

How to interpret creatine kinase level in neuromuscular conditions

Nermin Alashal

Nahin Hussain

Abstract

Creatine kinase (CK) is a screening diagnostic test for suspected neuromuscular disease. It is a sensitive indicator of muscle injury and is preferred to other skeletal muscle enzymes as it is least affected by haemolysis, is readily released in cellular injury and has a relative predominance in skeletal muscle. In a healthy individual the normal range varies between 22 and 200 IU/L (varies with laboratory), although gender and race can influence this range. CK can also be elevated in non-pathological transient situations such as cramps and post-exercise. It can increase up to three times the normal value after strenuous exercise, intramuscular injections, EMG studies and viral infections. Highest level of CK is seen in inflammatory myopathies and in early stages of DMD when patients are still ambulant. Occasionally CK is elevated in asymptomatic or mildly symptomatic children and this creates unwarranted anxiety and diagnostic uncertainties. The need for extensive ancillary investigations and muscle biopsy in clinically normal individuals with elevated CK remains an unresolved issue. This review discusses the diagnostic value of creatine kinase in neuromuscular conditions in children and offers practical advice about how results should be interpreted in different clinical situations.

Keywords Becker's muscular dystrophy (BMD); creatine kinase (CK); Duchenne's muscular dystrophy (DMD); electromyography (EMG); muscle; myopathy

Introduction

The enzyme creatine kinase (CK) is a widely used screening test for suspected neuromuscular disease. First identified in 1928, the enzyme has undergone intensive investigation over the last century. Unlike other muscle enzymes found in skeletal muscle (e.g. lactate dehydrogenase, aldolase, and transaminases), CK has relative predominance in skeletal muscle, and being unbound in cell cytoplasm is readily released in cellular injury.¹

Detection of increased CK in serum is an indicator of muscle injury, but elevation is not specific to the cause (e.g., trauma, inflammation, degeneration). Creatine kinase (CK) may create

diagnostic uncertainty when an elevated level is found in a mildly symptomatic or asymptomatic patient. To address diagnostic uncertainty in the use of serum CK levels this article describes the structure and function of CK, the common reasons for elevated CK levels in normal population as well as in those with neuromuscular disorders and proposes a diagnostic strategy for patients with suspected myopathies.

Background

Creatine phosphokinase (CPK), otherwise known as creatine kinase (CK), is found in a variety of striated, smooth muscles and brain. It is an important enzyme regulator of high-energy phosphate production and utilization within contractile tissues. CK has three isozymes (CK-MM, CK-MB and CK-BB) in cytoplasm and two isozymes (non-sarcomeric and sarcomeric) in mitochondria. Cytoplasmic CK is an 86,000 molecular weight dimer molecule that produces adenosine tri-phosphate (ATP) for use in muscle cells by catalysing the transfer of a high-energy phosphate bond from creatine phosphate to adenosine diphosphate (ADP). This is a near equilibrium reaction ($ADP + PCr + H^+ \leftrightarrow ATP + Cr$) (Figure 1). The primary function of the CK pathway is energy buffering during periods of increased ATP utilization.²

CK isoenzymes (CK-MM, CK-MB and CK-BB) can be distinguished electrophoretically. Total CK content is largely contained in skeletal muscle and 95% of this is in the form of CK-MM. CK-BB comprises most of the CK in brain tissue and CK-MB is the most abundant isoenzyme in the myocardium. CK from brain almost never crosses the blood-brain barrier. Serum CK is mainly derived from skeletal muscle and therefore is almost exclusively in the form of CK-MM.³

How we determine CK levels in blood

Serum CK in healthy individuals is derived from normal tissue leaking CK into lymphatic vessels and then into the blood stream. Therefore, serum CK levels are proportionate to the intracellular CK concentration.

In vitro testing involves spectrophotometric quantitative analysis of creatine kinase (CK). The test principle is based on determining the rate of reversible reaction catalysed by CK. Equimolar quantities of NADPH and ATP are formed during the rate limiting reaction. The rate of NADPH formation, measured photometrically at 340nm, is directly proportional to serum CK activity.

