An Ophthalmic Rating Scale to Assess Ocular Involvement in Juvenile *CLN3* Disease

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• PURPOSE: **Juvenile *CLN3* disease, the most prevalent form of Batten disease, is a progressive neurodegenerative disorder resulting from mutations in the *CLN3* gene. The objective of this study was to design an ophthalmic rating scale for *CLN3* disease in order to quantify disease progression.**

• DESIGN: **Retrospective, cross-sectional study.**

• METHODS: **Patients underwent ophthalmic evaluations including visual testing, optical coherence tomography and fundus imaging. Patients were also assessed using the Hamburg Juvenile Neuronal Ceroid Lipofuscinosis (JNCL) scoring system. Ophthalmic findings were divided into grades of severity ranging from 0 to 3, and the association between the extent of ocular disease and neurological function and age was assessed.**

• RESULTS: **Forty-two eyes of 21 patients were included. The mean age at the time of examination was 13.2 years (range, 5.3-21.9 years). The mean ophthalmic severity grade was 2.4 (range, 0-3). The mean neurological severity score was 9.9 (range, 4-14). Ophthalmic manifestations increased in severity with increasing age of the patients ($r = -0.84$; $P < .001$), and a strong correlation was found between the *CLN3* ophthalmic rating scale score and the Hamburg JNCL score ($r = 0.83$; $P < .001$).**

• CONCLUSIONS: **Ophthalmic manifestations of *CLN3* disease correlate closely with the severity of neurological symptoms and age of the patient. The newly established Hamburg *CLN3* ophthalmic rating scale may serve as an objective marker of ocular disease severity and progression and may be valuable tool for the evaluation of novel therapeutic strategies for *CLN3* disease. (Am J Ophthalmol 2020;220:64–71. © 2020 Elsevier Inc. All rights reserved.)**

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JUVENILE *CLN3* DISEASE IS A RARE AUTOSOMAL RECESSIVELY inherited lysosomal storage disease characterized by progressive neurodegeneration in brain and retina. It represents one of the main causes of childhood dementia. *CLN3* disease (formerly called juvenile neuronal ceroid lipofuscinosis [JNCL], Batten disease, or Vogt-Spielmeyer-Stock disease) is one of the most prevalent NCL forms and is caused by mutations in the *CLN3* gene (chromosome 16p.12.1).[1]

A clinical hallmark, and often the first symptom of *CLN3* disease, is a rapid deterioration of visual function starting at approximately 3-8 years of age.[2–4] A progressive cone-rod dystrophy with subsequent involvement of rod photoreceptors has been shown in previous morphological and electrophysiological reports.[4–7] Funduscopic features include optic disc pallor, macular orange pigment, vascular attenuation, and peripheral bone spicules at the late stage of the disease. Because juvenile *CLN3* disease is a rare cause of a cone-rod dystrophy in pediatric patients, the disease often remains undiagnosed or misinterpreted and becomes correctly diagnosed only with early genetic counseling or occurrence of additional neurological symptoms such as psychomotor decline and seizures in the previously healthy, developed children.[4] These symptoms of central nervous system degeneration start to become apparent at 7-12 years of age. Preterm death occurs in the third or fourth decade of life.[8–10]

To date, there is no approved treatment for *CLN3* disease. Several experimental therapeutic approaches are being tested in animal models. However, as the function of the CLN3 protein is still not completely understood, developing a cure remains a challenge. The AAV9-vector-based gene therapy trial has started recently, but results have not yet been reported (ClinicalTrials.gov title: Gene Therapy for Children With CLN3 Batten Disease [NCT03770572]). Another trial investigating the safety of mycophenolate in children with *CLN3* disease reported good safety data.[11]

Currently, the Hamburg JNCL score and the Unified Batten Disease Rating Scale are the gold standards used to quantify global disease progression in juvenile *CLN3* disease.[12,13] Although the Hamburg JNCL score includes a coarse grading of visual function, both rating systems lack a detailed ophthalmic evaluation, and thus do not consider

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TABLE 1. Characteristics of Patients with *CLN3* Disease Undergoing Clinical Rating

