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Disease impact on general well-being and therapeutic expectations of European Type II and Type III spinal muscular atrophy patients

Françoise Rouault [a,*], Vanessa Christie-Brown [b], Ria Broekgaarden [c], Nicole Gusset [d], Doug Henderson [e], Patryk Marczuk [f], Inge Schwersenz [g], Gil Bellis [h], Christian Cottet [a]

[a] AFM Telethon, 1 rue de l'Internationale, 91002 Evry, France
[b] SMA-Trust, 1c Atherstone Barns, Atherstone on Stour, Warwickshire CV37 8NE, United Kingdom
[c] Vereniging Spierziekten Nederland, Luitenant Generaal van Heutszlaan 6, 3743 JN Baarn, The Netherlands
[d] SMA Schweiz, Alpenstrasse 76, 3627 Heimberg, Switzerland
[e] SMA Support UK, 40 Cygnet Court, Timothy's Bridge Road, Stratford upon Avon, Warwickshire CV37 9NW, United Kingdom
[f] Fundacja SMA, Ul. Przy Forcie 10/99, 02-495 Warszawa, Poland
[g] Deutsche Gesellschaft fuer Muskelkranke, Im Moos 4, 79112 Freiburg, Germany
[h] Institut National d'Études Démographiques, 133 boulevard Davout, 75020 Paris, France

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Abstract

Spinal muscular atrophy (SMA) is a neurodegenerative disorder showing a broad clinical spectrum and no cure to date. To design and select evaluation criteria for the potential assessment of drugs currently being developed, the patient's perspective is critical. A survey, aiming to obtain a view on the current clinical state of European Type II and Type III SMA patients, the impact of this situation on their quality of life and their expectations regarding clinical development, was carried out by SMA-Europe member organizations in July 2015. A questionnaire was set up, translated into 8 European languages and sent out directly via electronic mailing to the targeted SMA patient population by the respective European patient organizations. We were able to collect 822 valid replies in less than two weeks. The questionnaire captured the current abilities of the respondents, their perception of the disease burden which appeared very similar across Europe despite some regional variations in care. According to the great majority of the respondents, stabilization of their current clinical state would represent a therapeutic progress for a compelling majority of the respondents to the questionnaire.

Keywords: Spinal muscular atrophy; Survey outcome; Patient's perspective

1. Introduction

Spinal muscular atrophy (SMA) is a rare (1:11,000 live births) [1] debilitating and incurable disease characterized by the degeneration of motor neurons in the spinal cord resulting in muscular atrophy and paralysis. Despite an improved understanding of this genetic disease, there is still no effective treatment for SMA patients [2].

Onset and severity of disease provide the basis for the classification of the different subtypes of SMA. The spectrum of severity may range from severe generalized weakness with respiratory failure in the neonatal period to mild proximal limb weakness noticed in adulthood. The onset and progression of weakness is usually characterized by rapidly progressive functional loss (lethal in Type I SMA – incidence about 58% of cases [3]), and a later slow phase of progression [4,5]. Type II SMA, representing about 29% of cases [3], typically has onset between ages 6 and 18 months. The ability to sit is usually achieved by 9 months, although this milestone may be delayed. By definition these children never stand or walk independently, but some patients are able to stand with the assistance of bracing or standing frame. Tongue atrophy with fasciculation is also a characteristic. Similar to the most severe and fatal Type I, facial and eye muscles are spared. Impaired swallowing and respiratory insufficiency are frequent in Type II, particularly in patients at the severe end of the Type II spectrum. SMA spares however the diaphragm and affects the intercostal muscles [6]. With disease progression, noninvasive ventilation (NIV) can be initiated at night in children with sleep-disordered breathing and later on during the day if daytime hypercapnia becomes an issue.

* Corresponding author. AFM Telethon, 1 rue de l'Internationale, 91002 Evry, France.
E-mail address: frouault@afm-telethon.fr (F. Rouault).

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For airway clearance and management, caregivers (mainly relatives) should learn to assist coughing when needed, through use of a cough-assist device [7]. Scoliosis occurs universally in this group and is a significant contributing factor to restrictive ventilation defects. In contrast to the majority of patients with severe generalized weakness with respiratory failure in the neonatal period, Type II SMA patients survive to age 25, and many patients live much longer due to improved and more aggressive supportive care. Type III SMA is associated with onset between ages 18 months and adulthood (calculated incidence at birth around 13% [3]). By definition standing or walking without support is achieved, although many patients lose these abilities later with disease progression. Abnormal gait characteristics are common in order to compensate for weakness, and many patients are able to continue ambulation despite severe weakness. Foot deformity may be seen in ambulatory patients. Lifespan is normal and a shift of the prevalence in favor of the Type III is observed among the SMA population with increasing age.

Respective type prevalence with increasing age in the SMA population depends on both the status at time of diagnosis and the individual natural history of the disease. In addition to the features of SMA related to motor unit loss, non-motor features may occasionally occur, when patients get older and in more severe cases. These may include sensory involvement, gastrointestinal and autonomic dysfunction, and endocrine abnormalities [8].

For all these reasons, a multidisciplinary team with experience in the care of SMA patients is required for proper delivery of care [2]. Disease burden is somewhat specific to the type of SMA, with more severe subtypes requiring more aggressive management [9]. It is important to understand the expected natural history of SMA to anticipate and stratify risk, to monitor function with appropriate measures, to determine the appropriate treatment options, and to deliver timely intervention. Proactive care and treatment decision-making by the professional care team and family are of utmost importance. This involves education of healthcare professionals and parents about the course and complications of the disease (e.g. the risk of aspiration, management of secretion, preventive measures such as routine immunizations against influenza, pneumococcus, and respiratory syncytial virus) [2,8,10]. It is also why the assessment of any therapeutic candidate requires extensive experience in the clinical management of SMA.

The objective of the present study is to provide an estimate of the disease impact on the general well-being of Type II and Type III SMA patients in Europe, and to appraise their expectations regarding the current therapeutic developments in SMA. This first large scale, multinational survey designed to prepare the way for a follow-up study would help identify meaningful therapeutic quality of life (QoL) outcomes during the course of therapeutic clinical trials.

Here we present the results of a large-scale exploratory survey which records the replies of patients and caregivers to a closed questionnaire across Europe. The goal was to get their views on certain key factors that would be useful to evaluators and which are currently lacking. In addition to the closed questions directly addressing the first set of objectives, the survey also included 2 open-ended questions and free text options which will help set-up a more in-depth survey.

2. Materials and methods

The questionnaire was prepared by a group of clinicians, researchers, caregivers and SMA patients. It consists of nine closed and two open-ended questions. The cover letter explaining the purpose of the survey, and the questionnaire itself, were translated by member organizations of the *SMA Europe* Consortium from the English version into 8 national languages spoken in across Europe (Appendix S1 for the English version).

