

# Symptomatic abnormalities of dark adaptation in patients with EFEMP1 retinal dystrophy (Malattia Leventinese/Doyme honeycomb retinal dystrophy)

R Haimovici<sup>1,2,3</sup>, J Wroblewski<sup>2</sup>, B Piguet<sup>2,4</sup>, FW Fitzke<sup>1</sup>, GE Holder<sup>1,2</sup>, GB Arden<sup>1,2</sup> and AC Bird<sup>1,2</sup>

## Abstract

**Purpose** To investigate the nature of symptomatic visual disturbance in patients with EFEMP1 retinal dystrophy in the absence of geographic atrophy or choroidal neovascularization.

**Methods** Patients presenting to a tertiary referral centre underwent clinical evaluation, fluorescein angiography, colour contrast sensitivity, focal, pattern, and standard electroretinography, electrooculography, scotopic threshold perimetry and dark adaptometry.

**Results** Clinical features included reduced central vision, difficulty passing from light to dark, and diffuse submacular and peripapillary deposits, which were hyperfluorescent by fluorescein angiography. Colour contrast thresholds were abnormal in all six patients studied and both pattern and focal electroretinograms were abnormal in five of six patients. The scotopic and mixed rod-cone single flash ERG was normal but two patients demonstrated reduced oscillatory potentials and one had borderline delayed 30 Hz responses. Scotopic thresholds were elevated and rod-mediated dark adaptation kinetics were markedly prolonged in all six patients when measured over the central visible confluent deposits.

**Conclusions** In patients with EFEMP1 retinal dystrophy with confluent macular deposits, scotopic sensitivity is reduced and dark adaptation kinetics are prolonged over the macular deposits but are normal elsewhere. These results emphasize the localised nature of functional deficits in

some patients with EFEMP1 retinal dystrophy and correlate well with the patient's visual symptoms. Symptomatic visual dysfunction may precede the development of clinically evident geographic atrophy or choroidal neovascularization in this disorder.

*Eye* (2002) 16, 7–15. DOI: 10.1038/sj/EYE/6700018

**Keywords:** retinal drusen; macular degeneration; EFEMP1 protein; dark adaptation; electroretinography; color vision defects

Historically, two well defined phenotypes have been described in which there is dominant inheritance of drusen, Malattia Leventinese (ML) and Doyme honeycomb retinal dystrophy (DHRD). Malattia Leventinese was described initially in inhabitants or descendants of the Leventine valley of Tessin Canton in Southern Switzerland.<sup>1–5</sup> It is described as having drusen-like deposits in the macula and around the optic nerve which are usually apparent by the age of 20 years.<sup>6,7</sup> Initially asymptomatic, these patients later develop more numerous and larger drusen which eventually coalesce to form a solid plaque at the level of Bruch's membrane. In rare cases only the peripapillary deposits develop.<sup>4</sup> The earliest visual symptoms include dyschromatopsia, metamorphopsia or relative scotomas and occur at age 30–40 years.<sup>5,7</sup> Central visual acuity usually deteriorates at about age

<sup>1</sup>Institute of Ophthalmology London, UK

<sup>2</sup>Moorfields Eye Hospital London, UK

<sup>3</sup>Department of Ophthalmology Boston University School of Medicine Boston, USA

<sup>4</sup>Hôpital Ophtalmique Jules Gonin Lausanne, Switzerland

Correspondence: R Haimovici Gundersen Eye Center DOB-10, 720 Harrison Ave Boston, MA 02118, USA Tel: 617 638 8393 Fax: 617 638 8342 E-mail: Robert.Haimovici@bmc.org

40–50<sup>4,5</sup> but may begin as early as age 30<sup>8</sup> or be delayed until age 60–70.<sup>4</sup> In the later stages of the disorder, patients develop loss of central vision and absolute scotomas, which are associated with the development of extensive pigmentary changes and geographic atrophy or choroidal neovascularisation in the region of the confluent macular drusen.

Doyme honeycomb retinal dystrophy was described initially in inhabitants of England.<sup>9,10</sup> The phenotype of DHRD<sup>10–13</sup> is similar to that of ML which led most investigators to consider that they represent the same disorder.<sup>6,8,14,15</sup> A characteristic fundus finding in ML is the presence of small radially orientated drusen<sup>4–6,16,17</sup> which are not identified in published photographs of Doyme's original families,<sup>11,12</sup> or from early written accounts of the family.<sup>18–20</sup> Subsequent descriptions show that they may occur in a small number of members of the Doyme family, but are not prominent.<sup>21</sup> Despite these discrepancies, genes from ML and DHRD families colocalise<sup>22,23</sup> and a single EFEMP1 (EGF containing fibrillin-like extracellular matrix protein 1) mutation is associated with both disorders.<sup>24</sup> We wish to report six patients with EFEMP1 retinal dystrophy (ML/DHRD) who presented with subjective visual loss in association with diffuse peripapillary and macular drusen and associated radially-orientated peripheral drusen. In these patients, visual symptoms could not be explained by the development of geographic atrophy or choroidal neovascularisation, known end-stage sequela of the disorder. To more fully characterize the nature of this visual dysfunction, fluorescein angiography, and extensive electrophysiological and psychophysical testing was performed.

