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Characterizing Upper Limb Function in the Context of Activities of Daily Living in CLN3 Disease

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Abstract

In CLN3 disease, impairments in motor function are frequently reported to have later onset compared to visual and cognitive decline, but upper limb motor function has yet to be explored in this population. In a cohort of 22 individuals with CLN3, we used a novel application of multiple measures to (1) characterize motor function, particularly of the upper limbs, in activities of daily living (ADLs), and (2) explore associations between motor function and age as well as visual ability, disease severity, and cognitive function, as evaluated by the Unified Batten Disease Rating Scale (UBDRS), a validated CLN3 disease measure. ADLs that required coordination, speed, and fine motor control were particularly challenging for children with CLN3 based on item-level performance across direct assessments [Jebsen-Taylor Hand Function Test (JTHFT) and MyoSet Tools] and caregiver reports [Pediatric Evaluation of Disability Inventory Computer Adaptive Testing (PEDI-CAT) and Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Upper Extremity]. Poorer visual ability, disease severity, and cognitive function were associated with worse performance on these measures, whereas age had limited impact. These findings support the need for children with CLN3 to receive skilled clinical evaluation and treatment tailored to their individual needs, particularly in the context of ADLs, as their symptom profile progresses.

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AUTHOR CONTRIBUTION STATEMENT

All authors have contributed substantially to conception and design, or acquisition of data, or analysis and interpretation of data; been involved in drafting or critically revising the manuscript for important intellectual content; given final approval of the version to be published; agreed to be accountable for all aspects of the work.

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Keywords

Neuronal Ceroid Lipofuscinoses; Batten; Occupational Therapy; Rehabilitation; Motor Function

INTRODUCTION

Neuronal ceroid lipofuscinoses (NCLs) make up a group of rare inherited genetic disorders of the nervous system (Rakheja, Narayan, & Bennett, 2007). These are fatal autosomal recessive lysosomal diseases and the most common inherited childhood neurodegenerative disease category (Schulz, Kohlschutter, Mink, Simonati, & Williams, 2013). NCLs are classified by the gene that causes the disorder (Williams & Mole, 2012). CLN3 disease, caused by pathogenic variants in the CLN3 gene found on chromosome 16 (Eiberg, Gardiner, & Mohr, 1989; Gardiner et al., 1990), is the most common form of NCLs. CLN3 symptom onset typically begins between four and seven years of age, beginning with the progression of vision loss and followed by cognitive and behavioral decline (~onset ages 6–8), speech impairment (~onset ages 11–17), and mobility problems (~onset ages 12–15) (Marshall et al., 2005; Ostergaard, 2016). This sequence suggests that motor skills might be preserved longer than other areas of function. Consequently, it is important to maximize this area of relative strength as the disease progresses. To date, relatively few studies have examined motor function impairment directly in CLN3 disease (Adams et al., 2007; Elmerskog & Hokkanen, 2019; Jarvela et al., 1997; Kuper et al., 2019; Kwon et al., 2011; Lamminranta et al., 2001; Santavuori et al., 1985).

Seizures and movement abnormalities are commonly reported in people with CLN3 disease (Haltia, 2003; Ostergaard, 2016; Schulz et al., 2013). Movement abnormalities include clumsiness (Wright et al., 2020), hunched posture (Wang, 2012), rigid or stiff muscles (Goebel, 1996), and slow/diminished movements (hypokinesia) (Wang, 2012). In addition, Parkinsonian-like movements, such as rigidity, bradykinesia, and tremor (rare) are reported (Ostergaard, 2016; Wisniewski et al., 2001). With disease progression, individuals exhibit increasing challenges with voluntary movement, which results in difficulty sitting and walking independently (Kuper et al., 2019; Ostergaard, 2016). Although it is acknowledged that lower limb function worsens with disease progression (Kuper et al., 2019; Ostergaard, 2016), no studies have focused on upper limb function in CLN3 disease.

To successfully participate in activities of daily living (ADLs) individuals with CLN3 may need to rely on upper limb function for their primary means of exploration and engagement as they lose vision, cognitive ability, speech, and mobility. Even though they may continue to use residual vision while engaging in ADLs, visual-motor integration is expected to be less effective as vision loss progresses. Therefore, the primary objective of this study was to examine individuals with CLN3 and (1) characterize their upper limb motor function profile in the context of ADLs, and (2) explore relationships between motor function and age, as well as visual ability, disease severity, and cognitive function, as measured by performance on the Unified Batten Disease Rating Scale (UBDRS). Characterizing the upper limb function in CLN3 disease is imperative for informing

caregiving strategies, Individualized Education Plans, and developing tailored therapies to optimize ADL participation throughout the disease course.

METHODS

Editorial Policies and Ethical Considerations

The Institutional Review Board at the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development approved this study (NCT03307304). Informed written consent was obtained from caregivers and verbal or written assent from participants ≥ age 7 prior to study participation.

Participants

This cross-sectional study is part of a broader natural history study (NCT03307304) aimed at obtaining clinical and biochemical markers that can later be used as outcome measures in treatment trials. This study enrolled individuals with molecularly confirmed diagnoses and clinical symptoms consistent with CLN3-related disorders. Study participants visited the National Institutes of Health Clinical Center for testing which included evaluation in the areas of neurology, neuropsychology, biomechanics, and occupational therapy. Prior to administering these evaluations, all providers were trained in the use of the corresponding measures. Twenty-two individuals were enrolled in this study between October 2017 and April 2019. Participants from this study will be presented across publications using the same identifiers (SP_._._) to allow for cross-sectional and longitudinal data comparisons.

Selection of Measures

Use of the measures described below has not been published in the CLN3 population for assessment of upper limb motor function in daily life, with the exception of the UBDRS Physical Assessment, against which we compared performance on novel measures. Due to anticipated variability in vision, cognition, behavior, and motor skills in this population, selection of measures was carefully considered. Test administration was modified (described below) when necessary to allow participants to successfully engage in procedures.

Description of Measures:

The **Jebsen-Taylor Hand Function Test (JTHFT)** is a widely-used standardized evaluation comprised of items that simulate common daily tasks designed to test unilateral hand function (Jebsen, Taylor, Trieschmann, Trotter, & Howard, 1969). It is comprised of seven subtests for both the non-dominant and dominant hands: writing, simulated page turning (ST1), lifting small objects (ST2), simulated feeding (ST3), stacking checkers (ST4), lifting large light objects (ST5), and lifting large heavy objects (ST6). We elected not to use the writing subtest since children with low vision have been shown to perform poorly on this task (Aki, Atasavun, & Kayihan, 2008), the subtest has multiple limitations (Beebe & Lang, 2009; Schaefer et al., 2018; Sears & Chung, 2010), and the skill being tested minimally translates to typical ADLs anticipated for the CLN3 cohort. Subtest scores (time in seconds to complete the task) and a total score (sum of scores for ST1-ST6) are calculated (Taylor, Sand, & Jebsen, 1973), with higher scores indicative of slowed/impaired function. The test was originally developed for adults ages 20 to 94 years, but it was later modified for use in

children ages 6 to 19 years. Normative data for individual subtest and total scores have been reported for individuals aged 5 to 94 years (Beagley, Reedman, Sakzewski, & Boyd, 2016; Jebsen et al., 1969; Reedman, Beagley, Sakzewski, & Boyd, 2016; Taylor et al., 1973), and test-retest reliability is good-to-excellent in 6–10 year-olds (Reedman et al., 2016) and in 18–65 years-olds (Sığırtmaç İ & Öksüz, 2020).