Serum or lithium heparin (plasma) samples can be used for CK analysis. Serum is the specimen of choice. CK in serum is stable for 48 hours at room temperature (18–25°C) and 7 days when refrigerated (2–8°C). The sample may be frozen (–15 to –25°C) for up to one month when protected against evaporation.⁴ Differences in the degree of haemolysis resulting from blood sampling procedure can lead to deviating results. The results also vary among laboratories because of different analytical methodology used and it is necessary for each laboratory to establish its own range of serum CK activity.

Normal CK levels and variability

Normal CK levels have a wide range due to a variety of factors including age, sex and race. Black men and South Asians usually

Nermin Alashal MBBS MRCPCH Paediatric Neurologist Registrar, Department of Paediatric Neurology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, UK. Conflicts of interest: none declared.

Nahin Hussain MBBS FRCPCH Paediatric Neurology Consultant, Department of Paediatric Neurology, Leicester Royal Infirmary, University Hospitals of Leicester NHS Trust, UK. Conflicts of interest: none declared.

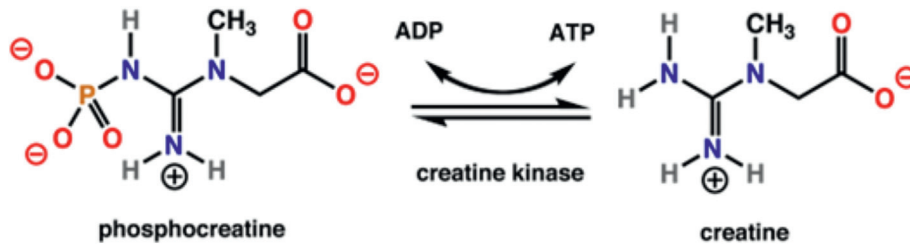


Figure 1 How creatinine kinase facilitates energy buffering.

have higher CK values. Additionally, males compared with females and people who are very active have a larger degree of muscle turnover, and therefore may have higher normal levels of creatine kinase.⁵ Newborn babies can have CK levels twice the adult value, up to 450 IU/L, which declines to near normal activity during the first week. There is no clear correlation between birth trauma and increase in serum CK level.⁶

Transient elevation of CK can be seen in children after injections, needle electromyography (EMG), and vigorous exertion. After muscle injury, CK levels rise within 12 hours and peak after 1–3 days. The elimination half-life is 36 hours. It is important to draw CK levels before EMG studies, as this can elevate CK levels by two to three-fold falsely suggesting myopathy, before returning to normal after 48–72 hours.⁷

One week of avoidance of exertional activity should be sufficient to ensure accurate measurement of CK levels in a frequently exercising patient.¹ Muscle cramps can also cause a substantial rise in CK levels. In one published case after a single severe cramp in a gastrocnemius muscle lasting several minutes, serum CK levels increased nearly threefold within 6 hours and nearly fivefold by 30 hours. Serum CK levels returned to normal 5 days after a single cramp.⁸

Indications and limitations

CK testing can be used to evaluate neuromuscular diseases in five basic ways:

1. To confirm a suspected muscle problem.
2. To determine whether symptoms of muscle weakness are caused by a muscle or a nerve problem.
3. To differentiate between some types of muscle disorders such as dystrophies versus congenital myopathies.
4. To detect "carriers" of neuromuscular disorders, particularly in Duchenne muscular dystrophy.
5. To follow the course of a disease that fluctuates (primarily the inflammatory myopathies), or to document episodes of acute muscle injury, as might occur in some metabolic myopathies.

These key concepts are studies in following clinical questions.

Does a normal CK level exclude neuromuscular conditions?

CK can be a useful marker for a few neuromuscular diseases, but not for those in which no degenerative changes occur or the process is so mild that renal clearance can compensate. Therefore normal CK does not rule out neuromuscular disease, but a normal CK does exclude DMD even in the pre-symptomatic child. Alternatively, elevated CK levels are not specific to neuromuscular condition either.

Excessive skeletal muscle exertion in convulsive seizures, dystonia and particularly status dystonicus, neuroleptic malignant syndrome, and acute psychosis can lead to elevated CK. Serum CK levels are also increased after cerebral ischaemia, cerebrovascular accidents and head injury. Hypothyroidism and patients on statins and dantrolene can have elevated CK. CK in severely asphyxiated newborns can be as high as 1000 IU/L secondary to acidosis.^{3,4}

Can the range of elevated CK levels help differentiate between various neuromuscular disorders?