Patient	Gender	Genotype	Age at Examination	Hamburg CLN3 Ophthalmic Rating Scale		Hamburg JNCL score
				Total score	Grade	Total Score
1	Female	Compound heterozygous 1 kb deletion and c.(790+1_791-1)_(1056+1_1057-1)del (p.?)	6.9	10	1	14
2	Male	compound heterozygous 1kb deletion and c.1054C>T (p.Gln352*)	5.3	10	1	14
3	Female	Homozygous 1-kb deletion	9.1	10	1	14
4	Female	Homozygous 1-kb deletion	9.7	11	1	11
5	Female	Compound heterozygous 1-kb deletion and c.424delG (p.Val142Leufs*39)	9.8	9	2	13
6	Female	Homozygous 1-kb deletion	8.5	9	2	13
7	Female	Homozygous 1-kb deletion	11.7	8	2	13
8	Female	Homozygous 1-kb deletion	10.1	8	2	13
9	Female	Homozygous 1-kb deletion	18.3	1	3	6
10	Male	Homozygous 1-kb deletion	21.9	3	3	8
11	Female	Homozygous 1-kb deletion	14.0	3	3	7
12	Female	Compound heterozygous 1-kb deletion and c.1054C>T (p.Q352*)	17.3	1	3	9
13	Female	Homozygous 1-kb deletion	14.4	4	3	9
14	Female	Compound heterozygous 1-kb deletion and c.105G>A (p.Trp35*)	15.4	2	3	6
15	Male	Homozygous 1-kb deletion	15.4	5	3	7
16	Female	Homozygous 1-kb deletion	18.0	2	3	5
17	Female	Compound heterozygous 1-kb deletion and c.1054C>T (p.Gln352*) and unknown deletion in intron 13	11.9	3	3	11
18	Female	Compound heterozygous 1-kb deletion and c.1054C>T (p.Gln352*)	14.2	2	3	9
19	Female	Homozygous 1-kb deletion	17.1	3	3	8
20	Male	Homozygous 1-kb deletion	11.0	4	3	13
21	Male	Homozygous 1-kb deletion	16.8	0	3	4

JNCL = juvenile neuronal ceroid lipofuscinosis.

the progressive deterioration of retinal structure and function during the course of the disease.

Hence, the aim of the current study was to establish an ophthalmic rating scale to precisely monitor progression of retinal degeneration in *CLN3* disease. The authors suggest that such ophthalmic data will serve as a useful reference for the assessment of future brain- or retina-directed experimental clinical trials. The suggested ocular rating scale is based on a concise clinical ocular evaluation without the need for invasive diagnostic tools, which are often troublesome and time-consuming for patients with *CLN3* diagnosis.

This paper proposes the combination of functional and morphological aspects (a best-corrected visual acuity [BCVA] test, a fundoscopy rating, and optical coherence tomography [OCT] assessment) for a comprehensive but easily applicable ophthalmic rating scale.

METHODS

THIS STUDY WAS APPROVED BY THE MEDICAL ETHICS COMmittee of the Ärztekammer Hamburg (PV7215), Germany. Patients' or parents' consent for evaluation of data was obtained according to the tenets of the Declaration of Helsinki (1991).

Twenty-one patients with genetically confirmed *CLN3* disease were included for retrospective evaluation. Forty-two eyes were examined during the annual follow-up visit at the Department of Ophthalmology and the Children's Hospital at University Medical Center Hamburg-Eppendorf.

Patient demographics including sex, genotype, and age at examination are presented in Table 1. The ocular examination of each patient included determination of BCVA, slit lamp examination, fundoscopy, fundus photography (Canon CX-1; Canon Medical Systems GmbH, Neuss,

TABLE 2. Hamburg *CLN3* Ophthalmic Rating Scale

	BCVA (Snellen fraction)	Score
Visual acuity	≥20/25	7
	≥20/63	6
	≥20/160	5
	≥20/400	4
	≥20/1000	3
	≥Counting fingers	2
	≥Hand motion	1
	Light perception/no light perception	0
	Fundus score	
Optic pallor	None	1
	Severe	0
Macular striae	None	1
	Presence	0
Macular orange pigment	None	1
	Presence	0
Peripheral bony spicules	None	1
	Presence	0
Vessel rarefication	None	1
	Presence	0
	OCT	
Ellipsoid zone	Intact	2
	Disruption in a diameter < 2000 um	1
	Complete loss	0
	Maximum Points	14 points
	Grade	Total score
	0 (unaffected)	14 points
	1 (affected)	10-13 points
	2 (severly affected)	5-9 points
	3 (end stage)	0-4 points

BCVA = best-correcte visual acuity; OCT = optical coherence tomography.

