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RESEARCH ARTICLE

Digital Gait Outcomes for Autosomal Recessive Spastic Ataxia of Charlevoix-Saguenay (ARSACS): Discriminative, Convergent, and Ecological Validity in a Multicenter Study (PROSPAX)

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ABSTRACT: Background: With treatment trials on the horizon, this study aimed to identify candidate digital-motor gait outcomes for autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS), capturable by wearable sensors with multicenter validity, and ideally also ecological validity during free walking outside laboratory settings.

Methods: Cross-sectional multicenter study (four centers), with gait assessments in 36 subjects (18 ARSACS patients; 18 controls) using three body-worn sensors (Opal, APDM) in laboratory settings and free walking in public spaces. Sensor gait measures were analyzed for discriminative validity from controls, and for convergent (ie, clinical and patient relevance) validity by correlations with $SPRS^{mobility}$ (primary outcome) and Scale for the Assessment and Rating of Ataxia (SARA), Spastic Paraplegia Rating Scale (SPRS), and activities of daily living subscore of the Friedreich Ataxia Rating Scale (FARS-ADL) (exploratory outcomes).

Results: Of 30 hypothesis-based digital gait measures, 14 measures discriminated ARSACS patients from controls with large effect sizes ($|\text{Cliff's } \delta| > 0.8$) in laboratory settings, with strongest discrimination by measures of spatiotemporal variability Lateral Step Deviation ($\delta = 0.98$), SPcmp ($\delta = 0.94$), and Swing CV ($\delta = 0.93$). Large correlations with the $SPRS^{mobility}$ were observed for Swing CV (Spearman's $\rho = 0.84$), Speed ($\rho = -0.63$), and Harmonic Ratio V ($\rho = -0.62$). During supervised free walking in a public space, 11/30 gait measures discriminated ARSACS from controls with large effect sizes. Large correlations with $SPRS^{mobility}$ were here observed for Swing CV ($\rho = 0.78$) and Speed ($\rho = -0.69$), without reductions in effect sizes compared with laboratory settings.

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Conclusions: We identified a promising set of digital-motor candidate gait outcomes for ARSACS, applicable in multicenter settings, correlating with patient-relevant health aspects, and with high validity also outside laboratory settings, thus simulating real-life walking with higher ecological validity. © 2024 The Author(s). *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society.

Key Words: ARSACS; wearable sensors; digital gait outcomes; spastic ataxia; outcome measures

Treatment trials are on the horizon for many spastic ataxias,[1] including autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) as one of the most frequent spastic ataxias worldwide.[2,3] ARSACS is a multisystemic neurodegenerative disease characterized by progressive cerebellar ataxia, spasticity, and peripheral neuropathy, with disease onset usually from early childhood to early adult years.[4] Treatment trials in slowly progressive diseases like ARSACS require sensitive outcome measures that capture change in relatively short trial-like time frames (eg, 1–2 years). While clinician-reported outcomes show only very limited sensitivity to change, sensor-based digital gait outcomes could be more sensitive, as recent findings from other genetic ataxias indicate.[5]

Digital gait outcomes obtained through wearable sensors have shown promising results in other genetic ataxias, with several cross-sectional studies demonstrating reliable discrimination between patients and controls, and correlation with clinical measures of disease severity[6-8]; and first longitudinal studies also demonstrating sensitivity to change.[5,9] In contrast, wearable sensor-based gait studies are still scarce in hereditary spastic paraplegias (HSPs),[10,11] and no genotype-specific studies on sensor-based gait measures have been conducted in spastic ataxias, let alone in spastic ataxias with prominent multisystemic involvement like ARSACS. Moreover, multicenter studies—as inevitably required for trials in such rare diseases—are very scarce in ataxias[7] and HSPs, demonstrating the urgent need for multicenter validation of performance and outcome validity. Finally, for measures to gain regulatory and patient acceptance as treatment outcomes, they must reflect health aspects that are relevant to patients,[12] such as mobility.[13-15] For sensor-based gait measures, this includes reflecting functional, patient-relevant disease-related impairments, ideally also with data acquired in patient-relevant settings, that is, conditions resembling patients' everyday lives such as, for example, public space.

To identify candidate digital-motor outcomes for future trials in ARSACS, this study evaluated gait measures capturable by body-worn sensors in an international, transatlantic, multicenter setting, assessing (i) discriminative validity against healthy controls; (ii) convergent validity with clinical measures of patient-relevant health aspects, general disease severity, and activities of daily living; and (iii) ecological validity by also assessing discriminative and convergent validity in free-walking settings in public spaces.

Methods

Participants

The study cohort was part of the PROSPAX study, a prospective, international, longitudinal, multicenter, natural progression study in spastic ataxias (ClinicalTrials.gov, No: NCT04297891). Of the overall PROSPAX study cohort, 24 patients with genetically confirmed ARSACS with available gait recordings and 50 healthy controls (HC) were recruited from four centers in four countries (Istanbul, Turkey; Pisa, Italy; Saguenay, Canada; Tübingen, Germany) where APDM recordings had been conducted based on the following inclusion criteria: (1) genetically confirmed and clinically manifest ARSACS; (2) ability to walk at least 10 m freely without any walking aid (45 ARSACS patients recruited by the four centers to the PROSPAX study failed this inclusion criterion); and (3) absence of severe comorbidities (due to ARSACS or unrelated) which present a major confounder for evaluation of gait and stance such as: amputation, blindness, severe dementia, severe joint deformities or contractures, or fixed orthoses (0 ARSACS patients recruited by the four centers to the PROSPAX study failed this inclusion criterion). HC had no history of any neurological or psychiatric disease, no family history of neurodegenerative disease, and did not show any neurological signs upon clinical examination. After exclusion of invalid gait recordings (damaged data files, unreliable step detection) recordings of 18 subjects from the lab-based walking condition (LBW) and 15 subjects from the supervised free walking condition (SFW) remained suitable for analysis (Fig. S1). To ensure comparability between patients and controls, the 18 eligible patients with valid gait recordings were matched with an equal number of 18 HC such that between-group age difference was minimized by selection of the 18 youngest HC. The Institutional Review Board of the University of Tübingen approved the study (AZ 824/2019BO2). All subjects provided written informed consent before participation according to the Declaration of Helsinki.

