Duchenne Gene Carrier as Cause of Asymptomatic HyperCKemia

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Asymptomatic hyperCKemia can be a clinical challenge for physicians, although its long-term prognosis seems benign. The causes usually include heavy exercise practice, muscle injury, drug-induced myopathy, chronic alcoholism, hypothyroidism, clinically silent myopathies, and susceptibility to malignant hyperthermia. A frequently missed cause in women is the carrier status of the Duchenne muscular dystrophy.

We report a case and discuss its investigational approach.

CASE

A 15-year-old girl was referred to us with asymptomatic hyperCKemia after an extensive prior investigation. The hyperCKemia was found after liver enzymes had been found mildly elevated during a fever work-up. There was no history of exercise intolerance, muscle injury, neuromuscular disease in the family, myotoxic drug use or personal and family history of anesthetic complications. She has an asymptomatic brother as well as no other family member has any history of neurological disorders. Resting CPK levels varied from 500 to 1400 U/L in the last three years. An electrophysiological study showed mild chronic myopathy represented by normal nerve conduction studies, no abnormal spontaneous activity, and moderate amount of polyphasic small amplitude and short duration motor unit potentials (MUP) with early recruitment (Fig 1). An extensive laboratory work-up was normal including CBC, sedimentation rate, ANA, TSH, free T4, PTH and electrolytes. A muscle biopsy performed in other medical center showed non-specific myopathic changes and a diagnosis of myotonic myopathy had been proposed, despite the absence of clinical or electrophysiological myotonia and negative genetic testing. A deletion in the exons 46-47 of the dystrophin gene was detected by Southern-blotting and PCR techniques. The CPK levels in other family members were normal. A cardiologic evaluation including routine as well as 24-hours electrocardiogram and echocardiogram were normal. Further genetic study in family members was denied. Genetic counseling and clinical follow-up are being provided on a regular basis.

The patient parents have agreed with this publication.

DISCUSSION

Idiopathic hyperCKemia (IH) is defined as elevated serum CK and no clinical, electrophysiological or pathological evidence of neuromuscular disease. Further exclusion criteria accepted nowadays include thyroid and parathyroid disease, pregnancy, muscle injury, heavy physical activity, family history of neuromuscular disease and use...
of myotoxic medications. Some authors believe that the diagnosis of IH only can be made after a normal muscle biopsy. Our patient did not fulfill the criteria for IH, since she had non-specific myopathic changes in the needle EMG and muscle biopsy. A better term to be used in this context could be “asymptomatic pathologic hyperCKemia.” In fact, most patients with persistent asymptomatic elevated CPK levels have an underlying muscle disease, usually with a benign course, although in a minority of cases the abnormality can precede an ominous neuromuscular disease. Our patient had received a diagnosis of myotonic dystrophy in other medical center based on the presence of excessive central nuclei in the muscle biopsy, despite the absence of clinical and electrophysiological myotonia and negative genetic testing for myotonic dystrophy.

Two usually underdiagnosed conditions associated with idiopathic or “asymptomatic pathologic” hyperCKemia are malignant hyperthermia susceptibility and dystrophin gene carrier status. Less frequently, caveolin-3 gene mutation and absence of dysferlin and sarcoglycans are found in patients with asymptomatic hyperCKemia, as well as patients with neuroacanthocytosis syndromes, including autosomal-recessive chorea-acanthocytosis and X-linked McLeod syndrome. In all these diseases, the CK elevation can predate by many years the neurological symptoms.

Malignant hyperthermia (MH) is a rare autosomal dominant disease associated with halogenated anesthetics and depolarizing neuromuscular blocking agents use. A study found MH susceptibility in half of patients with possible idiopathic hyperCKemia and recommended the caffeine-halothane contracture testing in all asymptomatic patients who undergo muscle biopsy due to persistently elevated CPK. Just a few centers in Brazil are able to perform this procedure.

Duchenne carrier status occurs in women with or without family history of Duchenne muscular dystrophy. Only a minority of them have “important weakness” and, when it is present, they are coined “manifesting genetic carriers.” Elevated CPK levels occur in up to 70% of carrier women of dystrophin gene. Dystrophin immunohistochemical staining should be included in the routine muscle biopsy.

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Fig 2. Suggested approach to the asymptomatic hyperCKemia.
study in patients with hyperCKemia to rule out Becker muscular dystrophy in men or dystrophin gene carrier status in women, regardless of family history. Typical findings include partially dystrophin-deficient fibers and mosaic pattern (dystrophin positive and dystrophin negative fibers) of staining. If such staining had been done in the muscle analysis of our patient, the correct diagnosis could have not been missed.

Genetic analysis of common deletions in the dystrophin gene is a feasible alternative to avoid muscle biopsy in patients with hyperCKemia. Molecular techniques detect carriers and permit prenatal diagnosis in 95% of the patients. The dystrophin gene is localized at the chromosome Xp21 and has 79 exons. About 70% of the patients have intragenic deletions of one or more exons, usually at the proximal or central regions of the gene. The deletions can be detected by PCR or Southern blotting using the patient’s blood. The diagnostic confirmation of the carrier status in females is hard by the presence of a normal copy of the gene in the other X chromosome and the relatively high incidence of point mutations. Another alternative is performing a DNA based linkage analysis using several polymorphic intragenic short tandem repeat markers. This method is a powerful helper in the diagnosis of the carrier status detection of deletional as well as non-deletional dystrophinopathy families. However, it requires a blood sample of the proband and other family members. In suspected patients with negative genetic tests, a muscle biopsy with dystrophin immunohistochemistry is indicated.

In dystrophin gene carrier women, periodid cardiologic evaluation is indicated, since some patients can show abnormalities in heart conduction and function. In the majority of the carriers cardiac abnormalities are asymptomatic, but close monitoring is recommended.

A suggested step by step approach for asymptomatic hyperCKemia can be seen in the Figure 2. When all such work up is negative, asymptomatic hyperCKemia is reasonable and the patient can be assured that the prognosis is benign.

REFERENCES