Each member organization of the European consortium was asked to invite their Type II and III SMA patients to participate in the survey. Together with the cover letter, an access link to the questionnaire was sent out to the patients and caregivers by personal e-mailings. The questionnaire was not published online to ensure that only the targeted populations would take part. Replies to the questionnaire were collected on a MODALISA software (Kynos, Paris, France), hosted by the AFM-Telethon patient organization. Each language had a separate access link. This survey was fully anonymous.

The survey was divided into 4 parts (see Appendix S1). The first part provided a general view of the population who answered the questionnaire, and ensured that it included only those respondents who belong to the Type II or Type III SMA populations. The second part was designed to reflect the impact of the disease on the daily life of these SMA patients. The third set of questions appraised the respondent expectations toward therapies. The final part consisted of two open questions.

This first survey was launched on July 22, 2015. The deadline for answers was short notice (12 days). After the removal of a few duplicates, some cases of very young infants most likely affected by Type I SMA, and 15 replies from outside Europe or without information on the country, 822 validated European answers to the survey were considered in this analysis.

Given the large number of answers, it was possible to stratify and cross-analyze them in terms of characteristics of the respondent (patient or caregiver), patient age, or regional origin. Two geographical regions were established, based on their SMA standard of care systems, namely, Western Europe (includes Austria, Belgium, Finland, France, Germany, Ireland, Italia, Spain, Sweden, Switzerland, and UK) and Eastern Europe (with Belarus, Moldavia, Poland, Russia, and Ukraine). In order to comply with statistical constrains, since the WHO 3-age classification was not sensitive enough, cross-analysis was based on 4 subsets of ages which better captures the SMA Type II and Type III context.

The results presented below summarized the replies of the SMA patient population who completed the questionnaire. The analysis was conducted using descriptive statistics and, in some cases, comparative statistics using chi-square test with significant value, $p < 0.05$. The statistical analyses were performed using SAS software version 9.4.

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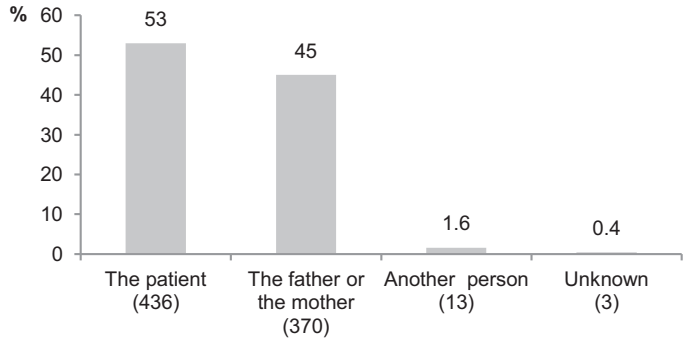

Fig. 1. Who completed the questionnaire. The graph represents the characteristics of the respondents as a percentage. The numbers of replies received are indicated in brackets.

Table 1
Origin of the replies.

Countries	Answers
Austria	4
Belarus	1
Belgium	3
Finland	1
France	208
Germany	185
Ireland	6
Italia	116
Moldavia	1
Poland	77
Russia	7
Spain	58
Sweden	14
Switzerland	29
United Kingdom	65
Ukraine	47
Total	822

Number of valid answers sorted by their geographical origin.

3. Results

3.1. A general view of the population who completed the questionnaire

Most of the respondents to this survey were either patients or parents (Fig. 1).

As expected since the questionnaire was not disseminated via Internet, the geographical origin of the respondents was directly correlated with the countries involved in SMA-Europe. Therefore, the breakdown is related to the dissemination procedure and does not reflect the respective incidence of SMA in these countries or across Europe (Table 1). A total of 822 completed questionnaires were considered as valid.

As shown in Fig. 2, in the columns '*caregiver*', the highest proportion of another person (parent or other, non-parent) answering on behalf of the patient was seen in the youngest category (ages 0–9). The same distribution pattern was observed between Western Europe and Eastern Europe suggesting that there was no regional difference in this respect. A total of 436 patients answered the survey themselves (Fig. 1). Ages ranged from 8 to 73 years. Only one child aged 9 years or less answered the survey alone. 383 caregivers (father, mother or another person) answered the questionnaire on behalf of the patient. The age range of the patients in this cohort was from infants to 47 years. 13 responses were obtained from a third party (other, non-parent). The patient ages ranged in this particular case from 2 to 65 years.

Nevertheless, the mean age of Eastern European patients who responded themselves (30.5 years old) was lower as compared to Western European patients (38.9 years old). This is probably due to the fact that a larger proportion of the respondents in Eastern Europe were aged 39 years or less (93.2% vs 73% in Western Europe, Table 2) and among them, a larger proportion of children

