Alport Syndrome
4.14.15
Sushma Bhusal
Nephrology Fellow
Case presentation

26 yo white Ukrainian male with no known PMH, sent to ED by PCP for
- Cr 12 with severe electrolytes abnormalities
- Pancytopenia
- HTN
HPI

- c/o fatigue, malaise and leg/hand cramping, post-prandial vomiting and pallor for months
- SOB with exertion over the past weeks, associated with LE swelling
- Easy bruising, several episodes of epistaxis
Constitutional: *fatigue, weakness, weight loss, night sweats*

HEENT: No sore throat, *hearing difficulties b/l*

Respiratory: *shortness of breath*, no cough

Cardiac: Negative for chest pain, orthopnea and palpitations

GI: Negative for abdominal pain, change in bowel habits, *nausea, vomiting +*

GU: Negative for dysuria, frequency, hematuria, frothy urine

Skin: *bruising +*

MSK: *Leg swelling*, negative for arthralgia, back pain

Neurological: *headaches*
History Contd..

PMH: *multiple common infection as a child*, mild hearing loss due to ear infection in childhood, multiple URI’s in last year

PSH: none

Home medication: none

Allergies: NKDA

PFH: no family h/o renal disease, Magnesium deficiency in mother

Social: Smoker : cigarette and marijuana
Physical Exam

**Vitals:** afebrile, BP: 150/90  HR: 94  sat 100% on RA

**General:** NAD, pleasant, comfortable

**HEENT:** pale conjunctiva, crusted blood in nostrils, no JVD, No lymphadenopathy

**CVS:** S1S2 normal, no audible murmur

**Pulmonary:** CTABL, no wheezing, no crackles

**Abdomen:** soft, non-tender, non-distended, no HSM

**Ext:** +1 edema to the knee, pitting, scattered ecchymotic patches
BMP

142 | 111 | 218

4.7 | <10 | 25.8

Ca: 6.5

Urine

UA: 3+ blood, 3+ prot, LE/nitrate neg, 30-50 RBCs.
Umicro: large blood, large protein, gluc+

Uprot/Ucr: 7.8 g/g

PO4: 12.6, Mg: 1.6

CBC

4.2

4.2 | 61

11.8

Labs
Differentials

Parvovirus B19 Collapsing GN
Alport syndrome/MYH9 Related disorders
Lupus Nephritis
IgA/Crescentic IgA
FSGS
Anti GBM, ANCA
TTP/HUS
Additional Labs

- PTH: 1500
- LFTs: WNL Alb: 3.4 Chol: 173
- Uric acid: 9.4
- Lactic acid: 0.6
- Retic: 2.88
- ESR: 80
- CRP: 3.57
- Hep B, Hep c serology neg
- C3 C4 WNL, ASO neg, P-ANCA, C-ANCA neg
- UPEP/SPEP neg,
- Parvovirus: + Ig G
Imaging

US Abdomen: RK: 10.5 cm, LK: 9.5 cm, no hydronephrosis, 20 mm RU pole cyst. Spleen: 10.3 cm, LUQ 15/12/15 cm avascular complex collection

CXR: Normal
MAB 5

POSITIVE CONTROL

PATIENT
Hospital Course

- Dialyzed
- Received blood and platelet transfusions
- Hematology involved for pancytopenia
ALPORT SYNDROME
Dr. Leonard Guthrie in 1902, described a family with members who had hematuria that “may vary in extent, liable to paroxysmal exacerbations with influenza-like symptoms, and not marked by edema.”

He called the syndrome **congenital hereditary family hematuria**, none of the affected individuals exhibited evidence of chronic renal damage at the time.

LB Guthrie Lancet, 1902
C Alport: BMJ 1927
Arthur Frederick Hurst in 1923 described the development of uremia in several members of this family.

In 1927, Dr. Cecil Alport followed 3 later generations of the same family and he recognized that deafness was a syndromic component and that the disorder tended to be more severe in males than females, that affected males died of uremia, while females lived to old age.

Subsequently, many more families were described and the disease was named Alport Syndrome (AS) in 1961.
Epidemiology

- Overall incidence in the general population is unknown.
- Accounts for 3% of children and 0.2 % of adults with ESRD, 0.6 % in Europe.
- Incidence varies from 1 to 11% depending upon the indications for biopsy.
- The gene frequency of AS in the US estimated at 1:5000 to 10,000, approx. 30,000 to 60,000 affected individuals in the US.
Each collagen IV chain has three domains:

- Short 7S domain at the N-terminal
- A long, collagenous domain occupying the midsection of the molecule
- Noncollagenous domain (NC1) positioned at the C terminal

JASN Oct 2004

NEJM 2003
• The α3, α4, α5 protomer forms a highly cross-linked network as a result of the high number of disulfide bridges between protomers.