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Clinical Assessments

All participants underwent detailed neurological examination. Disease severity was rated using the Scale for the Assessment and Rating of Ataxia (SARA)[16] and the Spastic Paraplegia Rating Scale (SPRS).[17] Mobility-relevant SPRS items 1–6 were combined into a subscore termed $SPRS^{mobility}$,[18] a clinical score to assess functional mobility across neurological systems. Activities of daily living were scored by the activities of daily living subscore of the Friedreich Ataxia Rating Scale (FARS-ADL).[19]

Gait Conditions, Data Acquisition, and Calculation of Gait Measures

Walking was assessed in two different conditions: (1) constrained walking in controlled laboratory conditions[20] (laboratory-based walking, LBW) and (2) largely unconstrained walking in public spaces, more closely resembling real-life walking by including. For example, pedestrian encounters and bypassing, turning around corners, and passing doors and stairs (supervised free walking, SFW). See supplementary Methods S1 for detailed descriptions of gait conditions.

Sensor data were captured with three inertial sensors (Opal, APDM Wearable Technologies Inc., Portland, OR, USA) attached on both feet and posterior trunk at the level of L5 with elastic Velcro bands. For further details on acquisition and processing of sensor data in LBW and SFW see supplementary Methods S2.

To obtain gait measures, non-parametric summary measures—namely median, normalized median absolute deviation (MADN = median absolute deviation/0.6745), and coefficient of variation (CV = MADN/median)—of gait features provided by *Mobility Lab* across strides were supplemented with one composite measure of spatial step variability (SPcmp, see later) and median harmonic ratio of pelvis linear acceleration in three directions (HR, see later). The composite measure SPcmp was formed from Stride Length CV and Lateral Step Deviation to capture spatial step variability in both anterior–posterior and medio-lateral directions in one measure, as described previously.[6] To quantify gait smoothness, HR of pelvis linear acceleration was determined from raw accelerometer signals of the lumbar sensor, as described previously by us[6] and others.[21]

Selection and Prioritization of Gait Measures

For analyzing discriminative validity, we considered a hypothesis-based selection of 30 gait measures out of all calculated measures based on previous studies and literature (from both the ataxia- and HSP-field) and clinical plausibility.[6-8,11,22-24] A list of these 30 gait measures—including their definitions—is provided in Table S1. For analyzing the convergent validity of gait sensor measures with clinical outcome assessments (COAs) in ARSACS, the correlation analyses of this study included one gait measure (out of the hypothesis-based set of 30 gait measures) of each key gait domain or subdomain established for gait disorders previously in the literature (for details of this prioritization process see Supplementary Methods S3). This led to identification of five gait measures, one for each gait domain or subdomain of interest: Speed (pace), Swing CV (temporal variability), Lateral Step Deviation (spatial variability), Pitch at Toe Off MADN (foot angle variability), and Harmonic ratio V (smoothness).

Statistics and Analysis

To assess the ability of gait measures to discriminate patients with ARSACS from HC, the effect size Cliff's δ between both groups[25] was calculated for all 30 gait measures and both conditions LBW and SFW. Effect sizes were reported as *small* ($\delta \geq 0.2$), *medium* ($\delta \geq 0.5$), or *large* ($\delta \geq 0.8$).[26] Significance of group differences was determined by the non-parametric Wilcoxon rank-sum test, with the significance level set to $P < 0.05/n = 30$: number of gait measures (Bonferroni-corrected for multiple comparisons). To assess convergent validity, Spearman correlations of prioritized gait measures with clinical- and patient-relevant COAs were examined. As primary outcome we used the patient-focused measure $SPRS^{mobility}$, because it allows the capture of patient-relevant functional mobility across neurological systems, with health aspects like gait speed or gait distance captured by the $SPRS^{mobility}$ top-ranked by spastic ataxia patients as most relevant health aspects (Saute et al., unpublished observations). Exploratory outcomes were ataxia- (SARA) or spasticity-focused (SPRS) disease severity measures; and an activity of daily living scale (FARS-ADL). Effect sizes ρ were given with 95% confidence intervals (determined by boot strapping using MATLAB's *bootci* function with 2000 samples) and p-values, and classified as *small* ($\rho \geq 0.1$), *medium* ($\rho \geq 0.3$), *large* ($\rho \geq 0.5$), or *very large* ($\rho \geq 0.7$).[26,27] Correlations with primary outcome $SPRS^{mobility}$ were reported as significant when $P < 0.05/n = 5$: number of prioritized gait measures (Bonferroni-corrected). Correlations with exploratory outcomes were deemed significant when $P < 0.05$. Further, Spearman correlations between the two walking conditions (LBW, SFW) were calculated for each gait measure. Statistical analysis was performed using MATLAB (version R2022a).

Results

Gait recordings of 18 ARSACS patients from the lab-based walking condition (LBW), and 15 ARSACS patients from the supervised free walking condition (SFW) were analyzed and compared with recordings of 18 HC from the PROSPAX cohort (LBW and SFW).

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Individual participant characteristics are displayed in Table S2.

Analysis of Gait Measures Discriminating Between ARSACS Patients and Controls

To identify gait measures discriminating between ARSACS patients and HC (discriminative validity), we considered a hypothesis-based selection of 30 candidate gait measures based on previous studies, literature search, and clinical plausibility. In LBW, 22 of the 30 measures discriminated ARSACS patients from HC with at least moderate effect sizes (|Cliff's δ| > 0.5) with all of them showing significant group differences ($P < 0.05/n = 30$: number gait measures; for overview see Table 1). Fourteen measures discriminated even with large effect sizes (|δ| > 0.8). The largest effect sizes were observed for measures of spatiotemporal gait variability such as Lateral Step Deviation ($\delta = 0.98$), SPcmp ($\delta = 0.94$), and Swing CV ($\delta = 0.93$). Further measures with particularly high discriminative power (|δ| > 0.9) belonged to the category of foot angles (Pitch at Initial Contact), foot angle variability (Pitch at Toe Off MADN), and gait smoothness (Harmonic Ratio V).

