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Dopplerographic and electrophysiologic studies of retinitis pigmentosa in young people

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The work concerns the study of retinitis pigmentosa (RP) – a hereditary generalized retinal dystrophy. Purpose: to study the changes in hemodynamic parameters in the eye vessels and ERG indexes and to implement a correlation analysis of young patients with various stages of RP. 100 patients (200 eyes) at the age from 15 to 24 years old with RP were examined, among them 41 patients – women, 59 patients – men. Patients were culled into 3 groups according to the functional disorders: I – 31 patients (62 eyes) with initial stage of RP, II – 40 patients (80 eyes) with medium severe stage of RP, III – 29 patients (58 eyes) with severe stage of RP. All patients underwent CDI on the apparatus Toshiba "NEMIO XG SSA-580A" (Japan) with ultrasound probe 8 mHz and ERG (standard combined, 30 Hz flicker, photopic) on the apparatus ROLAND CONSULT Super Color Ganz feld Q450 SC (Germany). The results of CDI and ERG indicate statistically significant changes in medium severe and severe stages of RP, also point to the disorders referred to the initial stage. CDI in the patients with RP allows detecting hemodynamic disorders timely. Analysis of ERG parameters indicates an impairment of photoreceptors function in parallel to ocular blood flow disorders. So, CDI and ERG are required for the purposes of early diagnostics and monitoring of patients with RP as well as for therapeutic and preventive measures.

Keywords: *Retinitis pigmentosa (RP), colour Doppler imaging (CDI), electroretinography (ERG)*

INTRODUCTION

In spite of rapid scientific and technical progress in all the branches of medicine, to date there are the fields in which undertaken attempts to suspend pathological process or restore impaired functions are not effective. One group of such serious pathologies in ophthalmology is hereditary diseases. Retinitis pigmentosa (RP) is a hereditary generalized retinal dystrophy. This pathology results in vision loss to the extent of blindness. The solution of this problem has not been found yet, hence, RP is the cause of disability of children and adults. (Гашимова и др., 2010; Шамшинова, 2001; Щуко и др., 2010; Hamblion et al., 2010).

There are many works aimed to the study of various aspects of RP (Robson et al., 2006; Sandberg et al., 2011; Eden et al., 2013; Riera et al., 2017). In recent years, the problem of vascular disorders in RP has also been studied. In ophthalmology and dopplerographic ultrasound examinations are widely used for evaluation of the vessel conditions. Colour Doppler imaging (CDI) is one of the methods of Doppler ultrasonography, which gives the opportunity to get reliable information about the eye hemodynamics. This method is non-invasive, convenient for implementation, does not require special training. However, to date, little studies are known concerning analysis the eye vessels hemodynamics in RP (Касимов и др., 2012; Parodi et al., 2017).

ERG is a leading method for the evaluation of functional condition of the retina, in particular photoreceptors, and gives an opportunity of detecting not only marked dystrophic changes of the retina, but also of diagnosing the functional disorders, which precede clinical manifestations of RP (Dolan et al., 2002; Seeliger et al., 1998; Marmor

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et al., 2009). For this reason, it is noteworthy implementation of complex of Dopplerographic and electrophysiologic studies in determining the severity of dystrophic process in RP (Киселева и др., 2015; Zhang et al., 2013).

The work objective concludes in study of the changes in hemodynamic parameters in the eye vessels and ERG indexes and in implementation of a correlation analysis in young patients with various stages of RP**.**

MATERIALS AND METHODS

100 patients (200 eyes) with RP at the ages of 15-24 were examined. Among them, 41 patients were female and 59 were male. The patients were culled into 3 groups. Group I included 31 patients (62 eyes) with initial stage of RP. During ophthalmoscopy, these patients had a deposition of single characteristic "bone bodies" on extreme and middle periphery of the eye fundus, the field of vision was restricted concentrically up to 40 degrees, and visual acuity in average referred to 0.95 ± 0.03. Group II included 40 patients (80 eyes) with medium severe stage of RP. During ophthalmoscopy, these patients had marked pigmentation by the type of "bone bodies" on extreme and middle periphery of the eye fundus, the field of vision was restricted concentrically from 40 to 20 degrees, and visual acuity at the average was 0.50±0.26. Group III included 29 patients (58 eyes) with severe RP stage. In this group of patients, during ophthalmoscopy, the marked pigmentation of the "bone bodies" type on extreme and middle periphery of the eye fundus was also revealed, the field of vision was restricted concentrically below 20 degrees, and visual acuity at the average was equal to 0.2±0.16.

