

Early Visual Symptom Patterns in Inherited Retinal Dystrophies

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Key Words

Age at onset · Best corrected visual acuity · Inherited retinal dystrophies · Visual field defects · Visual symptoms

Abstract

The present retrospective study compared initial visual symptom patterns in inherited retinal dystrophies (IRD) on the basis of records of 544 patients diagnosed with a wide variety of IRD at the Tuebingen University Eye Hospital from 2005 to 2008. Age at first onset of symptoms was noted, and the following clinical data were analyzed: visual acuity (VA), night vision disturbances, photophobia, onset of visual field defects, best corrected VA, and types of visual field defects. Median age at visual symptom onset was defined with 25th and 75th percentiles and compared in 15 IRD types. The main trends in VA changes in retinitis pigmentosa and cone-rod dystrophies were identified. This study was the first to combine disease history and clinical data analysis in such a wide variety of IRD. It showed that patterns of initial symptoms in IRD can provide extra clues for early differential diagnosis and inclusion of IRD patients in clinical trials.

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Introduction

Inherited retinal dystrophies (IRD) are heterogeneous disorders characterized by a progressive loss of visual acuity (VA) and deterioration of the visual field (VF). Hereditary retinal dystrophies are often monogenic [1]. They can manifest at any age, but mostly affect young people and lead to blindness when the patient is at his or her most productive age. To date, therapeutic possibilities for IRD are limited. Nevertheless, a few treatment approaches have shown promise, such as: RPE65 gene replacement therapy for Leber's congenital amaurosis (LCA) [2–5], genetic targeting of bipolar and/or ganglion cells with engineered photo-gates [6] or light-sensitive proteins such as channelrhodopsin-2 [7], exploitation of the protective effect of the neurotrophic factor [8], and microelectronic retinal prostheses [9, 10].

These advances in the treatment of IRD suggest that improved understanding of the onset of IRD will aid in the development of clinical applications. Epidemiological data on IRD in Europe is currently limited to blindness and the most common types of retinitis pigmentosa (RP) [11–15]. Only a few studies have reported on parameters

such as age at disease onset and geographic distribution [16, 17]. Age at the onset of night blindness in the most frequent types of IRD has been examined in an earlier study [18], which however was carried out on a relatively small group, and did not analyze other visual symptoms and focus on the different types of IRD.

A better understanding of symptomatic patterns at the time of disease onset and their differences in a variety of IRD should therefore make it possible to identify IRD patients who can benefit from treatment during early disease stages. The aim of our study was therefore to compare early patterns of typical visual symptoms onset in the different types of IRD.

Materials and Methods

Records of 544 patients with IRD at the University Eye Hospital in Tuebingen, Germany, from 2005 to 2008 were selected. Patients with the following diagnoses were included: RP; Stargardt disease (STD); central areolar choroidal dystrophy (CACD); cone dystrophies (CD); cone-rod dystrophies (CRD); pseudovitelliform, vitelliform and pattern macular dystrophy (MD), Bardet-Biedl syndrome (BBD); Usher syndrome I (USH I) and II (USH II); choroideremia (CHRD); LCA. Disease history was reported by the patient or collected from medical records using a standardized approach. The information on age of symptom onset as reported by the patient or parents (in the case of early-onset IRD), or as diagnosed by an ophthalmologist was recorded at the first visit to the hospital and checked for consistency on the subsequent visit. Records that did not contain a final diagnosis or a full history of the disease were excluded. The records were transferred to Ophthabase [19, 20]. General information included sex and age at first visit. This was necessary to compare sex distributions between IRD groups and to estimate the latency between VA decrease and ophthalmological examination. IRD-specific data included age at first onset of visual symptoms (i.e. noticeable loss of VA, night vision disturbances, glare sensitivity, signs of restricted VF), age at first clinical diagnosis, age at first experienced VA decrease, and age at first ophthalmological examination of patients with RP and CRD. Clinical data included best corrected VA (BCVA) in decimals and static and kinetic perimetry (Octopus 101 and Goldmann) as graded by the examining ophthalmologist. Some RP patients were genetically tested, and an inheritance mechanism was verified in a fraction of them. RP was described as simplex (SIM-RP) when no inheritance pattern was detected, and as non-specified inheritance (RP-NSI) when genetic testing was not done.

