BeSHG

Advanced Master in Clinical Genetics – Brussels, Nov 2022

Clinical Phenotype of Inherited Kidney Diseases

The Adult Nephrologist's Perspective

Johann Morelle, MD, PhD

Cliniques universitaires SAINT-LUC UCLouvain BRUXELLES

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Learning objectives

- To recognize 'common' phenotypes of kidney diseases
- To identify patients who should be offered genetic testing
- To understand the role of genetics in the pathogenesis of (some) kidney diseases
- To understand the clinical implications of genetic testing

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Clinical case: 32-year-old White female patient

- Unremarkable past medical history, no family history of kidney disease
- She presented to the emergency room with diarrheoa and vomiting
- Lab tests: acute kidney injury (sCreat 4.1), low platelet counts (31.10³/µl), hemolytic anemia (Hb 10.3 g/dl, haptoglobin <0.1 g/l, LDH 4xN, Coombs neg., schistocystes 4-10%), normal coagulation tests
- What is your hypothesis?
    A. Severe sepsis
    B. Acute leukemia
    C. Hantaan virus infection
    D. Thrombotic microangiopathy
    E. Disseminated intravascular coagulation

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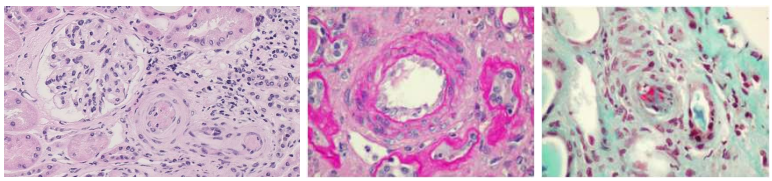
Diagnosis of thrombotic microangiopathy (TMA)

Clinical triad

- Non-immune, micro-angiopathic hemolytic anemia (MAHA);
- Thrombocytopenia (85% of cases);
- Organ damage (acute kidney injury and/or extra-renal damage)

and/or

Pathological lesion of TMA (biopsy of the kidney or another organ)



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Thrombotic microangiopathies:

Which etiologies?
Which workup?
Which treatment?

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Clinical case: 32-year-old White female patient

- Additional workup:
  - ADAMTS13: 83%
  - Negative screening for stx (PCR) on rectal swab/stools,
  - Returned negative: anti-nuclear or anti-phospholipid Ab, HIV testing, pregnancy test, hyperhomocysteinemia or methymalonic aciduria
  - No kidney biopsy performed
- Management: transient dialysis, PEX 5 days then C5 inhibitor
- Outcome: rapid improvement and complete remission
- Genetic testing: rare pathogenic variant in *CFH* gene (c.3486del)

What's your diagnosis?

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Atypical hemolytic uremic syndrome (aHUS) – complement-mediated TMA

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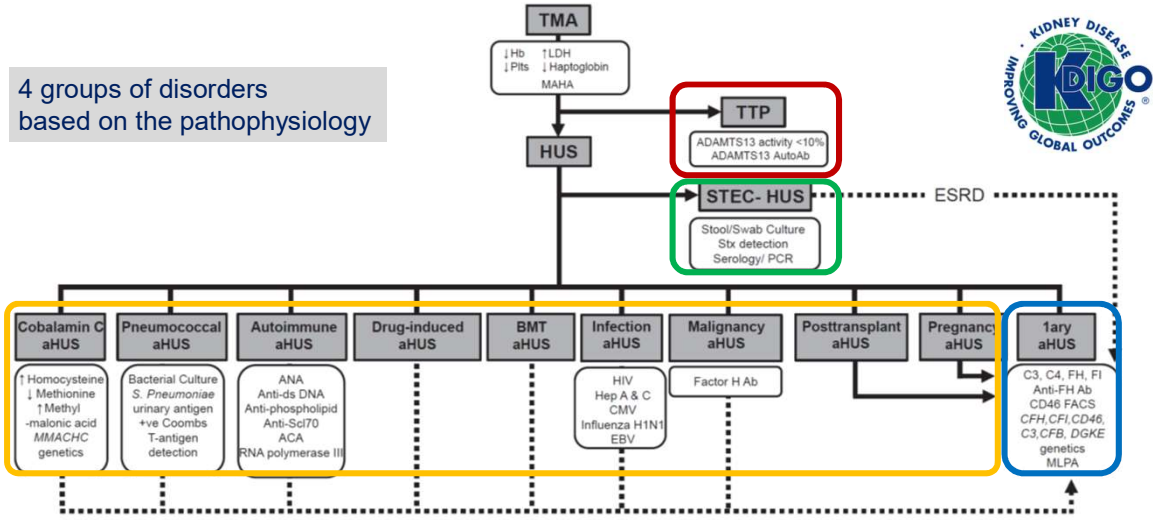
Etiologies of TMA

4 groups of disorders
based on the pathophysiology

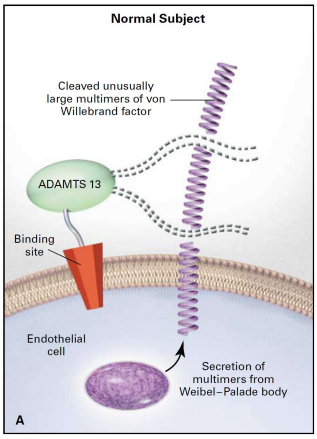


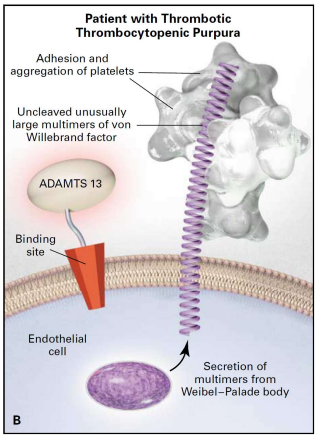
Goodship et al, *Kidney Int* 2016; Claes et al, *Acta Clin Belgica* 2018

Thrombotic thrombocytopenic purpura (TTP)

TTP = ADAMTS13 activity <10%
(vWF-cleaving metalloprotease)

- Acquired in most cases:
  anti-ADAMTS13 autoantibodies
  Treatment: PEX, immunosuppression, caplacizumab
- Rarely congenital and inherited (Upshaw-Schulman syndrome) :
  ADAMTS13 mutations
  (young children but also late onset associated with pregnancy)

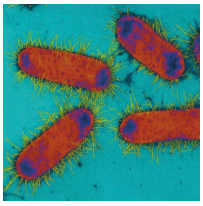


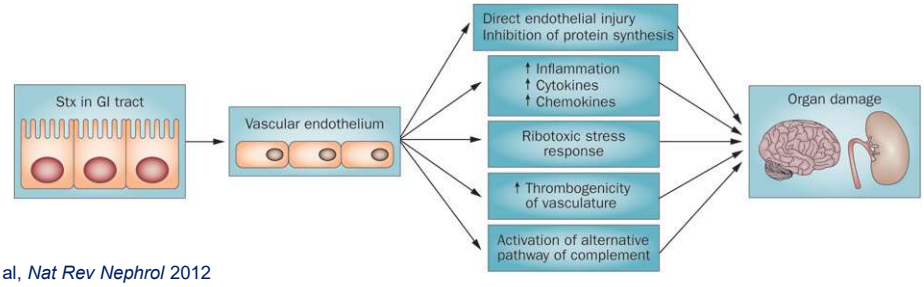


Low ADAMTS13 → Large multimers of vWF → Platelets adhesion/aggreg. → Microthrombi

Shigatoxin-associated HUS (ST-HUS)

- Food-borne disorder, 95% of all HUS in children, sometimes in adults
- Bloody diarrhoea followed (± 6 days) by abrupt onset TMA
- O_{157}:H_7 or other enterohaemorrhagic *E. coli* (TMA in 6% of infected patients)
- Diagnosis relies on identification of *stx* gene by PCR on stools/rectal swab
- Treatment: supportive



