Concise report

The value of routine creatine kinase and thyroid stimulating hormone testing in patients with suspected fibromyalgia: a cross-sectional study

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Abstract

Objective. The aim was to examine the prevalence of abnormal creatine kinase (CK) and thyroid stimulating hormone (TSH) values and previously unknown myopathy or thyroid disease in patients with suspected FM syndrome (FMS).

Methods. All adult patients with suspected FMS referred to the study hospital between November 2011 and April 2014 could participate. Patients with a history of myopathy or a previous diagnosis of thyroid disorder were excluded. Outcome measures were the percentages of abnormal CK and TSH values and the final diagnosis in those patients.

Results. Three hundred and seventy-three patients were included in this study (94% female, mean age 42 years). Of these patients, 7.5% (95% CI: 5.2, 10.6%) had an abnormal CK according to the local reference values. Applying the European Federation of the Neurological Societies guideline, this changed to 0.5% (95% CI: 0.2, 1.9%). In none of these patients was hyperCKaemia-related myopathy diagnosed, and the final diagnosis was FMS in 89% of the patients. Of the total number of patients, 3.5% (95% CI: 2.1, 5.9%) had an elevated TSH and 1.4% (95% CI: 0.6, 3.1%) a lowered TSH, with one patient having a somewhat lowered free thyroid hormone level. The final diagnosis was FMS in all these patients.

Conclusion. Abnormal CK and TSH values are rare in patients with suspected FMS and do not result in an alternative diagnosis. Therefore, it seems that routine testing of CK and TSH levels in patients with suspected FMS referred to secondary care does not contribute to the diagnostic process.

Key words: fibromyalgia, diagnostic value, creatine kinase, thyroid stimulating hormone

Introduction

FM syndrome (FMS) is a chronic pain syndrome mainly affecting women. The prevalence is around 2% and because of this high prevalence and its large impact on the quality of life of patients, FMS is a major health issue [1, 2]. In addition, owing to disputes about aetiology, pathogenesis and classification, FMS is still a somewhat controversial disease [3, 4]. FMS can be diagnosed using the preliminary 2010 ACR diagnostic criteria. One of those criteria is the absence of another disease that causes the complaints [5]. Although
not specifically included in these diagnostic criteria, numerous blood tests have been recommended as routine screening for patients with suspected FMS to exclude alternative diagnoses [6]. However, it is still unclear whether these tests contribute to the diagnostic process in patients with suspected FMS.

Both creatine kinase (CK) and thyroid stimulating hormone (TSH) are frequently mentioned tests in the routine diagnostic work-up of FMS owing to the presumed similarities between FMS and myopathies or hypothyroidism [4, 6–10]. However, the routine use of CK and TSH testing is, to our knowledge, not adequately supported by data. For example, there are no clear data to suggest that there is indeed a higher pre-test chance of myopathy or thyroid disease in patients with suspected FMS compared with the general population. Also, data are absent on the presumed increased chance of abnormal CK and TSH values in patients with suspected FMS compared with healthy controls. Finally, the added value of CK and TSH testing has not been assessed.

Our aim was therefore to explore the diagnostic value of CK and TSH testing in patients with suspected FMS. More specifically, we aimed to determine the prevalence of abnormal CK and TSH values and the prevalence of previously unknown myopathy or thyroid disease in patients with suspected FMS.

Methods

Study design

The present cross-sectional study used data obtained from a study that examined the prevalence of myotonic dystrophy type 2 among patients with suspected FMS. Details on the methods of the original study are described in a separate manuscript (J. van Vliet, A. Verrips, A. A. Tielemans, H. Scheffer, H. A. Cats, A. A. den Broeder, B. G. M. van Engelen, unpublished results). The methods relevant to our study will be described below. The local ethical committee approved both the original study and this study (CMO Nijmegen Arnhem: 3655109111), and all patients provided informed consent.

Setting and participants

All consecutive patients with suspected FMS referred to the outpatient clinic of the rheumatology department at the Sint Maartenskliniek (specialized hospital in rheumatology, orthopaedics and rehabilitation medicine; The Netherlands) between November 2011 and April 2014 were eligible for participation. Exclusion criteria were age <18 years, an established other diagnosis responsible for the pain and currently receiving cognitive behavioural therapy (as participation in the original study might interfere with its goals). In addition, we applied an extra exclusion criterion in the present study: having an established diagnosis of myopathy or thyroid disorder.