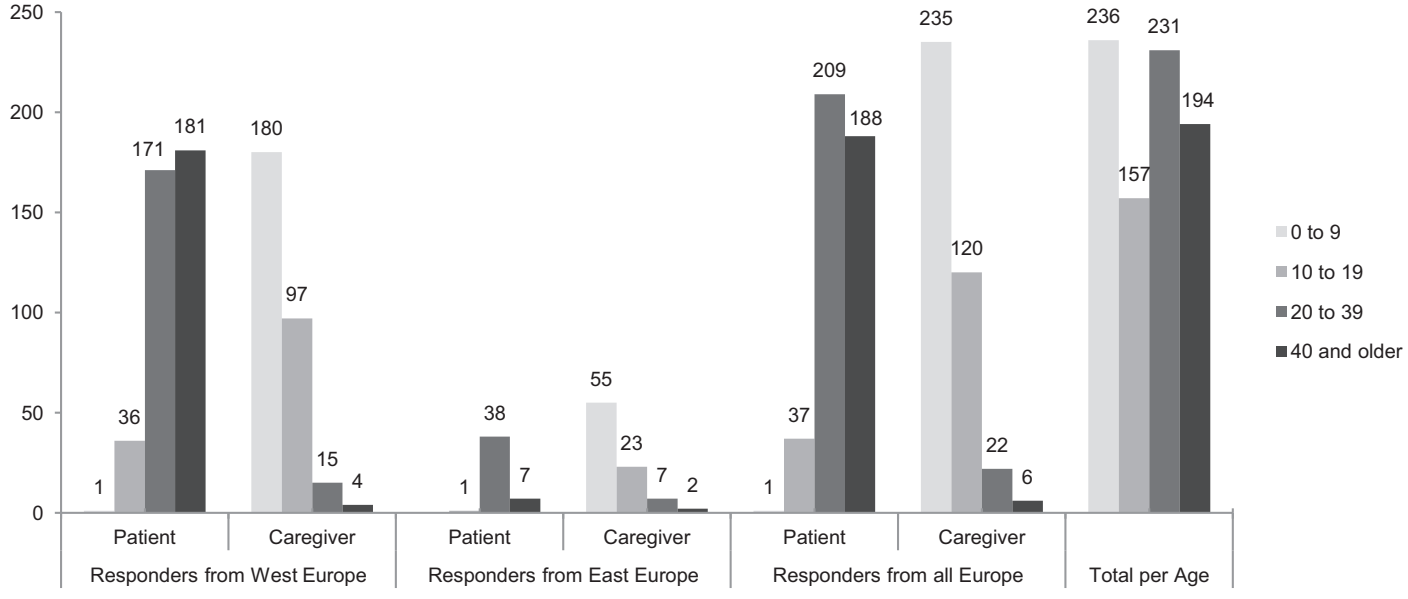

Fig. 2. Age distribution of the respondents. The graph summarizes the number of replies distributed by the characteristics of the respondent, patient age and regional origin. Caregivers are a parent (father or mother) or another person who completed the questionnaire on behalf of the patient. 818 replies indicating the age of the patient were included. 4 replies did not contain any information about the patient age.

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Table 2
Regional and age distribution of the respondents.

Region	0–9	10–19	20–39	40 and older
Western Europe	26.5	19.3	27.2	27.0
Eastern Europe	41.4	18.1	33.8	6.8
Europe	28.9	19.1	28.3	23.7

Percentage of respondents distributed by regional origin and age. Age is given in years.

were aged less than 9 years (41.3% vs 26.5%). Inversely, a larger proportion of older adults (27% vs 6.8%) were from the western part of Europe (Table 2). However, we cannot deduce from this observation, whether these differences reflect disease natural history or social aspects, such as more limited access to computers, or lower registration levels to a national patient association. Altogether Fig. 2 and Table 2 show that the study covers all age groups.

3.1.1. Mobility and respiratory functions

Since Type II and Type III SMA has a greater impact on lower limb muscles which strongly affects ambulation, the population was asked about the patient mobility status. The respondent answer rate to this question was between 83.4% and 86.6% (Fig. 3A). As expected, a decreasing proportion of the Type II and Type III SMA patients are able to sit unaided (50.5%), stand upright without help (20.8%) or are still ambulant (14.1%). When crossed this information with the age of the patient (Fig. 3B), the increasing proportion of ambulant respondents or of patients able to stand alone respectively probably reflects the disease status which is expected to be less severe in patients whose disease type allows them to live longer and with a milder burden [4,5]. The difference in life expectancy and morbidity between Type II SMA patients and Type III SMA patients most likely explains the apparently paradoxical observation (Fig. 3B).

Since loss of ambulation is experienced by the majority of SMA patients, the use of assistive devices was included in this survey (Fig. 4). As drawn from our survey, scooters are not commonly used within the SMA population who completed the questionnaire. Altogether only 30 respondents declared using a scooter, 21 from Western Europe (3.8% of the Western Europe respondents to this question) and 9 respondents from Eastern Europe (10.1% of the East European respondents to this question). As expected due to the disease burden, both manual and powered wheelchairs are commonly used by the SMA type

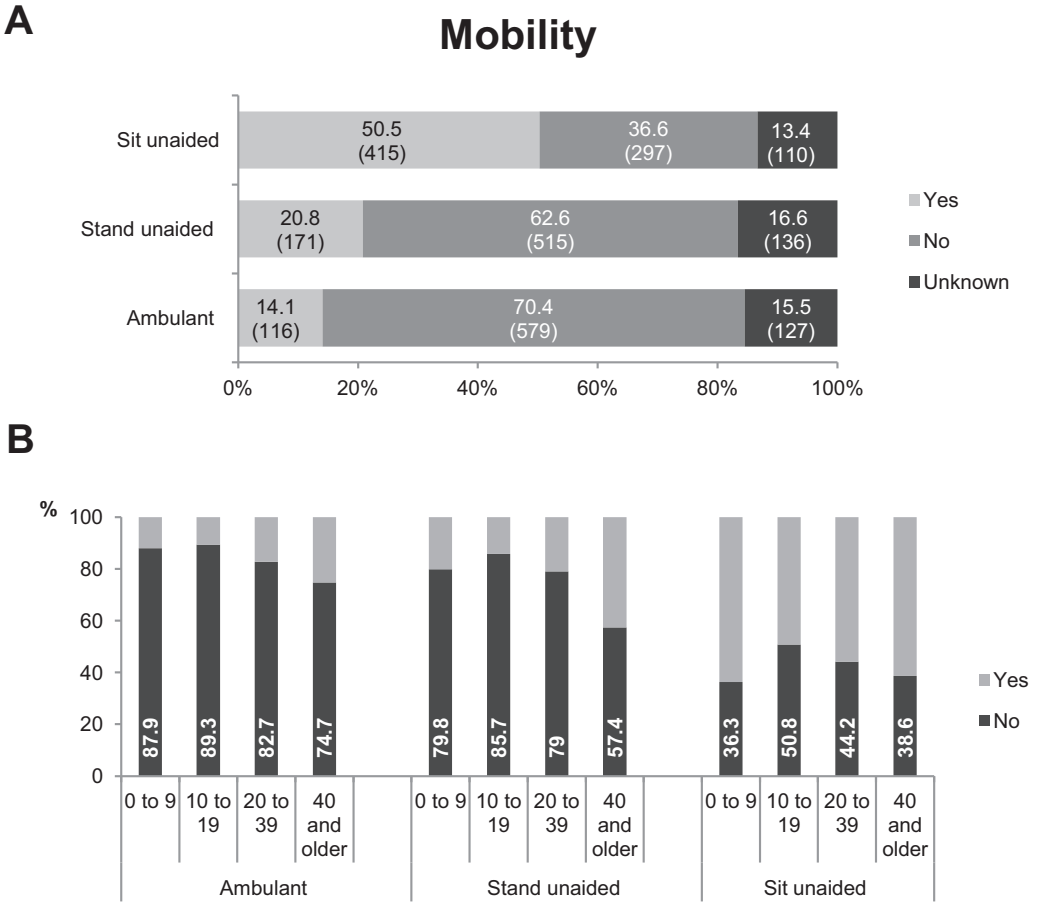

Fig. 3. Mobility status of the patients. (A) Level of mobility: the bars represent the percentage of patients per mobility function. The percentages are indicated as decimal numbers, while the respective number of answers collected per category is indicated in brackets. (B) The histograms represent the relative mobility as a percentage in relation to the age of the patient.

