British Journal of Ophthalmology 1995; 79: 746–752

# Severe course of cutaneous melanoma associated paraneoplastic retinopathy

Ulrich Kellner, Norbert Bornfeld, Michael H Foerster


## Abstract

***Background*—Melanoma associated retinopathy (MAR) is a paraneoplastic syndrome in metastatic cutaneous melanoma presenting with nightblindness, light sensations, mild visual loss, and reduced b-waves in the electroretinogram (ERG).**

***Methods*—A patient with MAR was followed for a period of 25 months with repeated examinations including visual field testing and recording of standard electro-oculography, standard ERG, and photopic On and Off responses.**

***Results*—A male patient with a very severe course of MAR is described. In addition to the clinical signs seen in previous patients, severe visual deterioration and vitreous inflammation were the predominant signs. The vitreous inflammation resolved after systemic corticosteroid therapy. Nightblindness and the reduced b-waves in the ERG remained unchanged during the follow up period. However, further visual deterioration and paracentral scotomas developed. Dark adaptation was markedly abnormal. Photopic On responses were reduced, but Off responses were preserved. Antibodies against retinal bipolar cells were isolated from blood samples of this patient.**

***Conclusion*—Vitreous inflammation may mask the diagnosis of MAR. ERG findings indicate that the more severe and progressive course is the result of local retinal changes and not progressive generalised retinal degeneration.**

(*Br J Ophthalmol* 1995; **79**: 746–752)


Since the report by Sawyer *et al*,[1] several patients with retinal degenerations associated with extraocular tumours have been described. Cancer associated retinopathies (CAR) can be distinguished from cutaneous melanoma associated retinopathies (MAR) both clinically and immunologically. CAR patients present with severe visual loss including complete blindness and severe reduced a- and b-wave amplitudes in the electroretinogram (ERG).[2–6] Autoantibodies reacting with photoreceptors and ganglion cells have been isolated from the blood sera of CAR patients.[3 7–13]

The cases of 16 MAR patients have been described in the literature to date.[14–25] Symptoms included mild visual loss, nightblindness, and shimmering or flickering light sensations; a b-wave reduction was observed in the ERG. This ERG waveform, called a 'negative ERG', can be found in disorders affecting neuronal transmission pathways beyond the photoreceptors or other cells within the inner retinal layers.[26–29] Autoantibodies reacting with retinal bipolar cells have been isolated from blood sera of all MAR patients examined.[23 25 30] Only one patient with a metastatic carcinoma developed signs similar to MAR.[31]

In contrast with previously reported patients with MAR, the male patient described in the present study showed progressive visual loss and signs of posterior uveitis.

**Freie Universität Berlin, Universitätsklinikum Benjamin Franklin, Augenklinik und Poliklinik, Berlin, Germany**
U Kellner
N Bornfeld
M H Foerster

Correspondence to:
Ulrich Kellner, MD, Augenklinik, Universitätsklinikum Benjamin Franklin, FU Berlin, Hindenburgdamm 30, 12200 Berlin, Germany.

Accepted for publication 27 February 1995

## Methods

### ELECTRORETINOGRAPHY

A negative ERG was first recorded in this patient in August 1992. Thereafter, the recording equipment was changed. For comparison during follow up, only ERG recordings with the new equipment were evaluated. The new technique corresponds to our technique described previously.[28 29]

The ERG recording protocol includes all recordings according to the standard for clinical electroretinography.[32] A Nicolet Spirit (Nicolet, Madison, USA) in combination with a Nicolet Ganzfeld was used for stimulation and recording. Recordings were done after 30 minutes of dark adaptation and with maximal dilated pupils (2·5% phenylephrine and 0·5% tropicamide). Stimulus duration was 0·1 ms. Four stimuli were used for recordings in the dark. The maximum light intensity was 10 cd s/m$^2$. Duration of light adaptation before recording was 10 minutes. Light adapted recordings were performed in the presence of white light adaptation of 30 cd/m$^2$ with white and chromatic stimuli of maximum light intensity. Kodak Wratten filters were used for chromatic stimuli (blue: No 47+47A+47B, maximum transmission at 445 nm, green: No 61, 538 nm; red: No 29, 630 nm). No averaging was done.

### ON/OFF RESPONSES

On and Off responses were recorded using red light emitting diodes (LEDs) (3 cd s/m$^2$) and flashes of long duration (256 ms). Recordings were done after 10 minutes of light adaptation (10 cd/m$^2$). Eight responses were averaged. The method has been described in detail by others.[33 34]

### ELECTRO-OCULOGRAPHY

Electro-oculography (EOG) was performed using a method described by Behrens *et al*[35] and according to the standard for clinical EOG.[36] A Ganzfeld with fixation lights was

*Table 1 Summary of clinical findings*

| Date | Visual acuity RE | Visual acuity LE | Visual fields RE | Visual fields LE | Vitreous haze (both eyes) | Fundus findings RE | Fundus findings LE | Treatment |
|---|---|---|---|---|---|---|---|---|
| Jan 91 | Visual loss | | ? | ? | – | ? | ? | None |
| Jun 91 | Visual loss | | ? | ? | ++ | ? | ? | Systemic corticosteroids |
| Jun 92 | 6/12 | 6/7·5 | ? | ? | + | Parac scar | Normal | None |
| Aug 92 | 5/60 | 6/12 | Concentric narrowing | | +++ | Parac scar | Normal | Systemic corticosteroids |
| Sep 92 | 6/36 | 6/7·5 | Concentric narrowing | | + | Parac scar | Normal | None |
| Jan 93 | 6/36 | 6/7·5 | Concentric narrowing | | + | Parac scar | Normal | None |
| Mar 93 | 1/60 | 6/12 | Central scotoma | Parac scot | (+) | Parac scar | Normal | Systemic corticosteroids |
| Jun 93 | 3/60 | 6/12 | Cent+parac scot | Parac scot | (+) | Parac scar | Normal | Systemic corticosteroids |
| Aug 93 | 1/60 | 6/24 | Cent+parac scot | Parac scot | – | Parac scar | Cystoid oedema | Acetazolamide+flurbiprofen |
| Nov 93 | 3/60 | 6/12 | Cent+parac scot | Parac scot | – | Parac scar | Cystoid oedema | Acetazolamide+flurbiprofen |
| Apr 94 | 3/60 | 6/12 | Cent+parac scot | Parac scot | – | Parac scar | Regressive cystoid oedema | None |
| Aug 94 | 3/60 | 6/12 | Cent+parac scot | Parac scot | – | Parac scar | Variable cystoid oedema | Acetazolamide+flurbiprofen |

