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Ocular Manifestations of the Alport Syndrome

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Introduction

Alport syndrome (AS) is a hereditary disease characterized by hearing impairment, kidney failure, and ocular abnormalities (Bamotra, Meenakshi, & Qayum, 2017). Because AS is a rare disease, it might remain undetected, meaning impacted individuals and their kin have low chances of being screened and receiving timely genetic counseling. This paper investigates ocular manifestations of AS and the prevalence of the disease. A majority of ocular abnormalities in AS do not impact vision but are essential in diagnosing the disease and evaluating how it was inherited (Savige et al., 2016). Diagnosis is critical since it can be used to predict whether other family members are impacted. Early detection and treatment of AS can delay complications and end-stage kidney failure. For instance, lenticonus often develops in middle-age years when kidney failure has already developed. Therefore, an early AS diagnosis may save the lives of affected individuals and their family members because it lowers the risk of early renal failure.

There are no clear statistics about the prevalence of AS across the world. Based on existing estimates, the prevalence varies from 1 in 5,000 to 1 in 53,000 people. Similarly, the situation in Baltic countries remains largely unknown (Savige et al., 2021). The prevalence of AS in Baltic countries can be estimated using the data related to renal failure. Alport syndrome is the second largest risk factor for inherited kidney failure (Savige et al., 2021). Patients with ocular manifestations, such as retinopathy, also tend to develop renal failure (Shaw et al., 2007). Baltic countries have a low prevalence of end-stage kidney failure. For instance, the incidence of renal failure in Estonia ranges from 22–85 persons per million (Thurlow et al., 2021). The people treated for end-stage kidney failure in Latvia range from 117–540 persons per million (Thurlow et al., 2021). This literature review focuses on the prevalence of AS in different countries and ocular manifestations.

Literature Review

Prevalence of the Disease in Different Countries

Alport syndrome has been studied widely, but there are no global figures about its incidence, prevalence, and related mortality. The aggregation of valid figures about the prevalence of AS is challenging because of the lack of broadly accepted diagnostic criteria (Hertz, 2009). In 2020, about 47 scientific and medical specialists from different continents held meetings in London to develop unified guidelines for genetic testing of AS in molecular laboratories (Savige et al., 2021). Despite holding two sessions, the scientists and medical specialists did not develop uniform diagnostic criteria. Amidst these challenges, there are sufficient data to predict AS's prevalence. The disease has been reported in different countries and affects people of different ethnic groups.

The prevalence of AS in the US is 1:5,000. This prevalence was developed following the discovery of 300 cases of AS in a population of 1,500,000 people across southern Idaho and Utah (Hertz, 2009). Furthermore, 77 cases of AS were reported in Rhode Island, where the population is approximately 1,000,000 people. Based on these new cases, the prevalence became 1:13,000 (Hertz, 2009). Over time, data on the prevalence of AS in the US have been updated to reflect new reports. The most recent data from the National Organization for Rare Disorders (NORD) estimate that AS affects about 1 in 5,000–10,000 persons in the US, meaning nearly 30,000–60,000 individuals in the US have the disease (Kashtan, 2020). This disease accounts for about 3% of all children with kidney disease and 0.2% of adults with end-stage kidney failure in the US (Kashtan, 2020).

The prevalence of the disease might be higher in certain European countries. An examination of 269 patients listed in Poland's Children National Registry for glomerular hematuria showed that 131 patients had X-linked AS (Żurowska et al., 2021). Also, the study identified that 195 adults related to these children were affected by AS (Żurowska et al., 2021). Poland is likely experiencing a high prevalence of AS across all age groups. In Finland, the prevalence is predicted at 1:53,000 people (Heidet & Lennon, 2020), and that of southern Sweden is 1:17,000 (Hertz, 2009). The disease affects about 1.3% of every 1,000 persons who undergo a kidney transplant in Sweden (Hertz, 2009). Across Europe, nearly 0.56% of all dialysis patients are diagnosed with AS (Hertz, 2009). These statistics suggest that AS is not widely prevalent in different countries around the world. However, the data does not account for

diagnostic difficulty, misdiagnosis, or undiagnosed disease. Uniform diagnostic criteria and classification of AS can produce actual data on global prevalence.

