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The yield of diagnostic work-up of patients presenting with myalgia, exercise intolerance, or fatigue
A prospective observational study

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Abstract

Myalgia, fatigue, and exercise intolerance are cause for referral to a neurologist. However, the diagnostic value of history, neurological examination, and ancillary investigations in patients with these symptoms is unknown. This study provides a sound footing for deciding which ancillary investigations should be conducted. A prospective observational study of the diagnostic approach in 187 patients with myalgia, exercise intolerance, or fatigue as their predominant symptom was performed. The primary outcomes were independent contribution of referral letter, history, examination, and ancillary investigations to a myopathy diagnosis. The secondary outcome was diagnostic value of combined ancillary investigations. 27% of patients had a myopathy. Positive family history (OR 3.2), progressive symptoms (OR 2.2), atrophy (OR 9.7), weakness (OR 10.9), and hyporeflexia (OR 4.4) were associated with a myopathy. Positive predictive values for myopathy were calculated for CK (0.32), EMG (0.66), ultrasound (0.47), and muscle biopsy (0.78). All contributed significantly in predicting myopathy. Multivariate analysis yielded a diagnostic algorithm facilitating a more efficient work-up in future patients. CK levels, EMG, ultrasound, and muscle biopsy independently contribute to predicting a myopathy. The diagnostic algorithm shows which combination of ancillary investigations should be employed in different subgroups and when to omit invasive techniques. This algorithm may drastically improve diagnostic efficiency.

Keywords: Myalgia; Myopathy; Muscle biopsy; Ultrasound; EMG; All neuromuscular diseases; Muscle disease; Mitochondrial disorders

1. Introduction

Muscle symptoms such as myalgia, fatigue, and exercise intolerance are prevalent in the general population and constitute a frequent cause for referral to a neurologist [1]. Most neurologists use a common-sense approach in addressing these patients, founding their decision whether and which ancillary investigations should be conducted on various aspects of the patient's history and physical examination.

However, the diagnostic value of ancillary investigations has only been studied separately and in specific subgroups, and results are not univocal. For instance, visual analysis of electromyographic (EMG) data has a sensitivity ranging from 47% to 85% in patients with known myopathies [2]. Conversely, in muscle biopsies of patients with isolated myalgia definite muscle pathology was found in only 4% [3,4]. Even though in recent years work-ups of hyperCKemia have been described, and recommendations regarding muscle biopsies have been made [1], the lack of literature on the diagnostic value of combinations of ancillary investigations renders the decision to conduct or refrain from these (sometimes invasive and expensive) investigations unfounded.

The aim of this study was to provide a scientifically sound footing for deciding which ancillary investigations should be conducted. Therefore we determined the prevalence of myopathies

Statistical analysis: Statistical analyses were conducted by Margot te Riele and Tim Schreuder. H. Groenewoud and G.J. van der Wilt contributed significantly to the multivariate logistic regression analysis.

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in a large cohort, and investigated the contributory value of widely employed diagnostic tools. We then created a statistical model to provide an evidence based decision algorithm for employing combined ancillary investigations in patients presenting with myalgia, fatigue, or exercise intolerance.

2. Methods

2.1. Patients

Between January 2009 and October 2011 a neuromuscular neurologist (BvE) screened all referral letters to our neuromuscular centre and included all patients aged ≥18 years with myalgia, exercise intolerance, or fatigue as their predominant symptom as indicated by the referring physician.

2.2. Data collection

The data from the medical charts were anonymously entered into an SPSS database after the visit.

2.3. Outcome measures

The primary outcome was the contribution of the referral letter, history, physical examination (in odds ratio (OR)), and the separate ancillary investigations (in OR and PPV (positive predictive value)) to the myopathy diagnosis. The secondary outcome was the diagnostic value of the combined ancillary investigations. The diagnostic value of the combined investigations was attained using multivariate logistic regression, resulting in a diagnostic algorithm.