The **MyoSet Tools** consist of three devices to assess upper limb strength and function: MyoGrip, MyoPinch, and MoviPlate (Seferian et al., 2015). The MyoGrip and the MyoPinch are precision dynamometers that measure maximum isometric grip (0.01 kg sensitivity) and key pinch strength (0.001 kg sensitivity), respectively (Servais et al., 2013). The MoviPlate is an electronic tool that assesses motor ability during repeated hand extension/flexion with an adjustable detection threshold (Servais et al., 2013). Lower scores on the MyoSet Tools are indicative of poorer performance. These devices were originally validated in non-ambulant individuals with Duchenne muscular dystrophy (ages 10–28 years) and age-matched controls, but they can be used with individuals ranging from healthy to extremely weak (Servais et al., 2013). There are no published norms for the MyoSet Tools. The mean and standard deviation values from the 30 male, age-matched, healthy control individuals in the study by Servais and colleagues were: 33.4 ± 10.9 (kg, grip strength), 6.4 ± 2.0 (kg, key pinch), and 74.7 ± 22.3 (# of taps, MoviPlate) (Servais et al., 2013). MyoSet Tools have been found to have excellent reliability (ICCs 0.89–0.98) in individuals ages 10–28 years with Duchenne muscular dystrophy and age-matched controls (Servais et al., 2013).

The **Dynavision™ D2™** (Performance Enterprises, Ontario, Canada) is a computerized device capable of assessing upper-body dynamic reaction time using a light-board (Wells et al., 2014). This height-adjustable 4×4-foot interactive light board contains 64 small target buttons arranged in five concentric circles. Mode A (self-paced) was used for this study, which entails specific target buttons illuminating one-at-a-time until the participant successfully strikes the button with either hand. The Dynavision was originally designed to train the sensory motor integration skills through the visual system of athletes and has since been adapted for clinical use in children as young as age two with visual and motor function impairments (Klavora, Warren, & Leung, 2006). Total accuracy scores (total number of lighted buttons struck) and average reaction times for button strikes are auto-calculated after trial completion, with lower scores and longer reaction times indicative of poorer performance. Normative reaction time values have been reported in adults ages 18–80 years (Blackwell et al., 2020), but not in children. The Dynavision Mode A has strong test-retest reliability (ICC of 0.88) in 19–26 year-olds (Klavora, Gaskovski, & Forsyth, 1995) and fair reliability in motor reaction time with sufficient practice (i.e., 3 familiarization trials) prior to testing (Wells et al., 2014).

The **Pediatric Evaluation of Disability Inventory - Computer Adaptive Testing (PEDI-CAT)** (Haley et al., 2011) Content-Balanced (“Comprehensive”) version is a questionnaire completed by a caregiver or clinician that consists of questions across three functional domains: daily activities (~30 total items), mobility (~30 total items), and social/cognitive (~30 total items). Only the daily activities domain was used in this study. A child’s level of difficulty in daily tasks is rated using one of the following responses: ‘unable’, ‘hard’, ‘a

little hard', 'easy', or 'I don't know'. Depending on the participant's age, sex, and mobility device, all respondents receive the same item first and the response to that item dictates which item they receive next based on a built-in algorithm (Haley, Coster, Dumas, Fragala-Pinkham, & Moed, 2012). After testing, the CAT program reports age percentiles, normative scores (T-scores), and scaled scores, with lower scores indicative of greater impairment. For T-scores, the mean for each age group is 50, with a standard deviation of 10, such that scores between 30 and 70 (i.e., mean ± 2 standard deviations) are within the expected range for age. The PEDI-CAT is intended for evaluation of children from birth to age 21 with a variety of conditions (Dumas, Fragala-Pinkham, Rosen, Lombard, & Farrell, 2015; Haley et al., 2011). The daily activities domain has been found to successfully differentiate between groups of children with and without disabilities and has excellent test-retest reliability (ICC=0.997) (Dumas et al., 2012).

The **Patient-Reported Outcomes Measurement Information System® (PROMIS) Pediatric Upper Extremity** questionnaire (Item Bank v2.0 – 28Jul2016) (Irwin et al., 2012) is a parent proxy report measure that assesses children's upper limb function during daily activities. This measure contains 29 questions for parents to rate their child's level of difficulty (27 questions) or frequency with which they performed such tasks (2 questions) over the past seven days. The response options for task difficulty are: 'with no trouble', 'with a little trouble', 'with some trouble', 'with a lot of trouble', 'not able to do', and for task frequency are: 'never', 'almost never', 'sometimes', 'often', 'almost always'. A raw score is generated by summing the scores for all 29 questions. Raw scores are then converted to standardized T-scores with a population mean of 50 and a standard deviation of 10. Lower T-scores are indicative of greater impairment. This questionnaire is intended for parents with children ages five to 17 years who are living with chronic conditions or developing typically (Irwin et al., 2012).

We used the **UBDRS** to assess the cohort's visual, physical, and cognitive impairments. The UBDRS was developed as a clinical rating scale for juvenile neuronal ceroid lipofuscinosis (Marshall et al., 2005) with proven validity (Kwon et al., 2011; Masten et al., 2020). We aimed to determine how task performance on novel measures in CLN3 (listed above) would compare against visual ability, disease severity, and cognitive function as assessed by performance on this validated measure. The UBDRS contains seven domains, but only the Physical Assessment domain (items #1–20) and the Clinical Global Impression (CGI) of Cognitive Function (item #63) are included in this paper. Visual ability was assessed using item #3 (Visual Acuity). Scores on the UBDRS items #1–20 range from 0–4 and on item #63 from 1–5, with higher scores indicative of greater impairment (Marshall et al., 2005). Weighted UBDRS Physical Assessment scores are calculated using the following formula: [total score for all completed items / (total possible score of all items – total possible score of missing items)] × total possible score of all items. The UBDRS Physical Assessment scores have been shown to correlate well with CLN3 disease severity (Kwon et al., 2011; Masten et al., 2020).

Procedure

Direct Assessment—The JTHFT was administered by a trained occupational therapist (H.H. or R.P.) and was completed in approximately 30 minutes. Standardized administration includes giving the subtests in numerical order, with each done first for the non-dominant followed by the dominant hand. Each task was timed using a stopwatch. As previous pediatric studies have done, one rehearsal of each subtest was offered prior to the timed trial to ensure object and space localization was achieved and the instructions were well-understood. Additional tactile and spatial orientation were provided due to visual limitations so participants could localize the objects prior to the timed trial. If participants made performance errors, subsequent timed trials were administered and used as the recorded measure (Beagley et al., 2016; Reedman et al., 2016). Another modification was a shortened ceiling time of 120 seconds instead of the originally-published 180-second limit (Taylor et al., 1973) to avoid fatigue. If a participant could not initiate the task within that time, the score was treated as missing data and reported as an incomplete performance.