### Patients and methods

Six patients were selected for study who had sub-retinal pigment epithelial deposits at the fovea. The criteria for diagnosis were visually symptomatic, early onset (prior to 40 years of age), symmetrical confluent plaque-like deposits at the level of Bruch's membrane, localised to the posterior pole but also surrounding the optic nerve, and small radially-orientated drusen at the periphery of this confluent plaque, visible either by fundus examination or fluorescein angiography. Five patients had a positive family history of visual loss with dominant inheritance on the basis of involvement of at least three generations and evidence of male-to-male transmission. One patient (patient 4) was adopted. Four patients were subsequently found to be members of the DHRD pedigree and one patient had a grandfather from the Levantine valley of Switzerland. Siblings and parents were examined when available.

None of the patients studied are the subject of previous reports.<sup>21</sup> Subsequent to the investigations described in this report, these patients were found to show the EFEMP1 mutation associated with both ML and DHRD.<sup>24</sup> All patients underwent a complete ophthalmologic evaluation, fundus photography, and fluorescein angiography. There was no history of systemic disease such as vitamin A or zinc deficiency, hepatic or biliary cirrhosis, chronic bowel disease, protein-energy malnutrition, or sickle cell anaemia that are known to cause abnormal dark adaptation.<sup>25–28</sup> All patients consented to additional investigations of visual function which occurred on two separate days. The eye with the better visual acuity was chosen for psychophysical testing. Colour contrast sensitivity was performed with a colour television monitor using a previously described system.<sup>29</sup>

Electroretinography (ERG) was performed in both eyes using a gold foil electrode and standard testing protocols.<sup>30,31</sup> The pattern ERG was recorded in one eye using a previously described protocol.<sup>32,33</sup> All ERG testing conformed to International Society for Electrophysiology of Vision (ISCEV) standards.<sup>34,35</sup> Focal ERGs were obtained with a Maculoscope (Diagnosys LLC, Littleton, MA, USA).<sup>36</sup> Electrooculography (EOG) was also performed.<sup>37</sup>

For measurements of scotopic threshold and dark adaptation kinetics, the pupil was dilated with 2.5% phenylephrine, and 1% cyclopentolate and patients were placed in a darkened room for 45 min. Scotopic threshold perimetry was performed with a modified Humphrey Field Analyser (HFA; Humphrey Instruments, San Leandro, CA, USA) to determine the magnitude and pattern of sensitivity loss.<sup>38,39</sup> The stimulus wavelength was 450 nm, 0.5 s duration, and Goldmann size V (102 min of arc). Measurements of dark adaptation kinetics were performed at two locations, one in which a threshold elevation had been demonstrated and another with normal final thresholds. Dark adaptation kinetics were measured on a modified HFA after a 2-min period of light adaptation (equivalent to viewing 6200 cd/m<sup>2</sup> through a 6 mm pupil), sufficient to bleach more than 95% of available rhodopsin using lamps installed in the HFA. The testing strategy used a method of ascending limits and was controlled by an external computer. The rod-cone break was determined by visual inspection. Datum points after this point were used to determine the time constant of rod adaptation using curve fitting software and an equation of the form  $\log(I) = A + B(e)^{-(t/c)}$ .<sup>40</sup> When possible, the cone time constant was derived in a similar fashion using datum points prior to the rod-cone break. Return to pre-bleach sensitivity was defined as the point at which the average of the

last five measurements came within 0.5 log units of the average of the pre-bleach measurements. Data from 30–50 year-old normal volunteers served as a comparison group.

## Results

### Clinical features

The study group consisted of six women ranging from 31 to 54 years of age (Table 1). All gave a history of slow onset of visual symptoms that usually began 5 or more years prior to presentation. Patients had a variety of visual complaints which included difficulty adjusting from a brightly to a dimly lit environment (patients 2,3,4, and 6), decreased night vision (patients 3 and 5), decreased vision in bright light (patient 2), or loss of visual acuity (patients 1 and 5).

The visual acuity ranged from 6/6 to 6/36 but all patients had one eye with visual acuity of at least 6/12 or better. Ophthalmoscopically, a roughly oval area of solid plaque-like deposition of yellow material at the level of Bruch's membrane was present in the macula, the margin of which also encompassed the optic nerve

(Figures 1a and 2a). There was no serous elevation of the overlying retina except in one patient who developed angiographically well-defined choroidal neovascularisation in one eye (patient 5; the fellow eye underwent the electrophysiologic and psychophysical testing). On fluorescein angiography the confluent plaque was mostly hyperfluorescent. Away from the centre, this plaque became less confluent and distinct soft drusen could be identified. At the periphery of this lesion there were small slender drusen, which appeared to radiate from the centre of the macula. These small drusen were sometimes difficult to appreciate clinically but were always brightly fluorescent and more clearly delineated in the early phases of the fluorescein angiogram. There were scattered areas of dense pigment on the surface of the plaque that were hypofluorescent on fluorescein angiography. The retinal vessels, peripheral fundus, and optic nerve were normal.

