ORIGINAL ARTICLE

Responsiveness of the Motor Function Measure in Patients With Spinal Muscular Atrophy

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Abstract
Objective: To assess the ability of the Motor Function Measure (MFM) to detect changes in the progression of spinal muscular atrophy (SMA).
Design: Observational, retrospective, multicenter cohort study.
Setting: Seventeen departments of pediatric physical medicine.
Participants: Volunteer patients with SMA (N = 112) aged 5.7 to 59 years with no treatment other than physical therapy and nutritional or respiratory assistance.
Interventions: Not applicable.
Main Outcome Measures: The distributions of the MFM scores (total score and 3 subscores) were analyzed per SMA subtype. The relationships between scores and age were studied. The slopes of score changes (reflecting MFM responsiveness) were estimated in patients with at least 6 months’ follow-up and 2 MFMs. Hypothetical sample sizes for specific effect sizes in clinical trial scenarios are given.
Results: In 12 patients with SMA type 2 and 19 with SMA type 3 (mean ± SD follow-up, 25.8 ± 19 mo), there was a moderate inverse relationship between age and the MFM total score. Patients with less than 6 months’ follow-up showed little score changes. Patients with longer follow-ups showed a slow deterioration (−0.9 points/y for type 2 and −0.6 points/y for type 3). Substantial responsiveness was obtained with the MFM Dimension 2 subscore (proximal and axial motricity) in patients with SMA type 2 (standardized response mean [SRM] =1.29), and with the MFM Dimension 1 subscore (standing and transfers) in patients with SMA type 3 aged 10 to 15 years (SRM = .94).
Conclusions: If further confirmed by larger studies, these preliminary results on the relative responsiveness of the MFM in SMA will foster its use in monitoring disease progression in patients who participate in clinical trials.

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Spinal muscular atrophy (SMA) is a recessively inherited neuromuscular disease characterized by a degeneration of the spinal cord motor neurons. The clinical spectrum of SMA is highly variable and ranges from early infant death to normal adult life. The severity of muscle weakness depends mainly on the patient’s age at disease onset and, most importantly, on the maximal motor milestone acquired (ability to hold head up, sit, or walk).1 This led some authors to propose defining SMA stages by the ability to sit or walk.2-5

The recent understanding of the pathogenesis of SMA raised hopes that specific therapeutic approaches might be possible.6 Many clinical trials—planned, in progress, or completed—have chosen motor function as the primary or secondary outcome.5 Indeed, in children with SMA, motor function assessment tools appeared to be more reliable than quantitative muscle testing in monitoring the course of the disease.7,8 Nonetheless, valid and responsive outcome measures are still needed to assess the effect of a treatment on the motor function of patients with SMA.9,10
Today, few clinical outcome measures, except survival, are available for patients with SMA type 1, the most severe form of the disease. Therefore, a motor function measure that allows an assessment of patients with SMA, regardless of the disease type, is welcome. Validation studies of many scales applied to SMA have already been published—for example, the Gross Motor Function Measure (GMFM),12 the Hammersmith Functional Motor Scale for SMA (HFMS),13,14 the Expanded HFMS (ExpHFMS),15,16 and the Upper Limb Module for Nonambulant SMA Patients. However, the validation processes of most scales lack specific responsiveness assessments (ie, sensitivity to change studies).18

Within the specific context of SMA, the HFMS and the Modified HFMS (MoHFMS)19 are used only in nonambulant patients with SMA types 2 and 3. The 6-minute walk test is now routinely used to assess patients with neuromuscular diseases, especially Duchenne muscular dystrophy and SMA. Although convenient and useful in patients with SMA type 3,20 this test becomes useless when ambulation is lost during follow-up, especially during a clinical trial. The ExpHFMS has added 13 items from the GMFM to capture various aspects of ambulation. Its reliability and validity have been validated in SMA types 2 and 3,15 but the methodology used for its construction has been the object of some criticism.18 The Motor Function Measure (MFM) is a reliable tool designed for most of the neuromuscular diseases and is applicable to a wide range of disease severities in ambulant and nonambulant patients between 6 and 60 years of age.21 The MFM showed good convergent validity and excellent correlations with the Vignos, Brooke, and FIM scales, as well as with a visual analog scale of overall motor impairment used by some physicians.19 The preliminary results concerning responsiveness in a population of 152 patients with various neuromuscular diseases (of whom 15 had SMA) showed good responsiveness, especially in Duchenne muscular dystrophy.22,23

