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Retinal dysfunction in eyes of patients with BRCA1 gene mutation

Dysfunkcja siatkówki w oczach pacjentek z mutacją genu BRCA1

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Summary: Purpose: To assess the retinal function in BRCA1 gene mutation carriers.
Material and methods: Thirty unaffected patients (60 eyes) with constitutional BRCA1 gene mutation were studied. Flash ERG recordings were performed in accordance with the International Society for Clinical Electrophysiology of Vision (ISCEV) standards.
Results: In ERGs, in the maximal response, amplitude of a-wave ($p<0.02$) was reduced. In the cone single- flash response, the amplitude of a-wave ($p<0.04$) was also reduced. In the scotopic oscillatory potentials (OPs), we noted: increased amplitude of OP2 ($p<0.0006$), increased index of OP amplitude (O1+O2+O3+O4) ($p<0.04$), and increased latencies of OP1 (<0.05) and OP3 ($p<0.004$) and OP4 ($p<0.03$).
Conclusions: Slight dysfunction of rods, cones and inner retinal layers is present in asymptomatic carriers of BRCA1 gene mutation.
Słowa kluczowe: mutacja genu BRCA1, siatkówka, ERG błyskowy.
Key words: BRCA1 gene mutation, retina, flash ERG.

Introduction

BRCA1 is one of major genes related to predisposition to familial cancer syndromes. BRCA1 is located on chromosome 17q21, its mRNA is 7.8 kb in length and 24 exons span almost 100 kbp of genomic DNA. Female carriers of BRCA1 mutations are of lifetime risk of breast /ovarian cancers achieving even 80-90%. For several ethnic groups a few founder mutations dominating entire populations have been described. It is estimated that the frequency of BRCA1 founder mutations among Askhenazi Jews is around 1: 100 and in Poland 1: 200 (1-5).

Purpose

Our initial ERG results (6) suggested that dysfunction of rods, cones and inner retinal layers is present in BRCA1 gene mutation carriers. In order to verify our preliminary findings, we decided to assess the retinal function in a two fold larger series of BRCA1 gene mutation carriers.

Patients and methods

The ERGs were performed on unaffected 30 females (60 eyes, mean age 34.5 ± 9.4 years) – carriers of BRCA1 gene mutation (exon 20-5382 ins C) from unrelated families diagnosed in Laboratory of Molecular Genetics of International Hereditary Cancer Center in Szczecin and 30 (60 eyes) healthy controls.

Mutations carriers and controls were matched as far as age, sex and refractive error were concerned.

Ocular findings in BRCA1 gene mutation group were as follows: Snellen visual acuity – 20/20 in all subjects; mean refractive error: -0.53 ± 1.0 D, normal anterior and posterior segment of the eye, normal color vision (Farnsworth Panel D-15- all 15 chips were ordered without any mistake by the patient according to color similarity) and normal visual field as measured by kinetic perimetry. Statistical analyses of electrophysiological parameters were performed for BRCA1 gene mutation carriers. Recordings of the full field flash ERG including scotopic oscillatory potentials (OPs) were performed with the use of UTAS-E 2000 system (LKC Technologies, Inc.). Parameters of stimulation as well as registration implemented in the test protocols of the system software were in agreement with the ISCEV standards [7].

Statistical analysis was performed using parametric (Shapiro – Wilk test, Student t – test), and non parametric (Mann – Whitney test) tests with significance level p Ł 0.05. This study was approved by the Committe of Medical Ethics of Pomeranian Medical University in Szczecin.

	Amplitude (μV)					Latency (ms)				
	N	BRCA1	N	C	p–value	N	BRCA1	N	C	p–value
Rod										
b – wave	+	177.2±40.0	+	182.9±44.4	NS	+	100.6±7.6	+	101.2±11.8	NS
Maximal										
a – wave	+	232.1±41.0	+	253.3±50.7	< 0.02	–	22.3±1.0	+	22.3±1.0	NS
b – wave	+	466.8±93.1	+	495.4±83.7	NS	–	44.6±2.7	+	45.6±3.0	NS
Cone										
a – wave	+	37.9±7.9	+	41.4±9.7	< 0.04	–	14.0±0.9	–	13.9±0.7	NS
b – wave	+	135.4±33.8	+	135.4±36.1	NS	–	30.1±0.9	+	30.1±0.9	NS
30 Hz flicker										
b – wave	+	96.7±20.4	+	96.8±24.4	NS	+	28.4±1.2	+	28.9±1.3	NS

BRCA1 – BRCA1 gene mutation group
C – control group
N – normal distibution. NS – not significant
Values are mean ± standard deviation

Tab. I. Statistical analysis of the flash ERG results in unaffected BRCA1 gene mutation carriers and healthy controls (n=60 eyes).