Ocular Manifestations

The most common ocular abnormalities in individuals with AS include fleck retinopathy, corneal dystrophy, and lenticonus. Vast research has been done on these three ocular abnormalities, revealing their prevalence and manifestations. Additional ocular manifestations that might develop among individuals with Alport syndrome include partial-thickness macular holes or lamellar and cataracts (Zhang & Ding, 2018).

Fleck Retinopathy

Peripheral or mid-peripheral retinopathy is common in men with X-linked AS and people with autosomal recessive disease (Shaw et al., 2007). Peripheral retinopathy develops in about 33% (3 in 9) individuals with X-linked AS and is more common compared to central retinopathy in women with X-linked AS carriers. Peripheral retinopathy can affect the periphery, mid-periphery, or both. Even though these might be sparse and localized, they can affect the entire periphery. Fleck retinopathy can have diverse symptoms or manifestations in affected persons (Image 1).

In their study, Shaw et al. (2007) stated that peripheral retinopathy consisted of diffuse confluent depigmented regions, and mid-peripheral retinopathy consisted of flecks and dots. Nevertheless, the patterns of appearance are likely to differ from one family member to another. According to Fawzi et al. (2009), mid-peripheral or peripheral flecks in the retina are less described in previous studies despite the possibility of being the only symptom among X-linked carriers.

Earlier studies had led to a flawed conclusion that retinopathy manifestations only appear in the inner retina because of mutations in genes responsible for type IV collagen, the core element of the internal limiting membrane (Fawzi et al., 2009). However, type IV collagen has also been discovered in Bruch’s membrane (Fawzi et al., 2009). Retinopathy mainly manifests as whitish-yellow flecks or dots and does not impact vision. Importantly, fleck retinopathy has no impact on visual acuity, and retinal function tests appear normal or show only minor abnormalities. Although retinopathy is often detected with ophthalmoscopy, it is documented

through photographs (Shaw et al., 2007). When eyes are not carefully examined, retinopathy might be missed or mischaracterized.

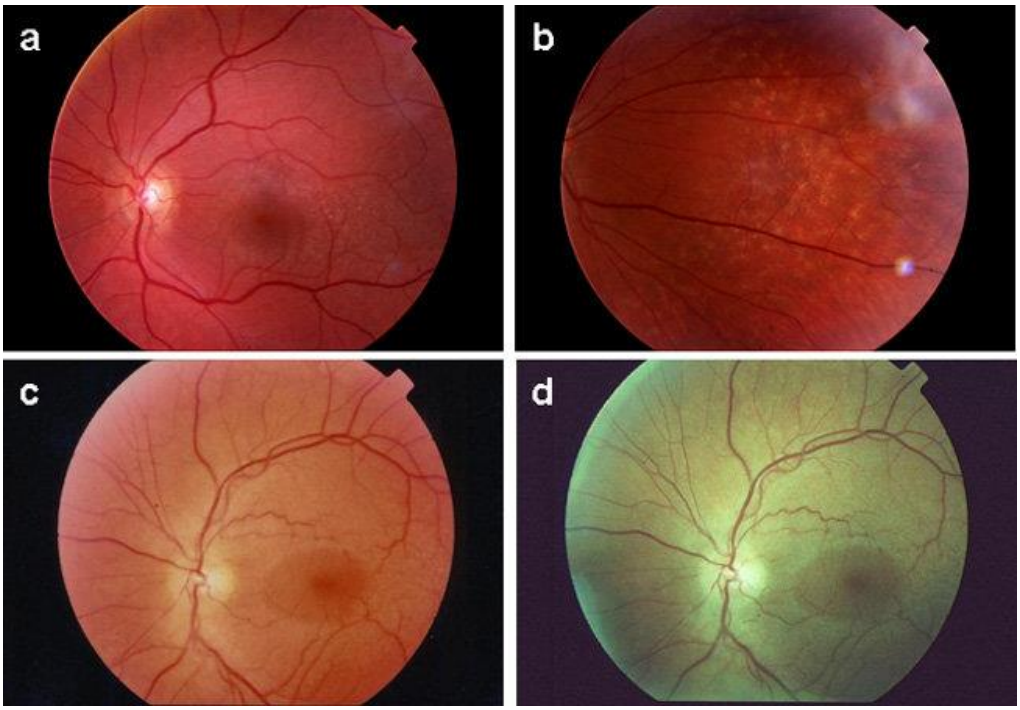

Image 1: (a) Typical perimacular dots and flecks, (b) peripheral retinopathy, (c) dull macular reflex (lozenge), and (d) red-free photograph demonstrating the dots and flecks in 1c more obviously. (Source: Savige et al., 2009)

