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RETINAL DISORDERS

An epidemiological approach for the estimation of disease onset in Central Europe in central and peripheral monogenic retinal dystrophies

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Abstract
Purpose To study clinical patterns of disease onset in monogenic retinal dystrophies (MRD), using an epidemiological approach.
Methods Records of patients with MRD, seen at the University Eye Hospital Tuebingen from 1994 to 1999, were selected from a database and retrospectively reviewed. For analysis, patients were divided into 2 groups by predominant part of visual field (VF) involvement: group 1 (predominantly central involvement) included Stargardt disease (ST), macular dystrophy (MD), and central areolar choroidal dystrophy (CACD), and group 2 (predominantly peripheral involvement) included Bardet–Biedl syndrome (BBD), Usher syndrome (USH) I and II, and choroideremia (CHD). Age, sex, age of first diagnosis, age of visual acuity (VA) decrease and VF emergence, night blindness and photophobia onset, types of VF defects and age of its onset, color discrimination defects and best corrected VA were analyzed.
Results Records of 259 patients were studied. Men were more prevalent than women. Mean age of the patients was 47.2 (SD=15.6) years old. Forty-five patients in the first group and 40 in the second were first diagnosed between 21 and 30 years of age. Ninety-four patients in the first group had VA decrease before 30 years of age; in the second group, 68 patients had VA decrease onset between 21 and 40 years of age. Forty-four patients in the first group noticed VF at an age between 21 and 30 years, and 74 patients between 11 and 30 years in the second group. Central scotoma was typical for the first group, and was detected in 115 patients. Concentric constriction was typical for the second group, and was found in 81 patients. Half of patients in both groups preserved best-corrected VA in the better eye at a level of 20/40 or better; 7% in the first group and 6% in the second group were registered as legally blind according to WHO criteria, having VA <1/50 or VF <5°. Diagnosis frequency was USH I and II—34%, ST—31%, MD—18%, CHD—14%, BBD—5%.
Conclusions An epidemiological approach to the estimation of the disease onset of various subtypes of monogenic retinal degenerations will be useful for detection of disease duration, its prognosis, rehabilitation and the researching of future treatment possibilities.

Keywords Hereditary retinal dystrophies · Disease onset · Epidemiology · Frequency of the disease · Blindness · Central Europe

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Introduction

Low vision and blindness are important public health problems not only in Germany, but worldwide [13]. Globally, in 2002 more than 161 million people were visually impaired, of whom 124 million had low vision and 37 million were blind [19]; 12.8% of the European population had low vision

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and 15.5% visual impairment [18]. According to the German Federation of Blind and Visually Impaired People, the number of blind people in Germany is about 145,000 and the number of partially sighted people is approximately 500,000 [8, 9].

The two most common retinal degenerative diseases that result in blindness secondary to photoreceptor loss are age-related macular degeneration and retinitis pigmentosa. Retinitis pigmentosa is more severe, and its symptoms appear earlier in life, but age-related macular degeneration is more prevalent [17].

Currently, there is no therapy that stops the evolution of monogenic retinal dystrophies [6, 17]. As the knowledge of molecular genetics and molecular biology increases, it may become possible to develop new treatment strategies [3] that will be based on pharmaceutical interventions such as topical treatment with alpha2-agonist [14], gene therapy such as RPE65 gene replacement [4], cell transplantation [2], and artificial retinal implants [20]. Due to this, a screening of monogenic retinal degenerations (MRD) at age at risk and identifying affected individuals in the early stages of the disease is necessary, and this shows the importance of epidemiological studies focused on disease and blindness onset estimation in MRD.

A retrospective longitudinal study of hereditary retinal degenerations (HRD) performed in Northern France showed the importance of such studies for establishment of HRD prevalence as well as the age of its diagnosis in the population [15]. Earlier epidemiological studies have been based on the information received from social services, and were focused on the estimation of the onset of blindness, but not of the disease itself [9, 10]. Disease and blindness onset in monogenic retinal degeneration need to be further investigated using an epidemiological approach as in the following study.

Materials and methods

Data from 3,787 patients with monogenic retinal degenerations, seen at the University Eye Hospital Tuebingen from 1994 to 1999, were stored in an RP-clinical access-based database. Records of 259 patients with hereditary retinal dystrophies were selected for the study from this database according to the inclusion criteria (diagnosis). Two groups of hereditary retinal dystrophies were selected for our study: the first group included pigment epithelial disorders (Stargardt and central areolar choroidal dystrophy (CACD)) and macular dystrophies with different age structure (Best's disease, pseudovetilliform macular dystrophy, pattern macular dystrophy and progressive macular dystrophy); the second group included syndromic degenerative diseases (Bardet-Biedl, Usher Syndrome I and II, choroideremia). A time frame from 1994 to 1999 was chosen for the study. During this period all clinical data was collected in a highly standardized manner, using an electronic database system.