The MyoSet tasks were led by a trained occupational therapist (H.H. or R.P.) and were completed in approximately 15 minutes. Standardized administration included scripted instructions, practice trials (only for MoviPlate), and one-minute rests between individual trials. For the MyoGrip, participants were instructed to grasp the MyoGrip handle as hard as they could. For the MyoPinch, they were asked to pinch the end of the tool using their thumb and index finger as tightly as they could. Participants completed a minimum of three trials. If they performed better on each consecutive trial, they performed a fourth trial. For the MoviPlate, the adjustable sensitivity threshold (Servais et al., 2013) was set to level ‘high’ for this study. After some rehearsal with the task, participants were instructed to perform alternating finger taps as quickly as they could (repeated wrist and finger flexion/extension movements) between two cylinders during a 30-second time period. Participants performed the task at least twice. If they improved their score from the first to second trial and were not fatigued, they were asked to complete a third trial (ceiling). Although MyoSet tasks can be administered using either hand, only the dominant hand was tested to limit fatigue. Accommodations for the MyoSet Tools included more time for tactile handling and orientation to the tools prior to test trials.

The Dynavision task was administered by a trained occupational therapist (T.N.) and was completed in approximately 30–45 minutes. Administration time was dependent on the amount of familiarization, instruction, and accommodations needed. Prior to testing, the height of the light board was adjusted so each child could comfortably reach and touch the outermost target buttons. During this time, all participants were encouraged to explore the light board using hand-over-hand tactile cues, spatial orientation cues, and residual vision. With assistance from the occupational therapist, this exploration allowed participants to learn the light board’s physical features so they could readily localize the target light buttons once testing began. We used all five circles during testing for the purpose of comparing our findings to published norms. Once ready to begin practice trials, participants were instructed to stand approximately 30 cm away and centered with the light board, with their legs shoulder-width apart. In preparation for the task, they were told that they would see buttons light up one-at-a-time on the board, and the goal was for them to touch the target

button as quickly as possible once they saw it light up. Once they touched the button, they were told a new button would light up in a different location on the board, and they would continue touching the buttons as quickly as possible. Most participants engaged in practice trials in this fashion until they seemed comfortable with the task. At that point, the occupational therapist told them they would be asked to repeat the same task they just practiced over the course of four minutes. If a participant could not do the entire four minutes or reach all five circles of buttons, the score was treated as missing data and reported as an incomplete performance. Each testing trial began with a verbal 5-second countdown from the light board's LCD screen. Once the test started, the occupational therapist provided interval verbal time cues (modification to standardized procedure to help with participant compliance) at every remaining minute mark until test completion (e.g., "Three minutes left"). If motivation or attention waned, more frequent verbal time cues were provided (e.g., "30 seconds left"). Testing trials were continued until the participant could no longer engage in the task.

Parent Report—The PEDI-CAT questionnaire was completed on a laptop (64-Bit, HP Elitebook, Windows 10) by a caregiver. Administration time was approximately 10 minutes and it was led by a physical therapist (J.M. or C.Z.). Parents were instructed that they would receive approximately 30 questions regarding their child's experience with daily activities, and that they would have five answer options to choose from to indicate the level of difficulty their child exhibits when performing the tasks.

The PROMIS questionnaire, paper-and-pencil version, was completed by a caregiver. Administration time was approximately 10 minutes and it was led by a clinical psychologist (A.T). Parents were instructed to answer 29 questions with five answer options regarding their child's difficulty/frequency with upper extremity tasks during daily activities over the past seven days.

Clinical Evaluations—Direct examination of participants was performed by a neurologist (A.S.) to complete the UBDRS using the paper-and-pencil 12/20/17 version.

Statistics

Spearman's rho correlations were run using SPSS (IBM, Armonk, NY) to test associations between each measure with age, visual ability, disease severity, and cognitive function. Strength of the correlations was interpreted as follows: weak correlations consisting of *rho*=0 to 0.39 and 0 to −0.39, moderate correlations ranging from *rho*=0.40 to 0.79 and −0.40 to −0.79, and strong correlations involving *rho*=0.80 to 1.00 and −0.80 to −1.00. Please note that for correlations involving the JTHFT ST1 scores were used in place of total scores since total scores were only available for some participants (n=8). ST1 was used, as opposed to other subtests, because it: 1) was the first test administered in the series so that performance fatigue was unlikely, 2) evaluated manual dexterity/fine motor skill (versus gross motor as in ST5 and ST6), 3) was relatively less dependent on visual ability (versus ST2, ST5, and ST6), and 4) was completed by the majority of participants (n=18). In addition, given the low number of completed assessments for the Dynavision (n=7), correlations were not calculated. PEDI-CAT T-scores that were '<10' were recoded

as ‘9’ for use in correlations. To account for multiple comparisons, a Bonferroni adjustment was used, with *alpha*=0.007.

RESULTS

Participants

Participant demographics are provided in Table 1. Participants’ average (mean ± standard deviation) age was 12.1 ± 4.3 years, duration of illness since first symptom was 7.3 ± 3.8 years, duration since vision loss began was 5.7 ± 4.0 years, and disease severity as measured by the UBDRS was 16.7 ± 17.9. The cohort includes four sibling pairs (SP5.2.1 and 5.2.2; SP10.2.1 and 10.2.5; SP12.2.1 and 12.2.2; SP16.2.1 and 16.2.2). Of note, SP5.2.1 and 5.2.2 have CLN3 genotype previously reported to present with non-syndromic, vision-only phenotype.

Direct Assessment

Jebsen-Taylor Hand Function Test—JTHFT subtest and total scores are provided for all 22 participants for the non-dominant and dominant hands in Figure 1. In general, CLN3 participants had lower performance scores than age- and sex-matched normative peers (Taylor et al., 1973). For this CLN3 cohort, the most difficult subtests were picking up small objects (ST2), simulated feeding (ST3), and stacking checkers (ST4). Subtest difficulty was based on the combined number of participants who performed at least two standard deviations below the norm, were unable to complete the task (incomplete), or could not be tested on the task due to cognitive, visual, or behavioral limitations (not tested).

For the non-dominant hand, poorer performance (higher scores) on the JTHFT ST1 was associated with poorer visual ability (*rho*=0.787), disease severity (*rho*=0.812), and cognitive function (*rho*=0.703), but no association was found with age. For the dominant hand, poorer performance (higher scores) was associated with poorer visual ability (*rho*=0.670), disease severity (*rho*=0.762), and cognitive function (*rho*=0.654), but no association was found with age (Table 2).

MyoSet Tools—Results for grip and pinch strength are reported in Figure 2. Mean and standard deviation values for the CLN3 cohort were much lower than those reported for the healthy male control cohort in the study by Servais and colleagues (Servais et al., 2013). Higher grip strength (higher scores) was associated with older age (*rho*=0.638), but no associations were found with visual ability, disease severity, or cognitive function. Pinch strength was not associated with age, visual ability, disease severity, or cognitive function (Table 2).

Results for the MoviPlate are reported in Figure 1, with the maximum number of taps reported based on 2–3 trials. Out of 22 participants, a portion of the participants performed 51–70 taps (n=5), 31–50 taps (n=9), 30 taps or less (n=4), or could not be tested (n=4). Similar to pinch and grip strength, mean and standard deviation values for the MoviPlate were much lower for the CLN3 cohort than healthy male controls (Servais et al., 2013). Poorer MoviPlate performance (lower scores) was associated with higher disease severity

(*rho*=−0.719), but no associations were found with age, visual ability, or cognitive function (Table 2).