2.4. Clinical evaluation

The diagnostic work-up was standardised and consisted of the following components: referral letter, medical history and neurological examination, laboratory investigations, needle EMG, quantitative muscle ultrasound, and muscle biopsy. Myopathies were diagnosed by two experienced neuromuscular neurologists (BvE, NV) in accordance with internationally accepted criteria [5–7].

The referral letter was evaluated for the following aspects: who referred the patient (specialist versus general practitioner), who initiated the referral (physician versus patient); the main reason for referral (confirmation versus exclusion of a neuromuscular disease (NMD)), and the predominant complaint (myalgia, exercise intolerance, or fatigue).

Medical history and neurological examination were performed by two neurologists (BvE, NV). The symptom the patient perceived as the most debilitating at the time of visit was defined as the 'predominant complaint'. Exercise intolerance was defined as onset or worsening of symptoms with physical activity. A positive family history was defined as having family members with a neuromuscular disease or muscular symptoms similar to those of the patient. Strength of proximal and distal limb muscles, and axial muscles was assessed using the Medical Research Council (MRC) scale.

2.5. Ancillary investigations

Laboratory investigations included: Creatine kinase (CK) (local normal values <200 U/L for male, <170 U/L for female patients), calcium (2.20–2.65 mmol/L), phosphate (1.3–1·9 mmol/L), magnesium (0.70–1.10 mmol/L), thyroid stimulating hormone (TSH; 0.4–4.0 mmol/L), and lactate; we classified a resting lactate level ≥2.5 mmol/L as indicative of a mitochondrial disease (specificity 1.00) [8].

Needle EMG was performed using a Synergy EMG system (Viasys Healthcare, Old Woking, United Kingdom). Motor unit potentials, spontaneous muscle fibre activity, and recruitment patterns were measured using a concentric needle electrode in at least four muscles, depending on which muscles were affected (mainly upper arms and legs). Results were categorised into four conclusive groups: 'normal', 'myopathic', 'neurogenic', or 'nonspecific'.

Quantitative muscle ultrasound (Philips IU22, Best, The Netherlands) was performed on seven muscles (depending on which muscles were affected) unilaterally using a Philips IU22 ultrasound system (Philips Healthcare, Best, The Netherlands) broadband linear 5–17 MHz transducer, as published previously [9]. Echo intensity (EI) and muscle thickness were measured; EI was determined using computer-assisted grey-scale analysis. Abnormal values were defined as EI above 3.5 SD in one muscle or 2.5 SD in two muscles or 1.5 SD in three muscles (98% specificity under 60 years of age, 92% above 60 years of age) [9,10].

Muscle biopsy specimens were obtained from the right vastus lateralis muscle and analysed as published previously [11]. We categorised an abnormal histological biopsy as 'nonspecific' (mild, non-specific changes), 'specific' (i.e. the biopsy directly led to a specific diagnosis, for example by showing muscle dystrophy with desmin accumulations leading to a myofibrillar myopathy diagnosis) or 'contributing' (i.e. definitely abnormal, myopathic or neurogenic, but not directly affording a neuromuscular diagnosis).

Biochemical analysis of the muscle tissue included the determination of the oxidation rates of radiolabelled substrates and the rate of ATP production from oxidation of pyruvate as previously described [12]. Abnormalities were further classified as 'mild' or 'severe'.

2.6. Statistical analysis

Statistical analyses were performed using IBM SPSS statistics 22 software (IBM, Chicago). For each variable, the number of cases was recorded and percentages were calculated, which, in case of missing data, were based on the number of available cases. For group comparison between patients with a myopathy and subjects without a diagnosis we used Pearson's χ^2 test for binary variables and Student's *t*-tests or Mann-Whitney U-tests for continuous variables, with significance set at $p < 0.05$. To determine the independent contribution of variables to the diagnosis of a myopathy, odds ratios were calculated for dichotomous variables using univariate logistic regression analysis ('diagnosis myopathy yes/no' as the dependent variable), and were presented alongside 95% confidence intervals. Furthermore,