

# HyperCKemia

Evaluation for elevated creatine kinase is a required skill for neurologists.

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Creatine kinase (CK) is critical for normal energy production in muscle, where it catalyzes creatine and adenosine triphosphate (ATP) to form phosphocreatine and adenosine diphosphate

(ADP). Multiple isoforms of CK are found throughout the body, including skeletal muscle (MM isoform), cardiac muscle (MB isoform), and brain (BB isoform). Some CK leaks from myocytes into the blood under normal physiologic conditions. Normal serum CK level varies by sex and race and is higher in men vs women and blacks vs whites or those of Asian descent.<sup>1</sup> Mean CK values also tend to decrease with age, likely secondary to sarcopenia. Definitions of elevated CK (hyperCKemia) differ in the literature; it is most simply defined as a persistent elevation in serum CK level, at least 2 standard deviations above the mean expected for a given population on at least 2 separate occasions. The European Federation of Neurological Sciences (EFNS) defines hyperCKemia as values more than 1.5 times the upper limit of normal using normative data that factors in gender and ethnicity.<sup>2,3</sup>

Elevation of CK occurs in myopathies, motor neuron disorders, cardiac disease, and trauma. A transient rise in CK levels can also be seen in people who are healthy after unaccustomed or strenuous physical exercise or heavy manual labor.

This article focuses on asymptomatic hyperCKemia, defined as a significant elevation in serum CK levels without a clear cause, symptoms or signs of muscle weakness, or severe exercise intolerance. *Paucisymptomatic hyperCKemia* denotes the presence of nonspecific symptoms (eg, myalgias, cramps, and/or fatigue with physical activity).<sup>4</sup>

## Causes of Asymptomatic HyperCKemia

Asymptomatic hyperCKemia has many causes including underlying systemic disorders, medications, neurogenic disorders (eg, motor neuron disease and rarely generalized polyneuropathies), and asymptomatic or latent myopathies.

### Systemic Diseases

Systemic causes from endocrine (eg, hyperthyroidism, hypothyroidism, or hypoparathyroidism) or connective tissue disorders, metabolic derangements (eg, hyponatremia, hypokalemia, or hypophosphatemia), pregnancy, renal disease,

malignancy, and viral illnesses have all been reported with asymptomatic hyperCKemia. These conditions are important to keep in mind because mild CK elevations in these contexts can be expected and may make further neurologic evaluation unnecessary. MacroCK is a macroenzyme, an enzyme complex with a higher molecular mass than that usually found in serum. MacroCK type 1 is a CK-IgG antibody complex, most often associated with autoimmune disorders and with a prevalence in the general population of about 1%. MacroCK type 2 is thought to be oligomeric mitochondrial CK, often seen in patients with malignancy or hepatic disease with a reported prevalence of 0.5% to 3%.<sup>5</sup> With quantitative serum assays, macroCK is indistinguishable from normal CK and falsely elevates the true CK level. Either form of macroCK can be distinguished from CK with protein electrophoresis, making this a useful test in otherwise unexplained hyperCKemia.

Statins, or 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors, can cause a variety of muscle disorders ranging from asymptomatic hyperCKemia to rhabdomyolysis; occurrence is more common in people with genetic polymorphisms predisposing them to metabolic muscle disease.<sup>6</sup> Other medications that lead to elevation in CK levels include fibrates, isotretinoin, beta-blockers, angiotensin receptor blockers, levetiracetam, clozapine, and hydroxychloroquine. Individuals with mild elevation in CK levels, who are taking these medications, likely need only periodic monitoring of CK values in the absence of symptoms or weakness on examination.

### Myopathies

Several forms of myopathy have been described that cause only CK level elevation without accompanying muscle weakness.<sup>4</sup> These include dystrophic muscle disorders (eg, dystrophinopathies [especially female carriers]) and various forms of limb girdle muscle dystrophies (LGMD) (eg, LGMD1C [caveolin-3], 2A [calpain], 2B [dysferlin], 2D [alpha-sarcoglycan], 2I [fukutin-related protein], and 2L [anoctamin 5]). Myofibrillar myopathies, desmin-related myopathy, and type 2 myotonic dystrophy have also been reported to cause isolated hyperCKemia, as have congenital myopathies including multicore, central core, and centronuclear myopathy.

