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Visual acuity changes in cone and cone-rod dystrophies

Elena Prokofyeva, Eric Troeger, Antje Bernd and Eberhart Zrenner

Centre for Ophthalmology, Institute for Ophthalmic Research, University of Tuebingen, Tuebingen, Germany

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Correspondence: Elena Prokofyeva
E-mail address: elena.prokofyeva@biomed-engineering.de

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Abstract

Purpose: The purpose of the study was to evaluate longitudinal visual acuity (VA) changes in cone (CD) and cone-rod dystrophies (CRD) in order to develop recommendations for follow-up strategies and to define an optimal time for potential therapeutic intervention.

Methods: Patients with clinically defined CD and CRD, who had at least three clinical examinations within a follow-up period of a minimum of 2 years, were included in the study. The observation period was divided into segments: between 1–2 visits and 2–3 visits in intervals of 2 years, and between 3–4 visits in 3-year intervals. Disease history was collected during the baseline examination. Median age of onset, age at first examination, and period between disease onset and 1st visit (latency) were estimated. Medians with 25th and 75th quantile of VA decrease in logMAR for each segment of observation were calculated. The median percentage of VA decrease was also calculated.

Results: Initial results of the Tuebingen longitudinal study of VA changes in CRD and CD are presented as medians with 25th and 75th quintiles. Twenty-nine patients (14 men and 15 women) were studied. Nineteen of them had CRD and 10 CD. Median age at the baseline visit was 18 (11, 31) years for CRD and 26 (8, 41.5) years for CD. Median age of disease onset was 9 (8, 25) years for CRD and 7.5 (5, 15) years for CD. The median latency was 6.5 (3; 8.25) years in CD and 4 (2, 10) years in CRD patients. VA in CD and CRD patients was significantly different only during the first visit ($p < 0.03$). VA decrease was highest in the period between 2–3 visits with a median VA decrease of 36%, for CDR and between 3–4 visits for CD with a median VA decrease of 80%. In the CRD group the rate of VA decline was fairly even over the four visits, whereas in the CD group the decline appeared to progressively increase towards the end of the follow-up.

Conclusion: CRD patients were younger than those with CD at a baseline visit and had a longer period of follow-up. A statistically significant difference in VA in CRD and CD was observed at the first ophthalmological examination only. VA decrease was most prominent in the second decade of life in CRD and in third decade in CD patients. CRD was characterized by a more progressive VA decrease than CD. CRD had a high decline of VA over the second and the third examination, whereas VA decline in CD progressed towards the end of follow-up period (fourth examination). These results should be considered when advising and following up such patients on a long-term basis.

Introduction

Cone rod dystrophies (CRD) and cone dystrophies (CD) are characterized by primary cone system involvement, which explains the early decrease of visual acuity (VA) in these diseases. The clinical course of CRD is often more severe and rapid than that in retinitis pigmentosa.[1,2] CD and CRD are eye diseases of high public health

importance, since they lead to disability at a young age. Proper follow-up strategies are required for the evaluation of CD and CRD progression, which is especially important in the light of new pre-clinical therapeutic developments such as gene therapy,[3,4] increase of neurotrophic factor expression,[5,6] and implantation of retinal prosthesis to restore vision.[7–10] Previous studies were mostly aimed at the evaluation of VA impairment in patients with retinitis pigmentosa at certain age and disease stages,[11–13] as well as at the estimation of yearly rates of rod and cone functional loss in RP and CRD.[14] Several articles were devoted to the correlation of the VA changes with type of mutations.[15,16] Despite the high value of these studies, most had a cross-sectional design and analyzed VA data for the patients' most recent visit to an ophthalmologist. A cross-sectional study design could potentially introduce a selection bias in the analysis, since patients might prefer to schedule a visit only when their visual function decreases. A prospective longitudinal design is often hampered by the loss of patients during follow-up, since these diseases require long follow-up periods to evaluate their progression. Furthermore most of the studies were focused on the evaluation of visual function changes in retinitis pigmentosa and only one included CRD, whereas to the best of our knowledge there were no studies that analyzed and compare the visual acuity changes in both CD and CRD.

