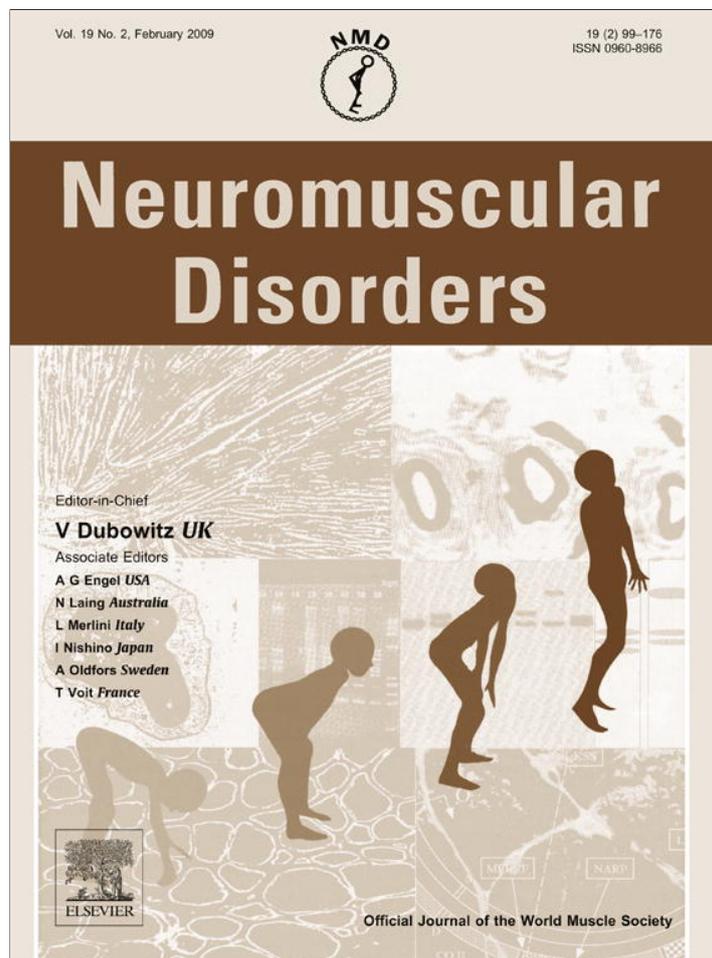


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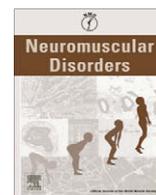
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## Neuromuscular Disorders

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## Activity limitations in patients with neuromuscular disorders: A responsiveness study of the ACTIVLIM questionnaire

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## ABSTRACT

Recently, a self-reported scale of activity limitations, the ACTIVLIM questionnaire, was developed and validated in patients with neuromuscular disorders (NMD). The purpose of this study was to investigate its sensitivity to change. One hundred thirty-two patients with NMD (mean age, range: 31, 6–80) were assessed twice, with  $21 \pm 4$  months in between, using the ACTIVLIM questionnaire. Mean score change, effect size, standardized response, mean paired *t*-test and an individual-level statistical approach were calculated for groups of patients according to their self-rated functional status evolution and for three main diagnostic groups (Ambulant and wheelchair-bound Duchenne muscular dystrophy patients, myotonic dystrophy patients, and patients with Charcot–Marie–Tooth neuropathy). The responsiveness indices showed that the change in activity measures was higher in patients who reported deteriorated functional status and in patients with Duchenne muscular dystrophy. The ACTIVLIM questionnaire showed a good sensitivity to change and could be useful in research settings to characterize the disease course of NMD.

