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Chapter 5

Alport Syndrome

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Abstract

Alport syndrome is a multisystem disorder including progressive renal disease, sensorineural deafness, and eye abnormalities. The high risk of cardiovascular pathology in patients with Alport syndrome was also described recently. The syndrome is caused by mutations in *COL4A3*, *COL4A4*, and *COL4A5* genes, which lead to defects in glomerular filtration barrier and other basement membrane. The diagnosis of Alport syndrome should be suspected in patients with glomerular hematuria and with family history of renal failure. The severity of the individual symptoms and renal prognosis are variable and depend on gene mutation type. The current standard of treatment is the use of angiotensin-converting enzyme inhibitors, which delay the progression of renal failure in Alport syndrome. The recent knowledge in pathogenesis of disease opens new therapeutic perspectives.

Keywords: Alport syndrome, *COL4A5*, *COL4A4*, *COL4A3*, kidney disease, glomerular basement membrane, hematuria, albuminuria, proteinuria, renal failure, sensorineural deafness, lenticonus, fleck retinopathy, corneal dystrophy, angiotensin-converting enzyme inhibitors

1. Introduction

Alport syndrome is the most frequent hereditary glomerulopathy affecting approximately 1 in 5000–53,000 people. The disease caused by mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes, which encode the α3, α4, and α5 chains of collagen type IV, a component of the basement membrane of the kidney, the eye, and the inner ear. The syndrome includes progressive nephropathy, ocular abnormalities, and high-tone sensorineural deafness. Clinical features and the prognosis of patients with Alport syndrome are known to depend on mutation type. The most frequent X-linked form of Alport syndrome is caused by *COL4A5* gene defects and

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detected in 85% of patients. Autosomal recessive inheritance is found in about 15% of patients; it can be caused either by homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4.* Patients who harbor only one pathogenic variant either in *COL4A3* or *COL4A4* gene are usually diagnosed with thin basement membrane nephropathy or autosomal dominant Alport syndrome. Digenic inheritance pattern of Alport syndrome has also been described. Current knowledge and future directions on Alport syndrome will be explored in this review.

2. Alport syndrome: genetic, pathogenesis, clinical presentation, prognosis, and treatment

2.1. Genetic and genotype-phenotype correlations in Alport syndrome

Several clinical cases of patients with hereditary familial congenital hemorrhagic nephritis were published by Arthur C. Alport in 1927. He was the first to recognize the link between nephritis and deafness, and he also noted ocular changes in one of these patients [1].

Alport syndrome (AS) is a multisystem disorder including progressive renal disease, sensorineural deafness, and eye abnormalities.

Alport syndrome is caused by mutations in the *COL4A3*, *COL4A4*, and *COL4A5* genes, which encode the α3, α4, and α5 chains of collagen type IV, a component of the glomerular basement membrane (GBM) in the kidney.

COL4A5 gene is located on chromosome X. More than 2300 *COL4A5* variants have been described to date [2]. Among the pathogenic variants, about 41% are missense mutations (with overwhelming majority of them being substitutions of glycine in the Gly-Xaa-Yaa triplet of the collagenous domain) which are the most frequent, followed by frameshift, splice site mutations, larger copy number variations, and nonsense mutations [3].

The *COL4A3* and *COL4A4* genes are located on chromosome 2 and share the same promoter (they are transcribed in opposite directions). Among *COL4A3* and *COL4A4* mutations, the distribution of mutation types is similar, in particular, glycine substitutions and missense mutations of other types still dominate. Incidence of pathogenic variants in the two genes is similar [4].

The abovementioned genes are known to have no mutation hotspots; however, some population-specific founder mutations have been described, e.g., *COL4A5* p.Leu649Arg mutation in the US [5], COL4A5 p.Gly624Asp mutation in the Slovenia, Hungary, and Greece [6–8], and deletion of exons 2–36 of COL4A5 in French Polynesia [9].

