

Observations in rare ophthalmic diseases

Effect of brachytherapy of uveal melanomas on corneal endothelium and characteristic lens morphology found in Alport syndrome Short thesis for the degree of doctor of philosophy (Ph.D.)

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Abbreviations

AJCC American Joint Committee on Cancer

AVG average cell size

CV coefficient of variation of cell area

ECD endothelial cell density

EOG elektrooculography

ERG elektroretinography

FLAG fluorescein angiography

HLA-I/II human leukocyte antigen I/II

IGF-1 insulin-like growth factor-1

OCT optical coherence tomography

PPMD posterior polymorph cornea dystrophy

UBM ultrasound biomicroscopy

1. Introduction

1.1 Uveal melanoma

Diseases of the anterior segment of the eye can be well known, easy to diagnose, but there are some rare diseases which can be diagnosed and treated only in special centers. Uveal melanoma is the most common primary malignant intraocular tumor in adulthood usually presenting in the 5-8. decades. It is a sight- and life-threatening disease with an incidence of 4-6/1 million/year. Its incidence has not changed in the last decades. Uvea consists of three parts: iris, ciliary body and choroid. About 85% of uveal melanomas arise from the choroid, 10% from the ciliary body and only 5% from the iris. Choroidal melanomas are usually asymptomatic or cause decreased visual acuity or visual field defect. Sometimes patients complain of floaters or very brief balls of light travelling across the visual field. Ciliary body tumors can grow for long asymptomatic behind the iris, finally causing visual field defect and visual impairment. The majority of iris melanomas arise from a pre-existing lesion. They usually grow slowly, are of low malignancy and easier diagnosed as they can be seen on the surface of the iris.

Treatment options of uveal melanomas depend on the location and size. If the tumor arises from the iris or ciliary body and not affects more than one quadrant iridectomy or iridocyclectomy can be done. Local resection should be followed by adjuvant irradiation. Brachytherapy itself can be used to treat intraocular tumors. The initiation of applicators containing radioactive particles meant a breakthrough in uveal melanoma therapy. They have made the treatment of eye tumors up to a certain height possible without enucleating the affected eye. The justification of brachytherapy was confirmed by a prospective, randomized study, the Collaborative Ocular Melanoma Study (COMS). Between 1989 and 2001 1317 patients with medium size uveal melanomas (2,5 – 10 mm thickness, 16 mm maximum basal diameter) were treated randomly by enucleation or I-125 brachytherapy. Patients were followed up 12 years, and there was no significant difference between the melanoma

related mortality of the patients treated with enucleation and brachytherapy. Local tumor control became an important question with the spreading and developing of globe salvage therapies. The University of California Department of Oncoradiology studied the local tumor control after brachytherapy and proton beam irradiation. After brachytherapy the local tumor control was 84% for 5 years and 79% for 12 years. After proton beam irradiation the local tumor control was found to be significantly better, 100% for 5 years and 98% for 12 years. Unfortunately, this kind of treatment is not available in Hungary, yet.

Beta-ray emitting applicators containing ^{106}Ru isotopes have been used at our department since 1986 for the treatment of uveal melanomas. ^{106}Ru ophthalmic plaques are suitable for the treatment of intraocular tumors defined by ophthalmologic ultrasound up to 6 mm. The explanation is the limited depth of penetration of emitted betaradiation. The effective amount of radiation to the apex is 100 Gy, which is limited by a maximum of 1,000 Gy to the sclera, in order to minimize complications, such as necrosis. Anterior segment tumors involving the iris and the ciliary body are mostly treated with round plaques placed directly on the cornea surface. In our practice, slotted plaques corresponding to the cornea are used, thus offering a lower irradiation dose on the cornea. Of course, the scatter of radiation also has to be taken into account.

There is no international agreement about how to treat tumors greater than 6 mm thickness. There are globe sparing therapies like endoresection after charged particle irradiation in case of tumors posterior to the equator or transscleral resection with adjuvant brachytherapy in case of tumors anterior to the equator, but fundamentally tumors thicker than 6 mm should be treated by enucleation.

