Approach to the Patient With HyperCKemia

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ABSTRACT

Purpose of Review: Neurologists commonly receive consultation requests regarding the evaluation of patients with an elevated serum creatine kinase (CK), a condition known as hyperCKemia. This article outlines an approach to the history and examination of patients with hyperCKemia in order to narrow the localization and differential of an elevated CK and guide possible next steps. This article aims to help clinicians identify treatable or reversible etiologies as well as those that will change management.

Recent Findings: An unrevealing patient history (assessing for acquired and hereditary etiologies) in an otherwise neurologically intact individual who has a normal nerve conduction study and EMG predicts that the likelihood of diagnosing the patient after further investigations will be quite low. After a comprehensive workup, a positive diagnosis is made in approximately 25% of cases of hyperCKemia.

Summary: The best predictors for added diagnostic yield with further testing in hyperCKemia are a higher level of CK and a younger age; the presence of weakness increases the likelihood of a specific cause other than idiopathic or familial hyperCKemia. Many etiologies do not yet have treatments that alter clinical outcomes, and, even in the absence of a specific diagnosis, good communication with patients and primary care providers remains essential to ensure longitudinal surveillance with expectant management for potential consequences. Many patients with hyperCKemia of uncertain etiology, however, will not develop significant muscle disease on longitudinal follow-up.

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INTRODUCTION

Limited clinical presentations of muscle disease occur (**Table 2-1**). Neurologists commonly receive consultation requests regarding the evaluation of patients with an elevated serum creatine kinase (CK), a condition known as hyperCKemia, regardless of whether associated symptoms and signs are present. An organized approach to the history followed by a thoughtful physical examination narrows the localization and differential for an elevated CK (**Table 2-2**). A useful framework to guide the next steps is to contemplate possible etiologies that are common, life-threatening, or that will change the course of disease management, while also recognizing that many referrals will be for asymptomatic or minimally symptomatic (eg, myalgia, fatigue, stiffness, cramps) patients.

Muscle disease is uncommon; therefore, considering acquired and inherited causes of elevated CK at the outset is essential in order to: (1) identify potentially treatable or reversible causes; (2) avoid exposure to unnecessary toxic medications used in the treatment of, for example, the immune-mediated myopathies; (3) provide appropriate genetic counseling; (4) identify necessary surveillance of cardiac and respiratory function where appropriate; and, ultimately, (5) provide accurate diagnoses.[2]

SERUM CREATINE KINASE

Serum CK reflects muscle membrane integrity and fluctuates with levels of activity. HyperCKemia is therefore a nonspecific marker of muscle damage. CK is an enzyme composed of muscle (M) and brain (B) monomers, resulting in

KEY POINTS

- Serum creatine kinase reflects muscle membrane integrity and fluctuates with levels of activity. HyperCKemia is therefore a nonspecific marker of muscle damage.
- Creatine kinase is an enzyme composed of muscle (M) and brain (B) monomers, resulting in MM, MB, and BB isoenzymes.

TABLE 2-1 Presentations of Muscle Disease

- ▶ Weakness and wasting
- ▶ Muscle pain/myalgia and stiffness/locking
- ▶ Exercise intolerance
- ▶ Myoglobinuria/rhabdomyolysis[1]
- ▶ Neuromuscular respiratory failure
- ▶ Cardiomyopathy or cardiac arrhythmias
- ▶ Hypotonia (in infants)
- ▶ Known family history
- ▶ HyperCKemia[2]

MM, MB, and BB isoenzymes.[2] Detailed knowledge of the underlying biochemistry and physiology is not necessary; in certain clinical presentations, however, it may be helpful to know that CK is essential for buffering cellular adenosine triphosphate (ATP) and adenosine diphosphate (ADP) through a rapid and reversible catalysis of high-energy phosphate bonds early in muscle excitation-contraction coupling. Total serum CK arises largely from skeletal muscle (mainly CK-MM), with minor amounts derived from cardiac muscle.[4] Therefore, elevated CK may be seen with cardiac and skeletal muscle injury that includes muscle, nerve (**Case 2-1**), and motor neuron disorders affecting skeletal muscle. However, myopathies with a normal serum CK occur and, conversely, no clear

TABLE 2-2 Differential for Elevated Creatine Kinase[a]

