Impact of Spinal Muscular Atrophy on Caregivers' Daily Activities and Health-related Quality of Life

Er Chen
Genentech Inc
Komal Bawa (BAWA.KOMAL@GENE.COM)
Genentech Inc https://orcid.org/0000-0001-7849-3720
Josh M. Noone
Ipsos
Sarah M. Whitmire
Ipsos
J. Daniel Buchenberger
ipsos
W. David Arnold
Ohio State University
Rosalina Mills
Ipsos
Stacy Dixon
University of Colorado Denver - Anschutz Medical Campus

Research

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Abstract

Background

Spinal muscular atrophy (SMA) is a genetic debilitating disease affecting approximately 10,000 individuals in the United States. Individuals with SMA frequently require caregiver support and care. Through a partnership with a large patient organization, we surveyed caregivers of individuals with SMA below 18 years of age to understand the impact of SMA on caregivers with respect to their daily activities and health-related quality of life (HRQoL). In addition to structured questions, a standardized HRQoL instrument, the EQ-5D-5L and visual analogue scale, were administered.

Results

The caregiver sample consisted of 45 unpaid caregivers of individuals with SMA. Of them, 22% reported that they were sole caregivers that received no additional caregiving support and 98% were parents of an affected individual. The majority of caregivers cared for individuals with type 2 (58%), followed by type 1 (38%) and type 3 (4%) SMA. Sixty-four percent of the individuals with SMA were able to sit without support or better, while 31% had some motor function and 5% reported no motor function. On average, caregivers reported spending 136 hours/month managing the overall treatment, care, and support for the affected individual. Most of the individuals (91%) were reported to have received nusinersen; caregivers reported spending 29 hours managing treatment in a typical month. Caregiver time investment correlated directly with disease severity measured by both SMA type and patient motor function level. On average, caregivers rated their overall health as 76 on a scale of 0-100 using the EQ-5D-5L HRQoL visual analogue scale. Specifically, 42% of caregivers reported any inability to do their usual activities and 73% reported any anxiety or depression.

Conclusions

SMA negatively affects caregiver’s daily activities and HRQoL and represents a substantial burden. Disease severity is associated with an increasing amount of time required for care and support for patients with SMA and caregiver’s own HRQoL. As treatments become available, economic evaluation of these treatments should include effects on the family as well.

Introduction

Spinal muscular atrophy (SMA) is a rare autosomal recessive neuromuscular disorder that results in progressive muscle weakness and atrophy [1, 2]. The disorder manifests due to a defect and/or deletion in the survival motor neuron 1 (SMN1) gene, resulting in low levels of the survival motor neuron (SMN) protein [1]. A second paralogous gene, SMN2, also produces low, insufficient levels of functional SMN protein due to alternative splicing that truncates the mRNA transcript. The number of copies of the SMN2 gene is inversely correlated with SMA severity in most cases [5]. As such, SMA has been a leading genetic

cause of morbidity in infants and young children, with an estimated incidence of approximately as 9.4 in 100,000 live births in the US [6].

There are multiple subtypes of SMA which are categorized as types 0–4 based on clinical criteria such as age of symptom onset and achievement (or failure) of motor milestones [3, 7]. Type 0 SMA is rare. It is characterized by a decrease in fetal movement during pregnancy and severe weakness and hypotonia at birth. Patients born with type 0 SMA usually could not survive beyond the age of 6 months. Type 1 SMA is the most common and severe subtype, which has an onset between 0–6 months. Based on natural history, these patients have severe hypotonia, cannot control their head movements, and will never sit independently [1]. Patients with type 1 SMA have severe impairment of swallowing, respiratory function and survival. Patients with type 2 or type 3 SMA experience disease onset before and after the age of 18 months, respectively. Those with type 2 SMA are unable to stand or walk without support, whereas patients with type 3 SMA are able to stand and walk until the disease progresses [1]. Patients with type 4 SMA are diagnosed in adulthood and have milder muscle weakness. As SMA progresses there is general loss of motor and respiratory function resulting in increased dependence on the caregiver. Fear of disease progression and respiratory complications could also lead to profound, emotional, and psychosocial consequences on caregivers and their families [8]. More generally, parents of children with SMA have been shown to exhibit higher levels of stress than parents of otherwise healthy children [9].

Historically, SMA management was limited only to supportive care. The landscape changed in December 2016 when the United States (US) Food and Drug Administration (FDA) approved Spinraza® (nusinersen), an SMN2 targeting anti-sense oligonucleotide, as a disease-modifying therapy (DMT) for SMA. Nusinersen is administered intrathecally, with four loading doses followed by maintenance doses every 4 months [10]. Additionally, a gene therapy, Zolgensma® (onasemnogene abeparvovec-xioi), which replaces the SMN1 gene received FDA approval in May 2019 for the treatment patients with SMA less than 2 years of age [11].

Since the advent of novel DMTs for a previously untreatable condition, the impact of the disease and disease management on caregivers may also change. Given the severity of SMA, it has previously been demonstrated there is a significant impact of caregivers' lives [12]. Studies have assessed the health-related quality of life (HRQoL) in SMA showing there is deterioration of HRQoL in SMA patients as well as their caregivers compared with the overall population [13, 14]. Qian et al. surveyed the impact of SMA on patients (n = 21) and their parents (n = 64) [12]. This study found there is a considerable impact SMA has on social-emotional aspects of parents' daily living such as loss of sleep or stress from the idea of premature death.

