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# CLINICAL MANIFESTATION AND PROGRESSIVE SENSORINEURAL HEARING LOSS IN THE PATIENTS WITH RETINITIS PIGMENTOSA

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**Abstract**

Retinitis pigmentosa (RP) is an inheritedretinal disorder characterized by progressive loss of photoreceptors and retinal pigment epithelium. RP is characterized by impaired night vision, slowly progressive peripheral to central visual field loss, and often a decline in visual acuity.

Aim: Clinical examination of patients with retinitis pigmentosa.

Material and method:From January 2006 to December 2017, 24 patients with retinitis pigmentosa (RP) were examined. The visual acuity, slip lamp and fundus examination, visual field, red cam investigation, FFA and OCT of the posterior segment were done. In the patients, the hearing condition was examined with vestibular testing. Most of the cases are still followed in the University Eye Clinic in Skopje.

Results: Clinical symptoms, FFA angiograms, OCT slides and visual fields results are discussed.All 24 patients showed either arteriolar attenuation, retinal bone-spicule pigmentation and/or waxy disc pallor, which result in progressive vision loss.18patients showed familiar characteristicpresentation of the disease and 6 patients showed sporadic cases.Myopiawas found in 62,5% (15 patients) and keratoconus in 25% (6 patients). On the posterior segment, fundus, drusen of the PNO in 20,8% (5 patients) and macular abnormalities (macular edema, macular atrophy, cellophanemaculopathy) in 16,7% (4 patients) was observed. Vitreous opacification 66,7% (16 patients) and cataract 62,5% (15 patients) were present and lead to additional deterioration of vision acuity. The open-angle glaucoma was found in 12,5% (3 patients). The results of the sensorineuralhearing tests suggest that most of the patients with RP havedifficulty communicating and socially inadequate hearing. Sensorineural hearing loss was observed in 62,5% (15 patients).In these 15 patients with hearing loss, alteration of vestibular function of peripheral type was found in80%(12 patients) and of mixed type in 20% (3 patients).

Conclusion:Treating the retinitis pigmentosa visual and hearing manifestations, as well as continuous following of the RP-affected patients is vital for preserving the vision acuity, auditory acuity and quality of life. Patients with neurosensory hearing loss of unknown genesis should necessarily undergo a preliminary eye examination to confirm or exclude the RP diagnosis.

Key words: retinitis pigmentosa, RP, visual loss, hearing loss, manifestations, therapy

# КЛИНИЧКА МАНИФЕСТАЦИЈА И ПРОГРЕСИВНО НЕВРОСЕНЗОРНО НАМАЛУВАЊЕ НА СЛУХОТ КАЈ ПАЦИЕНТИ СО РЕТИНИТИС ПИГМЕНТОЗА

**Апстракт**
Ретинитис пигментоза е наследно заболување на ретината кое се карактеризира со прогресивно оштетување на фоторецепторите и ретиналниот пигментен епител .Карактеристично е дека е нарушен ноќниот вид, постои бавно и прогресивно намалување на периферниот вид, а често и до губење на централниот вид и видната острина.Цел: Клиничко иследување на пациенти со ретинитис пигментоза.Материјал и метод: Од јануари 2006г. до декември 2017г.иследувани се 24 пациенти со ретинитиспигментоза. Кај пациентите беше иследувана видната острина, предниот и заден сегмент на очите, видно поле, нативна снимка на очното дно, флуоресцинска ангиографија(ФФА) и оптичка кохерентна томографија (ОКТ).Кај пациентите беше иследуван и слухот со помош на вестибуларен тест. Повеќето од пациентите и понатаму се следат во Клиниката заочни болести во Скопје.
Резултати: Иследени се клиничките знаци кај пациентите со РП,флуоресцинскитеангиограми, слајдови од ОКТ ивидните полиња. Кај сите 24 пациентибеа присутни стеснувањана артериските крвни садови, ретинална пигментација во облик на коска и /или восочно бела папила, кои доведуваат допрогресивно намалување на видот.Кај 18 од нив е забележана карактеристична клиничка слика, а кај 6 клиничката слика е со спорадична презентација на клиничките знаци.Миопија беше забележана кај 62,5% (15 пациенти), а кератоконус кај 25% (6 пациенти).На задниот сегмент забележани се друзи на ПНО кај 20,8% (5 пациенти), а кај 16,7% (4 пациенти) забележени се макуларни абнормалности (макуларен оток, атрофија и целофанска макулопатија).Витреалнозаматување беше забележано кај 66,7% (16 пациенти) и катаракта кај 62,5% (15 пациенти) кои дополнително доведоа до намалена видна острина.Глауком со отворен агол беше дијагностициран кај 12,5% (3 пациенти).Резултатите од иследувањето на слухот, покажуваат дека повеќето пациенти со РП имаат отежната комуникација и ограничен социјален живот. Невросензорно намалување наслухот е забележано кај 62,5% (15 пациенти).Кај овие 15 пациенти, намалување на вестибуларната функција од видот на периферно намалување беше забележано кај 80%(12 пациенти) и од мешан вид кај 20% (3 пациенти).
Заклучок: Значајно за зачувување на видната острина, слушната острина и квалитетот на живот кај пациентите со РП е лекувањето на визуелните и слушните манифестации и континуираното следење. Неопходен е очен преглед кај пациентите со невросензорно намалување на слухот од непозната генеза за да се потврди или исклучи дијагнозата на РП.

