ALPORTS SYNDROME

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ACADEMIC CORDINATOR - ECNG

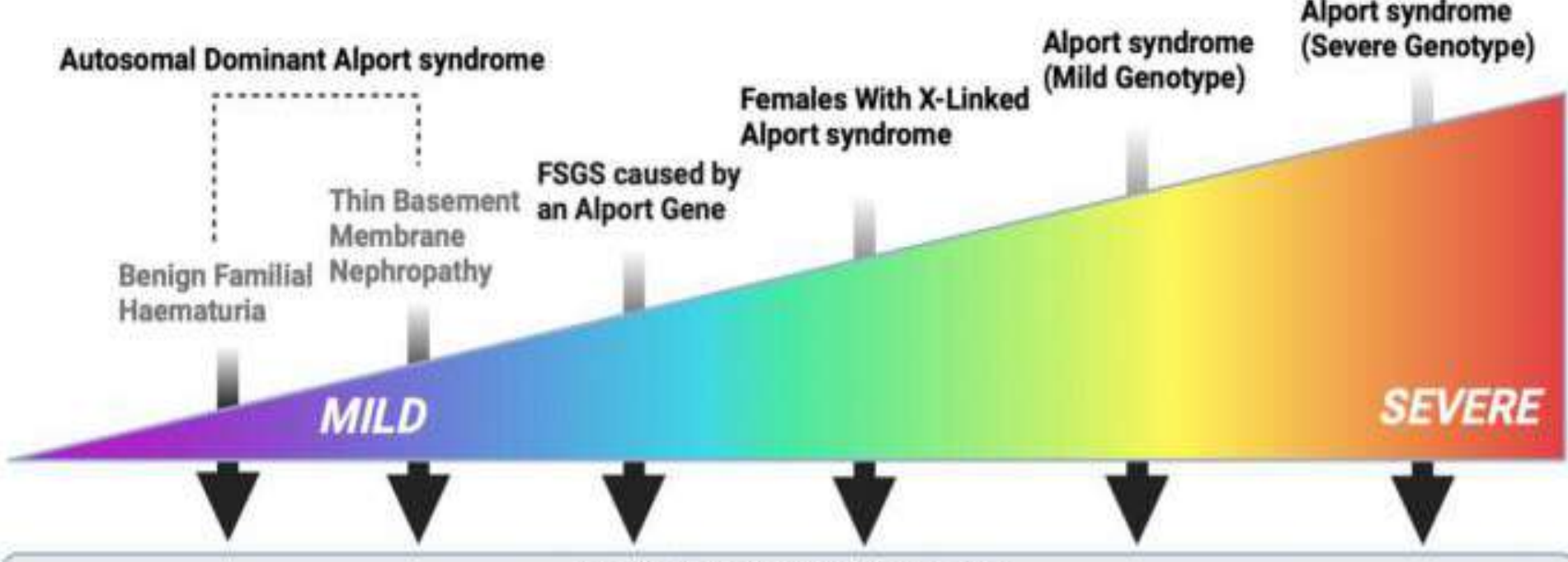
INTRODUCTION

- **Alport syndrome** : hereditary nephritis, is a genetic disorder arising from the mutations in the genes encoding alpha-3, alpha-4, and alpha-5 of type 4 collagen (COL4A3, COL4A4, COL4A5) or collagen 4 α345 network.

TYPES :-

- **XLAS** - caused by mutations in the *COL4A5* gene; 85% of cases of Alport syndrome.
- **ARAS** - due to mutations in *COL4A3* or *COL4A4* gene; leading to approximately 10-15% of cases.
- **ADAS** - caused by mutations in the *COL4A3* or *COL4A4* gene [rare].

- Alport syndrome affects about 1 in 50,000 newborns. Males are more symptomatic than females.