• Once secreted into the extracellular matrix, collagen IV protomers form networks through dimerization at their C-terminal NC1 domains and through tetramer formation at their N-terminal 7S domains.

JASN Oct 2004
Type IV Collagen genes

Figure 46.1 Genomic organization of type IV collagen genes.
Pathogenesis
Pathogenesis
Mechanisms of disease transmission and progression in AS

Pediatr Nephrol (2013)
### Inheritance Patterns

**Molecular Genetics of Alport’s Syndrome**

<table>
<thead>
<tr>
<th>Inheritance</th>
<th>Affected Locus</th>
<th>Gene Products</th>
<th>% Patients Affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>XLAS</td>
<td>COL4A5</td>
<td>α5(IV)</td>
<td>80-85%</td>
</tr>
<tr>
<td>ARAS</td>
<td>COL4A3 COL4A4</td>
<td>α3(IV) α4(IV)</td>
<td>10-15%</td>
</tr>
<tr>
<td>ADAS</td>
<td>COL4A3 or COL4A4</td>
<td>α3(IV) α4(IV)</td>
<td>Rare</td>
</tr>
</tbody>
</table>

Adapted from: Johnson Comprehensive Clinical Nephrology
X Linked Mutations

In the COL4A5 genes from the families with XLAS, more than 300 gene mutations have been reported.

Most COL4A5 mutations are small and include missense mutations, splice-site mutations, and small deletions where renal failure and deafness occur after 30 years of age (adult form).

Approximately 20% of the mutations are major rearrangements at the COL4A5 locus (i.e., large deletions, reading frame shifts, etc) in which patients are symptomatic before the age of 30 (juvenile form).

A rare large deletion spanning COL4A5 and COL4A6 genes is associated with a combination of XLAS and diffuse leiomyomatosis.

Johnson Comp Clinical Nephrology
Nature Reviews 2013
Autosomal Mutations

- To date, only 6 mutations in the \textit{COL4A3} gene and 12 mutations in the \textit{COL4A4} gene have been identified in patients with ARAS.

- ARAS patients are either homozygous or compound heterozygous for their mutations, and their parents are usually asymptomatic carriers.

- ADAS is more rare than XLAS or ARAS and is a result of a dominant negative mutation of the \textit{COL4A3} or \textit{COL4A4} genes whose gene product acts antagonistically to the wild-type allele.

Johnson Comp Clinical Nephrology
Nature Reviews 2013
Clinical Features

- Typical symptoms involve kidney, eye and ear

- **XLAS:**
  - Severe, early disease in males
  - Severity of disease in a female heterozygous for a COL4A5 mutation dependent primarily on the relative activities of the mutant and normal X chromosomes in renal, cochlear, and ocular tissues

- **ARAS:**
  - Disease is equally severe in male and female homozygotes
  - Suspect in patients with typical symptoms and absence of family history

- **ADAS:**
  - Typically result in asymptomatic hematuria but in some families may also be associated with progressive nephropathy (ADAS)
  - ADAS patients tend to have a slower course to ESRD than do those with XLAS or ARAS.
Renal Manifestations

Box 1 | Stages in the development of Alport syndrome

- Stage 0: microscopic haematuria (<30 mg albumin per g creatinine or per day)
- Stage 1: microalbuminuria (30–300 mg albumin per g creatinine or per day)
- Stage 2: gross proteinuria (>300 mg albumin per g creatinine or per day)
- Stage 3: impaired renal function (GFR <60 ml/min/1.73 m²)
- Stage 4: end-stage renal disease
## Renal Manifestations

<table>
<thead>
<tr>
<th>Hematuria</th>
<th>XLAS</th>
<th>ARAS</th>
</tr>
</thead>
</table>
| Cardinal finding of AS | Males:  
• Persistent μcopic hematuria  
• 60-70% Episodic gross hematuria, precipitated by URI  
Females:  
• > 90% have persistent or inter μcopic hematuria, absent in ~7% of obligate heterozygotes | • Persistent in both males and females  
• About 50% of carriers of COL4A3 or COL4A4 mutations have hematuria |

<table>
<thead>
<tr>
<th>Proteinuria</th>
<th>XLAS</th>
<th>ARAS</th>
</tr>
</thead>
</table>
| • Usually absent early in life  
• Increased risk of progressive nephropathy | • Develops in all males  
• Eventually in most heterozygote females  
• Increases progressively with age and may result in nephrotic syn (30%) | • Both males and females with ARAS  
• Also HTN follows similar course |