Dynavision—Results for the Dynavision are reported in Figure 1, which shows the average number of hits across 1–4 test trials and average time to perform those hits. Out of 22 participants, most participants either had an incomplete performance (n=2) or could not be tested (n=13). Of the participants who could complete the task (n=7), performance was highly varied with about half the participants performing relatively poorly and half performing relatively well.

Parent-Report

Pediatric Evaluation of Disability Inventory - Computer Adaptive Testing— Results for the PEDI-CAT are provided in Figure 2 (T-scores) and Supplementary Figure S1 (caregiver responses by category and task). Out of 18 caregivers who completed the PEDI-CAT, very few children were reported to perform within normal range (n=3), whereas the remaining children performed either one (n=5) or two standard deviations (n=10) below the norm (Figure 2). Since all caregivers did not receive the same questions (see methods for description of this computer adapted format), the percentage of caregiver responses regarding their child's difficulty with various tasks is arranged by PEDI-CAT category (Supplementary Figure S1a). Based on the combined percentage of caregivers who reported their children exhibit task difficulty of either 'hard' or 'unable', tasks within the *Home* category were the most difficult (55.1%), followed by *Keeping Clean* (45.5%), *Getting Dressed* (42.6%), and *Eating & Mealtime* (37.2%). In addition, the number of caregiver responses are provided for tasks within each category for items that at least 50% (n=11) of caregivers within our sample received (Supplementary Figure S1b). Based on the combined number of caregivers who reported their children exhibit task difficulty of 'hard' or 'unable', the most difficult tasks involved using kitchen utensils (n=11 had difficulty with cutting vegetables or meat with a fork and knife and n=10 had difficulty using a knife to butter bread and spread jam), coordinating a successful pour (n=8 had difficulty pouring liquid from a large carton into a glass), and putting on clothes (n=8 had difficulty putting on winter, sport, or work gloves and n=10 had difficulty putting on and buttoning front-button shirts). Poorer PEDI-CAT performance (lower scores) was associated with older age (*rho*=−0.753), poorer visual ability (*rho*=−0.861), greater disease severity (*rho*=−0.850), and poorer cognitive function (*rho*=−0.851) (Table 2).

Patient-Reported Outcomes Measurement Information System Pediatric Upper Extremity—Results for the PROMIS are provided in Figure 2 (T-scores) and Supplementary Figure S2 (caregiver responses by task). Out of 15 caregivers who completed the PROMIS, none of the children were reported to perform within normal range, and the remaining children performed at one (n=7) or two standard deviations (n=8) below the norm (Figure 2). The number of caregiver responses regarding their child's level of difficulty with each of the upper-extremity tasks on the PROMIS is provided in Supplementary Figure S2. Based on the combined number of caregivers who reported their children exhibit task difficulty of a '1' or '2' (1=a lot of trouble/often; 2=not able to do/almost always), the most difficult tasks for the cohort were tying shoelaces (n=12), dialing a phone (n=10),

taking a bath (n=8), and using a key to unlock a door (n=8). Poorer PROMIS performance (lower scores) was associated with poorer visual ability (*rho*=−0.818), disease severity (*rho*=−0.806), and cognitive function (*rho*=−0.725), but not with age (Table 2).

Unified Batten Disease Rating Scale—Results for the UBDRS are provided in Figures 2 and 3 (task performance by participant). Out of 22 participants who were evaluated, nine participants received a score of 13 or higher on the Physical Assessment domain, which is outside the range of early disease stages (0 and 1) and indicative of more advanced disease stages (Masten et al., 2020) (Figure 2). In Figure 3, the number of participants with specific impairments is displayed and categorized by body area. Based on the combined number of participants who were evaluated with a score of either '3' or '4' (exhibiting severe or complete impairment) on an item, items that had the worst performance for our cohort were visual acuity (n=12), heel stomping (right leg n=4; left leg n=5), hand tapping (right and left hand n=5), gait (n=5), and dysmetria (n=4). Of note, most participants had no impairment of arm (left n=21; right n=20) and leg power (both legs n=20).

DISCUSSION

This study provides a detailed characterization of upper limb motor function in CLN3 disease using a novel application of measures that assess routine ADL performance. The results showed that, in individuals with CLN3, 1) upper limb function was notably affected on measures that involved speed, coordination, and fine motor control, while gross motor skills were relatively spared, 2) successful function on common ADL tasks was closely related to visual ability and cognitive function with age having limited impact, and 3) the outcomes of measures with novel application in CLN3 correlated with disease severity. These findings identify specific areas of functional difficulty that may be remediable with clinical intervention. In addition, this study highlights modifications of standard measures found to be useful in this population.

Decreased Upper-Limb Function Was Found Despite Preserved Gross Motor Skills

Overall, **slower performance speed** was identified across relevant assessments (JTHFT, MoviPlate, Dynavision). The majority of the CLN3 cohort was markedly slower on the JTHFT compared to previously reported norms across all subtest scores. Slower performance has been reported in other studies, such as on tapping tests in individuals with CLN3 (Lamminranta et al., 2001) and on manual dexterity tasks in children with visual impairment (Houwen, Visscher, Lemmink, & Hartman, 2009). In the current study, all JTHFT average subtest times were faster for the dominant hand compared to the non-dominant hand. Similar to this finding, in individuals with Parkinson disease, longer performance times on the JTHFT have been moderately associated with greater impairment on the Unified Parkinson's Disease Rating Scale (the scale from which the UBDRS was derived) (Mak, Lau, Tam, Woo, & Yuen, 2015) for the non-dominant hand (*rho*=0.65, *p*=0.009) but not the dominant hand (*rho*=0.35, *p*=0.200). Despite overall deficits found in our cohort relative to the normative population, dominant hand function may remain relatively intact compared to non-dominant hand function in children with CLN3. However, reduced performance speed was also found in comparison to age-matched norms on the

MoviPlate, which is a dominant-hand task. This finding suggests that dominant hand function may still be impaired compared to typically developing peers, even though performance is better than for the non-dominant hand.

In addition to reduced performance speed, participants with CLN3 also exhibited **poorer coordination or fine motor control** in the context of ADLs in comparison to published norms (JTHFT and MoviPlate described above; PEDI-CAT and PROMIS) and healthy cohorts (MyoGrip, MyoPinch). On the PEDI-CAT and PROMIS, the majority of participants within the cohort performed at least two standard deviations below the expected normal range, suggesting upper-limb ADL performance is greatly impaired. From an item-level standpoint, the most difficult tasks on both of these measures were ones that involved fine motor control and coordination. Parents frequently reported that they believed their children had the motor ability to perform tasks but vision limited their ability to do so independently, leading parents to score their children at lower than perceived ability. For the MyoGrip and MyoPinch, although scores were lower than those reported in the literature (Servais et al., 2013), the control cohort consisted of only males who were slightly older than the present study's cohort, which limits the ability to make comparisons. However, the clinician's impression was that pinch and grip strength were less impacted than other skills that involved coordination and fine motor control.