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### 1. Introduction

Most neuromuscular disorders (NMD) have a progressive clinical course characterized by a decrease in muscle strength leading to impaired motor function [1]. Consequences of these diseases include fatigue, problems with locomotion and loss of functionality in daily activities. Difficulties in performing daily activities are defined by the World Health Organization as activity limitations [2]. Activity limitations in patients with NMD can be measured with a new scale, ACTIVLIM, which was recently developed and validated using the Rasch model [3]. This questionnaire presents excellent psychometric qualities, including reliability, construct validity, reproducibility, linearity and unidimensionality. Nevertheless, its sensitivity to change has not yet been studied. Sensitivity to change, or responsiveness, is defined as the ability of an instrument to detect important changes over time [4] and is a required psychometric quality for any instrument to be used in clinical trials and research designs [5,6].

The purpose of this study was to investigate the responsiveness of the ACTIVLIM questionnaire in relation with the natural evolution of the activity limitations in patients with NMD. The systematic use of a sensitive questionnaire dedicated to patients with

NMD could help characterizing the clinical course of the disorders and quantifying the effects of new treatments on their activity limitations.

### 2. Patients and methods

#### 2.1. Patients

This study was approved by the Medical Ethics Committees of the Université catholique de Louvain and the Katholieke Universiteit Leuven. The patients were recruited through the neuromuscular reference centers of two university hospitals. Adult patients and the parents of affected children gave written informed consent before evaluation. Fifty-three children (41 boys and 12 girls; mean age and range: 10 years, 6–15 years) and 79 adults (48 men and 31 women; mean age and range: 44 years, 16–80 years) diagnosed with NMD were included in this study. Three main diagnostic groups were identified, each of them including more than 10% of the patients: Duchenne muscular dystrophy (DMD) ( $n = 27$ , i.e., 20% of total sample), Charcot–Marie–Tooth neuropathy (CMT) ( $n = 20$ , i.e., 15% of total sample) and myotonic dystrophy with adult onset (MD) ( $n = 17$ , i.e., 13% of total sample). The patients not belonging to one of these groups were affected by another NMD such as Becker, limb-girdle or facio-scapulo-humeral muscular dystrophy, spinal muscular atrophy, Freidreich ataxia or

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post-polio syndrome for instance. The patients did not receive any particular treatment other than physical therapy or, for instance, drugs to ease pain. The sample description is given in Table 1.

## 2.2. Procedure

Patients were assessed twice, with  $21 \pm 4$  months in between (range: 11–27 months), using the ACTIVLIM questionnaire. This questionnaire consists of 22 daily activities presented in the questionnaire development study [3], and it was originally developed using the Rasch model, which allows the conversion of ordinal scores into linear measures located on a unidimensional scale [7]. These linear measures are expressed in logits (i.e., log-odd units), the constant measurement unit of the activity scale; a higher value in logits corresponds to a higher activity level of the patient.

The first (t1) and second (t2) activity measures were obtained by asking the adult patients and the parents of the affected children to note the difficulty they perceived in performing each activity on the ACTIVLIM questionnaire, without using human help. The parent who completed their child's questionnaire was the same for both evaluations. The questionnaire had a three-level scale: (0) impossible, (1) difficult and (2) easy. Moreover, during the second evaluation, patients were asked to provide personal perceptions of their functional status evolution since the first evaluation: (a) improvement, (b) stability or (c) deterioration.

## 2.3. Data analysis

The responses of both evaluations were first fitted to the Rasch model using the Rasch Unidimensional Measurement Models computer program (RUMM2020, RUMM Laboratory Pty Ltd., Perth, Western Australia). This software reported overall fit statistics that were close to the standardized normal distribution for item and person fit residuals. The mean and standard deviation of the item fit residuals were  $-0.324 \pm 0.684$  and  $-0.292 \pm 0.332$  for t1 and t2, respectively, while the mean and standard deviation of the person fit residual were  $-0.318 \pm 0.810$  and  $-0.263 \pm 0.706$  for t1 and t2, respectively. Moreover, the chi-square item-trait interactions were not significant ( $p = 0.13$  and  $0.98$  for t1 and t2, respectively). As a result, the ordinal total scores obtained from the ACTIVLIM questionnaire could be transformed into interval-level measures of activity limitations. Two linear measures of the patient's activity level (t1 and t2) were reported in such a way that they could be quantitatively compared and treated as a continuous variable. Moreover, standard errors of measurement associated with the activity level of each patient were displayed by the software.