Muscular disease

The degree of CK elevation in muscle disease is dependent on the underlying disease process, which includes myonecrosis or membrane defects¹ (Table 1).

Highest CK levels are seen with conditions in which muscle fibre necrosis occurs, such as dystrophinopathies, rhabdomyolysis, malignant hyperthermia, neuroleptic malignant syndrome and severe polymyositis. Myopathies, which have a more indolent course such as fascioscapulohumeral muscular dystrophy, myotonic dystrophy and inclusion body myositis, have a lesser degree of CK elevation. In conditions where muscle atrophy is the primary pathology rather than membrane damage, the CK levels are normal. These include steroid induced myopathy, hyperthyroidism, channelopathies and mitochondrial myopathies. Relapsing-remitting hyperCKemia is seen in polymyositis and dermatomyositis, correlating with the disease process.¹⁰ In polymyositis and dermatomyositis, CK levels improve on steroids, regardless of whether weakness improves and is not particularly useful to monitor treatment response. An acute increase in CK levels in these disorders, may be indicative of relapse. As patients with chronic myopathies lose muscle mass and strength, CK levels will drop and may approach normal in later stages of muscular dystrophy.

The time course of various myopathies in relation to level of serum CK is an important correlation to be aware of when interpreting elevated CK results (Figure 2).

Duchenne's muscular dystrophy (DMD) and Becker's muscular dystrophy (BMD) are caused by defects in the gigantic Xp21-linked gene, which codes for the dystrophin protein. These are the commonest muscular dystrophies. CK levels are markedly elevated in DMD and BMD patients from birth (before the onset of clinical signs) and the serum CK activity decreases with the progression of the dystrophic process¹¹ (Figure 3).

Serum CK levels in peripheral neuropathy

Serum CK levels are not commonly thought to be elevated in neurogenic disease such as mononeuropathy or polyneuropathy.

Expected serum CK levels in common myopathies

Normal CK	Congenital myopathy Channelopathies SMA type 1 Myasthenia
Mildly elevated CK (200–1000)	Hyper/hypothyroid myopathies Guillan-Barre syndrome CMT neuropathy
Moderately elevated CK (1000–8000)	Spinal muscular atrophy 2 & 3 Fascioscapulohumeral muscular dystrophy Emery Dreifuss muscular dystrophy Metabolic (e.g primary carnitine deficiency and fatty acid oxidation disorders)
Markedly elevated CK (>8000)	Congenital muscular dystrophy Glycogen storage disease DMD BMD LGMD Polymyositis/dematomyositis rhabdomyolysis Neuroleptic malignant syndrome Malignant hyperthermia

Adapted from reference 9.

Table 1

CPK value	Time course				
	Immediate	Acute	Sub acute	Chronic	Relapsing
Normal			Endocrine	Deconditioning/disuse	
2×	Cramp			Inclusion body myositis	
5×				Polymyositis, chronic	
10×			Polymyositis, acute	Limb-girdle dystrophy	
50×		Trauma		Duchenne dystrophy	Metabolic rhabdomyolysis

Figure 2 Serum CK level and time course of various myopathies. Adapted from reference 9.

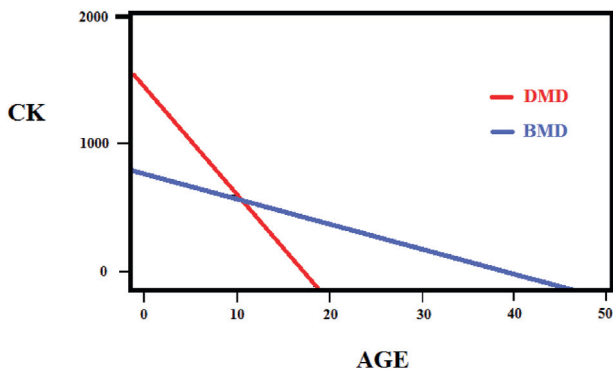


Figure 3 Decrease of serum CK activity as a function of age in DMD, compared to BMD. Reproduced from reference 12 with permission from Springer Nature.