However, to our knowledge, there is limited published data on the impact of SMA on a caregiver's HRQoL and the social implications of the disease in the US before and after the introduction of the disease modifying therapies. The aim of this study was to understand the impact of SMA on a caregiver's daily activities and HRQoL. This study provides valuable insight into caregivers' reports of overall HRQoL and potential challenges they face.

Note

Nusinersen was the only FDA approved treatment at the time this study was conducted, and as such, any treatment results described herein reflect experiences with nusinersen.

Methods

Data Source

De-identified data was directly collected from a survey with unpaid caregivers, of patients with SMA < 18 years old, who were routinely involved in the management of a patient's disease. The survey was administered electronically through an online platform and was fielded in February 2019.

Survey Design

Through partnership with a large patient organization, a survey was administered to 101 respondents (56 adult patients and 45 unpaid caregivers of a patient < 18 years of age). Any patients diagnosed with type 1–4 SMA who were ≥ 18 years and unpaid (non-professional) adult caregivers who were routinely involved in the care and management of a patient with SMA (< 18 years of age) were eligible for the study. This paper summarizes the findings reported exclusively by caregivers of patients < 18 years of age as related to their HRQoL and their daily activities. Other findings from this study are reported elsewhere.

To recruit participants, a survey e-link was distributed through an email listserv and posted on the patient organization's website between January to February 2019. The survey contained 45 structured questions, divided into multiple sections collating patient and caregiver demographics, patient health history, treatment and care, and their experience with treatment. A section was dedicated to collecting information on caregiver time to infer the impact of the disease and disease management on caregivers' daily activities. Attributes such as treatment, the amount of the time that came from paid work, unpaid work, and social activities (e.g., household chores, childcare, hobbies, or lifestyle activities) was included to understand the proportion of time spent on disease management.

In addition, the EQ-5D-5L (EuroQoL-5 Dimension-5 Level) and visual analogue scale (VAS) were administered to caregivers [15]. The EQ-5D, a simple validated instrument developed by a multi-disciplinary group of researchers, is commonly used to assess HRQoL in both the general population and a population with a disease [16]. The EQ-5D assesses five dimensions of health: mobility, self-care, usual activities (e.g., work, study, housework, or leisure activities), pain/discomfort, and anxiety/depression. It is also a common tool used in health economic evaluations to calculate utility values, which capture the change of a patient or caregivers' HRQoL, as related to a treatment. In the EQ-5D-5L, each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems [17]. The respondent results are scored ranging from 0 to 1, where 0 corresponds to death and 1 corresponds to perfect health (negative value may be possible in certain instances). In addition, an EQ VAS records the patient's self-rated health on a vertical scale, with the ends labelled 'The best health you can imagine' and 'The worst health you can imagine'. The EQ VAS can be used as a quantitative measure of health

outcomes that reflects the respondent's own judgement. A central Institutional Review Board reviewed and approved the study.

Quality Assurance and Data Analysis

The data quality assurance and quality control included multiple steps. From a programing standpoint, skip logic was implemented to ensure caregivers were only asked relevant questions. Similarly, range checks were included to minimize erroneous responses which were outside the valid range (e.g., an age of "136" instead of "36") and were inconsistent with previous responses. The survey was tested by multiple researchers using test links to ensure an accurate program. Further, a preliminary check of the program was conducted after approximately 10% of the sample had been recruited to ensure accuracy.

The caregiver sample was described with respect to demographics, and other characteristics of caregivers, as well as the demographics and clinical characterizes of the SMA patients less than 18 years old for whom they care. Descriptive statistics were used to characterize the study data. Frequencies and percentages were reported for categorical variables as well as means, medians, and standard deviations for continuous variables. The number of subgroup analyses performed was minimized due to the limited sample size. The two main sub-analyses performed were by type, (type 1 vs. type 2/3), and by current motor function status (minimal motor function, sitting, and standing/walking). All analyses remain descriptive; there was no attempt to conduct a statistical testing on these data. All results were reported for the total sample. The analysis was conducted in SAS version 9.3 and R version 3.3.

Results

Demographics of Caregivers and Patients

A total of 45 unpaid, primary caregivers with a mean age of 37 years (range 23–52) completed the survey. The caregivers were predominantly female (82%), non-Hispanic white (86.7%), and parents of children with SMA (98%) [Table 1]. Of the respondents, 22.1% reported that they were sole caregivers that received no additional caregiving support and 77.8% reported they received additional caregiving support that was paid (46.7%) or unpaid (31.1%). The patients with SMA under the care of caregivers ranged from under 1 year to 17 years old and 51% were female. These caregivers and patients were dispersed across the US.