The aim of the present study was to monitor motor function impairment in patients with SMA types 1, 2, and 3 using the MFM in order to study the responsiveness of the MFM in this disease and provide estimations of the number of patients with SMA needed for clinical trials to prove the effectiveness of a given drug.

Methods

Participants

For the present study, data were collected from patients followed up in 17 departments of pediatric physical medicine located in France, Belgium, and Switzerland. These centers use the MFM in the everyday management of patients with a wide variety of neuromuscular diseases, and their physiotherapists were given specific training in administering the MFM with a high interrater reliability.21 The protocol of the study was approved by the ethics committee of Hospices Civils de Lyon on June 26, 2009.

The inclusion criteria were as follows: (1) patients older than 5 years at first MFM testing; (2) a clinical diagnosis of SMA type 1, 2, or 3 with laboratory confirmation of a mutation of the survival motor neuron (SMN) gene; (3) at least 1 MFM testing by a trained physiotherapist during routine follow-up; and (4) no treatment other than physical therapy, nutritional assistance, and respiratory assistance.

In the present study, in agreement with the International SMA Consortium,1,24 SMA is classified into 3 clinical types: (1) SMA type 1 (severe) with onset between birth and 6 months of age (patients unable to sit without support and/or death occurring usually before 2y of age), (2) SMA type 2 (intermediate) with onset before 18 months of age (patients able to sit but unable to stand or walk unaided and/or death occurring usually after 2y of age); and (3) SMA type 3 (mild) with onset after 18 months of age (patients able to stand and walk and/or death occurring in adulthood).

Motor Function Measure-32

The MFM-32 consists of 32 task items in 3 dimensions that provide a detailed profile of the physical impairment: D1, standing and transfers; D2, axial and proximal motor function; and D3, distal motor function. The scoring of each task uses a 4-point Likert scale based on the subject’s maximal abilities without assistance: 0, cannot initiate the task or maintain the starting position; 1, performs the task partially; 2, performs the task incompletely or imperfectly (with compensatory/uncontrolled movements or slowness); and 3, performs the task fully and “normally.” The 32 scores are summed to yield a total score expressed as the percentage of the maximum possible score (the one obtained with no physical impairment); the lower the total score, the more severe the impairment.

In routine follow-up of patients with neuromuscular diseases, the MFM scores of each patient are automatically reported by the physiotherapist on a specific scoring sheet allowing a longitudinal follow-up. Furthermore, the cooperation of the patients is also rated as null, moderate, or optimal.

Data collection

By the end of 2009, the scores of MFM tests administered to 112 patients in the 17 centers between 2005 and June 30, 2008, were collected by a clinical research assistant. For each patient, a specific clinical questionnaire was filled out from the medical records; it included detailed information on motor deterioration milestones (eg, loss of ambulation, defined as the inability to walk 10 steps without assistance).

Statistical analysis

The MFM scores were presented as mean, SD, and range per SMA type and walking ability. The relationship between the MFM total score and age at first visit was analyzed in patients with SMA types 2 and 3 by using regression modeling. The assumption of homogeneity of the regression slopes was tested using an analysis of covariance.

The responsiveness was studied according to the SMA type (in types 2 and 3) by analyzing the slopes of change in patients with at least 6 months’ follow-up. Precisely, for each patient, the repeated
measurements of the MFM total score and the subscores were summarized by a slope of change expressed as an annual rate using the unweighted least-square estimate. These slopes were then expressed as standardized response means (SRMs) by calculating the ratios of the mean slopes to their SDs. These SRM values were considered high if >.80, moderate if ranging from .50 to .79, and low if <.50. These estimations helped in calculating the number of patients needed in a clinical trial to detect various outcome differences with various statistical powers.