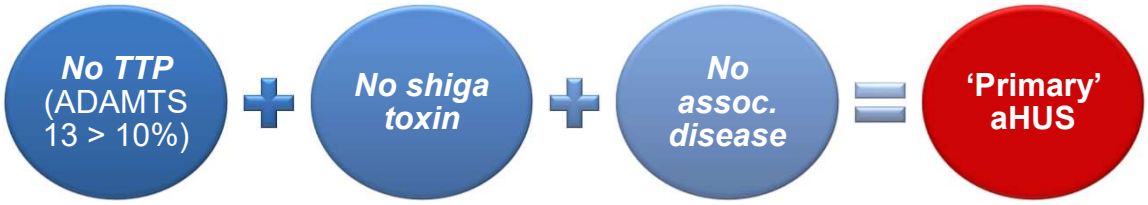


Trachtman et al, *Nat Rev Nephrol* 2012

Secondary HUS/HUS associated with a trigger

- HIV and other infections (*Strep. pneumoniae*)
- Pregnancy
- Connective tissue disorders (SLE, SSc)
- Antiphospholipid syndrome
- Drugs
- Cancer
- Malignant hypertension
- Hematopoietic stem-cell or solid-organ transplantation
- Monoclonal Igs
- Defective cobalamine metabolism

In a patient with TMA and…



Atypical HUS: clinical diagnosis, by exclusion!

Goodship et al, *Kidney Int* 2016; Claes et al, *Acta Clin Belgica* 2018

Kidney International, Vol. 53 (1998), pp. 836–844

GENETIC DISORDERS - DEVELOPMENT

Genetic studies into inherited and sporadic hemolytic uremic syndrome

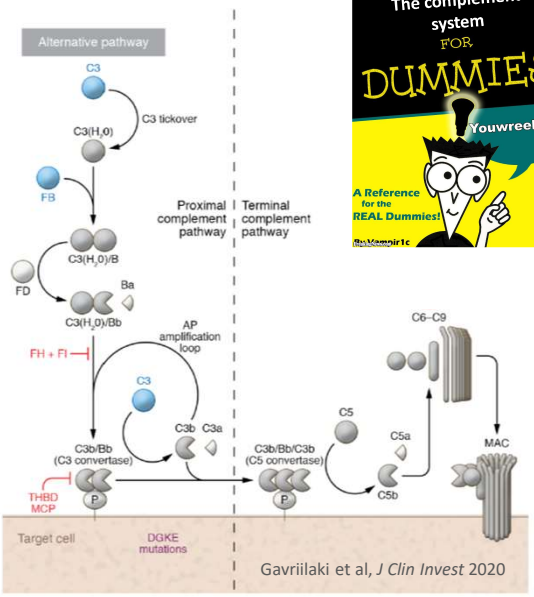
PAUL WARWICKER, TIMOTHY H.J. GOODSHIP, ROSEMARY L. DONNE, YVES PIRSON, ANTHONY NICHOLLS, ROY M. WARD, PETER TURNPENNY, and JUDITH A. GOODSHIP

Department of Medicine, and Department of Human Genetics, University of Newcastle upon Tyne, Newcastle upon Tyne, England, United Kingdom; Renal Unit, Cliniques Universitaires St. Luc, Universite' Catholique de Louvain, Brussels, Belgium; Renal Unit, and Clinical Genetics Service, Royal Devon and Exeter Hospital, Exeter, and Department of Immunology, Royal Victoria Infirmary Trust, Newcastle upon Tyne, England, United Kingdom

'The primary abnormality [in aHUS] is overactivity of the alternative complement pathway'
Locus at 1q32 segregated with the disease - mutation in *CFH*
Complement factor H - critical regulatory role in the alternative pathway of complement activation

The complement system

- Highly conserved component of the innate immune system, first-line of defense against pathogens
- Key roles
  - Generation of proinflammatory C3a - C5a
  - Production of the membrane attack complex C5b-9 (cell lysis)
  - Link to adaptive immunity
- Three pathways of activation:
  - Classical (immune complexes)
  - Lectin (mannose)
  - Alternative (spontaneous, 'tickover')
- Alternative pathway tightly controlled by regulatory proteins (FH, FI, MCP)



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The complement system

'Loss of function' variant in genes encoding for regulatory proteins (*CFH*, *CFI*, *MCP*)

or

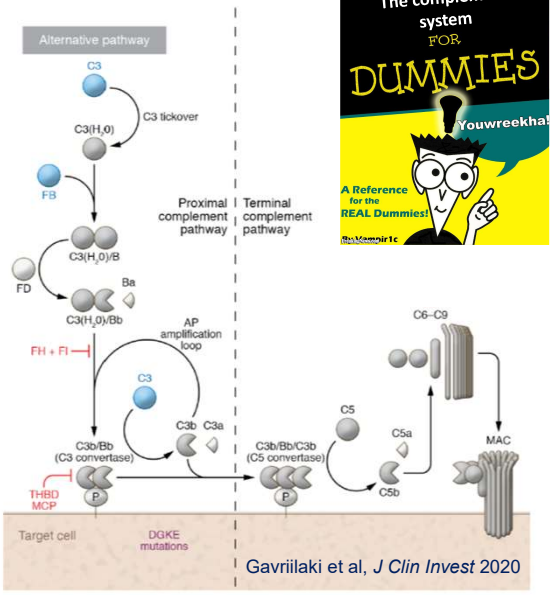
Anti-CFH autoantibodies

or

'Gain-of-function' variant in *C3* or *CFB*

↓

Overactivation of the alternative pathway of the compelment system



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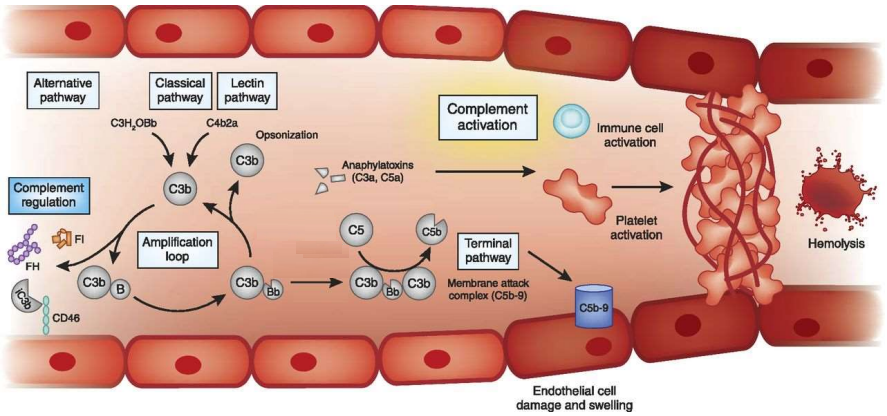
Atypical HUS ('complement-mediated TMA')

Overactivation of the complement system → endothelial injury → HUS



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Atypical HUS ('complement-mediated TMA')

- Ultra-rare disease - incidence ~0.5 per million per year
- Diagnosis is challenging
  - No reliable test or biomarker
  - Genetic or autoimmune abnormalities in only 50-60% of patients
- Before any treatment was available, aHUS was associated with a very poor outcome
  - ~50% kidney failure or death within 1 year
  - Pregnancy contraindicated (risk of relapse 20-30%)
  - High risk of recurrence on the kidney transplant…patients frequently on 'long-term' dialysis

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Atypical HUS, a prototype of 'precision medicine'

Understanding of the pathophysiology (role of the complement)