*Inflammatory Myopathies.* The prevalence of inflammatory myopathies in people with asymptomatic hyperCKemia is relatively low, although there are reports of polymyositis, mac-

rophagic myofasciitis, and inclusion body myositis. The inflammatory myopathies are important to diagnose because of the need for close clinical surveillance due to increased malignancy risk with some and, in the case of polymyositis, the potential benefits of treatment with immunotherapy.

**Metabolic Myopathies.** Metabolic myopathies reported to cause only hyperCKemia include disorders of carbohydrate metabolism (eg, myophosphorylase,  $\alpha$ -glucosidase, phosphofructokinase, and phosphorylase-b kinase deficiencies), lipid metabolism (eg, carnitine palmitoyltransferase type 2 deficiency), purine metabolism (myoadenylate deaminase deficiency), and mitochondrial cytopathies. Mutations in genes encoding the ryanodine receptor (*RYR1* and *CACNA1S*), which are more commonly associated with increased risk of malignant hyperthermia, have also been found in cases of asymptomatic hyperCKemia.<sup>7,8</sup> The risk of malignant hyperthermia in people with hyperCKemia has been addressed in only a few relatively small studies. The 2 largest yielded contradictory results, with demonstrated risks of 5.4% vs 49% for a positive in vitro contracture test in those with asymptomatic hyperCKemia; no participant in either study experienced an episode of malignant hyperthermia, and neither study tested for mutations in *RYR1* or *CACNA1S*.<sup>9,10</sup> Although this leaves the risk of malignant hyperthermia in people with hyperCKemia unknown, it is reasonable to consider genetic testing or, at the very least, alert anesthesiologists to this possibility before administering general anesthesia to a person with otherwise idiopathic hyperCKemia.

### Idiopathic HyperCKemia

Idiopathic hyperCKemia is a diagnosis of exclusion and a syndrome of persistent elevation in serum CK in the context of a normal neurologic examination and ancillary studies, including electromyography and muscle biopsy.<sup>11</sup> Studies have reported that it can be familial. The true incidence of idiopathic hyperCKemia is unknown, but studies suggest that it may affect approximately 1% of the general population.

### Diagnostic Studies

In the largest study of asymptomatic hyperCKemia, a retrospective review of 114 people with either asymptomatic or paucisymptomatic hyperCKemia,<sup>12</sup> 82% were male, mean age 33, and the mean CK level was 1,410 units per L. An EMG was done for 100 of the participants and had normal findings in 43, myopathic findings in 44, and abnormal, nonmyopathic findings in 13. Of the muscle biopsies, 44 were abnormal, of which 20 were diagnostic. The most common diagnoses were dystrophinopathy, partial CPT2 deficiency, and unspecified LGMD. In a follow-up study (mean follow-up duration 7.47 years, range 4-15 years)<sup>13</sup> an additional 6 people were diagnosed; only 1, who was diagnosed with a probable but genetically unconfirmed LGMD, became symptomatic.

In another study,<sup>14</sup> 104 people with asymptomatic or pauci-symptomatic hyperCKemia, 57 had EMG, and 18 had myopathic abnormalities. Muscle biopsy was done in all, and 83 had abnormal findings, 51 of which were diagnostic and 32 nonspecific. A probable or definitive diagnosis was made for 57 participants; the most common were McArdle's disease, dystrophinopathy,  $\alpha$ -glucosidase deficiency, polymyositis, macrophagic myofasciitis, and various forms of LGMD (eg, dysferlinopathy, caveolinopathy, FKRP, or calpainopathy).

Meta-analysis<sup>4</sup> shows 45.7% of EMGs in hyperCKemia were abnormal, ranging from neurogenic to myopathic, but it is unlikely that neurogenic findings completely explained hyperCKemia in many cases. The main question is if EMG is an adequate screening tool prior to more invasive muscle biopsy. Abnormal EMG was seen in 93% of those with abnormal muscle biopsy findings. Conversely, a minority of individuals had normal EMGs followed by abnormal muscle biopsy findings. Although muscle biopsy findings were abnormal in 66.1% of individuals, findings were diagnostic for only 23.3%. The relatively high proportion of nondiagnostic biopsies could be because of variability in skill of the interpreting physician, the quality of the specimens, limitations in testing performed on the specimens, or other factors. It seems reasonable to use EMG in hyperCKemia before muscle biopsy to avoid invasive testing for the few who may be diagnosed with EMG alone.