Results

Patients' characteristics

A total of 112 subjects (61 males, 51 females) with genetically confirmed SMA were evaluated. Their characteristics and MFM scores by SMA type are displayed in Table 1. Among patients with SMA type 3, 16 lost the ability to walk between the ages of 3 and 28 years (mean ± SD: 12.1±5.4y). Patients' cooperation was rated optimal in 90% of type 2 and 80% of type 3 patients.

Figure 1 shows the total MFM scores at first MFM testing according to age. A first finding from this figure is that there are areas where the scores of patients of different disease types overlap. Another finding is that the regression lines that fit the total scores of patients with SMA types 2 and 3 have a slow decrease with age. A third finding is that the lines that fit the total scores of patients with SMA types 2 and 3 (equations: MFM total score = [−.85 × age] + 49.77 and MFM total score = [−.67 × age] + 82.65, respectively) are almost parallel. This may be considered as a trend toward similar disease progressions along time in patients with SMA types 2 and 3 (analysis of covariance slope test P = .71). The number of patients with SMA type 1 was not sufficient to generate a reliable regression line.

MFM responsiveness

Overall, 164 MFM tests were carried out, and 40 patients were assessed at least twice. The mean ± SD follow-up duration was 21.6±18.8 months (range, 1.1–66.4mo). The number of patients analyzed for responsiveness was 31, with a mean ± SD follow-up of 25.8±18.9 months.

The scores of patients with short follow-ups (<6mo) showed little variation. Table 2 shows the slopes of change of the scores of patients with long follow-ups (>6mo) according to the SMA type. As expected, the slopes of change of the MFM total score in the latter patients showed slow deterioration: −0.9±1.45 points per year for patients with SMA type 2 (mean age ± SD, 9.67±3.24y), −0.6±4.0 points per year for all patients with SMA type 3 (mean age ± SD, 21.15±14.1y), and −2.9±3.3 for patients with SMA type 3 aged 10 to 15 years (mean age ± SD, 12.6±1.9y).

Figure 2 shows the changes in individual MFM subscore D2 according to age in patients with SMA type 2. These changes indicate a substantial responsiveness of this subscore in these patients (−3.25±2.52 points/y, SRM = 1.29).

Figure 3 shows the changes in individual MFM subscore D1 according to age in patients with SMA type 3. Here again, the changes indicate a substantial responsiveness of this subscore, especially in patients with SMA type 3 aged 10 to 15 years (−6.22±6.59 points/y, SRM = 9.4). As for the improvement found in several adult patients with SMA type 3 (n = 6), we may evoke 2 nonexclusive causes linked to the first MFM: (1) a learning effect; and (2) a motivation to get more exercise. However, these cases had only 2 assessments; thus, longer follow-ups are needed to obtain better estimates of motor function progression.

Estimation of the number of subjects to include in a clinical trial

Table 3 shows the estimated number of patients needed for a clinical trial to demonstrate the beneficial effect of a given treatment according to the desired effect of a 1-year active treatment versus placebo, statistical power, and alpha risk. For example, with 80% power and a 5% alpha risk, a stabilization of motor function would require 2 groups of 12 patients with SMA type 2 using the D2 subscore. In SMA type 3, 2 groups of 55 patients would be needed with the D1 subscore. If half the decrease in motor function in the treatment group versus the placebo group is to be reached, with 80% power and 5% alpha risk, 2 groups of 45 patients with SMA type 2 would be needed using the D2 subscore. In patients with SMA type 3, 2 groups of 210 patients would be needed with the D1 subscore.