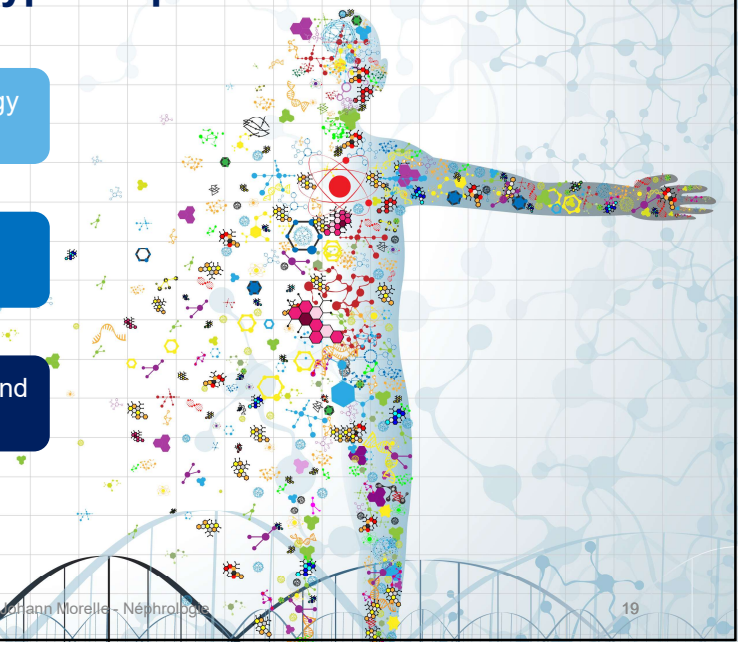
↓

Development of novel therapeutic and preventive strategies

↓

Improvement of patients' outcomes and QoL, reduction of adverse events

Jameson et al, *N Engl J Med* 2015



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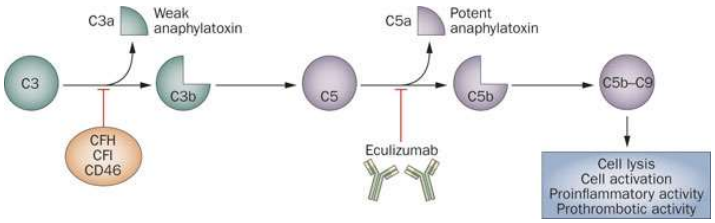
Atypical HUS, a prototype of 'precision medicine'

- Better understanding of the role of the complement in atypical HUS
  → Developement of eculizumab, monoclonal antibody targeting C5
- Approved by the FDA and EMA for the treatment of atypical HUS in 2011 based on the results of a non-randomized trial
- Major improvement in patients' outcomes and QoL



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Risk of death or kidney failure (dialysis) in aHUS - impact of eculizumab

	Children			Adults				
	Pre-eculizumab era		Eculizumab	Pre-eculizumab era		Eculizumab		
	French cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 3[139,140] (n=22)	French Cohort[2] (n=89)	Italian cohort[3] (n=149)	Trial 1[141,142] (n=17)	Trial 2[141,142] (n=20)	Trial 4[143,144] (n=41)
First episode	16%	..	..	46%	..	..	..	..
6-month follow-up	..	..	9%	..	..	6%	10%	15%
1-year follow-up	29%	..	9%	56%	..	6%	10%	15%
2-year follow-up	..	..	..	..	..	12%	10%	..
3-year follow-up	..	48%	..	..	67%	..	..	..
5-year follow-up	36%	..	..	64%	..	..	..	..

For a detailed table legend see the appendix (pp 27,28). HUS=haemolytic uraemic syndrome.

Table 2: **Percentage of patients with atypical HUS who progressed to end-stage renal disease or who died in four prospective trials of eculizumab compared with the Italian and French registries of the pre-eculizumab era**

Fakhouri et al, *Lancet* 2017

Peri-transplantation prophylaxis

- Risk of relapse post-transplantation
- Risk stratification based on the results of genetic testing
- Prophylactic use of eculizumab in the peritransplantation period (3-6 months, based on genetic results)

Prophylaxis in the peri-transplantation period

The risk of recurrence should be based on genetic screening, presence of anti-CFH antibodies and previous transplant history

Risk of recurrence	Conditions	Prophylactic eculizumab
Low	Isolated *MCP* mutation Previously positive anti-CFH antibodies *DGKE* mutation	None
Intermediate	No high-risk mutation No mutation found or auto-antibodies Variant with unknown functional significance *CFI* mutation Positive anti-CFH antibodies	3 months
High	*CFH* mutation or gene re-arrangements involving *CFH* and *CFHR* *C3* mutation *CFB* mutation Recurrence in previous transplant with graft loss due to TMA	6 months

In case of recurrence in previous allograft with graft loss due to the recurrence: duration decision case by case. Long-term treatment might be possible with yearly revision in the reimbursement college.

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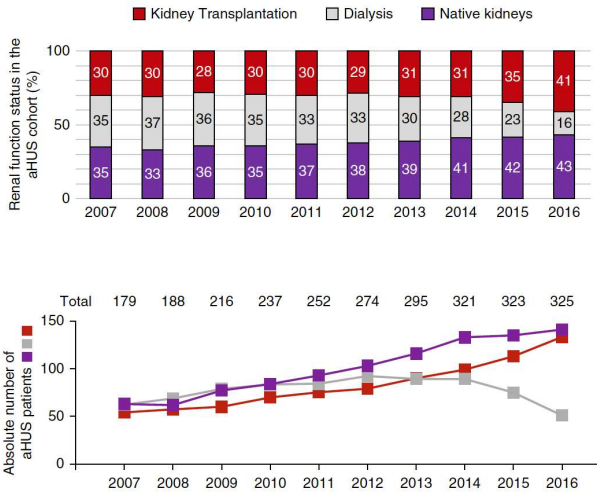
Claes et al, *Acta Clin Belgica* 2017 23

Impact of eculizumab on kidney outcomes



French registry

Increase in the proportion/number of patients with functioning native kidneys

Increase in the proportion/number of patients with functioning kidney allografts

Decrease in the proportion/number of patients with aHUS on dialysis

Zuber et al, *J Am Soc Nephrol* 2019

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Despite major advances, questions remains…

- Increased risk (x2000!) of severe infections caused by *Neisseria meningitidis, Haemophilus influenzae, Streptococcus pneumoniae*
  → vaccination/antibioprophylaxis!
- Expensive – in Belgium: ~500.000 €/year
- Burden of treatment – i.v. administration every other week (can be lifelong in some cases)
  - developement of ravulizumab (q 2 months)
- Effective in 'secondary' HUS?
- Optimal duration of treatment for aHUS?

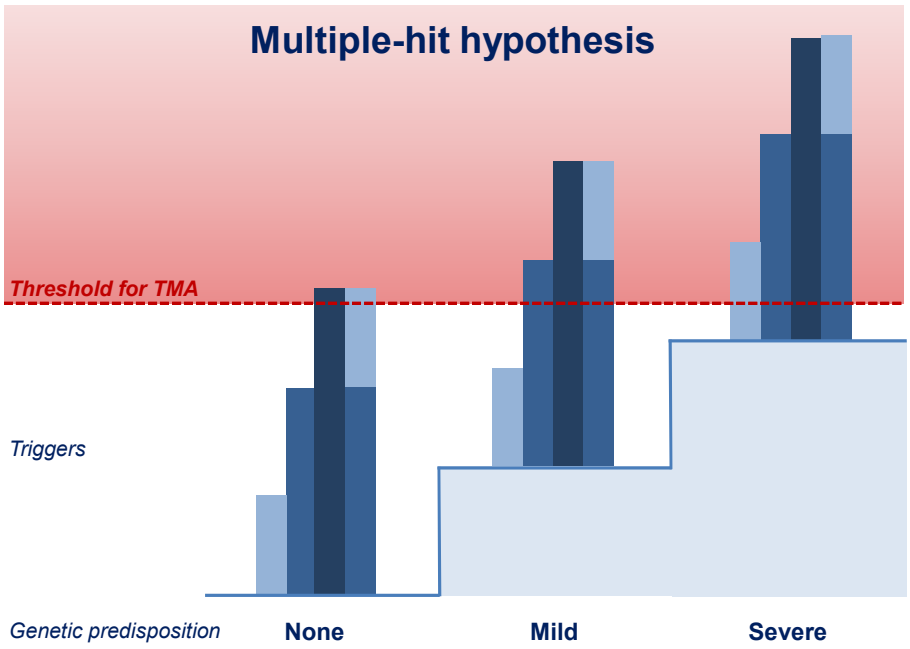
Towards a short duration treatment to reduce the risk of infection and costs related to treatment?