The most frequent X-linked form of AS is caused by *COL4A5* gene defects and detected in 85% of patients [10] (80% according to Kashtan [11]). It is dominant and more severe in males, whereas in females, penetrance depends on X chromosome inactivation pattern [12]. Patients demonstrate end-stage renal disease (ESRD) at the age of 8–60 years and usually have microhematuria with macrohematuria episodes from childhood [13]. About 80% of affected families demonstrate sensorineural hearing loss (at least in some patients) and about 50% are characterized by ocular abnormalities [13].

Autosomal recessive inheritance is found in about 15% of patients with their clinical course and ultrastructural changes being similar to those in X-linked form [14]. It can be caused either by homozygous or compound heterozygous mutations in *COL4A3* or *COL4A4* [15, 16].

Patients who harbor only one pathogenic variant either in *COL4A3* or *COL4A4* gene are usually diagnosed with thin basement membrane nephropathy (TBMN): benign familial hematuria not progressing to ESRD. It is still disputable if patients bearing only one pathogenic variant in either *COL4A3* or *COL4A4* gene who suffer from hematuria, lack hearing or ocular abnormalities, and potentially can develop ESRD in late age should be categorized to autosomal dominant AS or TBMN [17].

Digenic inheritance pattern of AS has also been described, which can be caused by two mutations in *COL4A3* and *COL4A4* genes each (either on the same chromosome or on homologous chromosomes) as well as by a combination of two mutations in *COL4A5* and *COL4A3* or *COL4A4* gene [18].

AS prognosis is known to depend on the mutation type. Associations have been shown both in males with X-linked inheritance and in autosomal recessive form (both sexes). Associations of genotype and phenotype have been extensively studied for the following conditions: age at onset of ESRD, hearing loss, and ocular abnormalities.

The expected ESRD age is similar for the two types of AS and comprises 23–25 years, excluding females with X-linked AS [4]. The risk of ESRD development in patients with X-linked AS by the age of 30 years is 70% in males, whereas only 5% in females; by the age of 40 years: 90 and 10%, respectively [19].

Phenotypic and clinical features in AS are known to depend on mutation type. Among patients with *COL4A5* variants, in males, the risk of development of ESRD by 30 years of age is the highest for subjects bearing "severe" mutations (nonsense, frameshift mutations, and multiexon deletions): 90%; lower for subjects bearing splice site variants: 70%; the lowest for patients bearing missense variants: 50% [19]. In females, there is no statistically significant difference neither for age at onset of ESRD nor for presence of hearing or ocular abnormalities [19].

Hearing and ocular abnormalities are also more prevalent in men than in women among X-linked AS subjects [20, 21]. Sensorineural hearing loss by the age of 30 is found in 60% of male patients with missense mutations compared to 90% of patients with mutations of other more severe types (including splice site mutations) [19]. Ocular abnormalities were shown to be 2–4 times less prevalent in males harboring pathogenic missense variants [20, 22, 23].

In patients with autosomal recessive AS, mutation type has similar effect on the clinical prognosis [4], which is significant both for women (unlike for X-linked type) and men.

2.2. Pathogenesis of Alport syndrome

Collagen type IV is composed of six different α chains, which assemble into three different protomers ($\alpha1\alpha1\alpha2$, $\alpha3\alpha4\alpha5$, and $\alpha5\alpha5\alpha6$) with a tissue-specific distribution [24, 25]. The absence of any one of these type IV collagen chains can result in the absence of the whole protomer in the GBM, presumably due to an obligatory association of the three chains in forming the type IV collagen superstructure [26].

The heterotrimers are essential for basement membrane structure and function [26]. The $\alpha3\alpha4\alpha5$ protomer in the GBM is only produced by podocytes [27], that is why podocytes are a key cell type affected by Alport syndrome pathology. The $\alpha1\alpha1\alpha2$ heterotrimer is produced by three cell types in the glomerulus: podocytes, endothelial cells, and mesangial cells [27]. The $\alpha1\alpha1\alpha2$ heterotrimer is ubiquitously distributed in all basement membranes during embryogenesis, and then in the process of development, there is a partial replacement of $\alpha1\alpha1\alpha2$ protomer by $\alpha3\alpha4\alpha5$ heterotrimer in the GBM, lungs, eyes, cochlea, and testes, and by the $\alpha5\alpha5\alpha6$ heterotrimer in skin, smooth muscle cells, kidney's Bowman capsules, and esophagus [28]. This substitution of collagen type IV heterotrimers leads to mechanical stability of basement membrane, as the $\alpha1\alpha1\alpha2$ chains are highly susceptible to endoproteolysis. In AS, assembly of the $\alpha3\alpha4\alpha5$ heterotrimer does not occur, resulting in decreased mechanical stability and splitting of the GBM, as well as other tissue-specific pathological changes.

