CASE REPORT

Rare Ocular Manifestation with Suspect Alport Syndrome

Krejčířová I.[1], Varadyová B.[1], Doležel Z.[2], Autrata R.[1], Matušová J.[3], Gregorová E.[3]

[1]Department of Paediatric Ophthalmology, University Hospital, Brno
Head: prof. MUDr. Rudolf Autrata, CSc., MBA
[2]Paediatric Clinic, University Hospital, Brno
Head: prof. MUDr. Zdeněk Doležel, CSc.
[3]Department of Ocular Diseases and Optometry, St. Anne's University Hospital, Brno
Head: doc. MUDr. Svatopluk Synek, CSc.

First author:
MUDr. Inka Krejčířová, Ph.D.
Department of Paediatric Ophthalmology, University Hospital, Brno
Černopolní 9
613 00 Brno
inka.krejcir@seznam.cz

SUMMARY

The authors mention a case report of a 13 year old girl with renal disease, who visited the outpatient Department of Pediatric Ophthalmology, University Hospital Brno with subjective complaints on decreased vision of both eyes. Ophthalmologic examination showed physiological foveolar reflex on fundus and very discrete changes of the retinal pigment epithelium in macula, the fundus periphery was without pathology. OCT images showed bilateral atrophy of central macula and changes at the level of the photoreceptors. The authors describe a rare ocular manifestation of macular atrophy with suspect Alport syndrome, which strengthened the suspicion of this disease. The authors also mention other possible ocular manifestations of Alport syndrome and compare the findings with the up to date international references.

Key words: Alport syndrome, X heterozygot Alport syndrome, macular atrophy, lentikonus

Čes. a slov. Oftal., 70, 2014, No. 3, p. 114–118

INTRODUCTION

Alport syndrome (AS) represents a hereditary disease, in which the function of the kidney glomeruli is affected. Their dysfunction resides in an attenuation of the basal membranes as a result of defective synthesis of chains of collagen type IV (3, 11, 12).
The most frequent cause of AS is mutation of the gene for the α5 chain of collagen IV (most often mutation of the gene COL4A5 on the X chromosome), and in 85% of cases this therefore concerns X-linked inheritance. In less common cases (10-15%), the disease is caused by a mutation of both alleles of the gene for the α3 or α4 chain of collagen IV; in this case it is autosomal recessive inheritance (3, 11, 12, 13).
The incidence of AS is approximately 1:5000 in live-born children (3, 8). In heterozygote women, as demonstrated by recent studies, there is a large variability of the disease, relating to both clinical and diagnostic findings (12, 17). Whereas 90% of affected men suffer chronic renal insufficiency before their 40th year of life, in heterozygote women this concerns only 12% of those affected (12).
In patients with classic AS, affliction of the renal function is typical (manifested as nephritic or nephrotic syndrome). Fully developed AS is also called progressive hereditary nephritis (3, 11). Disorders of hearing and also ocular manifestations are commonly associated with AS.
Clinical symptoms supporting the suspicion of AS include renal symptoms (microhematuria, proteinuria, hypertension and renal insufficiency), hearing disorders (bilateral loss of hearing at high frequencies) and ocular symptoms (3, 11). In addition to the basal membrane of kidney glomeruli, potentially afflicted tissues also include the basal membrane of the organ of Corti in the inner ear, the basal membrane of the capsule of the ocular lens, the internal limiting membrane of the retina (membrana limitans interna – MLI) and the basal membrane of the retinal pigment epithelium (RPE), which forms the Bruch's membrane (8, 13).
Internal determination of the diagnosis consists in a physical examination and anamnesis, a detailed family anamnesis and if applicable an analysis of urine from close relatives, an immunohistochemical examination of the basal membrane in renal or dermatological biopsy, examination of the renal biopsy using an electron microscope, and a molecular genetic examination of genes COL4A3, COL4A4 an COL4A5. If the doctor discovers microscopic haematuria, it is always necessary to consider AS (3, 11).
The variability of the disease in heterozygote women with X-linked AS is manifested in both clinical and diagnostic findings. The most recent studies have shown that histological findings in renal biopsy in heterozygote women vary widely in their appearance, with non-specific findings detected with the help of a light microscope. Immunohistological examination also demonstrates variable findings in heterozygote women. Sensorineural affliction of hearing, especially at high frequencies, occurs in 90% of affected men up to the age of 40 years, as against only 10% in the case of heterozygote women (12, 19).
Treatment of AS is only symptomatic, and consists in a treatment of hypertension and reduction of proteinuria. The only possible therapy in the terminal phase of renal failure in AS at present is haemodialysis or organ transplant of the kidney. For the future, treatment with the help of gene therapy is under consideration (3, 11).
In 1927, Alport first described the joint presence of hereditary nephritis with sensorineural hearing loss, observed in several generations. In 1954 deformation of the clear lens was first observed in patients with renal and hearing disorders. In 1961 Julien Marie described the presence of anterior lenticonus in patients with AS (8).
The most common ocular manifestations in AS include anterior lenticonus and perimacular or peripheral retinopathy ("fleck and dots retinopathy").