The purpose of the study was to evaluate longitudinal VA changes in CD and CRD in order to develop recommendations for follow-up strategies and to define an optimal period for therapeutic intervention, whenever available.

Materials and methods

The study had a retrospective longitudinal observational design. Patients with clinically defined CD and CRD who underwent at least three ophthalmological examinations at the University Eye Hospital, Tuebingen, Germany with a minimum of 2 year intervals between these visits (6 years of follow up) were included in the study. This inclusion criterion was based on the usual follow-up period in the special clinic for inherited retinal degenerations and was intended to maximize comparability between the groups. Special care was taken to identify any co-existing conditions that could have influenced or caused fluctuations of VA. This was excluded by detailed study of patients general and disease history, as well as clinical data and changes in ophthalmological parameters unrelated to CRD or CD. No such conditions were found in patients included into the study during the baseline and follow-up periods. Data from patients with follow-up periods shorter than 6 years or incomplete data were excluded from analysis. The study participants and those who were not included in the study did not differ in respect to age, sex or reason to visit an ophthalmologist. The observation period was divided into segments: between 1–2 visits, 2–3 visits in intervals of 2 years, and between 3–4 visits in 3 years intervals. Current and previous clinical examinations were compared for each patient. VA was first studied at a baseline and was classified into categories according to an international classification of visual impairment.[17] VA decrease was calculated in logMAR and percent of VA was calculated using the initial VA at the first examination and the decrease of VA during each follow-up period. VA was measured following the recommendations of the European Standard EN ISO 8596 (earlier DIN 58220). It was measured with Landolt-Ring optotypes (EN ISO8597) at a distance of 5 m. VA was measured with the patient's own spectacles with a subjective over-refraction using +0.50 DS and −0.50 DS being performed. If the lowest VA at 5 m (equal to 6/120 or 1.30 logMAR) was not achieved, VA was measured at a distance of 1 m. The measurements were initially presented in decimals, but were transformed into logMAR for further calculations.

Disease history was collected during the baseline examination by a senior ophthalmologist and continuously completed during follow up visits. Disease history was reported by the patient or collected from medical records by the senior ophthalmologist using a standardized approach and transferred to Ophthabase, a generic extensible patient registry system, for further data management.[18,19] The information on age of symptom onset as reported by the patient or diagnosed by the ophthalmologist was initially recorded at the first visit to the hospital and checked for consistency on the subsequent one. Median age of onset, age at first examination, and period between disease onset and first visit (latency) were estimated from such data. The median with 25th and 75th percentiles of VA decrease in logMAR for each segment of observation was calculated. Medians of VA at first visit of each follow-up period were compared using a non-parametric Kruskal–Wallis test. VA changes were also studied in respect to disease onset, age of first ophthalmological examination and latency.

Diagnosis of CRD and CD was based on a comprehensive analysis of medical history, clinical investigation including visual acuity, Goldmann or Semiautomatic kinetic perimeter (Octopus), colour testing (Panel D15 test), examination of anterior segment and funduscopy, fundus photography, Ganzfeld ERG (in every patient) and mfERG (in selected patients) according to current ISCEV protocols.

CRD were characterized by a decrease of visual acuity, colour vision defects, decreased sensitivity in the central

visual field, and later followed by progressive loss in peripheral visual field and night blindness in combination with family history and the particular fundoscopic signs. It is known that the typical course of CRD is usually more severe and rapid than other inherited retinal dystrophies; although CRD becomes similar to other inherited retinal dystrophies as it progresses and can be difficult to differentiate at later stages.