Table 1
Demographic information for caregivers of individuals with SMA

Caregiver age, yrs (SD)	**37 (7.1%)**
Unpaid status, n (%)	45 (100%)
Gender of caregiver, n (%)	
Female	37 (82.2%)
Male	8 (17.8%)
US region where caregiver resides, n (%)	
Northeast	9 (20%)
Midwest	17 (37.8%)
South	12 (26.7%)
West	7 (15.6%)
Race of caregiver, n (%)	
Non-Hispanic White	39 (86.7%)
Hispanic	1 (2.2%)
Black or African American	1 (2.2%)
Asian	3 (6.7%)
Mixed race/ethnicity	1 (2.2%)
SMA subtype of patients, n (%)	
Type 1	17 (37.8%)
Type 2	26 (57.8%)
Type 3	2 (4.4%)
Type 4	0 (0%)
Caregiver's household income, n (%)	
<$20,000	5 (11.1%)
$20,000 to $49,999	13 (28.9%)
$50,000 to $99,999	8 (17.8%)
≥ $100,000	18 (40%)

Caregiver age, yrs (SD)	**37 (7.1%)**
Prefer to not state	1 (2.2%)
Caregiver's education, n (%)	
Less than high school	1 (2.2%)
High school or GED equivalent	8 (17.8%)
Some college	11 (24.4)
Undergraduate degree	17 (37.8%)
Graduate degree	8 (17.8%)
Caregiver's insurance type*, n (%)	
Medicare	5 (11.1%)
Medicaid	24 (53.3%)
Private insurance (HMO)	12 (26.7%)
Private insurance (PPO)	21 (46.7%)
Other	2 (4.4%)
Uninsured	1 (2.2%)
*respondents may have selected more than one options	

A majority of responding caregivers held graduate and/or undergraduate degrees (56.0%), however, only 40% of respondents reported being employed full-time and 38% were full-time caregivers. Of these 45 caregivers, 18 (40.0%) noted a household income at or over $100,000 per year, 8 (17.8%) reported $50,000-$99,999 per year, 13 (28.9%) reported $20,000-$49,000 per year, 5 (11.1%) reported under $20,000 per year, and 1 respondent refrained from answering (2.2%). About a third (33.3%) of caregivers had only private medical insurance coverage through a preferred provider organization (PPO) or health maintenance organization (HMO) while 17.8% of the caregivers reported having Medicaid only. Fourteen caregivers (31.1%) reported having both Medicaid and private insurance [Table 1].

Patient Health History

A majority of caregivers cared for patients diagnosed with type 2 (57.8%), followed by type 1 (37.8%), and type 3 (4.4%) SMA. The SMA diagnosis was established in 33.3% of patients before 6 months of age, 55.6%% of patients between 6–18 months of age, and 11.1% of patients after they were 18 months old. Of the patients with type 1 SMA, 14 (82.4%) were diagnosed before the age of 6 months and of the 26 patients with type 2, 21 (80.8%) were diagnosed between 6–18 months of age. Sixty-four percent of patients achieved sitting without support or better; 31.1% were reported to have some motor function but

were unable to sit, and 4.4% reported having no motor function. At the time of the survey, 41 caregivers (91.1%) responded that their SMA patients were receiving treatment with nusinersen, of which 33 (80.5%) had been receiving treatment for over 1 year.

SMA Impact on Caregiver Activities of Daily Living and Time Burden

On average, caregivers reported spending 136 hours (SD 193.4) per month managing the care and supporting their patient with SMA. A sub-analysis of monthly time spent by SMA type found, caregivers expended an average of 143.9 (SD 188.1) and 131.25 (SD 199.8) hours managing the care of type 1 SMA and type 2/3 SMA, respectively. Similarly, the average time spent on monthly care correlated with the motor function status of the patient where more time was spent with those with minimal function compared with those who were sitting or standing/walking [Figure 1]. Caregivers of patients with minimal function reported spending an average 155 hours (SD 222.6) every month caregiving compared with 139 hours (SD 207) and 92 hours (SD 58.0) spent by caregivers of SMA patients who could sit or stand/walk, respectively.

Caregivers reported spending an average of 29.4 hours (SD 101.3) each week on SMA management. Thirty-eight percent of the respondents noted speaking with their insurance provider about medication access or medical bills at least once a month. Caregivers of patients receiving nusinersen treatment (n = 41) reported spending a monthly average 4.3 hours (SD 6.4) meeting with the medical team, 4.9 hours (SD 15.4) on driving to the treatment center, and 4.1 hours (SD 9.3) in post procedure recovery. Of note, a drive time of more than one hour to receive nusinersen treatment was reported by 56% of caregivers. Overall, treatment for type 1 SMA required a higher monthly time investment for treatment. Caregivers also reported that 14.6% (SD 25.7) of the time was taken from paid work and remaining 85.4% came from unpaid work and social activities.

SMA Impact on Caregiver's HRQoL

Caregivers also reported a mean perceived health status of 76.1 out of 100 (SD 16.97) using the EQ-5D VAS. Of the 45 respondents, 35 caregivers (77.7%) noted they did not have any concerns with mobility or self-care on the EQ-5D-5L [Figure 2]. Seventy-three percent and 53.3% of caregivers expressed they had some level of anxiety/depression and pain/discomfort, respectively. Moreover, while 57.8% of respondents did not identify any problems with performing their usual activities, the remaining caregivers (42.2%) noted varying levels of problems with completing usual activities. Notably, 8 respondents (17.8%) reported being unable to walk and perform activities of self-care. The mean overall caregiver HRQoL score was further assessed by SMA type and the motor function status of the patient [Figure 3]. A lower mean caregiver overall HRQoL score of 66.7 (SD 22.1) was found for caregivers of patients with type 1 SMA compared with 81.8 (SD 9.5) for those caring for type 2/3 SMA patients. Similarly, the overall score increased with improved motor function status. Caregivers of patients who had minimal or no motor function had a mean overall HRQoL score of 69.8 (SD 22.9) compared with 77.3 (SD 11.1) and 85.4 (SD 12.2) for caregivers of patients who achieved sitting and standing/walking, respectively.