Outcome measures and data collection

Outcome measures were the percentage of patients with abnormal CK and TSH values and the final diagnosis in those patients. Baseline patient characteristics were retrieved from the patients’ charts (age, sex, medical history, final diagnosis and whether the patient was referred to the study centre as a second opinion). The last of these characteristics was defined as the patient being seen in the last year by another secondary care specialist for the same complaints as presented during the first visit at the study centre. The final diagnosis (ICD-9 code) was determined by the treating rheumatologist using a protocolized diagnostic approach (history taking, physical examination, a neuromuscular questionnaire and the 2010 ACR FMS diagnostic criteria).

Serum CK and TSH were determined in all patients at the clinical laboratory of the study centre. The reference values used in the study centre for a normal CK in men and women were <200 and <170 U/l, respectively. As there is debate on the reference values for CK, we also used the hyperCKaemia values proposed by the European Federation of the Neurological Societies [11]. According to this guideline, hyperCKaemia is present when CK >504 U/l for non-black men and >325 U/l for non-black women [11]. CK levels may vary within individuals (e.g. after physical exercise); therefore, CK testing was repeated if the first test result was abnormal. A normal TSH was defined as a TSH between 0.4 and 4.0 mU/l. Free thyroid hormone (FT4) was assessed when TSH was abnormal (reference values for normal FT4: 8–22 pmol/l). In the event of abnormal TSH or FT4 values, no repeated testing was performed because TSH and FT4 values show no relevant day-to-day variation [12].

Data analysis

Statistical analysis was performed using STATA version 13.1. All outcome measures are given as percentages or means and include the 95% CI or s.d., as appropriate. A post hoc sensitivity analysis was performed, excluding patients seen as a second opinion.

Results

Setting and participants

All 398 patients included in the original study were considered for participation in the present study. We had to exclude 23 patients because of known previous myopathy or thyroid disorder (Fig. 1). As a result of missing data on CK and TSH values in two patients, 373 patients were included in the final analysis [mean age of 42 (11) years, 94% female]. Of the patients with a final ICD-9 diagnosis of FM, 92% fulfilled the ACR 2010 criteria (Table 1).

Results of CK and TSH testing

The mean CK in our study population was 96 (50) U/l (range: 23–470 U/l) and the mean TSH was 1.8 (1.4) mU/l (range: 0.1–17.6 mU/l). Twenty-eight (7.5%; 95% CI: 5.2, 10.6%) patients had an elevated CK according to the reference standard used at the study centre (range: 171–470 U/l). Using the European Federation of the Neurological Societies reference standard, two (0.5%; 95% CI: 0.2, 1.9%) patients had an abnormal CK (357 and 470 U/l, respectively). In both of these patients, a...
Repeated CK test was normal. No diagnosis of hyperCKaemia-related myopathy was given in any of the 28 patients with an abnormal CK, and their final diagnoses were FM (n = 25), osteoporosis (n = 1), arthropathy/arthralgia (n = 1) and AS (n = 1).

Eighteen patients had an abnormal TSH value, with 13 (3.5%; 95% CI: 2.1, 5.9%) patients having an elevated TSH and five (1.4%; 95% CI: 0.6, 3.1%) a lowered TSH. One patient with an elevated TSH had a slightly reduced FT4 (7.7 pmol/l). This was interpreted by the treating rheumatologist as subclinical hypothyroidism unrelated to the FMS complaints, and no further action was taken. The final diagnosis in all patients with abnormal TSH values was FM. A sensitivity analysis excluding all second opinion patients yielded similar results to the original analyses.

Discussion

This study suggests that relevant abnormal CK and TSH values and a final diagnosis of underlying thyroid disease or hyperCKaemia-related myopathy are rare in patients with suspected FMS. Therefore, it seems that routine testing of CK and TSH in secondary care patients with suspected FMS does not contribute positively to the diagnostic process.

To our knowledge, this is the first study assessing the diagnostic value of two commonly used tests in suspected FMS. Some strong points of our study are the prospective design, the well-defined patient population and the relatively large sample size. However, this study has some limitations. Firstly, we were not able to compare the CK and TSH results against a gold standard. For example, muscle biopsies could have been taken to serve as the gold standard for myopathies. However, this was not deemed feasible in the context of our study. Instead, we used a combination of history taking, physical examination, a neuromuscular checklist and the ACR 2010 FMS criteria in order to create, in our opinion, a reasonable surrogate gold standard.

