Clinical characterization of patients with Wilson Disease (WD) using performance and qualitative measures

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INTRODUCTON

- Wilson Disease (WD) is an autosomal recessive disorder of copper metabolism due to mutations in the *ATP7B* gene
- Liver disease, neurologic symptoms, and psychiatric disorders can result from cumulative copper buildup in the liver, brain, and other tissues

OBJECTIVES

- Describe the clinical presentation of WD using performance outcome assessments
- Evaluate the relevance and appropriateness of these assessments within the WD population
- Inform study design and endpoint selection for future trials

METHODS

- Physical therapists (PTs) at 5 participating sites completed video-based training for all assessments
- PTs practiced assessment administration with non-study participants
- Study participants were recruited from the 5 participating medical centers
- Following consent, each participant completed the assessments below in one session with instruction and assistance from a trained PT

Assessment	Description
Berg Balance Scale (BBS)	• 14-item objective measure to evaluate standing balance • Each item is scored using a five-point scale with a range of 0 (lowest level of function) to 4 (highest level of function)
Qualitative Gait Assessment	• Qualitative observations on use of a device/orthotics, cadence, step length and width, initial foot contact, arm swing, and mid-stance leg & trunk alignment
4-Meter Gait Speed Test (4MGST)	• Time to walk 4 meters at a comfortable/usual speed and at a maximum speed
6-Minute Walk Test (6MWT)	• Distance walked in 6 minutes
Grip Dynamometry	• 3 isometric grip force efforts were collected for each hand using a calibrated digital hand dynamometer
Manual Muscle Testing (MMT)	• 7 upper extremity muscle groups and 7 lower extremity muscle groups were assessed bilaterally following the modified MRC scoring from 0 (no palpable muscle activity) to 5 (normal strength)
Nine-Hole Peg Test (9HPT)	• Standardized quantitative assessment used to measure finger dexterity • Participants were timed removing and then replacing the pegs using their dominant and non-dominant hands
Bruininks-Oseretsky Test of Motor Proficiency 2nd Edition (BOT-2): Fine Motor Precision items 1–4	• Participants fill in a shape (circle and star) and quality is measured on a 0–3 scale [3 is the best and highest] • Participants use a pencil to follow a path (curved and crooked) and the number of errors is counted. The goal of the task is to make the lowest number of errors

Assessments are listed in the preferred order of administration

RESULTS

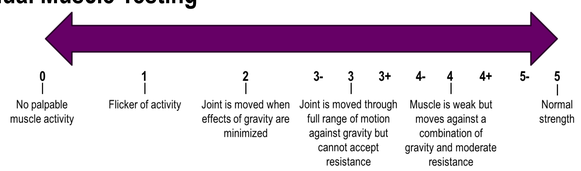
Patient Characteristics

- 16 of 17 participants completed all assessments
- Participant demographics and disease characteristics are shown below

Characteristic	N=17
Gender, n (%)	
Women	9 (53)
Men	8 (47)
Age, years	
Mean (SD)	35.5 (17.0)
Range	14–70
Age at WD diagnosis, years	
Mean (range)	20.9 (5–59)
BMI	
Mean (SD)	25.1 (3.2)
Range	18.7–30.3
Symptoms related to WD	
Neurologic, n (%)	9 (53)
Most reported symptoms	Cognitive impairment and tremor
Hepatic, n (%)	7 (41)
Most reported symptoms	Fatigue
Psychologic, n (%)	6 (35)
Most reported symptoms	Mood and behavior changes
Disease management, n (%)	
Managed with medicine	16 (94)
Managed with copper-restricted diet	12 (70.6)

Muscle Strength

Manual Muscle Testing



- MMT did not detect significant weakness in most participants
- 63% of participants had MMT grades >4
- 38% of participants had one or more muscles testing ≤3+
- Muscles testing weaker were primarily proximal hip muscle groups: hip extensors, flexors, and abductors

Grip Strength (average of 3 measurements)

- Most men had a grip strength close to age-matched peers (6/7: 86%)
- Many women had a grip strength below age-matched peers (4/9: 44.4%)