**Клучни зборови:**ретинитиспигментоза, РП, загуба на вид, загуба на слух, клиничка слика, терапија

**Introduction**
The retinitis pigmentosa (RP) is a hereditary disorder consisted of a heterogeneous group of retinopathies covering all retinal rod-con dystrophies presented with progressive bilateral degeneration of photoreceptors and retinal pigment deposits. The typical RP is described as a rod-cone dystrophy, photoreceptor rods being more affected than cones. RP is characterized by impaired night vision, slowly progressive peripheral to central visual field loss, and often a decline in visual acuity. Von Grafe first observed

the association of RP with hearing loss and deafness (1).Hearing loss may be the first complaint of patients with retinitis pigmentosa. There are different syndromes associated with various types of pigmentary retinopathies, the most frequent syndromes being Usher syndrome and BardetBiedl syndrome (BBS). The less frequent syndromes include renal abnormalities (SLS-Senior Loken syndrome, Alport syndrome), dysmorphic syndromes (Cohen syndrome, Jeune syndrome, Cockayne syndrome), metabolic diseases (Methylmalonic aciduria with homocystinuria, BassenKorntzweig disease, Bietti's disease, Cystinosis, Mucopolysaccharidoses, Zellweger syndrome, Hyperoxaluria type I, Neonatal adrenoleukodystrophy, Peroxisomal disorders, Infantile and Adult Refsum disease), neurological diseases (Neuronal ceroid lipofuscinosis, Joubert syndrome, Autosomal dominant cerebellar ataxia type, II, Myotonic dystrophy,Hallervorden-Spatz syndrome (2).
RP has an estimated worldwide prevalence of 1:3000 - 1:7000 persons. RP inheritance can be autosomal dominant, autosomal recessive, or X-linked, in addition to rare mitochondrial and digenic forms, and there is genetic heterogeneity within each group (3).Mutations in more than 50 genes are known to cause RP and more than 3100 mutations have been identified in these genes (4).

**Material and method**

From January 2006 to December 2017, 24 patients with retinitis pigmentosa (RP) were examined. Clinical examination of the 24 patients with RP started with complete medical history and family medical history, and was followed by physio-physical tests, best-corrected visual acuity, slit lamp and fundus examination, perimetry, red cam and fluorescein angiography (FFA), optical coherence tomography (OCT), audiometric and vestibular tests.
In addition, the 24 patients were tested on their hearing condition with vestibular testing and ontological history was taken, with special reference to other possible causes for any hearing loss. Most of the cases are still followed in the University Eye Clinic in Skopje.

**Results**

From the 24 patients, 14 patients were female and 10 patients were male. All 24 patients showed either arteriolar attenuation, retinal bone-spicule pigmentation and/or waxy disc pallor, which result in progressive vision loss (Figure 1, Figure 2, Figure 3).