PHENOTYPE AND GENOTYPE

Genetics*	Heterozygous COL4A3/4 variants	Heterozygous COL4A3/4 or FN1 variants	Heterozygous COL4A3/4 variants	Heterozygous COL4A5 variants	Heterozygous/homozygous COL4A3/4 or hemizygous COL4A5 variants	Homozygous COL4A3/4 or hemizygous COL4A5 variants
Haematuria?	Yes	Yes	Yes	Ranges from asymptomatic to isolated haematuria, to both haematuria with proteinuria, to proteinuria with CKD, to kidney failure (young or older onset)	Yes	Yes
Proteinuria?	No	Often and minimal	Yes		Yes	Yes
Kidney Function	Normal	Normal (may progress to CKD)	CKD, kidney failure (young or older onset)		Progressive CKD/late kidney failure	Progressive CKD, early kidney failure
Kidney Cysts?	No	Possible in proteinuric patients	Possible (few small)	Possible (few small)	Possible (few small)	Possible (few small)
Extra-renal manifestations?	No	Hypertension (some)	Mild or none	Can get eye defects and/or deafness or be asymptomatic	Variable eye and hearing defects	Eye defects and deafness (young onset). Hypertension.
Kidney Biopsy	Attenuated or normal GBM	Uniformly thinned GBM	FSGS	Mix of normal, thin and thick (lamellated) GBM	Early thin GBM. Later thick and lamellated	Early thin GBM. Later thick and lamellated

CLINICAL MANIFESTATION

Renal:

1. Gross or microscopic hematuria is the commonest and earliest sign of Alport syndrome , commonly seen in males ; commonly precipitated by upper respiratory infection, in the first two decades of life.

2. Proteinuria is generally absent in childhood but ultimately develops in males with XLAS and male and female patients with ARAS.

3.Hypertension develops by the second decade of life.

4.Edema and nephrotic syndrome are observed in 30 to 40% of young patients.

Hearing:

1`.Hearing loss is never congenital. Bilateral, high-frequency sensorineural deafness. Audiometry helps in diagnosis.