As rare ocular abnormalities, posterior lenticonus, posterior polymorphous corneal dystrophy, macular atrophy and macular hole have been described (2, 4, 6, 7, 8, 9, 13, 16, 19). Eye examination and a finding of an ocular manifestation may assist the diagnostics of AS (18).

CASE REPORT

At the end of 2012 a 13 year old girl came to the outpatient clinic of the Department of Paediatric Ophthalmology with a subjective complaint of bilateral deterioration of vision. Her personal ocular anamnesis contains nothing of significance. The girl has been in regular dispensary care at the Paediatric Clinic of the University Hospital in Brno since 2010 due to nephrotic syndrome, in which she has experienced a relapse of this condition six times over the course of the last 2 years. She has now been in a period of remission for 2 years on general corticosteroid therapy with Prednisone p.o., with the minimum doses of 5-10 mg every other day.

In 2010 a renal biopsy was performed with a conclusion of nephrotic syndrome, with an image of minimal changes of glomeruli and a non-specific finding for AS. During the period of remission of nephrotic syndrome, the girl was entirely without a finding of microscopic haematuria and proteinuria. In the phase of deterioration the image was always typical of advanced nephrotic syndrome. Before the finding of the ocular manifestation, no genetic examination for AS had so far been indicated from an internal perspective.

From the ocular clinical examination, vision OD 0.9 d.k.n; vision OS 0.7 d.k.n, according to cycloplegic refraction emmetropia, intraocular pressure within the norm, position parallel, movement unrestricted, pupil isocoric, without signs of afferent pupillary defect. Anterior segment biomicroscopically with entirely physiological finding, without pathological finding on cornea or lens.

On the fundus papilla of physiological appearance, capillaries of physiological course and filling, macula with preserved physiological foveolar reflex, only discrete changes perceptible at the level of the retinal pigment epithelium. Photographic documentation of the funds of the right and left eye of the patient is illustrated in Fig. 1 a and b.

Examination on an Amsler grid bilaterally without pathology.

Static perimeter implemented, in which minor relative central scotoma is visible in left eye. According to VEP only borderline latency of wavelength P100 without significant pathology.

The girl was subsequently sent for an OCT examination. The examination was performed on a Spectral OCT SLO OPKO. Bilateral macular atrophy determined, especially of the central part with regard to age (1, 5) with changes at the level of RPE and photoreceptors in Fig. 2 and table 1.

This was further supplemented with an instrument examination of colour-sensitivity (HMC anomaloscope, Oculus), which was bilaterally unaffected. Multifocal electroretinography demonstrated pronounced depressions of potentials of macular region bilaterally, with extended P-wave latency, which confirms atrophy in the central region. Result of analysis of laser scanning polarimetry (GDx) bilaterally within the standard limits.

Fig. 2a and 2b illustrate OCT of the macular region of the right and left eye (ODS): Foveolar depression preserved, visible umbo, visible attenuation of entire macular region of retina with regard to age, especially in central area, visible separation of RPE and border of outer and inner segments of photoreceptors.

The girl was sent also for examination by fluorescence angiography, but this examination was not indicated by the retinal specialist due to insufficient finding on the OCT image.

