Supplementary material - Statistics

1. Linear multilevel modelling was used to model progression of manual muscle testing (MMT), quantitative muscle testing (QMT) and Inclusion body myositis functional rating scale (IBMFRS) composite scores over time from onset of disease.

Multilevel models assume a hierarchical data set. In this case, they account for repeated measures within the same patient. The ordinary regression relationship for a single patient measure would be:

$y_i = a + bx_i + e_i$

where subscript *i* takes the value from 1 to the number of measures for a patient (Kirkwood et al., 2010). The intercept *a* is where the regression line meets the vertical axias and *b* its slope. The departure of the i^{th} measure from the predicted value is *e*, referred to as the residual, and it is not predicted by the fixed part of the model $a + bx$.

In the multilevel case of several patients we assume a regression relation for each patient;

$y_{ij} = a_j + bx_{ij} + e_{ij}$

where the subscript *j* takes the value from 1 to the number of patients in the data set. The multilevel model therefore accounts for within-patient as well as between-patient variation across repeated measures. Since patients are treated as a random sample, we re-express the equation as:

$y_{ij} = a_j + bx_{ij} + u_{ij} + e_{ij}$

where u is the departure of the j^{th} patient's intercept from the overall value, the latter forming the random part of the model.

Multilevel models assume the variables follow a normal distribution. Normal quantile-quantile plots were constructed to assess the normality of data in addition to formal significance testing using the Shapiro-Wilk test (Shapiro et al., 1965). Where the model residuals were not normally distributed we found suitable transformations to normality and homoscedasticity. Covariates included gender and age of onset of disease. Random effects were included for patient identifier and centre.

2. Assessment of muscle strength using MRC score by manual muscle testing (MMT)

Using adaptive LASSO, we are able to perform variable selection and are able to identify the covariates that are the best predictors for the time of onset on the logarithmic scale. In particular, the relevant covariates which result in a cross-validation error less than one standard error from the minimum consists of age (on the logarithmic scale), gender and five muscle groups: neck extensors, elbow flexors, long finger flexors, abductor pollicis brevis and knee extensors. We used canonical correlation analysis to obtain the loadings for these muscles that maximised its correlation with age of onset (log scale), gender and time of onset (log scale). This factor was then fitted as a response variable, using multilevel linear modelling, using covariates age of onset (log scale), gender, and time of onset (log scale). A

random effect was included for each patient ID to account for repeated measurements within the same patient over time. Cross-validation analysis confirms that using the logarithmic scale for both age and time minimises error.

3. Assessment of muscle strength by quantitative myometry scores

Similar to the procedure in 2., we use adaptive LASSO to perform variable selections for the models using muscles and grip, muscles only and grip only, where both the muscles and grip are measured as percentage of baseline. When we are considering both muscles and grip, the relevant covariates are age, gender, ankle dorsiflexors and grip. Involving additional covariates here leads to overfitting errors. When considering muscles only or grip only, all the covariates are relevant. The canonical correlation analysis and multilevel modelling used is same as in 2.

4. Survival analysis by Cox proportional hazards regression

The Cox model is expressed by the *hazard* function where $h(t)$ is the baseline hazard at time t, and x_1 to x_p are the p exposure variables:

$$\text{Log}(h(t)) = \log(h_0(t)) + \beta_1 x_1 + \beta_2 x_2 + \ldots + \beta_p x_p$$

Using this method, time to use of a mobility aid was modelled by age of onset and gender.