Practical approach

HUS & proteinuria

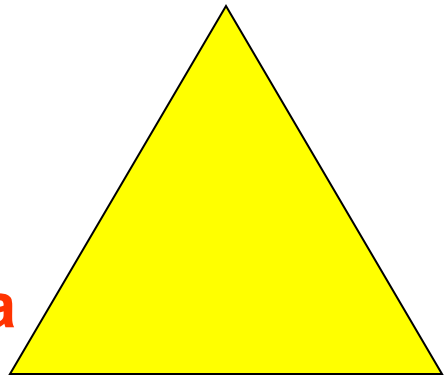
Maher Abdel-Hafez
Prof. and Head of Pediatric Nephrology
Tanta University

2023

HUS definition

Microangiopathic Hemolytic Anemia

Hb < 10 g/dl with
Reticulocytosis &
Schistocytes
Elevated LDH level
Decreased haptoglobin level



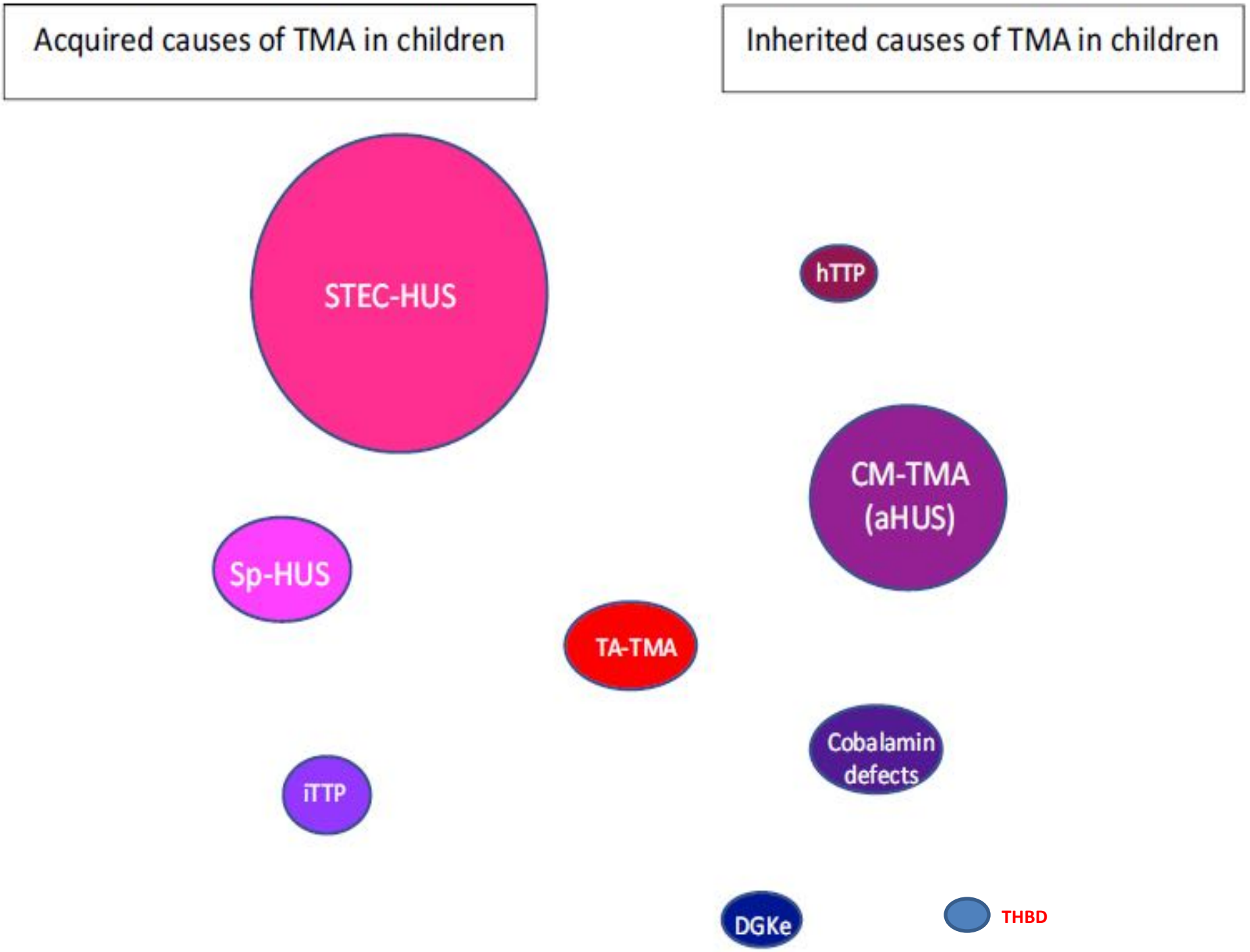
Thrombocytopenia

Platelet count <150,000/mm^3
or
> 25% decrease from baseline

Renal Impairment

GFR < 80 ml/min/1.73m^2

.


Acquired causes of TMA in children
Inherited causes of TMA in children
STEC-HUS
hTTP
CM-TMA
(aHUS)
Sp-HUS
TA-TMA
Cobalamin
defects
iTTP
DGKe
THBD

Clinical and laboratory findings that make STEC-HUS less likely

– Persistent thrombocytopenia beyond the first week
– Relapsing pattern of TMA after resolution of initial manifestation
– Kidney injury that persists for more than 4 to 6 weeks
– Absence of diarrhea and/or negative shigatoxin test
– Persistently low C3
- Persistent proteinuria