Ophthalmological research methods included visometry, refractometry, tonometry, perimetry, biomicroscopy, and ophthalmoscopy. As well, all the patients underwent ERG – total, rhythmic 30 Hz (RERG), macular (MERG) – with application of the device ROLAND CONSULT Super Colour Ganz feld Q450 SC (Germany).

Ultrasound examinations included B-scanning of the eyeball and Doppler ultrasonography of the eye vessels using the CDI method on the apparatus Toshiba “NEMIO XG SSA-580A” (Japan) with ultrasound probe 8 mHz. Ophthalmic artery (OA), central retinal artery (CRA) and posterior short ciliary arteries (PSCA) were studied. The velocity parameters Vmax (maximum systolic velocity of blood flow), Vmin (final diastolic velocity of blood flow) and RI (resistance index) were determined in these vessels. In order to determine standard age indicators, Doppler ultrasound examination of 50 practically healthy volunteers of 15-24-year-old, included into the control group, was performed.

Statistical data processing was performed using Microsoft Excel-2010. The reliability of the results was evaluated using the Student's t-test, and the differences between average values were accepted as reliable at $p<0.05$. In order to analysing statistical interrelation between the recorded parameters, the Pearson correlation calculation method was used.

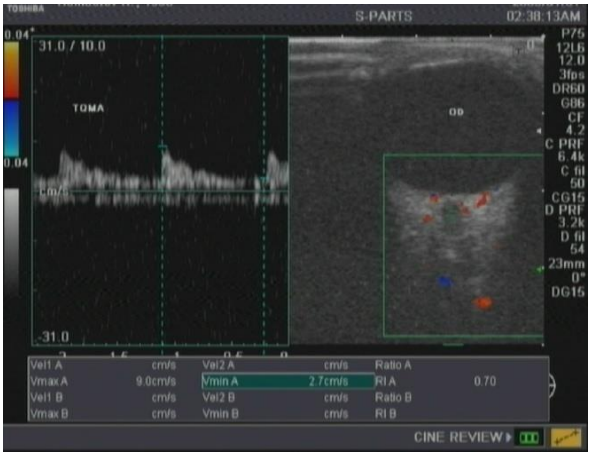
RESULTS AND DISCUSSION

In accordance to the results of CDI, various changes of hemodynamic parameters were observed in all the studied vessels. In OA, significant decrease in RI was found in the patients of group III. The values of Vmax and Vmin parameters of their vessels corresponded to the normative values in all studied groups. In CRA and PSCA significant changes in hemodynamic parameters were found in the patients of all the groups. Moreover, the most marked disturbances were observed in the patients of groups II and III (Table 1; Figure 1 and 2).

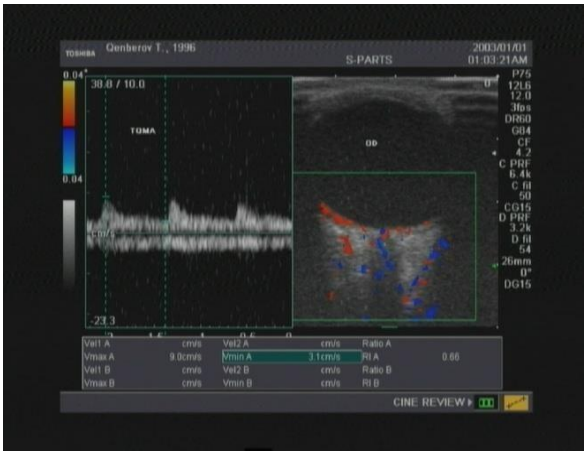
Thus, in OA of patients of group III, RI in average was equal to 0.71±0.02, and it was significant decrease with $p < 0.01$ (Table 1).