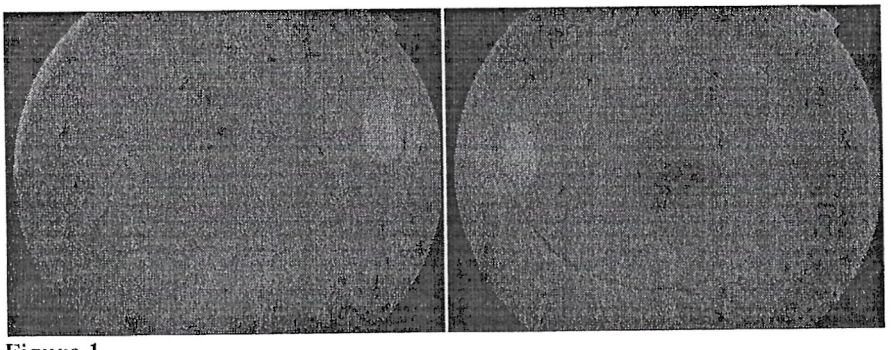

**Figure 1**

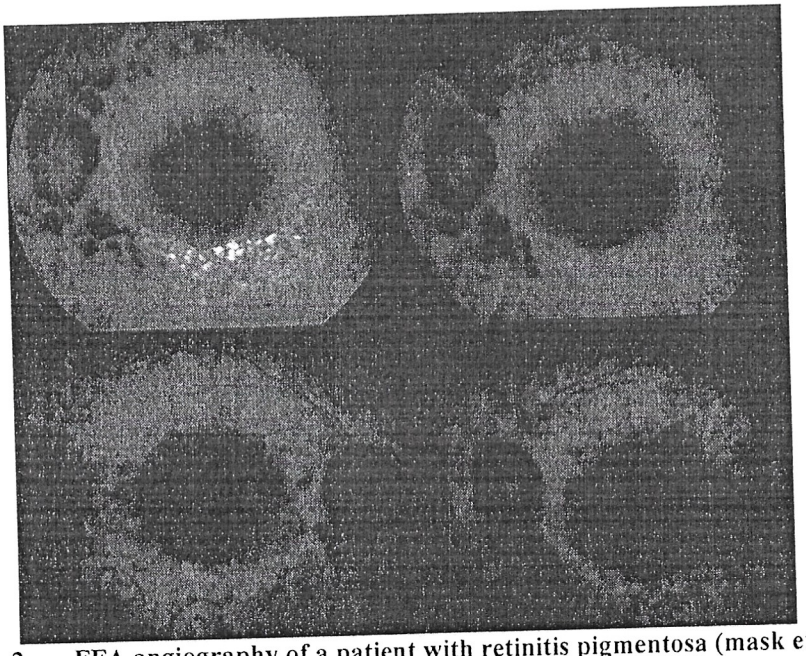

Figure 2 FFA angiography of a patient with retinitis pigmentosa (mask effect of the bone specular shape pigment epithelium, hyperfluorescence of retinal atrophy, narrowing blood vessels, pall circumferential optical disk, dark macular regia)

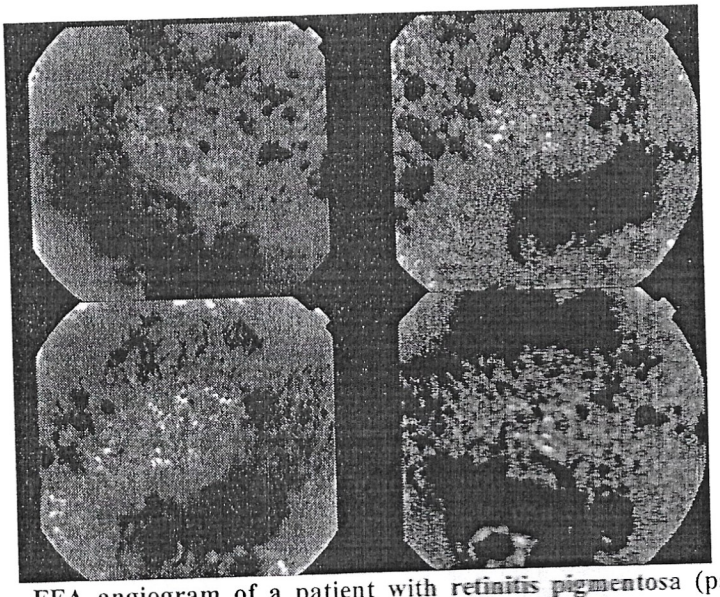

Figure 3 FFA angiogram of a patient with retinitis pigmentosa (pale optical disk, extremely narrowing vessels, wide zones of specular shape of pigment cells-mask effect and cellophane maculopathy)

18 patients showed familiar presentation of the disease and 6 patients showed sporadic cases. The patients were complaining of nyctalopia (night blindness), photophobia and/or impairment of the vision acuity especially in the late stages of RP. Myopia was found in 62,5% (15 patients) and keratoconus 25% (6 patients). On the posterior segment, fundus,drusen of the PNO in 20,8% (5 patients) and macular abnormalities (macular edema, macular atrophy, cellophanemaculopathy) in 16,7% (4 patients) was observed (Figure 4, Figure 5).