Even though the clinical picture of the renal disorder does not entirely typically correspond to AS, due to the absence of microscopic haematuria in the period of remission of nephrotic syndrome and the lack of a typical finding upon the renal biopsy, the finding of ocular macular pathology contributed to a confirmation of X-linked AS. There was anamnestically supplemented presence of possible renal disorder in the grandmother and grandmother of

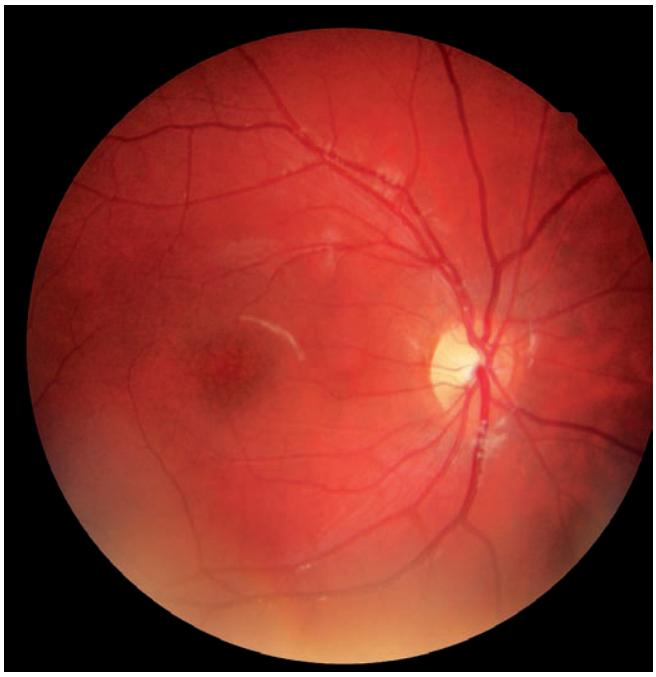

Fig. 1 a) Photo of fundus of right eye

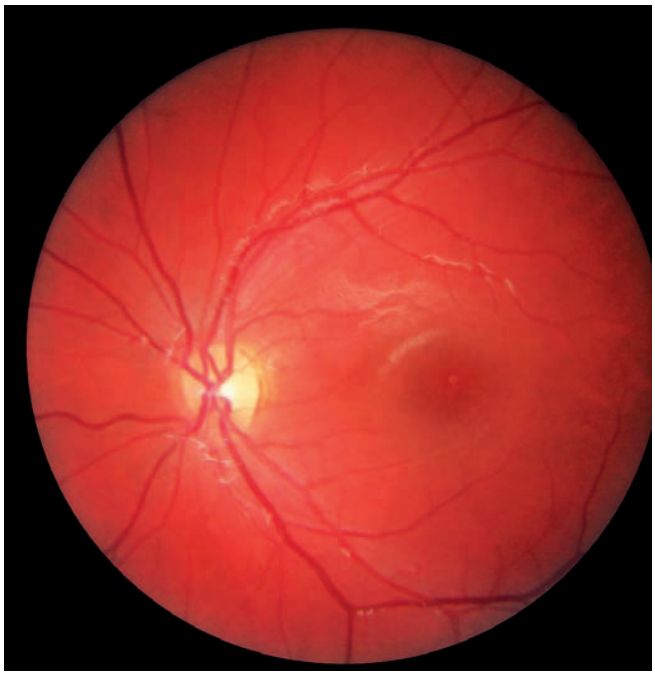

Fig. 1 b) Photo of fundus of left eye

Table 1 Macular thickness (MT) and volume in individual inner and outer segments in 13 year old girl with suspected Alport syndrome. Thinning primarily in the central regions of the macula in both eyes, more pronounced in left eye in comparison with normative data in healthy children (1, 5).

	OD		OS		Normative data in children	
	MT (μm)	Volume (μL)	MT (μm)	Volume (μL)	Ø MT (range) (μm)	Ø Volume (μL)
Centre	**110 !**		**109 !**		166 (130-194)	
Centre circle	**138 !**	0.11	**117 !**	0.09	204 (162-243)	1.8
Superior inner	**254 !**	0.40	**198 !**	0.31	282 (252-313)	0.9
Temporal inner	**221 !**	0.35	**198 !**	0.31	270 (242-294)	1.0
Inferior inner	**254 !**	0.40	**248 !**	0.39	281 (253-305)	0.9
Nasal inner	**229 !**	0.36	**214 !**	0.34	281 (247-322)	1.3
Superior outer	276	1.46	266	1.40	245 (219-277)	1.0
Temporal outer	232	1.23	233	1.23	231 (201-256)	1.3
Inferior outer	259	1.36	250	1.32	239 (207-269)	1.1
Nasal outer	287	1.52	273	1.44	263 (229-296)	1.1
Totals	255	7.18	242	6.83		

the girl. An audiological and ENT examination for the girl was also added with a conclusion of normacusis, the girl thus had no hearing disorder.