Lenticonus

Lenticonus manifests as a cone-shaped protrusion of the posterior or anterior lens (Bamotra, Meenakshi, & Qayum, 2017). Anterior lenticonus is perhaps the most common manifestation in patients with AS (Image 2). Zhang and Ding (2018) stated that anterior lenticonus develops in 25–50% of males with X-linked AS and is linked to early onset of kidney failure. The occurrence of lenticonus is highly associated with AS diagnosis. Slit-lamp examinations by experienced ophthalmologists are vital to detect lenticonus. If lenticonus is not identified early, it might worsen, leading to visual symptoms (Zhang & Ding, 2018).

Even though anterior lenticonus is prevalent, posterior and anterior might occur simultaneously. Nevertheless, simultaneous posterior and anterior lenticonus is an uncommon manifestation (Bamotra et al., 2017). Bamotra et al. (2017) reported simultaneous posterior and

anterior lenticonus presentation in a woman aged 22 years. The ocular examination resulted in the detection of AS in the 22-year-old woman. Posterior lenticonus is mostly unilateral and linked to Lowe's syndrome, while anterior lenticonus is usually bilateral and might be linked to AS. These kinds of ocular abnormalities involve the retina and the lens, but rarely the cornea (Bamotra et al., 2017).

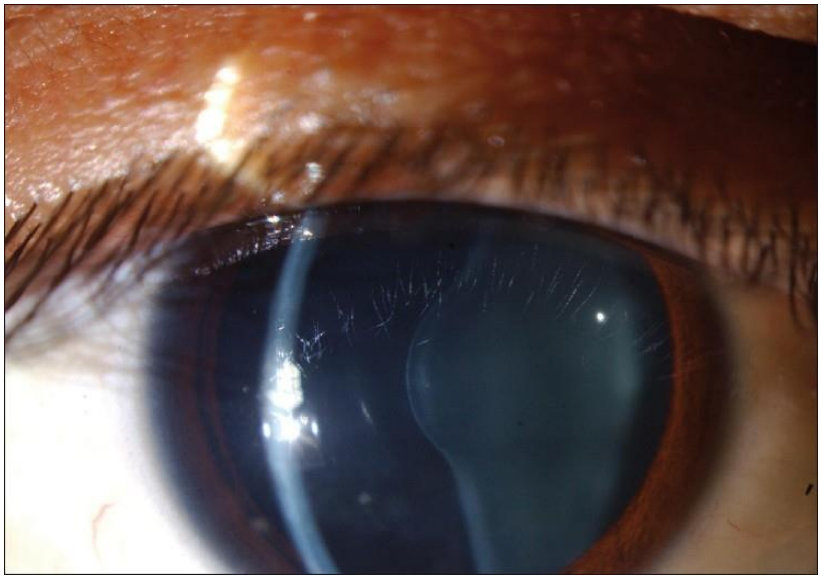

Image 2: Anterior lenticonus in the right eye in a patient with Alport syndrome. (Source: Al-Mahmood et al., 2010)

Corneal Dystrophy

Research has not placed a lot of attention on corneal dystrophy. In fact, corneal dystrophy has not been described widely compared to other ocular abnormalities in AS. According to Zhang and Ding (2018), corneal disease is rare in individuals with AS. Corneal erosions develop in less than 10% of all patients (Savige et al., 2015). On the contrary, another study indicated that nearly 20% of individuals with AS have experienced corneal erosion, which is characterized by attacks of blurred vision, lacrimation, acute ocular pain, and photophobia (Zhang & Ding, 2018). Corneal erosions are normally bilateral and frequently develop when Alport mutations are severe.

Erosions occur due to deformed Bowman's membrane within corneal subepithelial and posterior polymorphous corneal dystrophy because of deformed Descemet's membrane within the subendothelium (Image 3). These abnormal membranes are weak, do not have a collagen

IV α3α4α5 network, and attach weakly to the underlying stroma, endothelium, and epithelium (Savige et al., 2015).

Erosions might develop before a patient is diagnosed with AS, and this usually happens in the teenage years. They normally develop in persons with extrarenal features and early onset of kidney failure (Savige et al., 2015). In some cases, erosions can develop in members of the same family although they are not linked to precise mutations.