Potential Source	Examples
Normal	Laboratory values, sex, race, age, **muscle mass**, **physical activity**
Transient physiologic	**Exercise**,[3] **trauma**, seizure, acute psychosis, severe dyskinesia
Symptomatic	
Cardiac	Myocardial infarction, arrhythmia, myocarditis
Neurogenic	**Radiculopathy**, **motor neuron diseases**, multifocal motor neuropathy, mononeuritis multiplex
Myopathic	Acquired
	Myotoxic drugs (eg, **statins**, alcohol, chloroquine, cocaine)
	Endocrine (eg, **hypothyroidism or hyperthyroidism**, hypoparathyroidism, hypophosphatemia)
	Immune/**inflammatory** (eg, polymyositis, inclusion body myositis, immune-mediated necrotizing myopathies)
	Inherited
	Muscular dystrophies (eg, **dystrophinopathies**, facioscapulohumeral muscular dystrophy, limb-girdle muscular dystrophy)
	Myotonic dystrophies
	Metabolic myopathies (eg, **myophosphorylase deficiency**, carnitine palmitoyltransferase type II deficiency, mitochondrial cytopathies)
	Congenital myopathies
Idiopathic	**Sporadic** or familial (eg, caveolin/limb-girdle muscular dystrophy type 1C)

[a] Bolded text indicates most common sources and examples.

Case 2-1

A 48-year-old man was referred for assessment of leg pain and an elevated creatine kinase (CK) of 650 IU/L. He played hockey weekly and ran 5 km to 10 km every other day. He described a 6-month history of intermittent aching pain, primarily in the right calf more than in the left calf, with occasional involvement of the right posterior thigh. He had not experienced any weakness, sensory symptoms, or bowel or bladder dysfunction. The pain limited his enjoyment of running but did not prevent it. He had nocturnal calf and foot intrinsic cramping that had worsened during the past year. The remainder of the neurologic and functional inquiry was unrevealing; pertinent negative signs or symptoms included no pigmenturia and no symptoms of neurogenic claudication. He had a history of episodic low back pain that had not been problematic for several years. He was not on any medications and had never been exposed to a statin.

His examination was notable for asymmetric calves with the right larger than the left and a reduced right ankle reflex, but the patient was otherwise neurologically intact. Nerve conduction studies revealed normal bilateral sural and superficial peroneal sensory responses, reduced right tibial motor amplitude of 4.0 mV (left was 8.9 mV, with the lower limit of normal of 6 mV), and normal and equivalent common peroneal motor responses. Three-segment needle studies, including midthoracic paraspinals, revealed rapidly firing motor units of large amplitude and increased duration in the right medial gastrocnemius and long head of the biceps femoris, with fibrillation potentials and positive sharp waves seen in the gastrocnemius only. The electrodiagnostic studies were consistent with a chronic and active right S1 radiculopathy. An MRI of the lumbosacral spine showed mild degenerative disk disease, with foraminal narrowing and root impingement on the right at L5/S1. The examination, which was only minimally abnormal, supported conservative management, and after discussion with the patient, no surgical referral was recommended.

Comment. Mild elevations in CK (less than five to 10 times the upper limit of normal) may be seen with neurogenic etiologies such as radiculopathies and motor neuron disease. Providing an explanation to the referring physician is often sufficient, and the CK level can serve as a baseline going forward. Not all elevations in CK require intervention.

relationship with the serum CK level and the degree of weakness may exist (**Table 2-3** and **Case 2-2**).

Little agreement exists regarding what constitutes a clinically significant elevated CK. Normal laboratory values rarely consider sex, race, muscle mass, and activity level, which can influence CK levels.[2] The 2010 European Federation of Neurological Societies' guidelines for a diagnostic approach (based on literature review identifying only Class IV studies and expert consensus) to asymptomatic or minimally symptomatic hyperCKemia recommends investigation in patients who have CK levels more than three times the upper limit of normal.[5] The frequency of persistent hyperCKemia in the Norwegian general population older than 30 years of age was 1.3%.[6] A prospective case control study that evaluated these asymptomatic or minimally symptomatic (eg, muscle pain, stiffness, or cramps) participants after 3 days of rest found that 97% had CK values of less than three times the upper limit of normal.[7]

APPROACH TO HYPERCKEMIA

A systematic approach to the history and physical examination of patients with hyperCKemia is useful to narrow the

