Understanding the Spectrum of SCA1, SCA2, SCA3, and SCA6 Through the Eyes of Patients: Burden of Illness Perspectives

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CONCLUSIONS

- SCAs are a dominantly inherited group of ultra-rare diseases in which individuals experience progressive cerebellar neurodegeneration and associated symptoms that worsen over time.
- Data from this global, cross-sectional, mixed-methods study involving persons with SCA highlights the significant burden that gross motor challenges (including loss of enjoyable activities, impaired mobility, and lack of balance), issues related to independent living, and speech have on QOL.
- In all SCA types and in both phases of the study, mean summary scores on physical components of SF-36 were numerically lower than in the general population and worst in PWSCA3.
- This study captures burden-of-disease experiences of PWSA and a small number of caregivers to identify disease aspects that are most meaningful to PWSCA, with the goal of capturing their voices.
- Many participants indicated they could accept their current limitations if a remedy capable of stopping the disease progression were available.
- *"I wish there was something to halt the progression of the disease. Every day you lose your loved ones a little bit more and that's very hard. I wish something could be done for the next generation, especially because my daughter was also diagnosed." (Caregiver of a PWSCA2 who recently passed away)*

Disclosures: LS: consultation for Biohaven, Neurocrine Biosciences advisory board and research support, Teva research support; **MWB, MP, AN, TF, LH:** employed by and hold stock/stock options in Biohaven; **SJ, AL, PE:** employed by Engage Health (Engage Health was paid a fee by Biohaven for the service of conducting, fielding, and analyzing the study. Engage Health has or is conducting disease burden studies for: Amicus Therapeutics, Ayala Pharmaceuticals, Biohaven, the Jett Foundation, Little Hercules Foundation, the International Fibrodysplasia Ossificans Progressiva Association, KrabbeConnect, National Niemann-Pick Disease Foundation, Theranexus, and Inozyme Pharma. None of these studies, other than that for Biohaven, is specific to SCA, although the studies use similar methodologies.); **JG:** no disclosures to report; **GR:** provided paid consultation for Biohaven; **LM:** Biohaven has provided financial support to NAF through membership in NAF's Drug Development Collaborative. Biohaven has provided partial sponsorship for several NAF meetings, including the Annual Ataxia Conference for patients and family members (2020-2023), Ataxia Investigators Meeting (2020), and 2022 International Congress of Ataxia Research.

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Acknowledgments

We would like to thank the many patients and families who dedicated time and shared experiences to support this work; the teams at the National Ataxia Foundation, Ataxia UK, and the Coordination of Rare Diseases at Sanford (CoRDS) for their support with patient recruitment; and Eubio for medical writing assistance.

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Presented at World Orphan Drug Congress, USA • May 23-25, 2023 • Washington, DC

PURPOSE

This study aims to capture burden-of-disease experiences from persons with spinocerebellar ataxia (PWSCA) and their caregivers, to identify disease aspects that are most meaningful to them, and to augment the spinocerebellar ataxia (SCA) literature by incorporating the patient voice.

BACKGROUND

- SCAs are a group of ultra-rare neurodegenerative diseases of the cerebellum and spinal cord that are characterized clinically by progressive lack of voluntary motor coordination, gait impairment, loss of balance and associated falls, and speech and swallowing difficulties.[1-8]
- In addition to affecting physical functioning, SCA can significantly impact mental health, social well-being, and overall quality of life.[1,3]
- Of the more than 40 different SCA genotypes, each with a distinct pathophysiology and clinical profile, SCA genotypes 1, 2, 3, and 6 are most common in the US, Europe, and worldwide.[1,3,9]
- No disease-modifying treatments that can halt or limit the progression of SCA are available presently. As a result, SCA often causes significant disability and/or premature death.[1,2]
- It is important to understand patients' lived experiences with this disease as well as clinical outcome measures to both understand the impact and progression of SCA over time and identify opportunities for therapy and optimal provision of care.[10,11]
- In this global, cross-sectional, mixed-methods study involving PWSCA (including SCA1, SCA2, SCA3, and SCA6), we report data from both quantitative self-reported online assessments and qualitative structured interviews to capture participants' experiences and identify aspects of SCA that are paramount to them.[12]

METHODS

Study Participants & Recruitment

- Participants included individuals with a confirmed diagnosis of symptomatic SCA1, SCA2, SCA3, or SCA6 and proof of disease, including genetic diagnosis based on laboratory testing (68.8%), medical record (14.0%), or physician communication (17.2%).
- Eligible participants needed to be able to complete the invitation confirmation and structured interviews in English, French, German, or Portuguese and provide informed consent in ≥1 of these languages.
- Spouses or caregivers of PWSCA who were alive but had difficulty speaking or had died ≤2 years prior to study initiation were invited to participate to mitigate barriers to self-reporting.
- 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. 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, or SCA6. The targeted total sample size was 100.
- For Phase 2, a subset of individuals was selected to participate in qualitative semi-structured interviews. The study initially sought to obtain input from 15 PWSCA and/or caregivers representing each SCA type (1,2,3 and 6) (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.

