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EFNS GUIDELINES/CME ARTICLE

EFNS guidelines on the diagnostic approach to pauci- or asymptomatic hyperCKemia

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Objective: To provide evidence-based guidelines to general neurologists for the assessment of patients with pauci- or asymptomatic hyperCKemia.
Background: Recent epidemiologic studies show that up to 20% of 'normal' individuals have an elevated creatine kinase activity in the serum (sCK). The possibility of a subclinical myopathy is often raised, and patients may be unnecessarily denied treatment with statins.
Search strategy: Electronic databases including Medline, the Cochrane Library and the American Academy of Neurology were searched for existing guidelines. Articles dealing with series of patients investigated for asymptomatic/pauci-symptomatic hyperCKemia and articles dealing with myopathies that can present with asymptomatic hyperCKemia were identified and reviewed.
Results: The only guidelines found were those approved by the Italian Association of Myology Committee, and the only relevant articles identified describe class IV studies.
Recommendations: HyperCKemia needs to be redefined as values beyond 1.5 times the upper limit of normal (which itself needs to be appropriately defined). Pauci- or asymptomatic hyperCKemia with no apparent medical explanation may be investigated with a muscle biopsy if one or more of the following are present; the sCK is ≥3× normal, the electromyogram is myopathic or the patient is < 25 years of age. In addition, women with sCK < 3 times normal may be offered DNA testing because of the possibility of carrying a dystrophin mutation.

Objective

To provide evidence-based guidelines for the assessment of patients with pauci- or asymptomatic hyperCKemia.

Background

The normal values quoted for serum creatine kinase (sCK) are usually supplied by the manufacturer of the assay and have been derived from population samples that do not accurately reflect the entire population and do not take into account a number of extremely important variables which can affect sCK activity, notably gender, ethnic origin and the effects of exercise [1]. As a consequence, many normal individuals will wrongly be stated to have hyperCKemia and may be investigated unnecessarily or be denied treatment with statins because of unfounded concerns about the presence of subclinical muscle disease [2].

A practical definition of hyperCKemia

In the present context, we aim to define an upper reference value of creatine kinase (CK) above which further investigation for a possible subclinical myopathy may be appropriate.

Consideration has to be given to the sensitivity and specificity of measuring sCK. Sensitivity means the

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likelihood of there being an abnormal result in somebody with a muscle disease – thus an elevated sCK is a true positive result. Specificity relates to a normal individual being classified as having a normal CK – a true negative result. A low upper limit of normal (ULN) will increase sensitivity at the cost of reduced specificity – meaning in practice that more normal individuals will be investigated inappropriately. On the other hand, if the upper limit is set higher, it will reduce the sensitivity of the test but increase the specificity – fewer normal individuals will be investigated inappropriately, but some patients with muscle disease may be missed. Recent evidence suggests that adopting newly proposed upper reference limits has little practical clinical impact with respect to reducing sensitivity [3].

Therefore, the first priority is to establish appropriate 97.5th percentile values for each sex and ethnic group. Table 1 shows the 97.5th percentile values, broken down by gender and ethnicity, published in a recent study from the Netherlands, and we propose using these figures as a basis for defining practical upper reference limits for CK activity. This is the largest study to date looking at the distribution of CK in a large random population sample with standardization of exercise. Limited evidence suggests that these figures can be applied to patient populations in other countries [3]. Manufacturer quoted upper limits for serum CK activity should be replaced by these figures from Brewster *et al.* [4].

In routine clinical practice, laboratory results slightly above the defined upper limit (97.5th percentile) are often safely ignored, presumably reflecting the fact that by definition 2.5% of normal individuals will fall into this category and experience indicates that ignoring such values has little clinical impact. It may thus be reasonable, in a population of asymptomatic individuals, to set the level above which investigation is appropriate to a level higher than the 97.5th percentile. Brewster *et al.* (2007) [4], following personal contact, calculated the figures shown in Table 2.

If a figure of 1.5 times ULN is taken as the cut-off value for further investigation, as opposed to the 97.5th percentile, then it would approximately half the number of people being investigated, with probably only a small reduction in sensitivity.