### Table 1

<table>
<thead>
<tr>
<th>Variable</th>
<th>SMA Type 1</th>
<th>SMA Type 2</th>
<th>SMA Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>9</td>
<td>44</td>
<td>59</td>
</tr>
<tr>
<td>Males</td>
<td>6</td>
<td>24</td>
<td>31</td>
</tr>
<tr>
<td>Age (y)</td>
<td>10.2±2.7 (7.4–15.4)</td>
<td>11.5±5.0 (5.7–27)</td>
<td>18.7±12.3 (6.2–59)</td>
</tr>
<tr>
<td>Range of follow-up (mo)</td>
<td>3.6–28.8</td>
<td>2–62.4</td>
<td>1.2–66</td>
</tr>
<tr>
<td>Follow-up &gt;6mo</td>
<td>1</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>Patients with at least 2 MFM</td>
<td>3</td>
<td>14</td>
<td>23</td>
</tr>
<tr>
<td>Patients with more than 2 MFM</td>
<td>1 with 3 MFM</td>
<td>9 with 3 MFM</td>
<td>2 with 3 MFM</td>
</tr>
<tr>
<td></td>
<td>3 with 4 MFM</td>
<td>3 with 4 MFM</td>
<td>1 with 4 MFM</td>
</tr>
<tr>
<td>Optimal cooperation</td>
<td>6/6</td>
<td>34/38</td>
<td>38/47</td>
</tr>
</tbody>
</table>

NOTE. Values are n, mean ± SD (range), or as otherwise indicated.
Significant changes, SRM

different functional outcomes and progression rates, but the subtypes of SMA type 3 (3a and 3b). These subtypes certainly have never able to sit. The study did not consider patients with 2 different fact, of SMA “type 1b,” at borderline with type 2; that is, they were of pure classification (Munsat or Dubowitz), these patients are, in all receiving assisted ventilation, have prolonged survival. In terms the 2 types might not be negligible. Some patients with SMA type 1, proportion of patients with disease features intermediate between these scores decreased almost in parallel with age. Thus, the score was not reliably able to distinguish between patients with sample size was not large enough to consider this distinction.

The present results tend to confirm that SMA is a single disease entity with variable presentations and that it consists of a continuous spectrum of severities rather than clearly separated types. First, there were age ranges (8–12y and 17–19y) within which the total MFM score was not reliably able to distinguish between patients with SMA type 2 and type 3 (ie, where high-score patients with type 2 and low-score patients with type 3 were intermingled). Second, these scores decreased almost in parallel with age. Thus, the proportion of patients with disease features intermediate between the 2 types might not be negligible. Some patients with SMA type 1, all receiving assisted ventilation, have prolonged survival. In terms of pure classification (Munsat or Dubowitz), these patients are, in fact, of SMA “type 1b,” at borderline with type 2; that is, they were never able to sit. The study did not consider patients with 2 different subtypes of SMA type 3 (3a and 3b). These subtypes certainly have different functional outcomes and progression rates, but the sample size was not large enough to consider this distinction.

The classification of SMA has been amended to reflect the natural history of the disease, but this does not seem to have fully succeeded. According to a number of authors, all attempts to classify a disease are artificial, and classifications do not always correspond to pathophysiologic realities. The current classification of SMA should be used with caution for prognosis because the age at death is mainly influenced by exogenous factors such as pulmonary infections or inadequate medical care. Actually, the International Conference on SMA Standard of Care came to the consensus that the most appropriate care for patients with SMA should be tailored according to their current functional status rather than to the disease type.

The MFM allows the use of the same outcome measure in all patients with SMA whatever the disease type, whereas few outcome measures other than survival are available in patients with extreme muscle weakness, such as those with SMA type 1 or type 2. Myometry, the HFMS, or the MoHFMS are reliable in patients with SMA types 2 and 3 but not in those with type 1. The 6-minute walk test and other timed tests are not appropriate in nonambulant patients; they are applicable only to patients with SMA type 3. The recent module by Mazzone et al specifically designed to assess upper limb function in nonambulant patients with SMA, complements the current scales used in very weak SMA patients with severe contractures in the lower limbs, but still needs further validity and responsiveness studies.