In parallel to this general exploratory analysis of 30 candidate measures, five gait measures had been prioritized a priori (see section on 'Selection and Prioritization of Gait Measures'), each representing a separate key gait domain in ARSACS, thus allowing the capture of gait function in patients in a comprehensive, yet non-redundant, manner: pace; temporal, spatial, and foot angle variability; and smoothness. Four of these five measures were highly discriminative: Lateral Step Deviation, Swing CV, Harmonic Ratio V, Pitch at Toe Off MADN (|δ| ≥ 0.9), while only Speed was only moderately discriminative ($\delta = -0.74$) (Figs 1A and 2C).

Correlation Analyses of ARSACS Gait Measures with Mobility, Clinical Disease Severity, and Activities of Daily Living

We assessed convergent validity of the five a priori prioritized ARSACS gait measures by examining their correlations with a set of COAs differing in their degree of functional relevance and scope (for the underlying framework see Wilson and Cleary[28]). The $SPRS^{mobility}$ had been selected as the primary outcome, given that it measures mobility at a functional level of relevance for patients, and does so across neurological systems, which is especially important in a multisystemic disease like ARSACS. Among the five prioritized ARSACS gait measures, the $SPRS^{mobility}$ showed correlations of large to very large effect sizes for three of five measures: Swing CV ($\rho = 0.84$, $P = 1.6e\text{-}5$), Speed ($\rho = -0.63$, $P = 0.0050$), and Harmonic Ratio V ($\rho = -0.62$, $P = 0.0066$) (Fig. 3A,B,D,F; Table 2A).

As exploratory outcomes we used both more symptoms-oriented clinician-reported disease severity measures focusing primarily on ataxia (SARA) or pyramidal features (SPRS); and a more general activity of daily living scale going beyond just mobility (FARS-ADL). Of the five prioritized ARSACS gait measures, the top measure Swing CV also correlated with activities of daily living (FARS-ADL) ($\rho = 0.49$, $P = 0.040$), adding further support—in addition to its correlation with the $SPRS^{mobility}$—that Swing CV might capture patient-relevant health-aspects. In addition to Swing CV, also the other top measure Speed correlated with the SPRS (Swing CV: $\rho = 0.59$, $P = 0.010$; Speed: $\rho = -0.55$, $P = 0.018$), indicating an association with more general disease severity with a focus on pyramidal features. Of the five prioritized measures, only the foot angle variability measure Pitch at Toe Off MADN correlated with the SARA ($\rho = 0.61$, $P = 0.0075$) but not with the SPRS or $SPRS^{mobility}$, suggesting a potential specificity of this measure for ataxia rather than pyramidal features.

Analysis of Gait Measures Discriminating Between ARSACS Patients and Controls in Free Walking in Public Spaces

To evaluate gait measures under conditions with higher ecological validity—namely free walking in public spaces—they were next analyzed for their discriminative power and correlation with COAs in SFW. At least large correlations between the LBW and SFW conditions were observed for 28/30 gait measures (very large: 22, large: 6, medium: 1, small: 1) (Table S3). In SFW, 23/30 hypothesis-based candidate measures discriminated patients from HC with at least moderate effect sizes with 21 of them showing significant group differences. Eleven measures discriminated even with large effect sizes (Table 1). Significant group differences ($P < 0.05/n = 30$: number gait measures) were observed for all measures with at least moderate effect sizes except Elevation at Mid Swing and LRoM transverse CV. The highest discriminative effect size was observed for measures of temporal variability (Swing CV, $\delta = 0.99$), foot angle (Pitch at Initial Contact, $\delta = -0.97$), and gait smoothness (Harmonic Ratio V, $\delta = -0.96$). Seven of the 11 measures with large effect sizes captured gait variability (temporal, spatial, or foot angle). As in LBW, four of five a priori prioritized measures were highly discriminative, namely Swing CV, Harmonic Ratio V, Lateral Step Deviation, and Pitch at Toe Off MADN (|δ| > 0.8), while again only Speed demonstrated an only moderate effect size ($\delta = -0.74$) (Figs 1B and 2C).

However, compared with LBW, relevant reductions in effect size were observed in SFW for Lateral Step Deviation (SFW: 0.82; LBW: 0.98) and Pitch at

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TABLE 1 *Discrimination between autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) patients and healthy controls in lab-based walking and supervised free walking*