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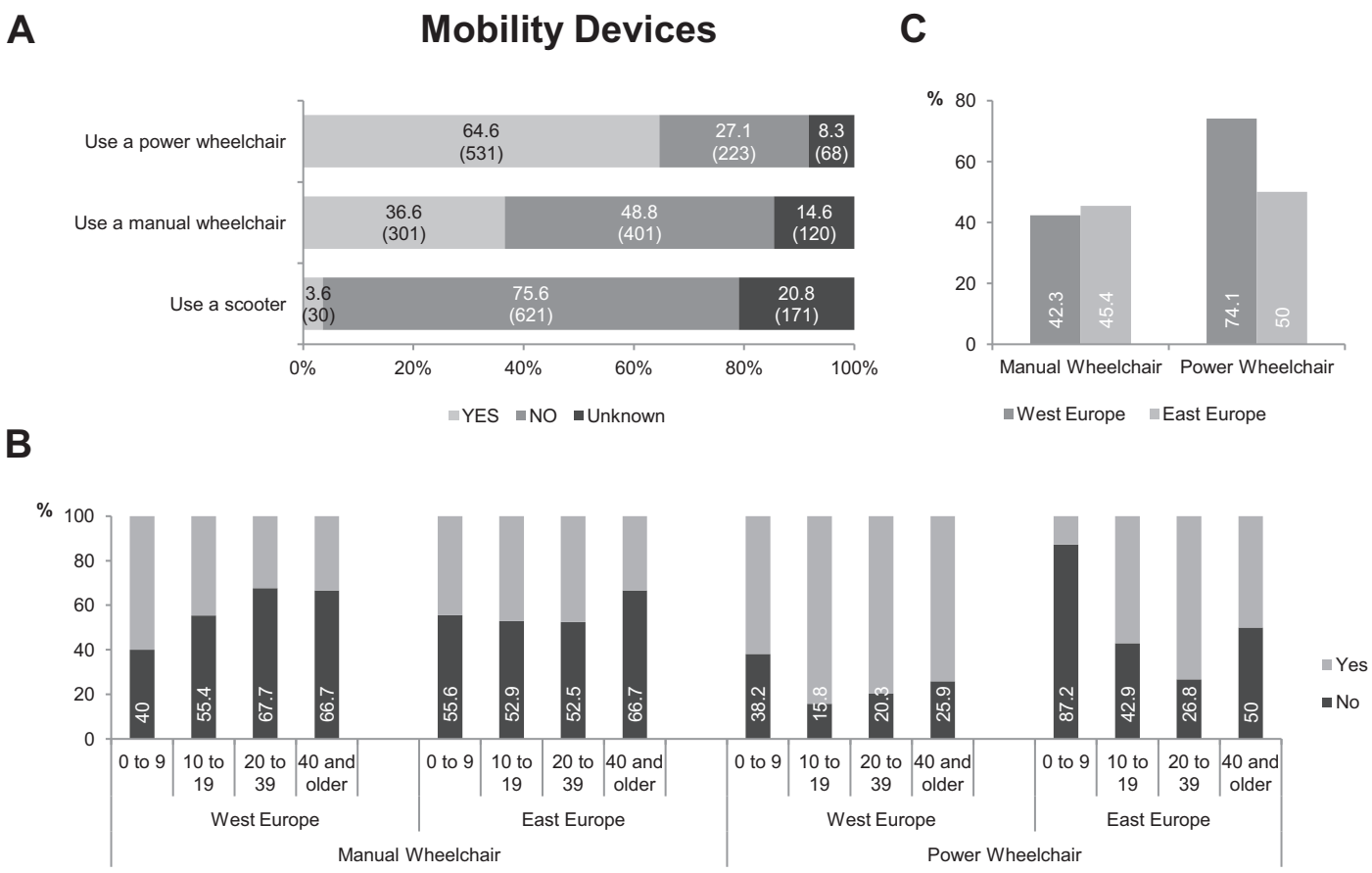

Fig. 4. Use of assistive devices. (A) Types of mobility devices: the bars represent the percentage of patients using a specific device. The percentages are indicated as decimal numbers, while the respective number of answers collected per category is indicated in brackets. (B) The histograms represent the relative utilization of manual or power wheelchairs across Europe. Respective percentages are given in each column. (C) Regional distribution of manual and power wheelchair usage: Results are given as a percentage.

II and type III populations. The data collected show an East-West difference in the respective use of these devices (Fig. 4B and C), especially power wheelchairs are under-represented in Eastern Europe in the 0–9 age category (Fig. 4B).

Although permanent noninvasive ventilation (NIV) seems not to be generalized within the Type II and III SMA European population (Table 3), the questionnaire reveals regional differences in care. A higher proportion of tracheostomy appears to be performed in Eastern Europe. NIV, 5–15 hours per day, is of more a general practice in Western Europe.

3.1.2. Ability of the respondents to perform some given actions

This survey focuses on the current ability of the respondents to perform given actions regardless of their SMA type. Fig. 5 summarizes the current level of mobility of the patients who responded to the questionnaire, based on a list of items related to daily life activities of Type II and Type III SMA patients. Most of the 822 respondents to the survey actively addressed these 10 sub-questions (answer rate of 98% per activity with the exception of 93.9% regarding the ability to transfer from wheelchair to bed alone).

Table 3
Regional distribution of ventilation assistance.

Region	Tracheostomy			Permanent NIV			NIV 5–15 hours/day			NIV less than 5 hours/day		
	Nb	Yes	% Yes	Nb	Yes	% Yes	Nb	Yes	% Yes	Nb	Yes	% Yes
Western Europe	511	40	7.3	530	11	2	456	116	20.3	495	61	11
Eastern Europe	85	13	13.3	92	2	2.1	89	5	5.3	91	3	3.2

Ventilation type and protocols are given. NIV means noninvasive ventilation. For each category, the number of replies is indicated. The column "% Yes" describes the respective percentage of users per region.

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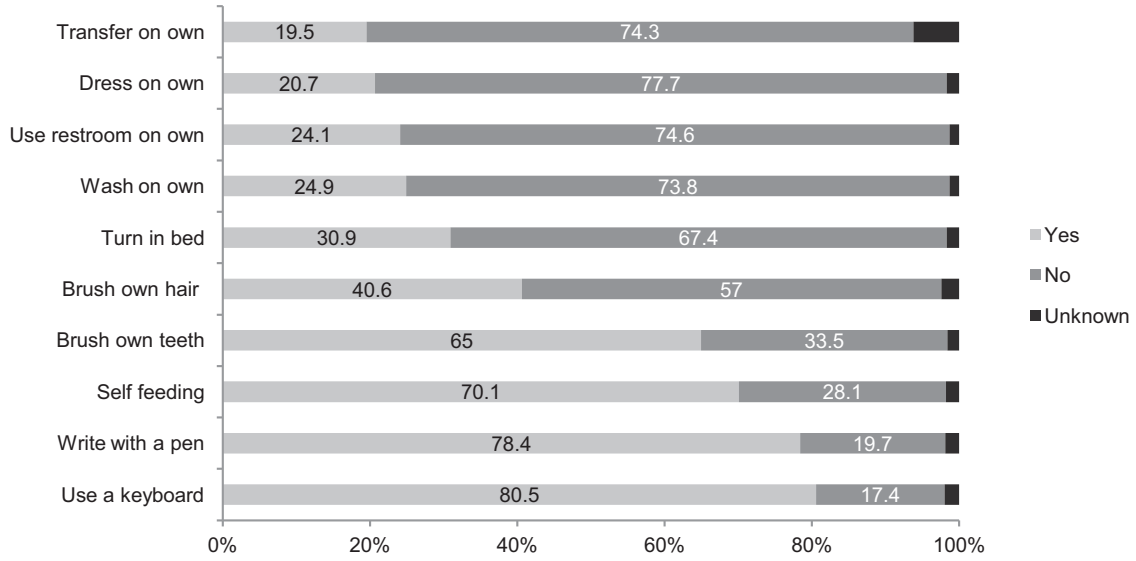