KEY POINTS

- A useful framework to guide the next steps in the evaluation of the patient with hyperCKemia is to contemplate possible etiologies that are common, life-threatening, or that will change the course of disease management, while also recognizing that many hyperCKemia referrals will be for asymptomatic or minimally symptomatic (eg, myalgia, fatigue, stiffness, cramps) patients.
- Total serum creatine kinase arises largely from skeletal muscle (mainly creatine kinase–MM), with minor amounts derived from cardiac muscle. Therefore, elevated creatine kinase may be seen with cardiac and skeletal muscle injury that includes muscle, nerve, and motor neuron disorders affecting skeletal muscle.
- Serum creatine kinase reflects muscle membrane integrity and fluctuates with levels of activity. HyperCKemia is therefore a nonspecific marker of muscle damage. Elevated creatine kinase may be seen with cardiac and skeletal muscle injury, including muscle, nerve, and motor neuron disorders affecting skeletal muscle.
- Normal laboratory values rarely consider sex, race, muscle mass, and activity level, which influence creatine kinase levels.

TABLE 2-3 Serum Creatine Kinase Levels

Creatine Kinase Fold Increase	Examples of Diagnostic Considerations
Normal	Facioscapulohumeral muscular dystrophy, milder limb-girdle muscular dystrophies, some metabolic myopathies at rest, rarely dermatomyositis
Mild (<5–10 times the upper limit of normal)	Exercise, neurogenic causes, Becker muscular dystrophy, facioscapulohumeral muscular dystrophy, many types of limb-girdle muscular dystrophy, myotonic dystrophy, advanced Duchenne muscular dystrophy, drug-induced, inflammatory myopathies, congenital and metabolic myopathies, congenital myasthenic syndromes
Marked (>20 times the upper limit of normal)	Duchenne muscular dystrophy/Becker muscular dystrophy, some types of limb-girdle muscular dystrophy (eg, types 2B, 2D, 2G) dermatomyositis, immune-mediated necrotizing myopathies, inherited and acquired causes of rhabdomyolysis and myoglobinuria

localization and differential of an elevated CK level and guide possible next steps.

History

Listening to patients' stories and judiciously probing for relevant details of the presenting symptoms will generate hypotheses. To exclude neurogenic, myocardial, and other causes such as metabolic or minor trauma, carrying out a focused neurologic and functional review of systems is helpful so that

Case 2-2

A 21-year-old woman was referred to the neuromuscular clinic by an orthopedic surgeon. The patient had left knee pain, and an MRI of the leg had revealed signal changes in the medial head of the left gastrocnemius. She had had normal developmental milestones, although she had toe walked for several years. She was athletic, played a number of sports, and rated herself ''at the front of the pack'' with respect to her teammates. Her left knee pain had begun insidiously 2 years prior without injury. She had not appreciated any weakness, pigmenturia, or more generalized muscle pain. The knee pain was limiting her ability to play soccer. Her parents were cousins, and she had no history of neuromuscular disorders in her extended family. She was otherwise healthy and not on any medications.

Her examination was remarkable only for a questionable exaggeration of the lumbar lordosis and an inability to hop on her left foot, which she attributed to knee pain. A serum creatine kinase (CK) had not been ordered previously. Her EMG studies revealed myopathic units in the thoracic paraspinals, the hamstrings, and the medial gastrocnemius. The patient's CK was greater than 5000 IU/L. She underwent an open muscle biopsy, which revealed inconsistent dysferlin staining. Molecular testing confirmed she was heterozygous for two deleterious mutations in dysferlin, consistent with a diagnosis of limb-girdle muscular dystrophy type 2B.

Comment. Consanguinity increases the likelihood of an autosomal recessive disorder. A CK level of greater than three to five times the upper limit of normal as well as an abnormal EMG warrants investigation even in the absence of definitive examination findings.

clinicians can look for features related to the limited clinical presentations of muscle disease (**Table 2-1**) and causes of elevated CK (**Table 2-2**). Ultimately, a clinician's goal is to decide whether an elevated CK is symptomatic, if it requires investigation and management, or if it is idiopathic, in which case reassurance and observation are more appropriate.