2. Hearing loss is always associated with renal involvement.

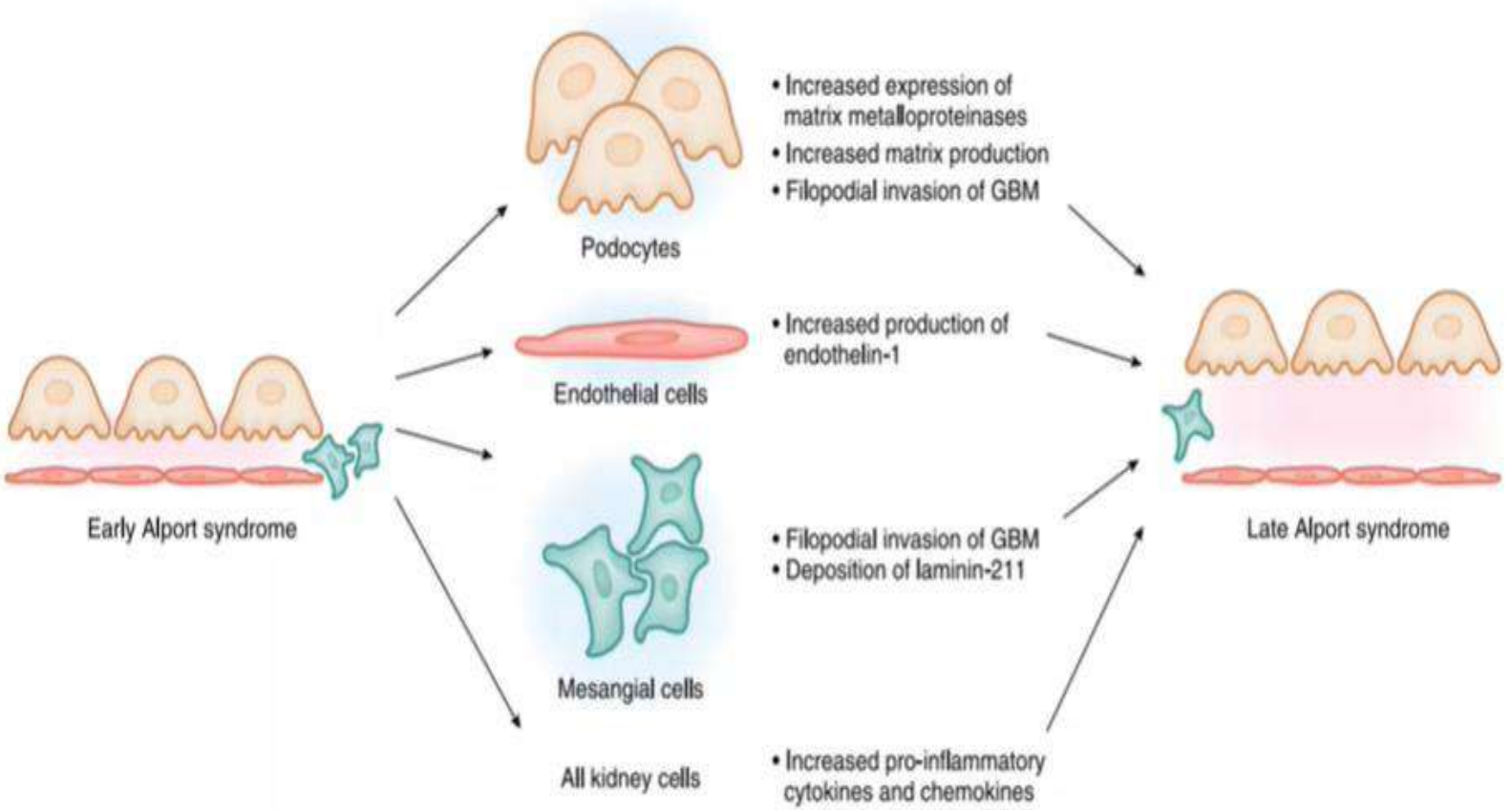
3. Approximately 50% of male patients with XLAS have sensorineural hearing impairment by the age of 25 years, and around 90% are deaf by 40 years.

Ocular:

`1. Anterior lenticonus, occurring in around 25% of patients with XLAS, is a characteristic feature of Alport syndrome diagnosed by slit lamp examination.

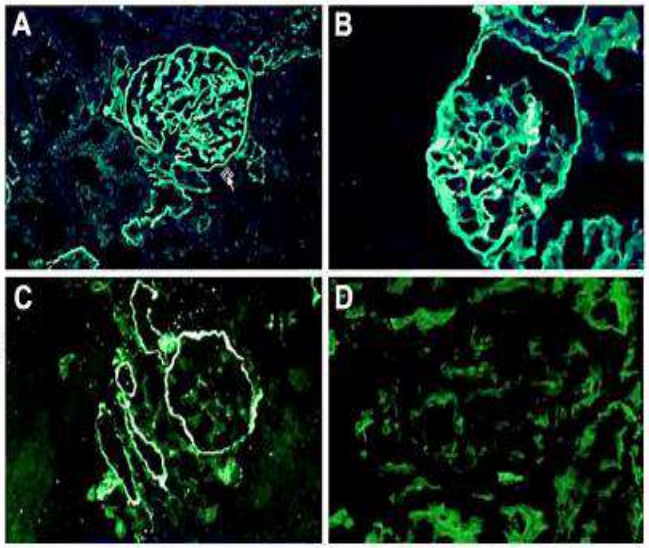
2.Dot-and-fleck retinopathy is the commonest ocular manifestation of Alport syndrome, occurring in around 85%