However, in conditions such as spinal muscular atrophy, Charcot-Marie-Tooth disease and Guillan-Barre syndrome there may be an elevation of CK, usually no more than five times normal. One proposed mechanism is damage due to increased work requirement on muscle fibres in weakened muscle. These neuropathies cause denervation of muscle fibres and the

on-going trophic changes to the muscle fibre membrane may result in leakage of CK. Another possibility is elevation of CK secondary to frequent cramping, a common symptom in acute neurogenic diseases such as Guillain-Barre syndrome.^{13,14}

Does a normal newborn screening result for CK exclude a diagnosis of muscular dystrophy?

Creatine kinase (CK) testing on dried blood spots has been attempted as a method of newborn screening (NBS) for DMD. CK is elevated at birth in individuals with muscular dystrophy and CK elevation is then validated by retesting blood at 4–6 weeks of age with subsequent DMD gene analysis to establish a definitive diagnosis.

There is a lag between first symptoms of DMD and diagnosis. In the UK median age at diagnosis is reported to be 4.1 years. In the time it takes for DMD to be diagnosed parents may have had more affected or carrier children and may justify newborn screening (NBS).

NBS for DMD had been used in New Zealand, Edinburgh, Germany, Canada, France, the USA (western Pennsylvania), Wales, Cyprus, and Belgium. Antwerp, Belgium is the only program that maintains NBS for DMD to this day. NBS was stopped in Wales in

November 2011. It has been difficult for programs to justify NBS for DMD because of the lack of evidence that early treatment (e.g. physiotherapy, steroids) improves the outcome of affected newborns. However, the non-medical benefits of early diagnosis have been highlighted. These include identification of behavioural and cognitive issues, avoidance of exposure to harmful interventions (e.g. general anaesthetics) allowing time to make emotional and practical preparations associated with the diagnosis, such as school selection, choice of home and employment opportunities and importantly consider prenatal diagnosis if desired.¹⁵

The Welsh newborn screening programme showed a sensitivity of about 83%, meaning that there is a relatively high rate of false negatives, with about 17% of DMD cases missed. Specificity was high (99.98%). However, the positive predictive value is about 41%, meaning that for every true positive there is roughly one false positive. The negative predictive value of the test is high at 99.997%. The test picked up mainly newborns with DMD, but also a smaller number of newborns with BMD and other dystrophies.¹⁶

Current UK national screening committee policy is that newborn screening for DMD is not recommended.

For newborn screening to be introduced for Duchenne muscular dystrophy, work will be needed to standardize the diagnostic test. At present, different laboratories perform the test differently and for the programme to be successful, the test would need to be consistent across the country. Further research into the screening test for DMD, cost effectiveness, new treatments for DMD, including long term follow up to assess efficacy which may be altered by early diagnosis through newborn screening is recommended.¹⁷

Can CK be used to identifying female carriers of DMD/BMD?

Assay of creatine phosphokinase (CPK) has also been used for the detection of carrier females in families with Duchenne-type pseudohypertrophic muscular dystrophy. However, creatine kinase activity can be normal in about a third of definite carriers and does not exclude the carrier state. CK is higher among young (less than 20 years old) compared to adult (greater than 20 years old) DMD/BMD carriers.

No statistically significant correlation is found between the proportion of skewed X inactivation in blood and serum creatine-kinase levels in Duchenne/Becker female carriers.¹⁸

Female carriers can have similar muscular weakness as affected males and for this reason are termed manifesting carriers. This condition can occur with no known family history of DMD, so all females who are suspected of having any form of muscular dystrophy should be tested to determine if they could be manifesting carriers because of the genetic implications.

It is estimated that at least 10% of female carriers may have problems, which can vary from a mild generalized weakness to an inability to walk, depending on how many muscles are affected. The weakness can be asymmetric. There is also growing evidence that the heart muscle can be affected in isolation, which may not become apparent until later in life.¹⁹ Ideally all known carriers should be assessed at the time of their child's diagnosis. Investigations should include an ECG and a cardiac assessment and possibly a muscle biopsy. General anaesthesia should be

avoided if possible, especially succinylcholine. Anaesthetists should be made aware of patient's genetic status.