Fig. 5. Ability of the patients to perform a given action. The bars represent the percentage of patients able or not able to perform a given action. Answer rate per activity: 98%; exception "ability to transfer from wheelchair to bed alone": 93.9%.

In coherence with what is known about Type II and III SMA, the functions requesting lower limbs are more affected than those requesting upper limbs and hands.

3.2. The SMA Type II and Type III patient perceptions on the disease impact on their daily life

3.2.1. Impact on QoL of the ability to perform daily life actions

In order to appraise the value given by the respondents to any therapeutic outcome, we first assessed the relative impact of the ability (or inability) to perform particular movements or functions. We used the same list of items as for Section 3.1.2.

The impact of the ability to carry out a given action on the patient QoL was assessed as follows: the respondents were asked, based on the functions listed, to indicate whether the patients were able to carry out a specific action (answer *Yes* or *No*) and what impact this action has on the patient quality of life (major, important or minor impact). Two separate sets of answers were analyzed according to the respective ability of the respondent to perform a given action (Fig. 6).

Fig. 6A shows in a decreasing order the perceived impact of the ability of a patient to perform the actions on his/her QoL. For patients who were able to achieve given actions, the following five actions appear to have a major impact on their quality of life: *Use the restrooms alone* (72%, use restroom on own), *Have a wash by themselves* (63.6%, wash on own), *Perform transfers on their own* (60.5%, transfer on own), *Self-feeding* (60%), and *Dressing alone* (55.5%, dress on own). For patients who reported inability to achieve given actions, the following five actions were having a major impact on their quality of life (Fig. 6B): *Use the restrooms alone* (70.7%), *Self-feeding* (65.4%), *Turn on her/his own in the bed* (59.8%, turn in bed), *Have a wash by themselves* (59.6%), and *Perform transfers on their own* (58.4%). Despite difference in impact perception and independently of the patient ability, four functions are selected by both groups as having a major impact on the QoL of the patients: *Use the restrooms alone*, *Self-feeding*, *Have a wash by themselves*, and *Perform transfers on their own*.

3.2.2. Functions to stabilize or to improve as a matter of priority

Participants were asked to choose from a list the three functions (ranked 1–3 in decreasing order of priority) they would most like to stabilize (Table 4) or to improve (Table 5).

Functions patients prioritized to be stabilized are shown in Table 4, which summarizes the number of answers for each action and the ranking of preferences based on the first priority. Of all 822 participants, 36.6% listed *Self-feeding* as one of the three most important functions. Among them, 57.8% ranked this as the most important function to preserve (174/301). This is followed by the ability to *Have a wash independently* (27.6% of which 44.9% priority 1), the ability to *Use the restrooms independently* (25.1% of which 51% priority 1) and *Performing transfers alone* (20% of which 50% priority 1).

While the stabilization data (Table 4) most probably correspond to patients who have retained the ability to perform a given action, those who express a need to improve a function in priority most likely means that the given functions are no longer possible, severely declining or achieved with difficulties. Table 5 shows in a decreasing order the functions patients prioritize to be improved. Patients wish to improve the ability to *Use the restroom independently* (48.4% of which 45% priority 1), *Have a wash independently* (39.2% of which 43.2% priority 1), *Perform their transfer on their own* (31.9% of which 45% priority 1), and *Turn in bed alone* (34.2% of which 39.9% priority 1) over *Self-feeding* (22.3% of which 48.1% priority 1). *Using a keyboard* and *Write with a pen* were nevertheless perceived as rather important to stabilize (25.8% and 24.3% respectively), but were of lower priority to improve (13.4% and

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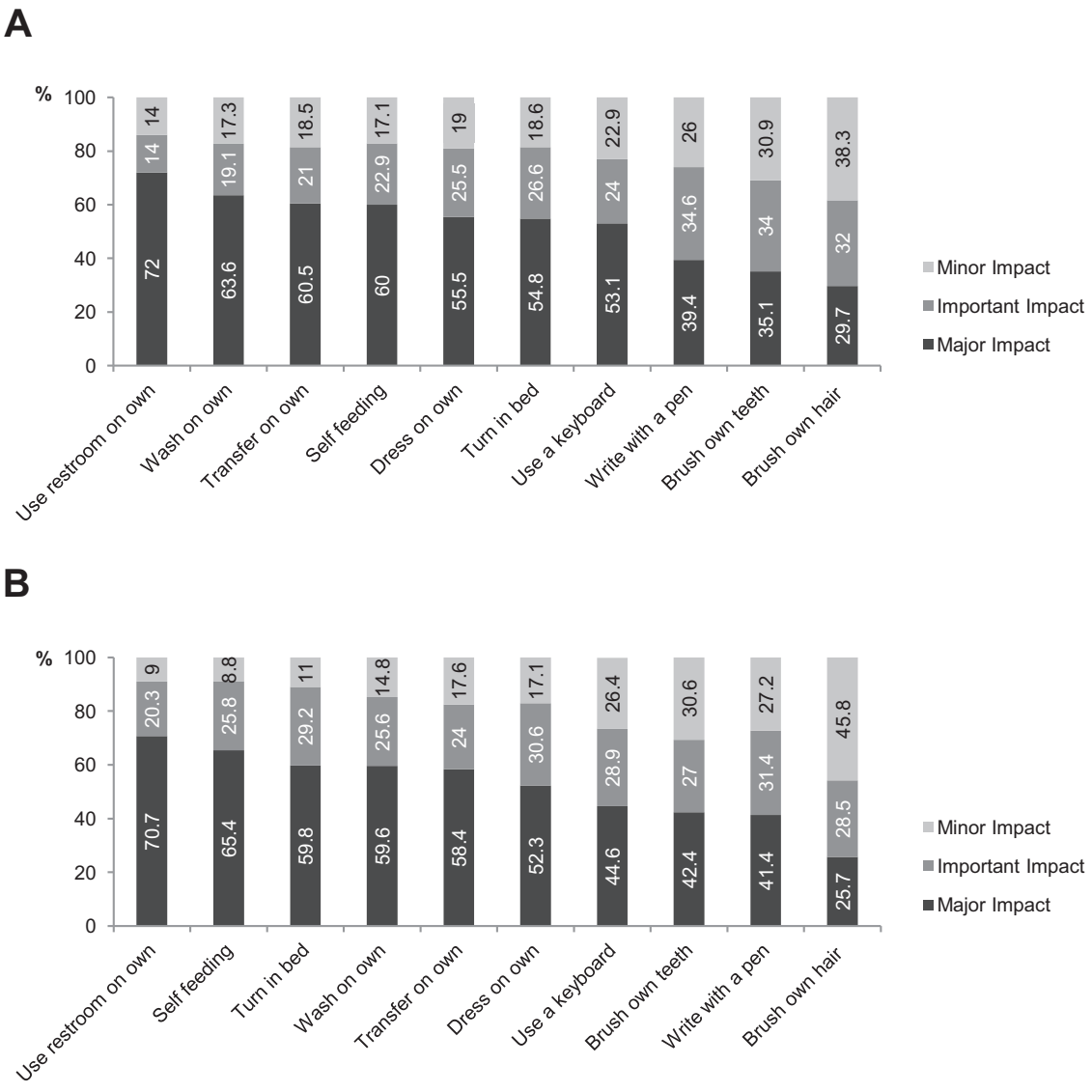