Germany), and OCT imaging (Spectralis, Heidelberg Engineering, Heidelberg, Germany). The ophthalmic rating scale was divided into 4 classes ranging from 0 (unaffected) to 3 (end stage).

Patients scaled with an ophthalmic grade of 0 had a BCVA ≥20/25, a normal fundus appearance without signs of retinal degeneration and showed no evidence of foveal atrophy on OCT. Patients scaled with an ophthalmic grade of 3, in comparison, were legally blind and presented with optic pallor, severe vascular attenuation, widespread bone spicules, and a pronounced macular atrophy on OCT imaging (Table 2). Functional assessment by BCVA and morphologic assessment by fundoscopic rating and OCT evaluation were chosen to determine the grade of disease severity.

A BCVA of ≥20/25 was assigned a score of 7; a BCVA range of <20/25-≥20/63 received a score of 6; a BCVA range of <20/63-≥20/160 received a 5; a BCVA range of <20/160-≥20/400 received a 4; a BCVA range of <20/400-≥20/1000 received a 3; a BCVA of <20/1000 and better than counting fingers received a score of 2; a BCVA worse than counting fingers but better than hand motion was assigned a score of 1; and light perception and below was assigned a score of 0 (Table 2).

Three retina specialists (S.D., Y.A., M.S.P.) graded the severity of the retinal degeneration in each of the 42 *CLN3* eyes in a blinded manner, using fundus imaging and OCT scans. The mean of the 3 independent ratings was used to determine the fundus and OCT imaging scores.

Fundoscopy scoring considered the presence of optic pallor: 1 point in case of no optic pallor; 0 points in the presence of optic pallor; 0 points in the presence of macular orange pigment; 0 points in macular striae; 0 points in identification of vascular attenuation; and 0 points in the presence of peripheral bone spicules.

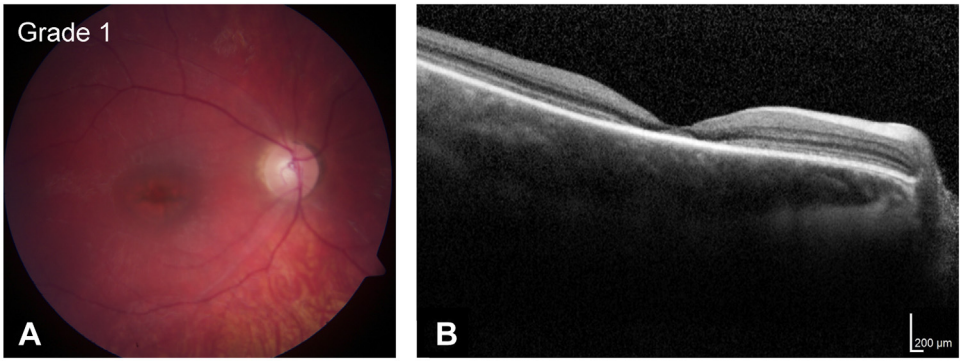

FIGURE 1. Hamburg *CLN3* ophthalmic grade 1. Patient 4 with a total score of 11 points and early manifestation of retinal degeneration in *CLN3* disease. Patient 4 can be found in Table 1.

The acquisition of complete macular volume OCT scans was often impeded during the course of the disease, thus making retinal thickness measurements by macular volume scans impossible. Therefore, only the disruption of the ellipsoid zone (EZ), a hallmark feature of photoreceptor degeneration, was assessed and scored. An intact EZ was scored with 2 points. Early foveal degeneration and the disruption of the subfoveal EZ in a diameter less than 2,000 µm was scored with 1 point. A complete loss of the EZ on foveal OCT scans was assigned 0 points.

In summary, the total scoring ranged between a minimum score of 0 points and a maximum score of 14 points. Based upon the total scoring, 4 grades were defined: patients with grade 0 (14 points) had no ocular involvement; those with grade 1 were affected (10-13 points); those with grade 2 were severely affected (5-9 points); and those with grade 3 represented end-stage ocular involvement (0-4 points).

Data of the *CLN3* ophthalmic rating scale were used for statistical analyses for correlation with age and the Hamburg JNCL score, a clinical scoring system for disease severity in *CLN3*, established by Kohlschütter and associates[13] consisting of 5 scoring items (motor function, language, intellect, vision, and epilepsy) with a total score of 15 points. Each category is scored from 3 points for normal function to 0 points for a total loss of function.