The first visit data were retrospectively analyzed, including general information, disease history and data about color discrimination defects and best-corrected VA of these patients. General information contained the main demographic characteristics of the study population: age, sex and nationality. Age of the patients was estimated as the age when they had their first visit to the special clinic for inherited retinal degenerations in Tuebingen. Disease history included information about disease onset and evolution of clinical appearance of the disease over time, such as the age of first diagnosis, age of visual acuity (VA) decrease, night blindness and photophobia onset, and types of VF defects and age of patient at its onset, which were reported by the patient. Age at onset of symptoms was defined as the age at which these symptoms were either first reported by the patient and/or diagnosed by the ophthalmologist. Age at first diagnosis was defined as the age at which the first correct diagnosis was made, as indicated by the patient. Final diagnosis was recorded as a diagnosis that was established during the last visit of the patient within the chosen follow-up period.

Diagnosis was established by a team of four senior resident ophthalmologists at the Eye University Hospital Tuebingen, and was based on a comprehensive analysis of medical history, clinical investigation including best-corrected visual acuity, Goldmann or semiautomatic kinetic perimetery, color testing (Panel D15 test), examination of anterior segment and funduscopy, Ganzfeld ERG (in every patient) and mfERG (in selected patients) according to current ISCEV protocols [7]. Only some of the patients could be genetically tested, and in a fraction of them it was possible to verify the diagnosis genetically.

Types of VF defects, color discrimination defects and best-corrected VA were obtained from the results of clinical examination. For the purpose of analysis, patients were divided into two homogenous groups according to predominant type of visual field defect: group 1 (with predominantly central involvement)including Stargardt disease, macular dystrophy, and CACD, and group 2 (predominantly peripheral involvement) including Bardet-Biedl syndrome, Usher Syndrome I and II, and choroideremia.

The study was designed with respect to ethical standards laid down in the 1964 Declaration of Helsinki. The study protocol was reviewed and approved by the Ethics Commission of the Medical Faculty, Eberhard-Karls University Tuebingen, Germany. All information was handled with the special guarantee of confidentiality in order to avoid unwanted back-tracing of participants.

For further analysis, data was extracted from an MS Access 2000-based RP-clinical database using Structured

Query Language (SQL) selection, and transferred to an Excel spreadsheet that was used for data management. Statistical analysis was performed using SPSS 11.00 for Windows. Descriptive statistics, including mean and standard deviation and frequency calculation, were used for data analysis. Data concerning age distribution, age at first diagnosis, age of night blindness, photophobia and VA decrease onset, and age of emergence of VF defects were further stratified by diagnosis, which made it possible to see the contribution of each diagnosis in each age group; VA distribution data was stratified by age. Frequency of diagnosis and blindness was defined as the number of patients with this condition divided by the study population.

Results

General information

General information about the study population included data about age, gender and nationality. Records of 259 patients were studied. In total, group 1 (predominantly central involvement) included 134 patients and group 2 (predominantly peripheral involvement) 125 patients.

Sex distribution: sex distribution analysis revealed that in both groups men predominated in comparison with women. The same trend was revealed when stratifying the data according to diagnosis in both groups (Figs. 1, 2a). Group 1 included 87 male and 47 female patients; group 2 included 72 male and 53 female patients. In the subgroup of patients with choroideremia, men are prevalent, as the disease is inherited via an X-linked recessive mechanism. At the same time, our data contained women who were mostly obligatory carriers of the disease with or without symptoms, and one case was diagnosed with choroideremia. The distribution of women in the choroideremia subgroup is shown in Fig. 2b.

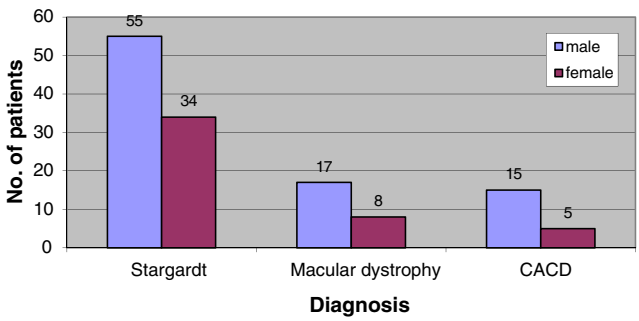

Fig. 1 Sex distribution of patients in group 1 (predominantly central retina involvement), stratified by diagnosis