RE=right eye; LE=left eye; Cent=central; Parac=paracentral; Scot=scotoma.

used for stimulus presentation and induction of eye movements. The duration of measurement was 56 minutes. Within the first 40 minutes, the luminance was decreased monotonically by four decades (2000 to 0·2 asb) in a logarithmic manner to become independent of the previous state of adaptation. After this adaptation procedure, a luminance step of four decades induced the light rise. The potentials were recorded with a DC amplifier. The response was described by the ratio between the maximum amplitude to the amplitude before the luminance was increased (light peak versus baseline).

DARK ADAPTATION

Dark adaptation was tested with the Goldmann-Weekers adaptometer. After a 10 minute bleach of 1400 cd/m$^2$ in a Ganzfeld sensitivity thresholds were determined over a period of 45 minutes.

## Clinical history

The clinical history of this 44-year-old man began in April 1989 when he presented with a cutaneous melanoma of the left leg. This lesion was locally excised and the patient was treated with systemic interferon. In March 1990, a local lymph node metastasis was excised; no further medical treatment was given. Regular follow up examinations during the next 4 years revealed no further evidence of metastatic disease. The patient was otherwise in good health with no personal or family history of eye disease. He denied difficulties with seeing at night or with colour vision before 1991.

In January 1991, the patient noted for the first time difficulties in seeing at night as well as a deterioration of visual acuity in the right eye. An overview of the ophthalmic findings by this and subsequent presentations is summarised in Table 1. Two to 3 weeks later, visual loss occurred in the left eye. A visual loss of unknown cause was diagnosed elsewhere. In

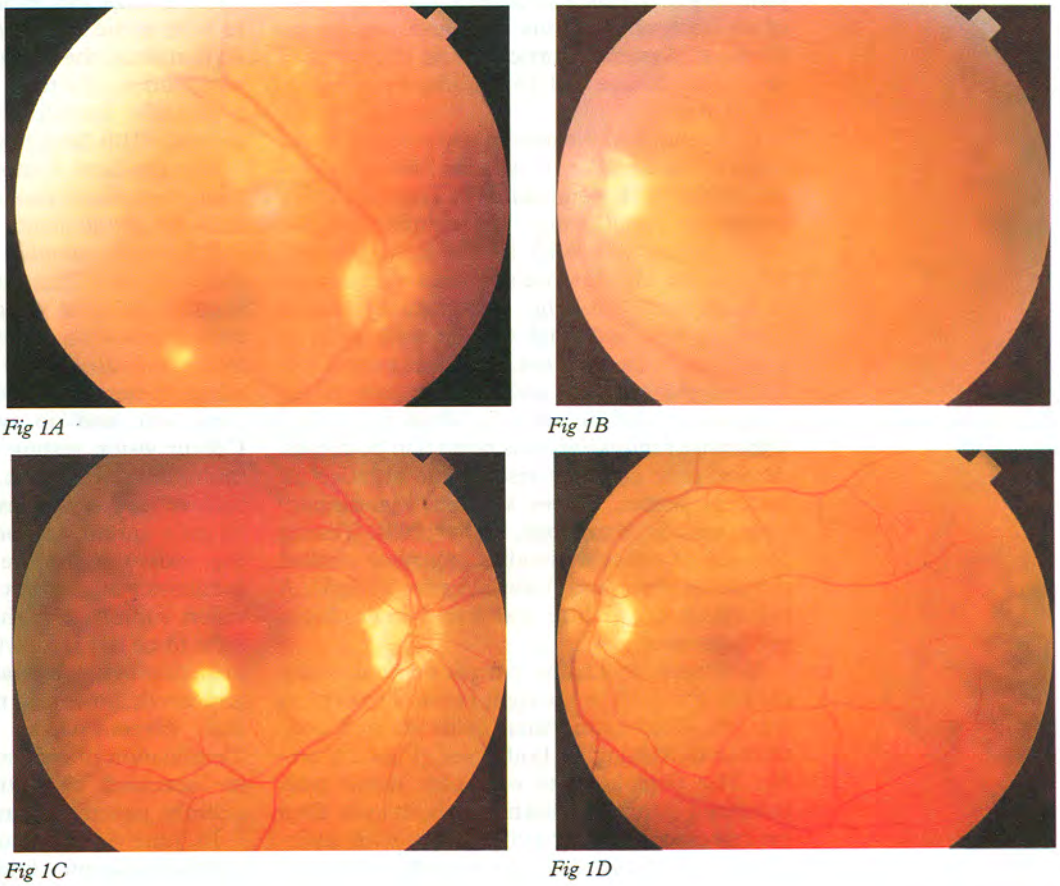

*Figure 1 Ophthalmoscopic findings in MAR. Vitreous haze reduced visibility of the posterior pole in August 1992 ((A) right eye, (B) left eye). In November 1993 fundus visibility was good ((C) right eye, (D) left eye). On the right eye the paracentral scar and the scar temporal to the optic disc were enlarged compared with August 1992.*