The sensitivity to change of the ACTIVLIM questionnaire was tested according to both group-level and individual-level approaches. The group-level approach consisted of computing

different responsiveness indices in groups of patients. In this study, groups of patients were constituted according to two criteria. The first criterion concerned a self-reported functional status evolution (improvement, stability or deterioration) and responsiveness indices were expected to be higher in groups of patients who reported an improved or deteriorated functional status than in patients who reported a stable functional status. The second criterion was concerned the natural evolution of patients included in the three main diagnoses in our sample (DMD, CMT and MD), constituting 48% of the total sample. The changes in activity limitations observed in patients from these three diagnosis groups were compared in order to determine whether they are supported by the natural evolution known in these patients. Because there is no agreement regarding how best to assess the sensitivity to change of measures, this study reported the most frequently cited indices in responsiveness studies [8]. Paired *t*-test, effect size and standardized response mean were calculated in each group of functional status evolution and in the three diagnostic groups. Paired *t*-tests were used to detect statistically significant changes in activity level between the first and the second evaluation. The null hypothesis was rejected when the *p*-value was below 0.05. However, paired *t*-tests are sensitive to sample size, and different sample sizes can lead to different decisions in terms of significance [8]. Effect size, on the other hand, enabled the comparison of responsiveness between different studies or outcome measures by standardizing the change effect in units of standard deviation without influence from the sample size [8]. This corresponded to the mean change divided by the standard deviation of the initial measures. Consequently, effect size was sensitive to the distribution of the measures obtained during the first evaluation. Standardized response mean also standardized the change in the same units independent of sample size but also incorporated information about change distribution [9]. Standardized response mean corresponded to the mean change divided by the standard deviation of the change scores. Higher effect sizes and standardized response means correspond to a higher magnitude of change between both evaluations.

The individual approach to testing sensitivity to change of the ACTIVLIM questionnaire consisted of taking into account the standard error of measurement associated with the patient's activity level obtained during both evaluations. A statistic for each patient could be computed to test the extent to which the activity measures had changed [10]:

$$t_{m12} = \frac{m_2 - m_1}{\sqrt{(SE_2)^2 + (SE_1)^2}} \sim N(0, 1)$$

where  $m_1$  and  $m_2$  are the activity measures at the first and the second evaluation, respectively, and  $SE_1$  and  $SE_2$  are their associated standard errors of measurement. Moreover, the distribution of this *t* statistic is approximately a standardized normal distribution [10].

**Table 1**  
Sample description ( $n = 132$ ).

	DMD <sup>a</sup> $n = 27$	MD <sup>a</sup> $n = 17$	CMT <sup>a</sup> $n = 20$	Others $n = 68$	Total sample $n = 132$
Age, years: mean (range)	10 (6–25)	36 (16–72)	21 (7–50)	40 (6–80)	31 (6–80)
<i>Gender</i>					
male, <i>n</i>	27	11	10	41	89
female, <i>n</i>	–	6	10	27	43
<i>Mobility level</i>					
Ambulant, <i>n</i>	16	17	18	47	98
Wheelchair-bound, <i>n</i>	11	–	2	21	34
Delay between both evaluations, months: mean (range)	17 (12–25)	22 (18–27)	19 (13–27)	22 (11–27)	21 (11–27)

<sup>a</sup> DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; CMT, Charcot–Marie–Tooth neuropathy.

Therefore, patients with a  $t$  statistic above 1.96 or below  $-1.96$  will show a statistically significant improvement or deterioration of their activity level, respectively.

### 3. Results

The mean activity level of the 132 patients was  $1.18 \pm 2.71$  logits at  $t_1$  and  $0.48 \pm 2.93$  logits at  $t_2$ . The paired  $t$ -test ( $t = 6.6$ ,  $p < 0.001$ ) indicated that the overall activity level of patients with NMD significantly decreased after  $21 \pm 4$  months. Effect size and standardized response mean were 0.25 and 0.57, respectively.