We agree with a recent opinion that SMA is a gradual process of muscular atrophy and weakness. Our results confirm this view, with significant decreases in MFM subscore D2 in patients with SMA type 2, and in MFM subscore D1 in ambulant patients with SMA type 3 at ages of loss of ambulation (10–15y). Thus, depending on the desired outcome, we consider it mandatory to analyze all MFM subscores and not only the total score. In specific conditions, such as in ambulant patients with no major status change, the D1 subscore will be more sensitive to change while the others will remain stable. Subscore D2 shows good responsiveness in patients with type 2 SMA, and subscore D1 shows good responsiveness in patients with type 3. In clinical trials, we propose to use only the subscores that show interesting changes.

![Fig 1](image-url)

The lines fitting the first MFM total score according to age in patients with SMA type 2 (dark squares) and type 3 (clear dots). Patients with SMA type 1 (gray triangles) are represented without fitting line.

### Discussion

The present results tend to confirm that SMA is a single disease entity with variable presentations and that it consists of a continuous spectrum of severities rather than clearly separated types. First, there were age ranges (8–12y and 17–19y) within which the total MFM score was not reliably able to distinguish between patients with SMA type 2 and type 3 (ie, where high-score patients with type 2 and low-score patients with type 3 were intermingled). Second, these scores decreased almost in parallel with age. Thus, the proportion of patients with disease features intermediate between the 2 types might not be negligible. Some patients with SMA type 1, all receiving assisted ventilation, have prolonged survival. In terms of pure classification (Munsat or Dubowitz), these patients are, in fact, of SMA “type 1b,” at borderline with type 2; that is, they were never able to sit. The study did not consider patients with 2 different subtypes of SMA type 3 (3a and 3b). These subtypes certainly have different functional outcomes and progression rates, but the sample size was not large enough to consider this distinction.

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### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>SMA Type 2</th>
<th>SMA Type 3</th>
<th>All Ages</th>
<th>SMA Type 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>12</td>
<td>19</td>
<td>21.15±14.14 (8–29)</td>
<td>12.6±1.9 (10–14.58)</td>
</tr>
<tr>
<td>Age (y)</td>
<td>9.67±3.24 (5.75–16)</td>
<td>18.5±14</td>
<td>22±19</td>
<td></td>
</tr>
<tr>
<td>Follow-up (mo)</td>
<td>37±20</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D1 score</td>
<td>-0.18±0.90</td>
<td>-1.95±6.98</td>
<td>-6.22±6.59</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.2</td>
<td>0.28</td>
<td>0.94</td>
<td></td>
</tr>
<tr>
<td>D2 score</td>
<td>-3.25±2.52</td>
<td>0.71±3.73</td>
<td>-0.72±2.69</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.29</td>
<td>0.19</td>
<td>0.27</td>
<td></td>
</tr>
<tr>
<td>D3 score</td>
<td>1.93±3.81</td>
<td>-0.13±4.53</td>
<td>-0.52±4.41</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.51</td>
<td>0.03</td>
<td>0.12</td>
<td></td>
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<tr>
<td>Total score</td>
<td>-0.86±1.45*</td>
<td>-0.55±3.99*</td>
<td>-2.91±3.33*</td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.6</td>
<td>0.14</td>
<td>0.87</td>
<td></td>
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</table>

* Significant changes, SRM>=0.6.
within shorter times (ie, D2 in SMA type 2 or D1 in SMA type 3). Distal motor function remains relatively preserved until the late stages of the disease; thus, subscore D3 seems the least useful subscore in patients with SMA.

