Cross-sectional Study of Visual Acuity and Electroretinogram in Two Types of Dominant Drusen

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PURPOSE. To compare the changes with increasing age of ERG parameters in relation to clinical data in two distinct phenotypes of genetically determined, dominantly inherited macular drusen: malattia leventinese (ML) and Zermatt macular dystrophy (ZMD).

METHODS. Ganzfeld rod- and cone-electroretinograms (ERGs) from 15 patients affected with ML and 14 patients with ZMD and clinical data were analyzed retrospectively. The patients' ages ranged from 20 to 77 years in the ML group and from 9 to 74 years in the ZMD group.

RESULTS. Both inherited macular degenerations caused a marked decrease in visual acuity, the latest after age 65. Most patients with ML retained good visual function (0.8–1.0) until the fifth decade, followed by a rapid decrease in the fifth or sixth decade. ZMD is characterized by a relatively continuous decrease in visual acuity with increasing age. Morphologically, in the juvenile stages in both entities, drusen were observed at the posterior pole. Rod-driven and cone-driven ERG b-wave amplitudes decreased nearly linearly in ML and ZMD in accord with the normal loss of amplitude with increasing age. Implicit times of cone b-waves for ML increased markedly with age, whereas in ZMD the values were always prolonged beyond the normal range with a slight increase with age.

CONCLUSIONS. In terms of visual acuity, the progression of both dominantly inherited macular dystrophies is quite different. This is not reflected in the amplitudes of the b-waves in the Ganzfeld ERGs, which decrease normally for both entities. Implicit times of the cone-b waves were more markedly prolonged in ML compared with ZMD. In-depth longitudinal documentation of the natural course of those dominantly inherited macular diseases should facilitate patient counseling. (*Invest Ophthalmol Vis Sci.* 2003;44:493–496) DOI:10.1167/iovs.01-0787

M acular degeneration is a major cause of legal blindness, not only for the elderly. Genetic predisposition for various subtypes of this disease has been postulated, often accompanied by other factors, such as oxidative stress, ultraviolet radiation, and accumulated light exposure. In this article, the natural course of two autosomal dominantly inherited macular drusen phenotypes is assessed. Both have been named after the geographical Swiss region, where the diseases are endemic: malattia leventinese (ML), identical with dominant drusen or Doyne honeycomb retinal dystrophy, and Zermatt macular dystrophy (ZMD). For ML, a single missense mutation at the residue 345 (R345W) of the *EFEMP1* gene, coding for the epidermal growth factor (EGF)-containing fibrillin-like extracellular matrix protein-1 was identified by Stone et al.[1] in 1999 as the disease-causing mutation. For ZMD, Piguet et al.[2] determined a single mutation at codon 172 (R172W) of the RDS/peripherin gene to be responsible for the development of the disease. Previously, R172W has been described as causing macular degeneration in a Japanese family.[3] Clinically, both genetic defects show complete penetrance. The hallmark of both degenerations is the presence of macular drusen already in the second decade of life, and patients in the advanced stages of disease have a significant decrease in visual acuity.[2,4–9] In Ganzfeld ERG recordings, decrease in b-wave amplitudes have also been described in both diseases.[2,6,8] The retinal pigment epithelium appears to be affected as well, thus leading to subtle alterations in the EOG.[10] The purpose of this study was to investigate whether the cross-sectionally examined changes with age of retinal function in either disease are similar. This work has been presented in abstract form.[11]

PATIENTS AND METHODS

We retrospectively examined and compared data from 15 patients with ML and 14 patients affected by ZMD. All patients gave informed consent for the clinical and genetic examinations, and the study was conducted in accordance with the tenets of the World Medical Association's Declaration of Helsinki. In all patients, the respective genetic mutation was tested and confirmed (Laboratory of Molecular Genetics, University Hospital, Lausanne, Switzerland).[1,2] The patients' ages at time of examination ranged from 20 to 74 years in the ML group and from 9 to 77 years in the ZMD group. No systemic diseases affecting the eye were present in any patient. All patients' data are summarized in Table 1.