The detailed pathogenetic mechanisms leading to progression of AS are not clear. As the GBM is a key component of the filtration barrier, patients with AS develop proteinuria [29] as a result of altered podocyte orientation, podocyte effacement, and disruption of slit diaphragms. However, interactions between integrins and the laminin $\alpha5\beta2\gamma1$ heterotrimer could disrupt the actin cytoskeleton and activate signaling mechanisms that result in an increase in matrix metalloproteinase expression and massive accumulation of extracellular matrix [25] as well as kidney fibrosis due to fibroblast formation by epithelial-mesenchymal transition, initiated as a physiological repair of injury response [30]. Invasion of mesangial filopodia may be responsible for deposition of the extracellular molecules in Alport GBM [31–33]. These changes could lead to progression of glomerulosclerosis, nephron loss, and hypertension. Increasing deposition of extracellular matrix and laminin $\alpha5$, upregulation of matrix metalloproteinase has been shown in the stria vascularis of ear in vivo.

Ultrastructural studies have demonstrated that the fundamental lesion of AS involves the GBM [29, 34]. The typical changes of GBM in AS are its thickening, splitting, and fragmentation of the lamina densa with formation of a characteristic "basket weave" pattern. The lesions may be focal (in the early stages of the disease) or widespread (in the late stages). The thinning or irregular appearance of the GBM (an alternation of thickening and thinning) is the prevalent changes in children with AS. Diffuse thinning of the GBM as the only morphological changes may be observed in 10–20% of patients with Alport syndrome, explaining why patients with thin basal membranes may have an unfavorable prognosis. Sometimes, it is possible to see the focal ruptures of the GBM and its reparation due to the synthesis of the new material of the glomerular basement membrane [35]. The light microscopy changes are not specific and vary from the normal renal tissue appearance or minimal glomerular changes in the early stages of the disease to focal mesangial proliferation, focal and segmental thickening of the capillary walls, and focal/global glomerulosclerosis in the late stages of the AS. These changes are associated with nonspecific tubulointerstitial lesions including foci of lipid-laden foam cells. Conventional immunofluorescence detects nothing or only faint or focal deposits of IgG, IgM, or complement C3.

The distribution of the different chains of collagen type IV in the basement membranes is very important for diagnosis of AS and especially for X-linked transmission's recognition.

Normally, *COL4A5* is expressed in the glomerular basement membranes, and the α5(IV) chain defect due to *COL4A5* mutation (absence or abnormal structure of α5(IV)) impairs protomer assembly and the normal collagen IV network formation. Immunohistological analysis reveals abnormal distribution of the α5(IV) chain in about two-thirds of patients with X-linked AS: in male patients, the α5(IV) antigen is not detected in the glomerular, capsular, and distal tubular basement membranes, while in female patients, the α5(IV) antigen has a discontinuous distribution. In addition, there is a lack of the α3(IV) and α4(IV) chains which participate in the α3α4α5(IV)-α3α4α5(IV) network formation. At the same time, the α1(IV) and α2(IV) chains normally confining to the mesangium and the subendothelial aspect of the GBM are widely expressed throughout the glomerular basement membrane in these patients. This immunohistological picture is typical for the fetal kidneys. But approximately, one-third of patients with AS do not have marked changes in the renal expression of α(IV) chains. The immunohistochemical picture is usually consistent within the family and correlates with the severity of the clinicopathological features of the disease [25, 36].