### Electrophysiology

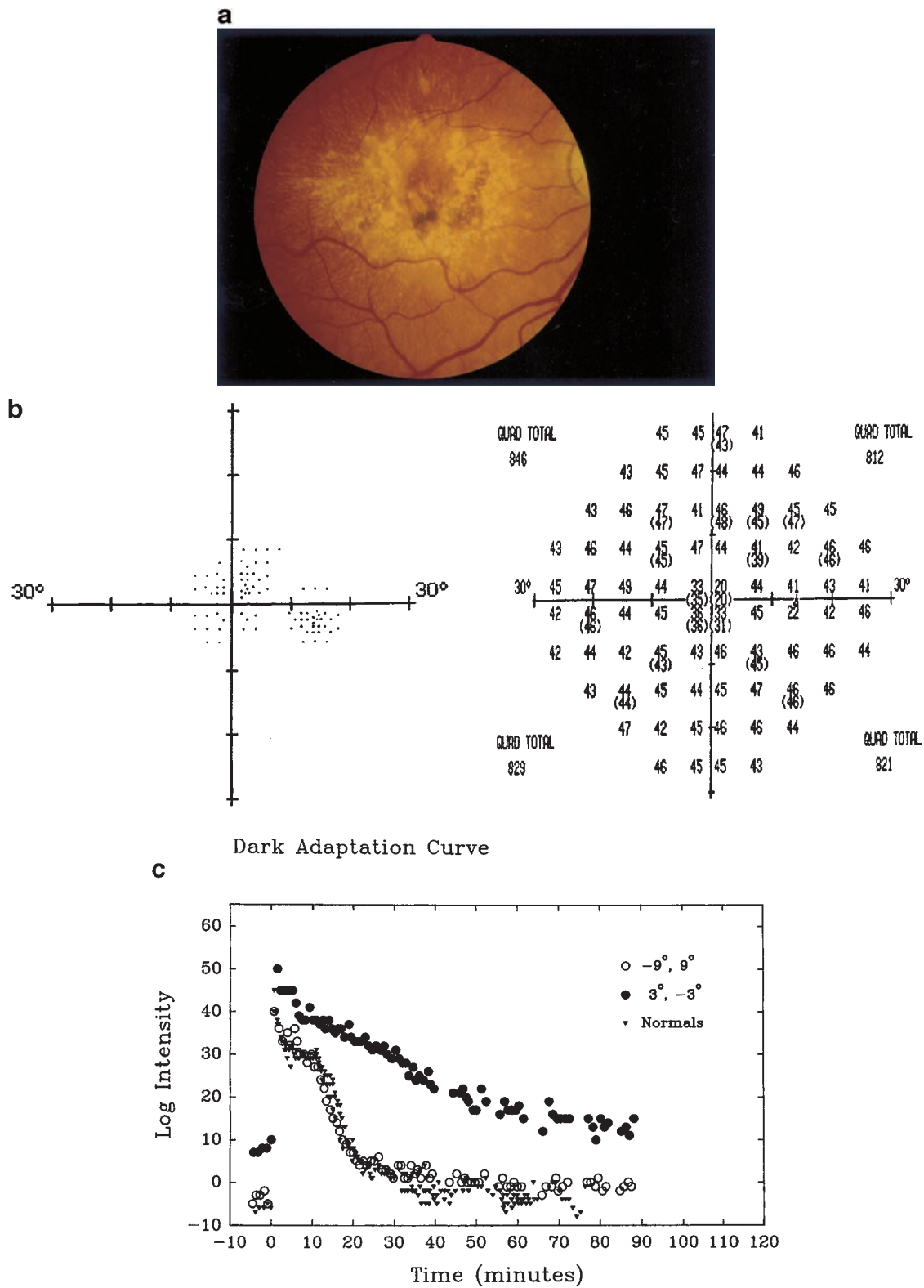
The scotopic rod and mixed rod-cone ERG was within normal limits for all six patients (Table 2). The 30 Hz

**Table 1** Clinical and fluorescein angiographic characteristics of patients with EFEMP1 retinal dystrophy (Malattia Leventinese/Doyme honeycomb retinal dystrophy)