Proteinuria in HUS

1- Rare mutations that present by proteinuria

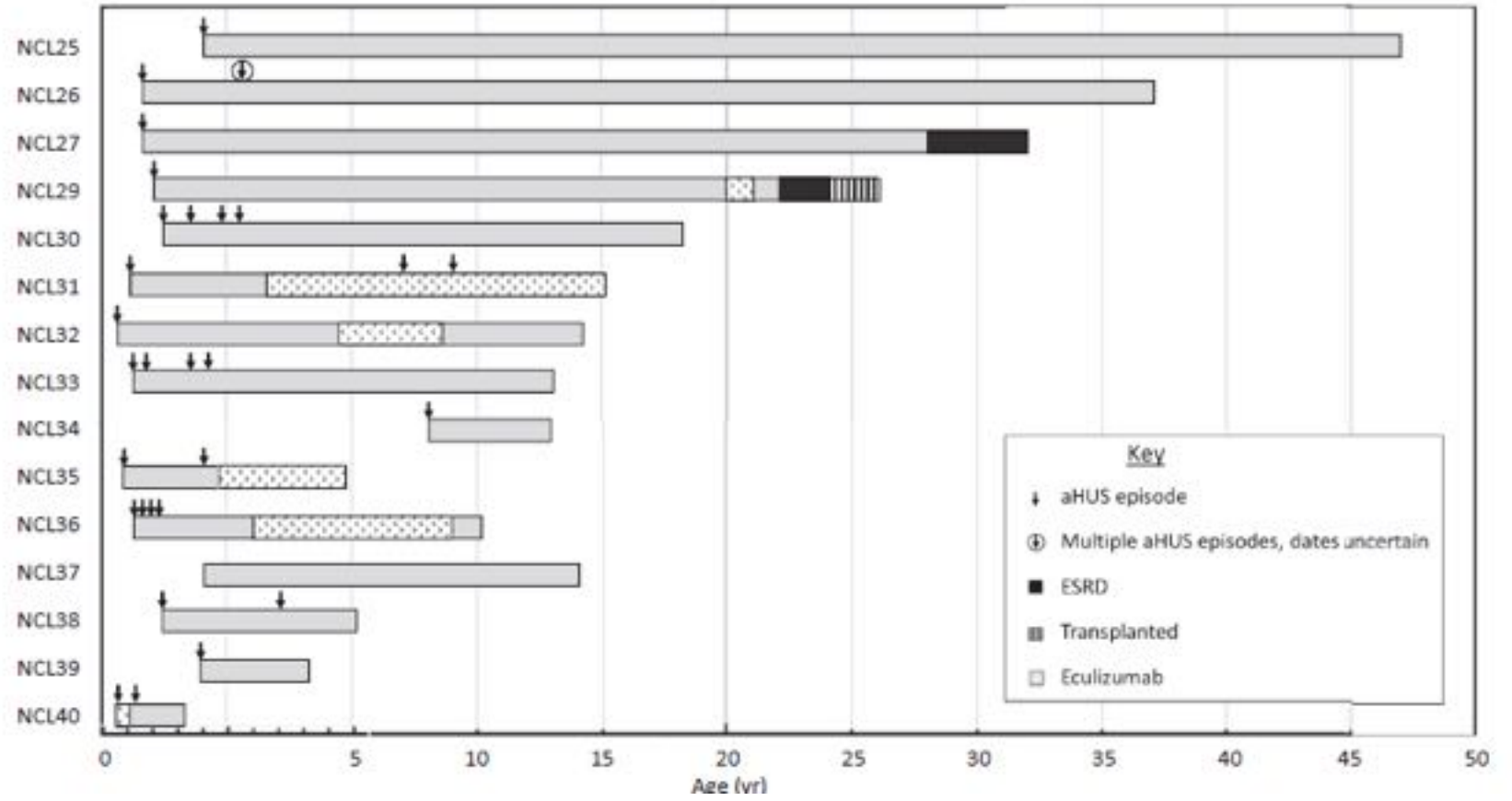
2- Glomerulopathy due to alteration of complement system

3- Sequelae of HUS

Diacylglycerol kinase epsilon nephropathy

- In 2013 recessive mutations in DGKE, which encodes (DGKE), were first reported to cause atypical hemolytic uremic syndrome (aHUS) and nephrotic syndrome, with (MPGN)
- The pathophysiological mechanisms remain poorly understood.
- the incidence of DGKE aHUS as 0.009/million/year
- DGKE MPGN as 0.006/million/year
- combined incidence of 0.015/million/year.
- DGKE-mediated aHUS is eculizumab non-responsive

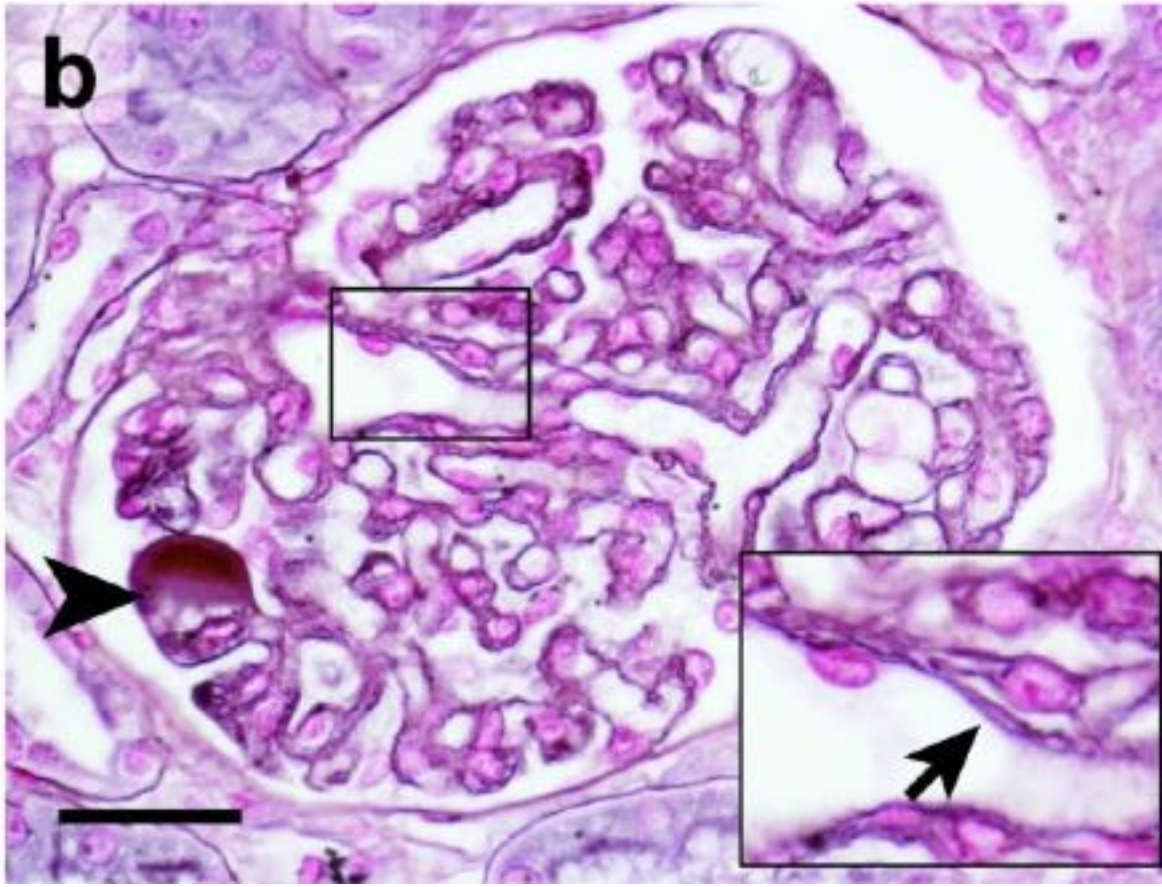
DGKE mutation: Age at presentation and clinical course



V Brocklebank et al Kidney International (2020)