Nicklason et al. (2020) designed a study involving males and females from eight families with X-linked AS to investigate the manifestation of corneal abnormalities. These family members were subjected to ophthalmological examinations, including corneal endothelial specular microscopy and slit-lamp examination. Based on the results, two males had experienced recurrent corneal erosions although they did not have a history of posterior polymorphous corneal dystrophy (Nicklason et al., 2020). Furthermore, one woman and her son had experienced corneal erosions. The findings concluded that corneal erosion occurs at the same rate for females and males with X-linked AS.

Despite the fact that corneal abnormalities are common in affected women, their correlation with AS might be overlooked (Savige et al., 2016). People tend to experience dry, scratchy eyes that may last several days and even recur.

The characteristics of attacks are tears, acute ocular pain, and photophobia. Attack triggers correlate with a dry ocular surface and include contact lens use, waking from sleep, prolonged screen time, and exposure to windy outdoor conditions (Nicklason et al., 2020). Other important precipitants are irritation from wind and computer screens (Savige et al., 2015). Individuals affected by AS usually start experiencing attacks during their teenage years, and an episode can last hours or even days (Nicklason et al., 2020). An examination can reveal red eyes. In some instances, corneal dystrophy progression can lead to vision loss. Supportive measures can help to reduce most attack episodes without needing serious treatment (Savige et al., 2015). Treatments for corneal erosion include lubrication and avoidance of trigger factors. In addition, an occlusive eye patch and occasional anti-inflammatory agents might be used as treatment (Nicklason et al., 2020). These products often produce good results for affected individuals when used appropriately.

Moreover, Zhang and Ding (2018) stated that patients with AS might experience posterior polymorphous corneal dystrophy and corneal clouding. Savige et al. (2016) attested

that posterior polymorphous corneal dystrophy is different from some corneal lesions that manifest in certain patients and has not been discovered in females with X-linked AS. This manifestation is more severe than typical erosions. A patient might be asymptomatic although some individuals complain of persistent episodes of watering, grittiness, and photophobia. Diagnosis is completed using specular microscopy or slit-lamp biomicroscopy (Savige et al., 2015).

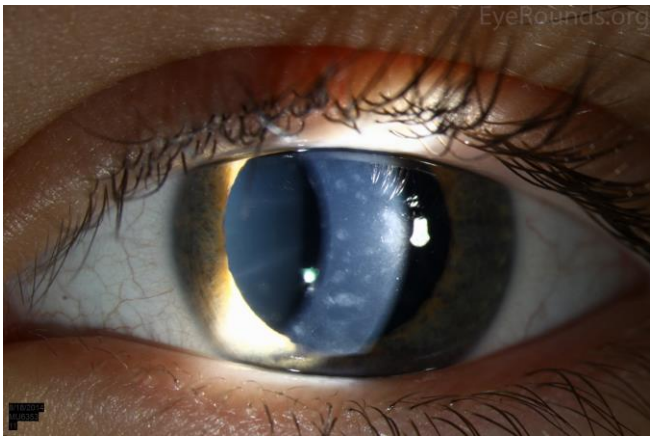

Image 3: Slit-lamp photos of a patient showing diffuse, geographic-shaped, discrete, gray lesions at the level of Descemet's membrane as seen by direct illumination. (Source: Dahrouj et al., 2015)

Macular Holes or Lamellar

Lamellar is less common in males with X-linked AS and females and males with recessive disease. Studies indicate that full-thickness holes are uncommon in all genders (Savige et al., 2015). Shah & Weinberg (2010) argued that cases of macular holes in previous studies were not appropriately correlated to AS. Macular holes develop early in life and are larger compared with instantaneous holes in individuals who have not been genetically diagnosed with AS. These holes might be unilateral, bilateral, or asymmetric (Savige et al., 2015). The occurrence of macular holes is procedural. It starts with minor defects on the inner limiting membrane and then microcystic fusion.

Studies have presented different pathways through which macular holes develop. Shah and Weinberg (2010) described a case of a patient who presented with a "giant macular hole" and AS diagnosis. The examination showed that many small macular holes emerged later after the giant hole had developed. The authors attested that the clinical progression and mechanism of the occurrence of giant macular holes is completely different from the mechanism and progression of idiopathic macular holes (Shah & Weinberg, 2010).

Full-thickness macular holes emerge from collagen IV abnormalities within Bruch's membrane, as well as the internal limiting membrane along with anterior lens capsule rupture, retinal detachment, and anomalous vitreoretinal traction (Savige et al., 2015; Shah & Weinberg, 2010).