Fig. 6. Impact on QoL of the ability or the inability to perform a given action. (A) Perceived impact of the patient's ability to perform a given action: the histograms represent the percentage of answers per point. (B) Perceived impact of the patient's inability to perform a given action: the histograms represent the percentage of answers per point.

Table 4
Priority of functions to be stabilized.

Stabilization	Total		Priority 1	Priority 2	Priority 3
	Nb	% of 822	Nb	Nb	Nb
Self-feeding	301	36.6	174	74	53
Wash on own	227	27.6	102	69	56
Use restroom on own	206	25.1	105	59	42
Transfer on own	164	20.0	82	34	48
Use a keyboard	212	25.8	64	74	74
Turn in bed	183	22.3	63	52	68
Write with a pen	200	24.3	57	79	64
Brush own teeth	149	18.1	46	42	61
Dress on own	149	18.1	37	46	66
Brush own hair	71	8.6	20	21	30

Participants were asked to choose the 3 functions, ranked 1–3 in decreasing order of priority, they would most like to stabilize. All numbers are the number of the respective answers received. The percentages given express the proportion of the total answers selecting the given function, irrespective of the priority order, among the 822 replies to the questionnaire.

Table 5
Priority of functions to be improved.

Improvement	Total		Priority 1	Priority 2	Priority 3
	Nb	% of 822	Nb	Nb	Nb
Use restroom on own	398	48.4	179	126	93
Wash on own	322	39.2	139	92	91
Transfer on own	262	31.9	118	61	83
Turn in bed	281	34.2	112	84	85
Self-feeding	183	22.3	88	48	47
Dress on own	275	33.4	63	87	125
Use a keyboard	110	13.4	47	34	29
Write with a pen	138	16.8	41	44	53
Brush own teeth	78	9.5	27	25	26
Brush own hair	68	8.3	21	16	31

Participants were asked to choose the 3 functions, ranked 1–3 in decreasing order of priority, they would most like to improve. All numbers are the number of the respective answers received. The percentages given express the proportion of the total answers selecting the given function, irrespective of the priority order, among the 822 replies to the questionnaire.

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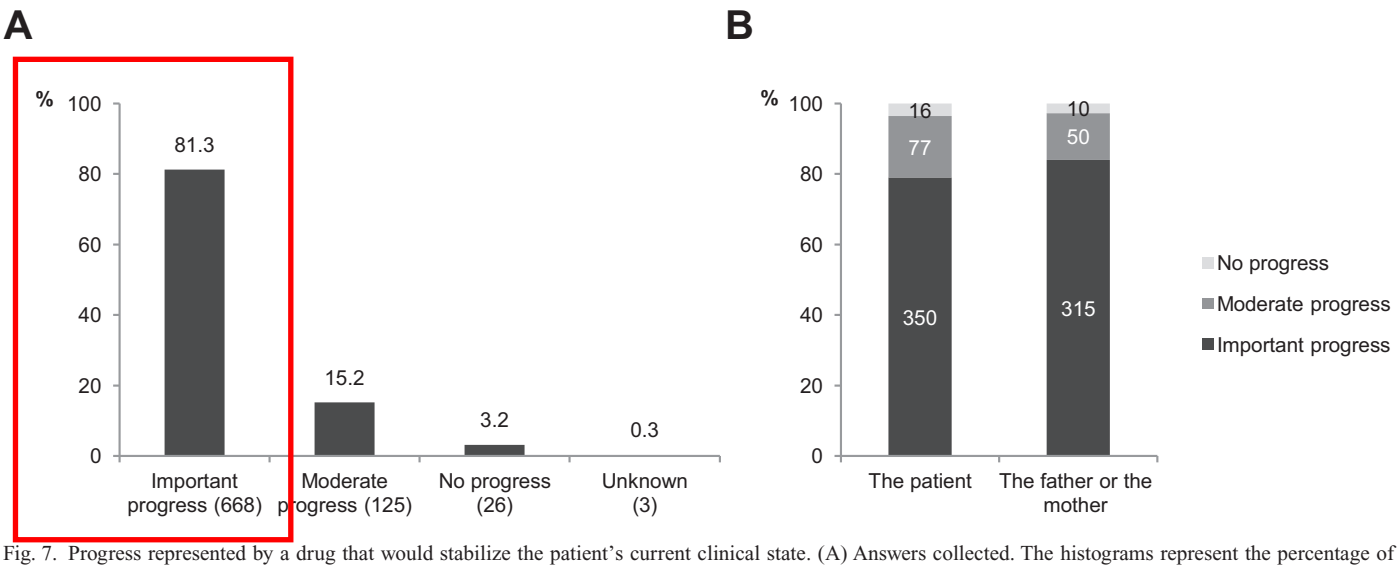

Fig. 7. Progress represented by a drug that would stabilize the patient's current clinical state. (A) Answers collected. The histograms represent the percentage of responses collected. The absolute number of responses is given in brackets. (B) Respondent effect. Only the replies given by the patient or a parent are included in this figure. The histograms represent the respective proportion of answer types. The number of replies for each category is indicated.

16.8% respectively). Inversely, *Dressing alone* is perceived as a low priority to stabilize (18.1%) and of higher priority to improve (33.4%) (Table 4 vs Table 5).