*Fig 1A* *Fig 1B*

*Fig 1C* *Fig 1D*

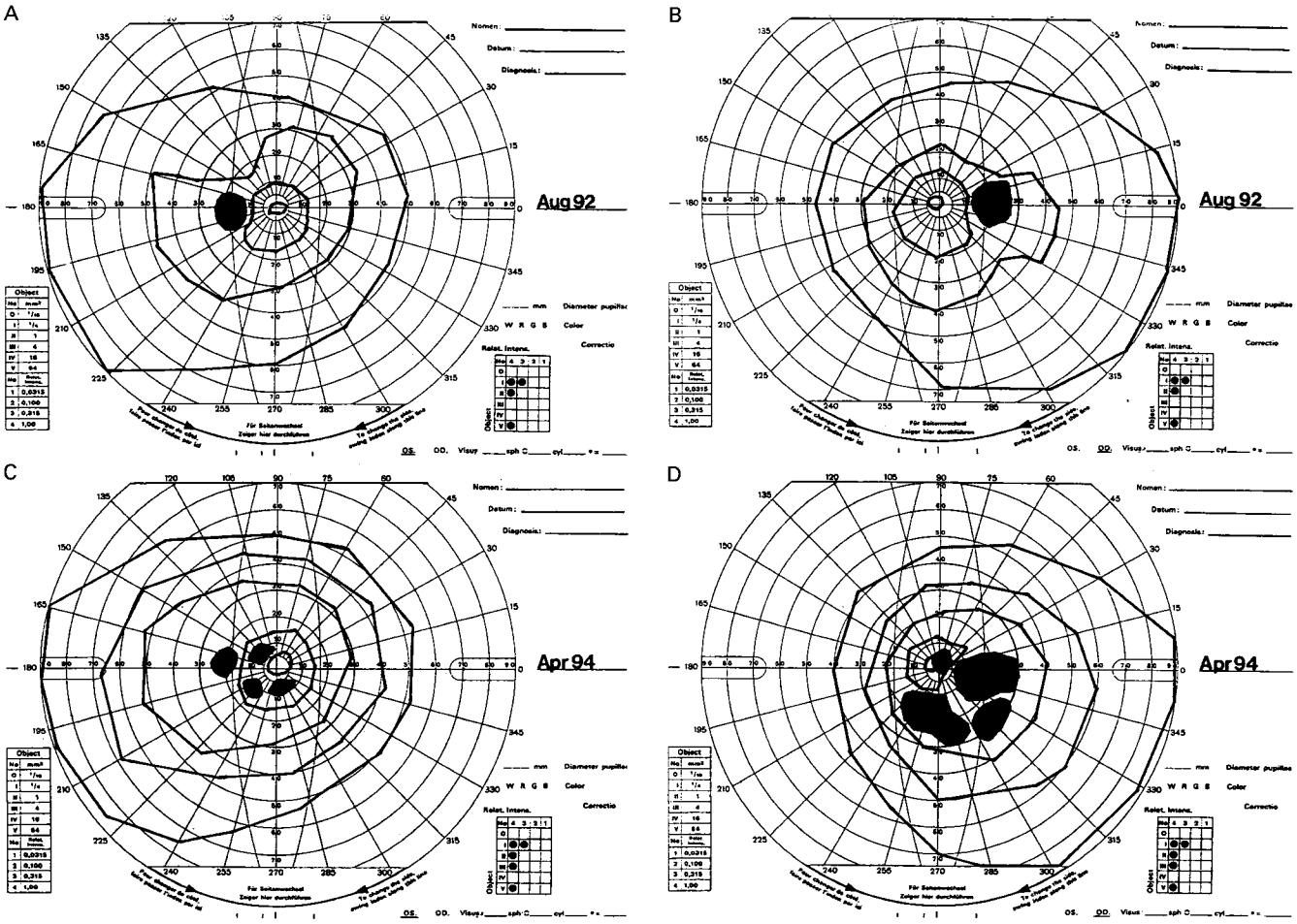


*Figure 2 Goldmann visual fields in MAR during follow up. When vitreous inflammation was present, concentric narrowing was seen on both eyes ((A) left eye, (B) right eye). In April 1994 vitreous inflammation had resolved. On the left eye (C) paracentral scotomas were present. The right eye (D) showed central and paracentral scotomas.*

June 1991, uveitis was diagnosed on the basis of an observed vitreous haze and cellular infiltration. Systemic corticosteroid treatment of unknown dosage led to an improvement of visual acuity.

One year later, the patient was referred to our department because of recurrent bilateral posterior uveitis. He complained of a further deterioration in visual acuity. On examination, the visual acuity was 6/12 in the right eye and 6/7·5 in the left. Anterior segments were normal in both eyes. Slit-lamp examination revealed vitreous haze and mild cellular infiltration in both eyes. In the right eye, there was a small scar located paracentrally and another one at the temporal side of the optic disc (Figs 1A and B). Otherwise funduscopy was normal in both eyes. At that time antibody testing was negative for varicella zoster, herpes simplex, cytomegalovirus, rubella, borreliosis, and syphilis. Testing for toxoplasma antibodies (enzyme linked immunosorbent assay) was negative for IgM. A low positive IgG titre was found indicating a previous infection.

In August 1992, the patient's visual acuity dropped to 5/60 in the right eye and to 6/12 in the left. Goldmann visual fields showed concentric narrowing in both eyes (Figs 2A and B). The vitreous haze was more dense with increased cellular infiltration in both eyes. Oral prednisolone (initially 100 mg/day) with tapering over 4 weeks resulted in resolution of the vitreous haze and improvement in visual acuity to 6/36 in the right eye and to 6/7·5 in the left. At that time, the ERG showed reduced b-wave amplitudes. Pattern visual evoked cortical potentials revealed low amplitudes with normal P100-latencies in both eyes.