There is no lymphatic drainage from inside the eyeball, uveal melanomas metastasize through haematogen way especially to the liver (89%), lung (29%) and bones (17%). In spite of successful treatment of the primary tumor metastasis develops in 50% of uveal

melanoma patients in ten years. The average survival after liver metastasis is 15 months. Although there was a great development in the local therapy of uveal melanoma in the last decades, the prognosis remained relatively unchanged. The reason is the early development of micrometastasis. Metastasis are estimated to appear three years before the diagnosis of primary uveal melanoma, but only two years after diagnosis become to be detectable. Development of metastasis is irrespective from the treatment of the primary tumor. Tumor related 5-year mortality of small tumors (thickness <2.5 mm) is 1%, of medium size tumors (thickness 2.5 mm-10.0 mm) is 11%, in case of large tumors 28%.

1.2 Alport syndrome

Ocular symptoms can be caused not only by ophthalmic diseases but some systemic diseases can have ophthalmological signs. Alport syndrome, historically referred to as hereditary glomerulonephritis with sensorineural hearing loss and anterior lenticonus, is a genetic multisystem disease resulting in renal failure. Alport syndrome is very rare with an estimated prevalence of one in 5,000. The causes of Alport syndrome are different mutations of $\alpha 3-5$ chains of type IV collagen. These collagen chains are important structural components of basement membranes in the kidney, cochlea and eye. The abnormal production or assembly of type IV collagen results in proteinuria and hematuria. Microscopic hematuria with hearing in young man is characteristic for Alport syndrome. Many patients have no other symptoms than blood and protein in the urine. As kidney disease progresses nephrotic or nephritic syndrome evolves leading to end-stage kidney disease usually in young or middle ages.

In 80% Alport syndrome is an X-linked hereditary disease (COL4A5 gene). Typical ophthalmological findings are: dot-and-fleck retinopathy in 85% of male patients, anterior lenticonus in 25% of patients and, on rare occasions, PPMD. Dot-and-fleck retinopathy in any individual with a family history of Alport syndrome or with end-

stage renal disease is highly suggestive for Alport syndrome. The presence of anterior lenticonus or PPMD in any individual is also highly suggestive for the diagnosis of Alport syndrome. Additional ocular features described in X-linked Alport syndrome include other corneal dystrophies, microcornea, arcus juvenilis, iris atrophy, cataract, spontaneous lens rupture, posterior lenticonus, poor macular reflex, fluorescein angiogram hyperfluorescence, electrooculogram and electroretinogram abnormalities, and retinal pigmentation.

In 15% of patients, Alport syndrome is autosomal recessive (COL4A3 or COL4A4 gene), while ophthalmological features are the same as in the X-linked type. There is also a dominant form, which arise from heterozygous mutation of COL4A3 or COL4A4, frequency is less than 5%, however next generation sequencing in Alport families suggest that may occur more frequently. Ocular findings are unusual.

2. Purpose

The anterior segment of the eye as an optical system plays a very important role in sharp vision. Structural deviations may lead to visual impairment. These deviations can be frequent and easy to diagnose, but there are some rare diseases or their treatment which can cause hardly recognizable alterations; however, these alterations can play an important diagnostic role or may take into account in interventions needed afterwards.

2.1 Uveal melanoma arising in the anterior segment is rare. In our practice, tumors involving the iris and the ciliary body are treated with slotted plaques corresponding to the cornea, thus offering a lower irradiation dose on the cornea. Of course, the scatter of radiation also has to be taken into account. The aim of our study was to examine whether plaque therapy for anterior segment tumors cause corneal damage, decrease in endothelial cell count or morphological changes.

2.2 Alport syndrome is a rare genetic multisystem disease with characteristic ocular symptoms. Our aim was to present ophthalmological findings regarding Alport syndrome and refractometry data, while finding early signs of the disease in order to enhance the diagnostic process. We also compared the results of different methods of refractometry, as well as analyzed their reliability.