3.3. Respondent expectations toward therapies

The participants were asked whether a medicine which could stabilize their current clinical state would represent a progress. Three options of answer were given: NO, YES sure, or a moderate YES.

Fig. 7 shows the high relevance of this issue for the respondents. Only three out of the 822 did not reply, leading to the highest answer rate to a question in the frame of this questionnaire (99.7%). The large majority of patients (81.3%) felt that a medicine which would stabilize their disease course would represent an important progress and almost all of the respondents a progress (96.5%, moderate or important) (Fig. 7A).The feedback is basically the same whether the patient or one parent completed the questionnaire (Fig. 7B).

Table 6 summarizes the age and regional distribution of the responses to the same question. Although the analysis of the outcome is meant to be descriptive only, a comparative statistical analysis was performed in this case, indicating that the opinion expressed is independent of both the geographical origin of the respondents and the age of the patients, i.e. non-significant difference using chi-square test.

3.4. Estimate of the disease impact on the general well-being

In the last part of the questionnaire, the respondents were asked two open questions (Appendix S1). The answers collected were categorized and grouped into more general sections to enable data comparison. Nevertheless, it was difficult to compare the answers, as some of them were very detailed, whereas other replies were kept on a very general level.

In the first open question "*Which functional activity or effect on your condition would you like to be preserved or to improve*

Table 6
Progress represented by a drug that would stabilize the patient's current clinical state.

Region	Age group	No progress		Important progress		Moderate progress		Total
		Nb	%	Nb	%	Nb	%	Nb
Western Europe	0–9	4	2.2	156	85.7	22	12.1	182
	10–19	5	3.8	102	77.3	25	18.9	132
	20–39	7	3.8	144	77.4	35	18.8	186
	40–74	6	3.2	157	84.4	23	12.4	186
	Total	**22**	**3.2**	**559**	**81.5**	**105**	**15.3**	**686**
Eastern Europe	0–9	2	3.6	49	89.1	4	7.3	55
	10–19	1	4.2	19	79.2	4	16.6	24
	20–39	1	2.2	34	75.6	10	22.2	45
	40–74			7	77.8	2	22.2	9
	Total	**4**	**3**	**109**	**82**	**20**	**15**	**133**

Age and regional distribution of the responses: the table summarizes the number of responses collected per point and the relative percentage associated per patient age and per geographical origin of the answer.

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as a priority through taking a medication?" a total of 689 replies were obtained. The most predominant answer (20%) referred to "*Respiratory functions (improvement or stabilization, including coughing and swallowing)*". This was followed by "*Improve proximal mobility/functionality (getting up, balancing, walking, jumping, running, climbing stairs)*" (16%) and "*Muscle strength stabilization/improvement*" (13%). It seems here that the respondents put higher priority to the factor, which could directly affect their life expectancy (respiratory functions), while the activities affecting their quality of life (such as mobility and muscle strength) were treated as secondary priorities.

The second open question "*What drug candidate effect should be taken into consideration and evaluated in a future trial?*" brought in a total of 567 replies. The most common answer (29%) related to "*Muscular strength – stabilization or improvement*", followed by "*Condition – stabilization or improvement*" (17%). This latter response is difficult to compare to others, as it could easily include all the other answers provided by the respondents. The next most popular answer (16%) related to "Muscular capacity". Interestingly, the most predominant response from the previous question ("*Respiratory functions*") was cited here only in 10% of answers. It is also worth noting that 46% of the replies to this question indicate that just the stabilization alone (both in terms of muscle function and general condition) of the SMA patient is already perceived as an important outcome measure, which should be taken into consideration in future clinical trials for SMA.

The replies to both open questions do not show any significant correlation between the geographical origin and expectations of the respondents. SMA patients and their caregivers participating in the questionnaire have the same pattern of responses, regardless of their country of origin.

4. Discussion and conclusions

This first large-scale survey is a descriptive analysis of the perception of Type II and Type III SMA patients toward their disease morbidity. This is of particular importance in view of their perception of any therapeutic intervention. In the recent years, a number of candidate SMA drugs are being developed [11]. They are still facing the critical need for meaningful outcome measures with a close link to the impact of the potential therapeutics on the patient QoL. In this respect the patient view is a key input that patient organizations may provide to drug developers and to regulators.

The quick feed-back from the patients contacted for the survey demonstrates the extremely high level of motivation of the SMA Type II and Type III population in Europe to contribute both to the general knowledge of SMA and to the development of therapeutics they desperately need.

The distribution in the number of respondents per different age classes shows that the teenagers may have been less prompt to answer to the questionnaire. The relatively high percentage of respondents, 10% of the participants to the questionnaire, who had already been volunteering in SMA clinical trials is indicative (with regard to the relatively low proportion of SMA patients who have so far been enrolled in clinical trials in Europe) of how active and informed the SMA population may be. Considering the period in year (launching on July 22 and reply deadline on August 3), the number of answers, collected in this rare disease community, over a very short period of time is another strong indicator of their motivation in contributing to initiatives that may advance knowledge and clinical development. Due to the short notice and this peculiar period in the year which led to technical complications, the response rate from UK was lower than expected. However the statistical patterns remained aligned with the other Western European countries (data not shown).

Even though they were not asked to specify their SMA Type, their mobility and autonomy profiles confirm that we indeed targeted the expected SMA population. As anticipated, the functions requesting lower limbs were more affected than those requiring the upper limbs.

The relative impact of the ability to perform a given function on the patient QoL appears to be independent of the regional origin of the respondent. Two other factors, however, may modulate this feed-back: the age of the patient and the characteristic of the respondent (patient or caregiver). As expected for a chronic disease, the impact of performing the gesture increases with age. Answers appear to slightly differ between patients and caregivers. Caregivers, usually a parent of the patient, are generally under-estimating the impact of the ability of a patient to perform a specific action on QoL (Fig. 8A). On the other hand, caregivers tend to over-estimate the impact on the QoL in the case a patient is unable to perform a given action (Fig. 8B). Considering these perceptional differences between these highly familiar parties, patients and caregivers, we would expect even more differences in the appreciation of these factors between patients and clinicians and between patients and regulators. This important point will have to be further explored and considered.

Interesting observations can be drawn from this survey that may be useful for drug developers as well as for the regulatory authorities. While the impact of the current clinical status and expectations of the patients are homogenously perceived by the respondents, differences in care system still exist across Europe. Geographical discrepancies in the standards of care (i.e. power wheelchairs or application of NIV) should be carefully considered when designing multicentric international trials. Discrepancies in terms of patient care between countries may impact upon the choice of given functions to be included in the outcome measures (for instance respiratory assistance vs lung function measurement).