First, it is important to understand the context and degree of the elevated CK. Not uncommonly, the elevated CK may be an incidental finding during routine blood work. The likelihood of making a specific diagnosis with any subsequent investigation is very low if the following apply: (1) the elevated CK is less than three to five times the upper limit of normal (less than 1000 IU/L), (2) the history is unrevealing, (3) the neuromuscular examination is normal, and (4) no abnormalities appear on the EMG assessment that includes sampling thoracic paraspinals.[2,5,8]

Individuals with insidious myopathies may see themselves as asymptomatic (their ''normal''), and probing for clues is often rewarding. This same information provides reassurance that a mild underlying process will not be missed. Gathering information about pregnancy and perinatal history (eg, fetal movements, feeding, sucking, crying, breathing), developmental milestones (age when first walked, history of toe walking), and athletic ability in school or involvement in sports relative to peers or siblings (front of the pack, average, or back of the pack) may be critical (**Case 2-3**). Family history including a three-generation pedigree, ethnicity, and presence of consanguinity are essential clues not to be missed (**Case 2-2**). Asking questions about relationships in kindreds in which consanguinity may be a cultural norm is usually not perceived as uncomfortable, whereas the converse is generally not true and emphasizes the need to frame the rationale behind the questions.

To determine whether an acute, subacute, or chronic process is involved, details must be teased out about age at onset (childhood, adolescence, early or late adulthood), progression, and functional limitations (if any) that relate to the following specific muscle groups: lower extremity (eg, falling, difficulty climbing stairs, tripping, or catching toes); trunk (eg, inability to roll over in bed or sit up from a lying position); upper extremity (eg, inability to lift arms overhead, fatigue with reaching, reduced grip or manual dexterity); oropharyngeal (eg, coughing or choking with solids, nasal speech, weight loss, recurrent aspiration); facial (eg, inability to whistle, soap in the eyes); ocular (eg, drooping eyelids, blurred vision); or cardiorespiratory (eg, symptoms of ineffective nighttime ventilation, orthopnea, swelling, palpitations, irregular heart beat). Clinicians should ask the patient (and then verify on the physical examination) whether he or she experiences equal involvement side to side, as conditions such as inclusion body myositis may be quite asymmetric. Explore any associated features along with aggravating or alleviating factors (**Table 2-4**).

The social and occupational history, details about current, recently started, or recently stopped prescription medications, over the counter and herbal preparations and supplements, illicit drug use, alcohol, and other potential toxic exposures, and hobbies may yield useful clues. Statins are a common culprit associated with an asymptomatic or mildly symptomatic rise in CK, although a complete assessment remains essential to avoid premature conclusions. For more information, refer to the article ''Toxic and Endocrine Myopathies'' by Hans D. Katzberg, MD, and Charles Kassardjian, MD,[9] in this issue of *Continuum*.

With the genetic era upon us, being aware of atypical, early, or late presentations of inherited disorders is critical,[10] and a dystrophinopathy is an

KEY POINTS

- To exclude neurogenic, myocardial, and other causes such as metabolic or minor trauma, carrying out a focused neurologic and functional review of systems is helpful so that clinicians can look for features related to the limited clinical presentations of muscle disease and causes of elevated creatine kinase.
- The likelihood of making a specific diagnosis of the cause of hyperCKemia with subsequent investigations is very low if the following apply: (1) the elevated creatine kinase level is less than three to five times the upper limit of normal, (2) the history is unrevealing, (3) the neuromuscular examination is normal, and (4) no abnormalities appear on the EMG assessment that includes sampling thoracic paraspinals.
- Family history including a three-generation pedigree, ethnicity, and presence of consanguinity are essential clues not to be missed when diagnosing hyperCKemia.

KEY POINTS

- With the genetic era upon us, being aware of atypical, early, or late presentations of inherited disorders is critical, and a dystrophinopathy is an important diagnosis not to overlook.
- Indolent processes can be relatively asymptomatic. Features such as ptosis, internal rotation of the shoulders, exaggerated lumbar lordosis, steppage gait, scapular winging, axillary creases, or contractures suggest chronicity that increases the likelihood of a diagnosis for the elevated creatine kinase.

Case 2-3

A 52-year-old man was referred to an EMG laboratory for an elevated creatine kinase (CK) of 252 IU/L (upper limit of normal of 180 IU/L) as his family physician wished to start a statin. The EMG revealed mild fibrillation potentials and positive sharp waves with small, polyphasic motor unit potentials in proximal and distal muscles; the report read ''consistent with a myopathy, consider inclusion body myositis given wasted quadriceps.'' The patient was then referred to the neuromuscular clinic for suspected inclusion body myositis. The patient had had insidious difficulty with stairs that had required him to use the railing for the past few years. He could no longer run but was not falling. He had no muscle pain, difficulty swallowing, or difficulty with activities such as buttoning clothing or using keys or utensils. He had had normal developmental milestones, but stated he was always clumsy and ''the last in gym class.'' He described always having skinny thighs and muscular calves. Family history was negative for consanguinity or known neuromuscular disorders; he had one healthy son.