The phenotypic image, according to recent studies (12, 9) observing heterozygote women with X-linked AS, may correspond to the large variability of AS, in which even the absence of microhaematuria and the non-specific finding of the renal biopsy does not exclude this disease (12, 19).

The ocular finding currently concluded as a rare ocular manifestation of macular atrophy in the case of suspect

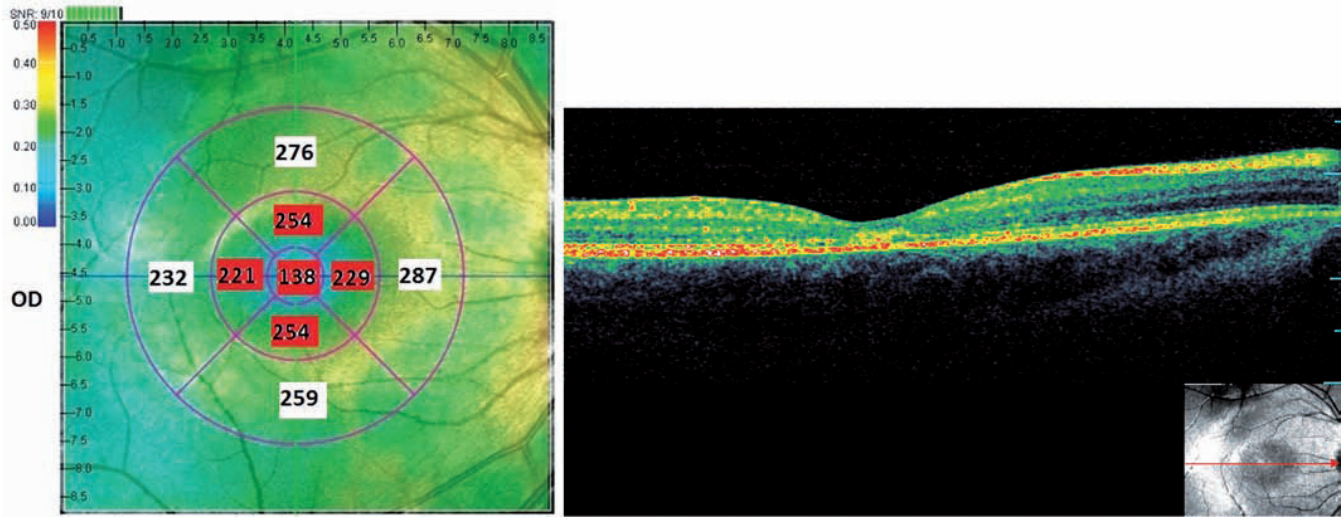

Fig. 2 a: On right eye (OD) central macular thickness 138 μm, inner temporal region of macula 221 μm

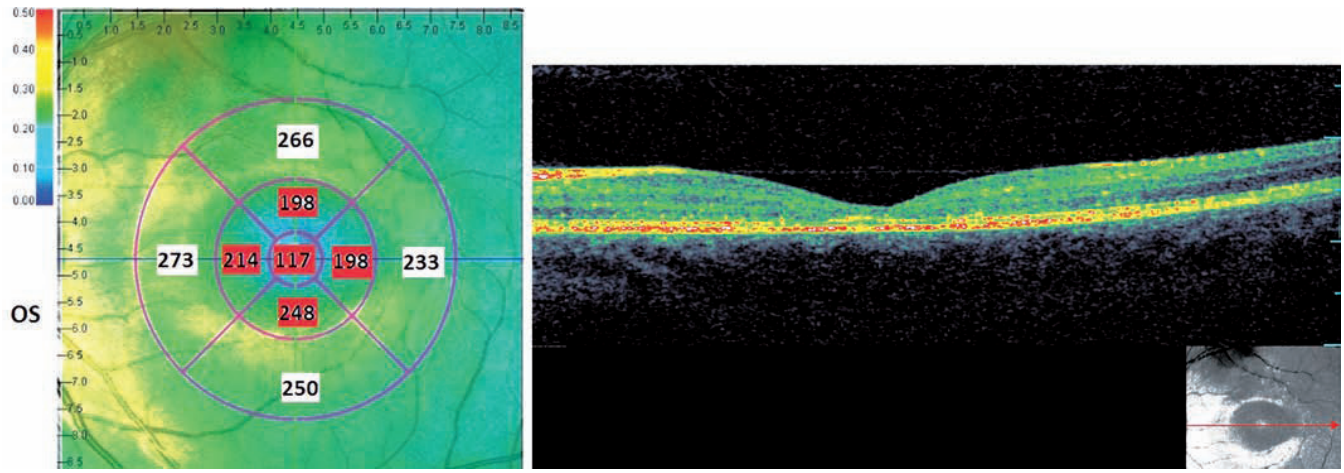

Fig. 2 b: On left eye (OS) central macular thickness 117 μm, inner temporal region of macula 198 μm