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, University of Tuebingen. Statistical analysis was performed with JMP 8.0.2 (SAS Institute Inc., Cary, N.C., USA). Non-normally distributed data were represented by medians (25th and 75th percentiles), and approximately normally distributed data by means (SD). Age at first diagnosis and first subjective visual symptoms were stratified by main ophthalmic diagnosis.

Results

Records of 544 patients with STD (n = 69), CACD (n = 7), CD (n = 37), CRD (n = 13), MD (n = 17), RP (n = 276), BBD (n = 13), USH I (n = 5), USH II (n = 18), CHRD (n = 21), and LCA (n = 15) were studied. Men (n = 302) were more prevalent than women (n = 242) in the study population (fig. 1a). Age distribution of the patients at first visit was approximately normal (fig. 1b): the mean age was 43.46 (SD = 18.34). The distribution at final diagnosis is shown in figure 1c. Genetic testing of RP patients showed that SIM-RP (n = 64, 41%) was the most frequent type of RP followed by X-linked (XL-RP) (n = 36, 23%), autosomal dominant (ADRP) (n = 30, 19%), and autosomal recessive (ARRP) (n = 27, 17%).

We obtained data on the number of genes causing different types of IRD from OMIM [21] and calculated a robust statistic of the variability in age at major visual symptom onset by taking the difference between the 75th and 25th percentiles. For each symptom, there is a very low correlation between the age at onset variability and the number of genes that cause the disease. Pearson's correlation coefficient ranged from 0.05 (for age at photophobia onset) to 0.34 (for age at VA onset).

An age comparison at the onset of night blindness and photophobia is shown in figure 1f and g, respectively. Figure 1h and i show a comparison of ages at the time of first-reported VA decrease and VF defects (both of which are strongly anti-correlated with the performance of daily activities [22]). A summary of median age at the onset of typical IRD symptoms is shown in table 1.

To highlight differences in the patterns of early symptoms of RP and CRD, BCVA was plotted vs. the difference between age at first visit to an ophthalmologist and the age of the first experienced decrease in VA in RP and CRD (fig. 1d, e). CRD patients (n = 66) and RP (n = 42) patients responded to written questions concerning first decrease in VA: ADRP (n = 6), ARRP (n = 5), early-onset RP (n = 18), SIM-RP (n = 9), and XL-RP (n = 4). Patient ages and BCVA at first visit were obtained from their records. Most patients had a combination of central (n_1) and peripheral

Fig. 1. a Sex distribution of the study population, stratified by diagnosis. **b** Age distribution of patients with IRD. **c** Distribution of final diagnosis. **d** A scatter plot showing BCVA versus the latent period in RP patients. **e** A scatter plot showing BCVA versus the latent period in CRD patients. **f** Box plots of age of night blindness onset in IRD. **g** Box plots of photophobia onset in IRD. **h** Box plots of age of initial VA decrease in IRD. **i** Box plots of age at onset of VF defects in IRD. **j** VF defects stratified by diagnosis.