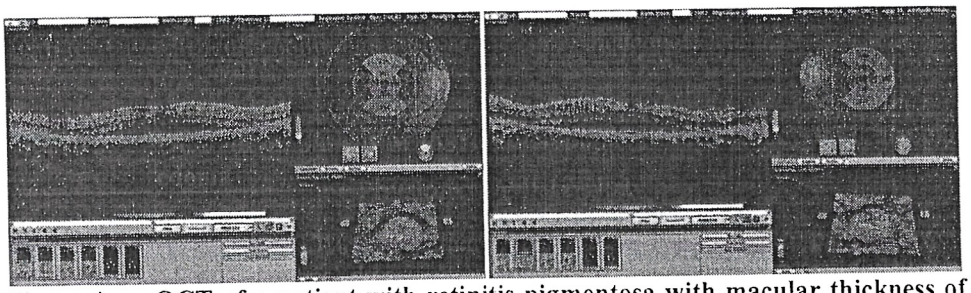

**Figure 4** **OCT of a patient with retinitis pigmentosa with macular thickness of neuro-retinal layers and applanation of the fovea**

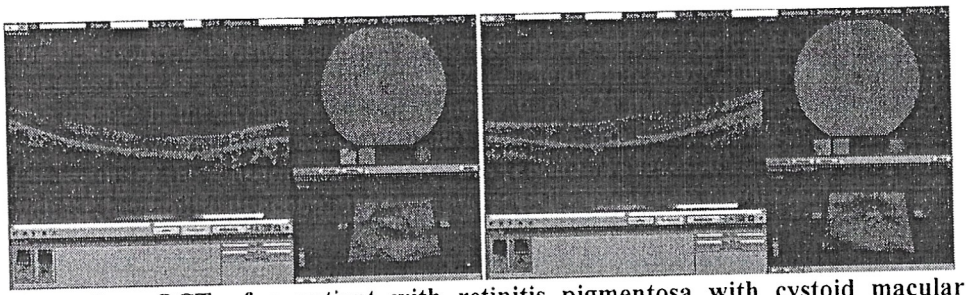

**Figure 5** **OCT of a patient with retinitis pigmentosa with cystoid macular edema**

Vitreous opacification 66,7% (16 patients) and cataract 62,5% (15 patients) were present and lead to additional deterioration of vision acuity. The open-angle glaucoma was found in 12,5% (3 patients). The visual field test (Figure 6) showed different RP indicators in the 24 patients, such as ring shape scotoma25% (6 patients), patchy losses of peripheral vision 45,8%(11patients)and tunnel vision 29,2% (7 patients)at the late stage of the disease.

The best-corrected visual acuity is preserved in most of the typical and advanced RP cases, as long as a small area of central visual field is preserved.The best visual acquit with glasses in the myopic and keratoconus patients (21 patients) was range from 0,5 to 1,0 c.c. and without correction (4 patients) was range from 0,6 to 1,0 s.c.
The results of the sensorineural hearing tests (Figure 7) suggest that most of the patients with RP have difficulty communicating and socially inadequate hearing.

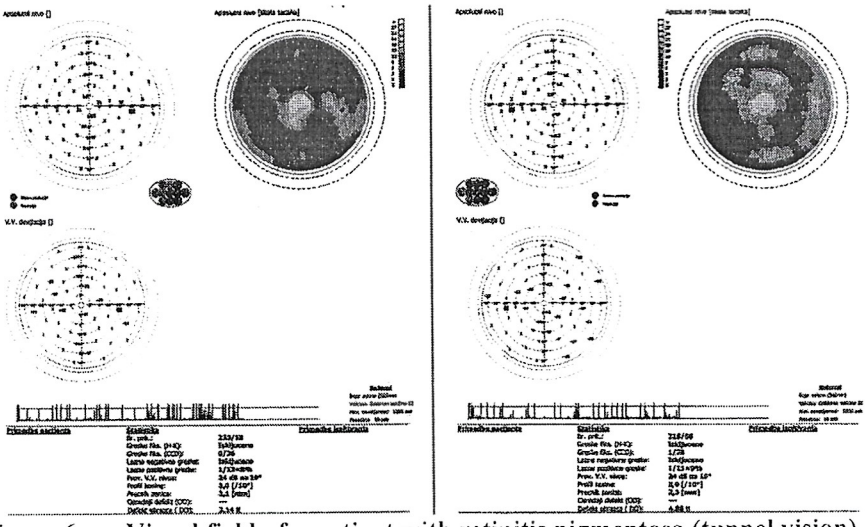

Figure 6 Visual field of a patient with retinitis pigmentosa (tunnel vision)

