Elevated creatine kinase is mainly harmless in children but persistent and severe hyperCKaemia should raise suspicions of serious muscle damage

The enzyme creatine kinase plays a crucial role in energy transfer and storage. It is mostly expressed in skeletal muscle, heart, brain and blood vessels. Normal serum ranges vary by ethnicity, gender and age.[1]

HyperCKaemia can point to conditions like muscular dystrophies, myopathies, spinal muscular atrophy, amyotrophic lateral sclerosis, rhabdomyolysis, metabolic diseases, neuroleptic malignant syndrome and hypoxic-ischaemic encephalopathy in newborns.[2,3] However, elevated creatine kinase can also be an accidental and reversible finding due to physical exercise.[3]

This retrospective study investigated the clinical significance of hyperCKaemia using serum creatine kinase measurements obtained by the IRCCS Burlo Garofolo Hospital in Trieste, Italy, from 2009 to 2016. The study was approved by the Institute's internal review board (grant ID RC 34/18).

We collected clinical information for all patients with at least one creatine kinase measurement above the 97.5th centile, which is more than three standard deviations over the mean and a reliable cut-off to increase specificity. Persistent hyperCKaemia was high creatine kinase levels at follow up and transient hyperCKaemia was subsequent normal levels. The highest level of persistent hyperCKaemia above 97.5th centile was used. We excluded newborns with a history of perinatal hypoxia, responsible for hyperCKaemia. Data included age, gender, ward, duration of hyperCKaemia, underlying disorder and final diagnosis. A sub-analysis focused on patients with creatine kinase levels of 95th–97.5th centiles to identify how many diagnoses of muscular disease would have been missed with just the 97.5th centile cut-off. The respective population-specific 95th and 97.5th percentiles for paediatric Caucasian patients[4] in mikrokat/L were 5.18 and 6.34 for males and 3.13 and 4.92 for females. Patients with creatine kinase levels >97.5th centile were divided into Group 1 (1–2 times the 97.5th centile), Group 2 (2–10 times), and Group 3 (more than 10 times). Muscular disease was defined as muscular dystrophies, including healthy female carriers, and metabolic, inflammatory or congenital myopathies. The chi-square test was used to study the correlation between creatine kinase levels and the considered events.

We obtained 6487 serum creatine kinase measurements from 3095 subjects and 238 (7.7%) had one value >97.5th centile. We excluded 62 newborns with a history of perinatal hypoxia. Of the remaining 148/210 subjects (64.2% male), with a median age of 11 (0–18) years, 34 (22.9%) had muscular disease (Table 1). The prevalence was 74.4% in patients with persistent hyperCKaemia, with a positive linear correlation between prevalence and severity, as shown in Table 1. All muscular diseases were characterised by persistent hyperCKaemia. None had transient hyperCKaemia.

We then analysed data on 167 patients with creatine kinase levels between 95 and 97.5th centile. There were clinical records for 118 patients (64.4% females) with a median age of 9 (0–18) years. Three (2.5%) had muscular disorders: two with persistent and one with transient hyperCKaemia.

HyperCKaemia was not rare in our study. Muscular disorders were common when creatine kinase was >97.5th centile, but significantly rare below this. Moreover, the few patients with a muscular disease and creatine kinase between 95 and 97.5th percentiles had significant symptoms leading to the diagnosis even without that increase. Notably, a patient with juvenile dermatomyositis just had transient hyperCKaemia, but presented with a heliotrope rash, periungual telangiectasias and Gottron's papules. Therefore, clinical manifestations clearly supported the suspicion of dermatomyositis independently of creatine kinase levels.

Not surprisingly, the first cause of hyperCKaemia in our study was an acute muscular injury, following a trauma or physical exercise, and this should always be the first hypothesis when creatine kinase is elevated, especially in asymptomatic subjects. The second cause was endocrinopathies: growth hormone deficiency, obesity, autoimmune thyroiditis, adrenal insufficiency, panhypopituitarism and hypoparathyroidism. Most (82.1%) of muscular injuries showed creatine kinase levels up to twice the 97.5th centile (Table 1).

Interestingly, the vast majority of patients with persistent hyperCKaemia had muscular disease, but only one case of transient hyperCKaemia had an underlying myopathy. Thus, transient hyperCKaemia with successive normalisation of creatine kinase levels seems to be reassuring.

Most patients with muscular disease were male (85.3%) because of predominant X-linked transmission. Thus, persistent hyperCKaemia is even more relevant in males.

Our study confirmed that the severity of elevated creatine kinase correlated with the prevalence of muscular disease. Notably, the

TABLE 1 Final diagnosis of patients with creatine kinase levels >97.5th centile.

Diagnosis	Creatine kinase levels			p
	Group 1 (78)	Group 2 (49)	Group 3 (21)	
Muscular disease[a]	9 (11.5%)	9 (18.4%)	16 (76.2%)	<0.00001
Acute muscular injury/ physical exercise	25	20	2	
Viral miositis	3	6	1	
Endocrinopathies[b]	23	5	0	
Drug-related hyperCKemia	1	1	1	

[a]Among muscular diseases, there was a positive linear correlation between prevalence and the severity of creatine kinase levels.

[b]Growth hormone deficiency (6), obesity (13), obesity + autoimmune thyroiditis (1), obesity + type 1 diabetes + panhypopituitarism (1), type 1 diabetes (3), type 1 diabetes + autoimmune thyroiditis (1), autoimmune thyroiditis (1), adrenal insufficiency (1), hypoparathyroidism (1).

diagnostic hyperCKaemia flowchart proposed by Saengpattrachai et al.[5] recommends the direct genetic analysis of dystrophin when persistent increases of creatine kinase are 10 times higher than the 97.5th centile. Our study did not include patients with spinal muscular atrophy, who usually show mild-to-moderate, persistent, elevated creatine kinase.

The limitations of our study were its retrospective nature, possible selection bias because our hospital is a reference centre for rare disorders, and the relatively small sample size. However, we believe that this is the first report on the prevalence of muscular disease in an unselected cohort of paediatric patients with hyperCKaemia.

Our study showed that transient elevated creatine kinase was mostly harmless, especially if the values were <97.5th centile. Persistent hyperCKaemia in children, particularly if severe, should raise the suspicion of a serious metabolic, inflammatory or congenital myopathy, therefore, these children should be referred to a tertiary paediatric centre for a complete diagnostic work-up.

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The authors have no conflict of interest.

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