Patient No./ Age/Sex	VA RE/LE	Symptoms	Fundus findings	Fluorescein angiogram	Inheritance
1/54/F	6/12+ 6/9–2	decreased vision	extensive confluent drusen (disc and macula); radial drusen, mild RPE changes	Drusen: hyperfluorescent RPE changes: hypofluorescent	AD
2/51/F	6/18+ 6/12	decreased vision in bright light delayed light to dark recovery	extensive confluent drusen (disc and macula); radial drusen, mild RPE changes	Drusen: hyperfluorescent RPE changes: hypofluorescent	AD
3/31/F	6/9–2 6/18	decreased night vision delayed light to dark recovery	extensive subconfluent drusen (macula only); radial drusen, mild RPE changes	Drusen: hyperfluorescent RPE changes: hypofluorescent	AD
4/50/F	6/9 6/6	dyschromatopsia delayed light to dark recovery	extensive confluent drusen (disc and macula); radial drusen, mild RPE changes	Drusen: hyperfluorescent RPE changes: hypofluorescent	adopted
5/47/F	6/12 6/36	decreased vision decreased night vision	extensive confluent drusen (disc and macula); radial drusen LE: serous macular detachment	Drusen: hyperfluorescent RPE changes: hypofluorescent LE: CNVM	AD
6/42/F	6/6 6/12	delayed light to dark recovery	extensive confluent drusen (disc and macula); radial drusen marked RPE changes	Drusen: hyperfluorescent RPE changes: hypofluorescent	AD

VA, Visual acuity.  
AD, Autosomal dominant.  
RE, right eye; LE, left eye.  
RPE, retinal pigment epithelium.  
CNVM, choroidal neovascular membrane.





**Figure 2** Case 6. (a) There are diffuse confluent Bruch's membrane deposits in the macula and around the optic nerve. Small radially orientated drusen are visible. (b) Modified Humphrey perimetry shows central scotopic threshold elevations of 1-2 log units over the confluent deposits. (c) Dark adaptation kinetics when compared with normal subjects (triangles) are abnormally prolonged over the confluent deposit (filled-in circles) with return to within 0.5 log unit of pre-bleach sensitivity at 80 min but are normal peripheral to this deposit (open circles).

**Table 2** Summary of electrophysiological findings in patients with EFEMP1 retinal dystrophy (Malattia Leventinese/Doyme honey-combe retinal dystrophy)

Patient No./ eye tested	Pattern ERG	Focal ERG	Electroretinogram (ERG)		30 Hz	Oscillatory potentials (OPs)	Electrooculogram
			Scotopic rod	Mixed rod/cone			
1/LE	moderate to severe reduction	could not be determined	normal	normal	normal	normal	normal
2/LE	moderate to severe reduction	mild reduction	normal	normal	borderline delayed timing	late OPs absent	normal
3/RE	normal	normal	normal	normal	normal	normal	borderline low light/dark ratio
4/LE	moderate reduction	mild reduction	normal	normal	normal	reduced amplitude	normal
5/RE	mild reduction	mild reduction	normal	normal	normal	normal	normal
6/RE	mild reduction	mild reduction	normal	normal	normal	normal	normal

flicker ERG was normal in five patients but the timing was borderline delayed but with normal amplitude in one patient (case 2). In the other five patients both the amplitude and timing were normal. The oscillatory potentials were abnormal in two patients. In one patient (case 2), the late oscillatory potentials were absent. In another patient, all oscillatory potentials were present but the amplitudes were reduced (case 4). The pattern ERG was normal in one patient, mildly depressed in two patients, moderately depressed in one patient and moderate to severely depressed in two patients. In these patients, the P50 and N95 waveforms were reduced but the P50 latency was not affected. The focal ERG was normal in one patient, mildly reduced in four patients, and technically unsatisfactory in one patient. The EOG light-peak to dark-trough (Arden Index) was borderline reduced in one patient (case 3).

#### Psychophysical tests

Colour contrast sensitivity gave elevated thresholds in protan, deuteran and tritan axes and ranged from mild (patients 3, 5 and 6) to severe (patients 1, 2 and 4) (Table 3). The results of scotopic perimetry and dark adaptation kinetics are summarised in Table 3. A 0.5–3 log-unit elevation of the scotopic threshold was detected at retinal eccentricities corresponding to the confluent deposit (Figure 1b and 2b). Peripheral to this, the scotopic threshold was normal. The kinetics of recovery of sensitivity following light adaptation showed severe delays in both the rods and cones in the three patients who were measured at the more central (3°, 3°) location corresponding to the confluent deposits (Figures 1c and 2c). Three patients could not

undergo testing of dark adaptation kinetics at the central (3°, 3°) location because of markedly elevated thresholds. At the more peripheral locations away from the confluent deposit the kinetics of cone and rod sensitivity were normal or nearly normal in all six patients.