The inter-rater reliability of the imaging-based fundus scoring was obtained using the random factorial ANOVA model. The corresponding confidence interval for inter-rater reliability is reported. The bivariate correlation was analyzed using ordinary least squares estimation. The coefficient estimates and their significance from these models as well as correlation coefficients are reported.

RESULTS

A TOTAL OF 42 EYES OF 21 *CLN3* PATIENTS WERE INCLUDED IN the analysis. The cohort included 16 female and 5 male patients. All 21 patients had genetically confirmed mutations in the CLN3 gene and were diagnosed with classic juvenile *CLN3* disease. Fourteen patients carried the common 1.02-kb deletion in the *CLN3* gene in the homozygous state, 6 were compound heterozygous for the common 1.02-kb *CLN3* deletion and another mutation in the *CLN3* gene, and 1 patient was compound heterozygous for another previously reported mutation and a novel deletion in intron 13. Detailed patient genotypes are listed in Table 1. All 42 eyes underwent a comprehensive ocular examination including color fundus photography and OCT imaging. At the time of examination, the patients' median age was 13.2 years (range, 5.3-21.9 years).

No anterior segment abnormalities were noted in any of the 42 eyes examined. The vitreous cavity in all eyes appeared normal with an optically clear vitreous. Posterior segment findings ranged from mild macular alteration to a severe, widespread retinal atrophy with complete absence of the outer retinal structures, complete foveal atrophy, massive vessel attenuation, and peripheral bone spicules. First signs of retinal degeneration were observed by OCT imaging in the fovea with a marked thinning of outer retinal layers. Centrifugal retinal degeneration with a loss of outer retinal layers progressed rapidly.

Of note, the ophthalmic scores of both eyes were identical in all *CLN3* patients examined; therefore a single scoring and grading result represents the ophthalmic status of each patient.

• **HAMBURG *CLN3* OPHTHALMIC RATING SCALE:** Using the findings from the ocular examinations and ancillary testing, the Hamburg *CLN3* ophthalmic rating scale was established (Table 2, Figures 1-3). A *CLN3* ophthalmic grade of 0 represents a normal fundus, regular macular profile and thickness on OCT scans, and a BCVA ≥20/25 (Table 2), whereas a grade of 3 denotes nearly complete retinal atrophy in both the posterior pole and the peripheral retina (Table 2, Figure 3).

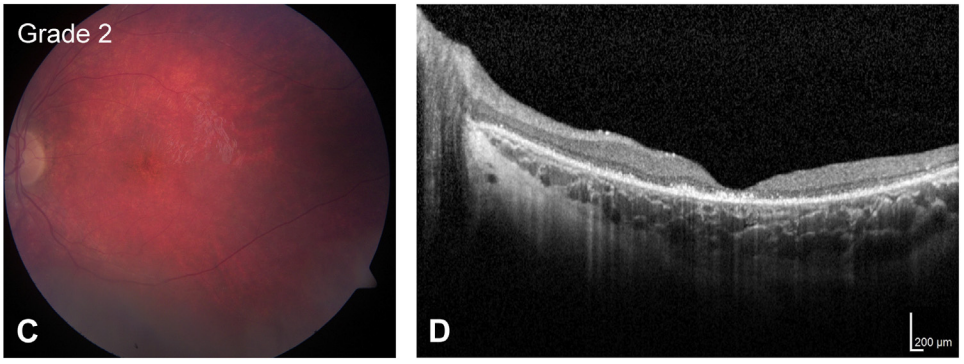

FIGURE 2. Hamburg *CLN3* ophthalmic grade 2. Patient 6 with a total score of 9 points presented with pronounced degeneration of the outer retinal layer on OCT imaging and classic macular atrophy and vessel attenuation on fundus photography. Patient 6 can be found in Table 1.