- No consensus on the optimal duration of treatment of aHUS
  - Lifelong as there might be constitutive genetic defects?
  - Ou transient as the disease has a low penetrance ('healthy carriers') and the prevailing hypothesis is a '*multiple hit model*' (genetic predisposition + environmental trigger)
- Belgian recommandation: 3-6 mo. then evaluation

No active disease Normalized platelets levels (+ LDH/Hb) Normalized/stabilized kidney function	→ **Stop eculizumab** after 3-6 mo. with thorough follow-up

Claes et al, *Acta Clin Belgica* 2017

Multiple-hit hypothesis



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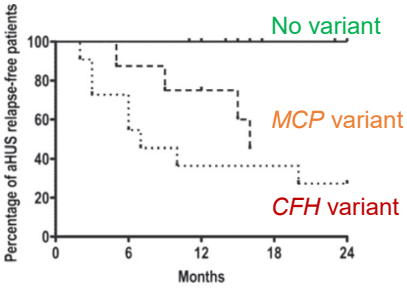
Evaluation of the risk of relapse based on genetic testing

French aHUS registry

Retrospective study 2010-2014

38 discontinued eculizumab (median duration 17.5 mo)

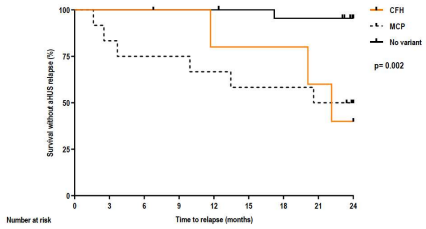


12 patients relapsed
- 0/16 (0%) with no rare variant
- 4/8 (50%) with *MCP* variants,
- 8/11 (72%) with *CFH* variants,

Fakhouri et al, *CJASN* 2017

Prospective study 2015-2019

55 discontinued eculizumab (median duration 16.5 mo)



13 patients relapsed
- 1/23 (8%) with no gene variant
- 6/12 (50%) with *MCP* variants
- 3/6 (50%) with *CFH* variants

Fakhouri et al, *Blood* 2020

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Thrombotic microangiopathy in aHUS and beyond: clinical clues from complement genetics

Fadi Fakhouri[1] ✉ and Véronique Frémeaux-Bacchi[2]

Knowledge of complement genetics and its contribution

- Better understanding of the disease
- Design of the first specific treatment for aHUS, eculizumab
- Guide therapeutic strategy (duration and peri-transplant prophylaxis)
- Reclassification of pregnancy-associated HUS within the spectrum of complement-mediated aHUS
- No link between constitutional complement dysregulation and secondary HUS
- Overlap between aHUS and other causes of malignant hypertension

Fakhouri and Fremaux-Bacchi, *Nat Rev Nephrol* 2021

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Thrombotic microangiopathy in aHUS and beyond: clinical clues from complement genetics

Fadi Fakhouri[1] ✉ and Véronique Frémeaux-Bacchi[2]

Interpretation of complement genetics results remains complex

- Even complement-mediated aHUS is not a classical monogenic disease (penetrance ~50%, familial forms ~20%, risk haplotypes *CFH*-H3 and MCP_{ggaac}, 'genetic susceptibility')
- HUS likely results from interactions between genetic susceptibility factors in and/or potentially outside the complement system and environmental factors (such as infections and injuries)
- Critical input of trained geneticists and experts with a comprehensive view of complement biology

Fakhouri and Fremaux-Bacchi, *Nat Rev Nephrol* 2021

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Complement Genetics in Atypical HUS

- Screening for rare variants in complement genes relies on combination of
  - NGS of at least five complement genes: *CFH, C3, CFI, CFB* and *MCP*,
  - Multiplex ligation-dependent probe amplification to identify potential *CFHR1−CFH* hybrid genes (nonallelic homologous recombination)
- To date, >500 variants in complement genes identified in aHUS patients
- Not all identified variants are involved in the pathophyisiology of aHUS
  - Depends upon the prevalence/enrichment in aHUS vs gen. population
  - Depends upon the impact of the variant on protein structure and function: null variant in a gene in which loss-of-function is a known mechanism of disease; *in vitro/in vivo* functional studies, *in silico* tools (e.g., Polyphen, SIFT Mutation Taster, CADD), localisation of variant in the protein, variant segregation

Fakhouri and Fremaux-Bacchi, *Nat Rev Nephrol* 2021

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Atypical HUS ('complement-TMA'): conclusions

- Ultrare disease characterized by overactivation of the complement system and thrombotic microangiopathy
- Poor outcomes (death and kidney failure) if left untreated – therapeutic emergency!
- Prototype of 'precision medicine'
  - Identification of pathogenic variants in genes of the complement system in 50-60% of cases
  - Understanding of the role of the complement
  - Developement of targeted therapy (eculizumab/ravulizumab)
  - Impact on outcomes and management

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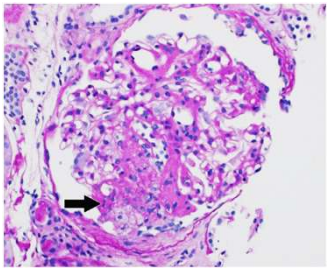
Clinical case

- 19-yo White female, no family history of kidney disease or albuminuria
- Albuminuria since the age of 12
- Nephrotic syndrome, no response to steroids
- Kidney biopsy: focal and segmental glomerulosclerosis



Progressed to kidney failure – candidate to transplantation
Risk of relapse after transplantation (FSGS)?
Living donation reasonable? What would you do next?

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Clinical case

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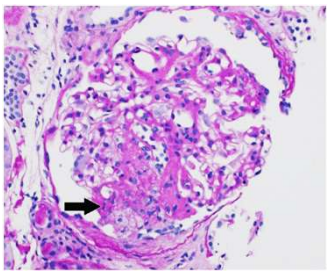

Genetic testing: compound heterozygous for *NPHS2* variants:
- Common R229Q variant, transmitted from the mother
- Rare pathogenic A288T variant, transmitted from the father

→ Inherited/monogenic podocytopathy – kidney transplantation from a living donor, no relapse

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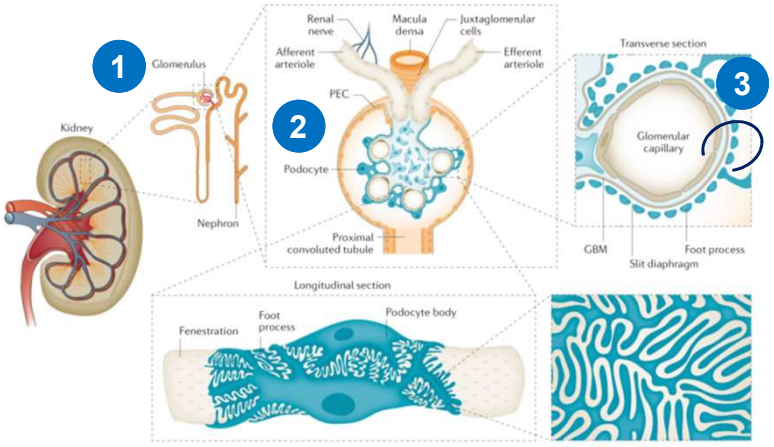
The glomerulus and the glomerular filtration barrier



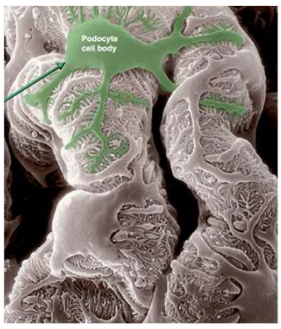
1. Nephron: functional unit of the kidney, glomerulus + tubule + vessels, ~1M per normal adult kidney