Biopsy of DGKE patient

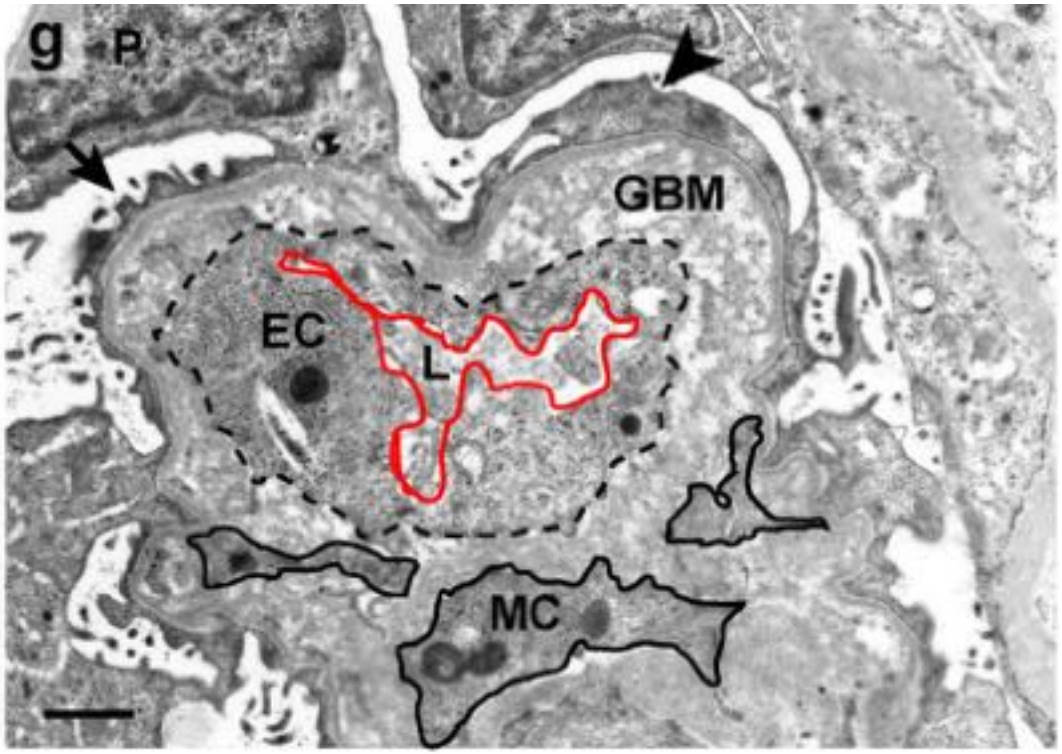
Glomerulus shows split GBM with debris accumulation in subendothelial space, and a dilated capillary filled with fibrinous material (arrowhead), consistent with a small thrombus (Jones' stain).



