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PO Box 117
221 00 Lund
+46 46-222 00 00

Full-field ERG, multifocal ERG and multifocal VEP in patients with retinitis pigmentosa and residual central visual fields

Lotta Gränse, Vesna Ponjavic and Sten Andréasson

Department of Ophthalmology, University Hospital of Lund, Lund, Sweden

ABSTRACT.

Purpose: To evaluate (with three different electrophysiological methods) the residual retinal function in a selected group of patients with retinitis pigmentosa and remaining small central visual fields.

Methods: Fourteen patients from several different genetic subgroups, who had been followed with visual acuity and visual field testing for periods up to 32 years, were examined. Ophthalmological examination included full-field electroretinography (ERG), multifocal electroretinography (mfERG) and multifocal visual evoked potential (mfVEP).

Results: The ERGs were severely reduced in all patients. The mfERGs demonstrated the residual central retinal function in five of the patients. The mfVEPs showed measurable amplitudes centrally in most of the patients. The follow-up examinations demonstrated the slowly progressive course of the disease with preservation or only slight further loss of visual fields over a period of 7–32 years.

Conclusion: Patients with retinitis pigmentosa may not always follow the typical natural course with progressive loss of visual fields, which may in some patients remain unaffected over several decades. Multifocal ERG and mfVEP may be clinically useful for evaluating remaining visual function in these patients.

Key words: retinitis pigmentosa – full-field electroretinography – multifocal electroretinography – multifocal visual evoked response – visual outcome

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Introduction

Retinitis pigmentosa (RP) is a progressive retinal degeneration characterized by nyctalopia, concentric visual field loss and glare and in some patients, reduced visual acuity (VA). More than 100 forms of RP with different genotypes and phenotypes are known, and the visual outcome varies between different

subtypes as well as between members of the same family (Fishman 1978; Marmor 1980, 1991; Berson et al. 1985; Farber et al. 1985; Berson 1993; Grover et al. 1998, 1999). Berson et al. (1985) described the natural course of RP in 100 patients, whom they followed for 4 years. They discovered that 23% of the patients experienced no significant decrease in retinal function during this period. However,

it is believed that all RP patients eventually lose their visual fields over a longer time period (Berson et al. 1985; Berson 1993).

There are several ways of monitoring the visual loss in patients with RP (Marmor 1980, 1991; Berson et al. 1985; Berson 1993; Grover et al. 1998). Objective electrophysiological tools have been of major importance for this purpose, of which probably the most important is the full-field electroretinogram (ERG) (Karpe 1945; Björk & Karpe 1951; Marmor 1979; Andréasson et al. 1988, 1997; Berson 1993). To assess the central retinal function only, pattern electroretinography has been used with valuable results (Holder 2001; Robson et al. 2003). Recently, two new electrophysiological methods, the multifocal electroretinogram (mfERG) (Sutter & Tran 1992; Barse & Sutter 1996; Gränse et al. 2001; Vajaranant et al. 2002) and the multifocal visual evoked response (mfVEP) (Baseler et al. 1994; Klistorner et al. 1998; Hood & Zhang 2000; Betsuin et al. 2001), have been introduced as methods for the same purpose for objective evaluation of function in the central part of the retina. Usually, deterioration of retinal function in RP patients initially involves the periphery and mid-periphery. In many adult RP patients, only the central visual fields are preserved. Therefore, we presumed that these new methods would give additional information on remaining visual function on re-examination of

patients previously examined with only full-field ERG.

For this study we selected from our RP register a group of patients with small central visual fields (< 20 degrees with object V₄) who had been previously examined on one or more occasions. We present the results from patients re-examined after 7–32 years with emphasis on the electrophysiological examinations.

Patients and Methods

Ophthalmological examination

Fourteen patients with different genetic forms of retinitis pigmentosa were studied (Table 1). They were between 21 and 85 years of age and had been followed for 7–32 years with VA and visual field testing and full-field ERG. Ophthalmological examination included assessment of best corrected VA, slit-lamp inspection, ophthalmoscopy and fundus photography. Kinetic perimetry was performed with a Goldmann perimeter using targets I₄ and V₄. The research procedures were carried out in accordance with insti-

tutional guidelines and the Declaration of Helsinki.