Alport disease mechanisms



Quinlan C and Rheault MN *CJASN* 2021 Jul;16(7):1101-1109

IF of collagen IV α5



Normal or Autosomal heterozyote

X-linked AS female patient

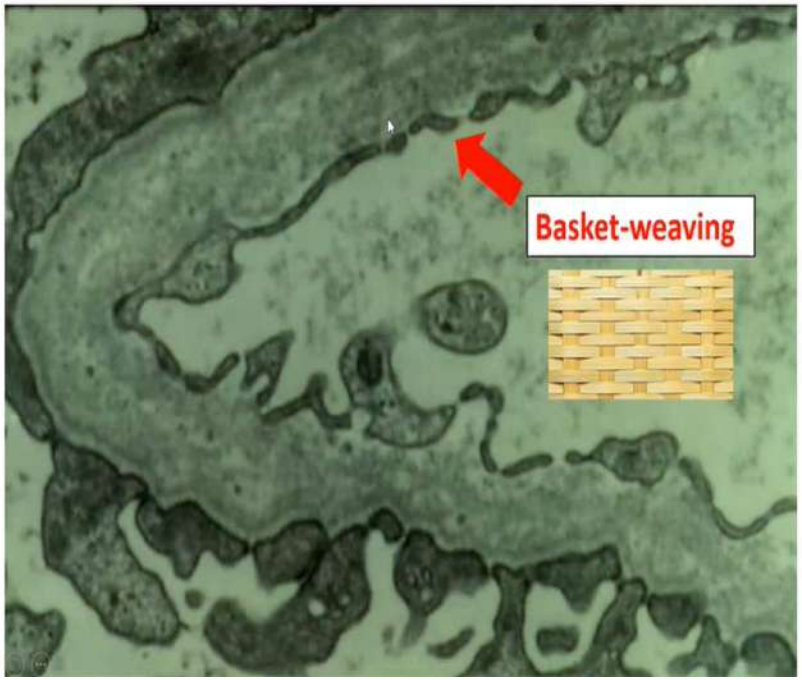
Autosomal recessive AS

X-linked AS male patient

Haas M, *Arch Pathol Lab Med* 2009, 133(2;224-232

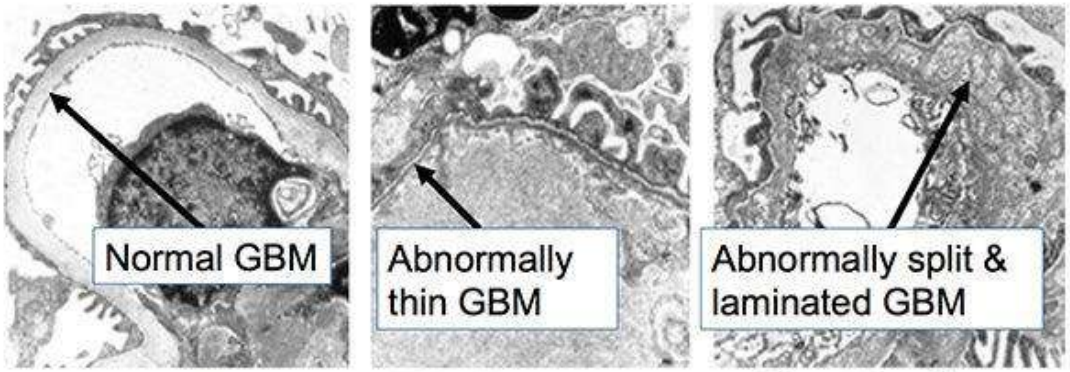
Liapis H, Gaut J. Alport Syndrome. In Colvin R.. & &. Kidney Diseases. 2019

EM in late Alport syndrome



Light microscopy : normal initially , later include focal and segmental glomerulosclerosis, tubular atrophy, interstitial fibrosis, and the presence of lymphocytes and plasma cells.

Immunofluorescence studies : negative . Patterns as in above figure.



Normal

Thin Basement Membrane Lesion

Alport Syndrome

BIOPSY

- Confirm the diagnosis when EM shows characteristic GBM changes (thinning → lamellation [BASKET –WEAVING]).
- Identify carriers (especially female X-linked carriers with mosaic pattern).
- Supports diagnosis when genetic testing is not immediately available or inconclusive.
- Prognostic value: Loss of α5 staining often correlates with more severe disease and faster progression.
- Skin biopsy IF (for α5 chain in epidermal basement membrane) can be a less invasive option, especially in males.