Should an asymptomatic child with mild to moderate hyperCKemia have muscle biopsy and EMG?

During routine blood tests for speech or developmental delay elevated CK levels may be identified in patients with no history of weakness. The discovery of a high serum CK, even when asymptomatic or pauci-symptomatic, raises the prospect of an underlying neuromuscular disorder and prompts a referral for further evaluation. Sometimes these children come to attention after they have been evaluated for abnormal liver function, with some even undergoing liver biopsy and later observed to have a raised CK levels, as other enzymes (such as AST) may be released from muscle.

It should be remembered that elevated CK in an asymptomatic child could be an indicator of pre-symptomatic muscle disease or carrier of DMD/BMD. If the serum CK level is elevated more than 10 times the normal levels prompt DNA analysis of the dystrophin gene is warranted, even in otherwise clinically asymptomatic males. The diagnosis of dystrophinopathy in patients with asymptomatic hyperCKemia has implications for cardiac monitoring, anaesthetic risks and genetic counseling. We recommend a muscle biopsy to exclude dystrophinopathy if the CK activity exceeds 5 times the upper limit of the normal range and dystrophin gene deletion is negative.^{20,21}

However, there is consensus on this approach. Some centres will simply monitor progress in asymptomatic children with an unexplained elevated CK level three to ten-times above normal. Depending on clinical context NCS/EMG studies can be helpful to differentiate neuropathies from myopathies causing mild to moderate rise in CK levels before embarking onto muscle biopsy.

If a normal EMG and muscle biopsy is available, the diagnosis of idiopathic hyperCKemia can be made. Idiopathic hyperCKemia (IHCK) is defined by "at least 3 serum CK levels more than twice normal that remain increased over at least 3 months in patients with no evidence of neuromuscular disease". However, in asymptomatic children the diagnostic yield of EMG and muscle biopsy is low and it may not add any benefit. In most cases, pathogenesis is unknown and clinical management is unclear. Though clinically asymptomatic, these subjects with hyperCKemia are potentially susceptible to malignant hyperthermia. With the advances of genetic tests, it is likely that more patients with this condition will have a defined neuromuscular disease or carrier state of such a disease. Hence, these children should be followed up for development of symptoms or signs suggestive of myopathy.²²

Our approach is summarized in [Figure 4](#).

Limitations

Creatine kinase has two main limitations in diagnosing muscular dystrophies, neither of which undermines its clinical value. Firstly, CK is not 100% specific to muscular dystrophies, with increased levels also occurring during various physiological and non-neuromuscular conditions. Secondly, CK levels are not elevated in all patients with dystrophinopathy. Therefore children with normal CK levels, but with a history of myalgia, toe-walking, or proximal muscle weakness should also be considered for the gene analysis for dystrophinopathy.

