Understanding the spectrum of SCA1, SCA2, SCA3 and SCA6 through the eyes of patients: burden of illness and quality of life

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POSTER

1. PURPOSE

- This study aims to capture burden-of-disease experiences from persons with spinocerebellar ataxia (PWSCA) and their caregivers.

2. BACKGROUND

- Spinocerebellar ataxias (SCAs) are a group of dominantly inherited, ultra-rare, progressively debilitating, neurodegenerative disorders with no available treatments to slow or halt disease progression.[1-5]
- PWSCA experience gait disturbances, lack of motor coordination, loss of balance and associated falls, challenges with speech and swallowing, and cognitive impairment, all of which worsen over time.[1-4,6-9]
- Furthermore, SCA can significantly impact mental and social well-being and overall quality of life (QOL).
- There are more than 40 distinct SCA genotypes, with genotypes 1, 2, 3, and 6 being the most common worldwide.[2,10]
- Lived experiences of PWSCA offer essential insights regarding care and treatment. More data regarding the lived experiences of PWSCA are needed, not only to understand the impact of disease progression over time but also to identify potential therapeutic goals and optimal modalities for care provision.[11]
- This global study describes burden-of-disease experiences of PWSCA, including those with SCA1, SCA2, SCA3, and SCA6 and their caregivers.

3. METHODS

Study Participants and Recruitment

- Individuals with symptomatic SCA1, SCA2, SCA3, or SCA6 and proof of disease were eligible to participate in the study.
  - Proof of SCA was confirmed by laboratory testing (68.8%), medical record (14.0%), or physician communication (17.2%).
- Surveys were conducted in English, French, German, or Portuguese with patients or caregivers. Caregivers and spouses were invited to participate if a PWSCA either had passed away within the 2 years prior to study initiation or was currently living but had difficulty speaking.
- Participants were recruited from the Coordination of Rare Diseases at Stanford (CoRDS) Registry, National Ataxia Foundation, Ataxia UK, and the Engage Health EnCompass® database, predominantly from the US, the UK, Canada, Australia, France, Germany, and Brazil.
- For Phase 1, the targeted total sample size was 100. For Phase 2, a subset of individuals was selected from Phase 1 to participate in qualitative semi-structured interviews. Quota sampling, purposive sampling, and saturation analysis were used to ensure a representative sample of SCA types and to increase the probability that the data collected in the study were representative of patients with SCA1, SCA2, SCA3, and SCA6. The study initially sought to obtain input from 15 PWSCA and/or caregivers representing each SCA type (SCA1, SCA2, SCA3 and SCA6) (quota sampling). Persons who volunteered to participate and provided proof of disease were scheduled for interviews (convenience sampling). After themes were coded by 2 independent coders and a saturation analysis was conducted to determine the saturation of themes, an additional 5 persons were sought for each SCA type, with priority given to those residing outside the US (purposive sampling). The targeted total sample size for Phase 2 was 60.
- All participants who spoke English or German and completed Phases 1 and 2 were invited to take part in follow-up surveys.
- This poster reports data from participants who completed both Phase 1 and Phase 2 of the study as well as those who completed the follow-up surveys.