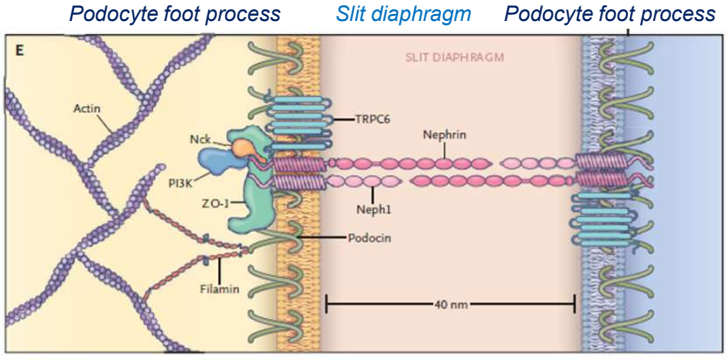
2. Glomerulus: tuft of fenestrated capillaries covered by specialized epithelial cells, the podocytes

3. Glomerular filtration barrier: includes endothelial cells, the glomerular basement membrane, and podocyte foot processes

Kopp et al, *Nat Rev Dis Primers* 2021

The podocyte and the slit diaphragm





- The podocyte is a specialized epithelial cell on the outer part of the GFB
- The slit diaphragm is a cell-cell junction connecting podocyte foot processes via proteins (nephrin/NPHS1, podocin/NPHS2,…) and the actin cytoskeleton
- They play a critical role in preventing the leak of plasma proteins into the primary urine

→ Dysfunction or injury to podocyte/slit diaphragm causes proteinuria

Benzing, Salant, *NEJM* 2021

Etiologies of podocytopathies

- Immune-mediated/circulating permeability factor: minimal change disease, primary FSGS
- Adaptive/hyperfiltration: low nephron number, obesity
- Drugs and toxins: interferon, heroin, pamidronate
- Viruses: HIV, COVID-19, parvovirus B19…
- Genetic
  - *APOL1* nephropathy (susceptibility factors)
  - Hereditary podocytopathies

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Immune-mediated (circ. permeability factor) vs. secondary/genetic podocytopathies

	Immune-med.	Secondary/Genetic
Nephrotic syndrome/low sAlb	Severe	Absent or moderate
Onset	Sudden	Progressive
Urinary protein	>3.5 g/day	Variable (NS rare)
Foot process effacement	Diffuse (>80%)	Segmental (<80%)
Response to RAS inhibitors	Poor	Quite good
Steroids/CNI	May lead to remission	Not efficient, potentially harmful
Post-TP recurrence	Common (>70%)	Rare

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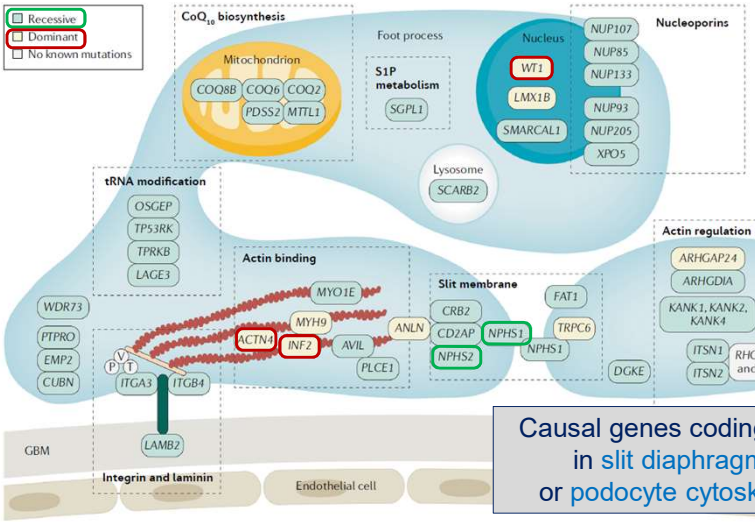
Etiologies of hereditary podocytopathies (>50 genes)



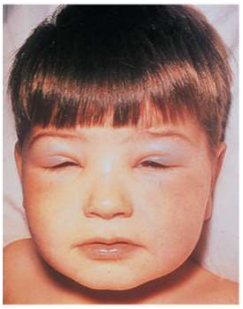
Genes and proteins
NPHS1 - nephrin
NPHS2 - podocin
ACTN4 – α-actinin 4
WT1 – Wilms tumor protein
INF2 – inverted formin-2
…

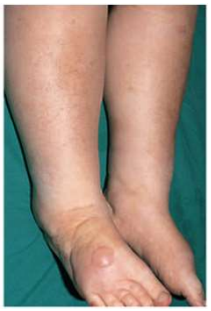
Causal genes coding for proteins expressed in slit diaphragm (NPHS1, NPHS2) or podocyte cytoskeleton (ACTN4, INF2)

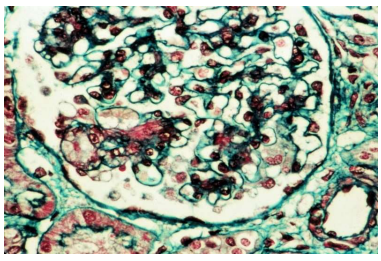
Kopp et al, *Nat Rev Dis Primers* 2020

Clinical presentation of hereditary podocytopathies

- Cardinal sign is proteinuria
- Typical presentations include
  - Congenital/infantile nephrotic syndrome (heavy proteinuria, low sAlb, edema, high cholesterol)
  - Steroid-resistant nephrotic syndrome
  - Lesions of focal and segmental glomerulosclerosis on kidney biopsy
  - Late-onset proteinuria

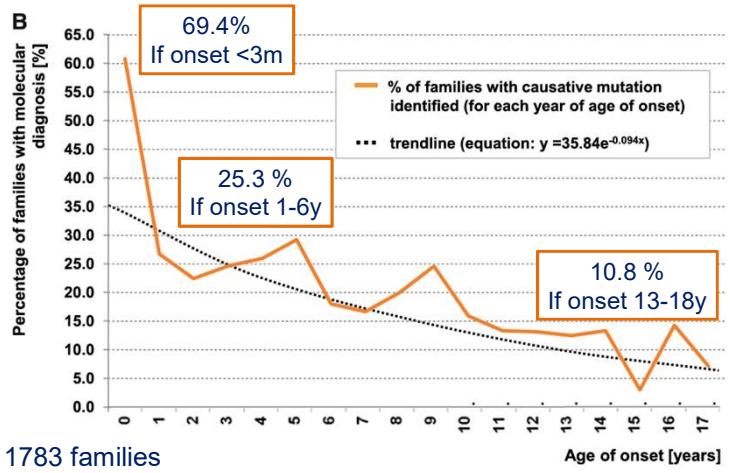






A Single-Gene Cause in 29.5% of Cases of Steroid-Resistant Nephrotic Syndrome

that manifested before the age of 25



1783 families

Sadowski at al, *JASN* 2015

Who & how to screen for hereditary podocytopathies?

- Who should be tested?
  - Infants with congenital NS (<3 months)
  - Children with steroid-resistant NS (resistance is not absolute)
  - All individuals with proteinuria before the age of 25?
  - Additional features increasing the likelihood of hereditary podocytopathy: young age, family history (autoD) or consanguinity (autoR), no recurrence post-transplant
  - Proteinuria/FSGS + extra-renal phenotype: nail patella (*LMX1B*), hypoacousia/hematuria (*COL4A3-5*), Charcot-Marie Tooth (*INF2*)…
- How?
  - NGS Panel for podocyte genes (~50 genes)

Why to screen for hereditary podocytopathies?