#### 3.1. Group approach

##### 3.1.1. Functional status evolution groups

Seven patients did not answer the question about their functional status evolution without giving any reason; therefore the data of these patients could not be analyzed according to this approach. Sixty-one patients reported a deteriorated functional status between both evaluations, and 60 patients reported a stable functional status. As only 4 patients reported an improved functional status, no responsiveness indices were calculated in this group of patients. Fig. 1 (left panel) shows the means and the standard deviations of the activity levels at  $t_1$  and  $t_2$  in patients who reported a stable or deteriorated functional status. Table 2 reports the responsiveness indices of the ACTIVLIM questionnaire in both of these groups. The change in activity level was higher in the group of patients who reported a deteriorated functional status than in the group of patients with stable functional status ( $-1.1$  logits and  $-0.35$  logits, respectively). The effect size, standardized response mean and paired  $t$ -test confirmed these observations.

##### 3.1.2. Diagnostic group

Fig. 1 (right panel) shows the means and the standard deviations of the activity levels at  $t_1$  and  $t_2$  in the three main diagnostic groups present in our sample (DMD, MD and CMT). Table 2 reports the responsiveness indices in these groups but also in the group of patients with other NMDs. The change in activity level was higher in the group of patients with DMD than in the groups of patients with MD or CMT ( $-1.18$  logits,  $-0.77$  logits and  $-0.08$  logits, respectively). The responsiveness indices confirmed these observa-

tions. The change in activity level and the responsiveness indices of the group "others" are similar to the total sample.

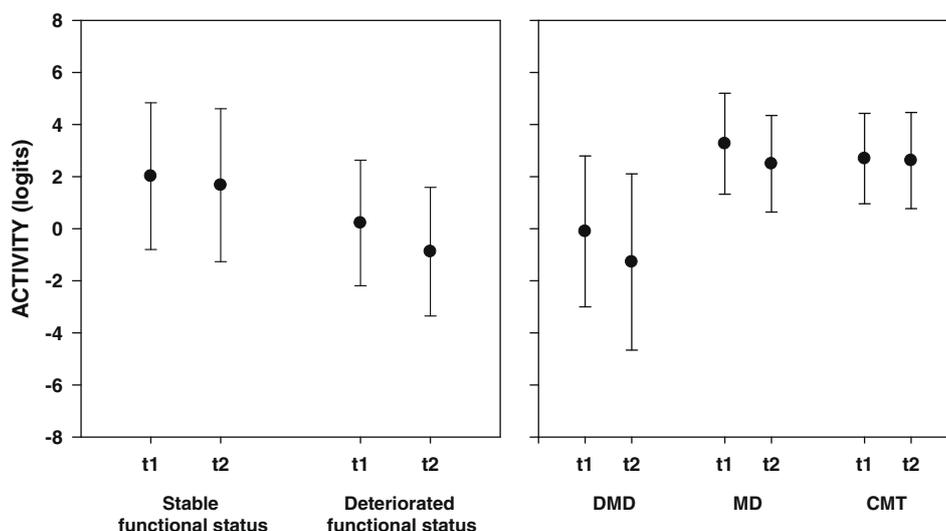
#### 3.2. Individual approach

The values of the  $t$  statistic obtained by each patient could be divided into five classes, according to limits of significance: (1)  $t > 1.96$ , (2)  $1.96 > t > 0$ , (3)  $t = 0$ , (4)  $0 > t > -1.96$  and (5)  $t < -1.96$ . Table 3 reports the proportions of patients in each of these classes and according to their self-reported functional status evolution or their diagnosis. The proportion of patients with a significant deterioration was higher in patients who reported a deteriorated functional status than in patients who reported a stable functional status (36.1% and 11.7%, respectively). Similarly, this proportion was also higher in patients with DMD than in patients with MD or CMT (44.5%, 11.8% and 5%, respectively).