Study Design

- Phase 1: Secured Online Quantitative Assessments
  - Using a secure, HIPAA/508/GDPR-compliant, multilingual online portal, participants were directed to provide demographic data, complete a modified version of the Klockgether Functional Staging of Ataxia questionnaire (a physician-administered tool that assesses SCA functional status, modified with patient-friendly language), and complete the SF-36® QOL measure.
    - The SF-36v2 utilizes norm-based scoring with a linear T-score transformation method such that each of the health domain scores and summary components have a mean of 50. Scores below or above 50 are reflective of scores below and above the 2009 US general population, respectively.[12]
    - Post-hoc ANOVAs of SF-36 scores were performed to calculate nominal P values comparing values between SCA types, where P <.05 indicated a significant difference (Excel 2016. Version 2308. Microsoft).
    - Linear correlation coefficients were calculated between the modified Klockgether Functional Staging of Ataxia questionnaire and SF-36 scores to evaluate the relationship between participants' self-assessment of functioning using the modified Klockgether Functional Staging of Ataxia scale and physical health measured by the SF-36 (Excel 2016. Version 2308. Microsoft).
    - Due to the self-reporting nature of the SF-36 assessment, only PWSCA were invited to complete the SF-36 QOL and associated measurements; caregivers were excluded.
- Phase 2: Semi-Structured Qualitative Interviews
  - Participants engaged in 90-minute, semi-structured telephone interviews administered by trained interviewers in the participant's native language. Interviews included open- and closed-ended questions regarding disease burden, which were developed through a comprehensive review of the medical literature and discussions with both disease experts and leaders of patient support organizations.
  - Skip logic was used to ensure that participants were only asked questions that pertained to them. Participants had the option to abstain from any question or discontinue the study at any time.
  - Participants were first asked in an unaided fashion about key disease-related burdens and ranked these burdens with scores of 0-100 points. Participants were then asked about symptoms associated with SCA, which were drawn from the medical literature, PROM-Ataxia, and transcripts of prior patient-focused meetings.
  - This qualitative methodology has previously been described and used in other forums.[13,14]
- Follow-Up Surveys
  - Follow-up surveys were shared to better understand participants' desired therapeutic outcomes and experiences related to falls.
  - Participants chose whether they preferred to complete the follow-up survey online, by phone, or via both online and phone.
  - Participants who did not previously report having a fall received surveys that excluded questions pertaining to experiences with falls.
- The study received institutional review board (IRB) and ethics approval from WCG IRB prior to initiation and again prior to the administration of follow-up surveys. Participants provided consent in their native language via the online portal prior to engaging in study activities.

4. RESULTS

Participant Disposition (Table 1)

- Of the 347 individuals who accessed the online site and provided preliminary information, including consent, 161 were excluded due to failure to complete the SF-36 assessment or the modified Klockgether Functional Staging of Ataxia questionnaire, lack of proof of disease, or proof of disease that was deemed insufficient for study enrollment.
- 86 individuals participated in Phase 1; 80 individuals participated in both Phase 1 and 2, including caregivers for 2 PWSCA who died and a caregiver who was a parent of a PWSCA.
- 77 participants were contacted to complete a follow-up survey pertaining to their experiences with falls and/or desired therapeutic outcomes; of whom 70 (90.9%) of completed surveys.

Table 1. Participant attrition

	n
Total number of people who visited the RSVP site, gave consent, and provided some information	**347**
People excluded because they did not complete the SF-36 or modified Klockgether Functional Staging of Ataxia measurement, did not provide proof of disease, or lacked proof of disease sufficient for enrollment	**161**
Completed Phase 1 of the study • Caregivers • Patients	**186** 3 183
Completed Phases 1 and 2 of the study • Caregivers • Patients	**80** 3 77
Follow-up surveys related to falls and/or desired therapeutic outcomes • Contacted for survey • Completed survey • Caregivers • Patients	 77 **70** 2 68

Demographics (Table 2)

- All 4 SCA types were equally represented (n = 20 for each SCA type). Three caregivers provided information on behalf of 1 PWSCA1, 1 PWSCA2, and 1 PWSCA3. No caregivers of PWSCA6 participated in the study.
- Females represented 57.5% of participants.
- Mean age ranged from 45.5 to 64.5 years. PWSCA6 were the oldest population and the oldest at diagnosis; PWSCA2 were the youngest population and the youngest at diagnosis.
- The majority of participants were from the Americas, including 45 (56.3%) from the US.

Table 2. Demographic data and SF-36 scores for study participants who completed Phase 1 and 2

	SCA1 (n =20)	SCA2 (n = 20)	SCA3 (n = 20)	SCA6 (n = 20)	P value
Female / male	14 / 6	10 /10	12 / 8	10 / 10	
Mean age (years) (range)	50.2 (28.0–75.0)	45.5 (26.9–74.3)	52.6 (31.6–73.9)	64.5 (48.9–86.0)	
Mean age at first clinical suspicion	43.9	35.8	41.6	56.2	
Mean age at genetic diagnosis	45.1	40.2	45.4	58.2	
Geography					
Americas	14	13	14	12	
Europe and UK	6	5	5	6	
Asia	0	2	0	0	
Africa / Middle East	0	0	0	0	
Australasia	0	0	1	2	
SF-36 physical summary	**44.7***	**42.8***	**36.7***	**40.7***	**0.11**
SF-36 mental summary	**47.8***	**47.5***	**45.4***	**48.7***	**0.85**
SF-36 physical functioning	52.4*	50.8*	32.9*	39.0*	0.14
SF-36 role, physical	66.5*	65.5*	37.8*	51.3*	0.02†
SF-36 bodily pain	79.6*	72.4*	59.3*	79.9*	0.05†
SF-36 general health	50.8*	49.8*	50.3*	54.0*	0.93
SF-36 vitality	54.3*	41.8*	43.4*	45.4*	0.38
SF-36 social functioning	67.8*	68.4*	55.3*	63.8*	0.44
SF-36 role, emotional	78.1*	78.1*	61.4*	74.2*	0.21
SF-36 mental health	66.1*	67.9*	63.4*	70.5*	0.82