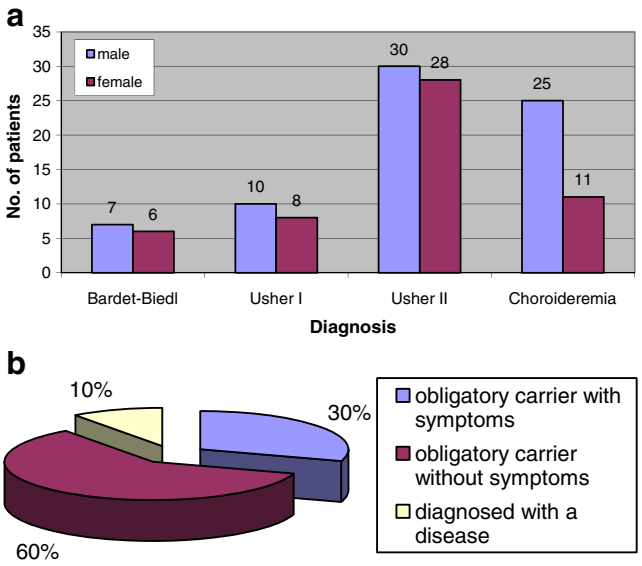

Fig. 2 **a** Sex distribution of the patients in Group 2 (predominantly peripheral involvement), stratified by diagnosis. **b** Distribution of women in choroideremia subgroup

Age distribution

Age distribution analysis showed that patients between 21 and 40 years old (n=53) represented the majority in group 1. The age group 41–60 years old included 42 patients in group 1; age groups 0–20, 61–80, and over 80 were presented by two, 34 and three patients respectively (Fig. 3a)

Fifty-two patients in group 2 were between 41 and 60 years old, 40 between 21 to 40 years old; 26 patients were aged between 61 and 80 years old, and there were no patients older than 80 (Fig. 3a). Mean age for the entire study population was 47.2 years old (SD=15.6).

A stratification of subgroups with specific diseases according to contribution of certain age groups of the patients is shown on the Fig. 3b.

Nationality distribution of the patients: German patients were predominant in both groups; in group 1 Germans represented 87 patients, and in group 2 76 patients. Forty-seven and 49 patients respectively originated from Central European countries.

History of the disease data

History of the disease data incorporated age at first diagnosis, age of visual acuity decrease, age of night blindness, photophobia onset and age of visual field defects emergence.

Age at first diagnosis showed the same trend for groups 1 and 2. In group 1 we observed that ten patients were diagnosed for the first time before 10 years old, 27 between 11 and 20 years old, 45 between 21 and 30, 17 between 31

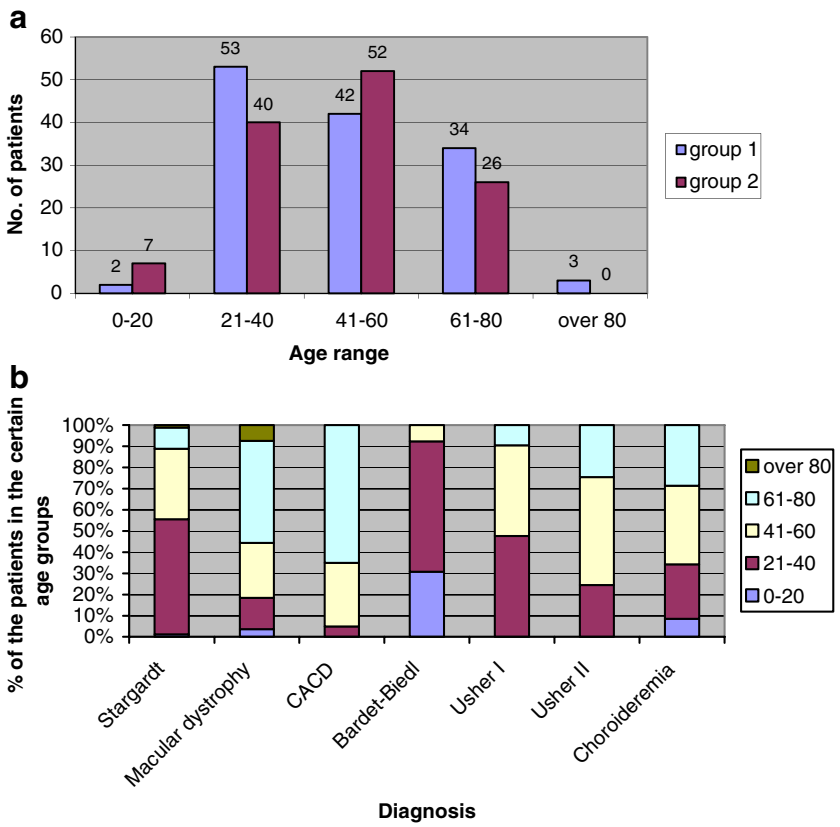

Fig. 3 **a** Age distribution of patients in groups 1 and 2. **b** A stratification of subgroups with specific diseases according to the age of the patients at first visit in the special clinic on inherited retinal degenerations in Tuebingen

and 40, 27 between 41 and 50, and eight patients between 51 and 60 years of age(Fig. 4a). In group 2, 17 patients were first diagnosed before age 10, 31 between 11 and 20 years old, 40 between 21 and 30 , 23 between 31 and 40, 12 between 41 and 50, and two were first diagnosed after 51 years of age (Fig. 4a).