For the next 7 months the patient's visual acuity remained stable. In March 1993, however, the visual acuity decreased to 1/60 in the right eye. It remained unchanged with 6/12 in the left eye. Examination of visual fields showed a central scotoma in the right eye and paracentral scotomas in the left. Dark adaptation, measured with a Goldmann-Weekers adaptometer, was monophasic with a small cone limb and no evidence for rod activity. Colour vision testing on the left eye revealed multiple errors on the desaturated Panel D-15 test without typical axis of confusion. On the Nagel's anomaloscope, the range of matches was extended to the protan side. Systemic corticosteroid therapy (50 mg/day) improved vision subjectively, the patient describing his sight to be less hazy without the disturbance of flickering lights. Visual fields were also slightly improved; however, the visual acuity, ERG, and vitreous haze remained unchanged. Termination of corticosteroid therapy resulted in increased subjective discomfort. Consequently, treatment was recommenced.

In June 1993, visual acuity, visual fields, ophthalmoscopic findings, and ERG were

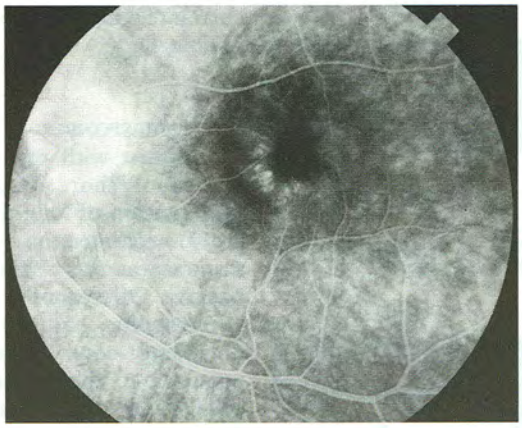

*Figure 3 Fluorescein angiography of the left eye in November 1993. In the late phase of the angiogram a cystoid macular oedema was revealed.*

unchanged compared with the findings in March 1993. The light sensations remained unchanged when treatment was discontinued after slow reduction of dosage.

In August 1993, visual acuity dropped to 6/24 in the left eye. Cystoid macular oedema was detected by angiography (Fig 3). Visual acuity improved after treatment with oral acetazolamide and local flurbiprofen. An attempt to discontinue this therapy resulted in recurrent visual loss within 10 days to 3 weeks. Consequently, the patient continued to receive the above regimen with few attempts at discontinuing to date. Upon examination in November 1993, visual acuity in the right eye increased to 3/60 and to 6/12 in the left. Visual acuity and visual fields remained unchanged in April and August 1994 (Figs 2C and D). Comparison of fundus photographs indicated that the scars in the right eye had slightly increased in size (Figs 1C and D). No other morphological changes were observed.

In April 1994, an EOG recording showed a reduction in the light peak versus baseline ratio: 127% in the right eye and 146% in the left one (normal ≥160%). Four months later, the coloured caps of the desaturated Panel D-15 test could not be distinguished by the patient. He had much less difficulty in performing the Farnsworth 100 hue test with saturated colours. The total error score was 80, within the normal range. The main errors were found along the tritan axis.

*Fig 4A*

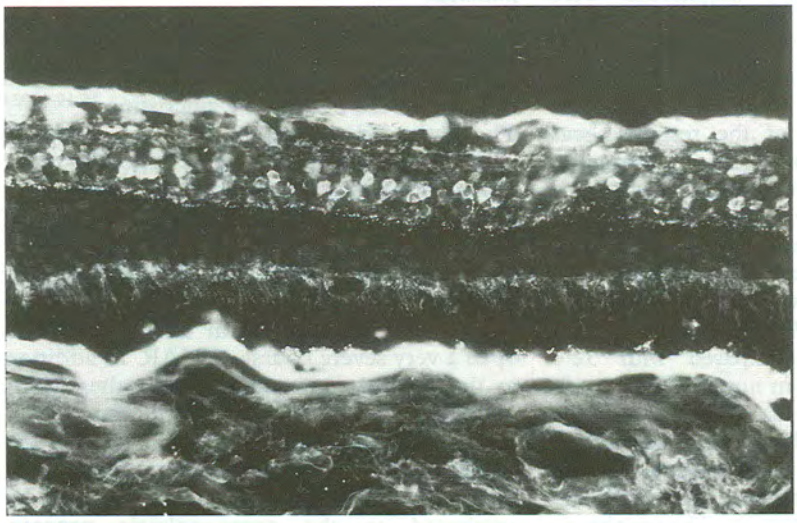

*Fig 4B*

*Figure 4 Immunolabelling of human retinas with IgG of a normal subject (A) and of our patient (B). Bright autofluorescence of lipofuscin granules can be seen in the retinal pigment epithelium and dim autofluorescence in the neurosensory retina. The sections treated with IgG from the normal subject showed no specific labelling throughout the retina. The sections treated with IgG of the MAR patient showed specific labelling of bipolar cells.[23] Magnification ×110. (This figure is presented by courtesy of Professor A H Milam.)*

## BLOOD EXAMINATION

In May 1993, serum of the patient was sent to A H Milam, University of Washington, Seattle, where it was prepared and examined as described previously.[23] Antibodies from this serum labelled rod bipolar cells similar to findings seen in other MAR patients[23 30] (Fig 4). An examination of a second blood sample in October 1994 gave identical results.