### 4. Discussion

The sensitivity to change of the ACTIVLIM questionnaire was investigated in 132 patients with NMD. The activity level of the whole sample significantly decreased after  $21 \pm 4$  months, confirming the progressive clinical course of the NMD [1].

The responsiveness study of the ACTIVLIM questionnaire was completed by group-level and individual-level approaches. In the group-level approach, different indexes were computed in groups of patients. First, patients were classified according to their self-reported functional status evolution. The change in the activity measures, the effect size and the standardized response mean were lower in patients who reported a stable functional status than in those who reported a deteriorated functional status between the two evaluations (Table 1). On the other hand, the paired  $t$ -test showed a  $p$ -value of 0.02 in patients with self-reported stable functional status, indicating a significant decrease of their activity level [11]. Nevertheless, despite the fact that this change was statistically significant, the patients did not consider this change as clinically meaningful [12]. In other words, the change self-reported by the patients on the 22 items of the ACTIVLIM questionnaire was more sensitive than the overall change self-reported by the same patients. In other words, the reduction of their activity level (mean change: 0.35 logits) was not as important, because these patients



**Fig. 1.** Means and standard deviations of the activity levels expressed in logits at first evaluation ( $t_1$ ) and second evaluation ( $t_2$ ) in patients with stable and deteriorated functional status (left panel) and in patients with Duchenne muscular dystrophy (DMD), myotonic dystrophy (MD) and Charcot-Marie-Tooth neuropathy (CMT) (right panel).

**Table 2**  
Responsiveness indices based on group approach.

	Functional status evolution		Diagnosis			
	Stable <i>n</i> = 60	Deteriorated <i>n</i> = 61	DMD <sup>a</sup> <i>n</i> = 27	MD <sup>a</sup> <i>n</i> = 17	CMT <sup>a</sup> <i>n</i> = 20	Others <i>n</i> = 68
Mean change (logits)	−0.35	−1.1	−1.18	−0.77	−0.08	−0.68
Paired <i>t</i> -test	<i>p</i> = 0.02	<i>p</i> < 0.001	<i>p</i> < 0.001	<i>p</i> = 0.01	<i>p</i> = 0.71	<i>p</i> < 0.001
Effect size	0.12	0.46	0.41	0.4	0.04	0.26
Standardized response mean	0.3	0.88	0.81	0.68	0.08	0.59

<sup>a</sup> DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; CMT, Charcot–Marie–Tooth neuropathy.

**Table 3**  
Responsiveness analysis based on individual approach.

	Functional status evolution		Diagnosis			
	Stable <i>n</i> = 60	Deteriorated <i>n</i> = 61	DMD <sup>a</sup> <i>n</i> = 27	MD <sup>a</sup> <i>n</i> = 17	CMT <sup>a</sup> <i>n</i> = 20	Others <i>n</i> = 68
Significant improvement,% ( <i>t</i> > 1.96)	1.7	0	0	0	0	3
Improvement,% (0 < <i>t</i> < 1.96)	25	11.5	14.8	5.9	25	17.6
No change,% ( <i>t</i> = 0)	18.3	14.8	18.5	29.4	20	10.3
Deterioration,% (0 > <i>t</i> > −1.96)	43.3	37.6	22.2	52.9	50	47.1
Significant deterioration,% ( <i>t</i> < −1.96)	11.7	36.1	44.5	11.8	5	22

<sup>a</sup> DMD, Duchenne muscular dystrophy; MD, myotonic dystrophy; CMT, Charcot–Marie–Tooth neuropathy.

did not notice, or the ACTIVLIM questionnaire could more sensitively reflect the change in activity than the patients' self-perception. Indeed, the use of the ACTIVLIM questionnaire will inform approximately how much the activity level has changed and will give a linear measure of activity level.