The distribution of α(IV) chains is also abnormal in skin basement membrane: the absence of the α5(IV) and the associated α6(IV) chains from the epidermal basement membrane is typical for male patients with X-linked AS and can be detected in about two-thirds of male patients. Observation of normal patterns of α5(IV) and α6(IV) localization does not facilitate definitive diagnosis in females because of the segmental distribution of the chains.

The peculiar immunohistochemical distribution pattern of α3(IV) to α6(IV) chains is observed in the skin and kidneys of most patients with autosomal recessive AS [31, 32, 35] and is characterized by the absence of α3, α4, and α5(IV) chains from the GBM contrasting with the persistence of α5(IV) chains in Bowman's capsules, collecting ducts, and epidermal basement membranes. These findings show that in autosomal recessive Alport patients, the expression of α5(IV) chains is defective only in those basement membranes in which the three chains are associated within the α3α4α5(IV)-α3α4α5(IV) network.

Expression of mutant collagen type IV results in splitting of the GBM, podocyte effacement, glomerulosclerosis, kidney fibrosis, and ESRD progression.

Men who are hemizygous for mutations in *COL4A5* causing X-linked AS have similar clinical presentation and prognosis to individuals homozygous for *COL4A3* and *COL4A4* mutations causing autosomal recessive AS. The median age of ESRD onset in untreated male patients with X-linked AS has been reported to be 22 years (range 7–39 years) [37, 38]. But, owing to imprinting (random inactivation on the two X chromosomes in female individuals) [39], female carriers of *COL4A5* mutations causing X-linked AS may have a higher risk of ESRD than do individuals who are heterozygous for autosomal recessive mutations in *COL4A3* and *COL4A4*.

2.3. Clinical presentation of Alport syndrome

The diagnosis of AS should be suspected in patients with family glomerular hematuria and with family history of renal failure. Children with AS syndrome can usually be diagnosed with mild hematuria with or no episodic macrohematuria and low-grade proteinuria. As the

disease progresses, patients gradually develop severe proteinuria and progressive renal failure. Irrespective of the mode of inheritance of the disorder, proteinuria indicates an increased risk of progressive renal disease, even in heterozygous carriers. Changes in the GBM that are pathognomonic for AS include splitting and enlargement of the GBM and podocyte effacement.

There are several clinical stages in the development of glomerulopathy in AS:

Stage 0: microscopic hematuria (albumin/creatinine rate <30 mg/g/day).

Stage 1: microalbuminuria (albumin/creatinine rate = 30–300 mg/g/day).

Stage 2: gross proteinuria (albumin/creatinine rate >300 mg/g/day).

Stage 3: impaired renal function (glomerular filtration rate <60 ml/min/1.73 m^2).

Stage 4: end-stage renal disease.

Diagnosis of AS can be made in most patients after a clinical examination on the basis of the typical symptoms including kidney, ear, and eye.

The sensorineural hearing loss in AS, which primarily affects high tones, occurs in 30–50% of relatives with renal disease. The severity of auditory and renal features does not correlate. The molecular defects that underlie the otopathology in this disease remain poorly understood. An animal model of X-linked AS showed complete absence of the $\alpha3\alpha4\alpha5$ network in the inner ear, suggesting that collagen type IV is vital to cochlear function as well as renal function. The generation of radial tension of the spiral ligament on the basilar membrane via the extracellular matrix is necessary for reception of high-frequency sound. The lateral aspect of the spiral ligament is populated by tension fibroblasts expressing nonmuscle myosin and α-smooth muscle actin [40]. On the basis of the foregoing, it was assumed that in AS, the loss of the $\alpha3\alpha4\alpha5$ network eventually weakens the interaction of fibroblasts with their extracellular matrix, resulting in reduced tension on the basilar membrane and the inability to respond to high-frequency sounds [40]. Findings in Alport mice suggest that the hearing loss may arise from dysfunction of the stria vascularis mediated through endothelin-1 [40, 41].