Discussion

The findings of this survey suggest that SMA has a substantial impact on caregivers' daily activities as well as their HRQoL. The vast majority of the caregivers reported their patients were receiving treatment with nusinersen. In the primary study of this survey (results reported elsewhere) the majority of these caregivers reported they were either 'very' or 'extremely satisfied' with the current DMT [18]. While caregivers valued the advancement in the treatment landscape, there continues to be a large time expenditure required in managing the treatment and care for their SMA patients. On average, caregivers reported spending nearly 17 working days, defined as 8 hours/day, each month managing the care and supporting their patient with SMA. The substantial time investment, on average 29 hours per month on SMA treatment remains high. The time burden may be attributed to the time caregivers spent working with insurance providers and managing treatment related details such as driving to a treatment center and administration of the available treatment.

Importantly, this study suggests that a more severe disease status, as measured by SMA type or patient motor function, was also associated with more time spent managing patient care and lower overall HRQoL for the caregivers. Caregivers of patients with type 1 SMA spent on average 13 additional hours per month managing the care of their patients compared with caregivers of patients with type 2/3 SMA. Similarly, caregivers of patients with minimal function reported spending an average of 63 additional hours every month caregiving compared with caregivers of SMA patients who could stand or walk. Our study shows a directional trend with regard to caregiver HRQoL, patient phenotype, and motor function ability. The HRQoL score reported for caregivers of type 1 SMA patients was approximately 15 points lower than for those with type 2/3 SMA patients. The corresponding difference by motor function was 16 points and 8 points lower for caregivers of patients who had minimal/no function compared with patients who could stand and sit, respectively.

Moreover, while the overall HRQoL score for SMA caregivers was similar to the US population average, the percentage of caregivers reporting anxiety or depression was three times as high as the US population and the percentage of caregivers reporting any problem with their usual activities was more than two times the US population [19]. Furthermore, the percentage of caregivers reporting any problem with self-care was 5.5 times higher than the US population [Figure 4] [19]. While it is difficult to establish a rationale for 8 caregivers reporting an inability to walk or perform activities of daily living, it is plausible that caregivers may have potentially misinterpreted the question or these caregivers may have a milder type of SMA themselves or that the caregiving burden prevents them from caring for themselves. The EQ-5D-5L methodology employed in this study has been utilized in other studies assessing caregiver outcomes in SMA [13]. López-Bastida et al. similarly noted a reduced HRQoL in caregivers of SMA patients from a Spanish population. A Dutch study utilizing the Caregiver Strain Index (CSI) also assessed perceived caregiver burden by mothers of SMA patients [20]. The study found 76% of mothers had a high caregiver burden, yet 77% also maintained paid employment.

It is also worth noting that a majority of respondents reported utilizing additional caregiving; this support was likely from another family member (unpaid) or a professional (paid). The need for additional support suggests our study may underestimate the impact of the disease on the family and the society. A recent health technology assessment for an SMA treatment acknowledged more than one caregiver may be involved in the care of patients, however as the HRQoL impact remains difficult to quantify for each caregiver, the final assessment only included one caregiver [21]. More research is needed in this area to better understand how the disease may affect multiple caregivers. For example, in our study only 40% of the respondents reported being employed full time, which suggests SMA may have a negative impact on caregiver productivity.

Furthermore, this study showed that despite reaching a higher educational threshold than the national average, as 56% of caregivers held an undergraduate and/or graduate degree compared with the national average of 31% in 2017 (US Census), only 40% were employed full-time [22]. Employed caregivers also reported about 15% of the time they spent caring for their patients was time spent away from paid work. Given the vast majority of caregivers in the survey were parents, the monthly time investment of 17 working days for the management and treatment of SMA may be seen as prohibitive to maintaining full time employment.

The results of this study indicate there is plausible rationale for lost productivity and absenteeism that are not formally assessed at present when therapies are evaluated for cost-effectiveness. The findings of this study are in line with other studies that have assessed caregiver burden and stress prior to the introduction of the disease modifying therapies [12, 13, 20].

Limitations

This survey was distributed by an email listserv from a patient advocacy group that may limit the generalizability of these results. The survey participants may have been more engaged with the advocacy group and therefore potentially more likely to take time to inform the study with their responses. As part of the survey design, caregivers of older patients (≥ 18 years old) were not recruited for this study. Additionally, the sample size was limited to 45 caregivers and the sample may not be representative of all SMA caregivers. Furthermore, the survey was limited to how respondents felt at a single point in time. Lastly, while most of SMA patients were receiving treatment with nusinersen, due to the small sample size and relatively short duration of treatment, it is premature to assess the impact of treatment on caregiver outcomes within this study. Future longitudinal studies are needed to further understand how the impact of the disease may change as the treatment landscape evolves and patient outcome continue to improve over time.

Conclusion

This study indicates that SMA has a significant impact on caregivers' daily activities and HRQoL, leading to substantial productivity loss and indirect cost. The overall time required to care for a patient with SMA

and the support for current treatment are evidence of the disease impact on families. Family spillover effects should therefore be considered as part of economic assessments for SMA treatments.