Examination was remarkable for hypertrophied calves and mild (4+) weakness of shoulder external rotators, hip flexors, and extensors. No scapular winging was present. When rising from a chair, he led with his buttocks. His thyroid-stimulating hormone (TSH) level was normal. Given the insidious onset of proximal weakness, the ''irritable'' EMG, and a mild increase in CK, his blood was sent for dystrophin analysis, which revealed deletion of exons 46 to 48, confirming a diagnosis of Becker muscular dystrophy. A referral to genetics was made to reinforce the discussion of risk to his son (none) and potential implications for other family members. Baseline ECG, echocardiogram, and pulmonary function tests were normal. He had biannual follow-up and surveillance for cardiorespiratory complications.

Comment. Without a clear history of an acquired process, clinicians should consider testing for dystrophin prior to muscle biopsy as Becker muscular dystrophy is the most commonly inherited myopathy presenting with proximal symmetric limb-girdle weakness. Be aware of the sensitivity of the molecular test ordered, which can range from 50% to 99%. A negative test does not rule out a dystrophinopathy, and dystrophin immunohistochemistry on muscle biopsy or sequencing of the gene should be considered.

important diagnosis not to overlook (**Case 2-3** and **Case 2-4**). For more information, refer to the article ''The Limb-Girdle Muscular Dystrophies and the Dystrophinopathies'' by Stanley Jones P. Iyadurai, MSc, PhD, MD, and John T. Kissel, MD, FAAN,[11] in this issue of *Continuum*.

Physical Examination

A thoughtful and focused examination tests the hypotheses generated during the history taking. This requires adequate exposure of the patient to facilitate directed observation (ie, inspection, percussion, palpation of muscles alongside the remainder of the neurologic and relevant physical examination) so that the clinician can look for clues that may be associated with the potential causes of hyperCKemia (**Table 2-2** and **Table 2-3**). Observation of posture and gait may be illuminating, even in the absence of clues from the history, as indolent processes can be relatively asymptomatic. Features such as internal rotation of the shoulders (thumbs to hips rather than forward), an exaggerated lumbar lordosis, Trendelenburg or steppage gait, scapular winging, scoliosis, axillary creases, horizontal clavicles, and contractures (eg, neck, elbow, fingers, knees, or ankles) suggest chronicity and increase the likelihood of a diagnosis for the elevated CK.

TABLE 2-4 Associated Features That May Accompany an Elevated Creatine Kinase

- Weakness: an inability to complete tasks or a functional limitation
- Atrophy or hypertrophied muscle
- Muscle pain at rest or during or after exercise/activity (note that isolated muscle pain is rarely neuromuscular)
- Cramps or contractures (note that cramps are most often neurogenic)
- Stiffness or locking of muscles (the delayed relaxation of myotonia), improves or worsens with repetition
- Relationship to exercise; symptoms may occur during or be delayed; can occur with brief duration high-intensity activity or sustained, low-intensity activity; fatigue
- Aggravation or alleviation with diet or temperature triggers
- Pigmenturia that is related to exercise, temperature, fever, diet, fasting, or illness
- General anesthetic; history of malignant hyperthermia, prolonged wean from ventilator
- Shortness of breath (bending over, lying flat, exertional, nocturnal)
- Ineffective nighttime ventilation (morning headaches, nocturnal anxiety, nightmares, memory impairment)
- Systemic symptoms (eg, rash, weight loss/gain, anorexia, fever, chills, night sweats, dry eyes/mouth, arthritis/arthralgia, visual loss, eye pain, cataracts, change in hair/skin texture, gastrointestinal symptoms, photosensitivity)
- Mitochondrial: cognitive involvement, seizures, hearing loss, short stature, diabetes, imbalance

A basic screen includes cranial nerve assessment for ptosis (head tilt, frontalis wrinkling); lid lag or twitch; weakness of the eyes, tongue, facial and oropharyngeal muscles; along with a description of any facial rashes. A systematic evaluation of all muscles including inspection, palpation (texture, atrophy, hypertrophy, fasciculations, rippling, myotonia—spontaneous or provoked), and strength testing will reveal any pattern of involved muscles and whether the process is symmetric or not. An initial assessment should be made of the following muscle groups: facial, nuchal, shoulder girdle, humeral, forearm, hand intrinsic, paraspinal, hip girdle, thigh, leg, and foot intrinsic muscles; evaluation of a complete set of muscles only requires a few minutes. The pattern and asymmetry/symmetry of muscle involvement is most helpful in the localization and diagnostic process (eg, hand and foot intrinsic wasting is most often neurogenic; asymmetric large calf muscles out of keeping with thigh muscles may be an important clue to a dystrophinopathy or to an S1 radiculopathy; preferential involvement of hip adductors may be seen in late-onset Pompe disease, calpainopathy, and Becker muscular dystrophy). More specific assessments may be tailored to the working diagnosis such as examining joints and listening for adventitious respiratory sounds with autoimmune/connective tissue disorders.