Although the present study did not use gross motor measures specifically, various items contained within the included measures assessed gross motor function. Accordingly, **gross motor skills appeared to be spared** in this CLN3 cohort, as evidenced by items on the PEDICAT, PROMIS, and UBDRS as well as subscales on the JTHFT (ST5, ST6). On the PEDI-CAT and PROMIS, ADL tasks that involved upper-limb gross motor skills tended to be the least impacted items. For the UBDRS, power and passive motion items suggested minimal deficit as compared to other physical assessment items, as the majority of participants were scored as having no impairment. Lastly, subtest performance on the JTHFT indicated that mean performance was better for the two subtests that involved gross motor skills (i.e., lifting light and heavy objects) as compared to the ones that required fine motor skill (i.e., stacking checkers).

Decreased Upper-Limb Function Associated with Poorer Vision and Cognitive Function

In CLN3, the onset of vision loss has been found to coincide with the onset of cognitive decline (Kuper et al., 2018). In our study, visual ability and cognitive function were related to participants' functional success and independence in upper limb ADLs for the JTHFT (ST1), PEDI-CAT, and PROMIS but not for any of the MyoSet Tools. While multiple studies have shown similar performance decrements between motor skills, physical health, and activity level in relation to visual impairment (Houwen, Hartman, & Visscher, 2009; Houwen, Visscher, et al., 2009; Lieberman, Byrne, Mattern, Watt, & Fernández-Vivó, 2010; Uysal et al., 2011), others have reported no difference in motor performance between children with mild versus severe visual impairment (Aslan, Calik, & Kitis, 2012; Houwen, Visscher, et al., 2009). Similarly, in individuals with Parkinson disease, some movement symptoms or skills (e.g., bradykinesia, rigidity, axial signs) have been found to correlate with cognitive impairment (Stojkovic et al., 2018; Wang et al., 2017; Yamawaki et al., 2018),

whereas others (postural instability, gait, tremor) have not (Domellöf, Elgh, & Forsgren, 2011). These conflicting findings may be attributable to variations in studied populations or methodology. While concurrent visual *and* neurocognitive deficits were not reported for participants in these cited studies, they occur in most individuals with CLN3 disease. Consequently, it remains challenging to tease apart the extent to which the functional problems observed in this study may be a result of these children's visual impairment versus neurocognitive deficits or likely a combination of both. There could also be motor control issues (Elmerskog & Hokkanen, 2019; Lamminranta et al., 2001; Ostergaard, 2016) related to parkinsonism influencing their upper-limb function, but investigating such concomitant issues was beyond the scope of this manuscript.

Poorer Upper-Limb Function Correlated with Higher Disease Severity

Except for a few reports, evaluation of physical ability and correlation to disease severity in individuals with CLN3 disease has mainly been done using clinician-reported measures (Adams et al., 2007; Cialone et al., 2012; Kwon et al., 2011; Lamminranta et al., 2001; Santavuori et al., 1985). In other CLN3 cohorts, increases in the UBDRS score correlated with age, disease duration, and poorer performance on neurological assessments (Adams et al., 2007; Cialone et al., 2012; Kwon et al., 2011). Direct assessment of motor ability in individuals with CLN3 included a report of decreased speed on a tapping test that did not improve with age as compared to a peer group (Lamminranta et al., 2001). In the present study's cohort, increased disease severity (as reflected by increased UBDRS scores) was associated with worse performance scores on direct (JTHFT, MoviPlate) and parent-reported (PEDI-CAT, and PROMIS) assessments, but this was not the case for strength assessments (MyoGrip, MyoPinch).

Clinical Implications

Although there is a dearth of rehabilitation assessments designed for use with people with visual and cognitive impairment, this study demonstrates that clinicians can use available measures of function to characterize ADL motor ability in CLN3 disease. The evaluations described herein contain the most extensive comparison of upper limb motor assessments in individuals with CLN3 disease. Since visual and cognitive limitations require the use of compensations in participants' daily activities, testing modifications reported here (i.e., familiarization of objects, task, and space) are believed to have yielded scores representative of participants' true upper-limb motor skills. We observed several participants with difficulty with in-hand manipulation, coordination of multiple objects, and moving a hand to a specific location. Other observed motor impairments included decreased passive range of motion (wrist and finger) and stiffness during rapid, repetitive movements. Since Parkinsonian-like symptoms have been frequently reported in CLN3, it is not surprising that these observations are consistent with a clinical picture of parkinsonism.

While further studies and carefully designed interventions are needed, application of intervention approaches for Parkinson disease (Farley et al., 2008; Foster et al., 2014; Welsby et al., 2019) may be warranted in children with CLN3. Individualized rehabilitation programs may integrate assessment outcomes from subtests or test items from the JTHFT, PEDI-CAT, and PROMIS to design exercises and adaptive approaches that promote

particular skills and performance. For example, children with mildly impaired visual ability may benefit from exercises that reflect skills tested in all six JTHFT subtests, whereas those with more severe visual impairment or more advanced disease severity may benefit from exercises designed to focus on skills tested in ST5 and ST6. For children with challenges that limit their ADLs as measured by the PEDI-CAT and PROMIS, specific therapeutic activities, adaptive strategies, and environmental modifications may be individualized to facilitate more successful performance in meaningful activities. Use of assistive augmentative communication alternatives such as auditory-based modalities may also be considered, similar to the approaches reported to have positive effects in Parkinson disease (Foster et al., 2014).

Engagement of affected individuals and their caregivers is critical to increase independence. Thus, incorporation of adaptations developed to retain independence in daily activities (e.g., use of two hands or fingers for self-feeding) is practical and may improve effectiveness of the interventions. Assisting caregivers to modify ADLs so that children with CLN3 can continue to participate (e.g., dividing a task into smaller action units to be done over time) will help provide opportunities for children with CLN3 to build and maintain their general sense of self, independence, and mental health (Houwen, Visscher, et al., 2009; Stuart, Lieberman, & Hand, 2006). Approaches based on analysis of target activities and the environment, similar to the techniques used to modify assessments in this study, will also help move toward this goal.

It is valuable for children with CLN3 to work with occupational and physical therapists who are trained to identify areas of difficulty that impede a child's participation (e.g., in the bath routine) and design treatment goals based on measures such as the parent questionnaires used here. In addition to the Individualized Education Plan, outside clinical services with a therapist experienced in working with people with visual and cognitive impairments should be considered to address non-academic goals. Early interventions, involvement of caregivers, and safe participation in adapted physical activities are anticipated to maintain higher physical function in children with visual impairment (da Cunha Furtado, Morato, Potenza, & Gutierrez, 2016; Elmerskog & Hokkanen, 2019; Ely & Ostrosky, 2018; Houwen, Visscher, et al., 2009; Karakoc, 2016; Stuart et al., 2006) and may have similar effects in children with CLN3.

Overall, we recommend that all children diagnosed with CLN3 receive developmental and routine comprehensive screening to determine if there is an existing or emerging need for rehabilitation services. In addition, we recommend that future studies in CLN3 incorporate measures that are adapted for those with visual impairment or cognitive impairment, such as the PEDI-NL (Dutch version of the PEDI-CAT) (Salavati et al., 2015). Otherwise, if adapted versions of assessments are not available, we recommend modifying testing in terms of the task approach, environment, and time allowance to ensure successful accomplishment of functional tasks. We also recommend using a very individualized approach to therapy when working with children with CLN3 that includes modifying ADL goals and methods to be based on the whole person (e.g., age, developmental level, visual ability, rate of cognitive decline and disease progression, families' goals and expectations). Finally, intervention

goals should be approached one at a time (or be limited in number), communicated using small units of information, and be repeated and relayed in alternative augmentative formats.