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 Klockgether questionnaire (a physician-administered tool that assesses SCA functional status, modified with patient-friendly language), and complete the SF-36® QOL measure.[13,14]
    - SF-36 data are reported as norm-based T-scores to aid in interpretation.
- 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.[15]

Standard Protocol Approvals, Registrations, and Patient Consents

- The study received institutional review board (IRB) and ethics approval from WCG IRB prior to initiation, and participants provided consent in their native language via the online portal prior to engaging in study activities.

RESULTS

Participant Disposition

- 347 individuals accessed the online site, gave consent, and provided some information; of these, 161 were excluded because they did not complete the SF-36 or modified Klockgether, did not provide proof of disease, or lacked proof of disease sufficient for study enrollment.
- A total of 186 participants were involved in Phase 1 of the study, including 3 caregivers who participated on behalf of 3 PWSCA (2 PWSCA who died and 1 child with SCA). Only PWSCA were invited to complete the SF-36 assessment.
- 80 participants, including 20 for each of the 4 SCA types, were recruited to complete Phase 2 of the study.

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, did not provide proof of disease, or lacked proof of disease sufficient for enrollment (eg, missing patient name or SCA type)	**161**
Completed Phase 1 of the study ○ Caregivers ○ Patients	**186** **3** **183**
Completed Phase 2 of the study ○ Caregivers ○ Patients	**80** **3** **77**

Demographics

- Phase 1 included more participants with SCA3 (n = 60) and SCA6 (n = 62) than SCA1 (n = 25) or SCA2 (n = 36). For Phase 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 across both phases. No caregivers of PWSCA6 participated in the study.
- Mean age ranged from 47.7 to 64.5 years in Phase 1 and from 50.2 to 64.5 years in Phase 2. In both phases, PWSCA6 were the oldest population and PWSCA2 were the youngest population.
- Females represented 59% of participants in Phase 1 and 57% of participants in Phase 2.
- In both phases of the study, the majority of participants were from the Americas, including 122 (66%) from the US in Phase 1 and 45 (56%) from the US in Phase 2.

SF-36 by SCA Type

- In both phases of the study, mean SF-36 summary scores on physical components were numerically lower compared to the general population for all SCA types and were lowest in PWSCA3.
  - General population scores on the SF-36 are 50.0.

Functional Status by SCA Type

- In both phases of the study, the majority of participants across all SCA types reported difficulty walking. In Phase 2, 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

- In both phases of the study, there was a direct correlation between scores on the modified Klockgether assessment and the physical component summary of SF-36 (Phase 1, R^2 = 0.3881; Phase 2, R^2 = 0.472). Data provided by caregivers were excluded from these analyses.

Table 2. Demographic Data of Study Participants

	Phase 1				Phase 2			
	SCA1 (n = 26)	SCA2 (n = 37)	SCA3 (n = 61)	SCA6 (n = 62)	SCA1 (n = 20)	SCA2 (n = 20)	SCA3 (n = 20)	SCA6 (n = 20)
Female / male	17 / 9	22 / 15	33 / 28	38 / 24	14 / 6	10 / 10	12 / 8	10 / 10
Mean age (yrs) (range)	49.6 (28.0–74.2)	47.7† (26.9–71.3)	50.1 (26.6–73.9)	64.5 (43.2–85.9)	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	n/a	n/a	n/a	n/a	43.9	35.8	41.6	56.2
Mean age at genetic diagnosis	n/a	n/a	n/a	n/a	45.1	40.2	45.4	58.2
Geography								
Americas	19	28	47	49	14	13	14	12
Europe & UK	7	6	10	9	6	5	5	6
Asia	0	2	3	0	0	2	0	0
Africa/Middle East	0	1	0	0	0	0	0	0
Australasia	0	0	1	4	0	0	1	2
SF-36 physical summary	46.6††	42.0††	37.9††	41.5††	44.7*	42.8*	36.7*	40.7*
SF-36 mental summary	47.3††	49.8††	47.9††	49.9††	47.8*	47.5*	45.4*	48.7*

n/a, not applicable.
‡ Excludes 1 deceased person (74.1 years).
†† n = 183 in Phase 1 (Caregivers of 1 PWSCA1, 1 PWSCA2, and 1 PWSCA3 were excluded.)
* n = 77 in Phase 2 (Caregivers of 1 PWSCA1, 1 PWSCA2, and 1 PWSCA3 were excluded.)

