Creatinine Kinase: A test done from muscle memory or clinical reasoning?

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Introduction

Creatinine kinase (CK) is a common lab ordered by generalists and specialists that is often misinterpreted. Given its prevalent use, we highlight a case that outlines pitfalls of the test. The case is of a gentleman who is referred to a neuromuscular clinic for weakness and an elevated CK. However, during the COVID-19 pandemic, this was initially a video visit, which then serves to highlight the challenges of video visits. In this report, we primarily aim to highlight an algorithm to evaluate CK in the presence of weakness. Secondary objectives include reviewing common pitfalls of CK testing, especially with the rising trend of video visits.

Practically, total CK enzyme activity (IU/L) is measured with a photometric assay utilizing the enzymatic rate method to calculate the rate of phosphate transfer from phosphocreatine to adenosine diphosphate per minute. Tissue isoform assays fractionate total CK using antibodies to CK-MM (skeletal muscle), CK-MB (cardiac muscle), or CK-BB (brain). Male sex, black race, younger age, and exercise are the most common reasons for normal physiologic increases in CK, possibly due to differences in muscle or total body mass and the permeability of the sarcolemma to CK.[1-3] Exercise causes transient increases in CK over 24-48 hours, followed by return to baseline over 7+ days.

Pathologic CK elevation is associated with myopathies or muscle injury, but can also occur in neurogenic disorders due to impaired muscle membrane integrity secondary to muscle degeneration from axonal loss.[4-6] Other causes of CK elevation include race, medication use, systemic disorders (e.g. acute renal failure, malignancy, viral illness), and endocrine abnormalities.[4, 5, 7] Of these, statin-induced CK elevation is most commonly observed.[3]

In clinical settings, assay manufacturers provide a CK reference range assuming a gaussian distribution (0-180 IU/L). This results in high false-positive rates as population CK distribution is skewed toward higher values.[5] For this reason, recent practice guidelines recommend using a upper limit of normal (ULN) threshold at the 97.5th percentile rather than manufacturer-quoted ULN (**Table 2**).[2,4,7,8] Using these guidelines, the prevalence of incidentally elevated CK in asymptomatic patients is 5.3%, with persistent unexplained elevation in 1.3%.[9] CK elevation can vary based on sex. In a cohort of musculoskeletal patients with elevated CK 29% were female (F) and 44% were male (M). Sensitivity using the 97.5th percentile versus manufacturer's guidelines was 29%(F)/60%(M) versus 50%(F)/80%(M) and sensitivity was 80%(F)/80%(M) versus 70%(F)/67%(M), respectively.[4] When using a cutoff of 1.5xULN instead of the 97.5th percentile, sensitivity for diagnosing myopathy decreased by 37%. CK > 1000 IU/L had a high likelihood for myopathy (11.0).[6,7] Thus, increasing the ULN improves specificity and decreases the false positive rate when evaluating CK elevation.[1,6,7] The cost of total CK to Medicare is $6.51. Total CK with isoenzymes is $13.39.

Case

A 72-year-old man with peripheral neuropathy and lumbosacral polyradiculopathy presented for a video visit with gradually progressive voice hoarseness, weakness, and an elevated CK over the past two years. Three years prior to his visit, he began having difficulty climbing stairs, making a closed fist, and standing from a seated position due to knee buckling. His symptoms progressed to include a right foot drop, right greater than left leg weakness with quadriceps atrophy, and left greater than right hand weakness with volar forearm atrophy, all evident on video examination. He denied dyspnea, pain, cramps, fasciculations, and fluctuations. Laboratory results are shown in **Table 1**. Previous magnetic resonance imaging of the spine showed multilevel cervical and lumbar degenerative changes without spinal cord signal changes.

Table 1. Patient's Laboratory Values

Laboratory Test	Patient's Values	Reference Value or Range
Creatine kinase (IU/L)	498	0-180
Thyroid stimulating hormone (mIU/L)	1.6	0.5-5
Vitamin B12 (pg/mL)	565	190-950
Vitamin D (ng/mL)	normal	20-40
Erythrocyte sedimentation rate (mm/h)	9	0-15 mmol/h
Serum protein electropheresis with immunofixation	Normal	N/A

Table 2: Upper limit of normal (IU/L; 97.5th percentile) for CK based on the current literature; *1.5 x 97.5th percentile of Brewster et al

	Manufacturer[4]	Brewster[8]	Kyriakides/EFNS*[7]	George[2]
Male	174			
Black		801	1201	1001
Non-black		336	504	
White				382
Hispanic				572
Asian				520
Female	140			
Black		414	621	487
Non-black		217	325	
White				295
Hispanic				279
Asian				194

This visit occurred early during the COVID-19 pandemic where in-person visits were very limited. While an in-person examination was clearly the most appropriate next step, other options were discussed with the patient including obtaining electrophysiologic and laboratory studies first. We jointly elected to have an in-person visit first, which clarified his diagnosis.

Discussion

An elevated CK in an elderly man with bulbar symptoms and chronic progressive, asymmetric distal arm and proximal leg weakness suggests a neuromuscular disorder, specifically inclusion body myositis (IBM); however, his pace of progression was too fast for such a diagnosis. An in-person physical exam is the best next step to narrow the broad differential associated with an elevated CK and weakness, especially since CK is not specific to primary myopathic processes.

