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Motor function impairment is an early sign of CLN3 disease

Willemijn F.E. Kuper, MD, Claudia van Alfen, MD, Linda van Eck, BSc, Barbara C.H. Huijgen, PhD, Edward E.S. Nieuwenhuis, MD, PhD, Marco van Brussel, PhD, and Peter M. van Hasselt, MD, PhD

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Abstract

Objective
To delineate timing of motor decline in CLN3 disease.

Methods
Motor function, assessed by the 6-Minute Walk Test (6MWT), was evaluated repeatedly in 15 patients with CLN3 disease, resulting in 65 test results and during one occasion in 2 control cohorts. One control cohort (n = 14) had isolated visual impairment; a second cohort (n = 12) exhibited visual impairment in combination with neurologic impairments. Based on 6MWT reference values in healthy sighted children, z scores of 6MWT results in patients with CLN3 disease and control cohort individuals were calculated. 6MWT results were correlated with age—including multilevel modeling analysis allowing assessment of imbalanced repeated measurements—and with Unified Batten Disease Rating Scale (UBDRS) scores.

Results
In CLN3 disease, 6MWT scores were already impaired from first testing near diagnosis (mean z scores of −3.6 and −4.7 at 7 and 8 years of age, respectively). Afterwards, 6MWT scores continuously declined with age ($r = −0.64, p < 0.0001$) and with increasing UBDRS scores ($r = −0.60, p = 0.0001$), confirming correlation with disease progression. The decrease was more pronounced at a later age, as shown by the nonlinear multilevel model for 6MWT results in CLN3 disease ($y = 409.18 − [0.52 \times \text{age}^2]$). In contrast, an upward trend of 6MWT scores with age was observed in the control cohort with isolated visual impairment ($r = 0.56; p = 0.04$) similar to healthy, sighted children. The control cohort with additional neurologic impairments displayed a slightly decreased 6MWT walking distance independent of age.

Conclusions
The 6MWT unveils early onset of motor decline in CLN3 disease.
CLN3 disease (OMIM #204200), formerly known as juvenile neuronal ceroid lipofuscinosis or Batten disease, is a neurodegenerative lysosomal storage disorder with childhood onset. Currently, there are no curative or disease-modifying treatments for CLN3 disease. As a consequence, patients usually die in their second or third decade of life.1 The most striking early clinical feature is vision loss. This was long assumed to precede progressive neurologic deterioration by a few years, implicating a therapeutic window for any future brain-targeting treatments.2–4 Recently, however, onset of vision loss was found to coincide with onset of cognitive decline, rather implying early brain involvement.5 This led us to hypothesize that motor function decline might also have its onset early in the disease course.

The 6-Minute Walk Test (6MWT) is a clinical evaluation tool to obtain an overall impression of motor functioning. The 6MWT is commonly used to assess disease progression in various clinical populations; however, to our knowledge, it has not yet been described in visually impaired individuals, including CLN3 disease.5,7

We used the 6MWT to delineate timing of motor function decline in CLN3 disease.

Methods

Study population

From 2012 to 2017, 15 patients with a genetically confirmed diagnosis of CLN3 disease (9 patients homozygous for the common 1.02 kb deletion, 4 patients compound heterozygous for the 1.02 kb deletion and a different deletion or missense mutation, 1 patient homozygous for a different deletion, and 1 patient homozygous for a nonsense mutation) performed a total of 65 6MWT tests (mean of 3.8 6MWT performances per patient with CLN3 disease). All patients with CLN3 disease had a severe visual impairment: around diagnosis at a median age of 7 years (range 5–12 years), visual acuity was without exception below 0.3—considered low vision according to WHO guidelines8—deteriorating to blindness in a few years (data not shown). To determine the effect of visual impairment on motor functioning, 2 control cohorts totaling 26 children from the affiliated school for visually impaired children also performed the 6MWT during one occasion using the same protocol. Fourteen of these 26 children had an isolated visual impairment, thus without additional neurologic impairments, and the remaining 12 exhibited visual impairment in combination with neurologic impairments. A complete overview of the control cohorts is provided in the table. Of note, visual acuity can be reported in fractions, a logarithmic scale, or decimals, often dependent on the assessment method used. To make the visual acuities comparable, we chose to recalculate all visual acuities in decimals (e.g., 20/200 equals 0.1) if not already reported so. Reference values for 6MWT distances in healthy sighted children were retrieved from Ulrich et al.,9 based on the decision tree described by Mylius et al.7