	Lab-based walking						Supervised free walking					
	ARSACS		HC				ARSACS		HC			
N (f/m)	18 (8/10)		18 (10/8)				15 (5/10)		18 (10/8)			
Demographic/clinical measures	**Median**	**MADN**	**Median**	**MADN**			**Median**	**MADN**	**Median**	**MADN**		
Age (years)	26.00	8.90	38.00	8.15			25.00	8.90	38.00	8.15		
Disease duration (years)	17.00	6.67					16.00	5.93				
$SPRS^{mobility}$	7.50	2.97	0.00	0.00			8.00	2.97	0.00	0.00		
SPRS	12.00	4.45	0.00	0.00			15.00	4.45	0.00	0.00		
SARA	11.75	2.22	0.00	0.00			12.00	2.22	0.00	0.00		
FARS-ADL	8.00	4.45	0.00	0.00			8.00	4.45	0.00	0.00		
Gait measures	**Median**	**MADN**	**Median**	**MADN**	**Cliff's δ**	***P*-value**	**Median**	**MADN**	**Median**	**MADN**	**Cliff's δ**	***P*-value**
Lateral step deviation (%)	4.29	0.66	2.08	0.51	0.98	5.3e-07★	5.08	1.62	3.02	0.66	0.82	6.5e-05★
SPcmp	0.444	0.160	0.131	0.044	0.94	1.6e-06★	0.510	0.192	0.218	0.084	0.81	8.8e-05★
Swing CV	0.0299	0.0167	0.0124	0.0052	0.93	2.2e-06★	0.0319	0.0094	0.0142	0.0030	0.99	1.7e-06★
Pitch at initial contact (°)	13.1	5.7	26.2	4.1	−0.92	7.3e-06★	11.0	8.0	26.6	4.1	−0.97	5.5e-06★
Harmonic ratio V	1.86	0.64	3.79	0.84	−0.91	3.1e-06★	1.92	0.30	3.62	0.90	−0.96	3.4e-06★
Pitch at toe off MADN	1.76	0.89	0.825	0.340	0.90	4.8e-06★	2.27	0.81	0.881	0.172	0.81	8.8e-05★
Stride length CV	0.0483	0.0207	0.0248	0.0070	0.89	5.6e-06★	0.0512	0.0145	0.0285	0.0074	0.85	3.5e-05★
Double support MADN	1.97	0.66	0.858	0.292	0.88	7.6e-06★	2.09	0.60	1.05	0.29	0.87	2.5e-05★
Harmonic ratio ML	1.56	0.52	2.50	0.29	−0.86	1.2e-05★	1.67	0.25	2.46	0.52	−0.72	0.00048★
LRoM transverse (°)	18.7	7.7	9.06	2.67	0.85	1.6e-05★	17.7	7.5	10.8	3.4	0.74	0.00032★
Pitch at initial contact MADN	2.12	0.85	0.989	0.223	0.84	4.3e-05★	1.99	0.64	1.38	0.53	0.68	0.0015★
Stride length (m)	1.03	0.11	1.34	0.20	−0.82	2.8e-05★	1.08	0.16	1.38	0.21	−0.76	0.00024★
Harmonic ratio AP	1.70	0.39	3.48	1.10	−0.81	3.2e-05★	1.72	0.33	3.34	0.72	−0.84	4.8e-05★
Toe out angle MADN	3.10	1.04	1.35	0.61	0.80	4.2e-05★	2.80	0.75	1.72	0.42	0.84	4.8e-05★
Pitch at toe off (°)	32.4	3.9	38.5	4.6	−0.79	5.5e-05★	34.6	5.8	40.1	3.3	−0.70	0.00072★

(Continues)

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TABLE 1 *Continued*

Gait measures	Median	MADN	Median	MADN	Cliff's δ	*P*-value	Median	MADN	Median	MADN	Cliff's δ	*P*-value
Elevation at midswing MADN	0.488	0.136	0.221	0.062	0.78	6.3e-05★	0.545	0.242	0.309	0.110	0.77	0.00018★
Stride time CV	0.0315	0.0182	0.0179	0.0066	0.78	7.2e-05★	0.0471	0.0123	0.0208	0.0047	0.79	0.00014★
Speed (m/s)	0.924	0.196	1.24	0.23	−0.74	0.00016★	0.949	0.173	1.27	0.25	−0.74	0.00032★
LRoM sagittal (°)	8.12	3.32	4.78	1.07	0.73	0.00018★	9.33	2.21	5.30	1.51	0.82	6.5e-05★
Elevation at mid swing (cm)	2.16	0.67	1.28	0.63	0.68	0.00053★	2.40	1.04	1.12	0.55	0.59	0.004
Swing (%)	38.0	2.5	40.5	1.4	−0.65	0.00095★	38.8	2.0	40.6	1.7	−0.66	0.0014★
Double support (%)	23.8	4.6	19.0	3.0	0.64	0.0011★	22.4	4.3	18.8	3.4	0.67	0.0012★
Circumduction	3.49	1.55	2.69	0.83	0.42	0.033	3.21	1.52	2.57	0.44	0.34	0.1
LRoM sagittal CV	0.209	0.074	0.155	0.051	0.41	0.035	0.181	0.049	0.220	0.058	−0.21	0.32
LRoM coronal CV	0.119	0.045	0.0927	0.0379	0.39	0.048	0.128	0.040	0.108	0.030	0.13	0.53
Stride time (s)	1.14	0.11	1.08	0.11	0.24	0.23	1.16	0.08	1.10	0.11	0.36	0.086
Toe out angle (°)	8.49	3.58	7.98	5.46	0.21	0.29	10.3	5.1	9.32	6.85	0.19	0.38
Pitch at mid swing (°)	17.2	8.3	16.3	3.5	0.15	0.46	16.9	7.6	16.9	4.0	0.17	0.42
LRoM coronal (°)	8.75	3.04	8.58	1.62	0.04	0.84	9.97	2.97	7.70	2.99	0.26	0.21
LRoM transverse CV	0.228	0.051	0.217	0.114	0.04	0.86	0.205	0.054	0.293	0.075	−0.51	0.013

Marked in light gray and labelled by ★$P < 0.05/n = 30$: number of gait measures (Bonferroni).

Abbreviations: FARS-ADL, activities of daily living subscore of the Friedreich Ataxia Rating Scale; HC, healthy controls; MADN, normalized median absolute deviation; SARA, Scale for the Assessment and Rating of Ataxia; SPRS, Spastic Paraplegia Rating Scale; $SPRS^{mobility}$, mobility subscore of the SPRS (items 1–6).