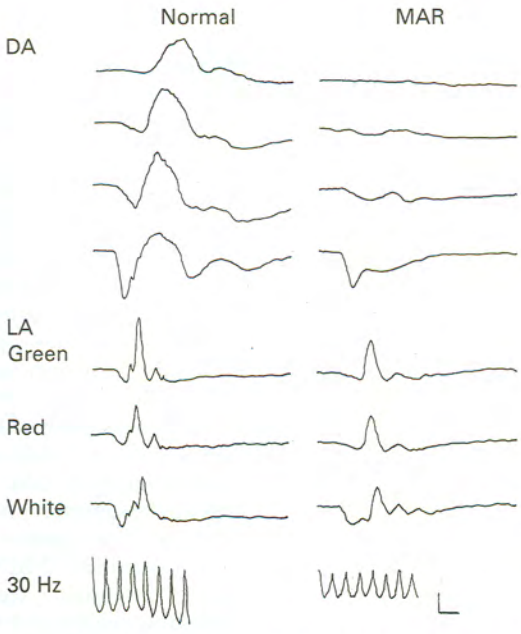


*Figure 5 ERG in response to white and chromatic stimuli of our patient compared with representative normal recordings. DA indicates four responses with increasing light intensity at dark adaptation. LA indicates responses at light adaptation. When dark adapted, the b-wave amplitudes were severely reduced in our patient. At light adaptation, b-waves were delayed and the 30 Hz flicker amplitude was reduced. Vertical calibration marks indicate 200 μV for DA recordings and 100 μV for LA and flicker recordings. Horizontal calibration is 20 ms for single flash recordings and 50 ms for flicker responses.*

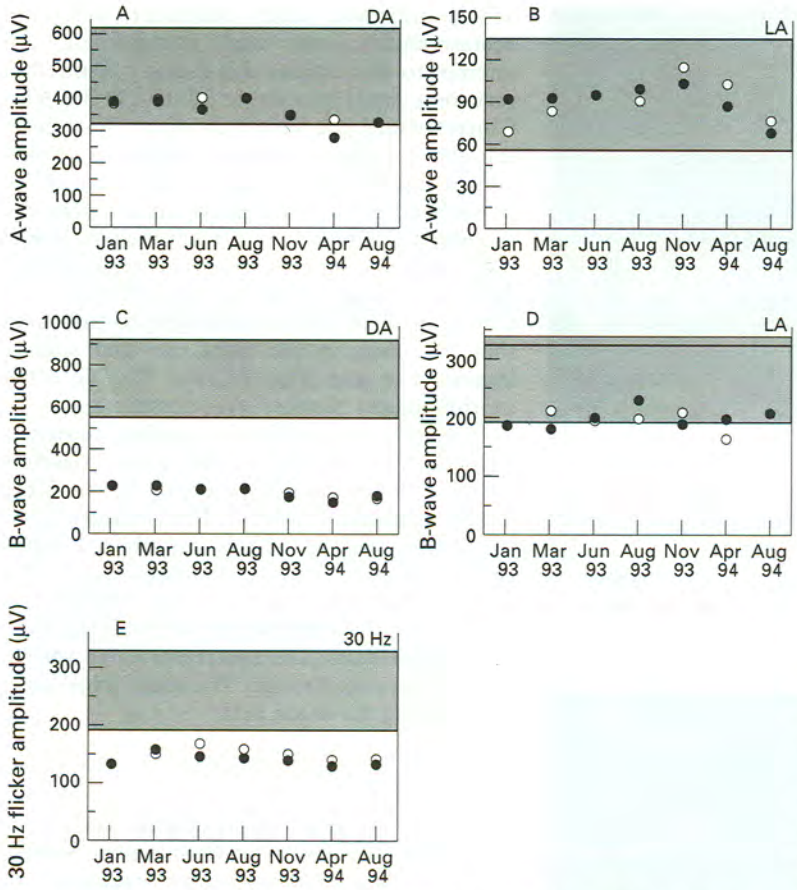


*Figure 6 Standard ERG recordings to white light during follow up. At dark adaptation (DA) only the amplitudes at maximum stimulus intensity are shown. The amplitudes of the right (filled circles) and left eye (open circles) are plotted separately. The shaded areas indicate the normal range (2 SD). A-wave amplitudes were normal at dark (A) and light adaptation (B). B-wave amplitudes were reduced to about one third at dark adaptation (C). When light adapted, b-wave amplitudes were borderline (D). The amplitudes of the 30 Hz flicker response were subnormal (E). Variation was low for all measured variables during follow up.*

## Results

ELECTRORETINOGRAPHIC FINDINGS

At dark adaptation, the a-wave amplitudes were normal and the b-wave amplitudes were reduced at all stimulus intensities, showing a negative ERG (Figs 5, 6). At maximum stimulus intensity, the b-wave amplitudes were about one third of the normal value. At light adaptation, the configuration of the response was altered. The a-wave amplitudes were normal to white and chromatic stimuli and had a normal time course. The b-wave amplitudes were borderline; however, the b-wave latencies and implicit times were markedly delayed. The b-wave implicit time was 40 ms (range at repeated examinations 39–40·8 ms; white stimulus) in the patient compared with 32·6 (1·4) ms (mean (2 SD)) in normals. The oscillatory potentials, seen as wavelets on the ascending limb of the b-wave in the normal response, were reduced to one small wavelet before the b-wave resulting in a broad negativity between the a- and the b-wave. The amplitude of the 30 Hz flicker response was subnormal.

In contrast with the clinical findings, the ERG findings were similar in both eyes (Fig 6). The ERG variables (amplitudes and latencies) showed only small changes during the course of the disease (Fig 6). They did not correlate with the variation of clinical findings (Table 1).

ON/OFF RESPONSES

In contrast with responses elicited with light flashes of short duration (0·1 ms, Fig 5), presentation of long duration flashes (250 ms, Fig 7) separates the b-wave into a positive On response at the beginning of the flash and a positive Off response at light cessation. The On response has been attributed to the depolarising cone bipolar cells and the Off response to the hyperpolarising cone bipolar cells.[34] In the patient, the On response was severely reduced and the Off response was normal (Fig 7).

## Discussion

To date, 16 patients with MAR have been described in the literature.[14–25] It should be noted, that the patient described by DuBois *et al*[16] was misdiagnosed initially and MAR was suspected later.[17] The patients described by Kim *et al*[22] and Wolf and Arden[37 38] are identical.