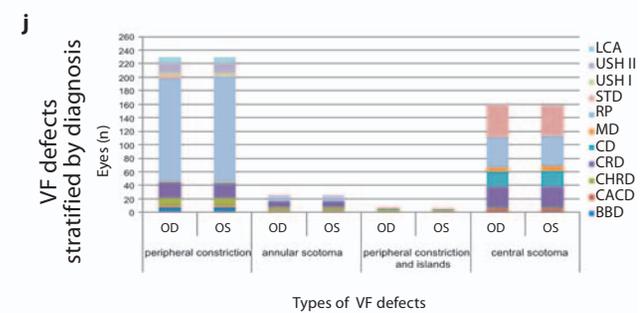
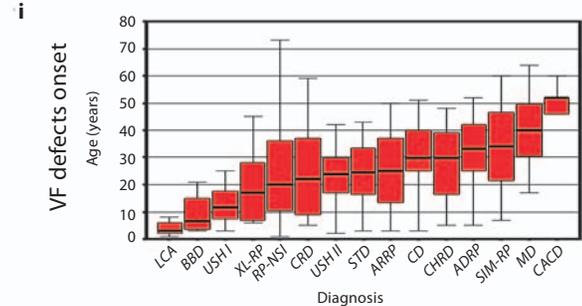
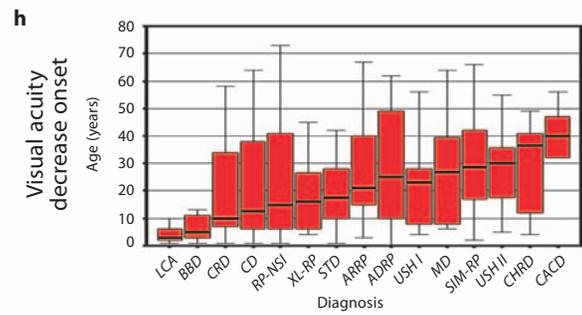
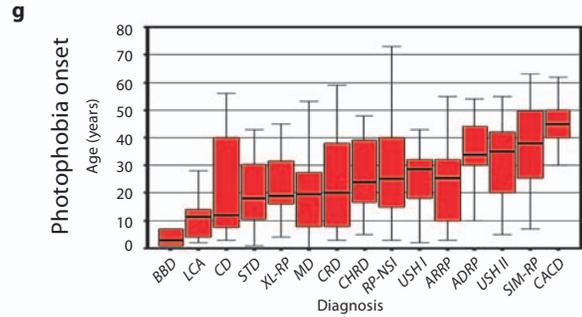
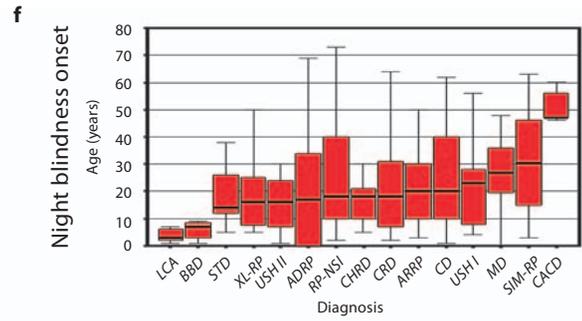
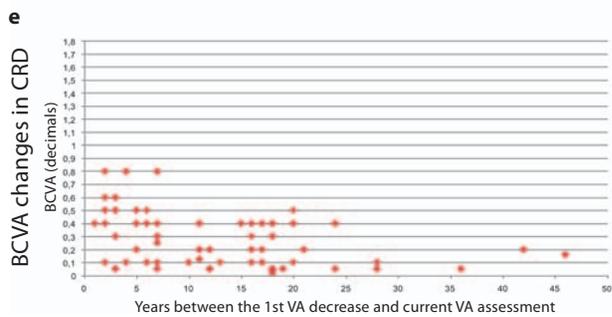
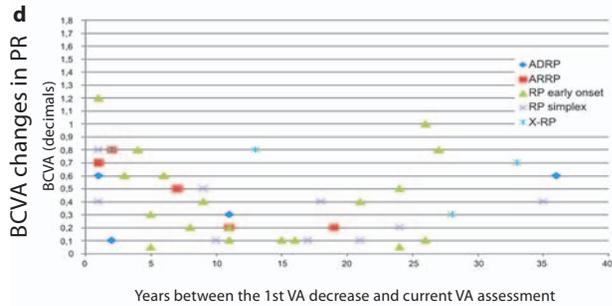
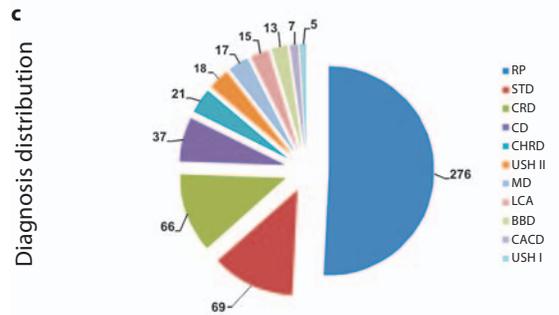
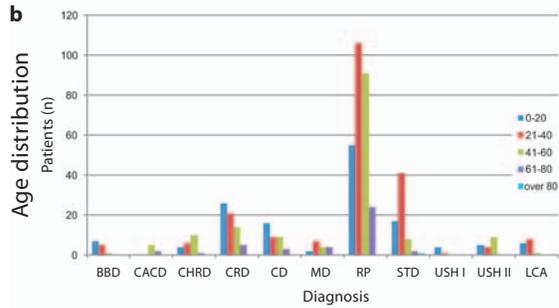
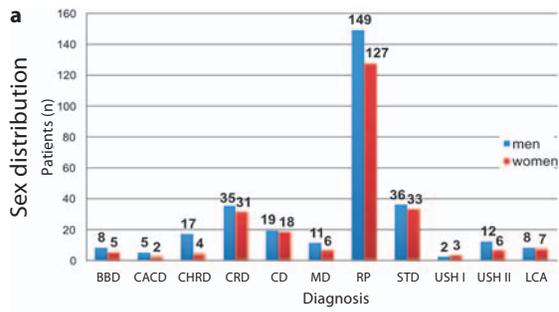