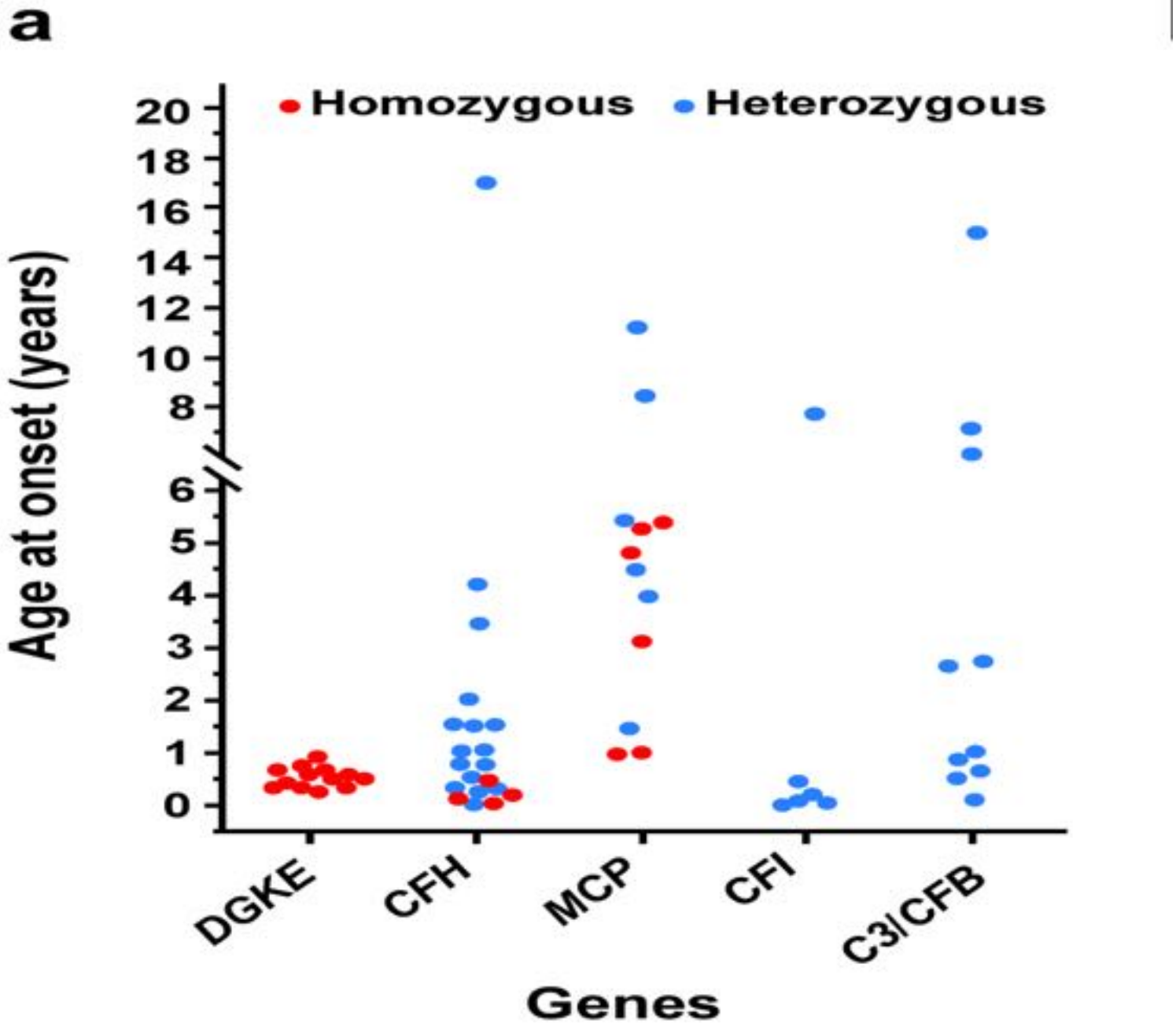
Lemaire et al. PMC 2013

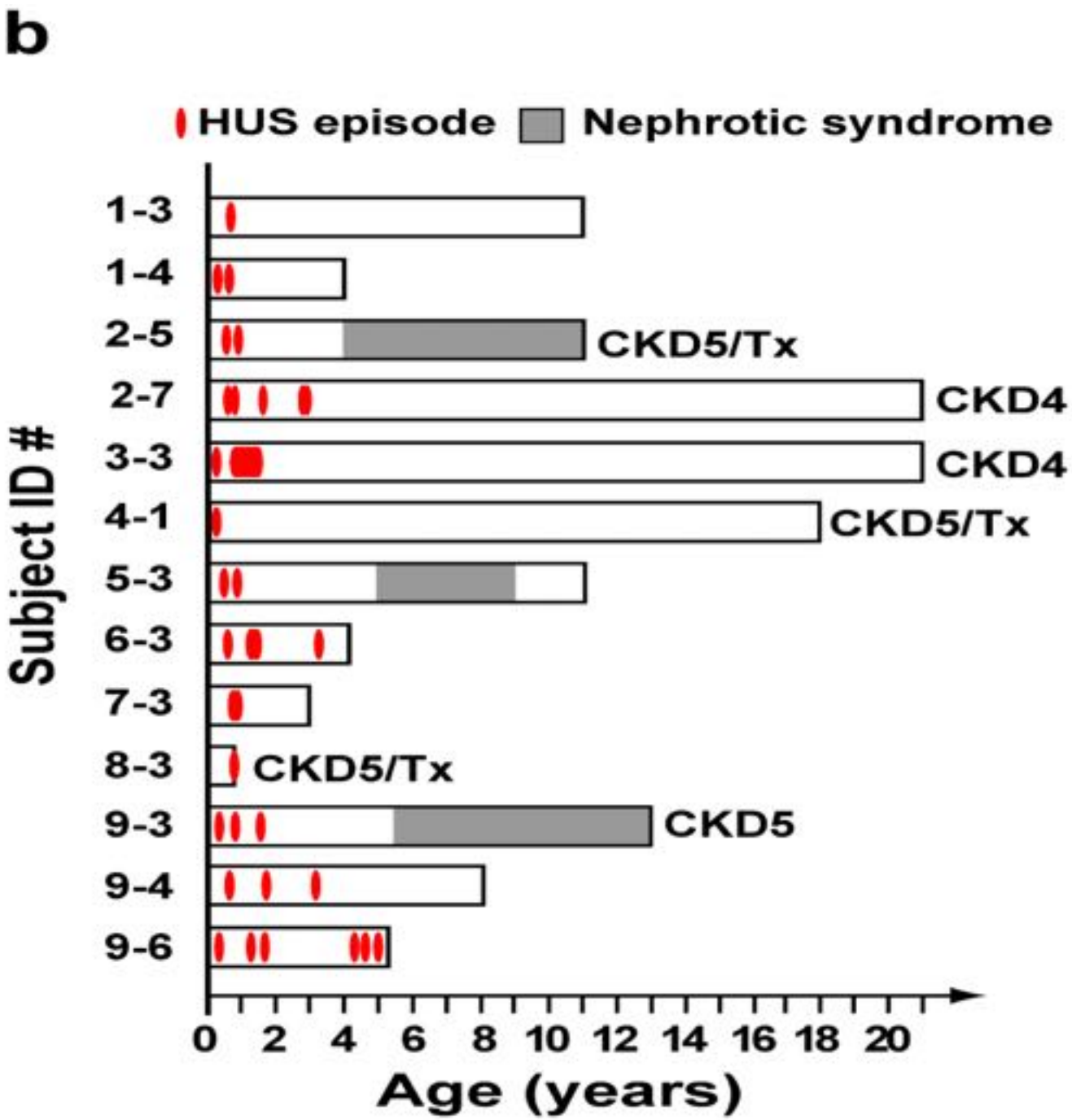
Electron micrograph

Narrow capillary lumen (L, red line) caused by GBM inner lamina rara expansion (devoid of electron-dense deposits) and hypertrophy of EC (black dotted line). There are also podocytes (P) with normal (arrow) or effaced (arrowhead) foot processes. Mesangial cell (MC; black line) processes are observed between EC and GBM, consistent with MC interposition (Lead citrate and uranyl acetate).



Lemaire et al. PMC 2013


a
Homozygous
Heterozygous
Age at onset (years)
20
18
16
14
12
10
8
6
5
4
3
2
1
0
DGKE
CFH
MCP
CFI
C3/CFB
Genes


b
HUS episode
Nephrotic syndrome
Subject ID #
1-3
1-4
2-5
CKD5/Tx
2-7
CKD4
3-3
CKD4
4-1
CKD5/Tx
5-3
6-3
7-3
8-3
CKD5/Tx
9-3
CKD5
9-4
9-6
0 2 4 6 8 10 12 14 16 18 20
Age (years)

c

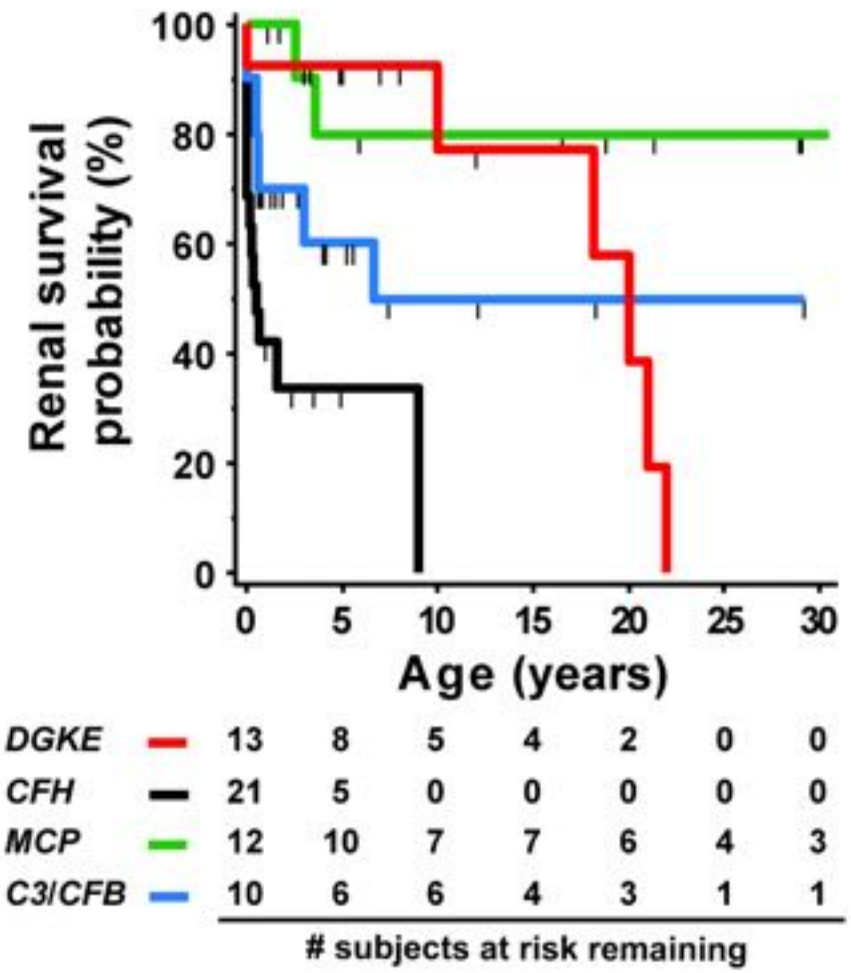
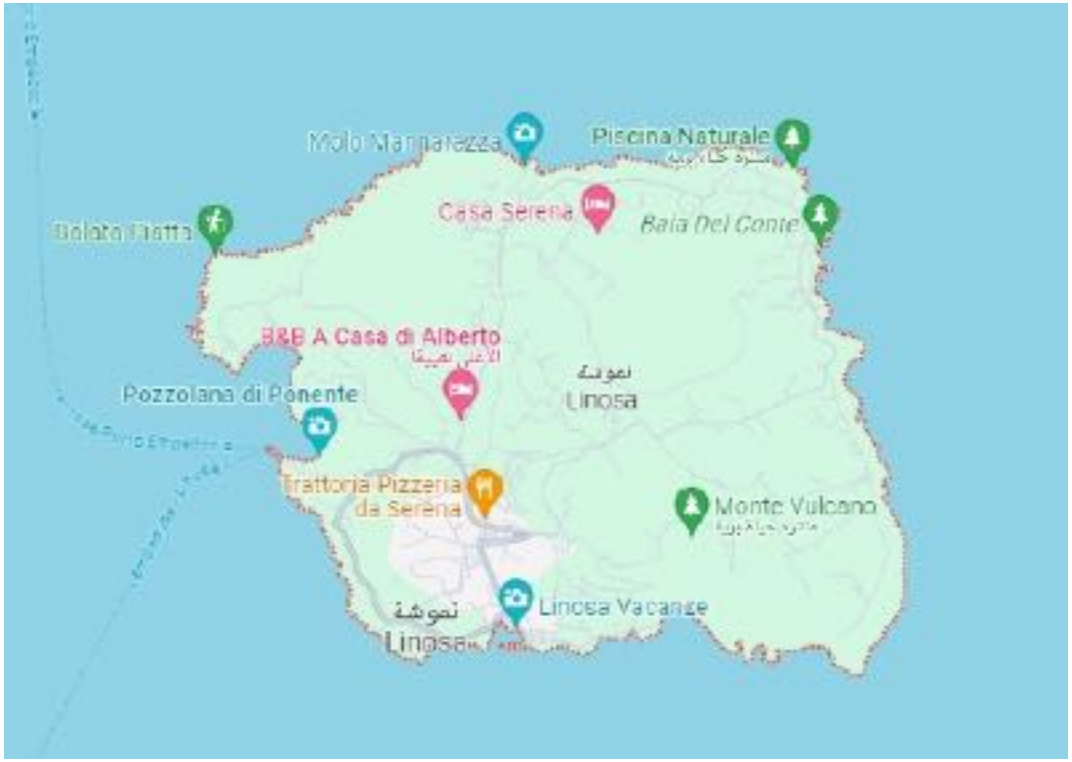