Ophthalmic signs were found either before or during the development of metastasis of a cutaneous melanoma. All patients had sensations of shimmering lights, difficulties with night vision, and reduced b-wave amplitudes in the ERG. In contrast with the current case, visual acuity was usually normal or only moderately reduced (not below 6/12). Only one patient developed severe visual loss with central scotomas[25]; paracentral scotomas were seen in two patients. In most patients, colour vision remained unchanged. Ophthalmoscopic findings were normal in most cases, with a few vitreous cells being described in one patient only.[23] The clinical courses showed progression of scotomas in one patient[24] and were stable up to 14 months in two other patients.[18 23]

In the first MAR patient described, a side effect of vincristine therapy was suspected,[14] however, findings in that patient were similar to others who did not receive vincristine.[15 19 20–23] The patient described in this study did not undergo treatment with vincristine. Systemic treatment with interferon may induce a retinopathy characterised by cotton wool spots, areas of non-perfusion, and haemorrhage.[39] Such alterations were not observed in our patient.

The patient described in this study developed a very severe course of MAR. In addition to the clinical signs reported in other MAR patients, our patient initially presented with ocular inflammation. This would explain the visual loss and visual field defects observed at that time. The posterior uveitis must be attributed to the paraneoplastic process. General history and immunological examinations revealed no indications for an unrelated cause of uveitis. The low IgG titre for toxoplasmosis is a sign of a previous infection. The clinical findings of bilateral uveitis without a localised chorioretinal inflammation would be

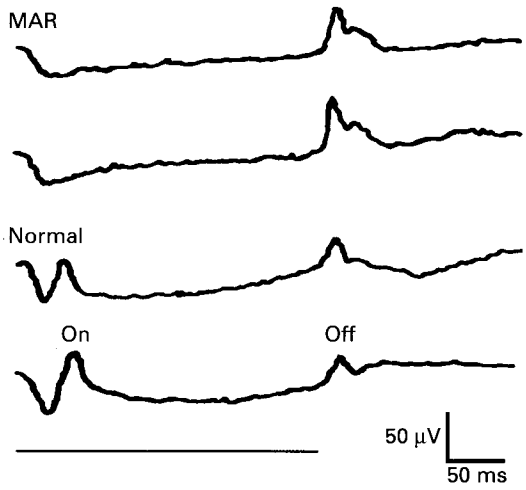


*Figure 7 On and Off responses of our patient compared with representative normal recordings. Two independent recordings of one eye are shown for the patient and the normal person. Stimulus duration was 256 ms. The On response was markedly reduced in the MAR patient, but the Off response was preserved.*

very atypical for ocular toxoplasmosis. The scar in the right eye enlarged during follow up without any signs of inflammation. During follow up examinations, the ocular inflammation gradually resolved and progressive visual loss and paracentral visual field defects occurred. Despite the difference in visual acuity, the ERG recordings were similar in both eyes. In contrast with the variable clinical course over the subsequent 20 months, little variation was observed in ERG variables. Therefore the visual loss and the paracentral scotomas detected in this patient could be attributed possibly to localised macular changes rather than to a progressive degeneration of the whole retina. One female MAR patient with severe visual loss has been reported recently.[25] She presented with central scotomas, moderately pale optic discs, and severely attenuated retinal vessels. Fluorescein angiography for differentiation of macular changes were not performed. It is not known whether vitreous inflammation was present during the early course of disease. Similar findings were not seen in other MAR patients.

The antibodies against rod bipolar cells isolated from the blood serum of our patient were similar to those seen in every MAR patient examined so far[23 25 30] (A Milam, personal communication). Similar antibodies could not be detected in other eye diseases or normals. The vitreous inflammation is consistent with the autoimmune mechanism of paraneoplastic retinopathy. An induction of vitreous inflammation has been demonstrated for several antibodies against retinal proteins.[40] In one MAR patient, fine vitreous cells were described.[23] In other patients with metastatic cutaneous melanoma, anterior uveitis[41 42] and a Vogt-Koyanagi-Harada syndrome[42 43] have been observed. Nightblindness was also reported in one of these patients.[43] The development of uveitic signs may depend on the severity of the autoimmune reaction directed against the bipolar cells (for example, a more severe breakdown of the blood-retinal barrier) or on individual variations in reactivity of the immune system. In our patient, ocular involvement started 9 months after diagnosis of a local metastasis. There was no indication that the recurrences of vitreous inflammation were associated with tumour activity elsewhere in the body. It has to be emphasised that the signs of inflammation delayed the correct diagnosis for approximately 1 year.

The ERG recordings in our patient and in other patients with MAR are in accordance with a defect of rod bipolar cells. When dark adapted, the a-wave amplitudes, indicating photoreceptor function, were normal. The b-wave amplitudes, indicating bipolar and Müller cell function, were reduced. The elevated thresholds at dark adaptation indicate a severe transmission defect in the rod pathway.

In our patient, the cone pathways were also affected. When light adapted, the b-wave amplitudes were borderline and the implicit times were prolonged. The 30 Hz flicker response was reduced. The On response was reduced and the Off response preserved in our patient (Fig 7). This has been described previously by Alexander *et al*[18] and is evidence for a defect of the depolarising cone bipolar cells.

Similar ERG findings are seen in congenital stationary nightblindness (CSNB).[18 44] MAR and CSNB have several features in common which may suggest that these diseases affect similar retinal structures. Some differences, however, indicate that MAR is not an acquired stationary nightblindness. For example, in contrast with patients with CSNB, the blue cones appear to be affected in MAR. Difficulties in detecting blue colours have been observed in our and other patients.[22] Further, the blue cone ERG can be severely reduced in MAR patients.[19 23] Extended psychophysical testing in two MAR patients revealed severe defects of the magnocellular pathway with preservation of the parvocellular pathways.[37 38] Our patient underwent similar psychophysical testing, the results of which will be presented in detail elsewhere (J Wolf and G Arden, in preparation). He had similar characteristics with achromatic low spatial frequency losses at low contrast corresponding to magnocellular losses. However, compared with the other MAR patients, he had greater losses in his achromatic high spatial frequencies, consistent with his reduced visual acuity (J Wolf and G Arden, personal communication). There are indications that the parvocellular and magnocellular pathways are separated on the level of the retinal bipolar cells.[45] It has been demonstrated recently that only a subset of about 30% of bipolar cells is labelled with antibodies of MAR patients.[25] One may speculate, that rod bipolar cells and cone bipolar cells of the magnocellular pathway express similar proteins which are not expressed by cone bipolar cells of the parvocellular pathways. Consequently, some bipolar cells could be more vulnerable to MAR antibodies than others. Two possible target proteins are protein kinase C[23] and a $G_0$ protein. In the cat, the $G_0$ protein could be detected in rod bipolar cells and depolarising cone bipolar cells which carry low spatial frequencies, but not in other depolarising cone bipolar cells.[46] A defect of the $G_0$ protein could explain the functional findings seen in MAR patients.