#### Discussion

All patients we report demonstrated the combination of small radially orientated drusen at the level of Bruch's membrane and more confluent deposits centrally. The confluent central deposits appear to occur as a secondary phenomenon, due possibly to the failure of material discharged from the retinal pigment epithelium to pass freely to the choroid through an abnormal Bruch's membrane. This pattern is consistently visible in some reported dominant drusen families<sup>4–7,15,22–24</sup> but is not present in others.<sup>11,12,15,41–49</sup> This phenotype has now been demonstrated in both ML and DHRD and is associated with the EFEMP1 mutation. There are superficial similarities between these small radial drusen and multiple small drusen of uniform size for which the term basal laminar or cuticular drusen has been used.<sup>50,51</sup> In these disorders, the drusen are of similar size, are brightly fluorescent and often more numerous by fluorescein angiography,<sup>16,51</sup> and may be associated with large confluent deposits in the macula but with preservation of relatively good visual acuity.

However, there are minor differences in appearance, which imply that these do not represent a single entity. The small drusen seen in our patients are thin, uniform in size, and radially aligned to the fovea whereas so

**Table 3** Results of psychophysical tests of vision in patients with EFEMP1 retinal dystrophy (Malattia Leventinese/Doyme honeycomb retinal dystrophy)

Patient No./ eye tested	Colour contrast threshold			Confluent deposit at test location chosen for dark adaptation kinetics	Scotopic threshold elevation (log units)	Rod-cone break (min)	Rod time constant Goldman size stimulus (III/V)	Time to final threshold (min)
	Protan (%)	Deuteran (%)	Tritan (%)					
1/LE	>100	>100	>100	yes	0.5–2.9	indeterminate	15.2/9.0	77 (still elevated 15 dB above threshold)
				no	none	11	8.6/5.3	
2/LE	>100	>100	>100	yes	0.5–3.0	indeterminate	45.6/27.6	52
				no	none	13	8.3/7.4	31
3/RE	21	20	39	yes	0.7–1.8	14	16.2/15.8	71
				no	none	11	8.8/8.7	28
4/LE	88	>100	>100	yes	0.5–1.4	12	indeterminate/5.9	46
				no	none	12	6.4/6.9	29
5/RE	25	25	23	yes	1.1–1.8	indeterminate	172/167	109
				no	none	13	11.3/10.4	39
6/RE	17	20	30	yes	0.9–2.5	indeterminate	38.5/32.3	80
				no	none	10	7.7/7.2	30
Normals	<7	<7	<7			10–12	<12	30–45

called basal laminar drusen are more likely to be round, are more variable in size, and are not aligned with the fovea. That these small drusen may differ is confirmed by histopathological studies. In some conditions, such as basal laminar drusen and type II mesangiocapillary glomerulonephritis,<sup>52</sup> the drusen are reported to be due to focal thickening of the basement membrane of the retinal pigment epithelium in which case the term basal laminar or cuticular drusen is appropriate. However in others with radial drusen,<sup>4,53,54</sup> including patients with ML,<sup>4</sup> the focal deposits are between the basement membrane of the retinal pigment epithelium and the inner collagenous layer of Bruch's membrane and are indistinguishable from typical hereditary or age-related hard drusen.<sup>49,55–57</sup> Genetic testing of patients with cuticular or basal laminar drusen for the EFEMP1 mutation should help to determine the relationship between this disorder and ML/DHRD.

There are conflicting reports regarding the functional attributes of various dominantly-inherited drusen syndromes with respect to the ERG and EOG,<sup>4–6,8,15,41,46,47,56,58–63</sup> colour vision,<sup>4,8,11,44,58,64</sup> and dark adaptation.<sup>4,6,8,41,44,46,58,63,65</sup> This disparity in findings may be related to several factors that include the definition of inherited *vs* age-related drusen,<sup>61,62</sup> the sensitivity of the tests employed, the stage of the disease, or whether they represent the same or different disorders. Electrophysiological tests performed in this study revealed a variety of modest

ERG abnormalities in some patients, which included reduced oscillatory potentials, a marginally delayed 30 Hz response cone b-wave. The pattern and focal ERGs were variably reduced in most patients. The EOG light-peak to dark-trough (Arden Index) was borderline reduced in one patient. Although only one patient complained of colour vision disturbance, colour contrast sensitivity testing revealed moderate to severe abnormalities of colour discrimination in all our patients. Psychophysical testing revealed relative central and paracentral threshold elevations<sup>58</sup> under both scotopic and mesopic conditions. The striking finding of this study was the very markedly prolonged dark adaptation kinetics when measurements were performed in a central location over the confluent deposit and the normal dark adaptation kinetics when measurements were performed peripheral to this deposit. The prolonged time required for these patients to return to their final or pre-bleach visual threshold provides objective evidence for the subjective complaint of difficulty passing from bright to dim environments. Our results highlight the importance of measuring the kinetics of dark adaptation at locations corresponding to the region of the retina primarily affected by the disease.