Figure 1. Functional Status by SCA Type

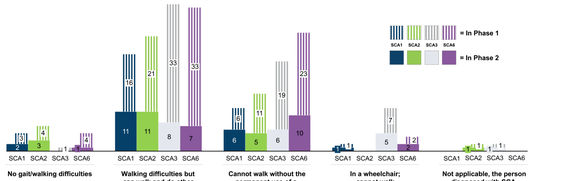


Figure 2. Relation Between Functional Status and SF-36 Scores

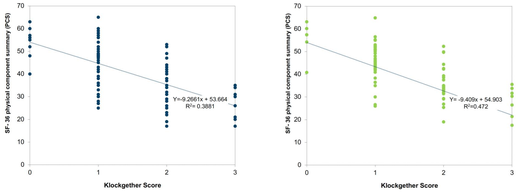
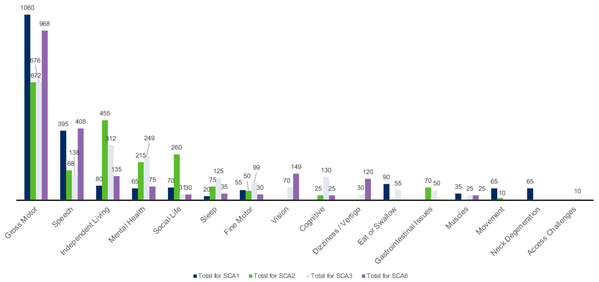


Figure 3. Most Important Disease-Related Burden Category Among Persons With SCA



Phase 2: Semi-Structured Interviews:

Several items were only reported in the Phase 2 semi-structured interviews, including assessing the first recognized symptom, the most important categories of disease-related burdens, and desired therapeutic outcomes.

First Recognized Symptom

- Difficulty with balance was consistently mentioned as the first recognized symptom, particularly among PWSCA2 and PWSCA3 (n = 10, 50% in both subtypes).
- Subsequently, abnormal gait (n = 8, 10% across all subtypes) and stumbling/falling (n = 4, 2 participants (10%) each among PWSCA1 and PWSCA6) were most commonly noted as the first recognized symptom. Decreased fine motor skills, difficulty changing direction, double vision, vertigo, and nystagmus were each reported by 3 individuals as their first recognized symptom.
- Mean ages at which participants began to have their first clinical suspicion for having SCA ranged from 35.8 years in PWSCA2 to 56.2 years in PWSCA6 (PWSCA3 = 42.6 years; PWSCA1 = 43.9 years).
- Nine (11%) participants reported that they were diagnosed with SCA prior to experiencing their first symptom.

Most Important Disease-Related Burden

- Across all SCA types, gross motor challenges were ranked as the most important burden. The second most important burden was identified as speech among PWSCA 1 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 (74%) spontaneously reported that they experienced a fall over the course of their disease.
- Among participants who reported having a caregiver (n = 54, 68%), household tasks, general help with mobility, and the mental impact of SCA were reported as the most important burdens faced by their caregivers.

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 desired that the therapy would address issues regarding mobility, speech, or balance.
- Of the participants in the study who addressed gain in functional burdens (n=70) most (62.9%) indicated that they could accept "not worsening" or "slowing/stopping progression" instead of functional improvements.

Table 3. Illustrative Quotes Regarding Gross Motor Burdens From Persons With SCA

Impaired Mobility	*"I can't walk without help, and I can't walk long distances. If I go shopping, I can't even walk back to the car. I feel that my energy is being drained all the time, and I get tired easily." (PWSCA1)*
Lack of Balance	*"I walk around as if I were drunk. I'm having near-falls every day. I lose my balance easily, especially when I'm turning directions. I live alone, and I'm surfing the walls and furniture to grab onto for balance." (PWSCA3)*
Loss of Enjoyable Physical Activities	*"I used to run a lot. I would get up at 5 AM every day for years and go on a 3- to 7-mile run. Now I wake up and hobble to the bathroom and have to sit down to put shoes and socks on. I do still get to go to the gym once a week tops and go for walks with my dog." (PWSCA2)*