The main clinical signs of CD were loss of visual acuity, photophobia, dyschromatopsia, and exclusive or predominant cone involvement in ERG. In contrast to CRD, rod responses are still recordable in the late stages of CD and macular lesions are absent or mild for many years, despite visual acuity decrease.[2]

Informed consent was obtained from all study participants in accordance with the Declaration of Helsinki. The study protocol was approved by the Ethics Commission of the Medical Faculty, Eberhard-Karls University, Tuebingen. Statistical analysis was performed in JMP 8.0.2 (SAS Institute Inc., http://www.sas.com/).

Results

A population of 29 patients was studied. Men ($n = 14$) and women ($n = 15$) were almost equally represented in the study population. Nineteen had CRD and 10 had CD. The patients' first visit to the eye hospital was due to the onset of symptoms or to knowledge of a family history of IRD. Patients with CRD often presented with the onset of visual acuity (VA) decrease followed by night blindness, whereas patients with CD tended to present with photophobia followed by the onset of VA decrease.[20] General study population characteristics are shown in *Table 1*.

Patients with CRD were younger than those with CD at the baseline visit. Patients with CRD had a later disease onset those with CD, but had a shorter latency (the period between subjective disease onset and first examination) and therefore tended to visit an ophthalmologist earlier after the disease onset in comparison with CD patients. CRD patients also had a statistically longer period of follow-up in comparison with CD patients.

Table 1. General description of the study population. Ages and durations are median values (25th, 75th percentile)

	Diagnosis		
Parameter	**CRD**	**CD**	**χ^2-test**
Male (*N*)	8	6	n/a
Female (*N*)	11	4	
Age at first visit (years)	18 (11–31)	26 (8–41.5)	0.82
Age at first diagnosis (years)	9 (8–25)	7.5 (5–15)	0.23
Disease duration (years)	4 (2–10)	6.5 (3–8.25)	0.38
Years of follow-up	11 (7–12)	6.5 (3–8.25)	0.036

Patients with CD had scotopic full-field electroretinograms (ERGs) within normal range with severely reduced/prolonged or non-detectable maximal, photopic and 30 Hz flicker, as well as reduced oscillatory potentials evoked by ISCEV (International Society for Clinical Electrophysiology of Vision) standard flashes (3 cds m^{-2}). In patients with CD, multifocal ERGs (mfERGs) were characterized by predominantly severe or moderate reduction of amplitudes, which was more noticeable in the central than in the peripheral mfERG responses. A relatively large number of eyes with cone dystrophy had normal implicit times in mfERG. Severely and moderately prolonged amplitude peaks were also present in all mfERG rings.

Patients with CRD had predominantly moderately reduced scotopic amplitudes and moderately prolonged scotopic implicit times in ISCEV standard rod response recordings, severely reduced and prolonged or nondetectable maximum, photopic 30 Hz flicker, and photopic single flash cone ERG, elicited with ISCEV standard flashes (3 cds m^{-2}). CRD patients' mfERGs were characterized by overall amplitude reduction and severe implicit time prolongation in all rings. The majority of CRD patients had severely prolonged implicit times that were often more marked in the periphery than in central rings. Observed peculiar changes of mfERG in CD (predominant amplitude reduction in the central rings) and in CRD (more noticeable implicit time prolongation on the periphery) underlines the high importance of mfERG in the differential diagnosis of these inherited retinal diseases. Overall, during the first three visits the majority of patients in the study population had VA $0.50 < \text{VA} \leq 1.00$ logMAR (between 6/18 and 6/60 Snellen), whereas from the third visit the majority of the study population transgressed into the group with more severe visual impairment with VA of $1.30 < \text{VA} \leq 1.80$ logMAR (between 6/120 and 6/380). No patients had VA worse than 1.80 logMAR and none of them were registered as legally blind. Distribution of the VA in the study population for each visit is shown in *Figure 1a*.