The paired *t*-test and standardized response mean indicated that the ACTIVLIM questionnaire also showed a good sensitivity to change taking into account the diagnosis of the patients (Table 2). The change in activity measures was higher in patients with DMD than in patients with MD or with CMT, confirming the deterioration rate of these diseases. CMT is a slowly progressive NMD [13], while the DMD progression is faster, even fatal in the third decade of life when patients are not appropriately treated [14]. As for the clinical course of MD with adult onset, it lies somewhere between CMT and DMD since patients could become severely disabled by their fifth or sixth decade of life [15]. This analysis therefore demonstrated that the ACTIVLIM questionnaire could characterize the natural evolution of the principal NMD. However, effect size was identical in the DMD and MD groups (0.41 and 0.4, respectively), whereas these values did not reflect the same change in the activity measures in both these groups (−1.18 and −0.77, respectively). This is due to the fact that effect size is sensitive to the standard deviation of the initial scores, and in the present study, the distribution of these scores is wider in patients with DMD than in patients with MD (SD at *t*1: 2.90 and 1.93 logits, respectively). Consequently, effect size in the DMD group did not proportionally reflect its higher change in activity measures. Effect size should therefore be carefully interpreted and is not the more relevant indicator of the ACTIVLIM responsiveness in comparing both groups. Nevertheless, these effect sizes were higher than the effect size of the CMT group (0.04), allowing the change in ACTIVLIM measure of patients with DMD or MD to be compared with the change in patients with CMT. The use of the effect size has been largely debated in the literature, and some authors have firmly recommended that its use should be completed by appropriate statistical tests and associated *p*-values to avoid misinterpretation of the magnitude of change [8,16,17]. In the present study, paired *t*-tests and standardized response means clearly reflect the sensitivity to change of the ACTIVLIM questionnaire when comparing groups of patients.

The responsiveness of ACTIVLIM was also investigated according to an individual-level approach because a standard error of

measurement was associated with the activity measure of each patient. Table 3 showed that the proportion of patients with a statistically significant decrease of activity level was higher in patients who reported a deteriorated functional status evolution (36.1%) and in patients with DMD (44.5%), which is consistent with the results of the group-level approach. Table 3 also showed a large proportion of patients with a deterioration of their activity level in each group of patients. This decrease in the ACTIVLIM measures, even if trivial, reflected the progressive clinical course of the NMD. For instance, 50% of patients with CMT experienced a deterioration of their activity level, but the *t* statistics of these patients ranged from −0.2 to −1.01 and are far from the limit of −1.96, confirming an insignificant change between both evaluations. On the other hand, the activity level of four patients with DMD improved between both evaluations but this increase was not statistically significant. However, the individual-level approach presents a considerable advantage compared to the group-level approach since it could report whether the activity level of a particular patient has significantly improved or decreased. Indeed, meaningful change for groups of patients may not have the same significance for individuals [17,18]. Consequently, the individual-level approach provides clinicians an alternative method of drawing conclusions from group results to individuals. Results can henceforth be interpreted patient by patient.

Further researches will be carried out to complete the present study. First, the sensitivity to change will be tested on shorter periods of time (6–12 months) and in clinical trials to document treatment intervention. Second, the responsiveness of the ACTIVLIM questionnaire will be investigated in larger sample of patients with spinal muscular atrophy, limb-girdle or Becker muscular dystrophies. Finally, the progression of the children's activity level when they moved into adulthood will be characterized when they will be able to self-complete the ACTIVLIM questionnaire instead of their parents.

In conclusion, this study shows that the ACTIVLIM questionnaire has good potential to objectively characterize the disease clinical course of patients with NMD in terms of activity limitations. It can be a useful instrument in research settings to measure, for instance, the specific benefit of neuromuscular centers in care and follow-up treatment of the patients.

Note. The ACTIVLIM questionnaire and its administration instructions can be downloaded from [www.rehab-scales.org](http://www.rehab-scales.org) in

English, French and Dutch. The website also allows total raw scores for the ACTIVLIM questionnaire to be converted into a linear measure of activity limitations, according to the Rasch model.

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