3. Patients and methods

3.1 Beta-ray emitting therapy of ciliary body tumors decreases central corneal endothelial cell density

In our prospective study, patients with ciliary body tumor with no history of any preliminary ophthalmologic treatments or events (inflammation, lesions) were examined. Melanomas arose in the lower temporal part of the ciliary body and developed behind the iris with no metastasis in the iris or anterior chamber. Slit-lamp examination revealed no cells in the chamber, not even with enlargement. Neither glaucoma nor secondary glaucoma was verified before and after therapy. During and after irradiation, no manifest uveitis developed, none of the patients' pupils coalesced to the anterior surface of the lens, and pupils remained well expandable. Patients not eligible for the conditions mentioned above were excluded from the study. According to these conditions and regarding the size of tumor, between 2004 and 2011, 15 eyes with ciliary body tumor of 15 patients (mean age 58 ± 17 years, 8 men and 7 women) were suitable for brachytherapy. Considering that melanomas arising in the ciliary body are usually detected later, the prominence of tumors subject to irradiation, defined with ultrasound biomicroscopy (UBM), was between 4 and 6 mm. In the center of the cornea of the 15 patients' affected eyes, ECD was measured prior to and 6 months after brachytherapy. Considering that the cornea area around the applicator is exposed to higher scatter radiation, after irradiation central ECD values were compared with peripheral ECD values measured around the plaque. ECD measurements were conducted with specular microscope (EM-1000; Tomey, Tennenlohe, Germany).

3.2 Alport patients without classic ocular symptoms have a smaller lens diameter

Seven patients (two male, five female, average age 29 years) with newly diagnosed Alport syndrome were referred to the Department of Ophthalmology at the University of Debrecen between January 1st, 2014, and December 31st, 2015. The data collected for evaluation included patient history, age, sex and best-corrected visual acuity. All patients underwent slit lamp evaluation and dilated fundus biomicroscopy for lenticonus and retinal changes. IOL Master (IOL Master 5.4.0002; Zeiss, Jena, Germany), Pentacam HR (Pentacam High Resolution; Oculus, Wetzlar, Germany) and ultrasound biomicroscopy (OTI Scan 3000; Optos, Hialeah, USA) were performed in order to assess keratometry, corneal thickness, anterior chamber depth, lens size and axial length data. Color fundus photography, optical coherence tomography and fluorescein angiography were also performed.

The studies were performed in accordance with the tenets of the Helsinki Declaration and informed consent was obtained from all patients.

Statistical analysis

Statistical analysis was performed using the MedCalc software (Version 10). Descriptive statistical results were described in terms of mean, standard deviation (SD) and 95% confidence interval (95% CI) for the mean. In the first case in the proband group, the differences in values of measurements prior to and after irradiation were analyzed by Wilcoxon test. In the second case data were analyzed using the Mann-Whitney test. A p-value below .05 was considered statistically significant.

4. Results

4.1 Beta-ray emitting therapy of ciliary body tumors decreases central corneal endothelial cell density

Eligible for the conditions mentioned above and in respect to the tumor size, 15 patients' 15 eyes with ciliary body tumor were suitable for brachytherapy. We concluded that brachytherapy for anterior segment tumor caused a significant ECD decrease in central cornea 6 months after radiation when compared to the baseline values ($p = 0.007$). The mean corrected ECD value prior to radiation was 2147 ± 128 cells/mm² and 2050 ± 108 cells/mm² after radiation. Considering that peripheral cornea around the plaque is exposed to higher scatter radiation dose, not only was central ECD measured 6 months after irradiation, but also peripheral cornea ECD around the applicator. The mean peripheral ECD value after irradiation was 2056 ± 101 cells/mm², meaning that although peripheral ECD was exposed to higher scatter radiation dose it showed no significant difference ($p = 0.86$) in comparison to central ECD. We counted out the scattered radiation dose at the measured points of the cornea. By the calculation the protocol of measurements of tissue absorption of the given plaque was used. The distribution of the ¹⁰⁶Ru isotope in the plaque is characteristic for each plaque and it is given by the firm. As the edge of the plaque was in the limbus, we used the distances from the limbus for the orientation on the cornea in our calculations. It can be seen that the periphery 2.0 mm from the limbus, i.e., 2.0 mm from the edge of the plaque, got higher scattered radiation than the center. (As the center is hard to define from the limbus radiation dose was counted out 5.0 and 6.0 mm from the limbus as well.) Images captured by the equipment clearly show that in untreated cases endothelial cells have normal structures, are of nearly the same size, and have a shape of a standard hexagon. After irradiation, a growth in cell size was observed

and an explicit pleomorphism was detected. Significantly higher AVG and CV values were observed in central cornea after irradiation when compared to the baseline results ($p = 0.03$, $p = 0.005$, respectively). No statistically significant difference was found between the peripheral and central AVG and CV values after irradiation ($p = 0.22$, $p = 0.27$, respectively). Statistical analysis did not find any significant changes in the central pachymetry results after the brachytherapy ($p = 0.74$).