When stratified by diagnosis, it was observed that during the first two visits VA between $0.50 < \text{VA} \leq 1.00$ was predominant in CRD patients, whereas an equal number of CD patients had $\text{VA} < 0.30$, $0.30 < \text{VA} \leq 0.50$, and $0.50 < \text{VA} \leq 1.00$ with slight predominance of $0.30 < \text{VA} \leq 0.50$ during the first visit to an ophthalmologist. The third and the fourth visits can be described as a transient period between better and worse VA. This trend can be clearly seen in both CRD and CD patients. These changes are shown in *Figure 1b*. Medians as well as 25th and 75th percentile of VA in CD and CRD patients for each visit are presented in *Table 2*.

As one of the aims of the current study was to define an optimal time for potential therapeutic intervention

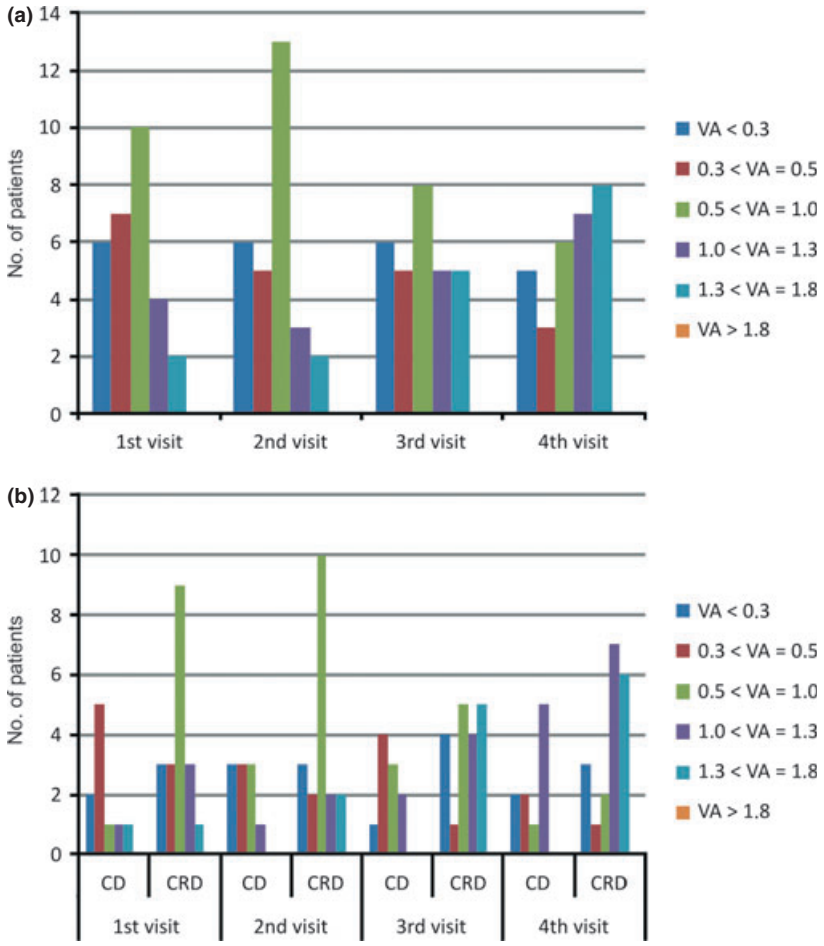

Figure 1. (a) Distribution of VA (in logMAR) in the study population according to an international classification of visual impairment at each visit. (b) Distribution of VA (in logMAR) according to an international classification of visual impairment at each visit stratified by diagnosis.

and for early differential diagnosis of CRD and CD, VA for each visit within a certain follow-up period was compared between patients with CD and CRD using a non-parametric Kruskal–Wallis test. Interestingly, differences between VA were shown to be statistically significant only for the first visit to an ophthalmologist ($p = 0.03$), whereas there was no statistically significant difference found for subsequent visits. Results of the comparison are shown in box-plots[21] in *Figure 2*. The box-plot shows the median and quartiles of the data.