Table 1 97.5th percentile for serum creatine kinase (CK) activity (iu/l). Derived from Brewster *et al.* 2007

	Non-black Female	Non-black Male	Black Female	Black Male
CK iu/l	217	336	414	801

Table 2 Percentage of normal individuals with creatine kinase activity above the upper limit of normal (ULN) (Personal communication Brewster *et al.* 2007)

	Non-black Female	Non-black Male	Black Female	Black Male
1.0 ULN	2.5	2.5	2.5	2.5
1.5 ULN	1.5 (325)	1.0 (504)	1.3 (621)	0.5 (1201)
2.0 ULN	0.2	0.8	0.5	0

The value in bracket represents 1.5× ULN

Non-myopathic hyperCKemia

Serum CK activity is commonly, but not always, elevated in patients with skeletal muscle disease. It also important to recognize that hyperCKemia can occur in those without a primary disorder of muscle. There may be secondary involvement of muscle as in neurogenic disorders such as amyotrophic lateral sclerosis, hereditary spinal muscular atrophy type III and IV, post-polio syndrome, bulbospinal muscular atrophy and some neuropathies. In these conditions, there are usually no diagnostic difficulties as additional features on examination, and the history, point to the correct interpretation. sCK may also be elevated in patients without primary neuromuscular disease (Tables 3 and 4).

These guidelines will consider the diagnostic approach in patients with pauci- or asymptomatic hyperCKemia who otherwise do not have an apparent medical explanation for their hyperCKemia. One of the aims is to provide the reader with guidelines to identify in which patients it is appropriate to perform a muscle biopsy.

Search strategy

The Task force members met on 21/3/2009 and decided on a search policy. This included a search for any

Table 3 Causes of hyperCKemia unrelated to a recognized neuromuscular disease

Medications
Strenuous muscle exercise (especially eccentric)
Trauma (electromyogram studies, IM injections)
Surgery
Toxins (alcohol, heroin, cocaine)
Endocrine (hypothyroidism, hypoparathyroidism)
Viral illness
Metabolic (hypokalaemia, hyponatraemia)
'Idiopathic' (sporadic and familial)
Race (black > non-black)
Sex (male > female)
Chronic cardiac disease (CK-MB)
Obstructive sleep apnoea
Neuroacanthocytosis syndromes
Macro-CK
Malignant hyperthermia syndrome

existing guidelines and articles dealing with series of patients that were investigated for asymptomatic/pauci-symptomatic hyperCKemia as well as articles dealing with myopathies that can present with asymptomatic hyperCKemia.

Medline 1966–2009 was searched and key terms included: CK, CK and high, CK and increase, hyperCKaemia/hyperCKemia and idiopathic, hyperCKaemia/hyperCKemia and asymptomatic, hyperCKaemia/hyperCKemia and biopsy, hyperCKaemia or hyperCKemia and investigation, CK elevation or elevated and idiopathic, CK elevation or elevated and asymptomatic, CK elevation or elevated and asymptomatic, CK elevation or elevated and idiopathic rhabdomyolysis and asymptomatic.

The Cochrane Library was accessed on 30/6/2009 and the American Academy of Neurology on the 7/7/2009 for any guidelines on the investigation of HyperCKemia and none were found. The only guidelines found were those approved by the Italian Association of Myology Committee [5].

Abstracts were reviewed and relevant articles identified and circulated amongst members of the task force. To evaluate articles, we followed the critical review of guidelines as recommended by the EFNS [6]. Only class IV studies were identified. A first draft was prepared and circulated to all members of the Task force for a consensus position. Several revisions to the first draft were made, and the Task Force met again on the 13/9/2009 to finalize the guidelines.

Patients and definitions

Once non-myopathic hyperCKemia has been excluded, pauci-symptomatic patients are those patients without any objective signs of muscle disease such as muscle weakness, atrophy, hypertrophy or myotonia but who have non-specific and vague neuromuscular symptoms such as myalgias, undue fatigue, exercise intolerance, cramps and stiffness. Patients with asymptomatic hyperCKemia are those who do not have any neuromuscular symptoms or signs. Patients with pauci- or asymptomatic hyperCKemia form a heterogeneous group including amongst others 'normal' individuals, patients with sub-clinical myopathy and patients with 'idiopathic hyperCKemia'. The latter term was initially coined by Rowland *et al*. and may be defined as those individuals who have persistent hyperCKemia but no clinical, neurophysiological or histopathological evidence of neuromuscular disease using current laboratory methodologies [7]. There is some evidence that 'idiopathic hyperCKemia' is sometimes familial and may be genetically determined [8].