List Of Abbreviations

5L 5-Level

DMT a disease-modifying therapy

EQ EuroQoL

EQ-5D EuroQoL-5 Dimension

FDA Food and Drug Administration

HMO health maintenance organization

HRQoL health-related quality of life

PPO preferred provider organization

QoL quality of life

SD standard deviation

SMA Spinal Muscular Atrophy

SMN survival motor neuron

US United States

VAS visual analogue scale

Declarations

Ethics approval and consent to participate: We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines. The study was reviewed and approved by Pearl Institutional Review Board (Pearl IRB, 29 E McCarty St, #100, Indianapolis, IN 46225) reference number 19-IPSO-123 on 1/24/2019.

Consent for publication: Not Applicable

Availability of data and material: The datasets generated and/or analyzed during the current study are not publicly available as this is proprietary information but are available from the corresponding author on reasonable request.

Competing interests / Conflict of Interest Disclosures: Authors KB and EC are employees of Genentech, Inc. All other authors declare that they have no competing interests.

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Authors' Contributions:

Er Chen MPP: Study lead has made substantial contributions to the conception; design of the work; the acquisition, analysis, and interpretation of data; substantively revised the manuscript.

Komal Bawa Pharm.D: Made substantial contributions to the study conception; analyzed and interpreted the data; and drafted the manuscript.

Josh M. Noone Ph.D: Made substantial contributions to the conception; design of the work; the acquisition, analysis, and interpretation of data.

Sarah M. Whitmire MS: Made substantial contributions to the conception; design of the work; the acquisition, analysis, and interpretation of data.

Daniel Buchenberger MS: Made substantial contributions to the conception; design of the work; the acquisition, analysis, and interpretation of data.

David Arnold MD: Made substantial contributions to the study conception; interpreted the data; and substantively revised the draft manuscript.

Rosalina Mills BA: Made substantial contributions to the conception; design of the work; the acquisition, analysis, and interpretation of data.

Stacy Dixon MD, PhD: Made substantial contributions to the study conception; interpreted the data; and substantively revised the draft manuscript.

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Author list and contact information: We confirm that all authors have reviewed and approved the manuscript for submission.

1. Er Chen MPP; Genentech Inc, San Francisco, CA, USA; chene19@gene.com (first author)
2. Komal Bawa Pharm.D; Genentech Inc, San Francisco, CA, USA; bawak@gene.com (corresponding author)
3. Josh M. Noone Ph.D; Ipsos Healthcare, New York, NY, USA; Noone@ipsos.com
4. Sarah M. Whitmire MS; Ipsos Healthcare, New York, NY, USA; smwhitmire@gmail.com
5. Daniel Buchenberger MS; Ipsos Healthcare, New York, NY, USA; Daniel.Buchenberger@ipsos.com

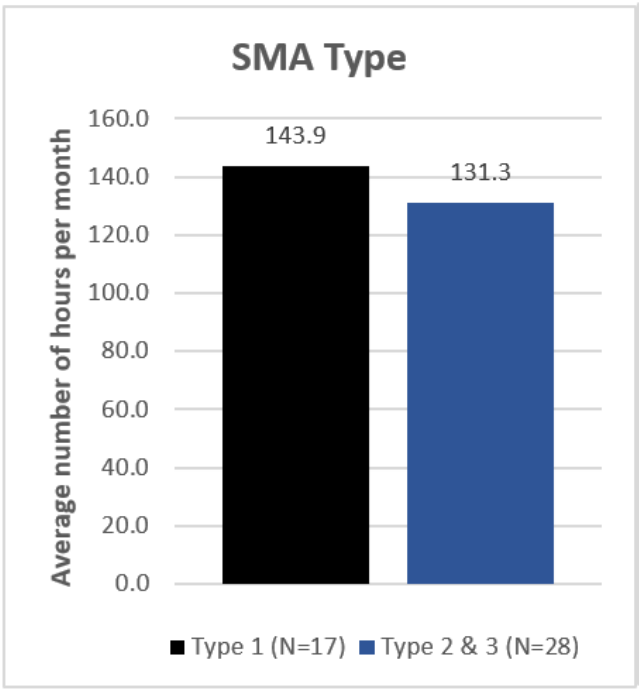
6. David Arnold MD; The Ohio State University Department of Neurology; William.Arnold@osumc.edu
7. Rosalina Mills BA; Ipsos Healthcare, New York, NY, USA; mills@hsc.wvu.edu
8. Stacy Dixon MD, PhD; University of Colorado School of Medicine, Department of Neurology; dixon@ucdenver.edu