We suppose that the course of MAR is initiated by circulating antibodies reacting with bipolar cells. This is reflected clinically by a rapid onset of the disease; for example, all MAR patients report a sudden onset of nightblindness. Although differences of onset between both eyes have been observed in our and other patients,[18 20 23] this time difference was short and never longer than 2 months. Apparently a certain number of bipolar cells have to be affected before nightblindness becomes clinically obvious. It may be suspected that the retinal damage occurs during this initial phase followed then by a stationary phase. This is indicated by a non-progressive clinical course in most MAR patients. Repeated ERGs in our patient were unchanged indicating that no progressive retinal degeneration was present. The progressive deterioration of visual acuity in this case must be attributed to localised macular changes secondary to posterior uveitis.

It remains puzzling how antibodies against rod bipolar cells can induce defects in the cone pathways. Further analysis is necessary to determine the meaning of severely reduced cone b-waves and missing On responses when psychophysical data indicate preservation of important cone functions as good visual acuity, normal colour vision, and intact parvocellular pathways in most patients. The origin of the flickering light sensations also remains unknown. Detailed evaluation of MAR patients may reveal new insights into retinal circuitry in the future.

We thank Mrs H Kraus for help with the ERG recordings and Mrs G Bröskamp for fundus photography. Immunological examination of the blood serum was done by Professor A H Milam (Department of Ophthalmology, University of Washington, Seattle). Detailed psychophysical examinations were performed by Dr J Wolf (Department of Optometry and Visual Science, City University, London) and Professor G B Arden (Moorfields Eye Hospital, London).