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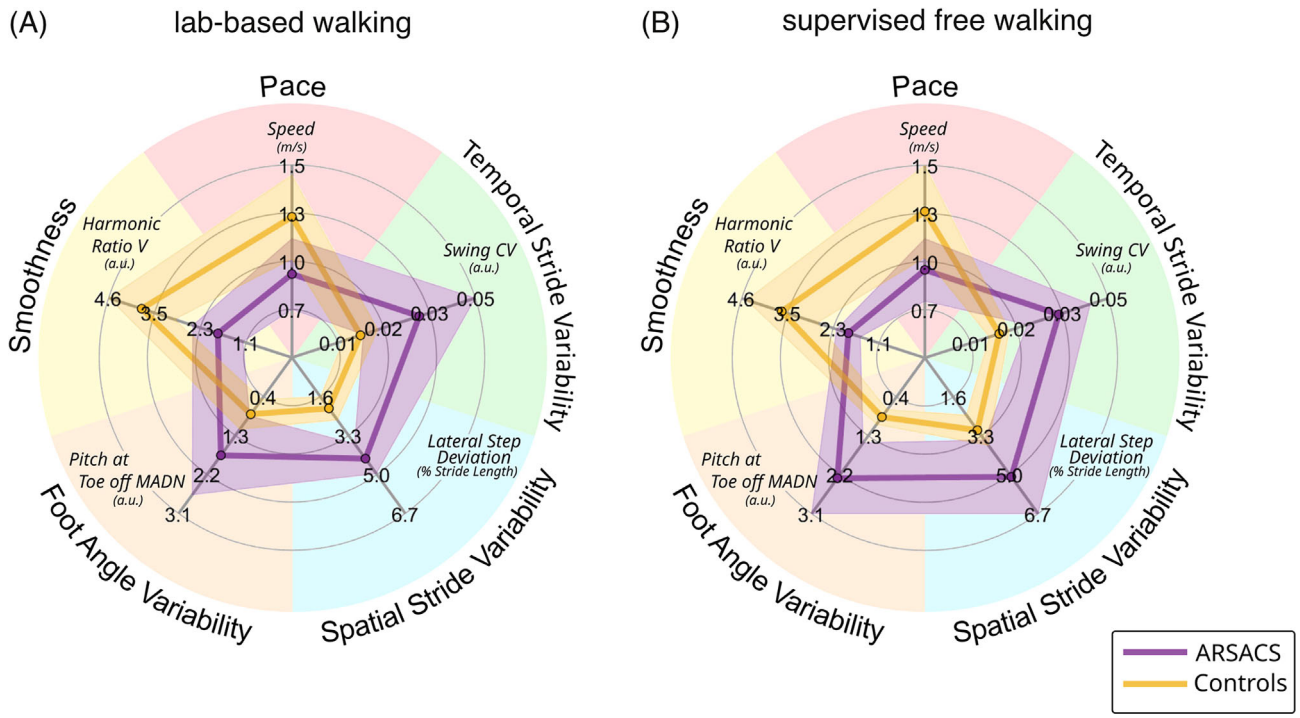


FIG. 1. Comparison of the five prioritized gait measures, each representing a key gait domain in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (outer circle), between ARSACS patients and controls in (A) lab-based walking and (B) supervised free walking. Group medians ± median absolute deviations (shaded areas) for the five gait measures. [Color figure can be viewed at wileyonlinelibrary.com]

Toe Off MADN (SFW: 0.81; LBW: 0.90), as depicted in Fig. 2C. This finding was driven primarily by two factors: relative to LBW, (1) Lateral Step Deviation in SFW increased more strongly in controls than in patients; and (2) interindividual variance increased substantially in both Lateral Step Deviation and Pitch at Toe Off MADN in SFW, in particular in patients (Fig. 2A,B).

Correlation Analyses of ARSACS Gait Measures in Free Walking with Clinical Variables

Among the five prioritized ARSACS gait measures, the primary outcome $SPRS^{mobility}$ showed correlations with large to very large effect sizes for the gait measures Swing CV ($\rho = 0.78$, $P = 0.00069$) and Speed ($\rho = 0.69$, $P = 0.0046$) also in SFW (Fig. 3A,C,E,G; Table 2B). Compared with LBW, the effect sizes were only slightly smaller for Swing CV and even larger for Speed in SFW (Fig. 3A), suggesting that the effect sizes of these top gait measures observed in LBW are largely preserved even in more real-life settings with higher degrees of freedom and noise. The correlation of the $SPRS^{mobility}$ with Harmonic Ratio V reached the same effect size in SFW as in LBW, but did formally not reach statistical significance here ($\rho = -0.62$, $P = 0.0137$).

In the analysis of the exploratory outcomes, the two top measures Swing CV ($\rho = 0.75$, $P = 0.0013$) and Speed ($\rho = -0.56$, $P = 0.029$) also correlated with the SPRS—like in LBW—thus further underlining the association of these two measures with more general disease severity with a focus on pyramidal features. Pitch at Toe Off MADN correlated with the SPRS ($\rho = 0.60$, $P = 0.017$), but not with the SARA in SFW (in contrast so LBW). No significant correlations of the five prioritized ARSACS gait measures in SFW were observed with the SARA or the FARS-ADL.

Discussion

This study presents the first multicenter study of digital gait outcomes in ARSACS, aiming to identify candidate digital gait outcomes for ARSACS applicable in multicenter settings and reflective of patient-relevant health aspects. With a clear focus on trial-readiness and ecological relevance, it focused on outcomes capturable by wearable sensors demonstrating their discriminative, convergent, and ecological validity—also during free-walking in public spaces.

Gait Measures Discriminate Patients with ARSACS from Controls with Large Effect Sizes

We identified 14 measures discriminating ARSACS patients from HC with large effect sizes ($|\delta| > 0.8$), with the top three measures—Lateral Step Deviation, SPcmp,