Individuals with macular holes experience challenges with metamorphopsia and central vision. Diagnosis of macular holes happens when a patient's visual impairment fails to improve even after undergoing surgery for lenticonus (Savige et al., 2015). Indeed, lamellar holes do not often improve through surgical treatment. Retinal photographs might fail to show lamellar holes, and ocular coherence tomography (OCT) might be needed for diagnosis (Savige et al., 2015). Serial clinical examination, fundus photographs, and visual acuity can also be used for diagnosis (Images 4 and 5) (Shah & Weinberg, 2010). An inaccurate diagnosis might confuse lamellar holes with a retinal lozenge.

Macular holes in patients with AS usually lead to permanent visual impairment since they respond poorly to surgical treatments (Zhang & Ding, 2018). Additionally, macular holes increase the risk of vision loss in patients diagnosed with AS.

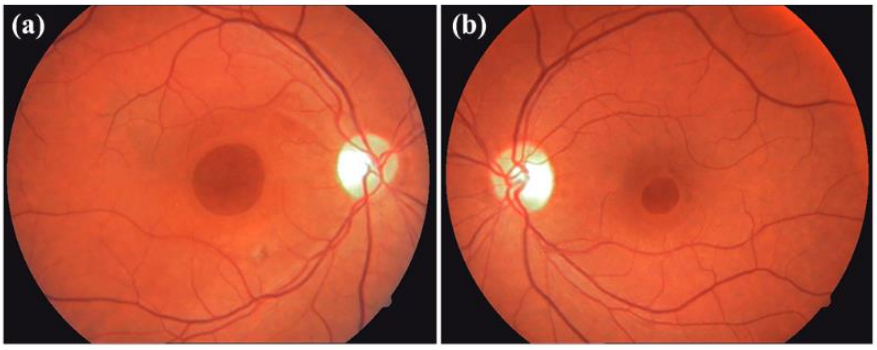

Image 4: Fundus photography of the right (a) and left eye (b) showing bilateral full-thickness giant macular holes. (Source: Raimundo et al., 2018)

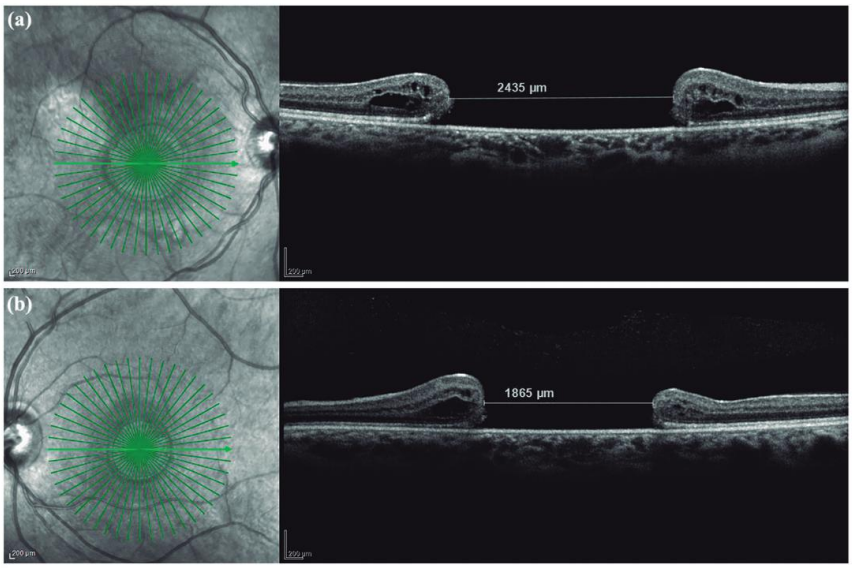

Image 5: Spectral domain optical coherence tomography showing bilateral full-thickness macular holes (Source: Raimundo et al., 2018).

Cataracts

Cataracts are often associated with lenticonus because they might co-occur in patients with AS. Lenticonus emerges from the conical bulging of the lens, specifically through the weakest and thinnest region of the capsule. Since the capsule lacks the α3α4α5 network, it incurs splits that might rupture (Savige et al., 2015). The healing of these minor instantaneous ruptures results in the development of cataracts. The formation of cataracts blocks the progression of lenticonus. Symptomatic cataracts are usually treated through lens removal and implantation of an intraocular lens (Savige et al., 2015). However, cataracts are not often symptomatic, and a patient might experience visual impairment without knowing the cause if an appropriate diagnosis is not made.