Renal survival probability (%)
100
80
60
40
20
0
0
5
10
15
20
25
30
Age (years)
DGKE 13 8 5 4 2 0 0
CFH 21 5 0 0 0 0 0
MCP 12 10 7 7 6 4 3
C3/CFB 10 6 6 4 3 1 1
subjects at risk remaining

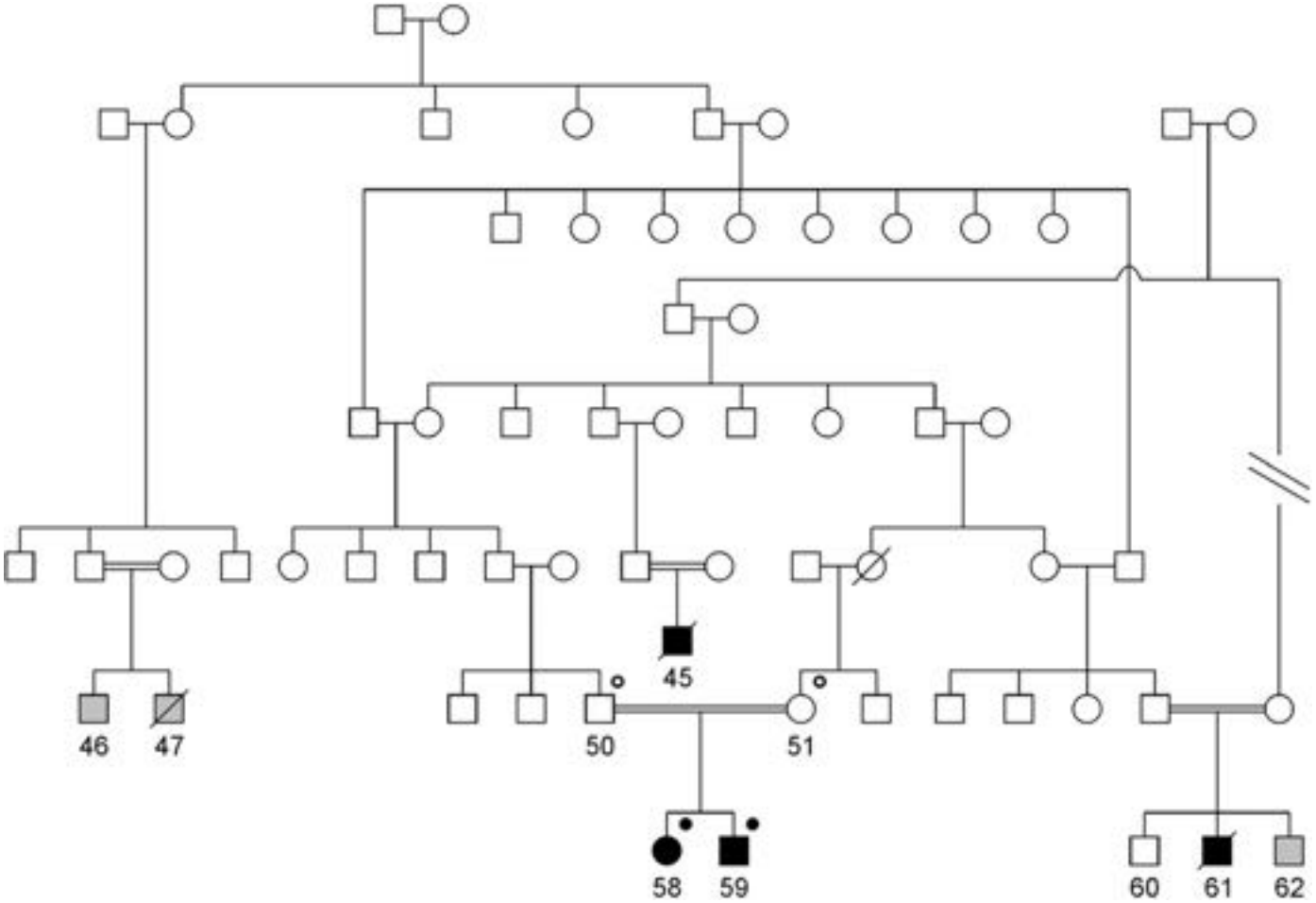
TABLE 1 Clinical characteristics of the aHUS patient with *DGKE* variant.

Characteristics	Laboratory value	Reference value	Unit
Hemoglobin	62	120–140	g/L
MCV	86	80–100	fL
Reticulocyte count	9.3	0.5–1.5	%
Schistocytes count	3	0	%
Platelet count	23	100–300	$\times 10^9$/L
SCr	0.62	0.20–0.40	mg/dl
BUN	5.66	2.9–8.2	mmol/L
Cystine	1.57	0.59–1.03	mg/L
C3	0.89	0.7–1.4	g/L
C4	0.21	0.1–0.4	g/L
LDH	585.1	172–382	U/L
Hematuria	4,627.9	0–4.5	/μl
Proteinuria	+++	− or ±	–
PT	36.2	11–14	s
APTT	58.6	28–45	s
Fibrinogen	4.26	2–4	g/L

APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; C3, serum complement C3 level; C4, serum complement C4 level; LDH, lactate dehydrogenase; MCV, mean corpuscular volume; PT, prothrombin time; SCr, serum creatinine.