The next step of the study was to estimate the median decrease of VA for each follow-up period. For this purpose the results of the VA measurement for the first and the last visit during each follow-up period were obtained. This data was used for the calculation of median VA decrease for each segment of the follow-up, as well as in percent of VA. VA decrease was highest in the period between 2–3 visits CRD (4 years after the first ophthalmological examination) and between 3–4 visits (6 years after the first visit to ophthalmologist) for CD, which corresponds roughly to the second decade of life in patients with CRD and to third decade of life in CD patients. It was also noted that in the CRD group the rate of decline was fairly even over the four visits, whereas in CD the

Table 2. Median visual acuity in logMAR with 25th and 75th percentiles in cone dystrophy (CD) and cone-rod dystrophy (CRD) patients

	Visit 1	Visit 2	Visit 3	Visit 4
CD	0.45 (0.10–0.50)	0.50 (0.20–0.75)	0.50 (0.40–1.00)	1.15 (0.30–1.80)
CRD	0.70 (0.60–1.30)	0.70 (0.50–1.00)	1.00 (0.60–1.40)	1.30 (0.60–1.70)

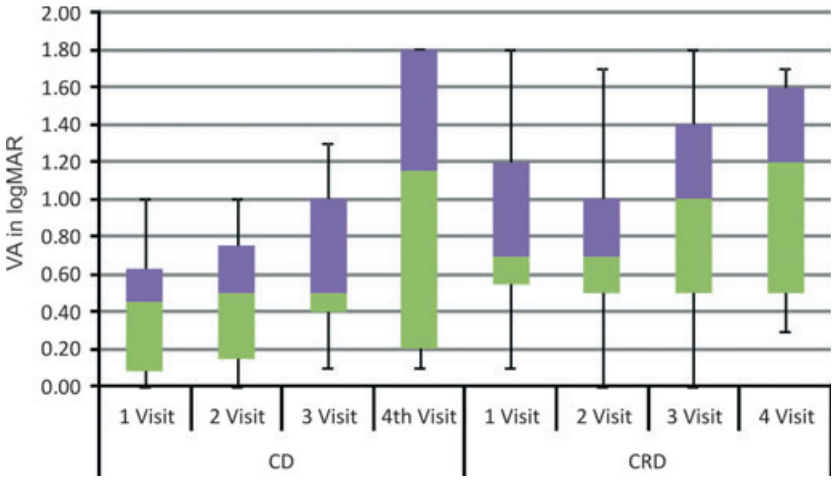

Figure 2. Comparison of VA (in logMAR) in CD and CRD during the first, second, third and fourth visit to an ophthalmologist.

decline appeared to be progressively increasing. The median VA decrease with 25th and 75th percentiles and VA decrease in percent are presented in *Table 3*.

Discussion

In the light of successful developments of new innovative therapies for inherited retinal dystrophies, knowledge concerning typical disease progression is essential for the detection of optimal times for therapeutic intervention. It is also of high importance for further disease follow-up, prognosis, advising patients and timely application of rehabilitation or treatment methods.

VA loss is an early clinical sign for both CD and CRD onset, and is highly correlated with patient's every day activities,[22] therefore the main focus of current study was longitudinal evaluation and comparison of VA changes in CD and CRD. It was found that patients with CRD were younger than those with CD at a baseline visit and had a longer period of follow-up, which corresponds to our knowledge of early and more severe onset of CRD in comparison with other IRD.[20] In contrast, CD patients were first diagnosed slightly earlier than those with CRD and therefore had longer median disease duration at baseline. Observed differences did not reach a significance, which may be explained by a similar pattern of disease onset, which makes differential diagnosis somewhat difficult.[1]