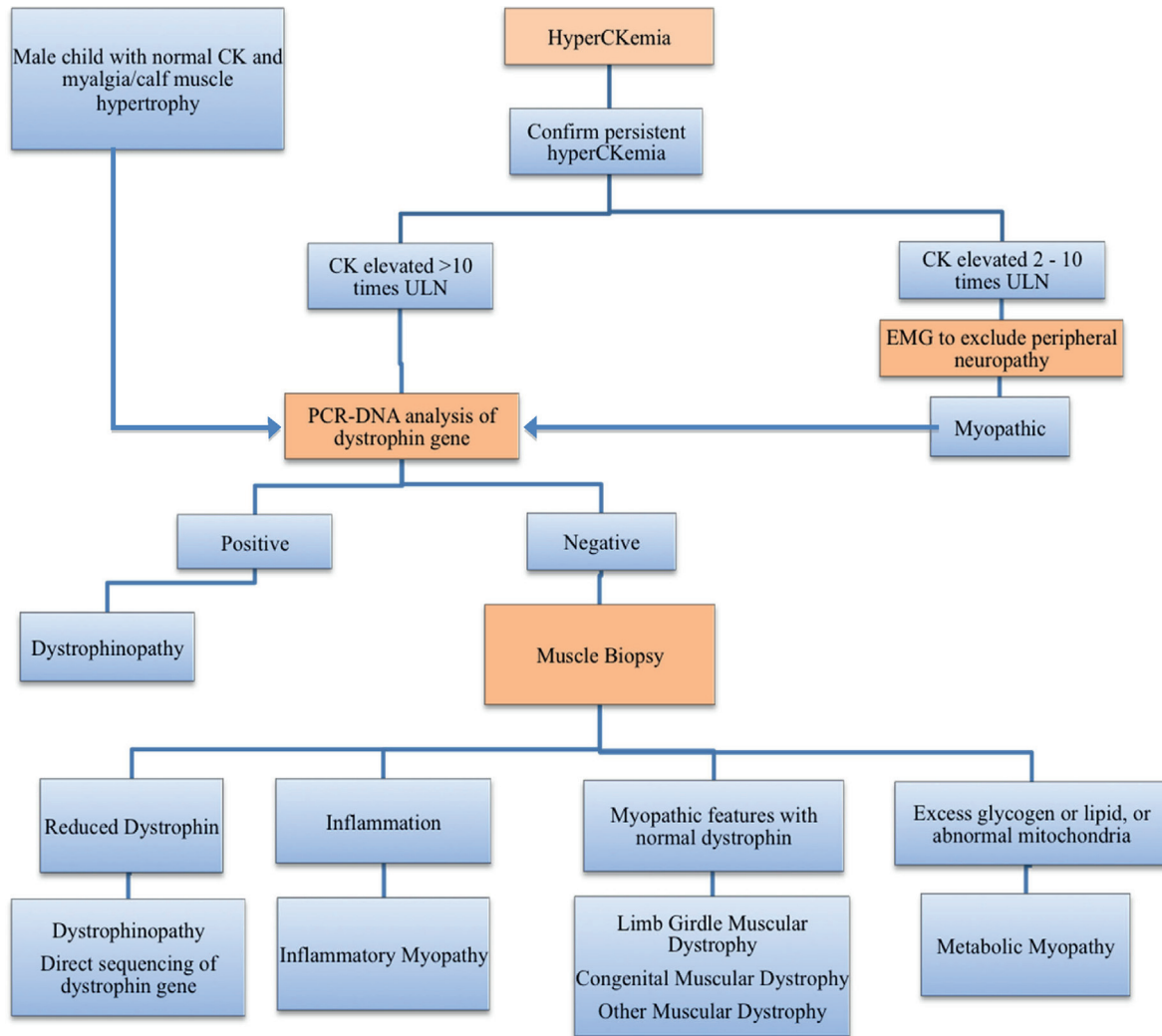


Figure 4 Proposed approach to persistent hyperCKemia in children.

Conclusion

HyperCKemia is defined as a CK level of more than twice the upper limit. For children presenting with this finding we recommend that healthcare professionals consider all non-neuromuscular other non-myopathic causes of hyperCKemia that might explain their high CK.

Before embarking on long and expensive investigations, it is advised that hyperCKemia is confirmed by repeat assay and that the possibility of normal physiological elevation is excluded.

Females with hyperCKemia, because of the possibility of Duchenne/Becker mutation carrier status, should undergo DNA analysis prior to muscle biopsy. Currently, multiple ligation probe amplification analysis will identify 70% of carriers.

Males with hyperCKemia and a CK less than 3 times normal may be offered a biopsy if there are serious concerns about neuromuscular disease. Alternatively they should be followed up in the neurology clinic to oversee any clinical development.

Further investigations may be needed, directed by the biopsy appearance, including western blotting, enzymology and mitochondrial DNA analysis; a frozen sample should be stored at the time of biopsy to be available for such studies.

Clinical bottom lines

- Serum CK is a useful screening test for suspected muscle disorders in children
- Diagnostic challenges occur when symptoms are absent/mild (isolated rise in serum CK levels).
- Elevated CK levels can occur as an incidental finding in healthy individuals and it is important to recognize it in order to avoid unnecessary specialist consultations and investigations.
- Markedly elevated (greater than 10 times ULN) CK levels should prompt dystrophin gene deletion/duplication testing even in clinically asymptomatic males.
- Highest CK levels are seen with conditions in which muscle fibre necrosis occurs, such as dystrophinopathies, rhabdomyolysis, malignant hyperthermia, neuroleptic malignant syndrome and severe polymyositis

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