Molo Marinaretta
Piscina Naturale
Casa Serena
Baia Del Conte
B&B A Casa di Alberto
Pozzolana di Ponente
Linosa
Trattoria Pizzeria
da Serena
Monte Vulcano
Linosa Vacanze
Linosa


Napoli
Cagliari
Palermo
Malta
Tunis
Izmir
Antalya



J Am Soc Nephrol 25: 1408–1414, 2014

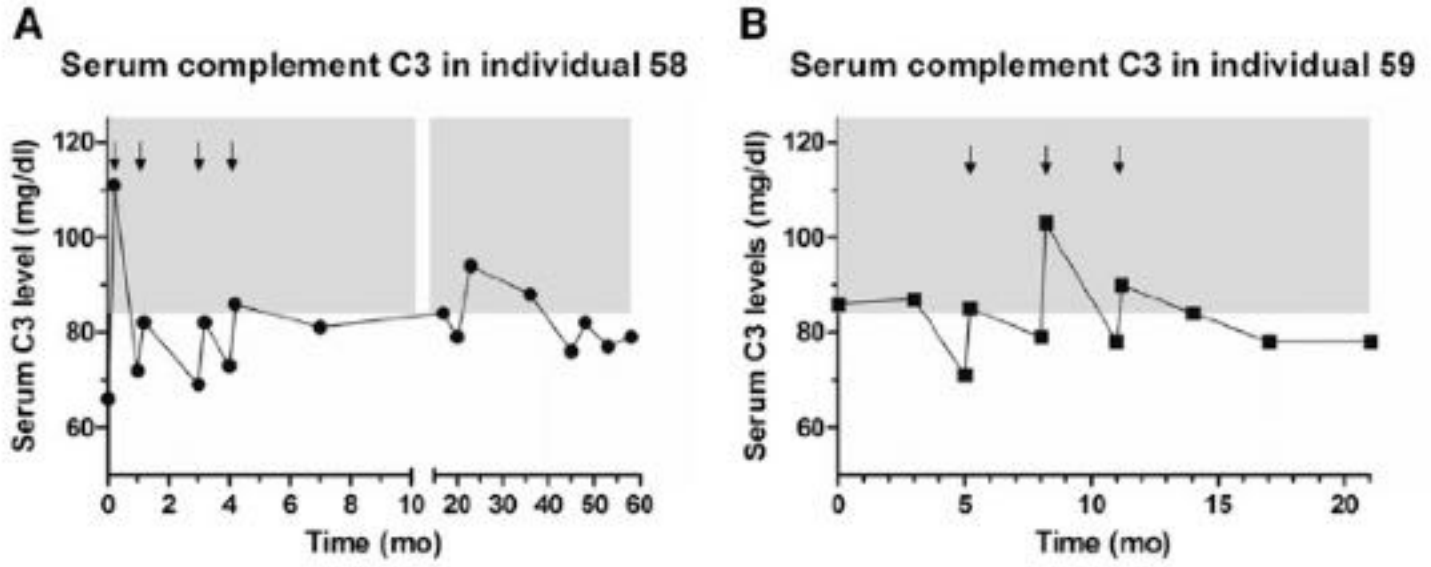
Table 1. Clinical characteristics of individuals 58 and 59 at presentation and last follow-up

	Individual 58 (Girl)		Individual 59 (Boy)	
	Presentation	Last Follow-Up	Presentation	Last Follow-Up
Age (yr)	0.8	5.3	0.7	3.4
SCr (mg/dl)	1.5	0.29	11.4	0.30
Platelet count ($\times 10^9$/L)	64	279	30	201
LDH (IU/L)	1923	414	2736	551
Haptoglobin	<2	46	<2	<2
C3 (mg/dl)	66	79	86	78
Proteinuria	Yes	Yes	Yes	No
Hematuria	Yes	Yes	Yes	Yes

Reference values for C3: 84–192 mg/dl. Proteinuria is defined as a protein-to-creatinine ratio greater than 0.2 mg/mg on a morning urine sample. Hematuria is defined as greater than 3 red blood cells/high power field on urinalysis. SCr, serum creatinine; LDH, lactic dehydrogenase; C3, serum complement C3 level.

J Am Soc Nephrol 25: 1408–1414, 2014

Longitudinal data on serum complement C3 levels



J Am Soc Nephrol 25: 1408–1414, 2014

- Dgke-null mice did not show overt renal disease or a thrombotic phenotype

- The mechanism by which mutations in DGKE result in complement activation is unclear.
- A possibility is that the effect of DGKE on protein kinase C activation

Interesting Case

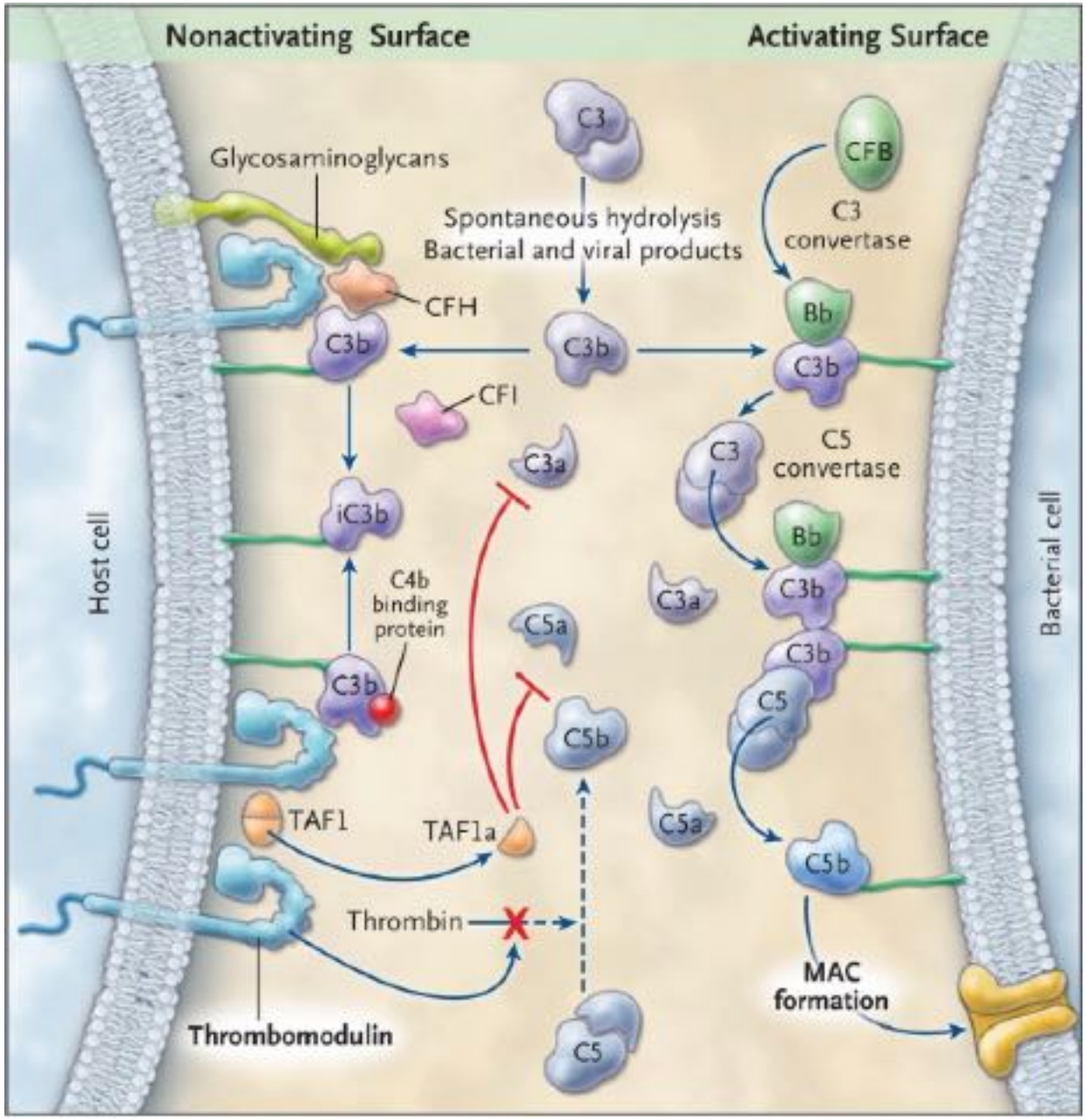
- **A girl aged 13 years and 9 months with no previous morbidity was referred to with a 2-week history of evident periorbital and pretibial edema, myalgia, and fatigue.**
- **Her blood pressure was 130/80 mm Hg, and urine dipstick testing showed pro-teinuria +++ and microhematuria ++.**
- **serum creatinine at 1.04 mg/dl, hemoglobin at 10.1 g/dl, and a normal platelet count. Serum electrolytes, albumin, and the lipid panel were within the normal range. Urine analysis showed proteinuria up to 2 g/24 h**
- **Renal ultrasound was unremarkable. The complement system components C3 and C4, hemolysis indices, antinuclear and antineutrophil cytoplasmic antibodies, prothrombin time, and acti-vated partial thromboplastin time were normal.**