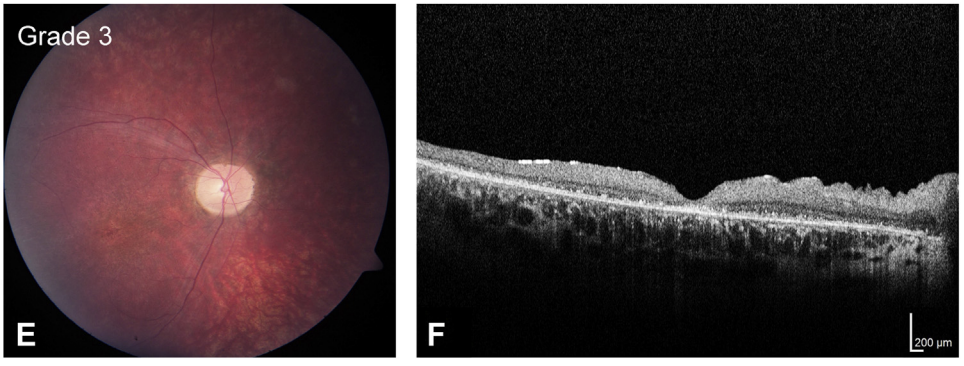

FIGURE 3. Hamburg *CLN3* ophthalmic grade 3. Advanced retinal degeneration with optic disc pallor, macular orange pigment and vessel attenuation on fundus photography. Complete loss of the outer retinal layers and macular striae on OCT imaging in patient 13 with a total score of 4 points. Patient 13 can be found in Table 1.

• **GRADE 0 (UNAFFECTED):** *CLN3* patients with a grade 0 showed no evidence of retinal degeneration on fundoscopy and OCT and had a BCVA of ≥20/25 on age-adapted testing. None of the *CLN3* patients examined in this study presented with a grade 0. A grade 0 is designated as a presymptomatic genetically diagnosed *CLN3* patients.

• **GRADE 1 (AFFECTED):** A total score of 10 to 13 points resembled an early manifestation of retinal degeneration in CLN3 disease. Patients with grade 1 had only subtle fundoscopic abnormalities. OCT imaging revealed foveal atrophy with intact perifoveal retinal tissue (Figure 1). In our cohort 4 patients had an ophthalmic grade of 1. The mean age of these patients was 7.7 years (range, 5.3-9.7).

• **GRADE 2 (SEVERELY AFFECTED):** Progressive retinal degeneration with loss of the outer nuclear layer and EZ band on OCT imaging, obvious macular atrophy on fundoscopy and functional decline were observed in 4 of 21 patients. The mean age of patients at examination was 10 years (range, 8.5-11.7 years) (Figure 2).

• **GRADE 3 (END STAGE):** A score with <5 points was assigned to patients that presented with end stage retinal degeneration and almost complete loss of visual function. Characteristic ocular abnormalities at this end stage of the disease included optic pallor, macular atrophy with orange pigment deposition, vessel attenuation and peripheral bone spicules. In this cohort of *CLN3* patients, 13 patients had an ophthalmic grade of 3 (Table 2). The mean age of these patients was 15.8 years (range, 11-21.9 years) (Figure 3).

• **RESULTS AND VALIDATION OF THE HAMBURG *CLN3* OPHTHALMIC RATING SCALE:** The present cohort of *CLN3* patients had a mean total ophthalmic score of 5.1 points (range, 0-11 points) and a mean grade of 2.4 (range, 0-3 points). Four patients presented with a grade of 1; 4 patients with a grade of 2; and 13 patients with a grade of 3.

In order to verify the reliability of the imaging-based fundus scoring, inter-rater reliability statistical analysis was performed. Substantial agreement was evident, with an inter-rater reliability of $P = .88$ (95% confidence

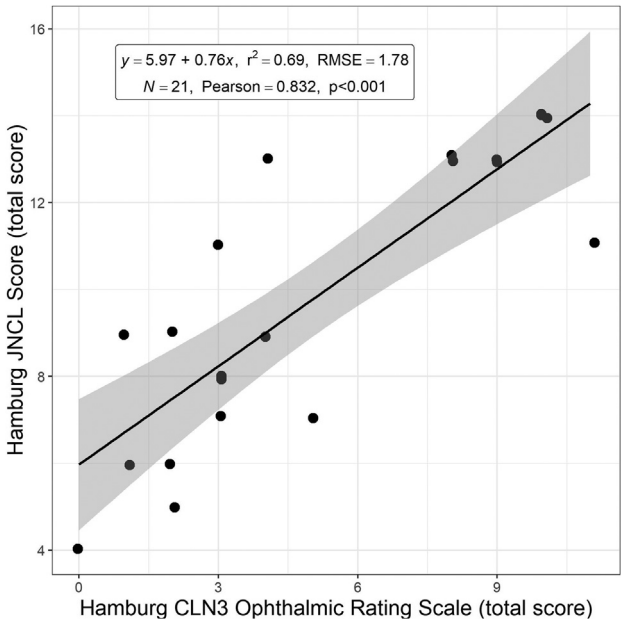

FIGURE 4. Correlation of the Hamburg *CLN3* ophthalmic rating scale (total score) and the Hamburg JNCL-Score (total score)