Both DHRD and ML are represented within our patient group, and as might be expected given their common genetic basis, electrophysiologic testing does not reveal any functional difference between the two nosological entities. The deficits correspond to the

physical location and density of the deposits, and do not appear to be intrinsic to the primary disorder, in that function outside the deposits appears to be normal. The marked functional deficits in patients with DHRD and ML reported in this study represent the more severe end of the spectrum for this disorder.<sup>21</sup> This is likely to be due to the presence of the confluent macular deposits in the subgroup studied. The basis of diminished retinal function over areas of confluent deposits are compatible with one or more of the following explanations: decreased outer retinal photopigment content,<sup>66</sup> photoreceptor misalignment,<sup>4,6,49,55</sup> retinal pigment epithelial dysfunction,<sup>56</sup> and delayed metabolic exchange across a thickened Bruch's membrane.<sup>67–69</sup> The mutated protein EFEMP1 identified in ML and DHRD, is homologous to fibulins, which are extracellular matrix glycoproteins that bind to elastic fibers<sup>70</sup> and through attachments to nidogen, interact with collagen IV and laminin in basement membranes.<sup>71</sup> If this mutation alters supramolecular assembly of basement membrane components within Bruch's membrane, this could contribute to the development of drusen in ML/DHRD. There is close similarity between the symptoms and functional loss in our patients and those associated with Sorsby fundus dystrophy<sup>67</sup> and age-related changes at the level of Bruch's membrane.<sup>68</sup> In these conditions the deficit has been ascribed to interference of metabolic exchange between the choroid and the retinal pigment epithelium by deposits in Bruch's membrane. This was supported by the observation that the deficit can be reversed by high supplementation of vitamin A, although the effect was not sustained after withdrawal of the supplement.<sup>69</sup> Thus, the functional similarities between our patients do not imply that they are the same primary condition, but reflect a non-specific result of Bruch's membrane change. Further molecular genetic studies should help to clarify the relationship between ML/DHRD and other types of dominantly inherited drusen.

## References

- Vogt A. *Graefes-Saemischs Hdb. d. ges. Augenheilk J.* Springer: Berlin, 3rd edn, 1925, p 13.
- Klainguti R. Die tapeto-retinale Degeneration im Kanton Tessin. *Klin Mbl Augenheilk* 1932; **89**: 253–254.
- Wagner HR, Klainguti R. Weitere Untersuchungen über die Malattia leventinese. *Ophthalmologica* 1943; **105**: 225–228.
- Forni S, Babel J. Etude clinique et histologique de la malattia leventinese. *Ophthalmologica* 1962; **143**: 313–322.
- Forni S. Nouvel arbre genealogique de degenerescence tapeto-retinienne de la region maculaire et peripapillaire, type 'Malattia leventinese'. *Bibl Ophthalm* 1957; **47**: 570–575.
- Franceschetti A, Francois J, Babel J. *Les Heredo-degenerescences Chorioretiniennes*. Masson: Paris, 1963, pp 494–515.
- Franceschetti A, Klein D, Forni S, Babel J. The tapetoretinal degenerations. *Acta XVI Concil Ophthalm Britan* 1950; **1**: 182.
- Niemeyer G. Rod and cone-function in Malattia Leventinese and in retinitis pigmentosa. *Doc Ophthalm Proc* 1978; **17**: 337–344.
- Doyne RW. *Trans Ophthalm Soc UK* 1899; **19**: 71.
- Doyne RW. *Trans Ophthalm Soc UK* 1910; **30**: 93–95.
- Tree M. Familial hyaline dystrophy in the fundus oculi or Doyne's family honeycomb 'choroiditis'. *Br J Ophthalmol* 1937; **21**: 65–91.
- Pearce WG. Doyne's honeycomb retinal degeneration. *Br J Ophthalmol* 1968; **52**: 73–78.
- Pearce WG. Genetic aspects of Doyne's honeycomb degeneration of the retina. *Ann Hum Genet Lond* 1967; **31**: 173–180.
- Waardenburg PJ. On macula-degeneration. *Ophthalmologica* 1948; **115**: 10.
- Deutman A. Dominant drusen of Bruch's membrane. In: *The Hereditary Dystrophies of the Posterior Pole of the Eye*. Van Gorcum: Assen, The Netherlands, 1971, pp 367–399.
- Babel J, Farpour H. Les lesions de la choroïde dans les heredo-degenerescences a la lumiere de la fluoro-retinographie. *Ophthalmologica* 1968; **156**: 305–312.
- Piguet B, Haimovici R, Bird AC. Dominantly inherited drusen represent more than one disorder: a historical review. *Eye* 1995; **9**: 34–41.
- Hutchinson J. *Roy Lond Ophthalm Hosp Repts* 1876 **7**: 231–244.
- Mould GT. Family choroiditis. *Trans Ophthalmol Soc UK* 1910; **30**: 189–190.
- Butler H. Family choroiditis. *Trans Ophthalmol Soc UK* 1910; **30**: 94.
- Evans K, Gregory CY, Wijesuriya SD, Kermani S, Jay MR, Plant C, Bird AC. Assessment of the phenotypic range seen in Doyne honeycomb retinal dystrophy. *Arch Ophthalmol* 1997; **115**: 904–910.
- Heon E, Piguet B, Munier F, Sneed SR, Morgan CM et al. Linkage of autosomal dominant radial drusen (Malattia Leventinese) to chromosome 2p16–21. *Arch Ophthalmol* 1996; **114**: 193–198.
- Gregory CY, Evans K, Wijesurya SD, Kermani S, Jay MR, Plant C, Cox N et al. The gene responsible for autosomal dominant Doyne's honeycomb retinal dystrophy map to chromosome 2p16. *Hum Mol Genet* 1996; **5**: 1055–1059.
- Stone EM, Lotery AJ, Munier F et al. A single EFEMP1 mutation associated with both Malattia Leventinese and Doyne honeycomb retinal dystrophy. *Nature Genet* 1999; **22**: 199–202.
- Herlong HF, Russell RM, Maddrey WC. Vitamin A and zinc therapy in primary biliary cirrhosis. *Hepatology* 1981; **1**: 348–351.
- Russell RM, Smith VC, Mutlack R et al. Dark adaptation for diagnosis of subclinical vitamin A deficiency and evaluation of therapy. *Lancet* 1973; **2**: 1161–1164.
- Dutta SK, Russell RM, Lakhnani V. Abnormal dark adaptation in adult patients with protein-energy malnutrition: correction by protein-energy repletion. *Nutr Res* 1981; **1**: 443–449.
- Warth JA, Prasad AS, Zwas F, Frank RN. Abnormal dark adaptation in sickle cell anemia. *J Lab Clin Med* 1981; **98**: 189–194.