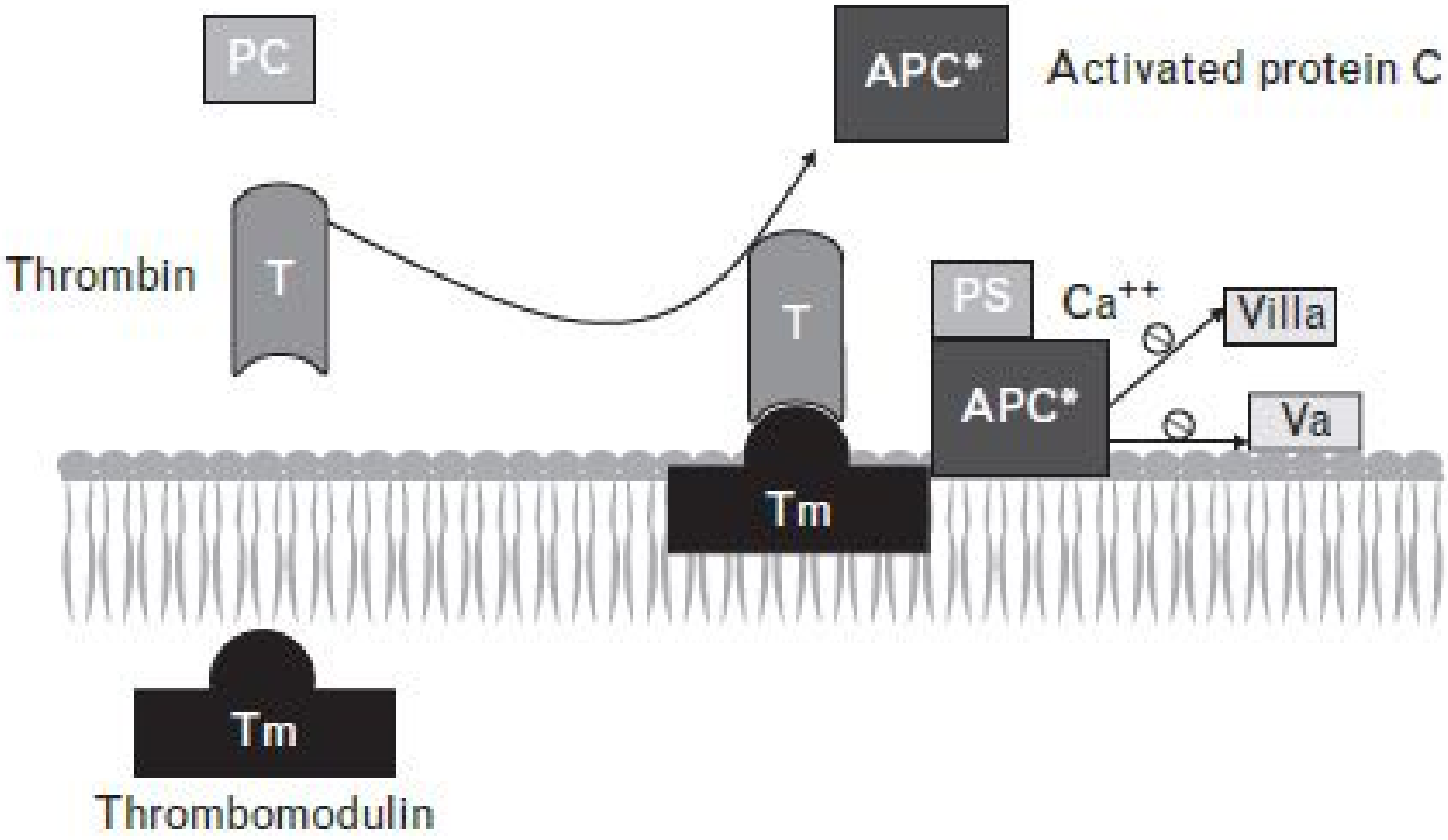
S. Karger AG, Basel 2016

- **Renal biopsy: Thrombotic microangiopathy (TMA).**
- **Normality of ADAMTS13**
- **Molecular analysis of the THBD gene, coding for thrombomodulin, showed a rare heterozygous missense mutation**