Full-field electroretinography (ERG)

Electroretinograms were recorded in a Nicolet Viking analysis system (Nicolet Biomedical Instruments, Madison, Wisconsin, USA), as described previously (Andréasson et al. 1997; Gränse et al. 2001) deviating from ISCEV standards by using a weaker flash (0.8 cd s/m²) than the standard flash (1.5–3.0 cd s/m²) and routinely using a notch filter, when examining RP patients. A Burian-Allen bipolar contact lens was applied on the topically anaesthetized cornea together with a ground electrode on the forehead. Responses were obtained with a wide-band filter (– 3 dB at 1 Hz and 500 Hz); stimulation was with single full-field flashes (30 µs) of dim blue light (Wratten filters 47, 47A and 47B) and white light (0.8 cd s/m²). If responses measuring less than 10 µV were recorded with single white flashes, recordings were also obtained with computer averaging (30 flashes), a bipolar artefact rejecter and a line frequency notch filter (50 Hz). Cone responses were obtained

with 30 Hz flickering white light (0.8 cd s/m²) averaged from 20 sweeps. To obtain small cone responses in the RP patients, the stimulation also included 200 flashes of flickering white light (30 Hz) and a digital narrow band-pass filter tuned to 30 Hz (Andréasson et al. 1988). These adjustments were not needed in the control group and therefore were not used.

On re-examination only the right eye of the patient was tested. Results of the full-field ERG responses were compared with normal values obtained from 70 normal subjects.

Multifocal electroretinography (mfERG)

Multifocal ERGs were recorded using the visual evoked response imaging system (VERIS) (EDI, San Mateo, California, USA), developed by Sutter et al. (Sutter & Tran 1992; Bearnse & Sutter 1996). The stimulus matrix consisted of 103 hexagonal elements displayed on a screen on the infra-red (IR) camera and driven at a 75 Hz frame rate. The sizes of the hexagons were scaled with eccentricity to elicit approximately equal amplitude responses at all locations. At a viewing distance of 5 cm the radius of the stimulus array subtended approximately 20–25 degrees. The luminance of each hexagon was independently alternated between black and white according to a pseudorandom binary m-sequence at 75 Hz. The responses were passed through a band-pass filter at between 10 Hz and 300 Hz. A small black fixation object was placed at the centre of the stimulus matrix. After dilation of the pupil and topical anaesthesia of the cornea, a gold bipolar ERG electrode was applied to the ocular surface and a ground electrode to the forehead. The camera part of the IR camera was used to control the fixation. The optical correction was made in the lens system of the camera for each patient.

Multifocal visual evoked potential (mfVEP)

Multifocal VEPs were recorded using the same VERIS system as above when recording mfERG (Baseler et al. 1994; Baseler & Sutter 1997). The visual stimuli on a screen in the IR camera had the appearance of a dartboard containing 60 segments. These segments were cortically scaled in order to produce 60 recordings of approximately

Table 1. Clinical characteristics and electrophysiological results in 14 patients with different types of RP and long persistent central visual fields. The 30 Hz flicker cone ERG responses were measured with the digital band-pass filter for all the patients but not for the controls. The 'mfERG central' is the response from ring 1 and 2 averaged together.

Patient	Age (years)	Geno type	Visual acuity	Years of follow-up	Goldmann field degree		30 Hz cone ERG (µV)	mfERG central (nV)	mfVEP central (nV/deg ²)
					V:4e/I:4e	Visit 1 Follow-up			
1	21	RP 2	20/20	12	20/10*	20/8*	2.8	14.1	21.1
2	26	RP 2	20/25	12	70/12	15/10*	1.9	8.5	13.9
3	32	RP 3	20/100	9	15/3*	7/3*	0.4	ND	6.8
4	34	RP 2	20/20	13	8/4*	8/4*	1.1	6.3	6.7
5	36	RP 3	20/100	9	10/3*	8/2*	0.9	ND	ND
6†	42	DOM	20/60	12	20/10	8/5	0.8	7.0	11.2
7	45	ISO	20/50	11	7/4	5/3	ND	ND	ND
8	46	AR	20/30	9	20/18	10/5	0.3	ND	5.1
9	48	ISO	20/30	32	12/8	5/3	0.6	ND	10.6
10	57	ISO	20/100	18	5/3	5/2	ND	ND	8.1
11	58	AR	30/40	8	15/10*	15/10	0.3	ND	5.9
12	62	DOM	20/200	10	10/4	10/8‡	1.3	ND	8.1
13	76	DOM	20/30	7	35/25	30/22	9.2	6.7	ND
14	82	ISO	20/60	9	15/10	10/7	5.4	ND	12.3
Mean (2SD) in 70 controls							63 (41)		
Mean (2SD) in 11 controls							25.8 (12.9)		
Normal in 10 controls									> 20

* Central field and a temporal crest.