	Amplitude (μV)					Latency (ms)				
	N	BRCA1	N	C	p-value	N	BRCA1	N	C	p-value
OP1	–	36.2±14.1	–	36.2±11.3	NS	–	18.4±0.7	–	18.2±0.6	<0.05
OP2	–	92.6±30.9	–	74.2±30.8	<0.0006	–	25.0±0.7	–	24.9±0.7	NS
OP3	–	55.9±20.2	–	56.0±18.5	NS	–	31.8±0.9	–	31.3±0.9	<0.004
OP4	–	24.8±11.1	–	28.6±18.9	NS	–	40.7±2.1	–	40.0±2.3	<0.03
O1+O2+O3+O4	–	209.5±57.2	–	195.0±64.0	<0.04					

BRCA 1 – BRCA1 gene mutation group
C – control group
N – normal distribution
NS – not significant
Values are mean ± standard deviation

Tab. II. Statistical analysis of the OPs results in unaffected BRCA1 gene carrier mutation and in healthy controls (n = 60 eyes).

Results

The flash ERG parameters as well as statistical analysis for BRCA1 gene mutation carriers and controls are shown in tables I and II.

During dark adaptation state, in mixed cone-rod ERG (Maximal response) reduced amplitude of the a- wave was obtained (a-wave: 232.1 ± 41.0 μV versus 253.3±50.7μV- p<0.02). The b-wave amplitude was also reduced but not statistically significant. Differences in latencies of a- and b- waves also were not statistically significant. Figure 1 ilustrates an example of abnormal mixed cone-rod ERG (Maximal response) with reduced amplitude of a-wave in unaffected BRCA1 gene mutation carrier.

Rod b-wave ERG was not altered. During light adaptation state, in cone single white flash ERG, reduced amplitude of a-wave was found (a-wave: 37.9 ± 7.9 μV versus 41.4 ± 9.7 μV- p<0.04). Differences of b-wave amplitude in single flash and flicker as well as latency of the a- and b-waves were not statistically significant (Tab. I).

In the OPs, statistically significant increase of OP2 amplitude (OP2-wave: 92.6 ± 30.9 μV versus 74.2 ± 30.8 μV- p<0.0006) and increase of index of OP amplitude (O1 +O2 +O3 +O4): 209.5 ± 57.2 versus 195.0 ± 64.0 μV- p<0.04) were obtained. Increase of latencies of OP1 (P1: 18.4 ± 0.7 ms versus 18.2 ± 0.6 ms- p< 0.05) OP3 as well as OP4 waves (OP3: 31.8 ± 0.9 ms versus 31.3 ± 0.9 ms- p<0.004; OP4: 40.7 ± 2.1 ms versus 40.0 ± 2.3 ms- p<0.03) were observed. Remaining OPs parameters were not altered (Tab. II).

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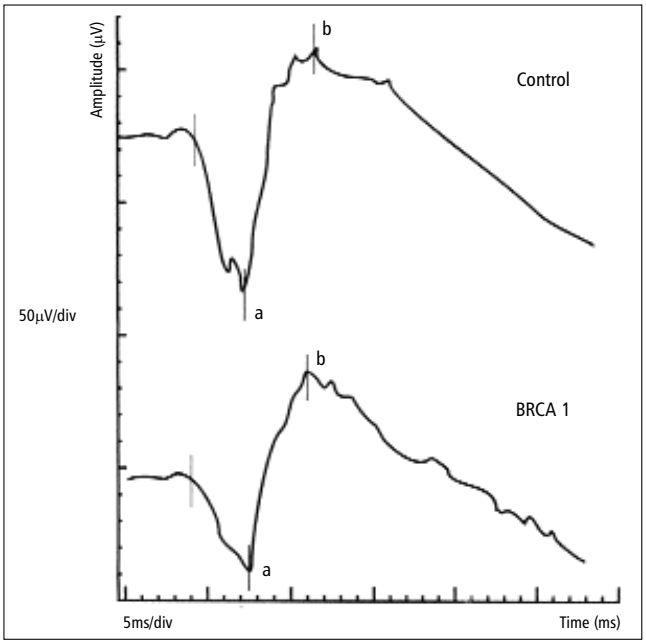