Particularly, we studied cross-sectionally the changes with age in ML and ZMD of visual acuity; extent of macular dystrophy signs, such as drusen or alterations in pigment epithelium; and Ganzfeld ERGs. The Ganzfeld ERGs were recorded according to the methods referred to in previous publications,[12–14] using Henke low-vacuum contact lens electrodes throughout. These methods were largely in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.[15,16] To facilitate comparison of the data, we set the mean normative values for each of the three methods to 100% and calculated the individual percentage change in the patients' data. After 20 minutes, at least, of dark adaptation, a red, a blue, and a bright white flash were used as stimuli, and the amplitude of the rod-driven b-wave and the maximum mixed rod–cone b-wave responses were measured. A photopic ERG was performed in the presence of a rod-desensitizing white background light, including a single orange, a blue-green, or a single white flash, as well as a 30-Hz white flicker stimulation, and the amplitudes of the b-waves were measured. Implicit times were measured for the single-flash responses of the cone system. In the results section, for brevity, only the rod-driven response to the red flash in dark adaptation and the cone-driven response to the blue-green or white flash in light adaptation are considered.

TABLE 1. Patients with Malattia Leventinese and Zermatt Maculopathy

| Patient | Age | Visual Acuity | | Electroretinogram | | | | Genetic Status |
| | | | | Dark-Adapted Red Flash | | Light-Adapted Blue-green or White Flash | | |
		OD	OS	OD	OS	OD	OS	ML: EFEMP1 ZMD: R172W
ML								
m1	20	1.25	1.25	270	270	130	120	M/W
m2	25	na	na	180	160	120	110	M/W
m3	26	1.00	1.00	125	130	160	175	M/W
m4	32	na	na	180	180	140	130	M/W
m5	33	na	na	270	275	120	120	M/W
m6	34	1.25	1.25	235	240	85	115	M/W
m7	40	na	na	210	210	120	130	M/W
m8	48	1.25	0.70	150*	120*	120*	140*	M/W
m9	54	0.10	0.80	220	270	90	110	M/W
m10	65	0.20	0.01	120*	130	40*	50*	M/W
m11	69	0.10	0.18	70*	60*	50*	55*	M/W
m12	69	0.20	0.16	165	170	80*	40*	M/W
m13	70	0.30	na	70*	45*	120	70*	M/M†
m14	74	0.10	0.10	100*	90*	90*	80*	M/W
m15	77	na	na	30*	30*	60*	50*	M/W
ZMD								
z1	9	1.00	1.00	na	250	300	270	M/W
z2	21	1.00	1.00	300	270	220	180	M/W
z3	24	1.25	1.00	150*	160*	145*	160*	M/W
z4	30	1.00	0.70	160*	212	195	160*	M/W
z5	31	1.00	1.25	160*	150*	160*	160*	M/W
z6	31	1.50	1.50	210	100*	140*	145*	M/W
z7	32	1.00	1.00	140*	225	212	215	M/W
z8	36	1.25	0.90	205	203*	224	220	M/W
z9	38	0.90	0.80	260	260	160*	180	M/W
z10	39	0.20	0.50	250	250	150*	130*	M/W
z11	48	0.30	0.30	280	180*	170	180	M/W
z12	56	0.02	0.02	150*	116*	118*	118*	M/W
z13	71	0.07	0.10	130*	140*	115*	105*	M/W
z14	74	0.02	0.05	100*	70*	70*	60*	M/W

Data are absolute values. ERG in microvolts. M, mutation of the respective allele; W, wild type of the respective allele.

* Pathologic reading (i.e. below mean ± 2SD) for the respective ERG method used. As three different methods have been used, pathologic readings differ sometimes significantly from one method to another.

† Homozygous patient, only OD measured, OS was lost to panophthalmia after surgery.

RESULTS

All patients, their visual acuity data, the ERG data, and their genetic status are presented in Table 1. All except 1 patient (m13), who had a homozygous mutation for ML, had a heterozygous mutation for either ZMD and ML, the second gene being of the normal wild type. The change in visual acuity with age in ML and ZMD of the patients studied is plotted in Figure 1.

Apparently, in the ML group the visual acuity remained stable (>0.8) until approximately the fifth decade of life, then it declined rapidly to 0.2 or lower. In some patients, it was observed that visual acuity decreased markedly within only a few weeks (Sergio Forni, personal communication). In contrast, the ZMD group was characterized by an earlier and more rapid decrease of visual function over time, starting at the third or fourth decade of life.