In CRA in the patients group II, Vmax was decreased significantly up to 8.1±0.07 cm/sec with $p<0.01$, and in group III – up to 7.0±0.1 with $p<0,001$. In the same vessels, Vmin in group II corresponded to average 3.05±0.1, and in group III – 2.2±0.01, both changes were significant with $p<0.01$. RI in the CRA was also recorded as reduced in all the groups and at average was 0.62±0.1 ($p<0.01$) in group II, and 0.60±0.03 ($p < 0.001$) in group III (Table 1).

(a) Group I patient



(b) Group II patient



(c) Group III patient

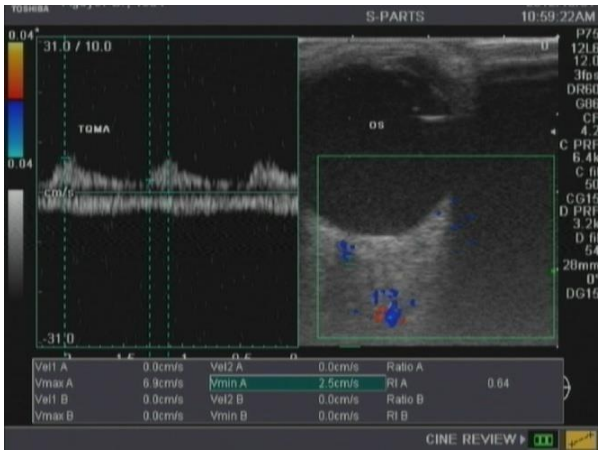
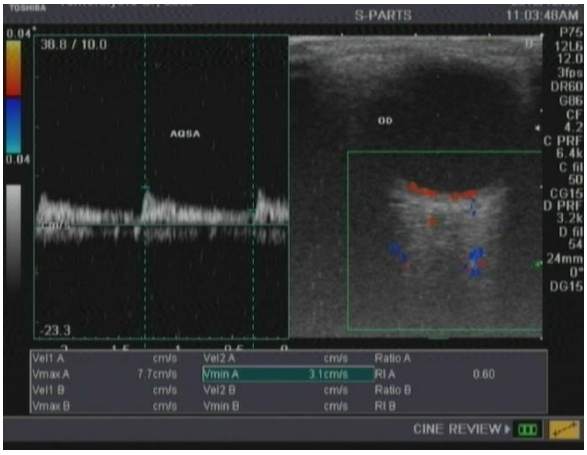
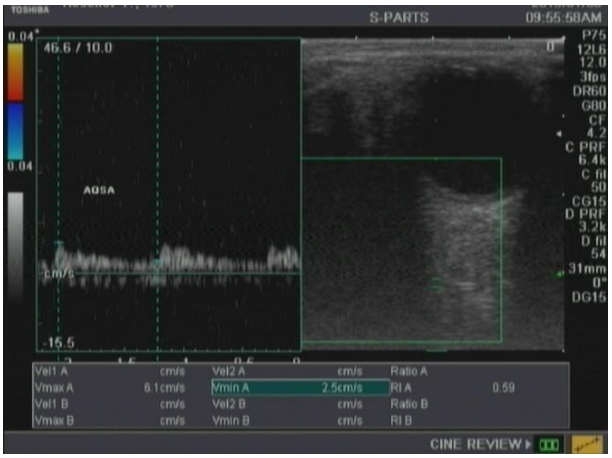


Figure 1. Sonograms of the CDI of the CRA.

(a) Group I patient



(b) Group II patient



(c) Group III patient

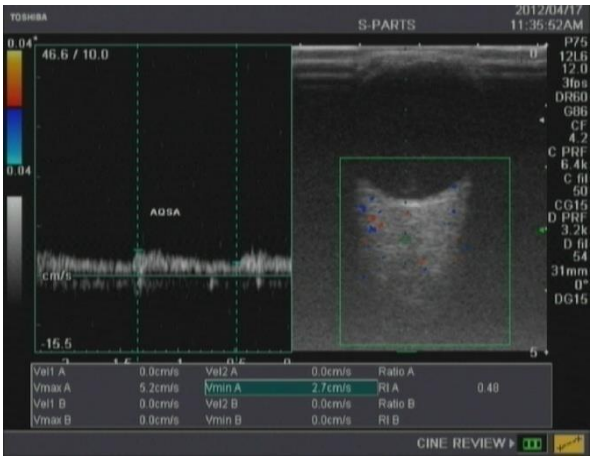


Figure 2. Sonograms of the CDI of the PSCA.