Table 4 Drugs frequently associated with chronic hyperCKemia

Statins (HMG-CoA reductase inhibitors)
Fibrates
Colchicine
Anti-psychotic drugs (including Neuroleptic malignant syndrome)
Zidovudine
Certain beta blockers
Isoretinoin

Table 5 Genetic myopathies that can present as isolated hyperCKemia

	References
Adult onset glycogenosis type II	[12]
Caveolinopathy (Caveolin-3)	[17–19]
Calpainopathy (Calpain-3)	[20,21]
Desminopathy	[22,23]
Dysferlinopathy (LGMD and Miyoshi)	[9,21,24,25]
Fukutin-related protein (FKRP) LGMD 2I	[25]
Dystrophinopathy (also female carriers)	[26–29]
Sarcoglycanopathy	[30]
Myotonic dystrophy type 2	[31]

Only selected references are given.

Results

Muscle biopsy diagnoses in patients with pauci- or asymptomatic hyperCKemia

Several genetically well-defined myopathies can rarely present with isolated hyperCKemia as shown in Table 5.

However, an indication of the relative frequencies of various myopathies that are diagnosed in patients with pauci- or asymptomatic hyperCKemia can be gleaned from several retrospective studies [9–16] and are summarized in Table 6.

Patients with non-neuromuscular causes of hyperCKemia and/or with a family history of documented neuromuscular disorder were excluded in these studies. Although none were prospective, patient inclusion was probably representative of everyday practice. The frequency of definitive or probable diagnoses provided by muscle biopsy varied from 8% to 63%.

The frequency of a normal biopsy result after all laboratory tests had been performed varied between 8% and 55%. What is perhaps distressing, to both patient and physician alike, is the frequency of non-specific myopathic abnormalities that did not allow a diagnosis to be made in 16–83% of patients.

There are several reasons for the discrepancy in reaching a final diagnosis between series including differences in the age of patients, in the level of

Table 6 Diagnoses in patients with pauci- or asymptomatic hyperCKemia

Diagnoses	Joy *et al.*, 1989	Reijneveld *et al.*, 2001	Prelle *et al.*, 2002	Simmons *et al.*, 2003	Fernandez *et al.*, 2006	Dabby *et al.*, 2006	Filosto *et al.*, 2007	Malan-drini *et al.* 2008	Total
Specific myopathies	12/19	6/37	21/114	6/20	55/104	3/40	15/105	3/37	121/460
Muscular dystrophies									25
Dystrophinopathy		2	5		9	3		1	17
Dysferlinopathy			1		1				2
Caveolinopathy					1				1
Calpainopathy					1				1
Sarcoglycanopathy		1							1
LGMD-unspecified			1						1
Fukutin-related protein					2				2
Metabolic myopathies									50
CPT 2 def.			4	2					6
Myophosphorylase	1	1			15				17
Phosphofructokinase def.							1		1
1 α, glucosidase def.					9		5		14
Glycogenoses (unspecified)					1				1
Phosphorylase-b kinase				3					3
Adenylate deaminase			1	1					2
Mitochondrial	2		2		1		1		6
Inflammatory myopathy									20
Polymyositis	5				6			1	12
Inclusion body myositis	1				2				3
Macrophagic myositis					5				5
Congenital myopathy									8
Central core	1	1	1				2	1	6
Centronuclear							1		1
Multicore	1								1
Miscellaneous									14
Malignant hyperthermia myopathy			3						3
Tubular aggregates		1	1				3		5
Myofibrillar myopathy					2				2
Lobulated fibre myopathy							2		2
Desminopathy			1						1
Sarcoid myopathy	1								1
Myotonia fluctuans			1						
Non-specific myopathic	3/19	24/37	18/114	3/20	26/104	19/40	68/105	29/37	190/460
Neurogenic			13/114		2/104		8/105	2/37	25/460
Normal	4/19	7/37	62/114	11/20	15/104	18/40	14/105	3/37	134/460

hyperCKemia and in the range of testing performed on muscle biopsies.

There are three large studies, with more than 100 patients each, which have included comprehensive testing, beyond routine histology and histochemistry, such as immunocytochemistry, respiratory chain and glycolytic enzyme assays [9,12,13]. Out of a total of 323 patients in these three studies, a specific diagnosis was made in 92 (28%), an abnormal non-specific myopathic biopsy was found in 138 (43%) and a normal biopsy in 93 (29%).