Functional testing is always useful, and in particular may identify subtle weakness not picked up with formal strength testing. Depending on the hypothesis, the clinician can have the patient rise from a chair or the floor,

KEY POINTS

- A systematic evaluation of all muscles including inspection, palpation (texture, atrophy, hypertrophy, fasciculations, rippling, myotonia–spontaneous or provoked), and strength testing will reveal any pattern of involved muscles and whether the process is symmetric or not.
- Functional testing is always useful, and in particular may identify subtle weakness not picked up with formal strength testing.

Case 2-4

A 42-year-old woman was referred for an asymptomatic elevated creatine kinase (CK) (approximately 2500 IU/L) with a normal thyroid-stimulating hormone (TSH) level. She was active, athletic, and worked out at the gym four to five times per week (a mixture of cardiovascular and light resistance weight training) without any functional limitations, myalgia, or pigmenturia. The patient's developmental and family history were unrevealing. She was healthy and was not taking any medications. She was a nonsmoker, enjoyed two to three glasses of wine per week, and did not use illicit drugs. Her neurologic and general physical examination was normal. After the initial assessment, the plan was to check random CK levels before and after usual exercise in addition to after a period of 1 week in which she would not exercise.

She had her electrodiagnostic studies the same day after the consultation, which revealed small-duration, low-amplitude early recruiting motor units and mild muscle membrane irritability and brief runs of unsustained fibrillation potentials only in the thoracic paraspinals with normal studies in the deltoid, bicep, flexor carpi radialis, iliopsoas, gluteus medius, vastus lateralis, and tibialis anterior. Based on the abnormal EMG findings, her blood was sent for dystrophin analysis, confirming a pathogenic deletion consistent with a dystrophin carrier. Genetic referral was made. Dystrophin carriers may have a normal CK or an elevated CK with or without myalgia. With 10% of carriers becoming symptomatic, she underwent baseline cardiorespiratory investigations, which were normal.

Comment. A CK value of greater than 10 times the upper limit of normal without clues from history or examination but with an abnormal EMG suggesting myopathy warrants dystrophin analysis. Dystrophin is the most likely explanation in these patients based on probability alone. The autosomal metabolic myopathies are less common.

elevate arms overhead, walk on heels and toes, hop on either foot, and perform an unassisted sit-up. The clinician can also note the time it takes the patient to walk 10 meters or climb four stairs, and can measure the patient's grip strength with a hand-held myometer. An abnormal examination supports the clinical suspicion of an underlying process causing the elevated CK. Similarly, an entirely normal examination that is associated with an unrevealing history lowers the diagnostic yield, but yet does not completely rule out an underlying explanation (**Case 2-4**).

Investigations

Health care costs have risen dramatically. It is imperative that physicians use a systematic approach in selecting relevant investigations aimed at the most likely diagnosis with consideration of how management will be affected. It is equally important to recognize that answers may not be possible (eg, availability of tests, patients' wishes [**Case 2-5**]), disease-modifying treatments may not be available even if an etiology is identified (eg, limb-girdle muscular dystrophy, facioscapulohumeral muscular dystrophy), and a focus on management of or surveillance for potential life-threatening consequences might be more appropriate (eg, cardiac arrhythmias, cardiomyopathy, chronic respiratory failure). If possible, electrodiagnostic studies should be done before laboratory tests, as an unrevealing history, a normal examination, and a normal nerve conduction study and EMG make the diagnostic yield of further investigations quite low. The negative predictive value of a normal EMG is reasonably good at approximately 75% in this setting.[5,8] Expectant management

Case 2-5

A 43-year-old man was referred for an asymptomatic elevation in creatine kinase (CK). He had had normal developmental milestones and had played basketball on a scholarship in college. No myalgia, cramps, or pigmenturia had occurred during or after physical activity. He climbed stairs easily to his third-floor apartment. The patient had had no exposure to myotoxic medications or substances, and his family history was unrevealing. Neurologic and systemic examination was normal. He had well-developed musculature without hypertrophy or atrophy. The patient's CK was 968 IU/L to 1494 IU/L (upper limit of normal of 180 IU/L) regardless of activity level. Thyroid-stimulating hormone (TSH) level was normal, and dystrophin polymerase chain reaction (PCR) (70% sensitive) was negative. Baseline cardiorespiratory investigations were normal. He did not wish to pursue muscle biopsy or further investigations. His examination remained normal at follow-up visits for the next 10 years.