<table>
<thead>
<tr>
<th>ESRD</th>
<th>XLAS</th>
<th>ARAS</th>
</tr>
</thead>
</table>
| Risk factors  
• gross hematuria in childhood  
• hearing loss  
• nephrotic range proteinuria  
• diffuse GBM lamellations | • All affected males by 2\textsuperscript{nd}/3\textsuperscript{rd} decade  
• 90% develop ESRD by age 40 years | • 12% developed ESRD < 40 yrs, increasing to 30% by age 60 years and 40% by age 80 years |
Hearing Deficits

- High tone sensironeural hearing loss present in up to 80% of males and 25% - 30% of females with the disease.

- Cause unknown, may reflect impaired adhesion of the Organ of Corti (which contain auditory sensory cells) to the basilar membrane of the inner ear.

- Never congenital, usually apparent by late childhood to early adolescence in boys with XLAS and in both boys and girls with ARAS.

- Hearing impairment always accompanied by evidence of renal involvement.

- No convincing evidence that deaf males lacking renal disease can transmit AS to their offspring.

- In its early stages, the hearing deficit is detectable only by audiometry, with bilateral reduction in sensitivity to tones in the range 2000 to 8000 Hz. In affected males, the deficit extends progressively to other frequencies, including those of conversational speech.

Johnson Comp Clinical Nephrology
Nature Reviews 2013
## Ocular Defects

<table>
<thead>
<tr>
<th>Ocular features</th>
<th>XLAS (%)</th>
<th>ARAS(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>Recurrent corneal ulcers</td>
<td>&lt;10</td>
<td>&lt;10</td>
</tr>
<tr>
<td>Post Polypmorphous Co dystrophy</td>
<td>Rare</td>
<td>Rare</td>
</tr>
<tr>
<td>Lenticonus</td>
<td>50</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Perimacular Fleck</td>
<td>70</td>
<td>20</td>
</tr>
<tr>
<td>Peripheral retinopathy</td>
<td>80</td>
<td>50</td>
</tr>
<tr>
<td>Temporal retinal thinning</td>
<td>55</td>
<td>30</td>
</tr>
<tr>
<td>Lamellar macular hole</td>
<td>&lt;5</td>
<td>Not described</td>
</tr>
<tr>
<td>Other maculopathies</td>
<td>&lt;5</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>
Ocular Findings: Perimacular Fleck Retinopathy

- The most common ocular manifestation of AS

- Present in 60% of men and at least 15% of women with XLAS, 50% of individuals with ARAS

- Poor prognostic factor for dev of ESRD < 30 yrs

- No interference with vision
Ocular Findings

- Conical protrusion of the lens anteriorly through the thinnest and weakest part of the capsule
- Pathognomonic of Alport (also Post polymorphous dystrophy)
- Often first seen in early middle age after the onset of renal failure. Patients have progressive difficulty in focusing because of their abnormal lens shape
- Worsens until visual symptoms require treatment, and most patients eventually require surgery.

CJASN  Feb 2015
Nature Rev March 2013
KI 2003
Leiomyomatosis

- Characterized by benign nodular tumors consisting of smooth muscle cells present in some families with Alport

- Can affect GI, trachea, bronchial tree and genital tract

- Genetic defect usually a large deletion in the COL4A5 gene, including COL4A6 gene, normally expressed in sm muscle cells of GE tract and encodes collagen α5 or α5α6 chains

- Symptoms usually appear in late childhood and include dysphagia, postprandial vomiting, substernal or epigastric pain, recurrent bronchitis, dyspnea, cough, and stridor

Nature Rev March 2013
Diagnosis

- Family history and typical symptoms

- UA, Slit lamp exam (presence of anterior lenticonus and posterior polymorphous corneal dystrophy pathognomonic) and audiometry for hearing loss

- Molecular genetic testing (gold std) in presymptomatic children

- Tissue biopsy: skin/kidney biopsy

Nature Rev March 2013
Skin Biopsy

Absence of $\alpha_5(IV)$ chains in the epidermal basement membrane on skin biopsy is diagnostic of XLAS (observed in only 80% of males with XLAS)

$\alpha_3(IV)$ and $\alpha_4(IV)$ chains are normally absent in the epidermal basement membrane, cannot diagnose ARAS and ADAS.
A: ARAS
B: Heterozygous female carrier of XLAS
C: Male XLAS
Renal Biopsy: LM

A: Podocyte hypertrophy on an early biopsy specimen
B: Rigidity and moderate thickening of GBM and segmental glomerular sclerosis
C: Irregular thickening of the GBM