Fig. 1. An example of abnormal mixed cone–rod ERG (Maximal response) with reduced amplitude of a–wave in unaffected BRCA1 gene mutation carrier.

Discussion

In this study, we showed that dysfunction of the rod and cone photoreceptors as well as inner retinal layer is present in BRCA1 gene mutation carriers.

Enlargement of the number of analysed eyes of patients with BRCA1 gene mutation (from 30 to 60 eyes) did not change significantly the ERG results obtained in the group of patients published previously (6). There is still slight dysfunction of rods, cones and inner retinal layers.

ERG abnormalities were observed already in carriers of several retinal diseases such as rod – cone dystrophy (retinitis pigmentosa in different genetic patterns), cone – rod dystrophy (8-9). In this study, abnormalities were detected in flash ERG – reduced amplitude of the a- wave in dark and light adapted state, and in OPs – hypernormal OP2 amplitude and increased latencies of OP3 and OP4 as well as hypernormal index of OP amplitude (O1 + O2 + O3 + O4).

It is well known that the absorption of light by visual pigment in photoreceptor outer segments initiates a sequence of molecular events that generates hyperpolarization of the photoreceptors leading to occurrence of the a – wave.

There is a suitable amount of evidence from different sources that the scotopic (dark adapted) ERG a-wave reflects essentially solely rod photoreceptor-cell activity but photopic ERG a – wave is mainly of cone photoreceptor origin (9). Obtained changes in scotopic and photopic a – waves suggest dysfunction of rod and cone photoreceptors.

The cellular origin of OPs in the retina is uncertain. Current data suggest that cells of the inner retina – amacrine or possibly interplexiform cells, are the generators of these potentials (10). The changes in OPs suggest amacrine cells dysfunction after cone system stimulation because responses obtained after the conditioning flash are from the cone system (he conditioning flash having adapted the rod system so that it does not contribute to the subsequent flash – elicited OPs) (11). Electrophysiological changes seen in OPs are probably secondary to photoreceptors dysfunction.

Up to now, there is no study describing retinal dysfunction in patients with BRCA1 gene mutation and/ or changes in cooperating genes except of c-myc gene (12).

C-myc gene interacts with BRCA1 protein close to nuclear localization signals region (13).

Al-Ubaidi and co-workers (14) have developed transgenic mouse lines expressing a human interphotoreceptor retinoid-binding protein (IRBP) promoter-c-myc construct.

Transgenic c-myc mice exhibited a rapid reduction of cone-mediated responses and gradual loss of the rod ERG a – wave resulting in cone and rod degeneration. The results from this study support the possibility that aberrant expression of oncogene c-myc may underlie some forms of human rod and cone – rod dystrophy.

It can be hypothesized, that observed retinal dysfunction in BRCA1 gene mutation carriers is due to photoreceptor abnormalities related to abnormal expression of c-myc.

Our data suggest that it is reasonable to take into consideration the possibility of modifying effects of alterted BRCA1 protein on penetrance/expression level in patients with rod and cone – rod dystrophies. Possibly, such syndromes in BRCA1 carriers will be characterized by more severe outcome.

Dawson et al. reported functional disturbances of retina in patients with breast cancer (15). In a group of ten patients not characterized for genetic predispositions, abnormalities clustered mainly about dark adaptation (rod cell sensitivity), the blue sensitive retinal cells and the oscillatory component of photopic ERG. Electroretinographic changes detected in our paper were certainly different because BRCA1 carriers were showing photoreceptor dysfunction only. Thus it seems that rod and cone ERG abnormalities are characteristic feature not for all breast cancer patients but to subgroup of women being BRCA1 mutation carriers.

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