	Dominant Hand			
	Right	Left	Right & Left	
Women's Grip Value	**n = 9**	**n = 0**	**n = 0**	
kg, mean (SD)	21.4 (4.4)	NA	NA	
kg, min to max	16.8–30.6	NA	NA	
% predicted, mean (SD)	76% (15)	NA	NA	
Men's Grip Value	**n = 5**	**n = 1**	**n = 1**	
			Right	Left
kg, mean (SD)	38.2 (6.8)	50.2 kg (NA)	50 (NA)	43.8 (NA)
kg, min to max	30.6–45.5	NA	NA	
% predicted, mean (SD)	87% (9)	90%	132%	110%

Standing Balance and Gait

Gait Quality

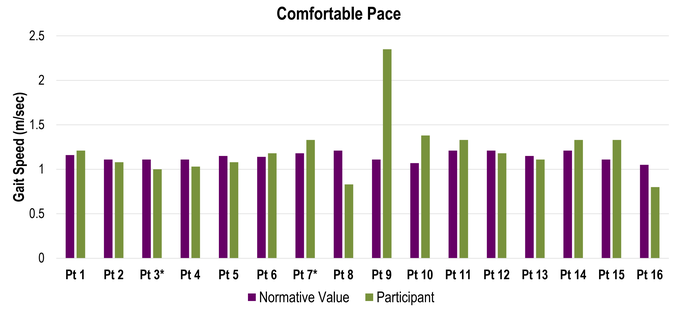
- No participants required a device to walk; no participant used a knee brace
- Arm swing
  - Decreased in 4/16 for both arms
  - Decreased in 4/16 for right arm
  - Arm swing absent in 1/16
- Step width was narrowed in 7/16 and widened in 1/16

Balance (BBS)

- BBS scores ranged from 49–56 out of 56
- These high scores indicated that these individuals were independent in their mobility and that none of the participants were at risk to fall

4-Meter Gait Speed Test

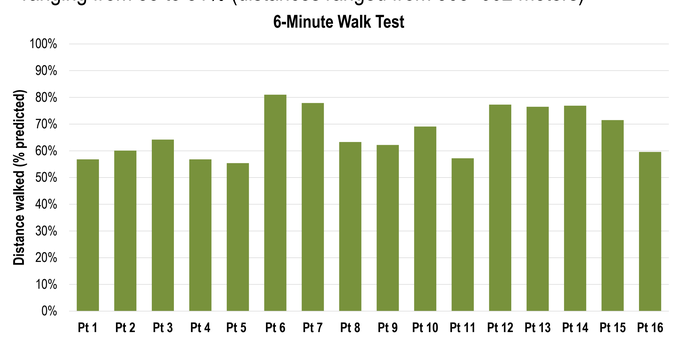
- Most participant's comfortable pace gait speeds were comparable to normed values
- Most max-speed gait speeds for participants were faster when compared to age/gender matched normed values



*Normative data were not available for patient age. Normative data for the closest age group is shown.

6-Minute Walk Test

- All participants walked less than predicted with percent predicted values ranging from 55 to 81% (distances ranged from 363–602 meters)



Fine Motor Precision and Dexterity

Fine Motor Precision

- Precision was good across most participants
- Most participants did not make errors when drawing lines through crooked and curved paths

FMP Item	Mean Score (SD)	Mean Errors (SD)
Filling in Shapes, circle	2.9 (0.3)	NA
Filling in Shapes, star	2.8 (0.4)	NA
Drawing lines through paths, crooked	NA	0.3 (0.8)
Drawing lines through paths, curved	NA	2.1 (2.9)

9-Hole Peg Test

- Most men performed the 9-HPT as fast or faster than their peers with their dominant and (4/7, 57%) and non-dominant hand (5/7, 71%).
- Most women were slower than their peers while performing the 9HPTwith the dominant (6/9, 67%) and non–dominant hand (6/9, 67%)

Limitations

- The study took place during COVID, and social distancing could be a confounding factor in enrollment and participation
- Only 16 participants completed all measures
- Enrollment and recruitment was limited to those receiving care from participating sites and may not be representative of all patients with WD

CONCLUSIONS

- Despite variability in some of the performance testing, all participants in this small group of WD patients had impaired walking capacity
- The 6MWT could potentially be used to assess the benefits of new and current therapies in WD
- This study provides an in-depth characterization of WD and may help inform endpoint selection for future studies

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