Figure 2 shows the rod-driven (Fig. 2A) and cone-driven (Fig. 2B) ERG b-wave amplitudes. The rod-driven b-wave amplitudes showed a large scattering and an overall decrease with age. The cone-driven b-wave showed a less variable decrease in amplitude with age. The decrease was approximately the same as it would be by age effect alone.[17]

As shown in Figure 3, the implicit times in patients with ML increased from normal to clearly pathologic levels with age, whereas in patients with ZMD, the values were always
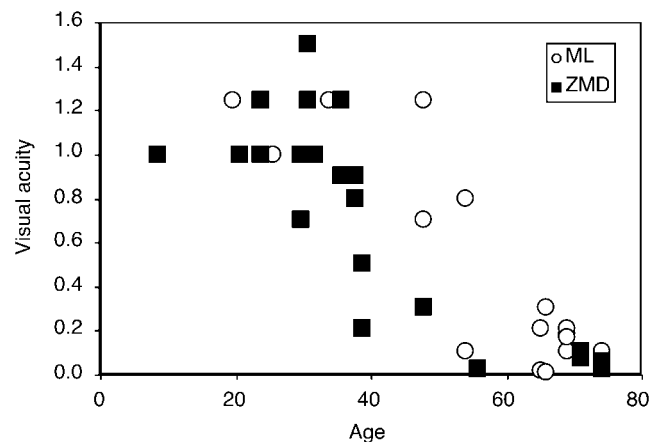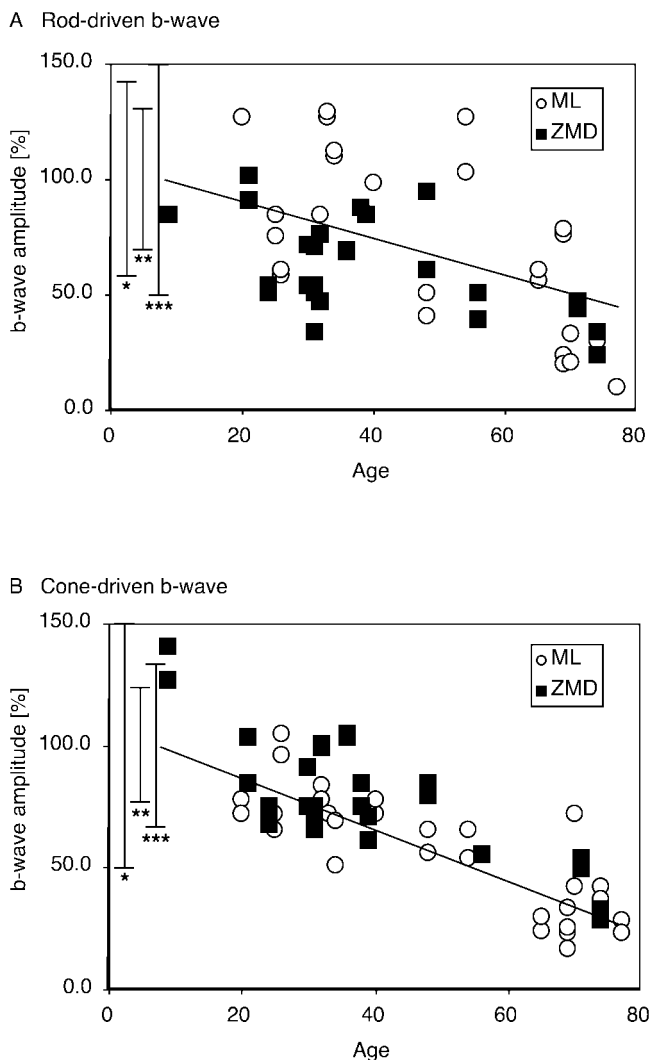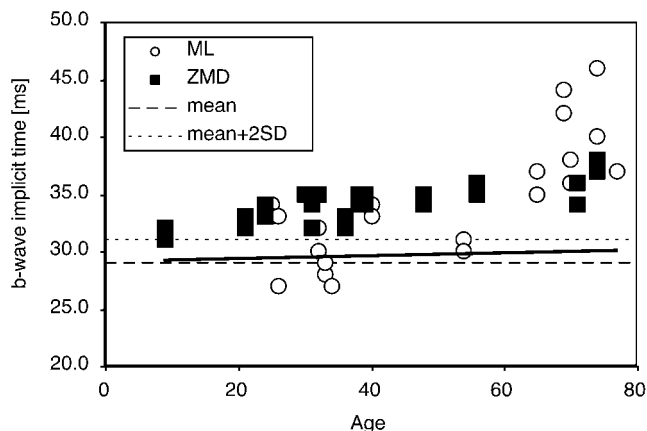

FIGURE 1.   Cross-sectional changes with age of visual acuity in persons with ML and ZMD.