The likelihood of making a definitive diagnosis in asymptomatic hyperCKemia using EMG and muscle biopsy is about 25% according to the meta-analysis.<sup>4</sup> It should be noted, however, that all of these studies were done before widespread availability of genetic testing that allows for higher diagnostic yields. Certain clinical features in these studies including younger age of onset and higher magnitude of CK elevation tended to predict whether a final diagnosis was made.

A large retrospective review of the diagnostic yield of muscle biopsy in almost 700 people found hyperCKemia alone was poorly predictive of diagnostic muscle biopsy, but weakness, myopathic EMG abnormalities, and hyperCKemia, combined, did correlate with positive biopsy findings.<sup>15</sup> The predictability of diagnostic muscle biopsy increased proportionally to the increase in serum CK level, consistent with previous studies.

### Recommended Diagnostic Workup

In general, and based on the available evidence, the following diagnostic work-up (Figure) is recommended in a patient referred for asymptomatic or paucisymptomatic hyperCKemia. The entire clinical context including age, comorbid medical conditions, family history, and potential genetic implications of a particular diagnosis should be taken into account when pursuing a diagnostic evaluation of asymptomatic hyperCKemia. It is recommended the patient be instructed to refrain from any strenuous physical activity for 7 days before repeating a CK test to ensure elevation was not due to exer-

cise. Both the total CK level and the levels of isoenzyme fractions are needed to confirm that MM isoenzyme from muscle is elevated. If the CK level normalizes after a period of rest, further evaluation is unnecessary. If the MB isoenzyme is elevated, refer the patient to cardiology. If the MM isoenzyme is

