Methods for Quantitative Gait Analysis in CLN3 Disease

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CLN3

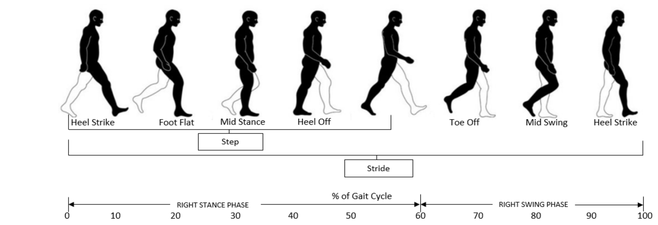
Background

- CLN3 disease (juvenile neuronal ceroid lipofuscinosis) is a genetic neurodegenerative disease of childhood onset, characterized by vision loss, epilepsy, dementia, and motor dysfunction[1].
- Motor decline begins between 10-12 years of age and demonstrates a gradual progression with age, to non-ambulation and then a bedridden state[2].
- Detailed quantitative gait data are limited.
- Spatiotemporal gait analysis is a way to measure characteristics of gait.

Definitions

Gait: A person's manner of walking	**Velocity**: The speed of walking
Footfall: Any time a foot contacts the ground	**Step length**: The distance between one heel strike to the next heel strike.
Stride width: The distance between the inside of one foot to the inside of the other foot.	**Stride length**: The distance between one heel strike and the next heel strike of the same foot.
Stance %: The amount of time spent in stance (foot on the ground) compared to swing (foot in the air) (*figure 1*). A typical individual will spend 60% of their gait cycle in stance.	**Step length ASI**: The difference between the step length of right and left feet. 0 indicates perfect symmetry. The +/- sign denotes the direction of any asymmetry.

FIGURE 1: The typical human gait cycle



Methods

- We analyzed gait characteristics in individuals with CLN3 disease using a portable ProtoKinetics Zeno™ 16' pressure sensing gait analysis system.
- Natural gait at a self selected pace was assessed over 4-6 videorecorded passes across the mat.
- A pass was deemed successful if the participant walked from one end of the mat to the other and back while remaining on the active sensor portion of the mat (32' of data per pass).
- Gait was also assessed using the gait item of the Unified Batten Disease Rating Scale (UBDRS), a validated disease-specific clinical measure of global disease progression. Possible gait scores were: 0-normal gait, 1-slow, small steps, 2-walks with difficulty, 3-requires assistance, 4-cannot walk[3].
- We compared spatiotemporal gait analysis data to two measures using bivariate correlation: 1) UBDRS gait score and 2) chronological age, a surrogate for disease duration.

FIGURE 2a: ProtoKinetics Zeno™ three-layered walkway (base, sensors, and surface).
FIGURE 2b: Research participant completing a pass across the mat.

a.

b.

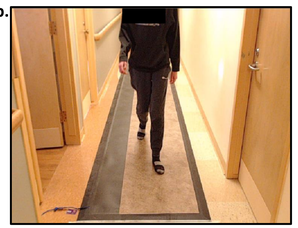
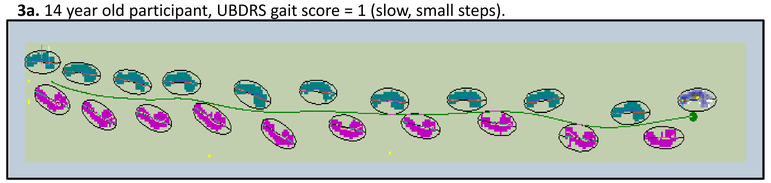
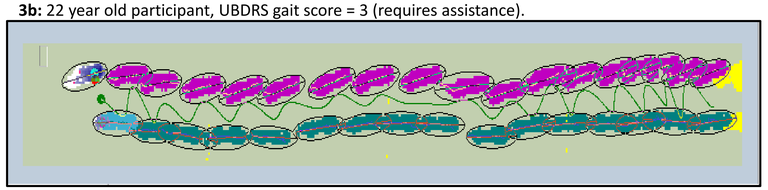


FIGURE 3: UBDRS gait score differences can be visualized with spatiotemporal gait analysis.

3a. 14 year old participant, UBDRS gait score = 1 (slow, small steps).



3b: 22 year old participant, UBDRS gait score = 3 (requires assistance).



Walkway display represents footfall images for a single direction pass across the mat in Figure 2.

Results

- 11 participants completed the assessments (mean age 11.7 years, range 2-22 years, female n=6)

TABLE 1: Higher UBDRS scores (worse function) are associated with smaller steps, higher left/right step asymmetry, slower speed, and wider base of gait.