Research Implications

Limited availability of pediatric motor and upper limb function outcome measures, especially for individuals with CLN3 disease or visual/cognitive impairment, remains a challenge. However, adaptation of standard tools have been used in several studies to enable exploratory research (Bakke, Cavalcante, de Oliveira, Sarinho, & Cattuzzo, 2019; Houwen, Hartman, et al., 2009; Houwen, Visscher, et al., 2009; Uysal et al., 2011). As shown in this study, concurrent assessments of a single well-characterized participant cohort using multiple evaluation modalities and tools, along with an established disease-specific measure such as the UBDRS, provide overlapping support of findings. Results from this study suggest that the JTHFT, MyoSet Tools, PEDI-CAT and PROMIS are useful measures for identifying upper limb impairments in individuals with CLN3, as they can be adapted to changes in visual, cognitive, and motor abilities. Longitudinal data are warranted to confirm how these initial findings will track over time. Additional evaluations of motor planning and kinesthesia to further describe upper limb function and visual-motor integration may elucidate potential compensatory strategies relevant to rehabilitative approaches.

Regarding the Dynavision, the majority of the CLN3 cohort was unable to perform the task due to visual, cognitive, or behavioral impairments. Of the participants who were able to perform the task, several of them were unable to complete three practice trials necessary to achieve performance reliability (Wells et al., 2014). In addition, the absence of normative data in children makes it difficult to interpret the findings for the children who were able to successfully engage in the task. Due to these reasons, we recommend against using the Dynavision in a heterogeneous group with CLN3 disease at this time. Should future treatment options change the natural history of CLN3 disease, this testing modality may be reconsidered.

With respect to the research community at large, we propose that future studies describe function in individuals with CLN3 by including standard measures that allow for modification as demonstrated in this study. In addition, should they become more readily available, functional outcome and ADL measures developed for individuals with visual and cognitive impairment should be considered for future studies. Another important research path would be to investigate the role of cognitive and mental (emotional) status associated with ADL function in these children.

CONCLUSION

Overall, slower performance speed, reduced coordination, and poorer fine motor control were highly prevalent within this CLN3 cohort and were further exacerbated as vision impairment, disease severity, and cognitive impairment increased. By contrast, gross motor skills were relatively preserved. It was clear from our findings that these children need clinical support from rehabilitation services. Future studies that include larger samples and longitudinal assessments are needed to confirm the findings reported here and ultimately help guide outcome selection in intervention studies.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Participant ID & Self-Reported Handedness	Jebsen Taylor Hand Function Task														Movi-Plate	Dynavision	
	Nondominant Hand Scores							Dominant Hand Scores									
	ST1	ST2	ST3	ST4	ST5	ST6	Total	ST1	ST2	ST3	ST4	ST5	ST6	Total	Max. Taps	Ave. Hits	Ave. Time
n=22	*n=18*	*n=17*	*n=8*	*n=14*	*n=19*	*n=19*	*n=8*	*n=18*	*n=17*	*n=8*	*n=14*	*n=19*	*n=19*	*n=8*	*n=18*	*n=7*	*n=7*
SP5.2.2 R	3.4	5.9	13.0	6.3	2.9	3.0	34.6	3.6	6.8	12.4	3.3	2.9	2.7	31.7	58.0	173.0	1.3
SP5.2.1 R	3.2	5.8	9.5	3.9	3.5	3.0	28.9	2.8	6.2	8.6	3.8	2.4	3.5	27.4	70.0	133.0	1.8
SP15.2.1 R	6.5	8.4	28.9	6.1	4.0	5.2	59.1	4.3	9.1	9.3	4.2	3.1	3.2	33.2	55.0	166.0	1.4
SP14.2.2 R	6.6	18.2	43.4	8.1	6.5	6.1	88.8	7.6	15.7	23.6	14.5	4.9	5.5	71.7	39.0	IC	IC
SP2.2.3 R	11.2	9.3	24.3	5.4	4.4	4.8	59.4	6.2	11.0	20.0	4.1	4.4	4.0	49.8	55.0	37.0	6.2
SP12.2.2 R	10.5	13.2	23.3	12.1	7.0	12.8	78.8	16.1	10.6	15.3	11.9	6.7	10.0	70.5	32.0	85.0	2.7
SP10.2.5 R	8.3	9.9	26.6	5.6	3.9	4.6	59.0	7.1	8.3	15.4	3.9	3.7	4.0	42.4	44.0	95.0	2.5
SP4.2.2 R	15.1	20.9	IC	53.2	5.9	6.0	--	7.6	21.7	IC	17.9	7.3	6.5	--	30.0	IC	IC
SP1.2.2 R	5.0	10.8	IC	7.3	4.0	4.6	--	4.2	10.1	IC	8.0	3.7	4.3	--	56.0	44.0	5.4
SP12.2.1 R	12.1	13.1	45.3	7.3	5.2	4.9	87.8	11.0	10.8	21.4	10.0	4.7	4.0	61.7	33.0	NT	NT
SP11.2.4 L	8.9	20.0	NT	22.8	15.5	8.2	--	7.1	18.4	NT	19.3	18.0	6.9	--	34.0	NT	NT
SP16.2.1 L	21.5	18.3	NT	NT	14.2	8.2	--	18.5	23.2	NT	NT	10.7	7.0	--	35.0	NT	NT
SP3.2.1 R	17.3	IC	NT	20.8	13.9	13.3	--	8.0	IC	NT	15.1	8.5	6.8	--	36.0	NT	NT
SP13.2.3 R	11.4	18.3	NT	21.0	7.9	7.1	--	14.5	18.8	NT	28.8	11.5	8.4	--	30.0	NT	NT
SP9.2.1 R	12.4	28.1	NT	17.2	12.5	9.9	--	10.1	16.2	NT	17.0	10.6	8.3	--	41.0	NT	NT
SP6.2.1 R	23.5	29.1	NT	IC	25.0	32.1	--	15.8	37.3	NT	IC	18.6	19.3	--	17.0	NT	NT
SP7.2.1 R	NT	NT	NT	NT	NT	NT	--	NT	NT	NT	NT	NT	NT	--	NT	NT	NT
SP18.2.1 R	NT	NT	NT	NT	14.9	14.3	--	NT	NT	NT	NT	13.8	14.8	--	NT	NT	NT
SP10.2.1 R	NT	NT	NT	NT	NT	NT	--	NT	NT	NT	NT	NT	NT	--	20.0	NT	NT
SP8.2.1 R	35.9	30.7	NT	NT	34.1	35.6	--	20.3	26.3	NT	NT	30.8	23.5	--	34.0	NT	NT
SP16.2.2 R	20.9	26.3	NT	IC	10.9	15.0	--	17.5	24.3	NT	IC	11.2	13.7	--	NT	NT	NT
SP17.2.1 R	NT	NT	NT	NT	NT	NT	--	NT	NT	NT	NT	NT	NT	--	NT	NT	NT
Average	*13.0*	*16.8*	*26.8*	*14.1*	*10.3*	*10.5*	*62.1*	*10.1*	*16.2*	*15.7*	*11.5*	*9.3*	*8.2*	*48.5*	*39.9*	*104.7*	*3.0*
SD	*8.3*	*8.2*	*12.7*	*13.0*	*8.2*	*9.1*	*22.5*	*5.6*	*8.4*	*5.6*	*7.6*	*7.2*	*5.8*	*17.7*	*13.9*	*54.7*	*2.0*
Quartile 1	*6.6*	*9.6*	*15.6*	*6.0*	*4.0*	*4.8*	*40.7*	*5.7*	*9.6*	*10.1*	*4.1*	*3.7*	*4.0*	*32.1*	*31.5*	*44.0*	*1.4*
Quartile 2	*11.3*	*18.2*	*25.5*	*7.7*	*7.0*	*7.1*	*59.3*	*7.8*	*15.7*	*15.3*	*10.9*	*7.3*	*6.8*	*46.1*	*35.5*	*95.0*	*2.5*
Quartile 3	*18.2*	*23.6*	*39.8*	*20.9*	*14.2*	*13.3*	*85.6*	*15.9*	*22.5*	*21.0*	*17.2*	*11.5*	*10.0*	*68.3*	*55.0*	*166.0*	*5.4*