4.2 Alport patients without classic ocular symptoms have a smaller lens diameter

One patient out of seven had ocular symptoms; she had a family history of Alport syndrome and had proteinuria and hematuria since childhood. PPMD and dot-and-fleck retinopathy were present. Although keratoconus could not be proven in this patient, remarkable astigmatism with high myopia was detected. Her corrected visual acuity in the right eye was 20/200, while it was 20/60 in the left eye. We could not identify any ophthalmological finding typical for Alport syndrome in the other six patients. All of them had proteinuria and hematuria, and two patients already had a moderately decreased glomerular filtration rate at diagnosis. Only one had a positive family history of kidney disease, but the electron microscopy examination of kidney biopsy specimen was typical for Alport syndrome in all cases. We compared the results of keratometry, corneal thickness, anterior chamber depth, lens parameters, and axial length with an age-matched control group. The control group consisted of seven healthy individuals (one male, six female, average age 29.6 years). There was no statistical difference between the visual acuity of the patient and control group ($p=0.9452$). The best corrected visual acuity was 20/20 for each eye. The average refractive error was $-1.21D$ in the patient group and $0.21D$ in the control group. Alport patients seemed to be myopic, but the difference was not significant ($p=0.18$). The Alport patients were found to have a significantly smaller lens diameter (on

average 7.82 ± 0.66 mm, $p=0.035$) than normal controls (average 8.65 ± 0.46 mm). Lens thickness was thicker in Alport patients (3.48 ± 0.19 mm), but not statistically significant when compared to normal age groups (3.4 ± 0.2 mm, $p=0.394$). The power of the lens was calculated and showed a significant difference ($p=0.026$), and Alport patients had lower lens power. IOL Master was used to calculate the artificial lens diopter in case of a cataract surgery to reach postoperative emmetropia. There was no significant difference between the other variables in the two groups analyzed using the Mann-Whitney test.

Keratometry and anterior chamber depth data, as measured by IOL Master, Pentacam HR, and ultrasound biomicroscopy, were compared to each other. No significant difference was found between the data measured by these three instruments.

5. Discussion

5.1 Beta-ray emitting therapy of ciliary body tumors decreases central corneal endothelial cell density

It is widely known that UVB radiation has a damaging effect on cornea, causing intraocular inflammation and photokeratitis. Research has been carried out to prove the damaging effect of UVB radiation on endothelium that induces programmed cell death (apoptosis). In several countries, a number of iris tumors are treated with Pd-103 or I-125 golden plaque, which partially covers the cornea. After irradiation, temporary exfoliation on the surface of the cornea and corneal abrasion can often be observed. Shields et al used custom-designed plaque radiotherapy using iodine 125 isotopes applied overlying the cornea in case of nonresectable iris melanoma. They found corneal epitheliopathy in 9% of the patients at 5-year follow-up as a radiation-related complication. They did not examine the ECD. We found only one publication investigating the effects of dose radiation therapy for anterior segment tumor on endothelial cells. However, in the worst case, a decrease in ECD and/or a morphologic change due to such irradiation may lead to the development of bullous keratopathy after a subsequent cataract surgery. Razzaq et al examined corneal ECD in patients with iris melanoma after ruthenium brachytherapy and with iris melanoma after ruthenium brachytherapy plus phacoemulsification in the tumor eye. They found a small but not significant decrease in central ECD after irradiation using the fellow eye as a control. However, a significant difference was found after phacoemulsification. Our study differs in that we measured the ECD before and after irradiation on the same eye, and also examined the peripheral ECD after irradiation. According to our measurements, plaque therapy for tumors in the anterior segment decreases ECD significantly, but not highly, even in case of plaques containing betaradiation isotope, and when the plaques are not placed directly