*n = 77 in Phase 2 (Caregivers of 1 PWSCA1, 1 PWSCA2, and 1 PWSCA3 were excluded.)
†P ≤ 0.05

SF-36 by SCA Type

- Mean SF-36 physical and mental summary scores were numerically lower compared to the general population for all SCA types and were lowest in PWSCA3. **Table 2**
  - PWSCA3 reported significantly lower scores than participants with other SCA types for bodily pain and physical role subscales.

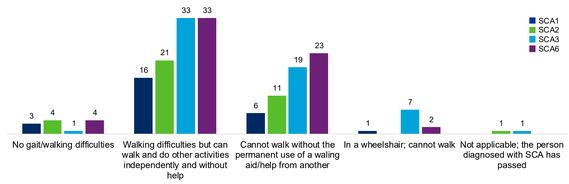
Functional Status by SCA Type

- Functional status, as measured by the modified Klockgether Functional Staging of Ataxia questionnaire, was chronicled for 78 of 80 PWSCA, as 2 PWSCA were deceased at the time of data gathering. **Figure 1**
  - PWSCA6 were most likely to need a walking aid, and PWSCA3 were most likely to be wheelchair-bound.

Relation Between Functional Status and SF-36

- There was a direct correlation between scores on the modified Klockgether Functional Staging of Ataxia assessment and the physical component summary of the SF-36 (R^2 = .472).

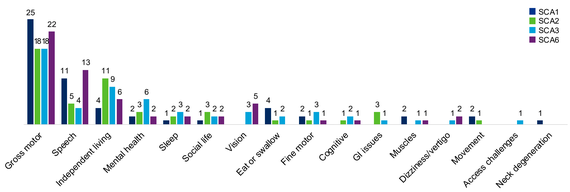
Figure 1. Functional status by SCA type



Most Important Disease-Related Burden (Figure 2)

- Across all SCA types, gross motor challenges were ranked as the most important burden. The second most important burden was identified as speech among PWSCA1 and PWSCA6 and challenges with independent living among PWSCA2 and PWSCA3.
- Of a possible 8000 points denoting burden, interview participants gave the highest scores to issues regarding gross motor function (42.2% of points), speech (13.9% of points), and independent living (12.3% of points). These 3 burdens ranked highest even when participants were given a comprehensive list of burdens to review and were then asked whether they wanted to change the rankings of their previously scored burdens.
- Of a possible 3376 points denoting burden for gross motor issues, participants gave the highest scores to impaired mobility (46.6% of points), loss of enjoyable activities (9.0% of points), and lack of balance (25.8% of points).
- Furthermore, 59 participants (73.8%) spontaneously reported that they experienced a fall over the course of their disease.

Figure 2. Most Important Disease-Related Burden Category Among Persons with SCA



Falls

- In follow-up surveys, 53 out of 70 participants (75.7%) reported experiencing at least 1 fall over the course of the past year. Among PWSCA3, 81.2% experienced at least 5 falls per year.
- In total, 53 participants experienced 2849 falls over the past year. Falls in PWSCA3 represented 71.5% of all falls reported. **Figure 3**
- The majority of injuries resulting from falls (2280, 99.2%) were minor (including broken tooth, cuts or lacerations, bumps and bruises, swelling, muscle pain/discomfort, and limited range of motion). However, there were 17 emergency room visits and 1 hospital admission reported.
- Participants reported increased reliance on others and changes in their daily routines as a result of falling.
- Many participants reported that fear of falling impacted their daily life; this included fear of injury, slower movement, and increased concentration on not falling. On a scale of 1-10, with 10 denoting *extreme impact, 30 (56.7%) rated the impact of fear of falling as 6 or higher, 36 (67.9%) rated the impact of fear of falling as 5 or higher*, and 46 (86.8%) rated it as 2 or higher. **Figure 4**