References

1. Lunn, M.R. and C.H. Wang, *Spinal muscular atrophy.* Lancet, 2008. **371**(9630): p. 2120-33.
2. Mercuri, E., et al., *Diagnosis and management of spinal muscular atrophy: Part 1: Recommendations for diagnosis, rehabilitation, orthopedic and nutritional care.* Neuromuscul Disord, 2018. **28**(2): p. 103-115.
3. Butchbach, M.E., *Copy Number Variations in the Survival Motor Neuron Genes: Implications for Spinal Muscular Atrophy and Other Neurodegenerative Diseases.* Front Mol Biosci, 2016. **3**: p. 7.
4. D'Amico, A., et al., *Spinal muscular atrophy.* Orphanet J Rare Dis, 2011. **6**: p. 71.
5. Prior, T.W., *Perspectives and diagnostic considerations in spinal muscular atrophy.* Genet Med, 2010. **12**(3): p. 145-52.
6. Lally, C., et al., *Indirect estimation of the prevalence of spinal muscular atrophy Type I, II, and III in the United States.* Orphanet J Rare Dis, 2017. **12**(1): p. 175.
7. Munsat, T.L. and K.E. Davies, *International SMA consortium meeting. (26-28 June 1992, Bonn, Germany).* Neuromuscul Disord, 1992. **2**(5-6): p. 423-8.
8. Farrar, M.A., et al. *Financial, opportunity and psychosocial costs of spinal muscular atrophy: an exploratory qualitative analysis of Australian carer perspectives*. BMJ open, 2018. **8**, e020907 DOI: 10.1136/bmjopen-2017-020907.
9. von Gontard, A., S. Rudnik-Schoneborn, and K. Zerres, *Stress and coping in parents of children and adolescents with spinal muscular atrophy.* Klin Padiatr, 2012. **224**(4): p. 247-51.
10. *FDA approves first drug for spinal muscular atrophy. Food and Drug Administration. https://www.fda.gov/newsevents/newsroom/pressannouncements/ucm534611.htm. Published December 23, 2016. Accessed June 20, 2019.*
11. *AveXis receives FDA approval for Zolgensma®, the first and only gene therapy for pediatric patients with spinal muscular atrophy (SMA). Novartis. https://www.novartis.com/news/media-releases/avexis-receives-fda-approval-zolgensma-first-and-only-gene-therapy-pediatric-patients-spinal-muscular-atrophy-sma Published May 24, 2019. Accessed June 25, 2019. .*
12. Qian, Y., et al., *Understanding the experiences and needs of individuals with Spinal Muscular Atrophy and their parents: a qualitative study.* BMC Neurol, 2015. **15**: p. 217.
13. López-Bastida, J., et al., *Social/economic costs and health-related quality of life in patients with spinal muscular atrophy (SMA) in Spain.* Orphanet Journal of Rare Diseases, 2017. **12**(1).
14. Klug, C., et al., *Disease burden of spinal muscular atrophy in Germany.* Orphanet Journal of Rare Diseases, 2016. **11**(1).

15. Szende, A. and B. Janssen, *Socio-demographic Indicators Based on EQ-5D*, in *Self-Reported Population Health: An International Perspective based on EQ-5D*, A. Szende, B. Janssen, and J. Cabases, Editors. 2014: Dordrecht. p. 37-46.
16. Brooks, R., *EuroQol: the current state of play.* Health Policy, 1996. **37**(1): p. 53-72.
17. Herdman, M., et al., *Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L).* Quality of Life Research, 2011. **20**(10): p. 1727-1736.
18. Noone JM, W.S., Buchenberger D, et al., *Clinical experience of spinal muscular atrophy (SMA) treatment: A combination of perspectives from a large survey. Presented at the SMA Researcher Meeting in Anaheim, CA; 2019 June 28-30. SMA Poster*
19. Janssen, B. and A. Szende, *Population Norms for the EQ-5D*, in *Self-Reported Population Health: An International Perspective based on EQ-5D*, A. Szende, B. Janssen, and J. Cabases, Editors. 2014: Dordrecht. p. 19-30.
20. Cremers, C.H., et al., *Participation and mental well-being of mothers of home-living patients with spinal muscular atrophy.* Neuromuscular Disorders, 2019. **29**(4): p. 321-329.
21. *National Institute for Health and Care Excellence. Final appraisal document: Nusinersen for treating spinal muscular atrophy. June 3, 2019. https://www.nice.org.uk/guidance/ta588/documents/final-appraisal-determination-document. Accessed September 25, 2019*
22. *The United States Census Bureau. Educational Attainment in the United States: 2017; Available at: https://www.census.gov/data/tables/2017/demo/education-attainment/cps-detailed-tables.html. Accessed August 1, 2019.*