on the cornea surface. We measured the peripheral ECD after irradiation and compared to the central ECD after therapy. We found no significant difference between peripheral and central ECD after irradiation although peripheral ECD was exposed to higher scatter radiation dose. We have 3 hypotheses. First, the limbal blood circulation decreased around the plaque by opening the conjunctiva, which could contribute to moderate the cell damage caused by the irradiation. Second, the applied topical steroid treatment after irradiation was more effective on the periphery, which could also contribute to moderate radiation damage. Third, Amann and colleagues studied the ECD in the paracentral and peripheral region of normal corneas, and found that peripheral ECD was 8.9% higher than central ECD measured with contact specular microscopy. Assuming that peripheral ECD of our patients was higher than central, and we found that the peripheral ECD was lower than the central ECD after irradiation (although the difference was not significant), we can conclude that the peripheral endothelial cells that were closer to the radioactive plaque had more damage than the central ones. The change in size and morphology of the cells was due to the decrease of ECD, considering the fact that the area has to be filled by a decreased number of endothelial cells. These endothelial alterations may cause no changes in corneal thickness or transparency, but may have an influence on a subsequent cataract surgery. Our results confirm the assumption that the corneal endothelium as a bradytrophic tissue is resistant to radiation damage. It is well known that due to irradiation, eye lens tends to turn opaque earlier, and in the instance of ciliary body melanomas, the lens is directly exposed to irradiation. In such cases, cataract is likely to develop earlier, and as patients have good visual acuity at the time of tumor detection that remains even after therapy, the gradual opacification has a disturbing effect. It is also well known that phacoemulsification decreases ECD. In case of cataract surgery on a patient who underwent plaque therapy, it should be considered that the irradiation has decreased the ECD. We plan to

examine patients with history of brachytherapy followed by cataract surgery and to investigate the rate of further ECD decrease due to phacoemulsification.

5.2 Alport patients without classic ocular symptoms have a smaller lens diameter

In accordance with the 2014 International Workshop on Alport Syndrome, our results support the importance of ophthalmological screening of patients with possible Alport syndrome. The regional center for Alport syndrome is located at the Department of Nephrology at the University of Debrecen. The diagnosis is based on kidney biopsy, electron microscopy, and immunofluorescence staining examinations. According to the 2015 International Workshop on Alport Syndrome, although genetic testing is generally replacing more invasive investigations such as kidney biopsy and skin biopsy, these investigations are still accepted in different parts of the world. In Hungary, genetic testing is available when kidney biopsy cannot be done or would not be informative. All new patients are referred to our department for ophthalmological examination. There were no ophthalmological findings for six out of seven patients. They underwent kidney biopsy. The diagnosis of the patient with typical ophthalmological features was based on the family history of Alport syndrome, patient history of renal failure, and ophthalmological findings. In this case, an invasive kidney biopsy or expensive genetic testing could be avoided.

The patient with eye abnormalities was an 18-year-old female who had PPMD and dot-and-fleck retinopathy. Although keratoconus was not present, she had high-degree myopia with remarkable astigmatism. Besides our cases, only one Alport syndrome case has been reported with the presence of PPMD and non-keratoconic astigmatism with high-degree myopia, while another has been

reported with PPMD, irregular astigmatism with superior steepening, and moderate myopia.

Kurt et al. reported the association of high-degree myopia, corneal dystrophy, and deafness as an individual hereditary disease. There are also reports on corneal steepening in PPMD and corneal dystrophies associated with progressive myopia. Although Raber et al. reported five patients with PPMD associated with non-keratoconic astigmatism and elongated axial length, they did not observe any connection between these clinical signs. Data were not available in the article on whether Alport syndrome was confirmed in these patients.