† Left eye examined.

‡ Cataract extraction undergone.

ND = non-detectable.

similar amplitude from the visual cortex. Each segment contained a checkerboard pattern with 16 checks, eight white and eight black, alternating in pseudorandom binary m-sequences at 75 Hz. The signals were amplified 100 000 times and passed through a band-pass filter at between 3 Hz and 100 Hz. The electrodes were placed on theinion and 4 cm above the inion and the ground electrode was placed behind the right ear. These electrode positions evoked a little more difference between the amplitudes from the upper and lower hemifields but there was much less muscle disturbance in the responses. The subjects were seated comfortably (to minimize muscle interactions), fixating the centre of the dartboard approximately 5 cm from the IR camera corresponding to a 20–25-degree segment of the visual field. To control the fixation, the camera part of the IR camera was used in the same way as above. The distance to the IR camera was easily controlled because the sharpness of the fixation control picture was altered by even very small movements. The pupils were undilated and the stimulation was monocular. A dim room light was used as background illumination.

Results

Ophthalmological examination

All the data collected were further analysed using results from the right eye. One patient had a previous injury of the right eye and therefore the results from the left eye were used. Visual acuity was at least 20/200, and in the majority of the patients better than 20/40 (Table 1). Fundus examination demonstrated changes typical of RP with attenuated vessels, bone-spicular pigmentations and different degrees of optic disc pallor. All the patients had a preserved macular residue without any sign of macular oedema. Comparison of visual fields was made to evaluate the progression rate of RP among the patients. The progression rate of the visual field defect was variable, but most patients progressed slowly. In one patient, who had been followed for 32 years, only minor changes of the residual visual field were detectable (Table 1). All patients had been examined for genotype. Three patients had the RP2

genotype (linkage RP2) and two the RP3 genotype (RPGRintron13splicing defect) (Table 1). The remaining patients are still under genetic investigation.

Full-field ERG

All patients had been previously examined with different ERG methods, which made comparison between them difficult. Using digital narrow band-pass filters and 30 Hz flicker full-field ERG, as described above, residual responses could be verified in 12 of 14 examined RP patients (Table 1).

Multifocal ERG

Multifocal ERG averages were measured from the three central areas and compared with those in 10 normal individuals. The most central area comprised rings 1 and 2 averaged together as 1+2 (Fig. 1) and identified as 'mfERG central' in Table 1. In five of the 14 examined patients, remaining central retinal function could be verified in this area with reliable responses over 5.0 nV using mfERG (Table 1). This is demonstrated in patient 1 (Fig. 1). These findings corresponded well with the visual fields and were in accordance with cone responses in the full-field ERG.

Multifocal VEP

All patients were examined with the mfVEP, which reflects the activity in the visual cortex cerebri. Because the registration is bipolar the results have opposite polarity in the upper and lower hemifields and there is then an elimination of the amplitudes in the horizontal mid-line (Fig. 1) (Klistorner et al. 1998; Hood & Greenstein 2003). The amplitudes in a defined central region of the cortical response, where we usually obtain the best results (Fig. 1) (Gränse et al. 2003), were measured and compared with those in 10 normal controls (Table 1). All but one of the patients had pathological and reduced responses in this central region and remaining cortical responses could be verified in 11 of 14 patients, demonstrating function within 5–10 degrees of the visual field. This also validates the theory that mfERG signals are propagated through the optic pathways to the visual cortex.

Discussion

Retinitis pigmentosa is a progressive retinal degeneration characterized by a severe loss of visual function, initially affecting night vision and peripheral visual fields. Recently, more than 100 genetic forms of this disorder have been identified. The visual outcome varies markedly between different genetic subtypes, but also between different members of the same family. Characterization and understanding of the visual loss is important for monitoring patients with RP and for predicting visual outcome; therefore different methods have been developed for this purpose (Berson 1993).

Electrophysiological findings in RP patients were reported as early as 1951 (Björk & Karpe 1951), demonstrating that the electroretinograms were often extinguished. As retinal function in these patients is often reduced more than 90%, it can be difficult to obtain residual retinal responses. Several attempts have been made to measure the residual response in patients with markedly reduced retinal function (Henkes et al. 1956; Sandberg et al. 1996; Sieving et al. 1998). Since 1985 the narrow band-pass 30 Hz flicker ERG has frequently been used for monitoring these patients (Berson 1993).