One study described a case of progressive, painless loss of vision in a male patient diagnosed with AS (Santiago-Cabán et al., 2008). Cataracts in this patient were only diagnosed after comprehensive ocular and history examination. Additionally, the study showed that cataracts might develop in patients with both diffuse leiomyomatosis (DL) and AS. Careful examination is needed in this case to rule out other potential causes of cataracts in patients. For instance, prolonged use of steroids can eventually lead to the formation of cataracts (Santiago-

Cabán et al., 2008). This finding means that patients with AS may develop cataracts because of steroid use rather than the disease.

Literature has delved deep into identifying the reasons certain ocular abnormalities in individuals with AS are usually overlooked. It is imperative to document current guidelines for diagnosing AS (Savige et al., 2015; Savige et al., 2021). For example, fleck retinopathy has no impact on a patient's vision and may be subtle and misdiagnosed for retinal sheen (Zhang & Ding, 2018). Ophthalmologists can detect a small retinal change during routine practice and fail to report this change unless a patient's vision is impacted. Ophthalmologists who perform ophthalmic examinations using slit-lamp examination and retinal OCT and photographic examination should be consulted when examining patients with potential AS. In molecular diagnostics, the assessments need to focus on the variants in the *COL4A4*, *COL4A5, and COL4A3* genes (Savige et al., 2021). These genes have certain traits that should be considered beyond the usual AS phenotype.

Slit-lamp examination is best suited to confirm corneal abnormalities (Savige et al., 2015). During an examination, lenticonus is diagnosed through retinoscope or ophthalmoscopy. Central retinopathy can be evident on red-free images and retinal photographs (Savige et al., 2015). Furthermore, peripheral retinopathy can be evident through classical retinal views although peripheral examinations might be needed. Temporal retinal thinning can be diagnosed using OCT (Savige et al., 2015). These guidelines have been highlighted in the literature as a way to help ophthalmologists avoid missing ocular manifestations.

Image 6: Posterior subcapsular cataract. (Source: Cabán et al., 2008)

Establishing the Diagnosis

Alport syndrome is characterized by abnormalities in the glomerular basement membrane (GBM, Figure 1 and Figure 2) along with the basement membranes of several other tissues, including the eyes and ears. The GBM is a sheet-like extracellular matrix (ECM) that plays a crucial role in restricting the movement of blood cells and blood-related proteins into the urinary space. The ECM consists of four major macromolecules, including type IV collagen, laminin, heparan sulfate proteoglycan (agrin), and nidogen. Type IV collagen constitutes about 50% of the total GBM mass. Type IV collagen chains have been found to be of six genetically distinct types, including α1 to α6 that join together to form three unique heterodimers, including α1α1α2, α3α4α5, and α5α5α6. In the case of AS, mutations appear in the genes, including *COL4A3*, *COL4A4*, or *COL4A5*, that lead to defects in type IV collagen α3, α4, or α5 chains, respectively. Nevertheless, it has been suggested that the transmission of AS takes place in an X-linked manner in a large number of cases. Considering this suggestion, an affected father rarely transmits the disease to his son. Furthermore, it has been found that the *COL4A5* gene is associated with X-linked mutations although mutations in *COL4A3* and *COL4A4* could also cause AS (Warady et al., 2020). The X-linked mutation is also referred to as X-linked Alport syndrome (XLAS), and the types of AS associated with mutations in *COL4A3*/*COL4A4* are also referred to as autosomal dominant AS (ADAS) and autosomal recessive AS (ARAS) (Nozu et al., 2019). The diagnosis of AS could be established considering these mutations.