Comment. Patient preferences guide investigations and management. In this case, the possibility of a mild dystrophinopathy or other hereditary myopathy remains, in addition to hyperCKemia of uncertain etiology. Longitudinal surveillance and expectant management is reasonable in the absence of any new or progressive symptoms and signs with cardiorespiratory tests repeated every 5 years.

KEY POINT

■ Essential blood work for patients with an elevated creatine kinase includes thyroid-stimulating hormone, as thyroid dysfunction is readily treatable. Obtaining blood work during vigorous exercise, mild activity, and after 5 to 7 sedentary days can be useful in determining whether the creatine kinase nadir is normal or always elevated.

would be reasonable if the elevated CK is less than approximately 1000 IU/L and thyroid-stimulating hormone (TSH) level is normal. If the CK is greater than 1000 IU/L, having a discussion and considering further investigations is a practical next step (**Case 2-2** and **Case 2-4**).

Depending on the working diagnosis after the clinical assessment, obtaining the serum CK levels of family members may be informative and provide support for a familial or hereditary process. Similarly, if the hyperCKemia is related to exercise, obtaining blood work during vigorous exercise, mild activity, and after 5 to 7 sedentary days (at which time the CK would be expected to normalize) can be useful in determining whether the CK nadir is normal or always elevated.[1] Essential blood work includes checking TSH as thyroid dysfunction is readily treatable (**Case 2-6**). If EMG abnormalities are found, molecular testing for dystrophin must be considered, with dystrophinopathies a likely cause of an asymptomatic to mildly symptomatic hyperCKemia (**Case 2-4**), and a blood draw is less invasive than a muscle biopsy. Additional blood work will be based on the history and examination and might include serum calcium, magnesium, phosphate, C-reactive protein, and a connective tissue screen with supplementary tests added as required (eg, serum lactate or acylcarnitine). A nonischemic forearm exercise test for glycogen disorders is best handled in an experienced center as it can be technically challenging. Myophosphorylase deficiency is readily identified on muscle biopsy, although proceeding directly to genetic testing for *PYGM* mutations in classic presentations with a second wind phenomenon is less invasive.[1] For more information, refer to the article ''Metabolic Myopathies'' by Mark A. Tarnopolsky, MD, PhD,[12] in this issue of *Continuum*.

Checking a serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) may be beneficial to preempt any consideration of liver disease in an otherwise asymptomatic individual. AST and ALT are also found within muscle and are generally elevated proportionately to the elevation of CK. Rarely, a patient will present for a

KEY POINT

- EMG studies must sample several proximal and distal muscles in an arm and leg as well as the thoracic paraspinals. The thoracic paraspinals are frequently abnormal, are unaffected by degenerative disk disease, and rarely may be the only abnormal muscle sampled in the workup of patients with an elevated creatine kinase that ultimately results in a specific diagnosis.

Case 2-6

A 56-year-old man was referred for possible myotonic dystrophy. He presented to a community neurologist with a head drop that had developed during the past 8 months. He was otherwise healthy and took no medications. The patient's developmental history was unremarkable, and he rated himself average at sports as a younger man. He denied muscle pain, pigmenturia, or any functional limitations. The patient had not experienced any changes in appetite or weight and had not had any myotoxic exposures such as statins or unhealthy alcohol use. He had no family history of neuromuscular disorders.

Examination was notable for male pattern baldness and a head drop with relatively preserved strength (4+) of neck flexion and extension. The patient had no ptosis or lid lag and had full extraocular movements. He had very mild weakness of shoulder abduction and hip flexion and questionable delayed relaxation on grip and percussion myotonia testing. When rising from a chair he led with his buttocks without using his arms. His nerve conduction study was normal, and the EMG revealed marked fibrillation potentials, positive sharp waves, complex repetitive discharges, and myotonia in all muscles sampled. Molecular testing was negative for myotonic dystrophy types 1 and 2. Subsequently, a creatine kinase (CK) draw revealed an elevated CK of 6000 IU/L. The CK level was too high for myotonic dystrophy, and thyroid-stimulating hormone (TSH) analysis was ordered, which came back markedly elevated at 97 mIU/L (the upper limit of normal being 5 mIU/L). He was diagnosed with a hypothyroid myopathy and was started on replacement therapy with gradual improvement over the next 6 months.