Age at first diagnosis stratified by diagnosis is shown in Fig. 4b.

Night blindness onset is one of the most important signs for detecting the disease onset of monogenic retinal degenerations. Information about night blindness onset was separately analyzed for groups 1 and 2. Forty-nine patients in group 1 first noticed night blindness when they were between 41 and 50 years old, 35 patients in this group noticed the presence of night blindness between 11 and 20 years of age, and 11 patients each between 1 and 10 and 31 and 40 years of age; the remaining three patients first experienced night blindness between 51 and 60 years of age. A different trend was observed in group 2: 38 patients in this group first noticed the presence of night blindness before 10 years of age, 44 between 11 and 20, 21 between 21 and 30 years of age, 11 between 31 and 40 years of age, five patients each between 41 and 50, and three between 51 and 60 years old (Fig. 5a).

A stratification of age of night blindness onset according to the disease is demonstrated in Fig. 5b.

Photophobia is one of the middle-stage symptoms of monogenic retinal degeneration. A similar tendency was observed in patients of both groups; the majority in both groups first noticed photophobia when they were younger than 30 years old. In group 1, ten patients first reported photophobia before the age of 10, 27 between 11 and 20 years old and 45 between 21 and 30 years old; of the remaining 52 patients, 17 patients first recognized photophobia between 31 and 40 years old, 27 between 41–50, and eight after the age of 51 years (Fig. 6a). In group 2, 17 patients first reported photophobia before the age of 10, 31 between 11 and 20 years old and 40 between 21 and 30 years old. 23 patients reported photophobia between 31 and 40 years of age, 12 between 41 and 50 years old, and two patients after 50 years old (Fig. 6a). Both groups were quite similar with respect to photophobia onset, and the mean age of onset for both groups was 26 years old (SD=15).

A stratification of age of photophobia onset in accordance to diagnosis is shown on Fig. 6b.

The age of onset of visual acuity decrease had different trends in the two groups. The data were collected for right and left eyes; results showed that there was no difference found in onset of visual acuity decrease between right and left eyes. In group 1, the majority of patients (n=94) noticed a decrease in visual acuity before 30 years old: 30 patients before 10, 33 between 11 and 20 years of age, and

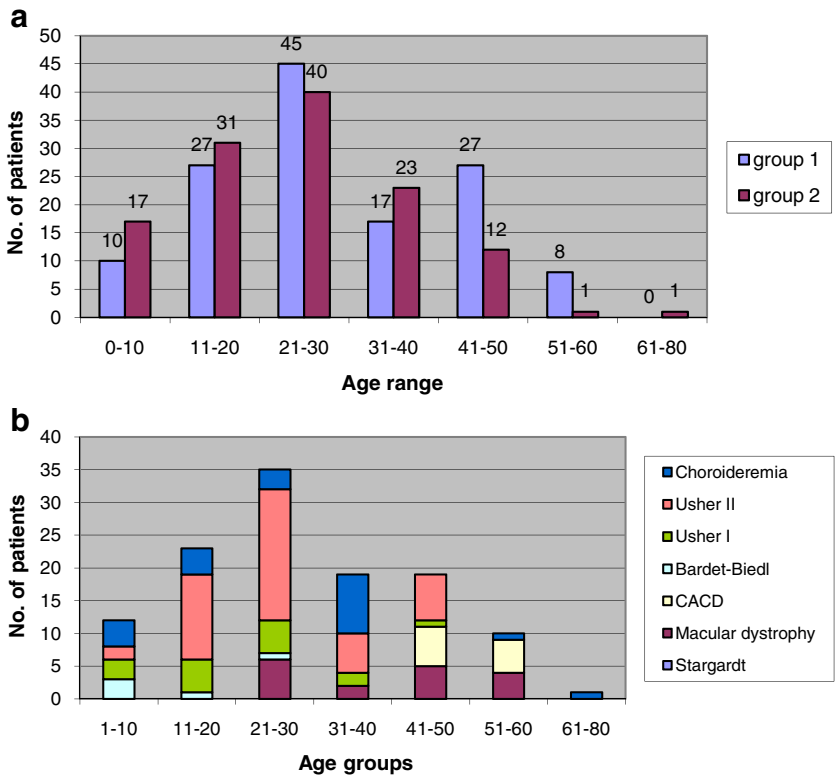

Fig. 4 **a** Age at first diagnosis in groups 1 and 2. **b** The age when the first correct diagnosis was made, as indicated by patients, stratified by diagnosis