A   Rod-driven b-wave

B   Cone-driven b-wave

FIGURE 2. Cross-sectional changes with age of normalized ERG b-wave amplitudes in the dark- and light-adapted states. (**A**) Rod-driven ERG b-wave amplitude elicited by a red flash. (**B**) Cone-driven ERG response to a single blue-green or white flash on a rod-desensitizing white background. Methods used: *Hatt et al.[12], **Knobel and Niemeyer,[13] and ***Steiner[14]. Data are the mean ± 2SD results of the three methods used. *Sloping line*: decrease of normal ERG amplitudes according to Weleber.[17] Our own age-related data showed a similar decrease in amplitude with age (data not shown).

higher than normal for ZMD with only a slight increase with age.

Clinically, ML was characterized by a typical, occasionally radial, pattern of drusen at the posterior pole extending frequently to regions nasal of the optic disc (Fig. 4). Macular and peripapillary drusen usually coexisted in the same patient, but peripapillary drusen was occasionally the only sign. Fluorescein angiography showed the radial distribution of drusen at the posterior pole, an observation made more frequently in the United States. (E. Stone, personal communication, May 2001). Subretinal choroidal neovascularization may occur.[18] One of our patients (m13 in Table 1) had homozygous mutations, but the parameters examined in her did not differ from those in patients with heterozygous genetic alteration. ZMD, in contrast, showed expanding dissemination of hard drusen and expanding atrophy of the retinal pigment epithelium at the posterior pole, but less on the nasal retina (Fig. 4). The most impressive difference between ML and ZMD was seen clinically


FIGURE 3. Cross-sectional changes with age of cone-driven b-wave implicit times in the light adapted state. *Thick line*: increase in normal ERG implicit times according to Weleber.[17] These normal data are in good correlation with the current results (data not shown).

in the intermediate stage of both diseases with more advanced visual loss in ZMD than in ML at 35 to 45 years of age. In late stages, both diseases showed comparable large atrophic degenerations at the entire posterior pole. Affected children usually showed minimal or no changes in the central fundus.

DISCUSSION

ERG amplitudes of ML and ZMD patients appeared to have largely the same pattern of decrease with increasing age, whereas the changes in visual acuity with increasing age is different for both diseases. The change in visual acuity nearly parallels the morphologic changes at the posterior pole. The changes in the implicit times of the cone-driven b-waves also show a different age-related course for both diseases. Compared with our own age-related data and the data found in the literature,[17,19] the amplitude decrease of both rod- and cone-ERG for ML and ZMD is not different from the age-related decrease alone. However, the increase of implicit times with age seems to be more important than it would be by age alone. These findings are similar to measurements of ERGs in early stages of degenerative diseases (e.g., retinitis pigmentosa), when amplitudes of cone b-waves are still normal and only prolonged implicit times indicate a pathologic process.[20] In addition, the functional deficit seen in the ERG may diverge from perimetric results, which is not uncommon in retinitis pigmentosa.[21]

On a cellular and molecular level, it is well possible that gene defects affect both cone and rod photoreceptors, al-
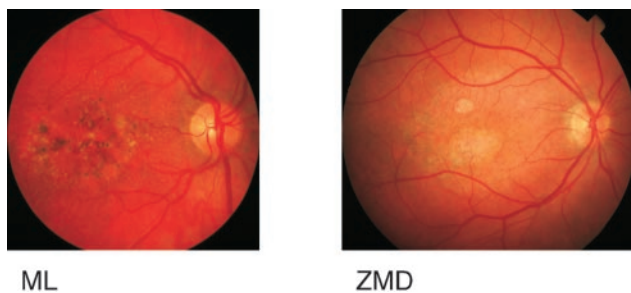
FIGURE 4. Examples of fundus photographs of ML (*left*) and ZMD (*right*) in intermediate stages of the disease. ML is characterized by drusen disseminated over the entire posterior pole. ZMD shows drusen as well as atrophy of the retinal pigment epithelium.

though one system may be more affected than the other. In both diseases the cone defect tends to become clinically more apparent as a significant decrease of visual acuity down to legal blindness, accompanied by the increasing spread of macular drusen and enlarging atrophy. In some cases of ML, visual acuity has been described to be normal (better than 0.8) after the eighth decade, despite the well-defined ML mutation (F. Munier, personal communication, February 2001). However, in the present study we found no patient with this particular phenotype. Changes in the visual fields have been described,[2,7] revealing central visual field defects without marked changes in the peripheral visual field. In our study population, the changes in the visual field were similar, although not all patients underwent detailed visual field examinations.