Table 2 documents cases of the retina thinning in patients with AS described by the authors.

Author/year	Number of patients	OD/OD BCVA	OD/OS MT (μm)	Age (years)	Sex
Usui (16) / 2004	1	1.0 1.0	59/62	38	M
Colville (2) / 2009	6	Not stated	Not stated	11-41	M
Fawzi (6) / 2009	1	0.5 0.4	Not stated	19	M
Savige (13) / 2010	10	Not stated	214 +- foveal	14-74	7M 3Z
Igami (8) / 2012	1	0.6 0.7	1 13/99	48	Z
Dolz-Marco R (4) / 2012	2	0.4/0.4 0.7/0.7	Not stated	35 36	M

AS. From an internal perspective, DNA analysis is subsequently indicated for the presence of mutation of COL4A genes due to suspect X-linked AS. A sample for the DNA analysis was sent as standard to the laboratory of the Department of Medical Genetics at the University Hospital in Ostrava, which conducts AS examinations. At the present time, i.e. more than one year after taking the sample, we do not yet have the result of the DNA analysis available.

DISCUSSION

The main ocular abnormalities in patients with AS include anterior lenticonus, and central and peripheral fleck and dots retinopathy. These two most common ocular manifestations occur in approximately 50% of men and 20% of women with X-linked AS (8, 13). Anterior lenticonus is caused by bulging of the lens as a consequence of attenuation of the lens capsule (13). Central retinopathy covers whitish-yellow perimacular flecks and dots, which are often present from the beginning of adolescence and are more frequent if renal dysfunction, hearing disorder and anterior lenticonus are present (13). Central and peripheral retinopathies may however occur separately, without the presence of anterior lenticonus in patients with AS, and mostly do not affect vision and do not require treatment (13). Central retinopathy ranges from a number of interspersed dots and flecks in the temporal part of the macula to (in the most severe cases) perimacular annulus composed of densely agglomerated points from the edges of the fovea to the remote vascular arcade. They may then form specific strips, which reflect the arrangement of the layer of bundles of nerve fibres (13). Sometimes flecks and dots produce an abnormal tapetal reflex (13), and their perifoveolar arrangement may thus influence the actual foveal and foveolar reflex, referred to in the literature as “lozenge or dull macular reflex” (2, 13).

In patients with AS, retinopathy afflicting the fovea and macular atrophy are rarely described (13). In patients with AS cases of thinning of the retina with a finding similar to cone dystrophy (14, 15), bull’s eye maculopathy or vitelliform maculopathy (6) have also been described in rare cases. Macular holes in connection with AS are also rare, are usually larger than classic idiopathic macular holes and respond poorly to surgical treatment (13, 9, 10).

The presence of chains of collagen type IV has been demonstrated on the retina by immunohistological analysis (13). They have been demonstrated in the MLI and in the basal membrane of the RPE Bruch’s membrane. In patients with AS, attenuation of the MLI / layer of nerve fibres and the Bruch’s membrane has been demonstrated (13). Perimacular “fleck and dots” retinopathy corresponds to hyperreflexia of the MLI / layer of nerve fibres (13). Macular hole and macular atrophy have a predilection in the temporal macular region (4, 8, 10, 13).

It is presumed that retinal abnormalities of AS are the result of thinning of the layer of the MLI / layer of nerve fibres and RPE basal membrane of the Bruch’s membrane. Attenuation of these layers contributes to the formation of fleck and dots maculopathy, as well as to rarer images of thinning of the retina and the occurrence of a macular hole. Probably through their influence on the nutrition and metabolism of the retina, they may influence the other layers, including the layer of the photoreceptors
2, 4, 6, 8, 9, 13, 16).