Table 1. Results of CDI in RP

Vessels	Parameters	I группа	II группа	III группа	Норма
OA	Vmax (sm/sec)	37.01 ± 0.7	37.25 ± 0.2	37.0±0.2	37.3 ±0.3
	Vmin (sm/sec)	8.9 ± 0.01	9.01 ± 0.1	9.1 ± 0.1	9.47 ±0.12
	RI	0.74±0.1	0.74±0.04	0.71±0.02**	0.75 ±0.002
CRA	Vmax (sm/sec)	11.2± 0.5*	8.1±0.07**	7.0±0.1***	13.2 ±0.1
	Vmin (sm/sec)	3.4 ± 0.02*	3.05 ± 0.1**	2.2 ± 0.01**	3.82 ±0.04
	RI	0.66±0.05**	0.62±0.1**	0.60±0.03***	0.71 ±0.002
PSCA	Vmax (sm/sec)	7.5 ± 0.09**	6.2±0.01***	5.0±0.8***	9.5 ±0.1
	Vmin (sm/sec)	3.2 ±0.2**	3.1± 0.05**	2.6±0.01***	3.67 ±0.04
	RI	0.55±0.01**	0.52±0.01***	0.47±0.02***	0.61 ±0.002

* - p < 0.05; ** - p < 0.01; ***- p < 0.001 – statistically significant difference in relation to the norm

Table 2. Indicators of total ERG, MERG and RERG

Indicators			Group I	Group II	Group III	Norm
Total ERG	a- wave	amplitude (μV)	98.3±11.4*	49.6±8.0***	15.3±7.1***	155-356
		latency (ms)	20.3±3.9	22.8± 4.2*	23.5±4.0*	14-22
	b-wave	amplitude (μV)	270.9±10.1*	114.4±8.2***	40.1±7.0***	290-654
		latency (ms)	43.5±3.1	44.7±2.3	51.0±2.2*	33-46
MERG	a- wave	amplitude (μV)	24.9 ± 4.7	22.0 ± 3.2*	19.3 ±4.0**	26-62
		latency (ms)	15.7 ± 2.3	19.6 ± 2.0*	25.1 ± 4.1**	13-16
	b-wave	amplitude (μV)	100.3 ± 6.1	61.2 ± 5.2**	34.7 ± 2.6***	103-250
		latency (ms)	32.1 ± 1.9	34.2 ± 6.0*	43.7 ± 4.0*	29-33
RERG	amplitude N1– P1 (μV)		53.3±3.5 *	40.1±4.3**	20.9±3.6**	57-223

* - p < 0.05; ** - p < 0.01; ***- p < 0.001 –statistically significant difference in relation to the norm

In the PSCA in the patients' group II, Vmax value corresponded to average of 6.2±0.001 (p<0.001), and in group III – 5.0±0.8 (p<0.001). Vmin values in PSCA in group II were equal to average of 3.1±0.05 (p<0.01), in group III – 2.6±0.01 (p<0,001). RIs of this vessel were also statistically significantly reduced to 0.52±0.01 with p<0.001 in group II, and to 0.47±0.02 with p < 0.001 in group III (Schedule 1).

Changes in ERG indicators were observed in all the studied patients groups, moreover statistically significant violations were registered even in the patients with initial stage of RP.

In accordance to total ERG data, significant disturbances were detected in the groups II and III (Table 2). The amplitude of the a-wave in the patients of group II was reduced to an average of 49.6±8.0 μV, and in patients group III – 15.3±7.1 μV. The amplitude of the b-wave in patients group II was reduced to average of 114.4±8.2 μV, and in patients group III – 40.1±7.0 μV. These changes were significant with p<0.001. In the patient group I, the amplitudes of a- and b-waves had statistical confidence values of p<0.05. The latency of a-wave in patients group II increased to an average of 22.8±4.2 msec (p<0.05), and in the patients group III – to 23.5± 4.0 msec (p<0.05). The latency of the b-wave in patients group II corresponded to 44.7±2.3 msec, which is statistically non-signifant change, and in patients group III it was increased to an average of 51.0±2.2 msec (p<0.01).