Therapeutic Recommendations for Alport Syndrome

Diagnostic Recommendations

Consider AS Diagnosis if
- Isolated persistent glomerular haematuria
- Normal complements
- Negative serology (ANA, ANCA, Anti-GBM etc.)

Genetic testing
- If family history of AS

Kidney Biopsy
- If no family history of AS
- Or genetic testing is inconclusive

When to start ACEi/ARB Treatment?

X-linked AS (XLAS) male
- At diagnosis (age > 12 to 24 m)

XLAS female
- Classify as Alport syndrome & NOT as carriers
- Microalbuminuria > 30 mg/g

Autosomal recessive AS (ARAS)
- At diagnosis (age > 12 to 24 m)

Autosomal dominant AS (ADAS)
- Microalbuminuria > 30 mg/g

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Conclusions: Earlier Diagnosis, regular monitoring and early treatment can delay progression in Alport Syndrome

Kashtan CE, Gross O. Clinica
diagnosis & management o
adolescents & young adults
2021.

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Ongoing clinical trials including patients with Alport syndrome

Trial name	Trial number	Drug	Mechanism of action	Ref
Atrasentan in patients with proteinuric Glomerular Disease (AFFINITY)	NCT04573920	**Atrasentan**	Haemodynamic: endothelin A receptor antagonist	216
Study of sparesentan treatment in pediatrics with proteinuric glomerular diseases (EPPIK)	NCT05003986	**Sparsentan**	Haemodynamic: dual endothelin A receptor antagonist and angiotensin receptor blocker	217
Study to evaluate R3R01 in patients with AS and patients with FSGS	NCT05267262	**R3R01**	Metabolic: promotes cholesterol efflux from cells by increasing ABCA1 levels	218
A Study of ELX-02 in patients with AS	NCT05448755	**ELX-02**	mRNA: premature termination codon readthrough	219
Phase 3 clinical trial with dapagliflozin in CKD in adolescents and young adult patients (DOUBLE_PROTECT)	NCT05944016	**Dapagliflozin**	Haemodynamic: sodium-glucose co-transporter 2 inhibitor	189
Effects of dapagliflozin on progression of AS	NCT06226896	**Dapagliflozin**	Hemodynamic: sodium-glucose co-transporter 2 inhibitor	220
A study to evaluate setanaxib in patients with AS	NCT06274489	**Setanaxib**	Anti-fibrotic: NOX1/4 inhibitor	221
Vonafexor Alport Syndrome efficacy & safety TRIAl-1 (ALPESTRIA-1)	NCT06425055	**Vonafexor**	Fibrolytic and anti-inflammatory: farnesoid X receptor agonist	222

Nat. Rev. Nephrol in press

TRANSPALNT - DONOR SELECTION

- Patients with Alport syndrome have no contraindication for renal transplantation.
- There is no recurrence of the primary disease, as the transplanted kidney would have normal GBM.

DONOR :

- Unrelated Donor -> No Alport Genes -> Preferred (Gold Standard).
- Unaffected Male Relative -> Tested Negative -> Excellent Choice.
- Heterozygous Mother/Sister -> 1 Mutation Carrier -> Last Resort.
- Only Symptomatic Relative -> Hematuria /Proteinuria -> Strictly Disqualified.

Post renal transplantation :

- 3% risk of de novo anti-GBM antibody disease or Alport post transplant nephritis in XLAS with COL4A3 .[ADAS less risk].
- The affected patients typically possess circulating anti-GBM antibodies leading to crescentic glomerulonephritis and graft loss.

- The treatment of post-transplant anti-GBM disease involves plasmapheresis along with cyclophosphamide and methylprednisolone with minimal benefit.

- Retransplantation in these patients has a high risk of recurrence.