The stratification of VA into groups according to the International Classification of Visual Impairment showed that during the first two visits CRD patients typically had VA between 0.50 and 1.00 logMAR (Snellen 6/18 to 6/60), whereas CD patients typically had VA between 0.30 and 0.50 logMAR (Snellen 6/12 to 6/18) during the first visit. The third and the fourth visits can be described as a transitional period between better and worse VA for both CD and CRD patients. These results are also in line with our findings of a rapid decrease of VA in CRD patients and a much slower decline in CD patients. Our results indicate that despite a progressive visual loss that is typical for early stages of these diseases, VA at first visit tends to be quite good. Furthermore, the comparison of VA in CRD and CD patients for each follow-up period showed a statistically significant difference in VA in these two groups for the first visit, but not for further examinations, indicating that the first visit to an ophthalmologist is an optimal time for early differential diagnosis and treatment.

Table 3. VA decrease during the follow-up periods in logMAR and in percent

	Follow-up											
	2nd Examination				3rd Examination				4th Examination			
Median/Percentile	CD	In %	CRD	In %	CD	In %	CRD	In %	CD	In %	CRD	In %
25th Percentile	0	0	0	0	0	0	0.03	6	0	0	0	0
Median	0.05	11	0.2	29	0.1	20	0.25	36	0.4	80	0.15	15
75th Percentile	0.18	29	0.3	23	0.3	40	0.38	38	1.025	100	0.20	14

The median decrease of VA for each follow-up period was calculated for each disease group. The highest decrease was noted for 4 years after the 1st visit (2–3 follow-up period) and 5 years after the 2nd visit (3–4 follow-up period) for CRD and 4 years after the 1st visit (3–4 follow-up period) in CD. These data correspond to previous studies on cone function loss in CRD, where it was shown that a significant decline in both VA and cone ERG amplitude was noted during the fourth year after the first observation.[14] Furthermore, this study showed that CRD had a high decline of VA between the second and the third examinations, whereas VA decline in CD progressed faster towards the end of the follow-up.

The present study has some limitations. Although inherited cone dystrophies are at the focus of ongoing preclinical trials of IRD, CRD and CD are relatively rare inherited retinal dystrophies, which led to a relatively small sample size in the current study. This can be explained by the low prevalence of CD and CRD in the population, as well as the high mobility of young CD and CRD patients, which makes it difficult to follow-up with these patients for a long period of time in one hospital. As this study is a hospital-based, its results cannot be generalized to the wider CD and CRD population. On the other hand, at least in Germany, most patients with IRD are referred by general ophthalmologists to one of the handful of clinics specialized for IRDs, like ours in the state of Baden-Wuerttemberg; therefore our data can be generalized at least to this geographically defined patient population. It was not possible to compare the rate of VA decrease between groups because of the small sample size in both groups. Nevertheless, due to strict inclusion criteria (similar follow-up periods) we were able to increase the comparability between groups.

The current study presents an analysis of VA changes in patients with rare inherited retinal dystrophies over a long period of follow-up. It enables us to define periods of higher VA decrease in both diseases, to define important signs for early differential diagnosis of these diseases, and to make some conclusions on the differences between VA decrease in CD and CRD patients.

Overall, the results of this study show that the disease history in CRD and CD patients is often similar, which makes differential diagnosis difficult. A majority of CD and CRD patients had quite good VA at the baseline visit. The first visit to an ophthalmologist was important for differential diagnosis. Furthermore, the highest VA decrease was found for follow-up periods 2–3 and 3–4 for CRD and 3–4 for CD. The rate of VA decline was shown to be progressively increasing in CRD patients, whereas CD patients had fairly even VA over different follow-up periods.

This study also showed that it is important to optimize diagnostic procedures and to start treatment, when it becomes available, before the periods of progressive vision loss that we identified. This is particularly important for CRD patients as their VA declines faster in comparison with CD patients. Furthermore this study identifies the further potential for studying visual function in patients with CRD and CD in prospective and retrospective longitudinal studies. In the future our work will be directed at obtaining a larger sample size of patients with CD and CRD, which will allow comparison of the progression and to predict the rate of decrease of VA in these two disease groups in more detail.

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