MERG indicators were impaired in the patients of groups II and III (Table 2). No statistically significant changes were observed in the patients of group I. The amplitude of the a-wave in the patients of group II was reduced to an average of 22.0±3.2 μV (p<0.05), and in the patient group III – to 19.3±4.0 μV (p<0.01). The amplitude of the b-wave in patients group II was reduced to an average of 61.2±5.2 μV (p < 0.01), and in the patient group III – to 34.7±2.6 μV (p<0,001). The latency of the a-wave in the patient group II was extended to an average of 19.6± .0 msec (p<0.05), and in the patient group III – to 25.1±4.1 msec (p<0.01). The latency of the b-wave in the patient group II corresponded to an average of 34.2±6.0 msec (p<0.05), and in the patient group III – 43.7±4.0 msec (p<0.05).

The N1– P1 amplitudes of RERG (Schedule 2) were statistically significantly reduced in all the 3 patients groups. In group I, these indicators corresponded to an average of 53.3 ± 3.5 μV ($p < 0,05$), in group II – 32.0±4.8 μV ($p < 0.01$), and in group III – 20.9 ± 3.6 μV ($p <0.01$).

The results of our research are consistent with the results of other authors (Steuer et al., 2005; Maquire et al., 1996; Akyol et al., 1995; Cellini et al., 2010). In these studies, hemodynamic parameters in the eye vessels were studied through CDI and the conclusion was made, that there was insufficient blood supply to outer and middle layers of the retina. The authors note significant decrease in the velocity of blood flow in the CRA and PSCA, Vmax and Vmin indicators, and a decrease of the resistance index in both vessels. Changes in hemodynamic parameters in the mentioned studies are consistent with the results of our study.

Based on the correlation analysis of the results, the interrelation between some hemodynamic parameters and ERG indicators was established. Direct correlation between Vmin and Vmax values in CRA and amplitudes of b-wave of total ERG (r=0.53; r=0.46, correspondingly), as well as between Vmax and Vmin values in PSCA and amplitudes of a-wave of total ERG (r = 0.80; r = 0.82, respectively) was found. Reverse correlation between Vmin and Vmax values in CRA and latency of b-waves of total ERG (r=-0.45; r=-0.47, correspondently), as well between Vmax and Vmin values in PSCA and latency of a-wave of total ERG (r=-0.47; r=-0.39, respectively) was found. Detected changes are statistically significant.

In the studies of Dolan and colleagues (2002), Seeliger and colleagues (1998), Marmor and colleagues (2009) the level of changes in functional status of central retina was analysed and studied, however, no studies were implemented depending on the stages of RP. Kisel'eva and colleagues (2015) studied the characteristics of the eye hemodynamics and retina electrogenesis in the adult patients group, but on smaller clinical material. The obtained results are in accordance with our own. In the work of Zhang and colleagues (2013) an interrelation between decreased blood flow of chorioretinal complex and impaired function of the eye photoreceptors based on MRI and ERG data was also established. However, there is no a correlation analysis and study of statistical reliability of the changes, implemented in the work.

CONCLUSION

The results of ERG and CDI show the presence of statistically significant changes in the cases of medium severe and severe stages of RP, as well indicate to advent of disturbances already in the initial stages. CDI of the patients with RP allows detecting timely hemodynamic disorders. Analysis of ERG data indicates the suppression of photoreceptors function in parallel to the disorders of blood flow in the eye vessels.

Thus, it is necessary to conduct EPS and dopplerographic studies for early diagnosis and monitoring of the patients with RP, as well for implementation of therapeutic and preventive measures.

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Pigmentli retinit zamanı cavan yaşlı pasiyentlərdə doppleroqrafik və elektrofizioloji tədqiqatlar

