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Four-year longitudinal study of clinical and functional endpoints in sporadic inclusion body myositis: Implications for therapeutic trials

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Abstract

Natural history studies in sporadic inclusion body myositis are of fundamental interest for future therapeutic trials. Previous works have demonstrated the particular relevance of knee extension strength in the follow-up of this disease. This work aimed to extend a preceding natural history over 9 months to a four year period. Thirteen patients were assessed using clinical and functional scales and dynamometry. Except wrist extension torque and manual muscle testing composite score, all the measurements presented a significant decline. The most important changes were observed for knee extension and ankle flexion and extension. The relative change in knee extension strength correlated with the level of strength at baseline. A non-linear correlation was found between 6-minute walk distance and knee extension strength. This study confirms that knee extension strength is particularly relevant to follow patients with sporadic inclusion body myositis. It also shows that a strength loss does not have linear consequences on motor ability. Finally strength and motor ability are complementing each other in the understanding of disease progression.

Keywords: Inclusion body myositis; Natural history; Outcome measures; Strength; Dynamometry

1. Introduction

Sporadic inclusion body myositis (sIBM) is the most common acquired inflammatory muscle disease in adulthood after the age of 50 years [1]. The pathological analysis shows the co-existence of auto-immune and degenerative mechanisms within the muscle yet the underlying etiology remains obscure [2] and to date there is no approved treatment [3]. Now several molecules are in sIBM clinical trials to assess safety and efficacy. Designing an efficient clinical trial requires the identification of a reliable outcome measures appropriate to the studied disease. These outcomes should be specific to sIBM since its features differ from the other myositides based on a unique muscular deficit phenotype with slow progression, usually asymmetry, and the absence of extra-muscular involvement. In addition outcome measures must be reliable, clinically meaningful, and sensitive to change.

Precise longitudinal data are of primary importance to construct the statistical analysis plan, including sample size estimation based on expected size of effect relative to precision of endpoints and duration of study. In sIBM, these key data are critically lacking. Recently, three

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independent studies have demonstrated that knee extension strength is a sensitive marker of disease progression in sIBM on a short term period ranging from 6 to 12 months [4–6]. The longest reported follow-up was achieved in eight patients in a 4-year-lasting study using manual muscle testing (MMT) [7]. However MMT has limitations in that it produces ordinal data that is not continuous nor scaled. In this study, MMT upper and lower composite scores decreased by 3.5 and 3.6%/year, respectively. Grip strength, as measured by dynamometry, decreased by 10.7%/year. Using the same methods, shorter studies demonstrated slower rate of decline [8,9]. Clinically meaningfulness of strength, either measured on individual muscles, either averaged from different muscles into composite scores, is not straightforward. The relationships between strength and motor abilities, and their consequences on functional outcome such as the 6-minute walking distance, or activities of daily living have not received much attention. Before starting any therapeutic clinical trial in sIBM, there is thus a critical need to identify and quantify adequate outcome measures through longitudinal natural history studies.

A few years ago, we initiated a study of 22 patients with sIBM. First results were published after a 9-month follow-up [4]. In order to demonstrate that short term changes could be extended in long-term follow-up, we conducted a 48 months evaluation of the same patients. A secondary objective of the study was to validate an inexpensive, portable, fast and simple measure of isometric quantitative knee extension strength, since this outcome measure was reported by our group and others to be a promising indicator of disease progression.

2. Materials and methods

2.1. Patients

Twenty-two patients with definite sIBM (based on muscle biopsies) were initially recruited in the first 9-month follow-up study [4] and 20 could be contacted to take part in the study. Thirteen accepted to come back 4 years after initial assessment for an additional comprehensive evaluation. None of them was treated by immunosuppressants nor immunumodulators for their IBM. The protocol was approved by the local Ethics Committee (CPP-Ile de France VI - ID RCB: 2012-A01634-39) and French regulatory authority. All patients signed an informed consent.

2.2. Clinical and functional evaluations

The protocol followed exactly the same experimental procedures than our previous follow-up study over 9 months [4]. Briefly, after complete medical examination, several clinical scales were used to assess the patients muscular conditions: Walton, Karnovsky, Rivermean Mobility Index (RMI), sIBM weakness composite index (IWCI including Barré, and Mingazzini functional tests) and Inclusion Body Myositis Functional Rating Scale (IBMFRS).

Strength was evaluated bilaterally using MMT on 17 muscle groups by the MRC (Medical Research Council) testing scale on 6 points (flexors of the ankle, knee, hip, wrist, elbow and neck, abductors of the hip and shoulder, adductors of the hip, extensors of the ankle, knee, fingers, wrist, elbow and neck, opponent of the thumb, palmar interosseous). Specific dynamometry was used to assess the maximal torques generated in the flexion and extension directions around the wrist, elbow, ankle and knee. Grip strength was also measured using the MyoGrip device. Strength values were expressed in percentage of predictive normal values from models already described (see [4]).

A six-minute walk test (6MWT) was performed in order to get the maximal distance covered during 6 minutes (6MWD) by walking. The same walking aids used in former evaluations were accepted. The 6MWT was performed in a corridor, between two cones separated by a distance of 25 m.

In addition to Biodex isometric assessment, knee extension was also measured using an isometric fixed portable dynamometer based on a strain gauge sensor (ZF-100, Scaime, Annemasse, France) with 10 g accuracy. The lever arm was carefully measured to the nearest half-centimeter using a measuring tape in order to compute the torque and to allow direct comparison between methods.

2.3. Data analysis

Composite MMT and QMT scores were computed for each patient as an average of the strength measured on all the muscle functions tested (expressed in MRC scale or in percentage of the predicted normal values, respectively). Wilcoxon signed rank test was used to test the difference between the baseline visit and the four-year visit. Depending on the linear pattern or not of the relationships between variables, correlations were assessed using either a Pearson's R or a Spearman's rho. Intraclass correlation coefficient (ICC) was computed to assess the reliability of fixed dynamometry to measure isometric knee extension strength as a single measure ICC with a two-way random-effect model (absolute agreement). Bland & Altman plot was also used to assess absolute agreement between methods. Standardized response mean (SRM) was calculated as the ratio between the mean and the standard deviation of the difference between the values obtained at the final visit and the baseline visit.