- Unequivocal cause-based diagnosis
- Avoidance of kidney biopsy in selected cases
- Personalized treatment ('precision medicine')
  - Nephrotic syndrome + 'high penetrance mutation' → no steroids (CNI?)
  - FSGS + recessive mutations in *COQ2*, *COQ6*, *ADCK4* → coenzyme Q_{10}
- Risk evaluation in kidney transplantation
  - Monogenic cause → low/no risk of recurrence after transplantation
  - Selection of living donors for kidney transplantation
- Genetic counseling
- Some genes associated with a syndrome, incl. extrarenal manifestations

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Mutations in *NPHS2* (podocin)

- Most frequent cause of autosomal recessive SRNS – as in our patient
- Podocin: important protein of the slit diaphragm, where it interacts with nephrin and TRPC6
- Mutations lead to congenital, childhood and late onset NS
- Most mutations provoke retention of mutant protein in endopl. reticulum
- Pharmacological chaperones may potentially slow progression of disease

Almost all adult-onset cases carry the p.R229Q (p.229Arg>Glu) non-neutral polymorphism (3%) associated with a pathogenic mutation on second allele

Slide courtesy Dr Demoulin

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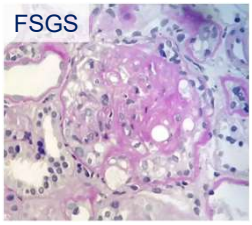
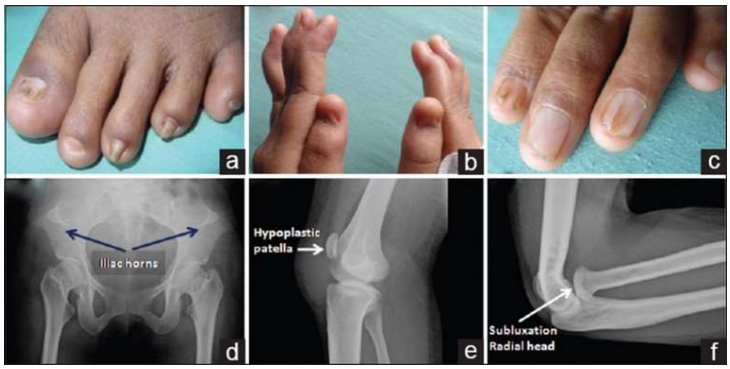
What's your diagnosis?

Proteinuria/FSGS – abnormalities of glomerular basement membranes – nail and distal digital abnormalities - hypoplastic patella – iliac horns

FSGS



Triangular *lunulae*



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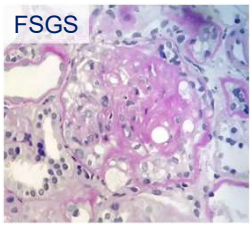
FSGS



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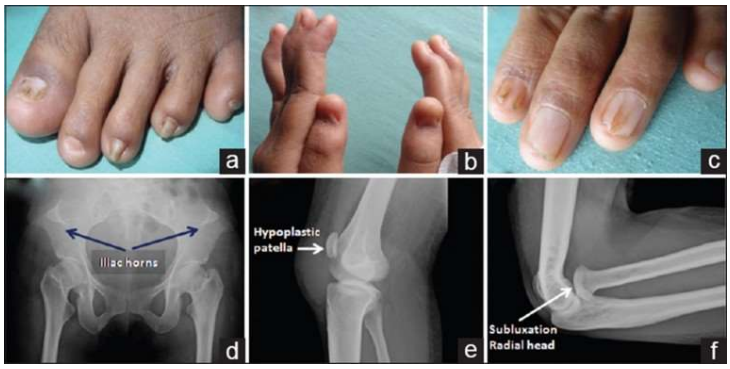

Nail-patella syndrome or hereditary osteo-onychodysplasia (HOOD) syndrome
Autosomal dominant, mutations of *LMX1B* (chr 9q, 15% de novo)

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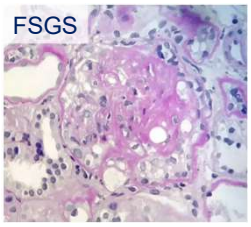
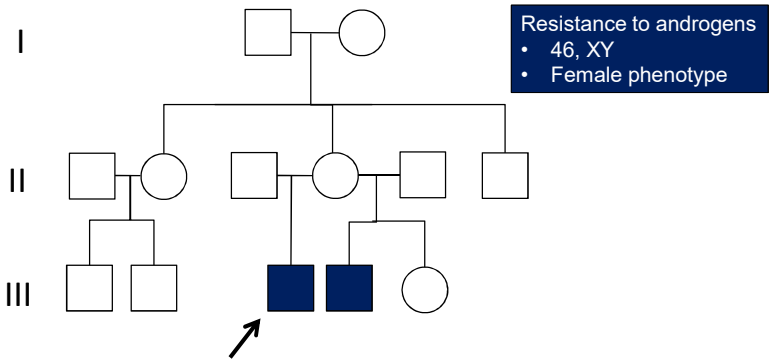
What's your diagnosis?

28 yo female – heavy proteinuria (18 g/day) - biospy: FSGS
The patient and her stepsister have androgen resistance: typical male chromosome pattern (46, XY) with female genitalia – coelioscopic removal of intraabdominal dysplastic testes at 18





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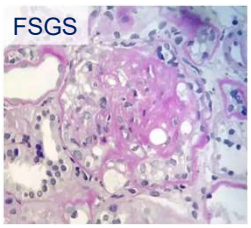

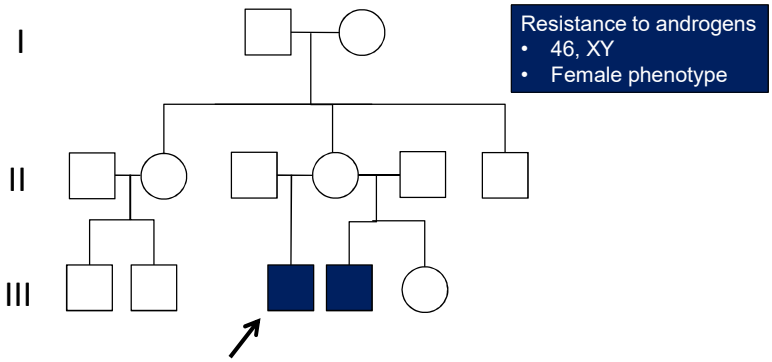

Frasier syndrome – mutations in the donor splice site in intron 9 of *WT1* gene

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‘Familial FSGS’ and microscopic hematuria…

Function of the gene product	Gene
Slit diaphragm proteins	*NPHS1, NPHS2, CD2AP, CRB2, TRPC6, FAT1*
Actin binding	*PLCE1, ACTN4, MYO1E, MYH9, INF2, ANLN, AVIL*
Actin regulation	*ARHGDIA, ARHGAP24, KANK1, KANK2, KANK4, MAGI2, DLC1, ITSN1, ITSN2, DAAM2*
Nuclear transcription factors	*LMX1B, WT1, SMARCAL1, NXF5*
Nuclear pore complex proteins	*NUP93, NUP85, NUP107, NUP133, NUP160, NUP205, XPO5*
Mitochondrial proteins	*COQ2, COQ6, COQ8B (ADCK4), PDSS2, MTTL1*
KEOPS complex (tRNA modification)	*OSGEP, TP53RK, TPRKB, LAGE3*
Lysosomal proteins	*SCARB2*
Adhesion proteins	*ITGA3, ITGB4, LAMB2*
Glomerular basement membrane proteins	*COL4A3, COL4A4, COL4A5, COL4A6, LAMA5*
Other	*SGPL1, CUBN, PTPRO, WDR73, EMP2, DGKE, ALG1*

…can be caused by pathogenic variants in *COL4A3*, *COL4A4* and *COL4A5*, and may reveal Alport syndrome

De Vriese et al, *Nat Rev Nephrol* 2021

Hereditary podocytopathies: conclusions

- Result from pathogenic variants in structural genes of the podocyte/slit diaphragm (>50 genes)
- Cause proteinuria/nephrotic syndrome, sometimes with extra-renal manifestations
- Genetic testing has important clinical implications

Clinical case

- A 52 year-old White woman with kidney failure of unknown etiology underwent deceased donor kidney transplantation
- Past medical history
  - Albuminuria since primary school
  - High blood pressure since adolescence
  - At the age of 30, kidney stones (+ subsequent episodes), never investigated
  - At the age of 50, fatigue and nausea, discovery of kidney failure - the patient was started on chronic hemodialysis
  - No family history of kidney stones or kidney disease
- Post-transplantation days 1-3: creatinine had dropped from 9 to 1.4 mg/dl
- Days 4-8: creatinine increases up to 4 mg/dl – kidney biopsy was performed