Several authors have already described the slow decline in motor function over time and related it to a loss of muscle strength. On the contrary, others related the deterioration in motor function to increased body size, contractures, and scoliosis without an increase in power to cope with these extra demands. Fannaccone et al reported that none of their patients lost strength but that they had some loss of motor function during the observation period. In a recent observational study of 71 patients with SMA types 2 and 3, the authors found no detectable mean change in motor function over the 12-month follow-up period as measured by the GMFM, the HFMS, or the ExpHFMS; they suggested a nonprogressive or a stable course of the disease. That conclusion is not consistent with the present results. One reason for the divergence could be an insufficient responsiveness (sensitivity to change) of the measures used to detect change. A longer follow-up of the patients is also needed to check the disease progression rate. We believe the individual course of the disease is probably not a slow continuous worsening but a succession of stable and worsening phases. One argument is that, in our sample, especially in patients with SMA type 3, the age range of 10 to 15 years was a crucial period during which the disease exacerbated the most; that is, the loss of motor function was the most obvious (−6.22±6.6 points/y on average for D1), and indeed, the loss of ambulation is often reported to occur 10 years after the disease onset.

The use of the MFM in our sample of patients with SMA was rather satisfactory despite the inclusion of patients with important muscle weakness. Indeed, patient cooperation was high whatever the SMA type, and there was no relationship between disease severity and the time required to complete the test. In previous independent investigations, the average MFM-32 test completion time in 34 patients with SMA aged ≥6 years was 39 minutes, and the average for the MFM-20 in 21 patients with SMA aged 2 to 6 years was 26 minutes. For comparison’s sake, O’Hagen et al reported that completion times for the ExpHFMS were between 20 minutes and 1 hour.

Studying changes in motor function in SMA has become increasingly important in light of future clinical trials. The reliable measurement of these changes over more than 1 year using the MFM (expressed as an annual rate of change) allowed us to estimate the number of subjects needed for a clinical trial according to the SMA type (though a disputed notion), the expected progress, and the desired study power. However, the above estimated sample sizes might be underestimated and should be compared with those provided by trials with placebo groups, because improved care to participating patients might change the expected rate of motor function decline. Also, even though the MFM total score was found to be less responsive than the MFM subscores, it is worth using as a first overall indicator of motor function impairment, and in phase III studies, it will capture a wide range of severities and different rates of disease progression.

### Study limitations

One limitation of this study is its retrospective nature. However, it showed interesting results because the patients were not treated and because increasing numbers of patients are being included in clinical trials while the measurement tools are still scarce. A Rasch analysis was not performed to evaluate the consistency of the MFM in the present study of patients with SMA because the sample size was not sufficient to yield conclusive results. Fatigue is a nonnegligible clinical aspect in patients with SMA that may interfere significantly with the completion of the MFM over nearly 30 minutes and sometimes up to 45 minutes or more. To better capture potential fatigue, some researchers have proposed to time this duration into account. However, in future large clinical trials, it is hoped that MFM duration and patient management between measures will be better controlled and that randomization will balance these and other factors. Besides, one may notice that some patients have reached the maximum subscores. This does interfere
with the objective of the present study because, past this maximum, the status of a given patient is deemed unable to improve; it can only worsen. Then subscores D1 and D2 may still be used in SMA types 3 and 2, respectively, to monitor state improvement after a given therapeutic intervention.

This small sample size and the very slow progress of the disease require that this preliminary study be extended in size and time for a more robust generalizability and power calculations for future clinical trials. At present, a large MFM database is collecting data from many centers in France and abroad, which will soon further test the validity and sensitivity to change of the MFM in untreated patients with SMA on a larger cohort. This will make it possible to carry out a specific analysis in every disease type. Finally, although we acknowledge a possible relationship between the SMN2 copy number and functional limitation, this copy number was not considered in the present study because of a lack of data.

Conclusions

In this investigation of the appropriateness of the MFM to assess the progression of motor function in SMA, the measure was able to show slight deteriorations in patients followed up more than 6 months, and 2 of its subscores were particularly responsive in patients with SMA types 2 and 3 during the period close to the loss of ambulation. The MFM is thus a good candidate among very few tools able to monitor disease progression in patients with SMA presenting with a wide range of disease severity who participate in clinical trials. Further studies will extend the present promising results to other neuromuscular diseases.

Keywords

Clinical trial; Mobility limitation; Muscle weakness; Muscular atrophy, spinal; Neuromuscular diseases; Rehabilitation

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