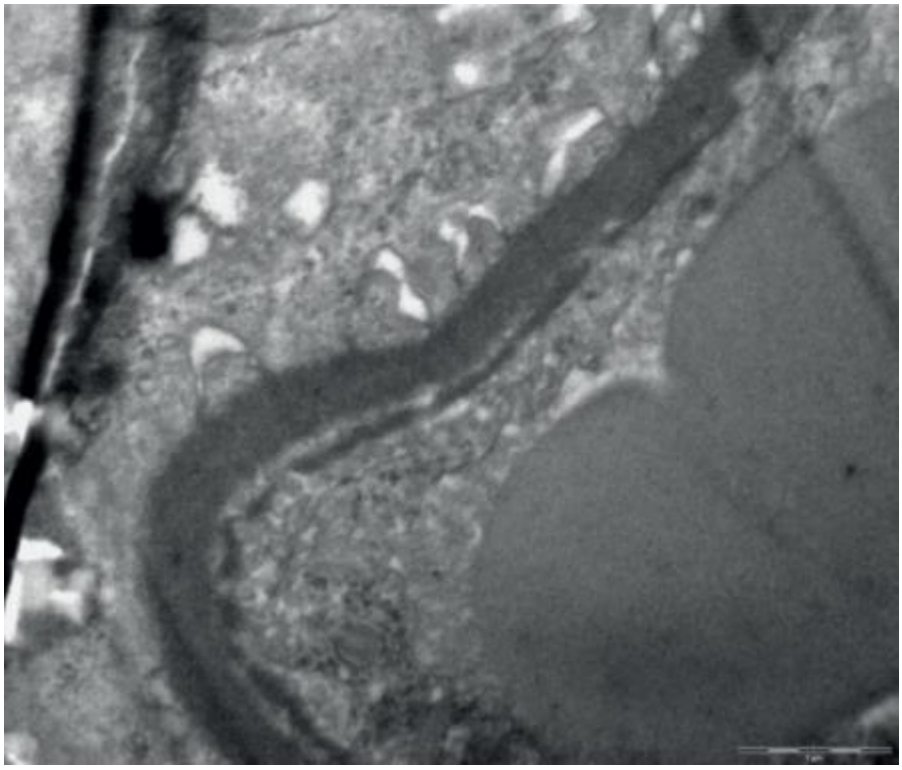

Image 7: Glomerular basement membrane showing its lamination with transmission electron microscopy (TEM). (Source: Tecellioglu et al., 2021)

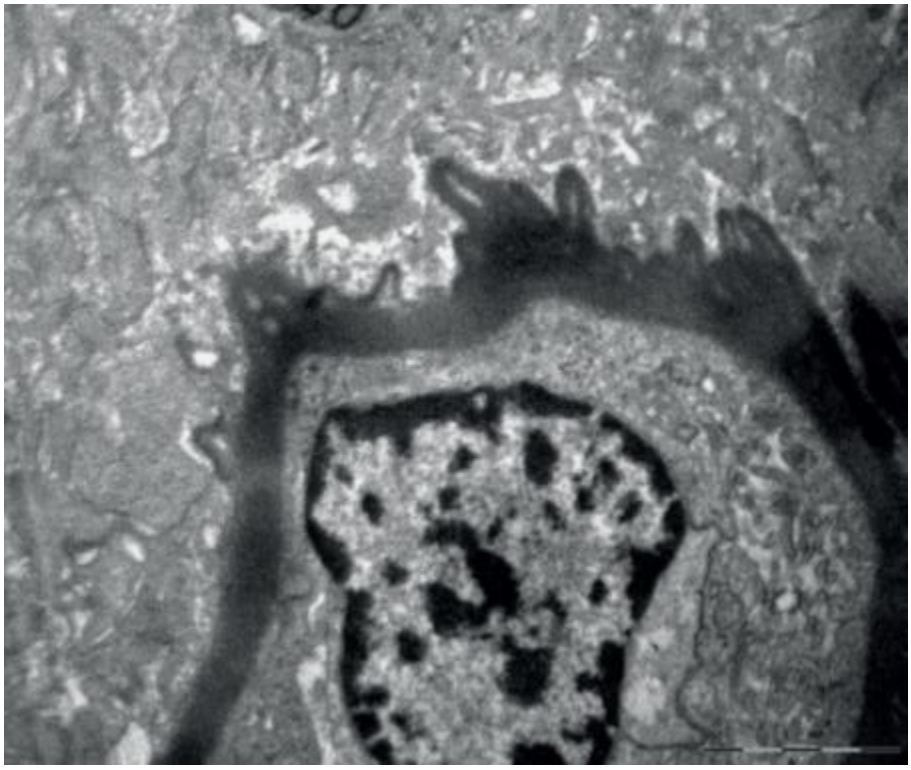

Figure 8: Glomerular basement membrane showing its duplication with transmission electron microscopy (TEM). (Source: Tecellioglu et al., 2021)

Differential Diagnosis

The differential diagnosis in different types of AS and other disorders/diseases based on type IV collagen, fibronectin, and laminin staining (Akihisa et al., 2019; Nozu et al., 2019; Tecellioglu et al., 2021) is presented in the Table 1.