Greater Visual Impairment

Key
JFHFT / Moviplate & D2
- Normal / Best
- 1+ SD / Intermediate
- 2+ SD / Worse
- Incomplete = IC
- Not Tested = NT

Greater Impairment

Figure 1.

Participant-level scores and performance gradings for the Jebsen-Taylor Hand Function Test (JTHFT), MoviPlate, and Dynavision in the CLN3 cohort. For the JTHFT test, the total scores are the sum of all six completed subtests as compared to age and sex normative values. For the MoviPlate, the maximum number of taps out of 2–3 trials is provided. For the Dynavision, the average number of hits and reaction time from 1–4 trials is provided. Shading of the cells indicates level of performance with darker colors representing poorer performance. Participants were sorted by increasing Unified Batten Disease Rating Scale (UBDRS) visual acuity score, followed by increasing UBDRS physical score, followed by increasing vision loss duration. L: left-handed. R: right-handed. SD: standard deviation. ST1: simulated page turning. ST2: picking up small objects. ST3: simulated feeding. ST4: stacking checkers. ST5: picking up large light objects. ST6: picking up large heavy objects. Use of '--' in cells: unable to calculate due to missing data. Dashed black lines indicate transition between levels of UBDRS visual acuity in participants, from top to bottom: mildly impaired, finger counting, light/dark perception, blind.

Participant ID	PEDI-CAT T-Score	PROMIS T-Score	UBDRS Physical Score	Max Grip Raw Score	Max Pinch Raw Score
n=22	*n=18*	*n=15*	*n=22*	*n=20*	*n=21*
SP5.2.2	61.0	NT	1.0	27.0	6.9
SP5.2.1	NT	NT	1.0	34.0	7.1
SP15.2.1	38.0	36.8	2.0	17.1	6.0
SP14.2.2	42.0	33.9	3.0	7.7	2.6
SP2.2.3	NT	36.5	3.0	7.3	3.3
SP12.2.2	39.0	31.5	4.0	5.0	3.5
SP10.2.5	49.0	33.7	5.0	14.3	3.2
SP4.2.2	38.0	NT	4.0	11.1	4.5
SP1.2.2	NT	NT	4.0	16.4	4.6
SP12.2.1	33.0	33.7	10.0	10.3	4.6
SP11.2.4	38.0	NT	6.0	16.5	4.8
SP16.2.1	<10.0	30.3	9.0	21.2	5.1
SP3.2.1	<10.0	23.7	10.8	10.0	2.9
SP13.2.3	29.0	23.3	19.0	7.0	3.8
SP9.2.1	<10.0	25.0	20.0	20.6	6.9
SP6.2.1	<10.0	23.8	33.0	20.4	8.4
SP7.2.1	NT	26.0	36.0	NT	NT
SP18.2.1	<10.0	21.7	37.3	11.4	4.1
SP10.2.1	<10.0	NT	58.0	13.7	3.6
SP8.2.1	<10.0	23.3	18.0	13.4	5.2
SP16.2.2	<10.0	24.1	22.0	16.2	7.1
SP17.2.1	<10.0	NT	61.0	NT	1.8
Average	--	--	*16.7*	*15.0*	*4.8*
SD	--	--	*17.9*	*7.2*	*1.8*
Quartile 1	--	--	*3.8*	*10.1*	*3.4*
Quartile 2	--	--	*9.5*	*14.0*	*4.6*
Quartile 3	--	--	*24.8*	*19.6*	*6.5*

Greater Visual Impairment

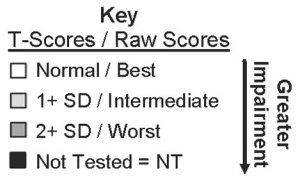

Figure 2.

Participant-level scores and performance gradings for the Pediatric Evaluation of Disability Inventory - Computer Adaptive Test (PEDI-CAT) and Patient-Reported Outcomes Measurement Information System (PROMIS) Pediatric Upper Extremity in the CLN3 cohort. T-scores are reported as compared to age normative values. Weighted scores for the Unified Batten Disease Rating Scale (UBDRS) Physical Assessment domain and raw scores (kg) for the MyoSet Tools maximum grip and pinch strength are reported. Poorer performance is reflected by lower scores on the PROMIS, PEDI-CAT, and MyoSet Tools and higher scores on the UBDRS. Shading of the cells indicates level of performance with darker colors representing poorer performance. Participants were sorted by increasing UBDRS visual acuity, then UBDRS physical scores, then by vision loss duration. Dashed black lines indicate transition between levels of UBDRS visual acuity in participants, from top to bottom: mildly impaired, finger counting, light/dark perception, blind.

