INTRODUCTION

Spinal muscular atrophy (SMA) is an autosomal recessive disorder that affects spinal cord neurons, and is clinically characterized by muscle weakness and genetically by mutations in the survival Motor Neuron (SMN) gene. Children with SMA experience weakness over a wide range of severity. Type 1 SMA are never able to sit independently and generally die in infancy. Type 2 SMA can sit but are never able to walk and often develop severe pulmonary and orthopaedic complications. SMA type 3 children acquire the ability to walk. SMA appears to be a slowly progressive disease confirmed by the progressively worsening course of restrictive respiratory insufficiency in all SMA type [loos, 2004]. Iannaccone et al. have shown in a long term prospective study that patients with SMA are very stable with regard to strength [Iannaccone, 2000]. Other studies have documented deterioration in motor function due to increase body size without an increase in power to cope with these extra demands. As a result a significant proportion of children with SMA type 3 lose the ability to walk independently [Barois, 2005, Crawford, 2004, Zerres, 1995]. Valid and sensitive outcomes measures are needed to precisely evaluate the natural history of the disease and the effect of treatments on motor function. The Motor Function Measure (MFM) is a reliable tool designed for all neuromuscular diseases and applicable to all degrees of disease severity in ambulant and non-ambulant patients. The MFM-32 consists of 32 items (tasks) classified in three dimensions: D1, standing and transfers; D2, axial and proximal motor capacity; D3, distal motor capacity [Berard, 2005]. A total score and a score for each dimension may be calculated.

AIMS OF THE RESEARCH

• To describe the population and to study applicability of the MFM to patients with spinal muscular atrophy type I, type II and type III and describe the course of the motor function impairment
• To estimate annual rate of change in scores according to subtype
• To estimate the number of subjects required in a therapeutic trial to show a difference in motor function at 12 months

PATIENTS AND METHODS

Results of 94 patients with SMA aged ≥ 6y, assessed at least once with the MFM and up to 5 years, were collected by research assistant in 18 neuromuscular clinics located in France, Belgium and Switzerland. These clinics use the MFM for their routine follow-up of patients. All MFM were performed by therapists trained with MFM. Cooperation of the patients and distributions of the MFM scores were analyzed within subtypes. Relation with age was studied and slopes of change for patients with at least one follow-up were estimated. Numbers of subjects required for inclusion in a therapeutic trial to demonstrate an effect on motor function have been estimated based on responsiveness of the MFM (SRM = Standard response mean).

RESULTS

A total of 164 MFM have been performed in 9 patients with SMA type I, 44 patients with SMA II and 59 patients with SMA III (table 1). Cooperation of patients has been rated as optimal in 86%. Forty patients were assessed at least twice with a follow-up ranging from 1 month to 5,5 years and 28 patients with a follow-up of at least 1 year.

In terms of motor function measured by the MFM, SMA appears as only one disease with different degrees of severity (Fig 1 and table 1).

SMA type III
• Difference between walking and non walking patients according to D1 (figure 2)
• 16 patients lost ability to walk at a mean age 12.1 y +/- 5.4
• Particular interest of D1 and Total score
• D1 subscore near 40% separates ambulant and non ambulant patients (figure 2)
• D1: mean decline : -5.2% / year (SRM=0.56)
• Total score: mean decline : -1.4% / year (SRM= 0.32)

Figure 2: Sub-score D1 in SMA type III

Table 1: Estimation of the number of subjects to include in a therapeutic trial

<table>
<thead>
<tr>
<th>SMA</th>
<th>Age M</th>
<th>Cooper.</th>
<th>D1</th>
<th>D2</th>
<th>D3</th>
<th>TS</th>
</tr>
</thead>
<tbody>
<tr>
<td>SMA I</td>
<td>10.2 + 2.7</td>
<td>6/3</td>
<td>6/6</td>
<td>2.3 + 2.4</td>
<td>35.7 + 7.7</td>
<td>30.9 + 15.5</td>
</tr>
<tr>
<td>SMA II</td>
<td>11.9 ± 5.5</td>
<td>24/29</td>
<td>34/38</td>
<td>3.5 ± 13.4</td>
<td>27.9 + 1.3</td>
<td>19.9 + 15.4</td>
</tr>
<tr>
<td>SMA III</td>
<td>12.0 ± 4.0</td>
<td>36/39</td>
<td>44/47</td>
<td>3.3 ± 11.0</td>
<td>23.1 - 0.3</td>
<td>11.1 - 1.0</td>
</tr>
</tbody>
</table>

SMA type II
• Particular interest of D2, D3 and Total score
• D2: mean decline: -3.05% / year (SRM=1.2) (figure 3)
• D3: mean decline: -4.28% / year (SRM=0.40)
• Total score: mean decline: -0.94% / year (SRM=0.63)

Figure 3: Sub-score D2 in SMA type II

DISCUSSION / CONCLUSIONS

These results show a continuum in terms of motor function among the 3 types of SMA with a slowly progressive decrease of motor function (whatever the type and the disease duration) and a similar rate of progression of the total score according to age for types II and III. If short test forms are needed, we suggest the particular interest of D1 in SMA type III who have not lost ambulation, and D2 and D3 in SMA type II and non-ambulant SMA type III.

The present results are also promising regarding the use of the MFM in clinical trials to demonstrate either deterioration of a patient's condition or a possible improvement due to treatment. The present results can be used to estimate the number of patients to include in a therapeutic trial. They can be used to design a prospective clinical trial. The number depends on the study design, on the required power, on the hypothesis concerning the outcome and on the patients' ability to walk.

The advantage of using the MFM for patients with SMA is to have a unique outcome measure whatever the walking ability and functional status change (for example SMA III becoming non ambulant). Validation of the MFM with only 20 items adapted to children between 2 and 6 years is on-going. Gathering of the MFM results on the databank connected via internet will facilitate the clinical studies. The user's manual translated in different languages can be downloaded from the website: www.mfm-nmd.org