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İrsi xəstəliklər tibbin digər sahələrində olduğu kimi, oftalmologiyanın ağır patologiyalarından sayılır. PR tor qişanın ümumi irsi distrofiyasıdır. Bu xəstəlik görmə funksiyalarının itməyinə və korluğa gətirib çıxarır. İşin məqsədi cavan yaşlı pasiyentlərdə PR-in müxtəlif mərhələləri zamanı göz damarlarında hemodinamik parametrlərin və ERQ göstəricilərinin dəyişikliklərinin korrelyasiyasının öyrənilməsi olmuşdur. PR diaqnozu ilə yaş həddi 15-24 arasında olan 100 pasiyentdə (200 göz) müayinə aparılmışdır. Onlardan 41-i qadın, 59-u kişi olmuşdur. PR zamanı funksional dəyişikliklərə görə pasiyentlər 3 qrupa ayrılmışdır: I qrup – başlanğıc mərhələlı pasiyentlər 31 nəfər (62 göz), II qrup – orta ağır mərhələli pasiyentlər 40 nəfər (80 göz), III qrup – ağır mərhələli pasiyentlər 29 nəfər (58 göz). Bütün xəstələrdə gözdə qan axınını

öyrənmək üçün RDK «TOSHIBA» firmasının «Nemio XG SSA-580A» ultrasəs diaqnostik aparatında 8 mHz xətti datçik vasitəsilə həyata keçirilmişdir. Həmçinin ROLAND CONSULT Super Color Ganz feld Q450 SC (Almaniya) aparatında ERQ (ümumi, ritmiki və makulyar) aparılmışdır. ERG və RDK nəticələri PR-in orta ağır və ağır mərhələlərində statistik dürüst dəyişikliklərin olduğunu göstərir, həmçinin başlanğıc mərhələdə də pozğunluqların olduğunu bildirir. RDK PR-də hemodinamik pozğunluqları zamanında aşkarlamağa imkan yaradır. ERG göstəricilərinin təhlili fotoreseptorların funksiyasının azalması göz damarlarında qan axınının pozulmasına paralel baş verdiyini bildirir. Beləliklə, PR zamanı pasiyentlərin erkən diaqnostikasında və monitorinqində, eləcə də müalicə-profilaktik tədbirlərin aparılması üçün dopplerоqrafik və elektrofizioloji müayinələrin aparılması zəruridir.

***Açar sözlər**: Pigmentli retinit (PR), rəngli doppler kartlaşdırılma (RDK), elektroretinoqrafiya (ERQ)*

Допплерографические и электрофизиологические исследования при пигментном ретините у лиц молодого возраста

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Одними из тяжелых патологий в офтальмологии, как и в других отраслях медицины, являются наследственные болезни. ПР представляет собой наследственную генерализованную дистрофию сетчатки. Эта патология приводит к потере зрения вплоть до слепоты. Цель работы – изучить изменения гемодинамических параметров в сосудах глаза и показателей ЭРГ и провести корреляционный анализ у пациентов молодого возраста с различными стадиями ПР**.** Обследованы 100 пациентов (200 глаз) с пигментным ретинитом в возрасте 15-24 лет: из них - 41 пациент женского пола, 59 – мужского пола. Пациенты были распределены на 3 группы. В I группу был включен 31 пациент (62 глаза) с начальной стадией ПР. Во II группу было включено 40 пациентов (80 глаз) со среднетяжелой стадией ПР. В III группу было включено 29 пациентов (58 глаз) с тяжелой стадией ПР. Всем пациентам проводилась ЭРГ – общая, ритмическая - 30 Гц (РЭРГ), макулярная (МЭРГ) – на аппарате ROLAND CONSULT Super Color Ganz feld Q450 SC (Германия). Ультразвуковые исследования включали В-сканирование глазного яблока и допплерографию сосудов глаза методом ЦДК. Исследовались глазная артерия (ГА), центральная артерия сетчатки (ЦАС) и задние короткие цилиарные артерии (ЗКЦА). Результаты ЭРГ и ЦДК показывают наличие статистически достоверных изменений при среднетяжелых и тяжелых стадиях ПР, а также указывают на наличие нарушений уже на начальных стадиях. ЦДК у пациентов с ПР позволяет своевременно выявить гемодинамические нарушения. Анализ данных ЭРГ указывает на угнетение функции фоторецепторов параллельно нарушениям кровотока в сосудах глаза. Таким образом, необходимо проведение электрофизиологических и допплерографических исследований для ранней диагностики и мониторинга пациентов с ПР, а также для проведения лечебно-профилактических мер.

***Ключевые слова:** Пигментный ретинит (ПР), цветовое допплеровское картирование (ЦДК), электроретинография (ЭРГ)*