Secondly, there was a relatively high proportion of second opinion patients in our study, probably higher than in other rheumatology departments. However, the sensitivity analyses with exclusion of second opinion patients showed similar results. Therefore, this does not seem to hamper the validity of our findings.

Thirdly, patients may already have had their CK and TSH tested by the general practitioner. This could have caused a selection bias leading to underestimation of the prevalence of abnormal CK and TSH testing and associated diseases in our study. This is because patients who were already diagnosed with thyroid disorder or hyperCKaemia-related myopathy would probably not have been referred to the rheumatologist for an FMS work-up. Although a valid concern, even if the majority of patients had received CK and TSH testing by the general practitioner this would not invalidate the generalizability of our results to other secondary care rheumatology departments. However, we would encourage the execution of a similar study in primary care.

In spite of widespread use of CK and TSH testing in suspected FMS and recommendations on this topic in some guidelines, our results do not contradict existing evidence. Although this may seem counterintuitive, this has to do with the aforementioned lack of data on CK and TSH testing in suspected FMS. Publications suggesting that routine CK or TSH testing is relevant in the diagnostic work-up of FMS [4, 6, 7] base this recommendation on the presumed similarity of symptoms between FMS and thyroid disease or myopathies. However, these recommendations are not based on prevalence data, as provided in our study, and also seem to ignore the very low prevalence of clinically relevant myopathies.

Furthermore, for both CK and TSH, studies on normal values in healthy controls are available. Regarding CK, the median value in healthy controls was 84 and 122 U/l for women and men, respectively [13]. With regard to TSH, the prevalence of abnormal TSH ranged from 7.3 to 10.4% [14–16]. As our results come close to these results in the normal population, they support our conclusion of not using routine CK and TSH testing in suspected FMS patients. Based on these studies, routine testing in suspected FMS patients would be as irrational as routine testing in the whole general population.

### Table 1 Characteristics of the patient population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Study population (n = 373)</th>
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<tbody>
<tr>
<td>Sex, female, n (%)</td>
<td>354 (94)</td>
</tr>
<tr>
<td>Age, mean (s.d.), years</td>
<td>42 (11)</td>
</tr>
<tr>
<td>Second opinion, n (%)</td>
<td>107 (29)</td>
</tr>
<tr>
<td>Final clinical diagnosis, n (%)</td>
<td></td>
</tr>
<tr>
<td>FM</td>
<td>358 (95)</td>
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<tr>
<td>Other&lt;sup&gt;a&lt;/sup&gt;</td>
<td>17 (5)</td>
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<sup>a</sup>Other diagnosis were as follows: mono-arthritis; polyarthropathy or polyarthritus unspecified; AS/Bechterev’s syndrome; spondylosis; osteo-arthritis; bursitis/enthesiopathy/synovitis; osteoporosis; arthropathy/arthralgia; hypermobility syndrome or Ehlers-Danlos syndrome and lumbago or neuralgia, neuritis or radiculitis, unspecified.
Finally, with regard to CK testing there are some additional limitations. Several studies claim that CK in general is not a good test because of its low specificity. There is a wide variation in serum CK levels in the healthy population, dependent on physiological factors such as sex, race and recent physical exercise [13, 17]. Therefore, the reference values for serum CK are subject to debate [11]. In our study, the use of either strict or liberal reference values had a large impact on the number of patients with abnormal values (28 vs 2 patients, respectively), with the two highest CK values turning out to be false positives after repeated testing. Furthermore, elevated serum CK can reflect a muscular disorder but can also occur in other conditions such as hypothyroidism, drug use, alcoholism, muscle trauma, infections and malignancies [18-20].

In summary, it seems that routine CK and TSH testing did not contribute to the diagnostic process in any of the studied patients. Therefore, we recommend against the routine use of CK and TSH testing in patients with suspected FMS seen at a secondary care centre. However, elective testing in patients with signs and or symptoms suggestive of muscular or thyroid disease should still be done and be followed by appropriate diagnostic or therapeutic steps.

Funding: No specific funding was received from any bodies in the public, commercial or not-for-profit sectors to carry out the work described in this manuscript.

Disclosure statement: The authors have declared no conflicts of interest.

References