- 29 Arden GB, Berninger T, Hogg CR, Perry S. A survey of colour discrimination in German ophthalmologists. *Ophthalmology* 1991; **98**: 567–575.
- 30 Arden GB et al. A modified ERG technique and the results obtained in X-linked retinitis pigmentosa. *Br J Ophthalmol* 1983; **67**: 419–430.
- 31 Marmor MF, Arden GB, Nilson SE, Zrenner E. Standard for clinical electroretinography. *Arch Ophthalmol* 1989; **107**: 816–819.
- 32 Arden GB, Vaegan. Electroretinograms evoked in man by local uniform and pattern stimulation. *J Physiol* 1983; **341**: 84–105.
- 33 O'Donoghue E, Arden GB, O'Sullivan F et al. The pattern electroretinogram in glaucoma and ocular hypertension. *Br J Ophthalmol* 1992; **76**: 387–394.
- 34 Marmor MF, Zrenner E. Standard for clinical electroretinography. *Doc Ophthalmol* 1999; **97**: 143–156.
- 35 Bach M, Hawlina M, Holder GE, Marmor MF, Meigen T, Vaegan, Miyake Y. Standard for pattern electroretinography. *Doc Ophthalmol* 2000; **101**: 11–18.
- 36 Fish GE, Birch DG. The focal electroretinograms in the clinical assessment of macular disease. *Ophthalmology* 1989; **96**: 109–114.
- 37 Arden GB, Barrada A, Kelsey JH. New clinical test of retinal function based upon the standing potential of the eye. *Br J Ophthalmol* 1962; **46**: 449–467.
- 38 Jacobson SG, Voight WJ, Parel J-M et al. Automated light- and dark-adapted perimetry for evaluating retinitis pigmentosa. *Ophthalmology* 1986; **93**: 1604.
- 39 Chen JC, Fitzke FW, Pauleikoff D, Bird AC. Functional loss in age-related Bruch's membrane change with choroidal perfusion defect. *Invest Ophthalmol Vis Sci* 1992; **33**: 334–340.
- 40 Pugh EN Jr. Rushton's paradox: rod dark adaptation after flash photolysis. *J Physiol* 1975; **248**: 413–431.
- 41 Deutman A, Jansen LMAA. Dominantly inherited drusen of Bruch's membrane. *Br J Ophthalmol* 1970; **54**: 373–382.
- 42 Alper MG, Alfano JA. Honeycomb colloid degeneration of the retina. *Arch Ophthalmol* 1953; **49**: 392–399.
- 43 Pajtas J. Honigwabenhähnliche Hyalinderdegeneration der Netzhaut als nosologische Einheit. *Ophthalmologica* 1957; **134**: 101–111.
- 44 Sanna M. Sulla Degenerazione colloide familiare della retina. *Atti Soc Oftal Lomb* 1957; **12**: 193–200.
- 45 Jost BF. Dominantly inherited drusen In: Newsome DA (ed). *Retinal Dystrophies and Degenerations*. Raven Press: New York, 1988, pp 105–113.
- 46 Marmor M. Dominant drusen. In: Ryan SJ (ed). *Retina*. CV Mosby: St Louis, 1989, pp 664–668.
- 47 Kasmann B, Volker HE. Familiäre Drusen der Makula. *Fortschr Ophthalmol* 1990; **87**: 567–570.
- 48 Marmor MF. Dominant drusen In: Heckenlively JR, Arden GB (eds). *Principles and Practice of Electrophysiology*. Mosby Yearbook: St Louis, 1991, pp 664–668.
- 49 Cagniat B, Theiler K. Hereditäre Drusen der Bruchschichten Membran. *Klin Mbl Augenheilk* 1987; **190**: 21–25.
- 50 Gass JDM. Specific choroidal diseases causing disciform macular detachment. In: *Stereoscopic Atlas of Macular Diseases*, 3rd edn. Mosby: St Louis, 1987, p 96.
- 51 Gass JDM, Jallow S, Davis B. Adult vitelliform macular detachment occurring in patients with basal laminar drusen. *Am J Ophthalmol* 1985; **99**: 445–459.