Distinguishing between ML and ZMD thus appears to be difficult when the ERG is used alone. Thorough clinical examination is needed to establish the differential diagnosis of macular dystrophies, followed by complementary examinations as visual field measurements and ERG testing. The family history can raise the suspicion of an inherited disorder. Differential diagnosis includes Stargardt disease, Stargardt-like dominant macular dystrophy, Best vitelliform macular dystrophy, pattern dystrophies, Sorsby macular dystrophy, and North Carolina macular dystrophy. Because it is possible to determine the genetic locus of ML and ZMD, identification of the suspected mutations should complement the clinical diagnosis. This would allow the ophthalmologist to counsel the patients with regard to the expected course of the disease as well as for occupational and family planning.

Acknowledgments

References

1. Stone EM, Lotery AJ, Munier FL, et al. A single EFEMP1 mutation associated with both malattia leventinese and Doyne honeycomb retinal dystrophy. *Nat Genet.* 1999;22:199–202.
2. Piguet B, Heon E, Munier FL, et al. Full characterization of the maculopathy associated with an Arg-172-Trp mutation in the RDS/peripherin gene. *Ophthalmic Genet.* 1996;17:175–186.
3. Nakazawa M, Wada Y, Tamai M. Macular dystrophy associated with monogenic Arg172Trp mutation of the peripherin/RDS gene in a Japanese family. *Retina.* 1995;15:518–523.
4. Klainguti R. Die tapeto-retinale Degeneration im Kanton Tessin. *Klin Monatsbl Augenheilkd.* 1932;89:253–254.
5. Forni S, Babel J. Etude clinique et histologique de la malattia leventinese. *Ophthalmologica.* 1962;143:313–322.
6. Niemeyer G. Rod- and cone-function in malattia leventinese and in retinitis pigmentosa. *Doc Ophthalmol Proc Ser.* 1978;17:337–343.
7. Scarpatetti A, Forni S, Niemeyer G. Die Netzhautfunktion bei Malattia leventinese (dominant drusen). *Klin Monatsbl Augenheilkd.* 1978;172:590–597.
8. Niemeyer G, Demant E. Cone and rod ERGs in degenerations of central retina. *Graefes Arch Clin Exp Ophthalmol.* 1983;220:201–208.
9. Heon E, Piguet B, Munier F, et al. Linkage of autosomal dominant radial drusen (malattia leventinese) to chromosome 2p16-21. *Arch Ophthalmol.* 1996;114:193–198.
10. Hess F, Niemeyer G. EOG changes in dominantly inherited Drusen (malattia leventinese). *Doc Ophthalmol Proc Series.* 1983;37:105–113.
11. Gerber DM, Munier FL, Piguet B, Niemeyer G. Divergent time course of acuity- and ERG-decrease in dominant drusen compared with Zermatt macular dystrophy [ARVO Abstract]. *Invest Ophthalmol Vis Sci.* 2001;42(4):S449. Abstract nr 2422.
12. Hatt M, Niemeyer G. Elektroretinographie bei Morbus Behcet. *Albrecht Von Graefes Arch Klin Exp Ophthalmol.* 1976;198:113–120.
13. Knobel U, Niemeyer G. Increase in the amplitude of the b-wave of the cone electroretinogram during light adaptation. *Klin Monatsbl Augenheilkd.* 1994;204:430–434.
14. Steiner B. Elektroretinogramm-Normwerte gesunder Probanden am "Universal Testing and Analysis System Electrophysiologic 3000"-Ganzfeldgerät. Faculty of Medicine. 1998, University of Zürich, Zürich, Switzerland. Thesis.
15. Marmor MF. An international standard for electroretinography. *Doc Ophthalmol.* 1989;73:299–302.
16. Marmor MF, Zrenner E. Standard for clinical electroretinography (1994 update). *Doc Ophthalmol.* 1995;89:199–210.
17. Weleber RG. The effect of age on human cone and rod ganzfeld electroretinograms. *Invest Ophthalmol Vis Sci.* 1981;20:392–399.
18. Zech JC, Zaouche S, Mourier F, et al. Macular dystrophy of malattia leventinese: a 25 year follow up. *Br J Ophthalmol.* 1999;83:1195–1196.
19. Birch DG, Anderson JL. Standardized full-field electroretinography: normal values and their variation with age. *Arch Ophthalmol.* 1992;110:1571–1576.
20. Berson EL, Gouras P, Hoff M. Temporal aspects of the electroretinogram. *Arch Ophthalmol.* 1969;81:207–214.
21. Niemeyer G, Schaefer A. Sehstörung bei unauffälligem Fundus und pathologisch verändertem Elektroretinogramm: Differentialdiagnosen. *Klin Monatsbl Augenheilkd.* 2002;219:259–263.