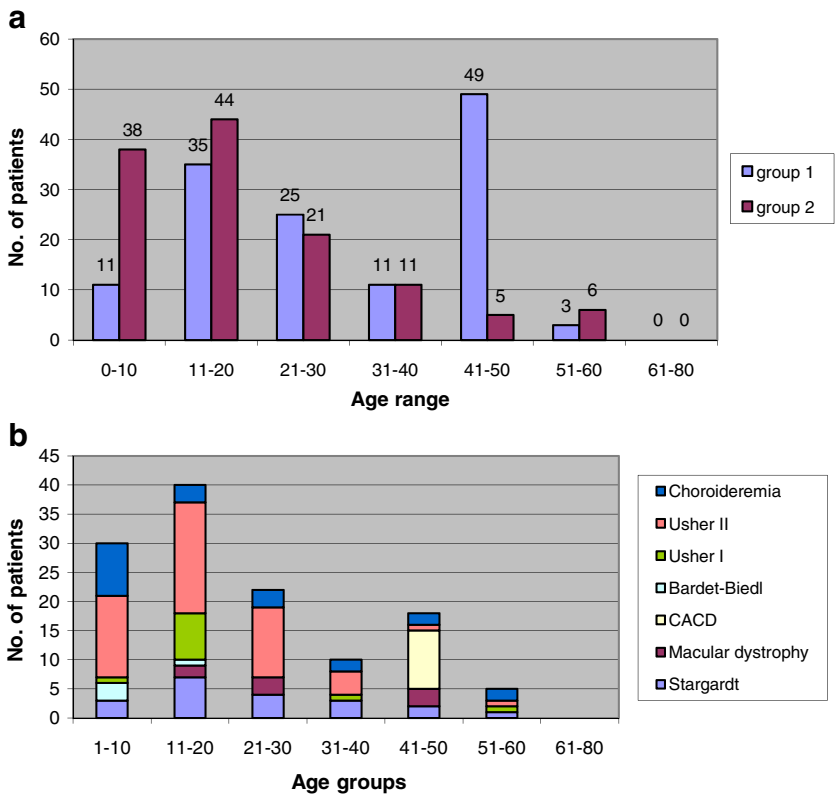

Fig. 5 **a** Age of night blindness onset in group 1 and group 2. **b** The age of night blindness onset stratified by diagnosis

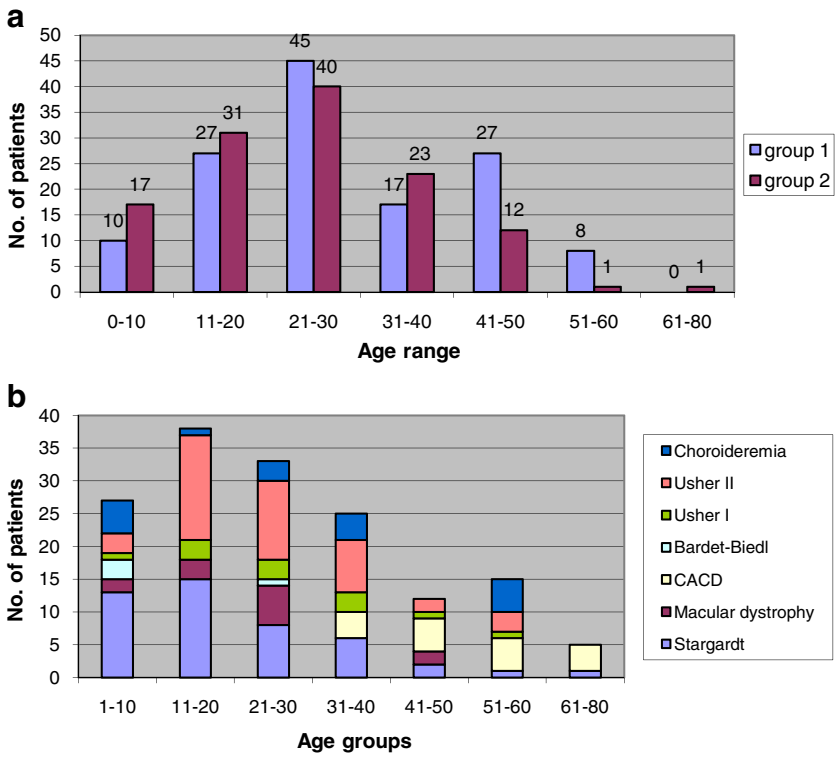

Fig. 6 **a** Age of photophobia onset in group 1 and 2. **b** Stratification of photophobia onset according to diagnosis

31 between 21 and 30 years old. The remaining 40 patients first noticed or were diagnosed with decreased visual acuity after 31 years of age: 16 patients between 31 and 40 years old, 22 between 41 and 50, and two patients after 51 years of age (Fig. 7a). In group 2, 36 patients had visual acuity decrease between 21 and 30 years old, and 32 between 31 and 40 years old. 36 patients noticed visual acuity decrease before 20 years old: 19 of them before 10, and 17 patients between 11 and 20 years old. A relatively high number of patients (n=17) recorded visual acuity decrease between 41 and 50 years of age and four patients after 51 years of age (Fig. 7a).