	Mean	Std. Dev.	Range	r-value
Step length (cm)	36.7	19.92	8.41-64.0	-0.36
Step length ASI (cm)	11.7	24.79	-14.95-67.68	0.32
Stride length (cm)	73.6	40.21	16.86-129.97	-0.36
Stride width (cm)*	12.3	6.13	2.10-20.23	0.78
Velocity (cm/sec)	76.6	47.72	10.26-136.79	-0.47
Stance %*	70.7	9.17	59.97-86.58	0.65

Pearson's r was used to assess the relationship between each listed gait metric and UBDRS gait score
* Represents p<0.007 (Bonferroni adjustment threshold).

FIGURE 4: Step length and velocity versus UBDRS gait score.

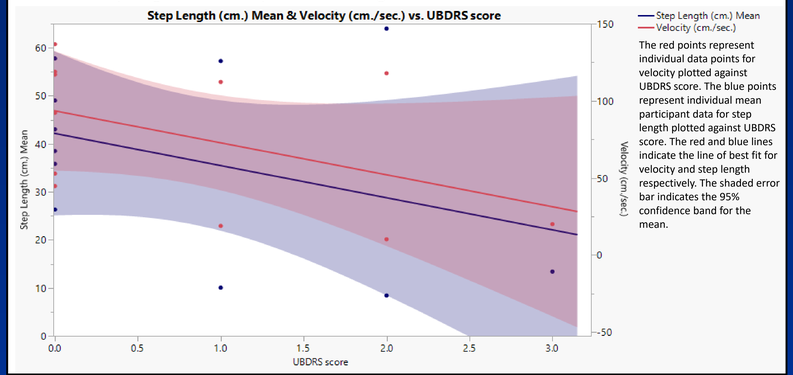
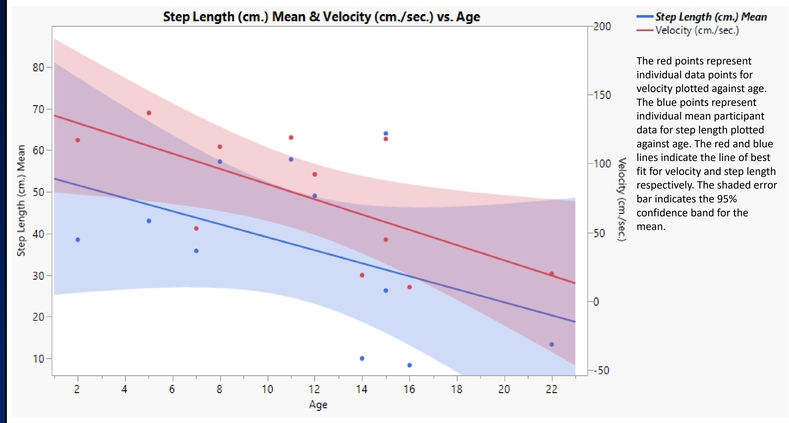


TABLE 2: Older age is associated with smaller steps, higher left/right step asymmetry, slower speed, and wider base of gait.

	Mean	Std. Dev.	Range	r-value
Step length (cm)	36.7	19.9	8.41-64.0	-0.45
Step length ASI (cm)	11.7	24.8	-14.95-67.68	0.32
Stride length (cm)	73.6	40.2	16.86-129.97	-0.44
Stride width (cm)*	12.3	6.13	2.10-20.23	0.78
Velocity (cm/sec) **	76.6	47.7	10.26-136.79	-0.66
Stance %*	70.7	9.17	59.97-86.58	0.79

Pearson's r was used to assess the relationship between each listed gait metric and age.
* Represents p<0.007; **p<0.05, ns after Bonferroni correction.

FIGURE 5: Step length and velocity versus age.



Discussion

- Spatiotemporal gait analysis is feasible in individuals with CLN3 disease, for whom visual impairment is a core symptom, and specific gait parameters can be quantified.
- Initial comparison of gait analysis data to age and UBDRS gait scores suggest that this may be a valid approach, based on known disease features of parkinsonism.
- Positive correlations between stance % and stride width with known surrogates for disease duration (age) and/or motor dysfunction (UBDRS gait score) may represent disease-associated gait instability. These associations may also be related to expected age-related growth and development.
- Larger, longitudinal studies are warranted to further assess the value of this approach and to examine the potential utility for measurement in clinical trials.
- Future analyses of this ongoing research will examine individual motor decline and will account for normal changes in gait patterns with age.

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References
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3. JM Kwon, HR Adams, PG Rothberg, EF Augustine, et al. Quantifying physical decline in juvenile neuronal ceroid lipofuscinosis (Batten disease). Neurology; 2011: 77(20), 1801-7.

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