The specific diagnoses made in 460 patients with pauci- or asymptomatic hyperCKemia are shown in Table 6. Out of the 121 specific diagnoses, the commonest was metabolic myopathies (42%) and subclinical muscular dystrophies (21%). The former was presumably asymptomatic or only minimally symptomatic whilst the latter was mostly diagnosed in the first two decades, presumably, prior to the appearance of the typical phenotypes. As can be seen from Table 6, although only a small minority of the myopathies have specific treatments, an accurate diagnosis of an untreatable condition is often enormously beneficial to the patient and the family, in terms of discussing prognosis, potential complications (which may be treatable e.g. cardiomyopathy and ventilatory muscle involvement) and genetic counselling.

Variables that increase the likelihood of a diagnostic muscle biopsy

The patient is best served if a muscle biopsy results in a specific diagnosis. A few studies have looked for clinical and laboratory indicators, which, if present, indicate

that muscle biopsy is more likely to give a specific diagnosis.

Level of hyperCKemia

Fernandez *et al*. identified that a CK of >10 times normal was statistically associated with an increased probability of arriving at a specific diagnosis following biopsy [12]. Similarly, a CK >5 times normal combined with an age of <24 years were found to be predictive of arriving at a specific diagnosis by Prelle *et al*. [9]. In the series of Filosto *et al*. [13] seven out of 105 had a metabolic myopathy, five myophosphorylase deficiency (glycogenosis type V), one phosphofructokinase deficiency and one mitochondrial myopathy. All six patients with a glycogenosis had a CK of >7 times normal.

The role of electromyography

With rare exceptions (e.g. myotonic dystrophy), the electromyogram (EMG) is not expected to provide any specific diagnosis other than to give information about motor unit physiology. There are several studies on the sensitivity and specificity of EMG in the literature but what is relevant in the context of pauci- or asymptomatic hyperCKemia can only be gleaned from the studies in this particular group of patients. The key questions that need to be answered are; does an abnormal EMG increase the likelihood of an abnormal biopsy and conversely does a normal EMG decrease the likelihood of an abnormal biopsy?

In the study by Prelle *et al*. [9] 100 patients had both EMG and biopsy. The sensitivity of EMG (the proportion of patients with an abnormal biopsy who also had an abnormal EMG) biopsy was 73%. Thus, an abnormal EMG increases the chances of obtaining an abnormal biopsy. The specificity of EMG (proportion of patients with normal biopsy who also have a normal EMG) was only 53%. Thus, an abnormal EMG may be associated with a normal biopsy. If one uses the data from Prelle *et al*., the positive predictive value of an abnormal EMG, i.e. the likelihood that an abnormal EMG will predict an abnormal biopsy in a group of patients with pauci- or asymptomatic hyperCKemia, is 51%. Similarly, the negative predictive value of a normal EMG, i.e. the likelihood that a normal EMG will predict a normal biopsy, is 74%.

If one considers the study by Joy and Oh, the sensitivity of an abnormal EMG was 92% and its specificity 100% [14]. The positive predictive value of an abnormal EMG in predicting an abnormal biopsy was 100%, whilst the negative predictive value of a normal EMG in predicting a normal biopsy was 80%. On the basis of our extensive personal experience, the figures from this much smaller study (only 19 patients) are far too optimistic. However, it is noteworthy that both studies agree on the high negative predictive value of a normal EMG (74–80%).

As far as can be ascertained, in none of the aforementioned studies was quantitative EMG employed and therefore its contribution in helping to select patients for biopsy is unknown.

Clinical parameters

Age below 15 was found to be statistically associated with a higher probability of reaching a specific diagnosis by Fernandez *et al*. 2006. Other variables that were associated with increased probability, but did not reach statistical significance, were women vs men (63% vs. 51%) and pauci-symptomatic vs asymptomatic (59% vs. 50%) [12]. Amongst pauci-symptomatic patients with hyperCKemia investigated by Filosto *et al*. [13] all six patients with glycogenosis had exercise-induced myalgias and no patients with isolated rest pain had a metabolic myopathy.