Age of onset of visual acuity decrease stratified by diagnosis is shown in Fig. 7b.

It was observed that in both groups visual field defects emergence was reported by the patient before the age of 30 years. In the first group, 44 patients reported emergence of visual field defects at an age between 21 and 30 years old, 31 between 11 and 20 years old, and 26 between 41 and 50 years old. The remaining patients reported early visual defects appearance: ten below 10 years of age, eight between 31 and 40 years old, and 15 between 51 and 60 years old (Fig. 8a). In group 2, 38 and 36 patients presented visual field defects at age periods 11–20 and 21–30 years old respectively; 23 patients in this group first observed visual field defects at an age before 10 years old, 22 at an age between 31 and 40, and six in the 41–50 age range. No patients in group 2 reported first onset of visual field defects beyond the age of 50 years (Fig. 8a). Visual defects appearance trends were quite similar between the groups, and mean age onset for both groups was 26 years old (SD=14.5).

A stratification of emergence of visual defects according to the diagnosis is shown in Fig. 8b.

Results concerning clinical data

The clinical data analyzed included best-corrected VA (BCVA), types of visual field defects and color perception problem diagnoses. BCVA was measured for both eyes of the patients. Visual acuity better than or equal to 20/40 was detected in 124 eyes in group 1 and 140 eyes in group 2; best-corrected visual acuity lower than 20/40 and higher than 20/200 was observed in 81 eyes in group 1 and 83 in group 2; lower than 20/200 was determined in 43 eyes from group 1 and 15 from the second group (Fig. 9a). We defined legally blind patients as having visual acuity lower than 20/400 or visual field less than 5° in the better eye, according to the WHO definition [16]. Twenty eyes in group 1 and 12 eyes in group 2 had a visual acuity that corresponded to the criteria for legal blindness (Fig. 9a). Overall, 7% of patients in group 1 and 6% in the second group were registered as legally blind.

Best-corrected visual acuity stratified by age is shown on Fig. 9b.

A stratification of BCVA by age showed an interesting pattern: BCVA higher or equal to 20/40 was observed in 35% of patients 41–60 years of age. Half of the patients

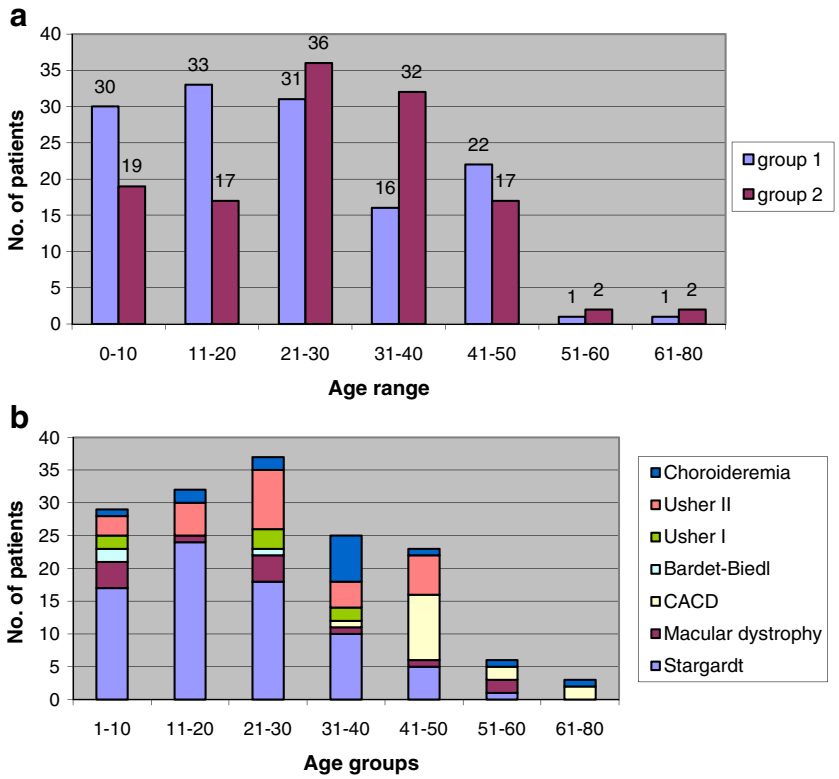

Fig. 7 **a** Age of visual acuity decrease onset in patients from Groups 1 and 2. **b** Age of onset of visual acuity decrease stratified by the diagnosis