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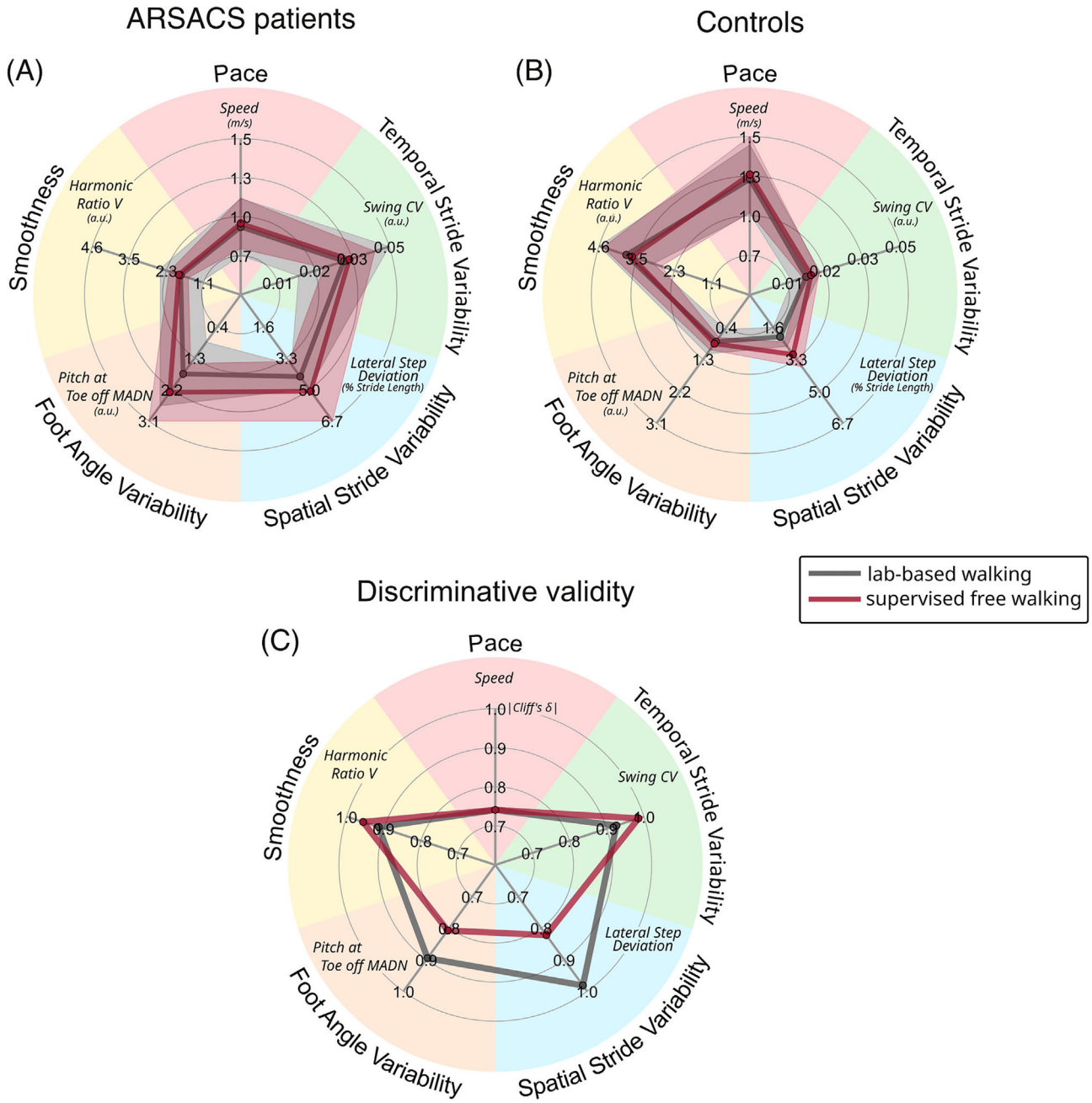


FIG. 2. Comparison of the absolute levels of the five prioritized gait measures in (A) autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) patients and (B) controls between lab-based versus supervised free walking, and of (C) their discriminative effect sizes of ARSACS patients from controls in lab-based versus supervised free walking (A, B). (A, B): group medians ± median absolute deviations (shaded areas) for ARSACS patients (A) and controls (B). (C): discriminative effect sizes Cliff's δ of ARSACS patients versus controls. [Color figure can be viewed at wileyonlinelibrary.com]

and Swing CV—all capturing aspects of spatiotemporal stride variability. Of note, discriminative effect sizes were large—even though the older age of HC likely reduced group differences due to naturally occurring aging-related gait changes.[29] The presented effect sizes thus likely present conservative (under-) estimates, of the true discriminative validity of the gait measures. This finding corroborates and extends previous studies, demonstrating that measures of spatiotemporal stride variability are increased in ataxia and HSP. Specifically, measures of spatial and temporal stride variability[5-7] and also foot angle variability[7] were increased in ataxias with effect sizes similar to those observed in the current study. Likewise, as in this ARSACS study, measures of gait smoothness like Harmonic Ratio were previously found altered in other ataxias.[6] Temporal stride variability was found to be increased also in HSP—though