Table 1. Age at onset of typical IRD symptoms

IRD types	Night blindness onset	Initial VA decrease	Photophobia onset	Onset of VF defects	First diagnosis
ADRP	17 (0, 35.5)	25 (8.8, 49.8)	34 (27.5, 44.5)	33 (21.5, 43.5)	27 (15.5, 57)
ARRP	20 (9, 30)	21 (13.5, 46.5)	25.5 (9.3, 33)	25 (13, 37)	16.5 (14.25, 22)
SIM-RP	30.5 (15, 46)	28.5 (16, 44)	38 (25.3, 9.8)	34 (21, 47)	31 (16.25, 70.3)
XL-RP	16 (7, 25)	16 (6, 28)	19 (16, 32.3)	17 (7, 30.3)	20 (20, 79.5)
RP-NSI	18 (10, 40)	15 (6, 41.5)	25 (24.8, 40.3)	20 (10, 37)	24.5 (24.5, 55)
BBD	7 (3, 8.75)	5 (2.5, 12)	3 (1, 15.5)	6.5 (3.3, 18)	5.6 (3.5, 7)
CACD	47 (46.5, 58)	44 (32, 49)	45 (35, 50)	52 (39, 56)	55.5 (43.25, 9.75)
CHRD	18 (10, 23)	36.5 (11.5, 42.8)	24 (15.8, 40)	30 (15, 41)	16.5 (10, 43)
CD	20 (10, 40)	12.5 (5.75, 38.3)	12 (5, 31)	30 (25, 40)	19 (10, 45.3)
CRD	18 (7, 32)	10 (6.5, 34)	20 (8, 40.5)	22 (9, 37.3)	12 (6, 26.5)
MD	27 (19.25, 36)	27 (7.5, 39.75)	19.5 (7.5, 27.8)	40 (30, 51)	33.5 (27.25, 51.75)
STD	14 (12, 28)	17.5 (10, 28)	18 (10, 31)	24.50 (15.8, 34.3)	23 (15, 32.5)
USH I	23 (7, 36.5)	25 (8.5, 37)	27.17 (16, 32)	11.5 (6.25, 17.8)	14 (7, 15)
USH II	16 (6, 24.5)	30 (16.3, 36.3)	35 (19.3, 42.8)	24 (17, 31.5)	23.50 (19, 34)
LCA	3 (2, 6)	3 (2, 6)	11.5 (4, 15.3)	3 (3, 6)	3 (3, 6)

Data presented as median ages (years) with 25th and 75th percentiles in parentheses.

(n_2) VF defects, i.e. RP ($n_1 = 152$ and $n_2 = 45$) and CRD ($n_1 = 23$ and $n_2 = 31$). Central scotoma was more typical in STD ($n = 48$), CD ($n = 23$), and MD ($n = 7$) (fig. 1f).

Discussion

Men were more prevalent than women (male/female ratio: 1:3), which corresponds to results obtained previously [15, 16]. The higher number of men can be explained by patients with X-linked retinal disorders such as CHRD and XL-RP in the study population. The majority of patients were between 21 and 40 years of age, which underscores the public health importance of IRD, and is in line with previous findings [23].

RP, STD, CRD, and CD were the most frequent diagnoses. Patients with USH II were 3 times more frequent than USH I patients, which is in line with earlier results [11]. SIM-RP was the most widespread form of RP, corresponding to previous studies [24], followed by XL-RP. A similar frequency of XL-RP was observed in a nationwide study in Denmark [25]. Our results showed a very low correlation between the age at onset variability and the number of genes that cause the disease.