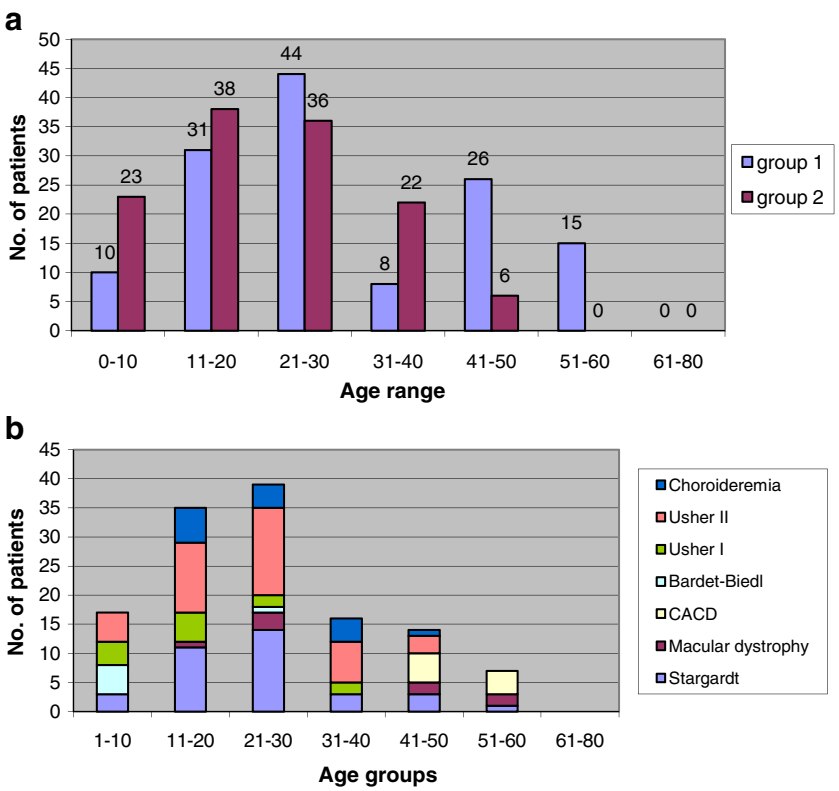

Fig. 8 **a** Age at visual field defects appearance. **b** Emergence of visual field defects stratified by diagnosis

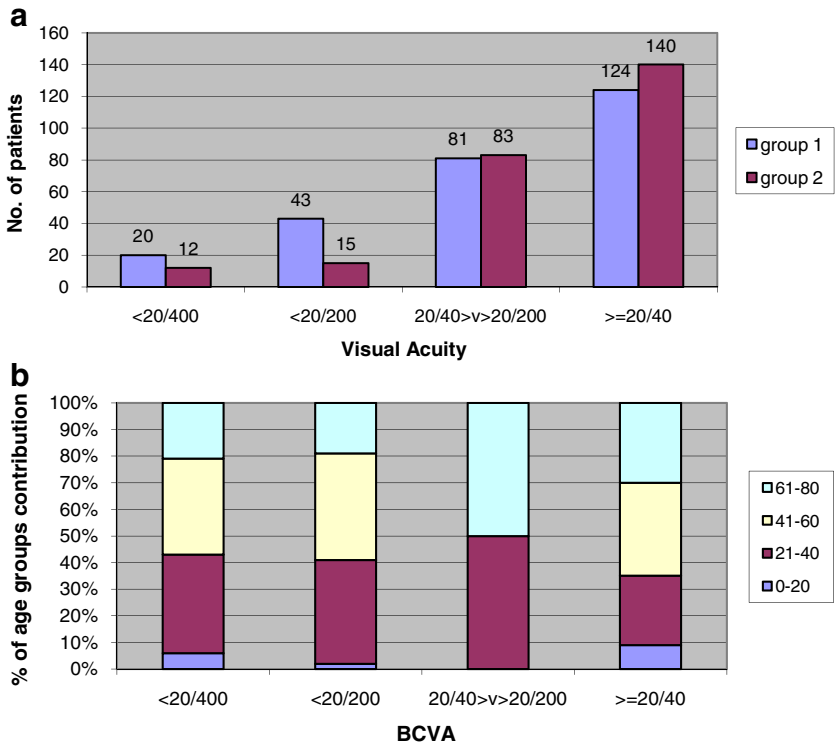

Fig. 9 **a** BCVA in group 1 and group 2. **b** BCVA stratified by age for both groups

with BCVA less than 20/40 but higher than 20/200 were in the 21–40 age range, while the other half was in the 61–80 age range. Forty percent of patients in the age group 41–60 and 39% in 21–40 had visual acuity less than 20/200. Thirty-seven percent of patients in age group 21–40 and 36% in age group 41–60 were registered as legally blind (Fig. 9b).