PPMD, abnormalities of the corneal shape (astigmatism, ectatic disorders), progressive myopia, sensorineural hearing loss, and Alport syndrome might have a similar background as for abnormalities in collagen at some level. Shen et al. suggested that the rare association of different abnormalities is the result of similar genetic anomalies. For further evidence, genetic testing of these patients would be necessary. We did not find any typical ophthalmological features in the other six Alport syndrome patients referred to our department. We compared the results of our measurements (keratometry, pachymetry, anterior chamber depth, lens morphology, and axial length) with the results of an age-matched control group. The Alport patients were found to have a significantly smaller lens diameter than normal controls. Although we observed a thicker lens in Alport patients compared to the normal controls, the difference was not significant. The power of the lens was calculated and showed a significant difference ($p=0.026$), meaning that Alport patients had lower lens power.

Our results suggest that Alport patients with no typical ophthalmological findings tend to have thicker lenses with a smaller diameter than in healthy controls. This presentation of spherophakia, which we found using ultrasound biomicroscopy, might represent one of the earliest ophthalmological signs of Alport syndrome. Only one paper has reported morphological changes to the lens in Alport syndrome; however, that study was published 20 years ago when no

examining method was available for precise measurements of the lens parameters. As such, using more advanced technology, our study suggests that the lens changes in Alport syndrome show signs of spherophakia. A more spherical lens results in myopia, which explains the myopia we found in Alport patients. We found that keratometric and axial length data showed no statistical significance, but the power of the lens was significantly smaller compared to normal controls, which is also a proof for myopia, and our study shows that morphological and parametrical changes of the lens can be the first ophthalmologic sign of Alport syndrome.

The possible background of spherophakia is the formation defect of type IV collagen, which is the same factor that causes classical ophthalmological findings, hearing loss, and kidney disorder in Alport syndrome. This defect causes structural damage in the basal membrane, which leads to its thinning and fracturing. Lens abnormalities might be described in a sequence, with changes in shape (thickening, smaller diameter, i.e., spherophakia) at first, followed by anterior lenticonus and posterior subcapsular cataract formation.

Spherophakia, as the first sign of Alport syndrome, can be diagnosed by ultrasound biomicroscopy, a noninvasive examination method. This finding also underlines the importance of ophthalmological testing in possible Alport patients, which, combined with ultrasound biomicroscopy, might be a diagnostic tool for the screening of patients with kidney abnormalities.

6. Summary of new results and their clinical relevance

6.1 Does beta-ray emitting therapy of ciliary body tumors decrease central corneal endothelial cell density?

Our results prove that corneal endothelial cells get damaged by beta irradiation, but there is no significant difference between the decrease of endothelial cell density in the center and the periphery. The extent of the damage can be moderated by using plaques with corneal cut. Another significance of our study is, that the corneal endothelium proved to be relatively resistant against radiation damage so in case of nonresectable tumors in the anterior chamber, round plaques covering the cornea can be used without risking endothelial damage.

6.2 Alport patients without classic ocular symptoms have a smaller lens diameter

Our results suggest that Alport patients with no typical ophthalmological findings tend to have thicker lenses with a smaller diameter than healthy controls. This presentation of spherophakia, might represent one of the earliest ophthalmological signs of Alport syndrome. Spherophakia can be diagnosed by ultrasound biomicroscopy, a noninvasive examination method. This finding also underlines the importance of ophthalmological testing in possible Alport patients, which, combined with ultrasound biomicroscopy, might be a diagnostic tool for the screening of patients with kidney abnormalities.

Keywords

Alport-syndrome, beta-radiation, ciliary body tumor, cornea, endothelial cell, lens, plaque therapy, spherophakia, ultrasound biomicroscopy.



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List of publications related to the dissertation

1. **Surányi, É.**, Nagy, V., Berta, A., Mátyus, J., Szalai, E., Ujhelyi, B., Meleg, J., Damjanovich, J.:
Alport Patients without Classic Ocular Symptoms Have Smaller Lens Diameter.
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2. **Surányi, É.**, Berta, A., Módis, L., Szalai, E., Damjanovich, J.: Does Beta-ray Emitting Therapy of
Ciliary Body Tumors Decrease Central Corneal Endothelial Cell Density?
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List of other publications

3. Damjanovich, J., **Surányi, É.**, Berta, A.: Az uvea melanómák kezelésének alapelvei.
Szemészet. 149 (1), 1-5, 2012.
4. **Surányi, É.**, Damjanovich, J., Berta, A.: Primer chorioidea-melanoma előfordulása 8 évvel
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