The ocular manifestations in Alport syndrome patients are caused by loss of the collagen IV $\alpha3\alpha4\alpha5$ network in basement membranes of the eyes due to mutations which lead to basement membrane thinning, lamellation, and a decrease in its mechanical stability. Most of the ocular features in AS do not lead to a visual impairment, but they have diagnostic and prognostic value: in some cases, the ocular symptoms suggest the mode of inheritance and the likelihood of early-onset renal failure. Such ocular features as central and peripheral retinopathy and lenticonus are typical for AS, and their presence confirms the diagnosis.

Anterior lenticonus can be detected in half of men (not women) with X-linked Alport syndrome. And its presence is associated with early-onset renal failure. The symptom is often found in autosomal recessive AS regardless of the patient's sex, and therefore, the presence of lenticonus in women with AS most likely indicates an autosomal recessive mode of disease inheritance [41, 42]. Lenticonus is the consequence of the conical protrusion of the lens anteriorly through the thinnest part of the capsule [43]; sometimes, the mechanical weakness of the

capsule due to the absence of the $\alpha 3\alpha 4\alpha 5$ network can lead to its spontaneous ruptures and secondary cataract developments [44, 45]. After cataract formation, lenticonus ceases to progress [46]. Posterior lenticonus is less common in patients with AS. Lenticonus is usually found in early middle-age patients with renal failure. The patients complain a progressive difficulty in focusing due to of their abnormal lens shape. The presence of an oil droplet sign on direct ophthalmoscopy or slit-lamp examination confirms the diagnosis. Visual symptoms progress with a time, and most patients eventually require surgery. The treatment for both symptomatic lenticonus and cataract includes the lens removal and intraocular lens implantation.

The central or perimacular fleck retinopathy and peripheral coalescing fleck retinopathy are common retinal abnormalities in patients with AS. The other retinal changes include manifestations of temporal thinning [47, 48]: lamellar and giant macular hole, a lozenge, loss of the foveal reflex, disturbances of foveal pigmentation, including a bull's eye or vitelliform maculopathy [48, 49]. Central fleck retinopathy is present in 60% of men and at least 15% of women with X-linked AS and 50% of individuals with recessive disease [50]. It is more common with early-onset renal failure and lenticonus [47]. The central retinopathy varies from scattered whitish-yellow dots and flecks to a dense, almost confluent annulus around the region of temporal retinal thinning. The fleck retinopathy is associated with an abnormal inner limiting membrane. Thinning of the inner limiting membrane/nerve fiber layer may interfere with the nutrition of the overlying cells, removal of debris, and maintenance of the watertight barrier. The central retinopathy is best seen with color photographs and red-free images centered on the macula. Specialized tests of retinal function, such as electroretinogram and electrooculogram, are normal or nearly normal. The peripheral fleck retinopathy is the most common retinal abnormality, occurring in most men and 25% of women with X-linked AS and most individuals with recessive disease [47, 48]. The asymmetric patches of confluent flecks are characteristic signs of peripheral retinopathy [50]. The appearance on optical coherence tomography (OCT) and fleck location in relation to the blood vessels suggests that their formation is related to pathological changes of the retinal pigment epithelium/Bruch's membrane. The peripheral retinopathy is a very important diagnostic and prognostic symptom of AS associated with early-onset renal failure, central retinopathy, and lenticonus. But the peripheral retinopathy can also be present in women with X-linked AS who have normal renal function [47]. The peripheral retinopathy is best seen on ophthalmic examination or with retinal photographs that extend beyond the standard views into the periphery and with red-free retinal images. Temporal retinal thinning is very common in men and women with X-linked AS, and in patients with recessive disease [41, 42, 47, 48]. The lozenge, dull macular reflex, foveopathy, and lamellar and macular holes all affect the temporal retina and reflect retinal thinning of both the inner limiting membrane and Bruch's membrane. Thinning is confirmed with retinal thickness measurements on OCT. However, thinning is common in all forms of Alport syndrome and less sensitive diagnostically than a peripheral retinopathy. Hypopigmentation occurred in Alport syndrome is often not diagnosed. It is usually present along with perimacular flecks or other ocular features and does not lead to the visual impairment. Severe forms, such as a bull's eye or vitelliform retinopathy, may be occasionally found. Lamellar, partial-thickness macular holes, and giant macular holes lamellar are uncommon in patients with X-linked and autosomal recessive AS. This sign is unspecific for