Table 1: Differential Diagnosis of Different Types of AS and Other Disorders/Diseases

Disorder/Disease		**Clinical/Pathological/Genetic features**	**Diagnostic Tool(s)**
XLAS	Male XLAS with truncating mutation	● α5 in Bowman's capsule and GBM shows weaker/negative staining.	● Type IV collagen staining
	Male XLAS with non-truncating mutation	● α5 in Bowman's capsule and GBM shows weaker/negative staining or mosaic expression.	● Type IV collagen staining
	Female XLAS	● α5 in Bowman's capsule and GBM shows weaker/negative staining or mosaic expression.	● Type IV collagen staining
ARAS	ARAS with homozygous truncating mutation	● α5 in Bowman's capsule shows positive staining. ● α5 in GBM shows negative/weaker staining.	● Type IV collagen staining
	ARAS with compound heterozygous truncating mutation and non-truncating mutation	● α5 in Bowman's capsule shows positive staining. ● α5 in GBM shows negative/weaker staining or mosaic expression.	● Type IV collagen staining
	ARAS with compound heterozygous non-truncating mutation	● α5 in Bowman's capsule shows positive staining. ● α5 in GBM shows negative/weaker staining or mosaic expression.	● Type IV collagen staining
ADAS	ADAS	● α5 in Bowman's capsule shows positive staining.	● Type IV collagen staining ● Laminin staining ● Fibronectin staining

		• α5 in GBM shows positive staining or mosaic expression. • α2 in GBM shows strongly positive staining.	
	Early Stage of ADAS / Thin basal membrane nephropathy (TBMN)	• α5 in Bowman's capsule shows positive staining. • α5 in GBM shows positive staining or mosaic expression. • α2 in GBM shows weakly positive staining.	• Type IV collagen staining • Laminin staining • Fibronectin staining
Thin basal membrane nephropathy (TBMN)		• Several aspects of TBMN are clinically and histopathologically similar to early onset AS. • TBMN has diffused thinning of the GBM that can be found through o an examination utilizing transmission electron microscopy (TEM) o *COL4A3*/*COL4A4* mutations.	• Diagnosis could be made with the help of collagen IV immunostaining and genetic studies.
Immunoglobulin A (IgA) nephropathy or nephritis		• IgA nephropathy may cause persistent hematuria that has almost identical features to that of TBMN. • Diffuse direct immunofluorescence (DIF) staining in the mesangium is one of the diagnostic markers of IgA nephritis.	• The TEM findings could be used, as these findings for IgA nephritis are different from that of AS in that they are not characterized by a change in the GBM. • Mesangial electron-dense deposits are commonly found utilizing TEM in the diagnosis of IgA nephritis.

		• Subendothelial electron-dense deposits could also be found in the active lesions.

Table 2: Usefulness of Ocular Features in Diagnosis, Predicting Early Onset Renal Failure, and Identifying Mode of Inheritance (Source: Savige et al., 2015)

Ocular feature	Diagnostic	Severe Mutations	Early onset renal failure	Distinguish Autosomal Recessive Alport Syndrome from X linked Alport Syndrome in Women
Posterior Polymorphous corneal dystrophy	Yes	Yes	Yes	?
Lenticonus	Yes	Yes	Yes	Yes
Central retinopathy	Yes	Yes	Yes	Yes
Retinal thinning	Yes	No	No	No
Giant macular hole	Yes	Yes	Yes	Yes
Peripheral retinopathy	Yes	No	No	No

Conclusion

Alport syndrome is not widely prevalent in Baltic countries, and even its global prevalence is low. Despite its low prevalence, the disease is associated with several ocular abnormalities that might or might not affect a patient's vision. Certain ocular manifestations, such as peripheral retinopathy, lenticonus, and corneal erosions, are common among individuals affected by AS. The presence of these ocular manifestations can be used as a confirmation for a positive diagnosis. On the other hand, less common ocular manifestations are cataracts and macular holes. The identification of these abnormalities can be used to determine the mode of inheritance and prevent early-onset kidney failure through treatment. Because some of these ocular manifestations may be subtle and asymptomatic, ophthalmologists should perform comprehensive examinations when assessing AS patients.

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