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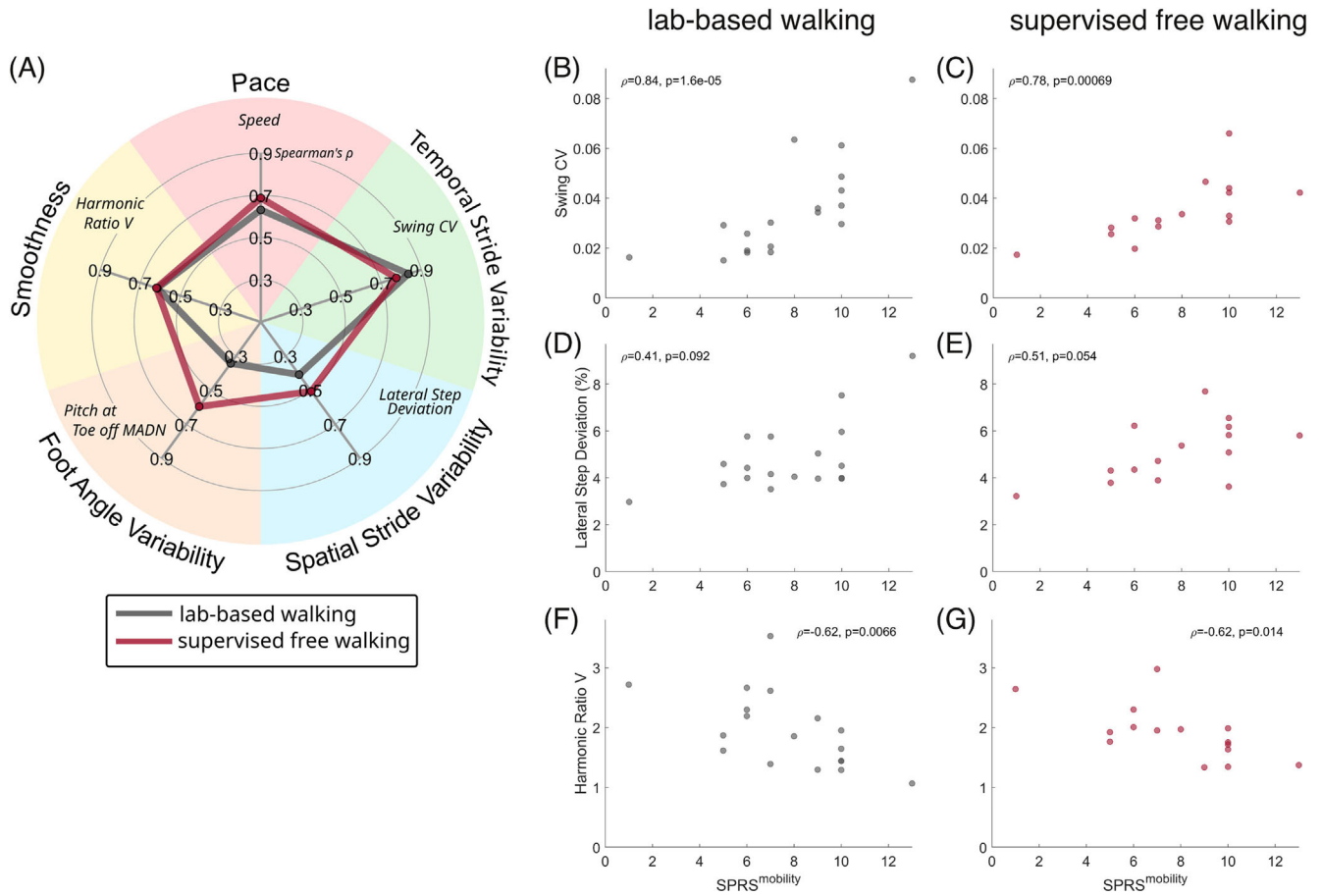


FIG. 3. (A) Degree of correlations of the five prioritized gait measures, each representing a key gait domain in autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) (outer circle), with $SPRS^{mobility}$ in lab-based walking (grey) versus supervised free walking (red) in ARSACS patients. (B-G). Scatter plots of three top measures versus $SPRS^{mobility}$ in lab-based walking (left) and supervised free walking (right): Swing CV (B + C), Lateral Step Deviation (D + E), and Harmonic Ratio V (F + G). [Color figure can be viewed at wileyonlinelibrary.com]

reported in only one study so far.[11] Here, we demonstrate the discriminative validity of these measures for the first time for ARSACS, a particular multisystemic disease combining not only ataxia and HSP features, but also severe neuropathy.

ARSACS Gait Measures Correlate with Patient-Relevant Health Aspects with Large Effect Size

Specific gait measures related to temporal stride variability (Swing CV), pace (Speed), and gait smoothness (Harmonic Ratio V) revealed correlations of large effect sizes with the $SPRS^{mobility}$, indicating convergent validity of these gait measures with a key patient-relevant COA. As opposed to classical clinician-reported scales focusing mainly on clinical symptoms, less on functions of patient relevance (like the SARA), or on general disease severity including a broad mixture of symptoms and functions (like the SPRS), the $SPRS^{mobility}$ genuinely focuses on patient-relevant functioning. It does so by (1) capturing health aspects like gait speed or gait distance top-ranked by spastic ataxia patients as most relevant health aspects (Saute et al., unpublished observations); (2) focusing on mobility-related functioning, as is key for showing convergent validity with sensor gait measures—which should inherently correlate more with mobility-related functions, rather than general disease functions (also including, eg, upper limb, speech or non-motor functions); and (3) by capturing disease-related mobility impairment across neurological systems—which is especially important in a multisystemic disease like ARSACS. Taken together, the high correlation of Swing CV, Speed, and Harmonic Ratio V with the $SPRS^{mobility}$ indicates that these gait measures might indeed be reflective of disease-related impairment of gait and mobility, a highly patient-relevant health aspect, as shown by various patients' voice surveys.[13-15] For achieving regulatory and patient acceptance, it is mandatory for digital-motor outcomes to demonstrate that they are closely reflective of such patient-relevant health aspects, as highlighted by the recent US Food & Drug Administration (FDA) guidance.[12]

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TABLE 2 *Correlation of gait measures with clinical measures in lab-based walking (A) and supervised free walking (B)*

	SPRS^{mobility}	SPRS	SARA	FARS-ADL
(A) Lab-based walking				
Speed (m/s)	**−0.63 [−0.87, −0.16]****	−0.55 [−0.87, 0.12]*	−0.46 [−0.81, 0.09]	−0.03 [−0.56, 0.47]
Lateral step deviation (%)	0.41 [−0.14, 0.80]	0.37 [−0.19, 0.76]	0.27 [−0.33, 0.72]	−0.16 [−0.64, 0.46]
Swing CV	**0.84 [0.63, 0.95]****	0.59 [0.19, 0.84]*	0.45 [−0.00, 0.78]	0.49 [−0.03, 0.79]*
Harmonic ratio V	**−0.62 [−0.85, −0.20]****	−0.45 [−0.77, 0.03]	−0.46 [−0.77, 0.09]	−0.18 [−0.65, 0.36]
Pitch at toe off MADN	0.34 [−0.17, 0.72]	0.28 [−0.35, 0.64]	0.61 [0.22, 0.81]**	0.10 [−0.50, 0.57]
(B) Supervised free walking				
Speed (m/s)	**−0.69 [−0.89, −0.21]****	−0.56 [−0.87, 0.01]*	0.00 [−0.60, 0.59]	0.08 [−0.55, 0.60]
Lateral step deviation (%)	0.51 [−0.13, 0.87]	0.41 [−0.40, 0.83]	0.24 [−0.39, 0.74]	−0.04 [−0.64, 0.61]
Swing CV	**0.78 [0.35, 0.93]****	0.75 [0.14, 0.94]**	0.30 [−0.37, 0.78]	0.21 [−0.51, 0.72]
Harmonic ratio V	−0.62 [−0.85, −0.19]*	−0.48 [−0.82, 0.06]	−0.28 [−0.73, 0.34]	−0.11 [−0.62, 0.46]
Pitch at toe off MADN	0.60 [0.03, 0.87]*	0.60 [−0.08, 0.92]*	0.42 [−0.14, 0.82]	0.09 [−0.53, 0.64]