The standardized full-field ERG, which reflects the total retinal response, in combination with computer averaging and the use of analogue and/or digital filters, has made it possible to estimate the small residual retinal response in most RP patients (Andréasson et al. 1988). These adjustments were not used in the control group and may, of course, influence the comparison of results. However, without this technique it would not be possible to obtain any recordable amplitude at all in many RP patients. Nonetheless, in these specific patients with only small central visual fields, the ERG may not be sensitive enough to detect the minimal regional response from the central retina. Pattern ERG (PERG) is an established technique to assess the central retinal function. The value of PERG in combination with autofluorescence when examining RP patients was described in a study by Robson et al. (2003). In the present study we have demonstrated that small remaining responses could also be measured

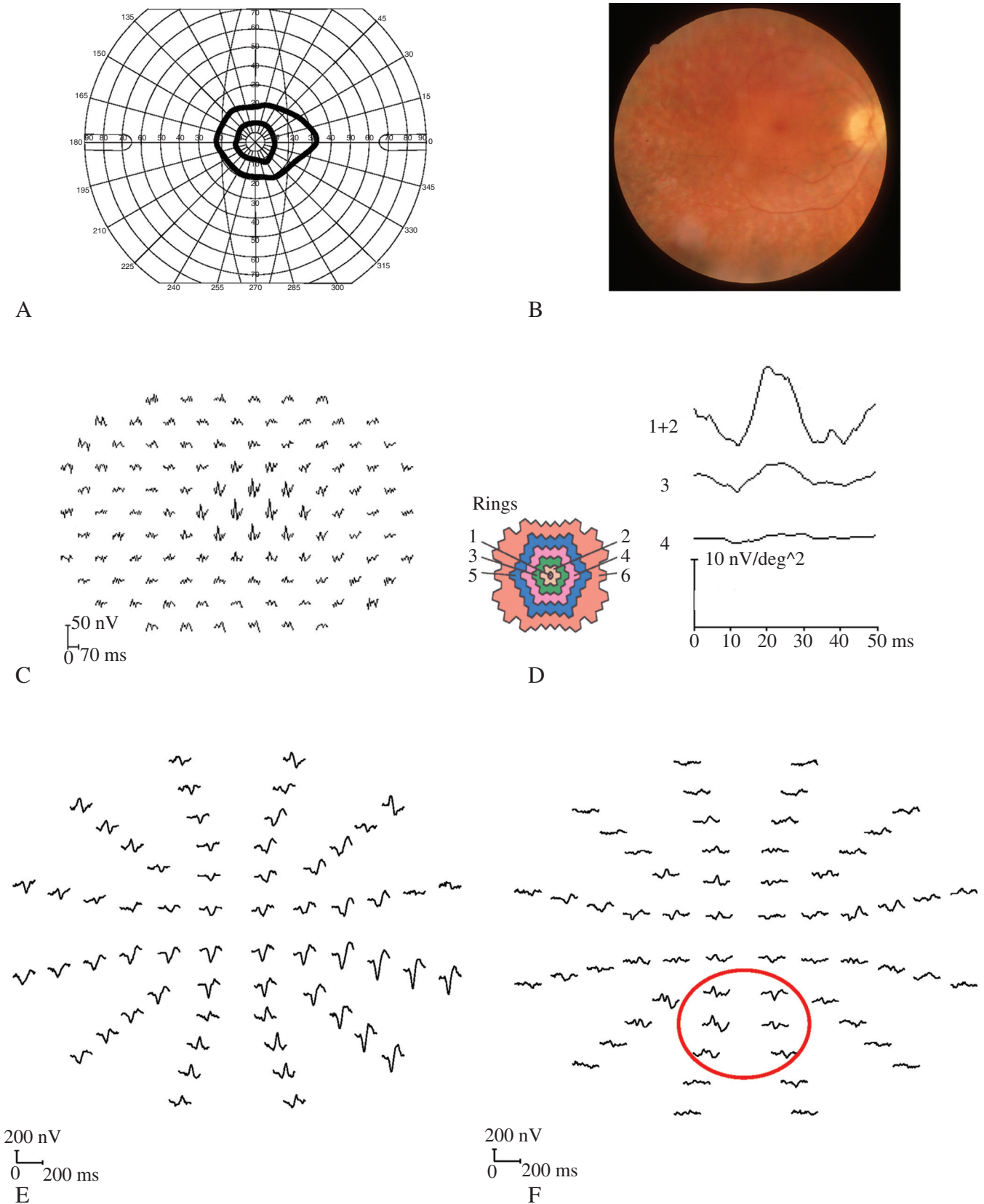


Fig. 1. Results, right eye, from one RP patient (patient 1) with lengthy follow-up (12 years). (A) The small remaining visual field. (B) The fundus picture. (C) The mfERG traces (field view). (D) Averages from the three central areas, where the amplitudes were measured. Rings 1 and 2 were averaged together as 1 + 2. (E) The mfVEP (field view) result from a normal subject for comparison. (F) The mfVEP (field view) result from the RP patient, demonstrating the corresponding cortical response to the remaining central retinal function. The red ring presents the region in the mfVEP where amplitudes were measured. Because of different polarity in the results from the upper and lower hemifields, there is an elimination of the registered amplitudes in the central horizontal line. The most peripheral amplitudes are reduced compared to the normal subject and show good correlation to the remaining central visual field.

with mfERG in some patients with RP. Similar findings were also described by Holopigian et al. (2001) and by Vajaranant et al. (2002), who demonstrated retinal function among carriers of X-linked retinitis pigmentosa. According to these studies, the mfERG may be another objective method for measuring residual function in RP patients with small residual function in the macular region and slight reduction in VA.

The mfERG can be combined with the mfVEP, another objective method used for measuring the cortical response from the central part of retina. Several studies have demonstrated the value of mfVEP in verifying visual field defects in various disorders (Klistorner et al. 1998; Hood & Zhang 2000; Betsuin et al. 2001), mainly in the optical pathway. In the present study of RP patients with remaining small visual fields, the cortical responses measured by mfVEP demonstrated a similar preservation of central amplitudes. As mentioned before, several attempts have been made to correlate ERG responses with the visual field (Sandberg et al. 1996). Multifocal VEP in combination with mfERG could be a valuable tool for better understanding the visual function of this group of patients. In both these methods we used the IR camera, both for the stimulation pattern and for fixation control at the same time. This has not been previously described for mfVEP and is an improvement compared to previous eye camera control of fixation.