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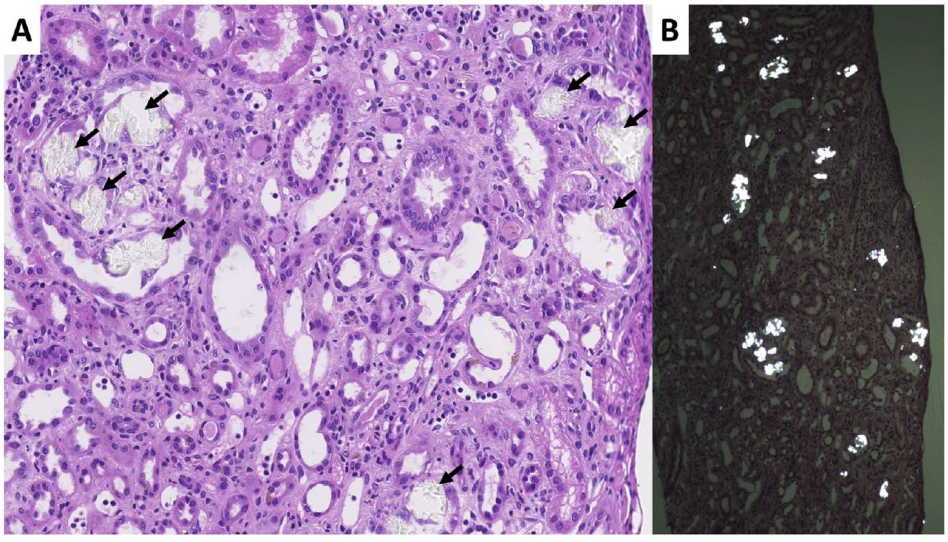

What do you see and what is your diagnosis?

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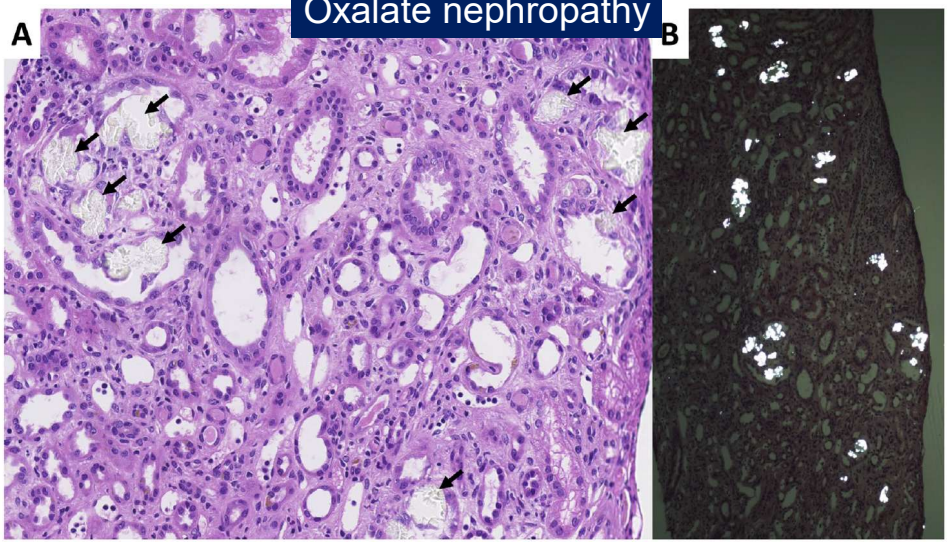
Oxalate nephropathy



(A) Light microscopy (H&E stain): intratubular translucent crystals, with acute tubular injury and mild interstitial inflammation. (B) Polarized light microscopy: crystals are birefringent.

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Clinical case (cont.)

- Genetic testing: homozygous for the p.Gly170Arg variant in *AGXT*, encoding for alanine-glyoxylate aminotransferase
- Consistent with the diagnosis of primary hyperoxaluria, type 1
- Stabilization of CKD using pyridoxine and massive hydration
- Started again on hemodialysis 7 years after transplantation
- Currently being discussed for a second transplant

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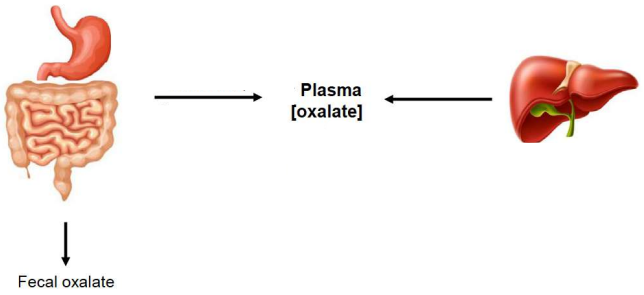
Metabolism of oxalate and etiologies of hyperoxaluria

Dietary intake: 20-40%
(vegetables, nut, tea, fruits)

Hepatic production: 60-80%
(from glyoxylate)



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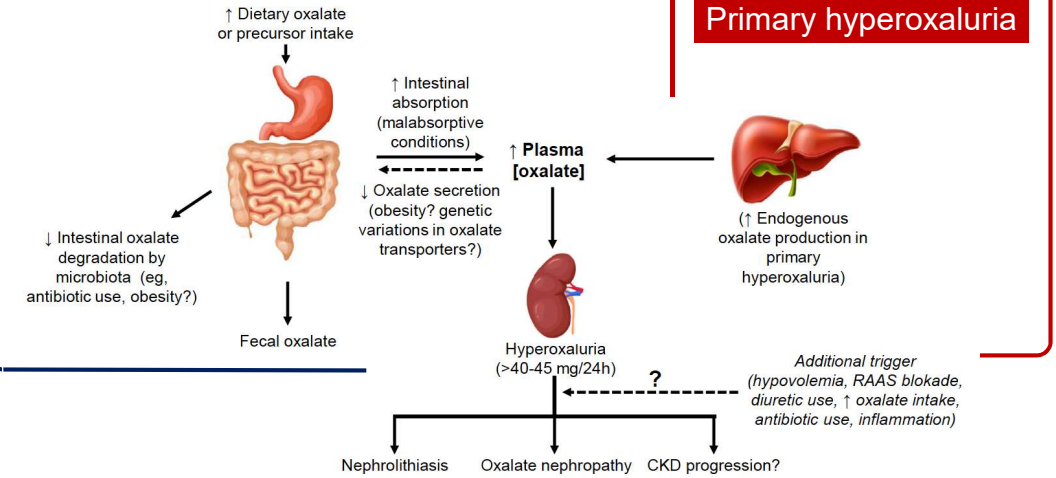
Metabolism of oxalate and etiologies of hyperoxaluria

Secondary hyperoxaluria

Primary hyperoxaluria



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Pathophysiology and Management of Hyperoxaluria and Oxalate Nephropathy: A Review

- **Hyperoxaluria results from either**
  - inherited disorders of glyoxylate metabolism leading to hepatic oxalate overproduction ('primary'), or
  - increased intestinal oxalate absorption ('secondary')
- **Hyperoxaluria may lead to** urinary supersaturation of calcium oxalate and crystal formation, causing
  - urolithiasis
  - deposition of calcium oxalate crystals in the kidney parenchyma, a condition termed oxalate nephropathy

Demoulin et al, *Am J Kidney Dis* 2022

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Primary hyperoxaluria (PH)

- Rare autosomal recessive inherited disorders of glyoxylate metabolism
- Caused by pathogenic variants in *AGXT* (PH1), *GRHPR* (PH2) or *HOGA1* (PH3)
- Inability to metabolize glyoxylate → excessive hepatic production of oxalate and accumulation in various organs, incl. the kidney (kidney stones, nephrocalcinosis and kidney failure)
- PH1 = most common and severe
  - Recurrent urolithiasis and kidney failure during the first 3 decades of life
  - Adult-onset PH1: Gly170Arg and Phe152Ile variants in *AGXT*