JASN 2009
G: Control
H: XLAS male
I: ARAS

Renal Biopsy : IF

JASN 2009
D: Irregular distribution of thick and split, and of thin GBM segments with lamellations
E: Diffusely thin GBM

JASN 2009
Treatment

Treatments targeting proteinuria
- RAAS Blockade
- Calcineurin Inhibitors

Treatments targeting inflammation and fibrosis
- Complement inhibition
- Chemokine receptor antagonists
- Bone morphogenetic protein-7
- Matrix metalloproteinase inhibitors

Treatments targeting the GBM pathology of Alport syndrome
- Discoidin domain receptor 1 and integrin α2β1 antagonism

Bone marrow transplant/stem cell therapy

Renal transplant
**Methods:** 12-week, double-blind multinational study investigated the effects of losartan 0.7–1.4 mg/kg/day compared with placebo (normotensive patients) or amlodipine 0.1–0.2 mg/kg/day up to 5 mg/day (hypertensive patients) on proteinuria [early morning-void (UPr/Cr), baseline 34 mg/mmol] in 30 children of up to 17 years of age with AS.

**Results:** 12 weeks of treatment with losartan significantly reduced proteinuria vs placebo/amlodipine:
Losartan 14.7 mg/mmol versus placebo/amlodipine 2.3 mg/mmol (26.0 to 18.1 mg/mmol), P< 0.01. Adverse event incidence was low and comparable between losartan and placebo/amlodipine groups.

**Conclusions:** Losartan significantly lowered proteinuria and was well tolerated after 12 weeks of treatment in children aged 1–17 years with proteinuria secondary to Alport syndrome with or without hypertension.
Clinical Study

Safety and Efficacy of the ACE-Inhibitor Ramipril in Alport Syndrome: The Double-Blind, Randomized, Placebo-Controlled, Multicenter Phase III EARLY PRO-TECT Alport Trial in Pediatric Patients

Oliver Gross,¹ Tim Friede,² Reinhard Hilgers,² Anke Görlitz,³ Karsten Gavénis,³ Raees Ahmed,³ and Ulrike Dürr³
The reported experience of cyclosporine in AS patients principally involves 3 case series involving a total of 32 patients.

Although a significant and sustained improvement in proteinuria was a consistent finding, this was associated with a significant reduction in GFR, calcineurin toxicity on renal biopsy, and hypertension.

Nephrotoxicity and hypertension likely preclude the use of cyclosporine in AS.

The mechanisms by which cyclosporine might have a beneficial or harmful effect on Alport kidney disease remain uncertain. Cyclosporine may interfere with alterations in the podocyte cytoskeleton or type IV collagen turnover.
Treatments targeting inflammation and fibrosis and GBM Pathology

Pediatr Nephrol (2013)
Stem Cell Based Therapies

- Could potentially be “Holy Grail” in the treatment of AS

- Several groups have claimed podocyte differentiation from stem cells in Alport mice, these publications still need validation and do not convincingly demonstrate that podocyte differentiation and consequent restoration of the GBM really occurs.

- Differentiation of injected stem cells (amniotic fluid stem cells) into podocytes does not occur in vivo in an animal model of AS, despite significant protection of glomerular structure and function.  
  
  Gross et al. NDT 2014
Schematic representation of possible mechanisms of injury repair in AS by stem cells and progenitors

- Paracrine activity (possibly affecting the TGFβ axis) leading to attenuation of fibrosis and chronic inflammation (main).

- Stimulating ingress of ‘healing’ type II macrophages (M2).

- Seem to induce blockade of the angiotensin II pathway that prevents further damage to the glomeruli and favours preservation of podocyte number.

Gross et al. NDT 2014
Renal Transplant

AS is essentially cured with renal transplantation

The most significant and devastating, albeit rare, complication of transplantation is antiglomerular basement membrane nephritis.

Approximately 3-5% of patients with Alport syndrome who receive a transplant develop anti-GBM antibody to the NC1 component of the α3(IV) chain.

Post-transplant anti-GBM nephritis usually develops within the first year of the transplant.

Renal Transplant

- Low risk: normal hearing, late progression to ESRD, or females with XLAS.

- Unlike de novo anti-GBM nephritis, pulmonary hemorrhage is never observed because the patient's lung tissue does not contain the antigen.

- Treatment with plasmapheresis and cyclophosphamide is usually unsuccessful, and most patients lose the allograft.

- Re-transplantation in most patients results in recurrence of anti-GBM nephritis despite the absence of detectable circulating anti-GBM antibodies before transplantation.

Thank You