AS. But in AS, the macular holes are larger (giant holes) and occur at a younger age than the spontaneous holes in patients who do not have AS. Holes may be asymmetric, unilateral, or bilateral. Beginning with multiple small defects, they hollow out from the surface of the inner limiting membrane in the consequence of accelerated passage of fluid through the defective Bruch's membrane, and followed by microcysts formation due to membrane breaking [50]. Patients with macular holes suffer from metamorphopsia (where straight lines are distorted) and impairment of central vision. In some patients, holes only become evident when there is no improvement in vision after surgery for lenticonus. Lamellar holes might be overlooked by retinal photographs; the OCT is required for their demonstration. Holes in AS do not respond well to surgical closure and often lead to a permanent loss of vision.

Posterior polymorphous corneal dystrophy and macular hole are rare but also suggest the Alport syndrome. Corneal disease is recognized infrequently in Alport syndrome. Erosions result from an abnormal Bowman's membrane in the corneal subepithelium and posterior polymorphous corneal dystrophy from an abnormal Descemet's membrane in the subendothelium [41]. The affected membranes lack the collagen IV $\alpha 3\alpha 4\alpha 5$ network, are weak, and adhere poorly to the epithelium, endothelium, and underlying stroma. Superficial corneal erosions occur in 10% of patients, but they are intermittent and hence. Their onset may precede the diagnosis of AS and is often in the late teenage years. They typically occur in individuals with early-onset renal failure and other extrarenal features. Posterior polymorphous corneal dystrophy is rare and more serious than the corneal erosions. Patients may be asymptomatic or have photophobia, watering, and grittiness. The diagnosis is based on high-resolution anterior segment OCT, slit-lamp biomicroscopy, specular microscopy, or in vivo confocal microscopy: there are multiple clusters of vesicles ("doughnuts") or bands ("snail tracks") at the posterior corneal surface. The vesicles result from vacuolar degeneration of dying cells or multilayered epithelial cell protuberances from Descemet's membrane. Treatment is usually symptomatic; sometimes, the dystrophy progresses, and corneal transplantation is required.

Ocular features are less sensitive but more specific than hearing loss in diagnostic of AS, because hearing loss occurs also in other inherited renal diseases and in dialysis patients. In addition, ocular symptoms may help distinguish between X-linked and autosomal recessive inheritance. Central retinopathy, lenticonus, and macular hole are rare in women with X-linked AS. The presence of any of these futures in a woman with hematuria leads to suspected autosomal recessive AS. Furthermore, revealed peripheral retinopathy in the mother of a boy with hematuria indicates the diagnosis of AS and also X-linked inheritance of the disease. Some ocular features have a prognostic value because they are associated with early-onset renal failure. Thus, central retinopathy and lenticonus usually indicate the onset of renal failure before the age of 30 years. Therefore, it is important to conduct a thorough ophthalmologic examination (slit-lamp examination, retinal photography, and OCT) in assessing patients with suspected AS. These tests are acceptable to patients, noninvasive, inexpensive, and widely available.

Other features of Alport syndrome include gastroesophageal leiomyomatosis and vascular abnormalities. Gastroesophageal leiomyomatosis is a very rare pathology characterized by benign nodular tumors with smooth muscle cells origin. The condition clinically presents by

dysphagia. Leiomyomatosis can also affect the tracheobronchial tree and the genital tract. Leiomyomatosis in AS is a consequence of a large deletion in the *COL4A5* and *COL4A6* genes, which encode collagen α5 (IV) or α5α6 (IV) chains in smooth muscle cells of the gastroesophageal tract [51, 52]. The α5 and α6 chains of type IV collagen are also found in the basement membranes surrounding vascular smooth muscle cells in the intima and media of aorta and other arteries in mice model [53]. Seki et al. [53] believed that α5 and α6 chains of type IV collagen in the basement membranes may have particular function in the arteries which are required to tolerate strong pulse and blood pressure such as the aorta. AS is associated with aortic abnormalities including aortic dilatation, ruptured ascending aortic aneurysm, aortic dissection, aortic insufficiency, and bicuspid aortic valve and coronary artery pathology including spontaneous coronary artery dissection in male patients [54–56].