Figures



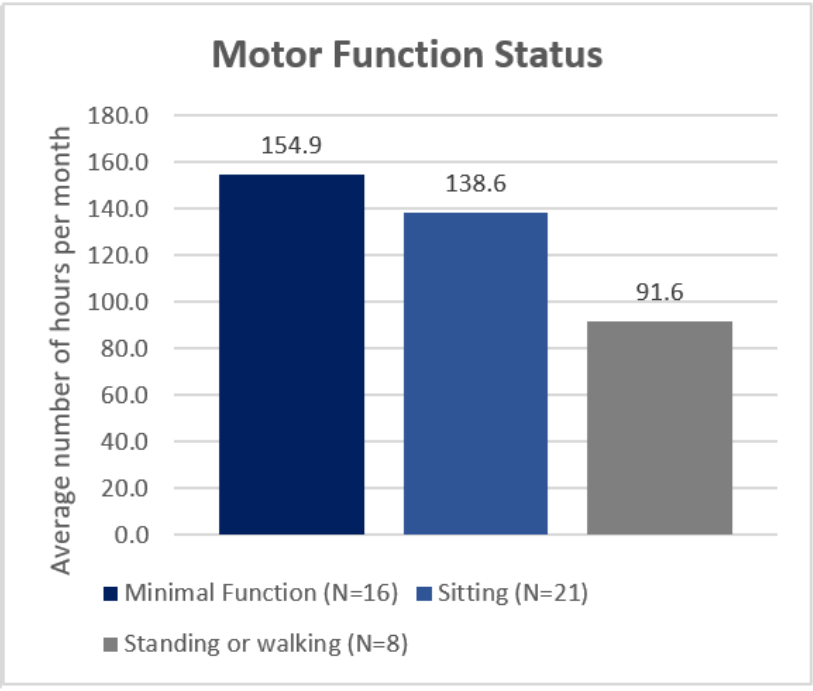


Figure 1

Average number of caregiver hours per month spent on managing care by SMA type and current motor function status, n=45

