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Alport Patients without Classic Ocular Symptoms Have Smaller Lens Diameter

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Background: The aim of this study was to present ophthalmological findings regarding Alport syndrome and report refractometry data and to present possible early signs of the syndrome.

Material/Methods: Seven patients suffering from Alport syndrome were referred to the Department of Ophthalmology at the University of Debrecen between January 1st, 2014, and December 31st, 2015. All patients underwent slit lamp evaluation and dilated fundus biomicroscopy, with special attention paid to lenticonus and retinal changes. IOL Master, Pentacam HR, and ultrasound biomicroscopy were performed to assess keratometry, corneal thickness, anterior chamber depth, lens size, and axial length data.

Results: One patient out of seven had ocular symptoms. Posterior polymorphous corneal dystrophy (PPMD) and dot-and-fleck retinopathy were seen. Meanwhile, although keratoconus was not proven, remarkable astigmatism with high myopia was detected. The other six patients were found to have a significantly smaller lens diameter (an average of 7.82±0.66 mm, p=0.035) compared to normal controls (an average of 8.65±0.46 mm). Lenses also tended to be thicker in Alport patients (3.48±0.19 mm) compared to controls (3.4±0.2 mm), although the difference was not significant (p=0.394). The power of the lens also showed a significant difference (p=0.026), with Alport patients having lower lens power.

Conclusions: Alport syndrome patients without classical ophthalmological findings have smaller crystalline lens diameter and lower lens power. These signs may support the diagnosis of Alport syndrome. Ophthalmologists should not only seek for the known classic signs, but also the parameters of the crystalline lens, especially if genetic testing is not available.

MeSH Keywords: Cornea • Microscopy, Acoustic • Nephritis, Hereditary

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Background

Alport syndrome, historically referred to as hereditary glomerulonephritis with sensorineural hearing loss and anterior lenticonus, is a genetic multisystem disease resulting in renal failure [1]. Alport syndrome is very rare, with an estimated prevalence of one in 5000. The causes of Alport syndrome are different mutations of α3–5 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 men is characteristic of 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-aged individuals.

In 80% of patients 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 [2]. 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 [3]. The presence of anterior lenticonus or PPMD in any individual is also highly suggestive for the diagnosis of Alport syndrome [2]. 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 arises from heterozygous mutation of COL4A3 or COL4A4; its prevalence is less than 5%, but next-generation sequencing in Alport families suggests that it may occur more frequently. Ocular findings are unusual.

Our aim here 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 and analyzed their reliability.

Material and Methods

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 study was performed in accordance with the tenets of the Helsinki Declaration and informed consent was obtained from all patients. 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. We used the IOL Master (IOL Master 5.4.0002; Zeiss, Jena, Germany), Pentacam HR (Pentacam High Resolution; Oculus, Wentzler, Germany), and ultrasound biomicroscopy (OTI Scan 3000; Optos, Hialeah, USA) 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.

Statistical analysis was performed using 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. Data were analyzed using the Mann-Whitney test. A p-value below.05 was considered statistically significant.

Results

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

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Table 1. Lens diameter, thickness and power, keratometry, corneal thickness, anterior chamber depth, axial length in Alport patients and in normal controls.

	Alport-syndrome			Normal control			P
	Mean	95% CI	SD	Mean	95% CI	SD	
Lens diameter (mm)	7.817	7.119–8.514	0.6644	8.651	8.224–9.079	0.4627	0.035
Lens thickness (mm)	3.48	3.279–3.681	0.1914	3.407	3.189–3.624	0.2073	0.3939
Lens power (D)	21.167	17.066–25.267	3.9073	22.571	18.689–26.453	4.1975	0.4452
K1 (D)	44.193	41.972–46.414	2.4014	44.279	41.886–46.671	2.5873	0.9491
K2 (D)	45.69	42.727–48.653	3.2035	45.193	42.999–47.386	2.3718	0.848
Corneal thickness (µm)	529.286	497.07–561.50	34.831	540.571	513.699–567.444	29.057	0.4433
Anterior chamber depth (µm)	3.607	3.255–3.960	0.381	3.399	3.034–3.763	0.3942	0.2774
Axial length (mm)	23.627	22.015–25.239	1.7427	22.623	21.219–24.026	1.5175	0.2774

Table 2. Keratometry and anterior chamber depth data measured by IOL Master, Pentacam HR and Ultrasound biomicroscopy.

	IOL Master			Pentacam HR			Ultrasound biomicroscopy			P
	Mean	95% CI	SD	Mean	95% CI	SD	Mean	95% CI	SD	
K1 (D)	44.279	41.886–46.671	2.5873	44.014	41.624–46.404	2.5842				0.62
K2 (D)	45.193	42.999–47.386	2.3718	44.914	42.763–47.066	2.3262				0.62
Anterior chamber depth (µm)	3.363	2.990–3.735	0.4027	3.399	3.034–3.763	0.3942				0.8048
	3.363	2.990–3.735	0.4027				3.386	3.025–3.747	0.3905	1
				3.399	3.034–3.763	0.3942	3.386	3.025–3.747	0.3905	0.7104

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. There was no significant difference between the other variables in the two groups analyzed using the Mann-Whitney test (Table 1).

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 (Table 2).

Discussion

In accordance with the 2014 International Workshop on Alport Syndrome, our results support the importance of ophthalmological screening of patients with possible Alport syndrome [1]. 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 [4]. 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 [5]. 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 [6], while another has been reported with PPMD, irregular astigmatism with superior steepening, and moderate myopia [7].

Kurt et al. reported the association of high-degree myopia, corneal dystrophy, and deafness as an individual hereditary

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disease [8]. There are also reports on corneal steepening in PPMD [9–11] and corneal dystrophies associated with progressive myopia [12]. 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 [10]. 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 [6]. 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.

Conclusions

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 [2]. 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 [13]. 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.

Conflict of interests

None.

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