The types of visual field defects are as important as the age of their onset, since they define the level of decrease of the patient's quality of life and the effectiveness of further rehabilitation. Patients from group 1 had a higher frequency of central scotoma (n=115), whereas concentric constriction (n=13) and ring scotoma (n=6) were detected less frequently. By contrast, in group 2 concentric constrictions were observed in 81 patients, central scotoma in 34, and ring scotoma in ten patients.

Both groups showed a quite similar tendency concerning the presence of color perception problems. In group 1, color perception problems were present in 68 patients and absent in 68, while in group 2 color perception defects were detected in 60 and were absent in 54.

The frequencies of main diagnoses in the study population were analyzed for both groups together. Diagnosis frequency was Usher I and II 34%, Stargardt disease 31%, macular dystrophy 10%, CACD 8%, and Bardet-Biedl syndrome 5%.

Eighty-two patients (out of a total of 134) in group 1 and 89 patients (out of a total of 125) in group 2 were genetically tested in the Genetic Department of the University Eye Hospital Tuebingen. In the first group, 51 patients were genetically verified to have Stargardt disease; ten macular dystrophy, including six patients with Best's disease; and 21 central choroidal dystrophy (CACD). In the second group, six patients were genetically verified to have Bardet-Biedl syndrome; 18 Usher syndrome I; 51 Usher syndroms II, and 14 patients had choroideremia.

Discussion

The results of the current study suggest that monogenic retinal degenerations are more frequent among men than among women. This corresponds to the conclusion formed by Krumpaszky in his study of inherited retinal degenerations in the Baden-Württemberg region in 1999 [10]. This may be due to X-recessive inheritance mechanism of some of the diseases, such as macular dystrophy and choroideremia.

The majority of patients in the study population were first diagnosed by an ophthalmologist with monogenic retinal dystrophy at an age between 11 and 30 years old, which is in line with the results obtained by Tsujikawa et al. in the study of age onset curves of retinitis pigmentosa [17].

A large number of patients in both groups retain good visual acuity equal or better to 20/40, 124 eyes in group 1 and 140 eyes in second group. This result is in line with other studies conducted earlier [5, 12]. Despite this stratification, BCVA for both groups by age showed that

37% of patients in age group 21–40 and 36% in age group 41–60 were registered as legally blind, indicating a strong impact of monogenic retinal degenerations on incidence of blindness principally in a productive age group.

Color perception problems didn't appear to be a very specific symptom in either group, since an equal number of patients in both groups indicated presence and absence of color vision problems. This is surprising, since color vision discrimination problems should be more common in primary diseases affecting central retina than in diseases affecting periphery. This may be a consequence of the "bystander effect", when cones are effected secondarily because of rod degeneration and production of rod-derived cone viability factor (RdCVF) [11].

Usher syndrome I and II (34%), Stargardt disease (31%), and choroideremia (14%) were the most frequent diagnoses in our study. This corresponds to the results of other studies, where Usher syndrome types I and II were found to be the most frequent types of monogenic retinal dystrophies in Germany and in Spain [1, 9, 10].

This study has some limitations. It was designed as a retrospective cross-sectional study, and the data was obtained from a clinical database which wasn't initially designed for research purposes. That limited us to the analysis of the data that were available. Furthermore, the age of symptoms onset estimation was based on the patients' perception, and therefore could be subjective. However, the current study was based on clinical data obtained from the database and included all patients with a diagnosis of interest, whereas the study performed by Krumpatszky derived data from social services and focused only on those patients that were already registered as blind. Our study included a high percentage of patients originating from other countries, which will make it possible to more effectively compare with other non-German studies performed in the future. Furthermore, examinations of the patients from the study population were conducted by the team of four senior resident ophthalmologists, who had homogenous diagnosis criteria, which ensures high data reliability.

Overall, the results of our study showed that these monogenic retinal dystrophies are more frequent among men than among women. We also found that relatively high numbers of patients in both groups retained quite good visual acuity, which shows that early and properly planned rehabilitation strategies could be beneficial in order to increase quality of life for these patients. Moreover, for both groups an age for optimal therapeutic intervention was defined. It is recommended that this should be taken into account while screening for patients to take part in clinical trials for testing new treatment strategies. It was also shown in the study that color perception problems didn't appear to be a very specific symptom in both groups; this may be a consequence of the "bystander effect".

Furthermore, our study showed that the age of disease onset can be estimated on the basis of an epidemiological approach, which is based on epidemiological analysis of age at main symptoms onset, derived from the history of the disease, and main clinical parameters. An epidemiological approach to the estimation of the disease onset could be used by clinicians for detecting the duration of the disease and its prognosis, planning rehabilitation measures, and for researching the future possibilities for treatment. Further long-term follow-up studies of clinical parameters are needed for the establishment of a decision-making algorithm for estimation of disease prognosis and rehabilitation possibilities.

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