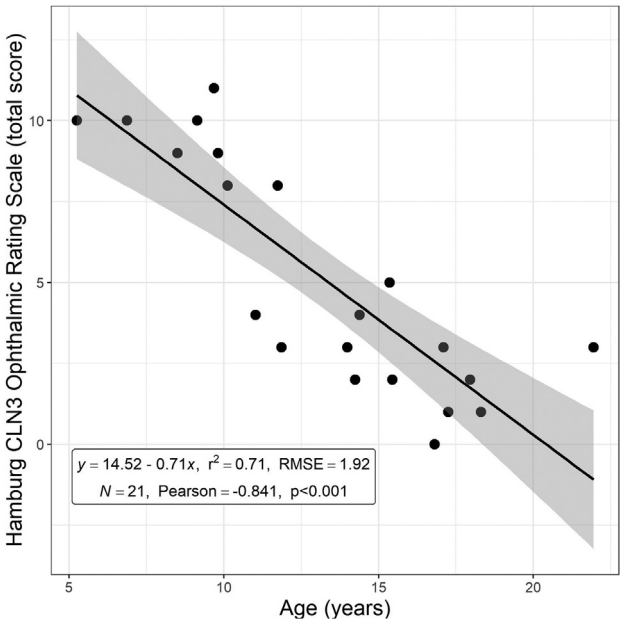

FIGURE 5. Correlation of the Hamburg *CLN3* ophthalmic rating scale (total score) with age.

interval [CI], 0.774-0.946) with an overall mean rating of 3.444 among all 3 examiners. Mean scoring results for each patient are summarized in Table 1, and detailed scoring results are shown in the Supplemental Table.

The fundus-based scoring correlated significantly with the results of the BCVA scoring ($r = 0.734$; $P < .01$) and the OCT-based scoring ($r = 0.703$; $P < .01$). A decrease in the fundus score correlated significantly with an increase of the patient's age, as expected. In addition, BCVA scoring results correlated significantly ($r = 0.80$; $P < .01$) with the OCT scoring (Figure 4).

The disease severity of patients was evaluated using the Hamburg JNCL score. This analysis revealed a mean score of 9.9 points (range, 4-14) (Table 1).

A strong correlation ($r = 0.832$; $P < .001$) was found between the newly established Hamburg *CLN3* ophthalmic rating scale and the previously established clinical scoring system with the Hamburg JNCL score (Figure 4). A strong negative correlation ($r = -0.84$; $P < .001$) was also found between age and the total score of the Hamburg *CLN3* ophthalmic rating scale (Figure 5), with older patients presenting with more severe ophthalmic manifestations.

DISCUSSION

A PROGRESSIVE VISUAL DECLINE DUE TO RETINAL DEGENERation is a key feature of juvenile *CLN3* disease, in addition to neurological and cognitive symptoms. In the present study, we established an ophthalmic rating scale for *CLN3* patients as a potential noninvasive measurement of disease progression. The authors suggest that the newly established Hamburg *CLN3* ophthalmic rating scale may serve as a useful tool to estimate the efficacy of future brain- or retina-directed therapeutic interventions.

Characteristic fundoscopic features of *CLN3* patients include optic pallor, macular orange pigment, vessel attenuation, and peripheral bone spicules.[2,5,14,15] An early foveal and macular involvement can be detected by OCT imaging.[3,16] Degeneration of the outer retinal layers starts in the foveal region and is accompanied by centrifugal progression and presumably secondary inner retinal degeneration with increased inner retinal reflectivity and with macular striae.[4,5]

The Hamburg *CLN3* ophthalmic rating scale is based upon 3 basic ophthalmic assessments the results of which are divided into 4 grades (0-3, from no to severe ophthalmic involvement).

Patients with a grade of 0 showed no apparent ophthalmic abnormalities and no visual impairment. Patients with a grade of 3, in comparison, presented with pronounced retinal degeneration and almost complete loss of retinal function.