Comment. Clinicians should always order a TSH when the CK is elevated as thyroid myopathies are treatable.

neuromuscular workup after he or she has had a normal liver biopsy.

Electrodiagnostic studies are helpful in confirming clinical localization to motor neuron, root, nerve, or muscle and supplement the history and examination. Normal studies do not exclude a myopathy, however, and EMG is rarely diagnostic by itself. Motor and sensory nerve conduction studies are frequently normal in myopathies, and needle studies sampling several proximal and distal muscles in an arm and leg (including clinically affected and unaffected muscles) as well as the thoracic paraspinals provide the most information.[13] In the author's experience, the thoracic paraspinals are frequently abnormal, are unaffected by degenerative disk disease, and rarely may be the only abnormal muscle sampled in the workup of patients with an elevated CK that ultimately results in a specific diagnosis (**Case 2-4**). In addition to the underlying pathophysiology (myopathic or neurogenic), abnormal needle studies identify a muscle to biopsy (avoid the site needled for at least 3 months or biopsy the other side if considering a treatable immune-mediated myopathy) and can reveal muscle membrane instability/necrosis (fibrillation potentials, positive sharp waves) or chronicity (myotonia, complex repetitive discharges). Caution is needed in interpretation, however, as small motor units recruited early associated with fibrillation potentials and positive sharp waves may be seen with immune-mediated as well as toxic, endocrine, and hereditary myopathies.

Synthesizing information from the history, examination, and electrodiagnostic studies into a working clinical diagnosis will then guide any additional investigations, such as MRI of the lumbosacral spine in the case of an S1 radiculopathy (**Case 2-1**) or blood work for molecular diagnosis in muscular dystrophies (eg,

tests for dystrophin, facioscapulohumeral muscular dystrophy, myotonic dystrophy types 1 and 2, and oculopharyngeal muscular dystrophy are readily clinically available), and it is reasonable to order a dried blood spot screening for late-onset Pompe disease when looking to support a working diagnosis of this disorder. Otherwise, a muscle biopsy is the next step.[13] Even with the absence of clues from the history and examination, if the CK level is greater than three to five times the upper limit of normal, and the patient is younger than 30 years of age, and/or the EMG is abnormal, a muscle biopsy could be considered[2,5,14,15] after dystrophin DNA analysis has been completed. The greatest yield on muscle biopsy, however, is with proximal weakness, an elevated CK, and an abnormal EMG.[13] It is important to recognize that the pathology may reveal nonspecific myopathic changes in the majority of asymptomatic or mildly symptomatic hyperCKemia cases.[15] After a comprehensive workup, a positive diagnosis is ultimately made in approximately 25% of cases of hyperCKemia[2,5] with weakness increasing the diagnostic yield up to approximately 75%.[13]

CONCLUSION

HyperCKemia is a relatively common reason for consultation requests, and even mildly elevated values may be of concern to the general practitioner and patient. An organized approach to the initial history, examination, and investigations will determine whether clues indicate an underlying diagnosis that will identify an etiology or change in management. Considering common etiologies alongside diagnoses that are potentially life limiting or have implications for family members will guide decision making. In the event of an unrevealing history and a normal examination and EMG, the diagnostic yield of further investigations is very low. The higher the CK level and the younger the patient is, the better chance that further testing will result in a specific diagnosis. Patients may very well have an idiopathic or familial hyperCKemia. Some individuals will not wish further investigation (**Case 2-5**).

In the absence of a specific diagnosis, good communication with patients and primary care providers is essential for longitudinal surveillance, with expectant management for potential consequences of an as yet undiagnosed etiology. It would be reasonable in all such patients to ensure anesthetic precautions as there are hereditary myopathies that carry an increased risk of malignant hyperthermia. Finally, many individuals will have hyperCKemia without a specific etiology determined and will not develop significant muscle disease on longitudinal follow-up, which is useful information to discuss with patients.[8]

KEY POINT

- After a comprehensive workup, a positive diagnosis is ultimately made in approximately 25% of cases of hyperCKemia, with weakness increasing the diagnostic yield of biopsy and genetics to approximately 75%.

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