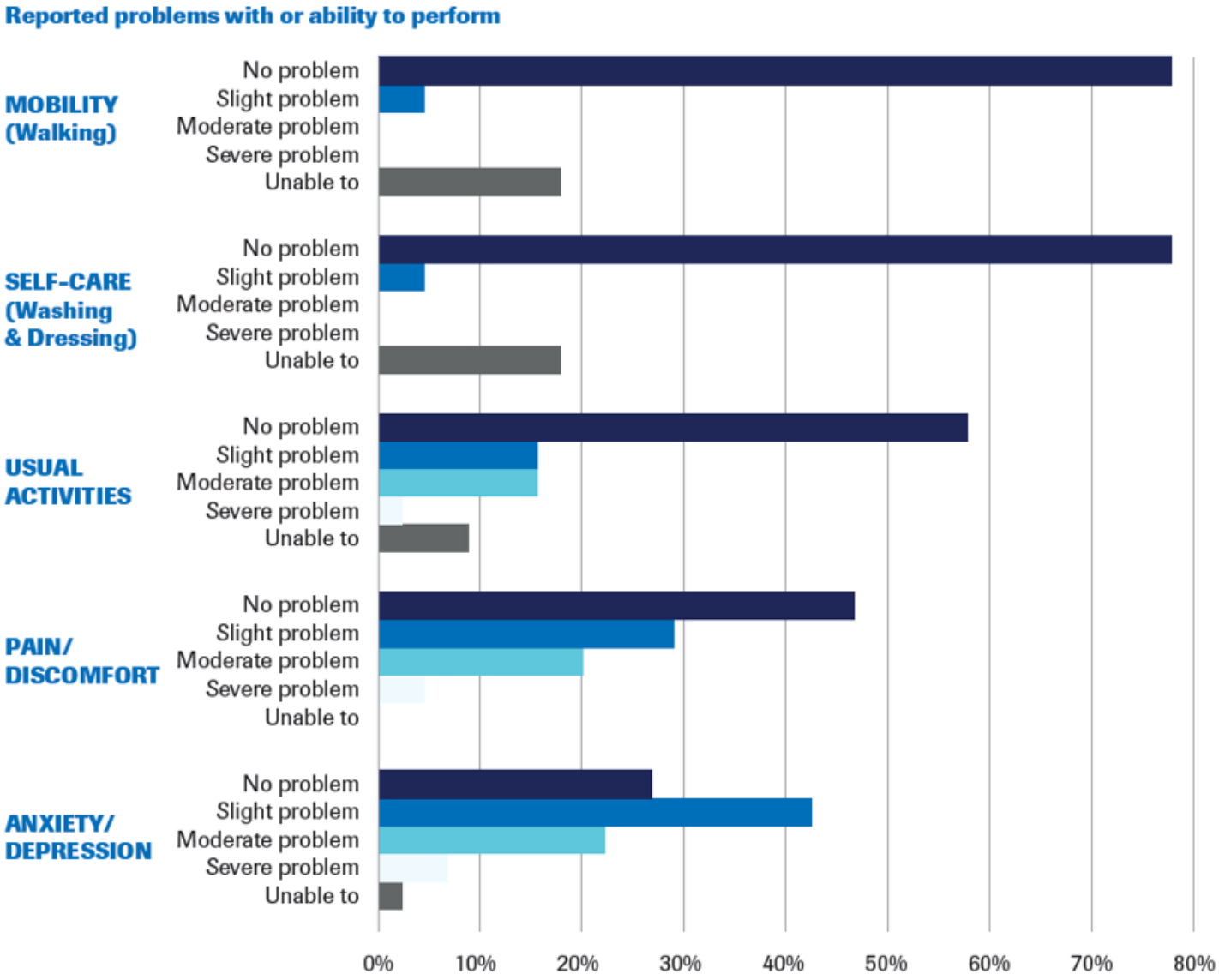


Figure 2

Caregiver EQ-5D-5L responses

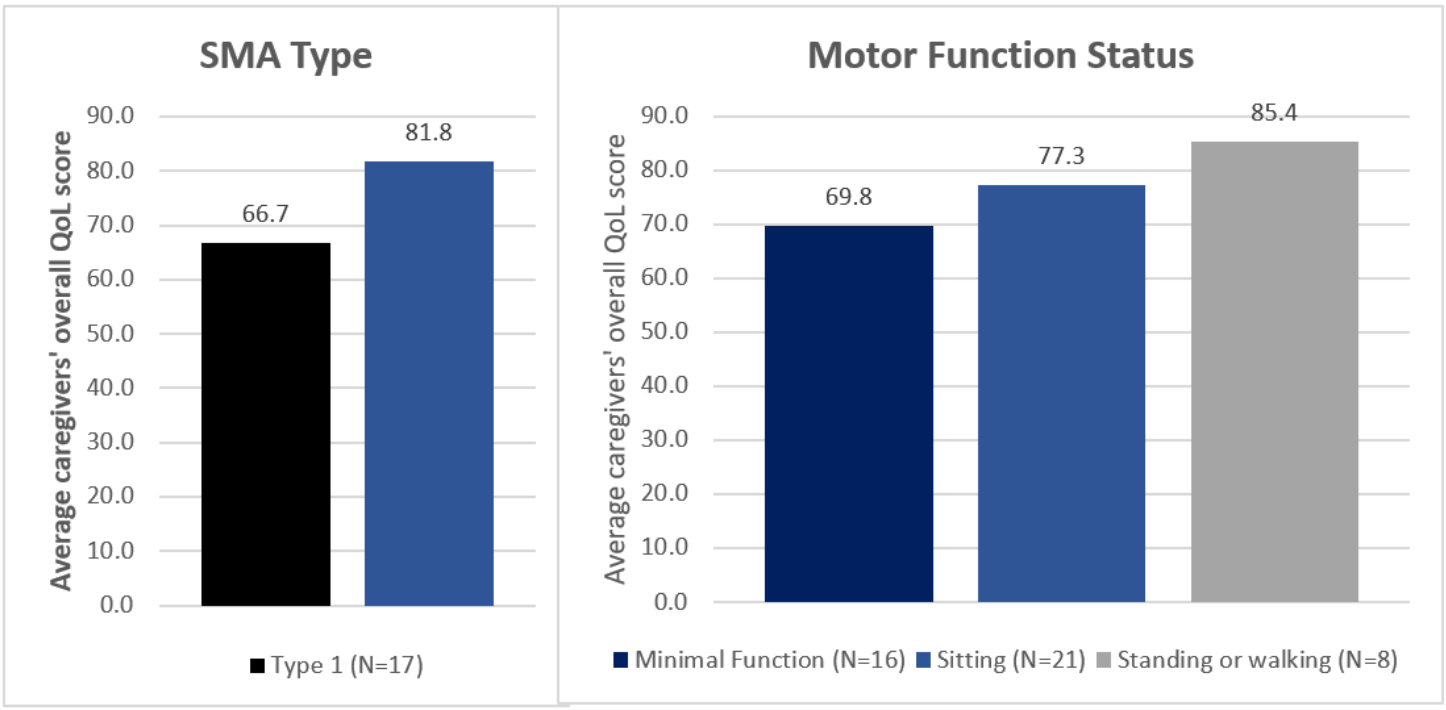


Figure 3

Average Caregiver HRQoL score by SMA type and motor function status

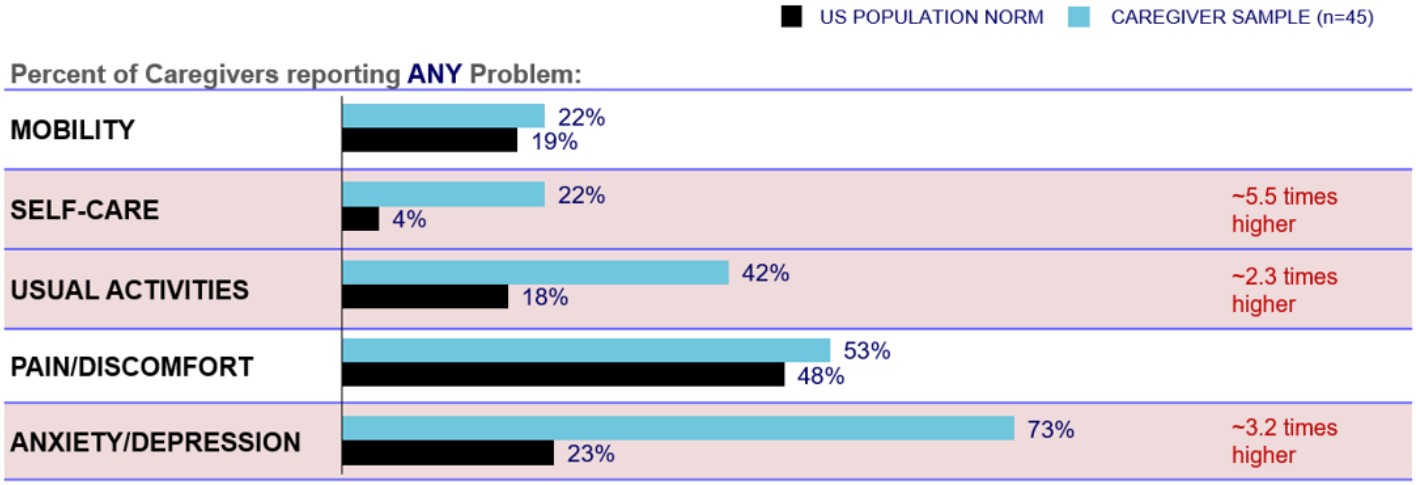


Figure 4

Caregiver Quality of Life compared to US Norms [19]