AGT, alanine-glyoxylate aminotransferase; GRHPR, glyoxylate reductase-hydroxypyruvate reductase; HOGA, 4-hydroxy-2-oxoglutarate aldolase

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Primary hyperoxaluria Type 1, a too often missed diagnosis and potentially treatable cause of end-stage renal disease in adults: results of the Dutch cohort

- p.Gly170Arg variant in *AGXT* in >50% of adult-diagnosed patients
- Largely underdiagnosed
- Pyridoxine-sensitive
- Patients may have previously only developed a few calculi
- Some of them diagnosed only after recurrence of oxalate deposition in kidney graft – as in our patient

Adult patients with CKD of unknown etiology and history of nephrolithiasis → assess oxaluria (Gly170Arg *AGXT* variant)

Nephrol Dial Transplant (2012) 27: 3855–3862

Current treatment of primary hyperoxaluria

- Conservative therapeutic options :
  - Massive fluid intake
  - Calcium oxalate crystallization inhibitors
  - Vitamin B6 (pyridoxine) in PH1
- Liver transplantation is currently the only 'curative' therapy - as it corrects the metabolic defect
- In patients with PH1 and CKD, liver-kidney transplantation (simultaneously or sequentially) is the current SOC - ideally before development of systemic oxalosis

New promising therapeutic agents: RNA interference (RNAi)-based therapy

- RNA interference: using synthetic small interfering RNA (siRNA) to prevent mRNA from being translated into proteins
- Lumasiran (Oxlumo®, Alnylam) blocks the synthesis of glycolate oxidase and reduces oxidation of glycolate to glyoxylate, the direct precursor of oxalate
- Phase 3 ILLUMINATE-A study: lumasiran reduced urinary oxalate excretion after 6 months in comparison with the placebo group
- FDA/EMA recently approved lumasiran for the treatment of PH1 - will be available soon (2023) in Belgium
- Potential to replace liver transplantation to 'cure the disease'

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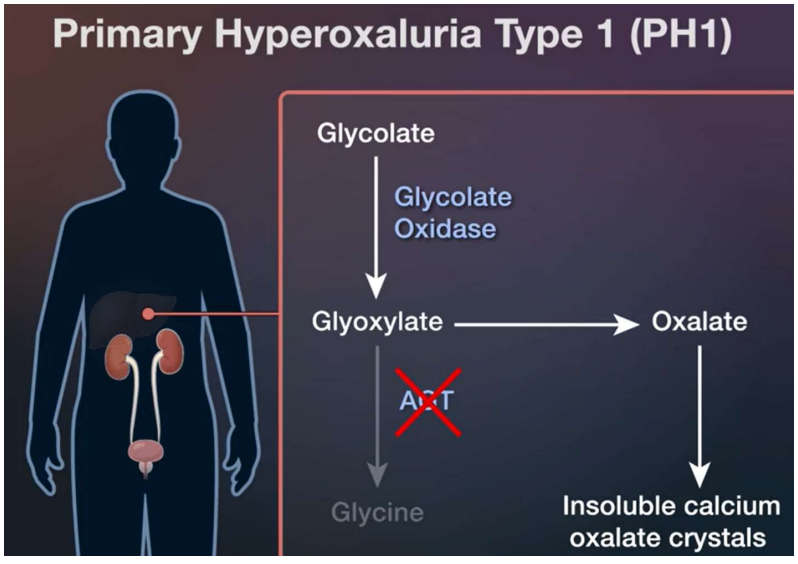

AGT, alanine-glyoxylate aminotransferase

Garrelfs et al, *NEJM* 2021

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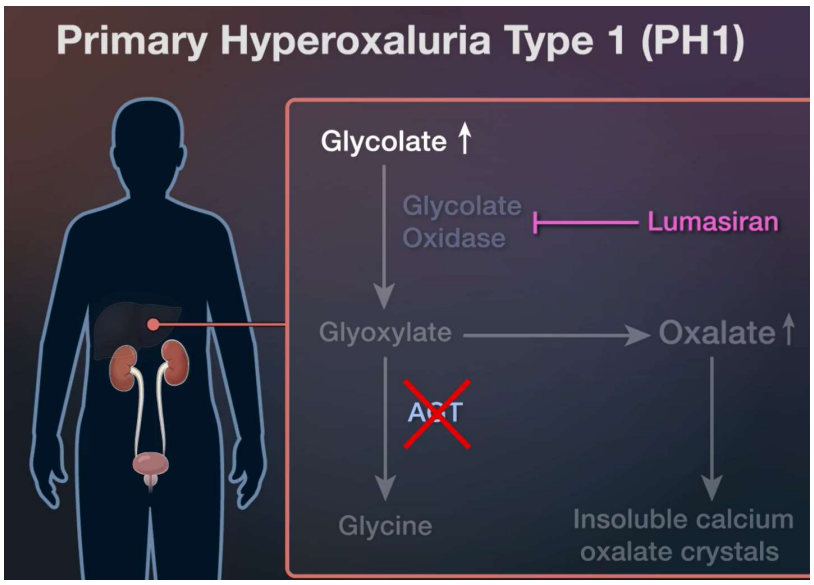

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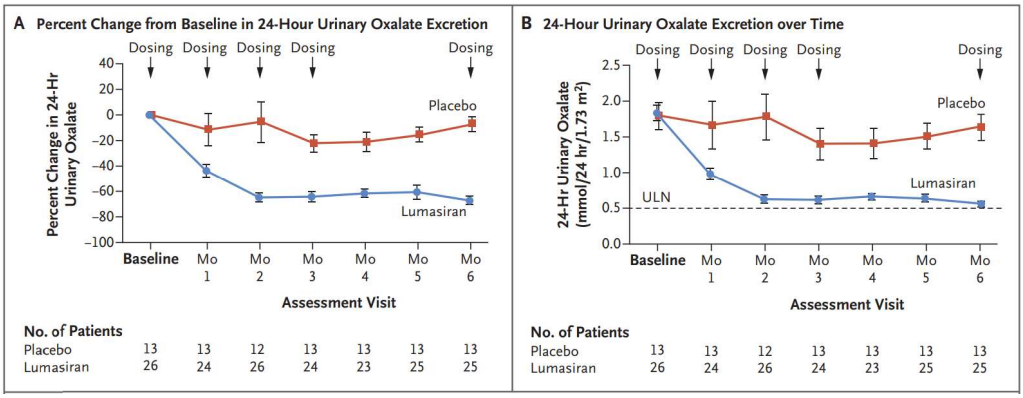
Garrelfs et al, *NEJM* 2021

Lumasiran, an RNAi Therapeutic for Primary Hyperoxaluria Type 1

ILLUMINATE-A: double blind, phase 3 trial, 39 patients with PH1 randomized (2:1) to lumasiran vs placebo
Lumasiran reduced urinary oxalate excretion, the cause of progressive kidney failure in PH1



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Garrelfs et al, *NEJM* 2021

Primary hyperoxaluria: conclusions

- Rare cause of urolithiasis, CKD and kidney failure
- Mostly in children and young adults
- Late-onset PH1 (adults): p.Gly170Arg variant in *AGXT*
- Most important: raise the hypothesis (urolithiasis + CKDu or kidney failure)
- Quantify oxaluria and perform genetic testing
- Novel promising treatments (RNA interference) available soon!

Clinical Phenotype of Inherited Kidney Diseases

- Three different diseases – three phenotypes
  - Atypical HUS - vascular phenotype/TMA
  - Hereditary podocytopathies - glomerular phenotype/proteinuria
  - Primary hyperoxaluria - crystallopathy
- Differential diagnosis is broad for each of these diseases – thorough, systematic workup is required, incl. genetic testing
- Importance of the interactions between clinical nephrologists and expert geneticists
- Genetic testing has huge implications for the management and outcomes of patients with kidney diseases