Berson et al. (1985) found that 23% of a group of patients with retinitis pigmentosa did not have any progression (further loss of visual fields) during a period of 3–4 years. In the present study, with its genetically different subgroups, we found an evident progression of visual field loss in some patients, while other patients, with different genetic backgrounds, demonstrated an extremely slow progression of visual field loss over a period of several decades. The genetic background is probably important for the prognosis, but we have still not been able to achieve an exact genetic diagnosis in two of the patients, in whom visual function seems to have remained stable for several decades (patients 9 and 10) (Table 1).

In a published study by Flynn et al. (2001), the authors found, by examining

longitudinal data, that the presence or absence of a macular lesion at the patient's initial visit was an important determinant of VA loss in this cohort of RP patients. These findings are of value when counselling RP patients regarding their prognosis for preservation of VA. The results imply that an mfERG should be assessed at the first visit, for objective documentation of the macular function and prediction of the prognosis.

A well studied phenomenon is the retinal rod–cone interaction that explains why diseases that selectively affect the rods lead to secondary cone degeneration. This phenomenon may also explain the remaining visual fields in some patients who do not follow the typical progressive natural course of retinitis pigmentosa. If we assume that all rods are degenerated before the apoptotic mechanism has been initiated in all cones, then the remaining healthy cones (especially the isolated macular cones, which are not surrounded by rods) may survive for the rest of the patient's life (Sandberg et al. 1981; Li et al. 1996; Curcio 2001).

In summary, this study demonstrates two new electrophysiological methods, mfERG and mfVEP, that might be of clinical importance for evaluating and monitoring the residual central retinal function and small remaining central visual fields in patients with retinitis pigmentosa. The results also demonstrate that some patients with an atypical disease course may retain their central visual fields for many years, up to four decades.

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Correspondence:
Dr Lotta Gränse
Department of Ophthalmology
University Hospital of Lund
S-221 85 Lund
Sweden
Tel: +46 46 17 14 70
Fax: +46 46 211 50 74
Email: lotta.granse@telia.com