- 52 Duval-Young J, MacDonald M, McKechnie N. Fundus changes in (type II) mesangiocapillary glomerulonephritis simulating drusen: a histopathologic report. *Br J Ophthalmol* 1989; **73**: 297–302.
- 53 Streicher T, Schmidt K, Dusek J. Hereditäre Drusen der Bruchschichten Membran I. Klinische und lichtmikroskopische Beobachtungen. *Klin Mbl Augenheilk* 1982; **181**: 27–31.
- 54 Dusek J, Streicher T, Schmidt K. Hereditäre Drusen der Bruch's Membran. II Untersuchung von Semidünnschnitten und elektronenmikroskopischen Ergebnissen. *Klin Mbl Augenheilk* 1982; **181**: 79–83.
- 55 Collins ET. A pathological report upon a case of Dooyne's choroiditis. *Ophthalmoscope* 1913; **11**: 537–538.
- 56 Farkas T, Krill AE, Sylvester VM, Archer D. Familial and secondary drusen: histologic and functional correlations. *Tr Am Acad Ophth and Otol* 1971; **75**: 333–343.
- 57 Holz FG, Owens SL, Marks J, Haimovici R, Bird AC. Ultrastructural findings in autosomal dominant drusen. *Arch Ophthalmol* 1997; **115**: 788–792.
- 58 Scarpatetti A, Forni S, Niemeyer G. Die Netzhautfunktion bei Malattia leventinese (dominant drusen). *Klin Mbl Augenheilk* 1978; **172**: 590–597.
- 59 Rover J, Bach M. C-wave versus electrooculogram in diseases of the retinal pigment epithelium. *Doc Ophthalmol* 1987; **65**: 385–391.
- 60 Niemeyer G, Demant E. Cone and rod ERG's in degenerations of central retina. *Graefes Arch Clin Exp Ophthalmol* 1983; **220**: 201–208.
- 61 Gass JDM. Drusen and disciform macular detachment. *Arch Ophthalmol* 1973; **90**: 206–217.
- 62 Fishman GA, Carrasco C, Fishman M. The electroretinogram in diffuse (familial) drusen. *Arch Ophthalmol* 1976; **94**: 231–233.
- 63 Krill AE, Klein BA. Flecked retina syndrome. *Arch Ophthalmol* 1965; **74**: 496–508.
- 64 Krill AE. Flecked retinal diseases. In: Krill AE, Archer DB (eds). *Krill's Hereditary Retinal and Choroidal Diseases*, Vol II. Harper Row: New York, 1977, pp 787–817.
- 65 Pajtas J. Pripad Dooyne's family honeycomb 'choroiditis'. *Ceskoslov oftal* 1950; **6**: 282–286.
- 66 Liem ATA, Keunen JEE, van Norren D. Foveal densitometry in adult-onset diffuse drusen. *Am J Ophthalmol* 1992; **114**: 149–157.
- 67 Steinmetz RL, Polkinghorne PC, Fitzke FW, Kemp CM, Bird AC. Abnormal dark adaptation and rhodopsin kinetics in Sorsby's fundus dystrophy. *Invest Ophthalmol Vis Sci* 1992; **33**: 1633–1636.
- 68 Steinmetz RL, Haimovici R, Jubb C, Fitzke FW, Bird AC. Symptomatic abnormalities of dark adaptation in patients with age-related Bruch's membrane change. *Br J Ophthalmol* 1993; **77**: 549–554.
- 69 Jacobson SG, Cideciyan AV, Regunath G, Rodriguez FJ, Vandenberg K et al. Night blindness in Sorsby's fundus dystrophy reversed by vitamin A. *Nature Genet* 1995; **11**: 27–32.
- 70 Sasaki T, Göhring W, Miosge N et al. Tropoelastin binding to fibulins, nidogen-2 and other extracellular matrix proteins. *FEBS Lett* 1999; **460**: 280–284.
- 71 Timpl R, Brown JC. Supermolecular assembly of basement membranes. *Bioessays* 1996; **18**: 123–132.