Early night blindness was detected in patients with LCA, BBD, STD, XL-RP, USH I, and RP-NSI; this corresponds to previous findings [18]. Considerable age variation was noted at the onset of night blindness in patients

with ADRP; this is in line with data obtained at the University of California Los Angeles, where the mean age at first examination was 35 years, with a mean disease duration of 19.2 years. CD and CRD patients had an earlier onset of photophobia and VA decrease than those with other diseases because of the predominant involvement of the cones [26]. Patients with XL-RP reported a VA decrease and VF defects earlier than those with other types of RP; this is supported by other studies which have reported on severe and/or early VA decrease and VF loss and night blindness onset in such patients [27–29].

Analysis of BCVA measured at first visit versus latency showed that patients with RP and better BCVA tended to delay their visit to the ophthalmologist for many years. The fact that some patients with a good BCVA visited an ophthalmologist early on in the disease can be explained by the onset of other major symptoms. Two main observations are apparent in figure 1d and e: (1) there is a wide variation in the period between onset of symptoms and first visit to an ophthalmologist, both for RP and CRD, and (2) there is a trend relating BCVA and latency for CRD, but this trend is less apparent for RP. Patients with early-onset RP and SIM-RP generally had a more stable BCVA than those with other RP types. CRD patients had both a shorter latent period than those with RP and on average a worse BCVA at their first visit. Our findings indicate that patients with CRD normally experience a severe VA loss earlier than those with RP [26]. Previous

studies in RP patients have shown that VA can remain normal in individuals with advanced stages of the disease, even when only a small island of the VF remains [23]. Since patients with RP are known to suffer irreversible and progressive loss of VF as they age [30], we speculate that the early decrease in VA and the shorter latent period found in some RP patients can be explained by a combination of central and peripheral VF defects that can lead to the subjective perception of lowered VA. Interestingly, the trend we observed when plotting BCVA versus the latent period in CRD was very similar to the trend of VF areas plotted against the period between first experience of VF defects and the time of the ophthalmological examination in RP. The trend of VF changes in RP patients was first noted by Massof et al. [31], who used a two-stage hypothesis to explain the natural course of RP.

Overall, the study identifies variability in age at onset of major visual symptoms in fifteen IRD types and defines the diagnostic reliability of these parameters for each IRD group. To the best of our knowledge there are no other studies that have performed a similar comparative analysis using such a wide variety of IRD diagnoses. The results of this analysis suggest that patients with RP tend to delay their first visit to an ophthalmologist, whereas others undergo ophthalmological examination even if their BCVA is relatively good. Clinical data suggest that early visits to an ophthalmologist can be explained by a combination of central and peripheral VF defects.

This study also showed that patients with CRD tend to have worse BCVA and visit an ophthalmologist earlier than those with RP. Interestingly, we observed a similarity between the trend of BCVA change in CRD and VF change in RP patients, which was not previously noted in the literature.

This study underlines the phenotypical heterogeneity observed between different RP types and suggests that

XL-RP patients had a rapid BCVA decrease and onset of VF defects, whereas early-onset RP and SIM-RP had more stable BCVA. Previous publications have mostly focused on phenotypical peculiarities in RP patients that carry a certain genetic mutation [32–34]. These studies did not compare symptom onsets or disease progression between different types of IRD. In contrast, our study provides new information on disease onset patterns and a comparison of age at symptoms onset in different IRD types, which can be useful in clinical practice as a diagnostic clue prior to genetic testing.

Our study had some limitations: it was retrospective and genetic data was available from a limited number of patients. Data on the history of the disease were mostly based on the patients' subjective perceptions. Nevertheless, the data were collected over a 4-year period in a highly standardized manner, which enabled us to include a relatively large sample size of patients with rare forms of IRD. Patients from all over Germany were represented in the study population, indicating that the results of the study will generalize. Our future research will be devoted to the linkage of phenotypical data with detailed genetic testing results in a wide variety of IRD, which will allow a more precise phenotype-genotype differentiation.

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Disclosure Statement

No conflicts of interest exist on the part of any of the authors.

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