Furthermore, patients with AS and mitral valve prolapse or ventricular septal defects and ruptured intracranial and coronary artery aneurysms have also been described [54, 57]. Therefore, the vascular imaging techniques could be included in the examination of patients with AS, especially in cases of family history of vascular abnormalities.

2.4. Differential diagnosis of Alport syndrome

In cases where the diagnosis of AS was not confirmed by clinical workup, morphology, or genetic test, other diseases with similar symptoms should be considered. A combination of kidney pathology and hearing loss can be associated with mutations of gene encoding mitochondrial and cytoskeletal proteins, ion channels, and receptors.

Patients with mitochondriopathy associated with mutations in the *COQ6* gene develop early-onset steroid-resistant nephrotic syndrome and sensorineural deafness [58]. The mutation leads to deficiency of ubiquinone biosynthesis monooxygenase COQ6 protein, localized in the Golgi apparatus of the stria vascularis and glomerular podocytes, and to upregulation of proapoptotic factors [58].

Alström syndrome is characterized by a defect of the primary cilium that is caused by mutations in *ALMS1* and leads to renal failure, sensorineural deafness in young adulthood, and vision loss in adulthood [59].

MYH-9-related disease should be considered in patients presenting with proteinuria and thrombocytopenia [60]. *MYH-9*-related disease (the gene for the heavy chain of nonmuscle myosin IIA) is a rare inherited autosomal dominant condition characterized by progressive nephritis (39%), macrothrombocytopenia (100%), Dohle-like leukocyte inclusions (100%), high-tone sensorineural deafness (49%), and cataract (54%) [60, 61]. Renal disease ranged from microscopic hematuria to end-stage renal failure necessitating dialysis and kidney transplantation. The most striking difference between hearing loss in *MYH-9*-related disease (or Fechtner syndrome) and that in AS was that the vast majority of hearing disorders in the latter occur in male patients. Hearing loss in *MYH-9*-related disease develops from the second decade of life and progresses slowly with several episodes of sudden deafness [60]. Renal biopsy findings are consistent with those of AS. Chronic renal failure can occur at a young age in patients with *MYH-9*-related disease.

A recent report described a *COL4A1* frameshift mutation in a family with autosomal dominant hematuria, GBM thinning, kidney cysts, and progressive kidney disease [62, 63]. The syndrome is characterized by hereditary angiopathy with retinal tortuosities, aneurysms, muscular cramps, and nephropathy manifesting as hematuria or cysts (HANAC). As such, investigation of patients with unexplained hematuria should include a search for extrarenal symptoms of HANAC, especially retinal abnormalities.

2.5. Renal prognosis

The expected ESRD age is similar for the males with X-linked and patients with autosomal recessive AS and comprises 23–25 years [4]. The risk of ESRD development in patients with X-linked AS by the age of 20 years is 70% in males, whereas only 5% in females; by the age of 40 years: 90 and 10%, respectively [19]. For many years, female members of Alport families who had hematuria were considered to be carriers who were not at risk for ESRD, despite reports of ESRD in female Alport patients. But review of clinical outcomes of nearly 300 girls and women with confirmed heterozygous *COL4A5* mutations showed that 12 and 30% of female have the probability of developing ESRD before the age of 40 and 60 years, respectively [19]. The 95% of heterozygous females had hematuria, the 75%—proteinuria; in addition, it was found that the proteinuria increased the risk of ESRD.

Patients with heterozygous mutations compared to patients with mutations in both alleles of *COL4A3* or *COL4A4* (autosomal recessive Alport syndrome) or hemizygous mutations in *COL4A5* (males with X-linked Alport syndrome) usually have milder renal involvement with late ESRD development and do not have extrarenal manifestations (ocular changes and hearing loss). But, lifetime risk of ESRD in heterozygous patients is higher than in the general population [64].