The algorithm to evaluate CK (**Figure 1**) first branches based on the presence of weakness. The pattern of weakness can establish risk factors for physiologic or toxic etiologies and help localize pathology along the motor unit. Myopathies typically present with symmetric, proximal weakness, with some exceptions (e.g. IBM and facioscapulohumeral dystrophy). Non-myopathic neurogenic etiologies should also be considered. Fluctuating or fatigable weakness points toward a neuromuscular junction disorder, whereas cramps, fasciculations, sensory symptoms, or weakness in the distribution of specific nerves suggest a neurogenic etiology (e.g. peripheral neuropathy, radiculopathy, plexopathy, or motor neuron disease (MND)). EMG is a tool for localization within the peripheral nervous system. Tests to identify the specific cause of CK elevation include antibody testing, muscle biopsy, and/or genetic testing.

The patient's exam revealed lower motor neuron signs: diffuse fasciculations in the arms/abdomen/legs, reduced reflexes, and asymmetric extremity weakness. He had upper motor neuron (UMN) signs: increased muscle tone in the legs with the presence of the Babinski sign. He had spastic-flaccid dysarthria. By the Awaji Criteria, the patient had clinically probable ALS. To confirm, EMG was performed showing widespread active denervation changes, including in the thoracic paraspinal muscles, with additional reinnervation changes in the cervical and lumbosacral regions. Given the diagnosis of ALS, CK was not checked again. In one series of 30 patients with ALS, CK was elevated in 43% of patients with a CK range of 5-423 U/L. CK level was higher in limb onset rather than bulbar onset ALS, but did not significantly differ based on disease duration or severity[11]. He was treated symptomatically.

In subsequent visits, the patient's strength worsened, and he developed an upper motor neuron sign in the cervical region (positive Hoffman's sign in the right hand), confirming the diagnosis of ALS. He passed away 4 years after symptom onset. The case highlights that the work-up for an elevated CK begins with the history to identify potential risk factors and the exam to characterize strength. CK evaluation has several pitfalls, most important being that the ULN is physiologically higher than the manufacturer-provided reference limits, and varies by age, sex, race, and activity-level. Importantly, elevated CK, with or without weakness, has a broad differential diagnosis, including several non-myopathic causes such as neurogenic etiologies. Lastly, as video visits become more common, significant challenges

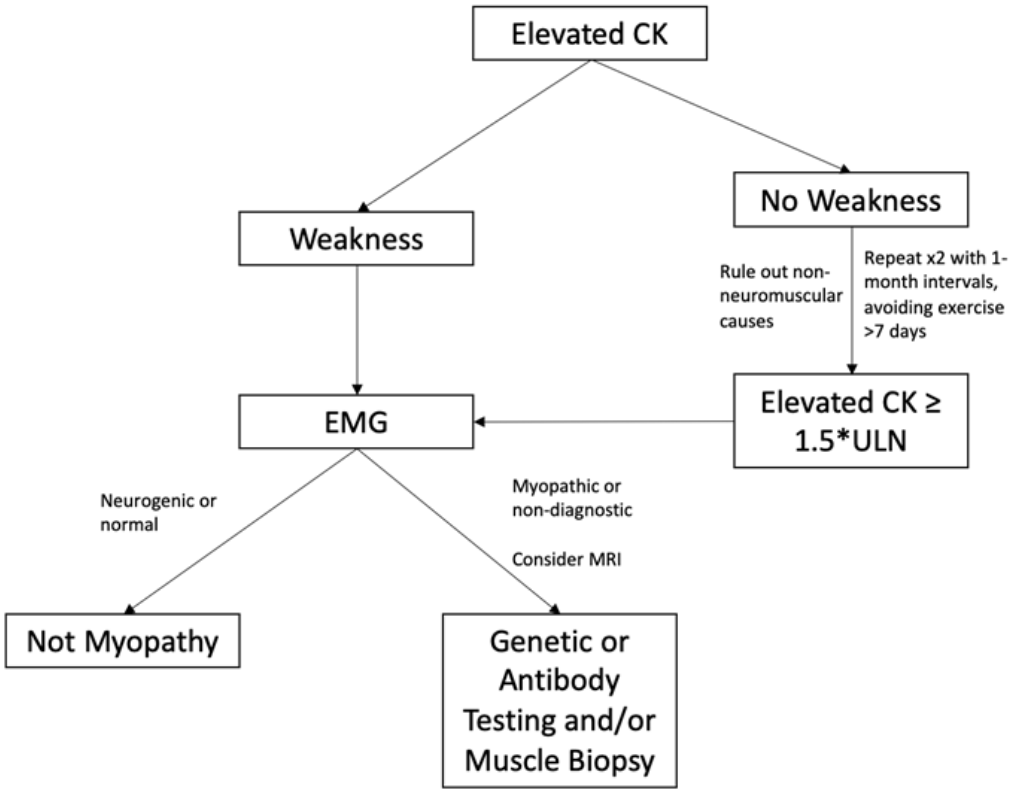

Figure 1: Approach to evaluating an elevated CK.

are increasingly encountered by neuromuscular specialists. While gross motor function and laboratory/imaging results can be reviewed, it is challenging to objectively assess sensation, muscle strength, and function without an in-person physical exam. While we navigate clinical practice through virtual platforms, we are once again reminded that our physical exam is indispensable.

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