The present study demonstrates the importance of stabilization to the patients with SMA, irrespective of their age and origin. It is also consistent with the overwhelming answer rate of 96.5% of the respondents believing that stabilization of their current clinical state through a drug would represent a progress (81.3%, a major progress). Such a largely shared opinion should definitely be taken into consideration by both clinicians and regulators when discussing the potential benefit of new drugs. This is especially true in the case of a slowly degenerative disease with unmet medical needs like SMA,

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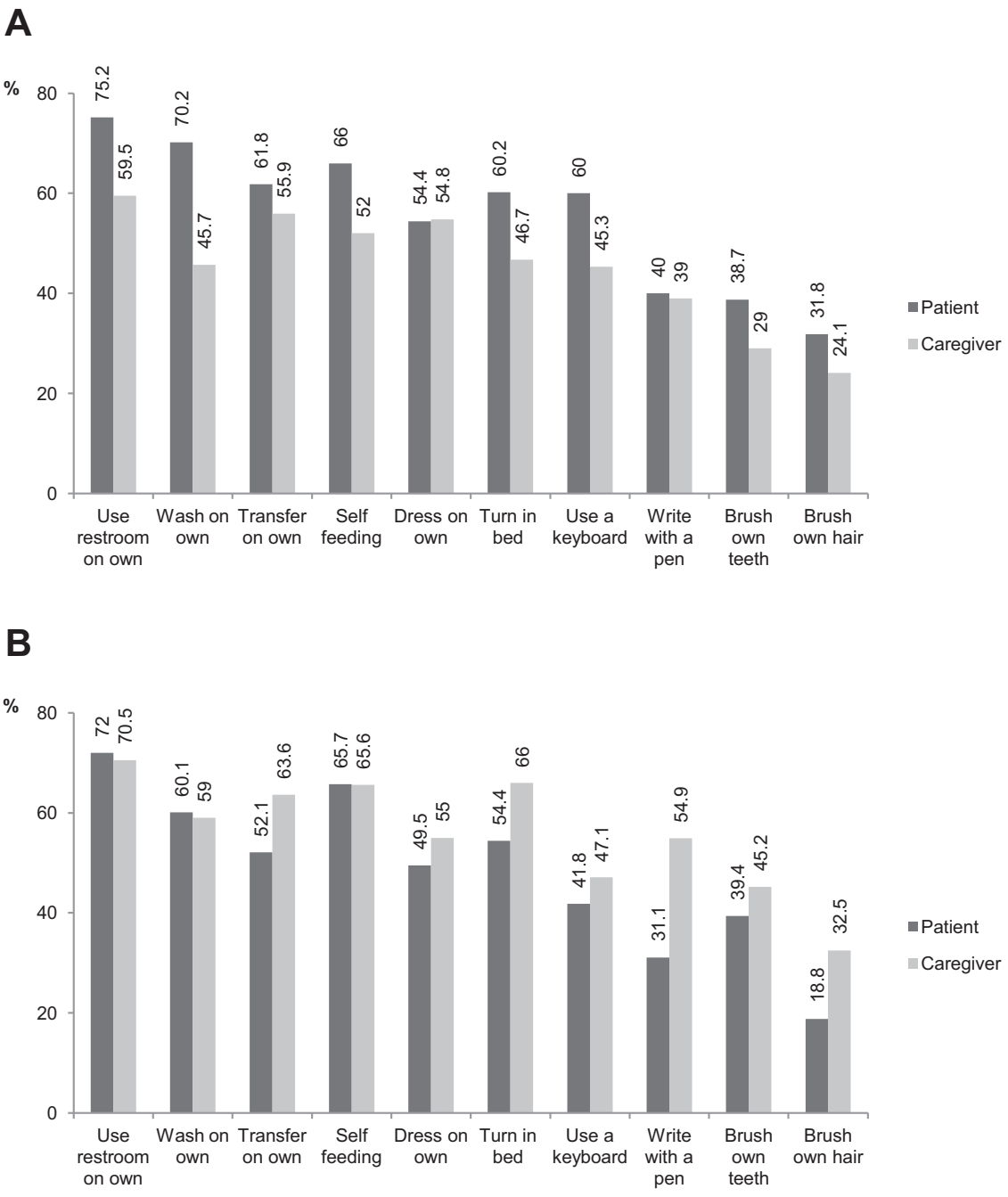

Fig. 8. Perceived major impact on QoL of the patient's ability or inability to perform a given action. The relative major impact on QOL of the patient's ability or inability to achieve a given action was evaluated (Section 3.2.1). The patient perception is represented whether the patient or the caregiver responded. Caregivers are a parent (father or mother) or another person who completed the questionnaire on behalf of the patient. The results are given in percentage of major impact for each given action respectively. (A) Relative major impact perceived by the respondent when the patient is able to achieve the given action. (B) Relative major impact perceived by the respondent when the patient is unable to achieve the given action.

where changes or stabilization is usually challenging to demonstrate in clinical trial setups. This may also drive drug developers to introduce some refinements in their clinical trials (size of patient cohorts, duration of the follow-up studies). During drug assessment, gestures that turn out to be of high importance for the respondents may require special attention and precise measurements. Outcome measures for motor assessment of ambulant and nonambulant SMA patients, currently used in clinical trials, have issues [12]. Motor assessment tools for non-ambulant patients with SMA aged more than 14 years have been recently validated and could be considered for trials [13]. Nevertheless tools are still needed that measure the functionality and that can be translated to daily life actions of importance for the patients.

This clear feed-back from the initial survey of the European SMA patient community now deserves further developments

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such as a more specific questionnaire administered to a larger cohort of SMA patients. Although the present study has already brought important and novel insights on the SMA patient's perspective, this prospective survey has also revealed some limitations and opportunities that could be usefully addressed in a more elaborate follow-up study.

The observation of a lower answer rate to some questions (mostly the questions relative to mobility and ventilation assistance) has drawn our attention. Since the motivation of the respondents was clearly high, the lower answer rates obtained in some cases might indicate a flaw in the way these particular questions were posed. Ambiguity inherent to those questions may have confused some respondents. This will enable to refine our future questionnaire. Simpler questions on personal disease status with little room for interpretation will facilitate cross-studies on patient mobility and age. On the other hand, the success of this first study has demonstrated that questionnaires directly sent to the targeted population by coordinated patient organizations can be a powerful tool for acquiring fast, reliable information needed by therapeutic developers and by regulatory authorities. Based on our present experience, a new survey can now be designed to define more precisely movements or specific gestures that would reflect the natural history of the disease and help us to develop clinically meaningful outcome measures. Investigators should work on establishing measurable tests that would model some of the functions of the daily life that were demonstrated by our patient population in order to preserve priority. More importantly, since patients are the real experts both of their disease and of its management, patients and their caregivers together with patient organizations should be included in this process.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.nmd.2017.01.018.

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