AS accounted for 0.5% of all cases of ESRD and was found to be associated with superior dialysis patient survival, superior posttransplant patient survival, and potentially superior renal allograft survival to matched controls with other causes of ESRD [65–67]. An incidence rate of anti-GBM antibody disease after kidney transplantation comprises 1–5% [65–67].

2.6. Treatment of Alport syndrome

Early diagnosis of AS is important, since therapeutic blockade of the renin-angiotensin-aldosterone system can slow the progression to ESRD depending on the stage of the disease when therapy is initiated. Angiotensin-converting enzyme (ACE) inhibitors are not a specific therapy for AS. The antihypertensive and antiproteinuric properties of ACE inhibitors lead to their nephroprotective effect. The animal models of AS have shown a major role of altered composition of the GBM and of podocytes (their cytoskeleton and their collagen receptors) with activation of profibrotic factors in disease progression [32, 33]. ACE inhibitors seem to be able to downregulate profibrotic factors independently from blood pressure and the amount of proteinuria in the Alport animal model [68].

The Alport Syndrome Research Collaborative recommends use of ACE inhibitors in all affected individuals with microalbuminuria or proteinuria, and underlines the importance of

using standardized dosing regimens and monitoring microalbuminuria during the treatment [69]. The ACE inhibitor ramipril is recommended as the first-line therapy; in cases of adverse effects associated with use of ramipril, the treatment with angiotensin-1-receptor antagonists will be recommended [69, 70]. The Alport Syndrome Research Collaborative guidelines suggest, therefore, that therapy with ACE inhibitors can be considered as early as stages 0 and 1 of the disease [69].

The age at progression from microalbuminuria to proteinuria in children with Alport syndrome is an important prognostic marker—the earlier this transition occurs, the worse the prognosis [71].

Currently, the only recruiting trial is the prospective, randomized placebo-controlled EARLY PRO-TECT Alport trial, enrolling pediatric patients with stages 0 and 1 Alport syndrome [72]. The goal of this trial is to clarify whether an early start of therapy delays renal failure more effectively than later onset of therapy and, above all, whether therapy in the early stages of Alport syndrome is safe. The trial will also investigate a potential protective effect of ramipril against the hearing loss as a secondary end point [72]. It seems to be very important because currently there are no therapies that can prevent the ocular changes or hearing loss development and progression in patients with AS.

Studies in animal models have revealed many potential new therapies for use in Alport syndrome: inhibitors of proinflammatory factors (for example, TGF-β1 and MMPs) [73, 74]; statins [75]; BX471 (a chemokine receptor-1 blocker) [76]; and upregulation of the expression of bone morphogenetic protein 7 [77]. A phase II study of antimicroRNA-21 treatment of patients with Alport syndrome 18 years of age or older with glomerular filtration rates of 45–90 ml/min/1.73 m^2 will be start; its primary goal will be determining the glomerular filtration rate decline during therapy [78]. In transgenic Alport mice, antimicroRNA-21 treatment reduced glomerular inflammation and impaired renal fibrotic pathways. A phase II/III study of the efficacy and safety of bardoxolone methyl for Alport syndrome patients with chronic kidney disease (CARDINAL) has been started [79].

3. Conclusion

Alport syndrome is a multisystem hereditary disorder characterized by progressive renal disease, sensorineural deafness, and eye abnormalities. Diagnosis of AS can be made on the basis of the typical symptoms, renal morphology, and/or genetic tests. Early diagnosis of Alport syndrome is very important, since therapeutic blockade of the renin-angiotensin-aldosterone system can slow the progression to ESRD.

Conflict of interest

The authors declare no conflict of interest.

Appendices and Nomenclature

AS	Alport syndrome
ACE	angiotensin-converting enzyme
GBM	glomerular basement membrane
ESRD	end-stage renal disease
OCT	optical coherence tomography
TBMN	thin basement membrane nephropathy

Author details

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