1 Sawyer RA, Selhorts JB, Zimmerman LE. Blindness caused by photoreceptor degeneration as a remote effect of cancer. *Am J Ophthalmol* 1976; **81:** 606–13.
2 Jacobson DM, Thirkill CE, Tipping SJ. A clinical triad to diagnose paraneoplastic retinopathy. *Ann Neurol* 1990; **28:** 162–7.
3 Keltner JL, Rith AM, Chang S. Photoreceptor degeneration. Possible autoimmune disorder. *Arch Ophthalmol* 1983; **101:** 564–9.
4 Keltner JE, Thirkill CE, Tyler NK, Roth AM. Management and monitoring of cancer associated retinopathy. *Arch Ophthalmol* 1992; **110:** 48–53.
5 Matsui Y, Mehta MC, Katsumi O, Brodie SE, Hirose T. Electrophysiological findings in paraneoplastic retinopathy. *Graefes Arch Clin Exp Ophthalmol* 1992; **230:** 324–8.
6 Thirkill CE, Roth AM, Keltner JL. Cancer-associated retinopathy. *Arch Ophthalmol* 1987; **105:** 372–5.
7 Adamus G, Guy J, Schmied JL, Arendt A, Hargrave P. Role of anti-recoverin autoantibodies in cancer-associated retinopathy. *Invest Ophthalmol Vis Sci* 1993; **34:** 2626–33.
8 Grunwald GB, Kornguth SE, Towfighi J, Sassani J, Simmonds MA, Housman CM, *et al.* Autoimmune basis for visual paraneoplastic syndrome in patients with small cell lung carcinoma. Retinal immune deposits and ablation of retinal ganglion cells. *Cancer* 1987; **60:** 780–6.
9 Kornguth SE, Kalinke T, Grunwald GB, Schutta H, Dahl D. Anti-neurofilament antibodies in the sera of patients with small cell carcinoma of the lung and with visual paraneoplastic syndrome. *Cancer Res* 1986; **46:** 2588–95.
10 Polans AS, Buczylko J, Crabb J, Palczewski K. A photoreceptor calcium binding protein is recognized by autoantibodies obtained from patients with cancer-associated retinopathy. *J Cell Biol* 1991; **112:** 981–9.
11 Polans AS, Burton MD, Haley TL, Crabb JW, Palczewski K. Recoverin, but not visinin, is an autoantigen in the human retina identified with a cancer-associated retinopathy. *Invest Ophthalmol Vis Sci* 1993; **34:** 81–90.
12 Thirkill CE, Fitzgerald P, Sergott RC, Roth AM, Tyler NK, Keltner JL. Cancer associated retinopathy (CAR syndrome) with antibodies reacting with retinal, optic nerve, and cancer cells. *N Engl J Med* 1989; **321:** 1589–94.
13 Thirkill CE, Keltner JL, Tyler NK, Roth AM. Antibody reactions with retina and cancer associated antigens in 10 patients with cancer associated retinopathy. *Arch Ophthalmol* 1993; **111:** 931–7.
14 Ripps H, Carr RE, Siegel IM, Greenstein VC. Functional abnormalities in vincristine-induced night blindness. *Invest Ophthalmol Vis Sci* 1984; **25:** 787–94.
15 Berson EL, Lessell S. Paraneoplastic night blindness with malignant melanoma. *Am J Ophthalmol* 1988; **106:** 307–11.
16 DuBois LG, Sadun AA, Lawton TB. Inner retinal layer loss in complicated migraine. *Arch Ophthalmol* 1988; **106:** 1035–7.
17 DuBois LG, Sadun AA. Retinitis pigmentosa misdiagnosed as complicated migraine – in reply. *Arch Ophthalmol* 1991; **109:** 175.
18 Alexander KR, Fishman GA, Peachey NS, Marchese AL, Tso MO. 'On' response defect in paraneoplastic night blindness with cutaneous malignant melanoma. *Invest Ophthalmol Vis Sci* 1992; **33:** 477–83.
19 Mackay CJ, Gouras P, Yamamoto S. S-cone and rod ERGs in paraneoplastic retinal degeneration. *Invest Ophthalmol Vis Sci* 1992; **33:** 1074.
20 Pollock S, Kuwashima L, Kelman S, Tiedeman J. Melanoma associated retinopathy. San Diego: North American Neuro-Ophthalmologic Society, 1992: Feb 23–7.
21 Andreasson S, Ponjavic V, Ehinger B. Full-field electroretinogram in a patient with cutaneous melanoma-associated retinopathy. *Acta Ophthalmol* 1993; **71:** 487–90.
22 Kim RY, Retsas S, Fitzke FW, Arden G, Bird AC. Cutaneous melanoma-associated retinopathy. *Ophthalmology* 1994; **101:** 1837–43.
23 Milam AH, Saari JC, Jacobson SG, Lubinski WP, Feun LG, Alexander KR. Autoantibodies against retinal bipolar cells in cutaneous melanoma-associated retinopathy. *Invest Ophthalmol Vis Sci* 1993; **34:** 91–100.
24 Rush JA. Paraneoplastic retinopathy in malignant melanoma. *Am J Ophthalmol* 1993; **115:** 390–1.
25 Weinstein JM, Kelman SE, Bresnick GH, Kornguth SE. Paraneoplastic retinopathy associated with antiretinal bipolar cell antibodies in cutaneous malignant melanoma. *Ophthalmology* 1994; **101:** 1236–43.
26 Cideciyan AV, Jacobson SG. Negative electroretinograms in retinitis pigmentosa. *Invest Ophthalmol Vis Sci* 1993; **34:** 3253–63.
27 Ripps H. Night blindness revisited: from man to molecules. *Invest Ophthalmol Vis Sci* 1982; **23:** 588–609.
28 Kellner U, Brümmer S, Foerster MH, Wessing A. X-linked congenital retinoschisis. *Graefes Arch Clin Exp Ophthalmol* 1990; **228:** 432–7.
29 Kellner U, Foerster MH. Cone dystrophies with negative photopic electroretinogram. *Br J Ophthalmol* 1993; **77:** 404–9.
30 Milam AH, Saari JC. Autoantibodies against retinal rod bipolar cells in melanoma associated retinopathy. *Invest Ophthalmol Vis Sci* 1994; **35:** 2116.
31 Shults WT, Weleber RG. Retinitis pigmentosa and allied disorders. In: Ryan SJ, ed. *Retina.* St Louis: Mosby, 1994: 444–5.
32 Marmor MF, Arden GB, Nilsson SEG, Zrenner E. Standard for clinical electroretinography. *Arch Ophthalmol* 1989; **107:** 816–9.
33 Frishman LJ, Karwoski C. The d-wave. In: Heckenlively JR, Arden GB, ed. *Principles and practice of clinical electrophysiology of vision.* St Louis: Mosby, 1991: 112–4.
34 Sieving PA. Photopic ON- and OFF-pathway abnormalities in retinal dystrophies. *Trans Am Ophthalmol Soc* 1993; **91:** 701–73.
35 Behrens F, Foerster MH, Petsch J, Weiss LR. A new apparatus measuring the clinical electrooculogram (DC-EOG) automatically. *German J Ophthalmol* 1993; **2:** 382.
36 Marmor MF, Zrenner E. Standard for clinical electrooculography. *Arch Ophthalmol* 1993; **111:** 601–4.
37 Wolf J, Arden GB. Selective loss of magnocellular function in a patient suffering from melanoma-associated retinopathy (MAR). *J Physiol* 1994; **475:** 42P.
38 Wolf J, Arden GB. Selective loss of magnocellular function in melanoma associated retinopathy. *Invest Ophthalmol Vis Sci* 1994; **35:** 2117.
39 Guyer DR, Tiedemann J, Yannuzzi LA, Slakter JS, Parke D, Kelley J, *et al.* Interferon-associated retinopathy. *Arch Ophthalmol* 1993; **111:** 350–6.
40 Rao NA, Biswas J. Retinal autoimmunity. In: Ryan SJ, ed. *Retina.* St Louis: Mosby, 1994: 187–99.
41 Albert DM, Sober AJ, Fitzpatrick TB. Iritis in patients with cutaneous melanoma and vitiligo. *Arch Ophthalmol* 1978; **96:** 2081–4.
42 Donaldson RC, Canaan SA, McLean RB, Ackerman LV. Uveitis and vitiligo associated with BCG treatment for malignant melanoma. *Surgery* 1974; **76:** 771–8.
43 Gass JDM. Acute Vogt-Koyanagi-Harada-like syndrome occurring in a patient with metastatic cutaneous melanoma. In: Saari KH, ed. *Proceedings of the international symposium on uveitis.* Amsterdam: Elsevier, 1984: 407–8.
44 Miyake Y, Yagasaki K, Horiguchi M, Kawase Y, Kanda T. Congenital stationary night blindness with negative electroretinogram. A new classification. *Arch Ophthalmol* 1986; **104:** 1013–20.
45 Gouras P. Retinal circuitry and its relevance to diagnostic psychophysics and electrophysiology. *Curr Opin Ophthalmol* 1992; **3:** 803–12.
46 Vardi N, Matesic DF, Manning DR, Liebman PA, Sterling P. Identification of a G-protein in depolarizing rod bipolar cells. *Vis Neurosci* 1993; **10:** 473–8.