Scoring was based upon ophthalmic assessments of BCVA, evaluation of fundus photography, and OCT imaging. Although an electroretinogram (ERG) plays an important role in the evaluation of differential diagnosis, repeated ERG recordings are often troublesome for *CLN3* patients. Furthermore, ERG recordings have the risk to induce epileptic seizures. Most importantly, they do not add relevant longitudinal outcome measurement as the ERG amplitudes diminish early in the course of the disease.

Therefore, the functional outcome measurement is based on BCVA as additional tests such as full-field perimetry are often hampered by the cognitive decline of the patients during the course of the disease. BCVA thresholds (Table 2) were determined based on the World Health Organization classification of visual impairment,[17] where severe visual impairment is defined as visual acuity <20/63, and further limits were set 0.4 steps in logMAR values. In addition, all patients in this cohort presenting with BCVA scores of 4-6 points demonstrated with a total grade of 1 in the Hamburg *CLN3* ophthalmic rating scale, underlining the early retinal disease progression and the potential suitability to measure longitudinal ophthalmic disease in an interventional clinical trial.

Fundoscopic features of *CLN3* disease and the present proposed scoring system (Table 2) are based on the present authors' clinical experience and on previous reports.[5,15,18] Retrospective analysis was performed by rating fundus photography and was therefore dependent on subjective evaluation of raters; accordingly, an inter-rater reliability analysis was performed which revealed substantial agreement between independent raters, indicating the reliability of this subjective method.

OCT imaging in patients with juvenile *CLN3* disease is challenging as the progression of cognitive impairment and visual decline during the course of the disease leads to inaccurate macular volume scans due to reduced compliance. Even modern swept-source OCT systems with fast scanning speed are often incapable of imaging precise macular thickness and volume scans. Therefore, a single high-quality foveal scan was used to evaluate macular pathology and to determine disruption or loss of the EZ, an established predictor of vision loss.[19–21] Present data verify the relationship of the EZ and vision loss in juvenile *CLN3* patients by showing a strong correlation ($r = 0.80$; $P < .001$) between the BCVA and OCT scoring in 21 juvenile *CLN3* patients.

Data from the present study indicate that data from ophthalmic examinations represent a useful measurement for the general progression of *CLN3* disease. In the 21 patients evaluated in this study, there was a strong positive correlation between the Hamburg *CLN3* ophthalmic rating scale and the Hamburg JNCL score, as well as the age of patients at the date of examination. For instance, the most severe deterioration of retina structure and function was noted in patients with the most severe general neurological symptoms and older age. Visual decline and retinal degeneration progressed, as previously stated, independently from the underlying genotype of the disease.[22]

The clinical scoring system for disease severity developed by Kohlschütter and associates[13] considers neurological functions as well as basic visual abilities of patients. Visual ability is usually assessed by pediatricians and is scored according to the patient's ability to recognize or grab objects or to perceive light. Although this was a useful initial step to independently evaluate visual function in pediatrics, neither an ophthalmic examination nor any ancillary ophthalmic testing was a part of this study.

The current study analyzed the ophthalmic manifestation in juvenile *CLN3* disease and established a novel and easily applied ophthalmic rating scale as a potential measurement of general disease progression.

The noninvasive nature of the ophthalmic examinations, the rapid assessment of data, and the feasibility to perform all diagnostic procedures in patients at advanced stages of the disease make this rating scale a useful tool to monitor *CLN3* patients over the complete course of the disease.

The combined consideration of morphological and functional parameters in a single rating scale addresses the regulatory demands for meaningful outcome measurements in interventional clinical trials in *CLN3* patients. It is anticipated that a standardized ophthalmic rating scale will facilitate the assessment of treatment efficacy in upcoming clinical trials, such as that currently active phase I/II gene therapy trial with intrathecal administration of AAV9-*CLN3* (NCT03770572). A retrospective, longitudinal multicenter study is currently being initiated that will apply the Hamburg *CLN3* ocular rating scale to a large *CLN3* cohort to generate robust natural history data of the eye and to validate the proposed rating scale.

CONCLUSIONS

ON THE BASIS OF A VALIDATED OCULAR RATING SYSTEM and with the aid of a large ophthalmic natural history group, the eye may serve as surrogate endpoint in clinical trials related to *CLN3* to either prove the retina- or brain-directed therapeutic approaches.

ALL AUTHORS HAVE COMPLETED AND SUBMITTED THE ICMJE FORM FOR DISCLOSURE OF POTENTIAL CONFLICTS OF INTEREST and none were reported.

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