies, an acute and symptomatic increase of CK in the context of disease or other stressors is a frequent finding.<sup>3</sup>

Among the subtypes of IMD, the disorders that involve primarily energy metabolism are the ones typically related to myopathies and CK elevation triggered by events like infection, intense exercise, or fasting, which are responsible for catabolic stress.<sup>8,10</sup>

To our knowledge, there is no other study that aimed to compare the degree of CK elevation between patients with a metabolic myopathy diagnosis and the ones without it. The most similar study was one from 2015 by Adler M. et al reported a resting CK value in children and adolescents >1000 UI/L in nearly all patients with a glycogen storage disease type V.<sup>11</sup>

It is well known that muscular myopathies predispose to recurrent rhabdomyolysis.<sup>8,10,11,12</sup> This was confirmed in our study by showing a statistically significant association between having a metabolic myopathy and the recurrence of CK >1000 IU/L.

Among the most common triggers for CK elevation, the most frequently reported cause for rhabdomyolysis in patients with IMD diagnosis was vigorous physical exercise.<sup>8,10,11</sup> In our study the leading cause for CK elevation was the occurrence of an infectious disease, mostly acute gastroenteritis, with physical exercise being the second more common cause. This can be explained by the fact that the referred studies evaluate mainly adult populations, while our study was performed in paediatric population, in which acute infectious diseases with systemic repercussions are more common.

Concerning the study limitations, the small sample size, especially among the patients' group, may hinder the extrapolation of the results to the general population.

### Conclusion

In conclusion, our results support the establishment of a CK threshold value above which one should be suspicious about the possibility of a metabolic myopathy. It is crucial for the everyday paediatrician to be aware that even though an increased CK value

cannot be interpreted by itself, its absolute value should always be considered along with the recurrence of CK high values and other accompanying clinical symptoms. As patients with MM present static and dynamic symptoms and CK values, we considered that all patients with the finding of a CK value  $\geq 2709$  IU/L should be further evaluated in a medical appointment to follow clinical and laboratory evolution.

### Compliance with Ethical Standards

Funding None

Conflict of Interest None

### References:

1. Silvestri JN, Wolfe GI. Asymptomatic/pauci-symptomatic creatine kinase elevations (hyperckemia). *Muscle Nerve*.2013; 47: 805-815.
2. Moghadam-Kia S, Oddis C, Aggarwal R. Approach to asymptomatic creatine kinase elevation. *Cleve Clin J Med*.2016; 83(1): 37-42.
3. Stahl K, Rastelli E, Schoser B. A systematic review on the definition of rhabdomyolysis. *J Neurol*. 2020 Apr;267(4):877-882.
4. Magee H., Goldman R. Viral myositis in children. *Can Fam Physician*. 2017 May;63(5):365-368.
5. Agyeman P., Duppenhaler A., Heining U., Aebi C. Influenza-Associated Myositis in Children. *Infection* 2004; 32: 199-203.
6. Darras BT, Friedman NR. Metabolic Myopathies: a clinical approach: part 1. *Pediatr Neurol*. 2000 Feb;22(2):87-97.
7. El-Hattab A. Inborn Errors of Metabolism. *Clin Perinatol*. 2015 Jun;42(2):413-39.
8. Lilleker JB, Keh YS, Roncaroli F, et al. Metabolic Myopathies: a practical approach. *Pract Neurol*. 2017; 1-13.
9. K. Burton B. Inborn Errors of Metabolism in Infancy: A Guide to Diagnosis. *Pediatrics* 1998;102:e69
10. Saudubray JM., Garcia-Cazorla A. Inborn Errors of Metabolism Overview Pathophysiology, Manifestations, Evaluation, and Management. *Pediatr Clin North Am*. 2018; Apr;65(2):179-208.
11. Adler M, Shieh P. Metabolic Myopathies. *Semin Neurol*. 2015;35:385-397
12. Ferreira C., Karnebeek C. Inborn errors of metabolism. In: *Handbook of Clinical Neurology*, Vol. 162, 3rd edition. L.S. de Vries and H.C. Glass, Editors; 2019; Chapter 22.