Prognosis in patients with pauci- or asymptomatic hyperCKemia

Prelle *et al*. reported a 6-year follow-up study on 55 (38 were lost to follow-up) of the 93 undiagnosed patients with asymptomatic hyperCKemia of their original cohort [32]. Most patients (43/55 or 78%) still had persistent hyperCKemia but at a lower level. CK had normalized in 12/55 (22%). Statistical analysis revealed a correlation between CK normalization and a normal biopsy. One patient out of the 55 was diagnosed to have limb girdle muscular dystrophy and one to be a dystrophinopathy carrier. Thus, long-term prognosis for the whole group was favourable.

An earlier, long-term follow-up study (mean 7.2 years) on 23 out of the original 31 idiopathic hyperCKemia patients also provided a benign prognosis with none of the patients developing neurological abnormalities except for one patient who developed an axonal neuropathy [33]. The mean values of CK did not differ significantly at follow-up.

Risk for malignant hyperthermia

Malignant hyperthermia (MH) susceptibility may be seen in association with central core disease, in which case additional features of myopathy may be present, but can also occur in isolation. In the latter group of asymptomatic patients, some, but not all, may have hyperCKemia. Therefore, the question arises as to the possibility of MH susceptibility in an individual with asymptomatic hyperCKemia in whom all other investigations have failed to reveal a cause. There are

practical problems in that confirmation of MH susceptibility involves what will usually be a second muscle biopsy, few centres offer such testing and even then there are limits to sensitivity and specificity.

There have been few large studies. Weglinski *et al.* (1997) [34] reported that 24/49 (49%) of patients with asymptomatic hyperCKemia had positive contracture tests. More recently, Malandrini *et al.* [16] found one susceptible and one equivocal subject in 37 patients with asymptomatic hyperCKemia.

The facility for MH testing varies enormously between neuromuscular centres and countries. We advise that local guidelines be followed but that a pragmatic approach is to advise patients with otherwise unexplained hyperCKemia that they may be MH susceptible and appropriate anaesthetic guidelines should be followed. Consideration also has to be given to assessing and advising other family members.

Recommendations

The recommendations are based on the limited number of class IV studies available and the expert opinion of the panel and as a result can be viewed as level C recommendations. They outline the sequential steps in a diagnostic approach to pauci- or asymptomatic hyperCKemia.

1. HyperCKemia is defined as sCK >1.5 times the ULN (see revised values in Table 2).

2. Consider all non-neuromuscular causes in Tables 3 and 4 and other non-myopathic causes of hyperCKemia that might explain their high sCK.

3. Enquire about any family history of neuromuscular disease, hyperCKemia or MH.

4. Before embarking on long and expensive investigations, it is advised that hyperCKemia is confirmed by repeat assay and that the possibility of normal exercise-induced elevation is excluded. Therefore, the patient should be advised to avoid strenuous exercise for 7 days prior to sampling and at least two samples 1 month apart should be taken.

5. If hyperCKemia is confirmed to perform a nerve conduction study and EMG.

6. A biopsy may be performed in a patient with hyperCKemia if one or more applies:

(i) If the EMG is abnormal (myopathic)
(ii) If sCK is ≥3 times normal.
(iii) If the age of the patient is <25 years.
(iv) Exercised-induced pain or exercise intolerance.
(v) Women with hyperCKemia but sCK <3 times normal (because of the possibility of Duchenne/Becker mutation carrier status). However, prior to biopsy, DNA analysis on blood lymphocytes should be undertaken. Currently, multiple ligation probe amplification analysis will identify ~70% of carriers. Developing technology is probably to improve that and all such cases should be discussed with local genetic services.

Table 7 Minimal muscle biopsy investigations

Histology and histochemistry
Haematoxylin & eosin, modified Gomori trichrome, Oil red O, periodic acid-schiff, adenosine triphosphatase (9.4, 4.2, and 4.6), succinate dehydrogenase (SDH), Nicotinamide Adenine Dinucleotide Hydrogenase (NADH), cytochrome c oxidase, myophosphorylase, acid phosphatase
Immunohistochemistry
Dystrophin, α, β, γ and δ sarcoglycans, dysferlin, caveolin-3, MHC-1, α-dystroglycan

7. Men with hyperCKemia and a sCK <3 times normal may be offered a biopsy if they are seriously concerned about neuromuscular disease or alternatively they may be followed up in the neurology clinic.

8. The extent of diagnostic work up to be performed on a muscle biopsy will vary but must include histology, histochemistry and immunohistochemistry (Table 7). 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.

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