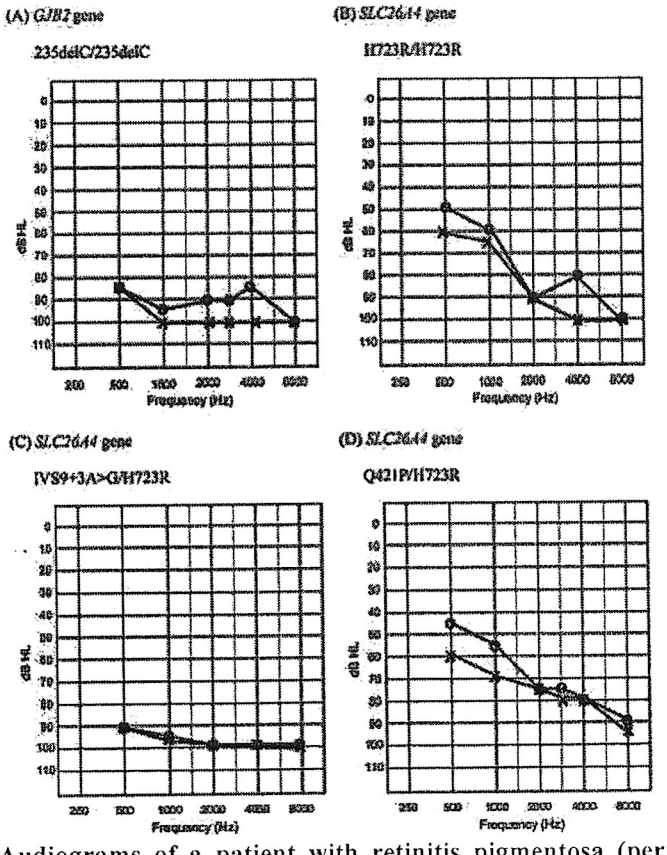


Figure 7 Audiograms of a patient with retinitis pigmentosa (peripheral type and mix type

Sensorineural hearing loss was observed in 62,5% (15 patients). In these 15 patients with hearing loss, alteration of vestibular function of peripheral type was found in80% (12 patients) and of mixed type in 20% (3 patients).

**Discussion**

Franceschetti and Klein suggested that the association between RP and deafness is due to the common origin of the retinal pigment epithelium (RTE) and the organ of Corti(5).De Robertiscarried outseveral experiments and provedthat there is evidence that retinal photoreceptors are modified cilia (6). Other researchers, such as Arden and Fox,examined samples ofnasal cilia from RP patients and found increased incidence of cilia with abnormal axonemal micro tubular structures, and also of compound cilia(7). All of this suggests that furtherstudieshave to be done on the other ciliated epithelium in the body of the patients with RP.

The results of the sensorineural hearing testssuggest that most of the patients with RP have a socially inadequate hearing. Sensorineural hearing loss was observed in 62,5% (15 patients) with alteration of vestibular function.

Results of the retina may vary with the stage of RP and may initially be normal. The earliest change in the retina is associated with fine, dust-like granularity of the retinal pigment epithelium (RPE), pigment mottling and normal vasculature. In the middle stage of the disease, patchy loss of the RPE and the beginning of retinal vessel attenuation are evident. Advanced RP is characterized by arteriolar narrowing, waxy pallor of the optic nerve head and photoreceptor cell death accompanied with migration of intraretinal pigment epithelium (termed bone spicule deposits).

FFA detects the changes in the pigment epithelium and the morphological changes of the macula associated with RP. In FFA hyperfluorescence is observed of small spots that are characterized by a window effect, associated with atrophy of the pigment epithelium.In contrast, the pigment piling zones mask the fluorescence and most commonly show in the form of bone cells. Even if there are hyperfluorescent spots on the fundus, good visual acuity can be achieved.

On the FFA angiogram, the macula usually remains dark for a protracted time period during the exam. FFA can detect degeneration of the retinal pigment epithelium in the macular region and the rest of the retina. The macular atrophy is most commonly encountered in late stages of RP and in older individuals usually between 40-50 years of age.Rare forms of macular degenerationmay be observed as well, such as microcystoid degeneration, lamellar hole and macular edema.