Figure 3. Number of falls by SCA type in the past year

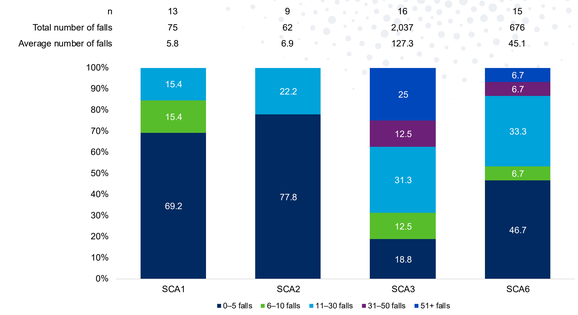
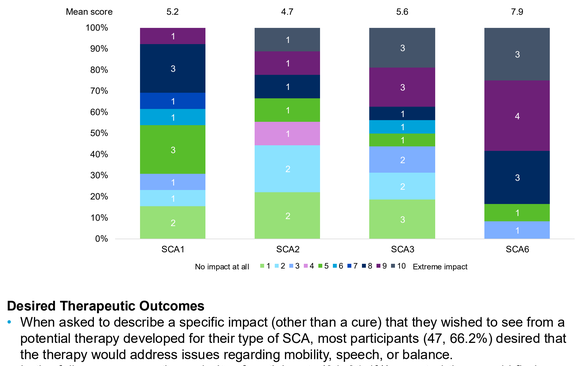


Figure 4. Impact of fear of falling on lives of PWSCA



Desired Therapeutic Outcomes

- When asked to describe a specific impact (other than a cure) that they wished to see from a potential therapy developed for their type of SCA, most participants (47, 66.2%) desired that the therapy would address issues regarding mobility, speech, or balance.
- In the follow-up survey, the majority of participants (64, 91.4%) reported they would find an approved medication that slowed or stabilized disease progression as *"extremely meaningful"* (5 on a scale of 0-5).
  - In particular, the majority of PWSCA3 and PWSCA6 (≥50% in each group) rated the importance of falling as an outcome of an approved therapy as 10, *"extremely important"* on a scale of 1-10.
- Participants reported that a medicine that slowed or stabilized disease progression would provide hope, the ability to maintain their daily physical activities and QOL, and, as a result, potentially improve their mental well-being.

Table 3. Illustrative quotes regarding falls and desired therapeutic outcomes

Falls	*"I have been cautioned by my doctors not to fall, as my symptoms get worse after each one and I do not recover to the point where I was previously. I need someone to help me go up a curb or step if there is no rail or if I can't find a cutout in the sidewalk. I have to think about where to sit in places like theaters or church because I need to be able to get there safely and stand back up. It is becoming harder to remain independent out of my home." (PWSCA1)*
Fear of falling	"I am extremely careful to NOT fall. I use a walker frequently, go up and down stairs 1 step at a time, etc. My daily life consists of BEING CAREFUL to avoid falls." (PWSCA6)
Therapeutic outcomes	"It would be amazing to have a drug that slowed the progression of this disease. Knowing I have it [SCA] and now waiting for symptoms to develop has impacted my mental health. Having the ability to slow/stop this would allow me to **live a normal and hopefully carefree life** to the fullest." (PWSCA6)

5. CONCLUSIONS

- Data from this global, cross-sectional, mixed-methods study involving persons with SCA highlight the significant burden that gross motor challenges (including loss of enjoyable activities, impaired mobility, lack of balance and falls) have on QOL.
- In all SCA types, mean summary scores for physical and mental components of the SF-36 were numerically lower than in the general population and lowest in PWSCA3. PWSCA3 also were most likely to be wheelchair-bound.
- In follow-up surveys, 53 out of 70 participants (75.7%) reported experiencing at least 1 fall during the past year. Among PWSCA3, 81.2% experienced at least 5 falls per year. Most participants indicated that fear of falls affected their daily lives.
- The majority of participants reported that they would find an approved medication that slowed or stabilized the progression of SCA to be "extremely meaningful." Furthermore, most PWSCA3 and PWSCA6 rated falling as an outcome of an approved therapy "extremely important."
- "If I was not so fearful of falls (and the potential damage that the fall may inflict on me), this could open up a steadily closing door in my activities." (PWSCA3)
- "To have medication available would improve the life of myself and family. I constantly worry about the future. We are not able to plan because I don't know how my health will be." (PWSCA6)

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