6MWT protocol

The 6MWT was performed biannually during our multidisciplinary CLN3 disease follow-up meetings under the guidance of the same experienced physical therapist (L.v.E.). We applied a slightly adapted protocol derived from the standard American Thoracic Society guidelines.6 The assessments were performed indoors on a smooth, uncluttered surface in the physical rehabilitation accommodations at the Bartiméus center. Due to limitations of space, lanes of 10 meters rather than the standard 30 meters were marked on which the patients and the control group individuals had to walk back and forth. However, as both the patients and the control group individuals had to walk on these shorter lanes, any speed loss and thus 6MWT results impairment should not have affected the comparative analysis. Due to the visual impairments present in both the patients and control cohorts, they were allowed to—dependent on their preferences and abilities—walk independently, with a walking cane, or with physical assistance of the physical therapist. In all cases, the individual tested determined the tempo.

Data analysis

For data analysis, we retrieved distance walked in meters and age at testing. Based on the 6MWT reference values in healthy sighted children, we calculated z scores of the 6MWT results in patients with CLN3 disease and control cohort individuals. 6MWT results were correlated with age. To account for repeated measurements with missing data in the patients with CLN3 disease, multilevel analysis was used. Multilevel analysis, modeling all measurements (level 1) within patients (level 2) with CLN3 disease, was performed with 6MWT scores as the outcome measurement. Age was added to the multilevel model, to validate a possible relation between 6MWT scores and age.10 Both age and quadratic age were entered in the model to find the best model fit. This indicates if the best model fit is a linear or a quadratic curve relationship.

The Unified Batten Disease Rating Scale (UBDRS) assesses multiple domains of disease in detail—including a physical assessment, seizure assessment, and capability assessment including school performance—and provides a clinical global impression score of these disease domains.11 If during the same visit both the 6MWT and the UBDRS were applied, we correlated 6MWT scores with the sum of the UBDRS clinical global impression scores.
Statistical analyses were performed using Graphpad Prism version 7.02 and MLwiN version 3.01 software. For correlation analyses, Pearson R coefficient was used. p Values <0.05 were considered statistically significant.

**Standard protocol approvals, registrations, and patient consents**
The study was approved by the Medical Ethical Review Committee of the University Medical Center Utrecht (17-269/C).

**Data availability**
Anonymized data will be shared by request from any qualified investigator.

**Results**
In patients with CLN3 disease, 6MWT scores were already impaired around diagnosis (mean z score of −3.6 [n = 3] at 7 years of age; mean z score of −4.7 at 8 years of age [n = 5]) (figure 1 6MWT scores in CLN3 disease and figure 2 corresponding z scores). Afterwards, a continuous decline with increasing age was seen (r = −0.64, p < 0.0001) (figure 1). Correspondingly, 6MWT scores decreased with increasing UBDRS scores, confirming correlation with disease progression (n = 37 corresponding 6MWT and UBDRS measurements, r = −0.60, p = 0.0001) (data not shown).
Although 6MWT results already decreased in the early stages of the disease ($r = -0.46$ up to and including 13 years of age, $p = 0.005$), the decrease in motor function was as expected more pronounced at a later age, indicating that a linear regression model may not provide the most accurate model to use the 6MWT as a follow-up marker. To account for this nonlinear decrease with age, we therefore used a nonlinear multilevel model that provided us with the following equation for 6MWT results decline in CLN3 disease: $y = 409.18 - (0.52 \times \text{age}^2)$.