Spearman's ρ [95% CI]. **$P < 0.01$ (Bonferroni-corrected for five comparisons), *$P < 0.05$. Significant correlations with primary outcome SPRS^{mobility} ($P < 0.01$) highlighted in bold.
Abbreviations: FARS-ADL, activities of daily living subscore of the Friedreich Ataxia Rating Scale; SARA, Scale for the Assessment and Rating of Ataxia; SPRS, Spastic Paraplegia Rating Scale; SPRS^{mobility}, mobility subscore of the SPRS (items 1–6).

Correlations in the exploratory analysis of the five prioritized ARSACS gait measures with the COAs SPRS, SARA, and FARS-ADL exhibited smaller effect sizes, with only few reaching statistical significance. This was in accordance with our expectations, as these COAs focus mainly on clinical symptoms, less on functions of patient relevance (SARA); or on general disease severity including a broad mixture of symptoms and functions (SPRS); or on broader concepts of activities of daily living (FARS-ADL). Additionally, all of them go substantially beyond mobility, as was to be reflected by gait measures. Nevertheless, Swing CV—the measure exhibiting the largest correlation with the SPRS^{mobility}—also correlated with the FARS-ADL and SPRS. This adds further support that Swing CV might capture patient-relevant health aspects—in addition to its correlation with the SPRS^{mobility}—and even more broadly in the sense of the wide ADL spectrum captured by the FARS-ADL. It might also reflect general disease, at least as captured by a clinician-reported disease severity scale focusing on pyramidal symptoms and functioning.

Gait Measures Discriminate ARSACS from Controls and Correlate with Patient-Relevant Health Aspects with High Effect Size—Also in Free Walking in Public Spaces

Also, in settings of free walking in public spaces (SFW), 11 gait measures with high discriminative effect size were identified, with the highest effect size again observed for measures capturing aspects of gait variability (temporal: Swing CV; spatial: Stride Length CV; foot angle: Pitch at Initial Contact) and gait smoothness (Harmonic Ratio V). This finding is remarkable as this setting—while ecologically more relevant, as closer to patients' real life—is inherently characterized by higher degrees of freedom, noise, and confounders, compared with the quiet, non-public, highly standardized laboratory setting (LBW). This finding is even more remarkable considering that, in addition, the walking routes in free walking naturally differed between the multiple participating centers. Indeed, a small reduction of discriminative power was observed for many measures, likely attributable to an increase of interindividual variation in gait under free walking settings among both patients and controls that had already been observed in a previous study in other ataxia conditions.[6] Yet, the same four of the five a priori prioritized ARSACS gait measures (Swing CV, Harmonic Ratio V, Lateral Step Deviation, Pitch at Toe Off MADN, all $|\delta| > 0.8$), were highly discriminative in SFW as in LBW. Taken together, these findings validate not only the applicability of free walking test protocols in multicenter settings; but also the discriminative validity of the top-ranked ARSACS gait measures, observed in lab-based settings, in such—ecologically more relevant—free walking settings.

Moreover, similar to their performance in lab-based settings, the top gait measures related to pace (Speed), temporal variability (Swing CV), and smoothness (Harmonic Ratio V, though with $P = 0.014$, not statistically significant after Bonferroni-correction) also showed correlations of large to very large effect size with the SPRS^{mobility}—with no relevant decreases in effect size compared with lab settings. In fact, effect

sizes for Speed were even larger in SFW than in LBW. These findings not only validate the *convergent* validity of the top-ranked ARSACS gait measures observed in lab-based settings, also for such free walking settings—despite the higher degrees of freedom and noise. They also demonstrate a high degree of *ecological* validity of these outcome measures, as they combine in fact *two* features of patient relevance: these outcomes both reflect patient-relevant aspects of health (disease-related mobility) and are acquired in ecologically relevant contexts (walking in public spaces). This combined convergent and ecological validity of our top-ranked gait measures will be key for achieving regulatory and patient acceptance, as highlighted by the FDA guidance on patient-focused drug development.[12]

Limitations of the Study

This study has several limitations. While this study presents the first multicenter—and largest—study of any digital-motor outcome in ARSACS, our findings need to be confirmed in larger ARSACS disease cohorts of still ambulatory patients. Furthermore, for some of the participants, no valid gait recordings could be obtained due to technical difficulties (unreliable step detection, corrupted data files), eligibility errors, and failure in recording gait. Future studies need even more thorough eligibility and quality control training across all participating sites than already applied in the current study. While this study focused on the analysis of straight walking, future studies are warranted to also analyze turns, here ideally including tasks that cover and maximize a sizeable number of turns. As a further limitation, test–retest reliability of gait measures specifically for ARSACS was not assessed in this study. While good to excellent test–retest reliability has already been shown in ataxia populations in earlier studies for the most sensitive and specific gait measures also highlighted in the current study,[5,7] future studies are warranted to demonstrate test–retest reliability also specifically for ARSACS. Finally, given its cross-sectional design, our study could not evaluate sensitivity to longitudinal change.

Conclusions

This study identified a promising set of digital-motor candidate gait outcomes for ARSACS, applicable in multicenter settings, that exhibited high discriminative and convergent validity in both laboratory-based and free walking settings, in each setting highly correlated to patient-relevant health aspects. If their sensitivity to change is validated longitudinally, these digital gait measures might serve as outcome measures in upcoming treatment trials for ARSACS and potentially also other diseases from the >200 spastic ataxias. ●

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Data Availability Statement

Data will be made available upon reasonable request and as patient consent allows.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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