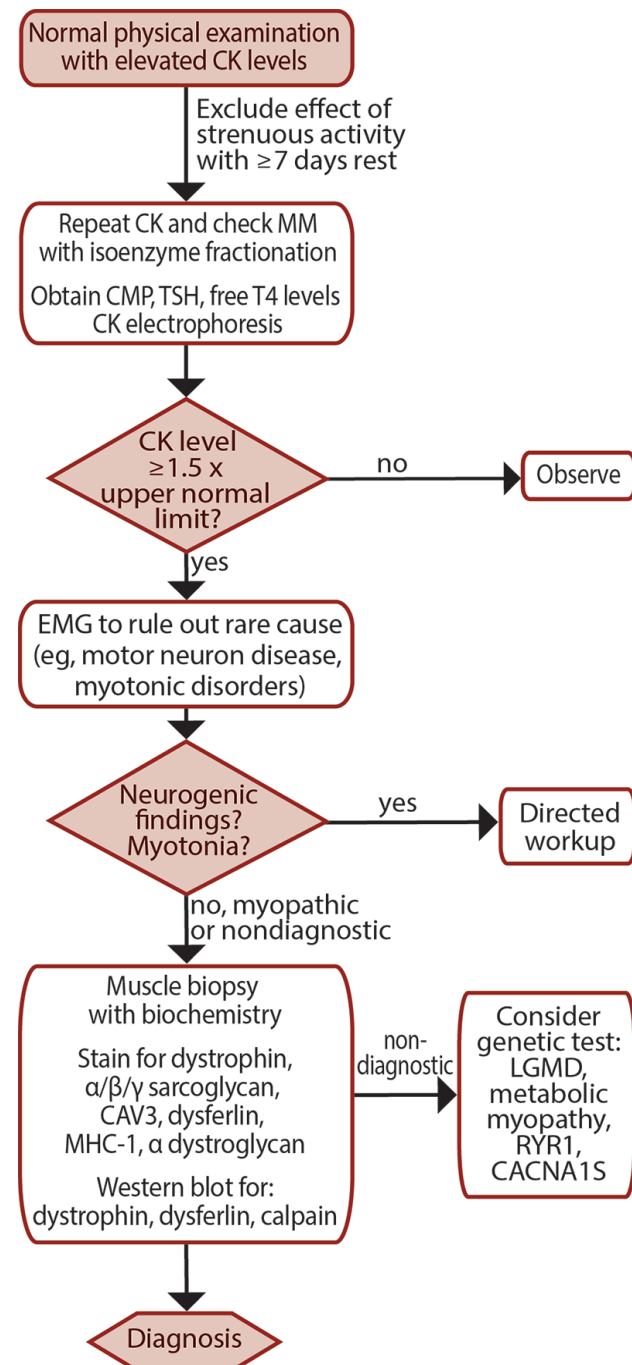


**Figure: Diagnostic Algorithm for Asymptomatic HyperCKemia.** Abbreviations: CK, creatine kinases; CMP, comprehensive metabolic panel; LGMD, limb girdle muscle dystrophies; TSH, thyroid-stimulating hormone.

persistently elevated, the next step is to exclude nonneurologic causes by reviewing medications for drugs known to cause hyperCKemia and order lab tests to exclude systemic causes, including comprehensive metabolic profile, thyroid stimulating hormone and free thyroxine levels, parathyroid hormone level, and CK electrophoresis, the latter to evaluate for the presence of macroCK. If CK levels are not more than 1.5 times the upper limit of normal for gender and race, based on EFNS guidelines (Table),<sup>3</sup> observation with neurologic re-evaluation and repeat CK level testing in 3 to 6 months is suggested. If CK levels are more than 1.5 times the upper limit of normal for gender and race, EMG should be performed to evaluate for disorders known to elevate CK levels, including motor neuron disorders, myotonic disorders, and myopathy. In people who undergo EMG and have either myopathic or nonspecific findings, the next step is muscle biopsy with biochemical analysis and routine staining as well as staining for major histocompatibility complex 1 (MHC-1), dystrophin, sarcoglycan, dysferlin,  $\alpha$ -dystroglycan, and Western blot for dystrophin, dysferlin, and calpain. If these tests are nondiagnostic, genetic testing for LGMD, more common metabolic myopathies (eg, myophosphorylase, CPT2, myoadenylate deaminase deficiencies), and malignant hyperthermia susceptibility (eg, *RYR1* and *CACNA1S* mutations) is recommended in the appropriate clinical context.

## Prognosis

Because the yield of a reasonable diagnostic evaluation in individuals with asymptomatic hyperCKemia is relatively low, several studies have evaluated what the prognosis is after an initial nondiagnostic evaluation. Prospective follow up over a mean of 7.2 years<sup>16</sup> of 23 patients who had been evaluated for elevated CK levels found the magnitude of CK elevation was not significantly changed at follow up. Of these individuals, 70% had normal EMG and 77% had muscle biopsy findings of nonspecific myopathic changes. Only 1 person was diagnosed with an idiopathic chronic sensory axonal neuropathy, determined to be unrelated to elevated CK levels. The authors of this study concluded that long-term follow-up is probably unnecessary in individuals with a normal initial evaluation. A subsequent study from the same group, however, found caveolin-3 mutations in 2 of 29 patients available for follow-up.<sup>17</sup> Considering these and other findings described, it is reasonable to discharge these people with asymptomatic hyperCKemia

**TABLE: ELEVATED CREATINE KINASE NORMATIVE VALUES BY SEX AND RACE**

| Descriptor     | Creatine kinase (CK) (U/L) |
|----------------|----------------------------|
| Black women    | 621                        |
| Black men      | 1,201                      |
| Nonblack women | 325                        |
| Nonblack men   | 504                        |

after a reasonable evaluation, instructing them to return for reevaluation if neurologic symptoms, particularly muscle weakness or exercise intolerance, develop.<sup>13</sup>

## Conclusion

More people with idiopathic hyperCKemia are likely to be found to harbor occult neuromuscular or metabolic disorders as research evolves and new conditions are identified. Until then, evaluation of asymptomatic or paucisymptomatic hyperCKemia will remain a frequent consultation for the practicing neuromuscular neurologist, and knowledge of the appropriate diagnostic evaluation is therefore practical and important. ■

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### Disclosures

The authors report no disclosures.