OCT was introduced to ophthalmology more than 20years and it has become the standard for assessing anatomical abnormalities using high-resolution tomographic images.Changes revealed by OCT have provided insights into the pathology of RP as well as for predicting the prognosis of RP. Previous studies of RP verified that the earliest histopathological changes were the shortening of the photoreceptor outer segments (8, 9, 10). The three reflective lines are the external limiting membrane (ELM), ellipsoid zone (EZ), and interdigition zone (IZ) from the inner to the outer retina, which are commonly used to evaluate the integrity of the photoreceptor segments (11).In RP, the photoreceptor lines are shortened with the degeneration of photoreceptors. Rod photoreceptor death is followed by degeneration of the RPE cells and eventually leads to the loss of the cones (12). In advances RP patients, it is difficult to identify the border between the retinal layers. Therefore, it is ideal to make optimal use of macular volume and retinal macular thickness to assess the condition of the retina. An increase or decrease in the retinal thickness has been reported in a study (13),

which observed that cell loss led to retinal thinning and retinal edema led to retinal thickening. Compared with the general population, macular abnormalities were more prevalent in RP patients (14, 15) and were observed in 45,1% of RP eyes (16). In clinical studies, cystoids spaces were present from 5,5% - 24,5% (15, 16), and the prevalence of epiretinal membrane was reported in 15,6% (14).

OCT has been shown to be parallel to or even more sensitive than fluorescence angiography in detecting cystoid macular edema in RP (15). In eyes with RP, macular edema showed central location and presentation. Macular edema in RP eyes showed little dye accumulation in fluorescence angiography, but the mechanism was not clear (15). In RP patients, spatial distribution of the cystoid spaces was found mainly in the inner-nuclear layers INL, but sometimes in the outer nuclear layers/ outer plexiform layer (ONL/OPL) and the ganglion cell layer (16).

There are many reasons for the preferential spatial distribution in RP. In normal retina, intraretinal fluid distribution is restricted by the inner plexiform layer and outher plexiform layer (IPL and OPL), and serum leakage from intraretinal vessels is mediated by Müller and RPE cells (17). So it was supposed that the degeneration of RPE and Müller cells accounted for the preferential distribution of cystoid spaces in the inner retina in RP patients. Intraretinal layers, a barrier, stopped fluid movement, but with the atrophy of the retinal layers, the barrier damage contributed to the formation of cystoid spaces in the inner retina (18). The ELM is another barrier that limits the diffusion of large molecules (19). However, with the loss of Müller cells and photoreceptor segments, the ELM barrier is destructed. So in RP patients, retinal atrophy and the destruction of retinal layers led to macular edema, while the disrupted blood retinal barrier mainly accounted for macular edema in vascular diseases.

The most frequent manifestation of other findings in thisstudy is cataract and myopia.

The occurrence of myopia was high, but a genetic exam was not done on the patients with RP to determine whether the myopia is in association with X-linked RP.

Most of the cataracts in patients with RP were central in the posteriorcapsular lens and characterized with blurred vision, which in turngenerates photophobia. Some of cataracts were operated using phacoemulsification with intraocular lens implantation.The early development of a cataract is common feature in RP, although the reason for the capsular opacification remains poorly understood and may be due to vitreous changes and modification of blood ocular barrier (20). In addition, compared to age-related cataracts, RP patients tend to develop zonular instability and posterior capsular opacification requiring Yag laser (21).

The visual prognosis of RP patients depends onthe level of the macular abnormalities and the opacification of the lens.The scans of the OCTshowed different sings of macula abnormalities depending on the stage of the RP. Observed were cystic macular lesions, macular edema, aplanatic fovea, macular peripheral ring of depigmentation and complete disturbance of all NR and pigment epithelium in the macular region.Macular edema occurs frequently and is usually chronic. Cystoid macular edema is reported in 40% of cases (22). In addition, atrophic changes in the macula may also be observed early in some cases and represent another cause of early decrease in visual acuity in RP alongside cystoid macular edema, cellophanemaculopathyand cataract (23).

The vitreous opacification and cells within the vitreous are common (24). In this study, vitreous opacification usuallywas associated with macular edema and cataract.Keratoconus is rare and is usually encountered in the early stages of the disease.In the literature, the keratoconus is not associated with RP. However, 6 patients