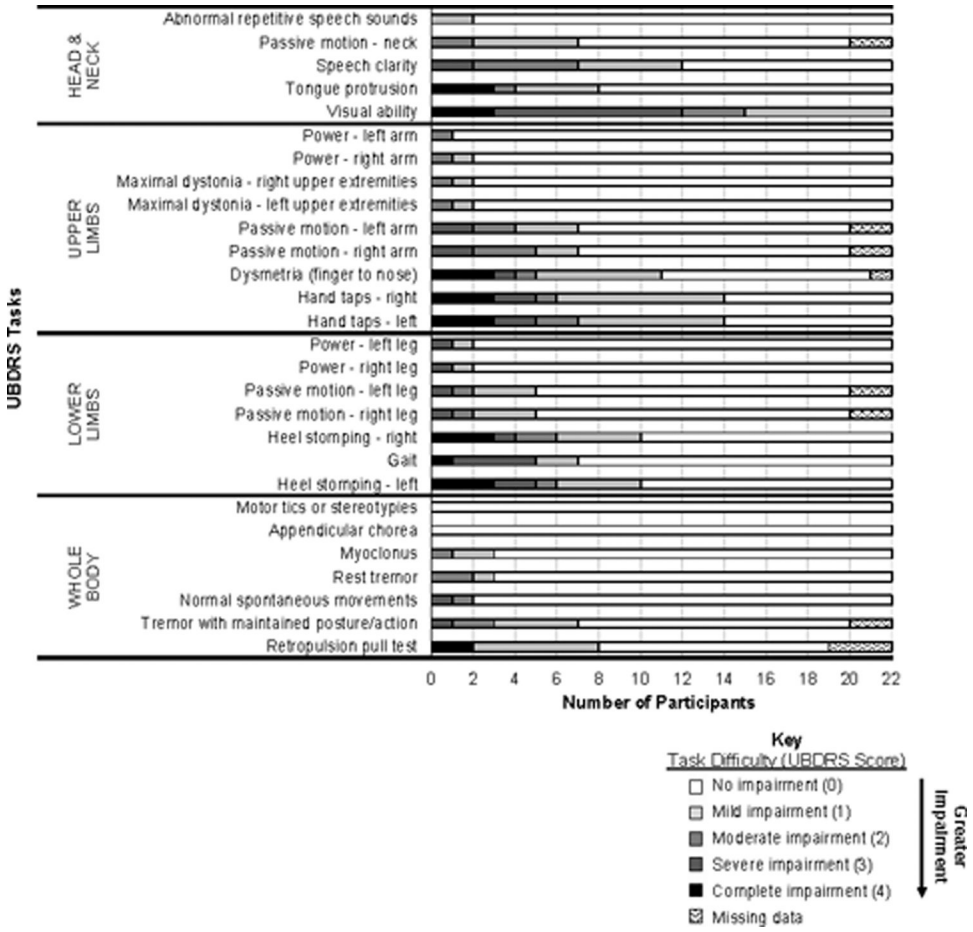

Figure 3.

Group-level scores and performance gradings for the Unified Batten Disease Rating Scale (UBDRS) Physical Assessment domain in CLN3 participants. The number of participants with specific impairments is displayed and categorized by body area. Within each category, number of reported difficulties (based on the total number of participants who received scores of ‘3’ or ‘4’) is arranged from top to bottom (least to most difficult).

Table 1.

Demographics, handedness and disease parameters in CLN3 participants. Participants are first arranged by increasing Unified Batten Disease Rating Scale (UBDRS) visual acuity score, followed by increasing UBDRS physical score (for participants whose visual acuity scores were equal), followed by increasing vision loss duration (for participants whose visual acuity scores and UBDRS physical scores were equal). Note: vision loss duration for participants SP4.2.2 and SP1.2.2 are 3.27 and 3.29 years, respectively.

Participant ID	Sex	Race	Ethnicity	Age (yrs)	Handed-ness	UBDRS Visual Acuity	Vision Loss Duration (yrs)	UBDRS Physical Score	UBDRS Cognitive Function
SP5.2.2	Male	Caucasian	Not Hispanic or Latino	13.2	Right	1	3.7	1.0	1
SP5.2.1	Female	Caucasian	Not Hispanic or Latino	17.7	Right	1	11.7	1.0	1
SP15.2.1	Female	Caucasian	Not Hispanic or Latino	10.0	Right	1	1.4	2.0	3
SP14.2.2	Male	Caucasian	Not Hispanic or Latino	6.8	Right	1	1.0	3.0	1
SP2.2.3	Male	Asian	Not Hispanic or Latino	9.0	Right	1	3.5	3.0	3
SP12.2.2	Female	Caucasian	Not Hispanic or Latino	7.5	Right	1	1.9	4.0	2
SP10.2.5	Male	Caucasian	Not Hispanic or Latino	6.8	Right	1	0.8	5.0	2
SP4.2.2	Male	Caucasian	Not Hispanic or Latino	7.3	Right	2	3.3	4.0	1
SP1.2.2	Male	Caucasian	Not Hispanic or Latino	13.3	Right	2	3.3	4.0	2
SP12.2.1	Female	Caucasian	Not Hispanic or Latino	9.3	Right	2	2.9	10.0	3
SP11.2.4	Male	Caucasian	Not Hispanic or Latino	7.8	Left	3	2.8	6.0	2
SP16.2.1	Female	Caucasian	Not Hispanic or Latino	16.1	Left	3	10.1	9.0	3
SP3.2.1	Female	Caucasian	Hispanic or Latino	9.5	Right	3	3.5	10.8	3
SP13.2.3	Male	Asian	Not Hispanic or Latino	7.7	Right	3	0.9	19.0	4
SP9.2.1	Male	Caucasian	Not Hispanic or Latino	16.6	Right	3	9.6	20.0	4
SP6.2.1	Male	Multiple	Not Hispanic or Latino	15.4	Right	3	9.9	33.0	4
SP7.2.1	Female	Caucasian	Hispanic or Latino	11.4	Right	3	8.4	36.0	4
SP18.2.1	Female	Multiple	Hispanic or Latino	11.6	Right	3	6.6	37.3	4
SP10.2.1	Female	Caucasian	Not Hispanic or Latino	20.7	Right	3	13.7	58.0	4
SP8.2.1	Female	Caucasian	Hispanic or Latino	16.6	Right	4	7.6	18.0	4
SP16.2.2	Female	Caucasian	Not Hispanic or Latino	15.1	Right	4	11.1	22.0	4
SP17.2.1	Male	Multiple	Hispanic or Latino	17.5	Right	4	7.5	61.0	4

UBDRS visual acuity: 0=normal; 1=mildly impaired; 2=finger counting only; 3=light/dark perception; 4=blind. Vision loss duration was calculated as the duration from parental report of first visual symptom to study enrollment. UBDRS Clinical Global Impression cognitive function: 1=no impairment, 2=minimally impaired, 3=mildly impaired, 4=moderately impaired, 5=severely impaired. Dashed black lines indicate transition between levels of UBDRS visual acuity in participants.

Table 2.

Correlations for evaluated measures with age, the Unified Batten Disease Rating Scale (UBDRS) visual acuity, Physical Assessment domain and Clinical Global Impression cognitive function scores. Significance is set to $p<0.007$ based on Bonferroni corrections. JTHFT: Jebsen-Taylor Hand Function Test. PEDI-CAT: Pediatric Evaluation of Disability Inventory - Computer Adaptive Testing. PROMIS: Patient-Reported Outcomes Measurement Information System. ST: subtest. UBDRS: Unified Batten Disease Rating Scale.

	Participant's Age		**UBDRS Visual Acuity**		**UBDRS Physical Assessment**		**UBDRS Cognitive Function**	
	rho	***p-value***	***rho***	***p-value***	***rho***	***p-value***	***rho***	***p-value***
JTHFT Non-Dominant ST1 Score	0.234	0.349*	0.787	<0.001*	0.812	<0.001*	0.703	0.001*
JTHFT Dominant ST1 Score	0.112	0.657*	0.670	0.002*	0.762	<0.001*	0.654	0.003*
MyoGrip Score	0.638	0.002*	0.057	0.813	−0.116	0.626*	−0.080	0.736
MyoPinch Score	0.460	0.036	0.137	0.553	−0.068	0.769*	0.106	0.649
MoviPlate #Taps	0.113	0.656	−0.568	0.014	−0.719	0.001*	−0.472	0.048
PEDI-CAT T-Score	−0.753	<0.001*	−0.861	<0.001*	−0.850	<0.001*	−0.851	<0.001*
PROMIS T-Score	−0.472	0.075	−0.818	<0.001*	−0.806	<0.001*	−0.725	0.002*