To assess whether the decreased 6MWT walking distance could be attributed to the visual impairment, we additionally performed the 6MWT in the first control cohort with a severe but isolated visual impairment (table). In contrast with the test results in patients with CLN3 disease, 6MWT scores in children with an isolated visual impairment showed an upward trend with age ($r = 0.56; p = 0.04$) similar to healthy sighted children (mean $z$ score −0.38) (figure 3). There was no correlation between the degree of visual impairment and 6MWT $z$ score (data not shown), indicating that the degree of visual impairment did not directly affect 6MWT results. To assess the effect of neurologic impairment on 6MWT walking distance, we also performed the 6MWT in a control cohort displaying mild visual impairment in addition to non-progressive neurologic impairments (table). Within this control cohort, 6MWT scores were slightly impaired (mean $z$ score −1.26) without an upward or downward trend with age ($r = -0.29; p = 0.36$) (figure 3).

Discussion

We provide evidence that in CLN3 disease, motor function is already impaired at the time of diagnosis.

The decreased 6MWT distance walked by patients with CLN3 disease cannot be explained by their visual impairment. The control cohort of individuals with a severe but isolated visual impairment performed the 6MWT similarly well compared to their sighted peers. Conversely, the group with mild impairments of visual acuity but accompanying neurologic impairments displayed a decreased 6MWT walking distance. Of note, they still outperformed patients with CLN3 disease—even those early in the disease course—underlining the severity of motor impairment in CLN3 disease as detected by the 6MWT.

As the 6MWT assesses functional exercise capacity deriving from multiple aspects involved in disease, it is not possible to...

**Figure 1** Six-Minute Walk Test (6MWT) performance in patients with CLN3 disease

![Graph showing 6MWT scores over time in patients with CLN3 disease.](image1)

6MWT scores over time in patients with CLN3 disease ($n = 65$ test scores from $n = 15$ patients, $r = -0.64, p < 0.0001$). Median age at first 6MWT was 13 years (range 7–18 years); median age at last 6MWT was 14 years (range 9–20 years). First measurement per patient is shown in red squares. Subsequent measurements are shown in black circles. Official reference values in healthy sighted children are provided in gray (mean ± 2 SD). The nonlinear multilevel model is provided in blue ($y = 409.18 - (0.52 \times \text{age}^2)$).

**Figure 2** Six-Minute Walk Test (6MWT) $z$ scores in CLN3 disease

![Graph showing 6MWT $z$ scores over time in CLN3 disease.](image2)

$z$ Scores derived from 6MWT scores in patients with CLN3 disease compared to the reference values in healthy sighted children ($r = 0.70; p < 0.0001$).

**Figure 3** Six-Minute Walk Test (6MWT) performance in (isolated) visually impaired children

![Graph showing 6MWT scores over time in visually impaired children.](image3)

6MWT scores over time in children with a visual impairment (see table for individual diagnoses and test results). Test results from children with an isolated visual impairment are shown in blue circles ($n = 14, r = 0.56; p = 0.04$). Test results from children with visual and neurologic impairments are shown in black triangles ($n = 12, r = -0.29; p = 0.36$). Official reference values in healthy sighted children are provided in gray (mean ± 2 SD).
retrieve a single cause for impaired 6WMT scores. As CLN3 disease is known to cause a parkinsonism-like motor dysfunction—a combination of reduced walking speed, smaller steps, and start–stop problems—it is tempting to speculate that the gradual decrease in ambulation from early in the disease course onwards reflects subclinical parkinsonism. Attention span may also be a relevant factor, particularly early in the disease. Indeed, the physical therapist who guided all 6MWTs mentioned that the patients with CLN3 disease, already from an early age, seemed easily distracted and hence seemed to have difficulties keeping themselves focused on the task. Of note, while neuronal loss is the main cause of its deteriorating course, CLN3 disease is a systemic disease. Signs of accumulation in skeletal muscle have been described, but without any clear clinical implications. In contrast, cardiac muscle involvement has been described late in the disease course. Therefore, we cannot exclude a role for cardiac or even skeletal muscle impairment in the decreased functional exercise capacity earlier in the disease course.

We show that motor decline has its onset early in the disease course of CLN3 disease, which is quantifiable using the 6MWT and cannot be explained by decreased visual acuity. We encourage using the 6MWT for CLN3 disease progression assessment in clinical follow-up and future therapeutic studies.

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Appendix (continued)

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