CONCLUSION

The case of rare ocular manifestation of bilateral macular atrophy in a 13 year old girl highlights the relation of this retinal affliction to AS, and emphasises the importance of correct diagnosis, of benefit especially for heterozygote women, in whom there is large variability of the X-linked syndrome, and the presence of this retinal or other anomaly may strengthen suspicion of this general disease and assist overall diagnosis of a systemic disorder. It is evident that a finding of macular atrophy has an influence on central visual acuity, which cannot be influenced therapeutically or otherwise (8, 13). Retinal abnormalities in connection with AS may also represent a higher risk of future progression of renal disorder (2, 12).

LITERATURE

1. **Altemir, I. et al.:** Reproducibility of optical coherence tomography measurements in children. Am J Ophthalmol, 2013 Jan; 155(1): 171–176.
2. **Colville, D., Wang, YY., Tan, R. et al.:** The retinal “lozenge” or “dull macular reflex” in Alport syndrome may be associated with a severe retinopathy and early-onset renal silure, Br J Ophthalmol, 2009; 93(3): 383–6.
3. **Češka, R., Tesař, V., Dítě, P. et al.:** Interna, 1. vydání, Praha: TRITON, 2010, 855, s. 541–542.
4. **Dolz-Marco, R., Gallego-Pinazo, R., Francés-Munoz, E., et al.:** New macular tomography findings in Alport syndrome. Arch Soc Esp Oftalmol, 2012; 87(2): 55–6.
5. **Eriksson, U., Holmstrom, G., Alm, A. et al.:** A population-based study of macular thickness in full-term children

assessed with Stratus OCT: normative data and repeatability. Acta Ophthalmol, 2009; 87(7): 741–5.
6. **Fawzi, AA., Lee, NG., Eliott, D. et al.:** Retinal findings in patients with Alport Syndrome: expanding the clinical spektrum. Br J Ophthalmol, 2009;93(12): 1606–11.
7. **Hentati, N., Sellami, D., Makni, K., et al.:** Ocular findings in Alport syndrome: 32 case studies. J Fr Ophtalmol, 2008; 31: 597–604.
8. **Igami, TZ., Lavezzo, MM., Ferraz, DA., et. al:** Unusual macular thickness in Alport syndrome: case report. Arq Bras Oftalmol, 2012; 75(4): 283–5.
9. **Mete, UO., Karaaslan, C., Ozbilgin, MK., et al.:** Alport's syndrome with bilateral macular hole, Acta Ophthalmol Scand., 1996;74(1):77–80.
10. **Mercé, E., Korobelnik, JF., Delyfer, MN., et al.:** A new case of giant macular hole in a patient with Alport syndrome. J Fr Ophthalmol, 2012; 35(8): 573–9.
11. **Povýšil, C., Šteiner, I., Dušek, P., et al.:** speciální patologie. 2 vydání, Praha: Galén: Karolinum, 2007, 430.
12. **Rheault, MN.:** Women and Alport syndrome. Pediatr Nephrol, 2012; 27(1): 41-6.
13. **Savige, J., Liu, J., DeBuc, DC., et al.:** Retinal basement membrane abnormalities and the retinopathy of Alport syndrome. Invest Ophthalmol Vis Sci., 2010; 51(3): 1621–7.
14. **Setälä, K., Ruusuvaara, P.:** Alport syndrome with hereditary macular degeneration. Acta Ophthalmol (Copenh),1989; Aug;67(4): 409–14.
15. **Spraul, CW., Lang, GE.:** Cone dystrophy associated with Alport syndrome. Klin Monbl Augenheilkd, 2000 Sep; 217(3): 194–7.
16. **Usui, T., Ichibe, M., Hasegawa, S., et al.:** Symmetrical reduced retinal thickness in a patient with Alport syndrome, Retina, 2004; 24(6): 977–9.
17. **Xu, JM., Zhang, SS., Zhang, Q., et al.:** Ocular manifestation of Alport syndrome. Int J Ophthalmol, 2010; 3(2): 149–51.
18. **Zhang, KW., Colville, D., Tan, R., et al.:** The use of ocular abnormalities to diagnose X-linked Alport syndrome in children. Pediatr Nephrol., 2008 Aug; 23(8): 1245–50.
19. **Zhao, C., Wang, F., Zhang, Y., et al.:** A novel splice site mutation in the COL4A5 gene in a Chinese female patients with rare ocular abnormalities. Mol Vis, 2012; 18: 2205–12.