One year after disease onset

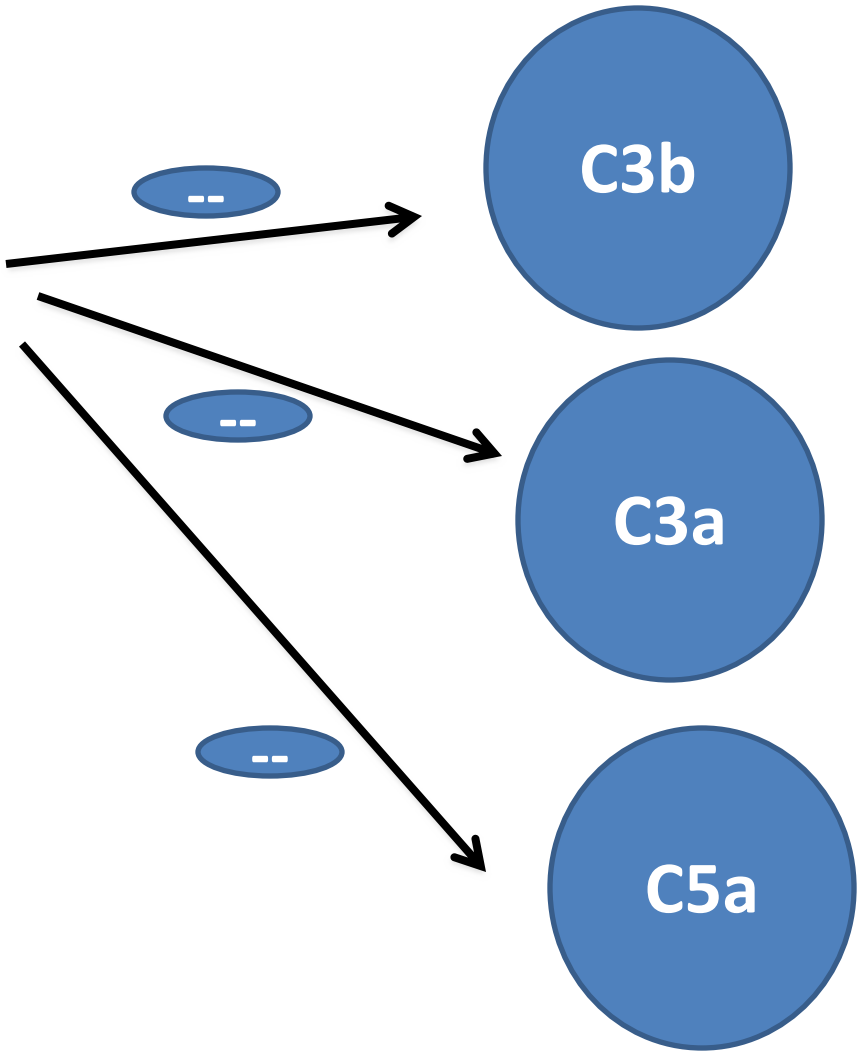
- **The patient presented severe microangiopathic hemolytic anemia [hemoglobin 7.2 g/dl, unconjugated bilirubinemia 1.62 mg/dl, lactate dehydrogenase (LDH) mildly increased to 500 U/l, haptoglobin <1 mg/dl, and reticulocytes 11%]**


Nonactivating Surface
Activating Surface
C3
CFB
Glycosaminoglycans
Spontaneous hydrolysis
Bacterial and viral products
C3
convertase
CFH
Bb
C3b
C3b
C3b
CFI
C3a
C3
C5
convertase
iC3b
Host cell
Bacterial cell
Bb
C4b
binding
protein
C3a
C3b
C5a
C3b
C3b
C5
C5b
TAF1
TAF1a
C5a
C5b
Thrombin
MAC
formation
Thrombomodulin
C5



The protein C pathway. PS, protein S.

- **Thrombomodulin**



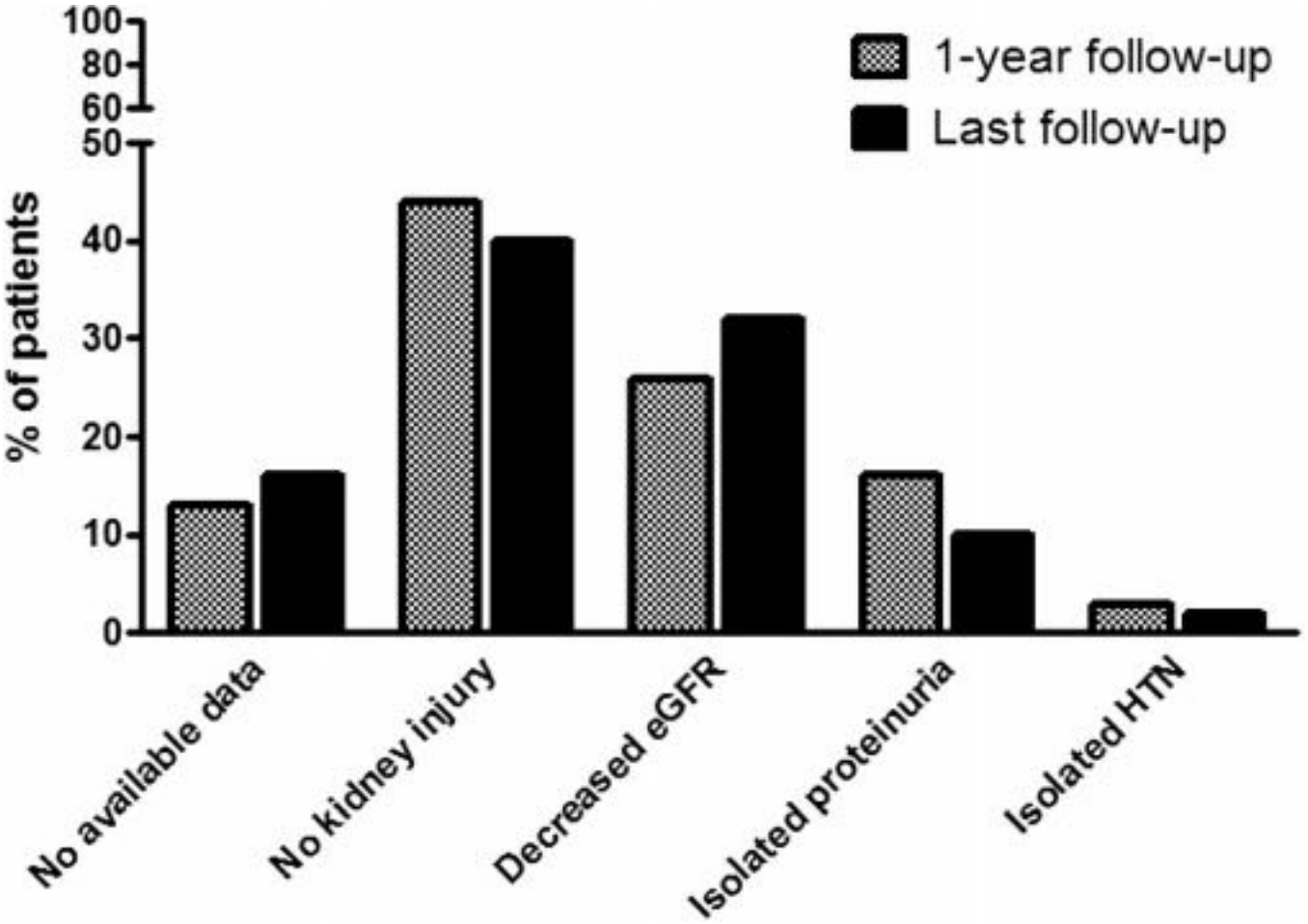
2-Glomerulopathy due to alteration of complement system

Phynotypes of complement dysregulation

a HUS	MPGN
2 children with CFH deficiency and aHUS have been reported to develop C3G after kidney transplantation.	a homozygous mutation in CFH associated with undetectable circulating CFH levels has been documented in a patient who first developed C3G and later aHUS
TMA	Hematuria + Proteinuria
Respond to Eculizumab	poor response to Eculizumab
Low to normal C3	Persistent low C3
Anti-CFH autoantibodies the autoantibodies bind the CFH carboxy-terminal surface recognition domain	Anti-CFH autoantibodies the autoantibodies bind to the amino-terminal complement regulatory domain of CFH
surface-restricted complement dysregulation	fluid – restricted complement dysregulation

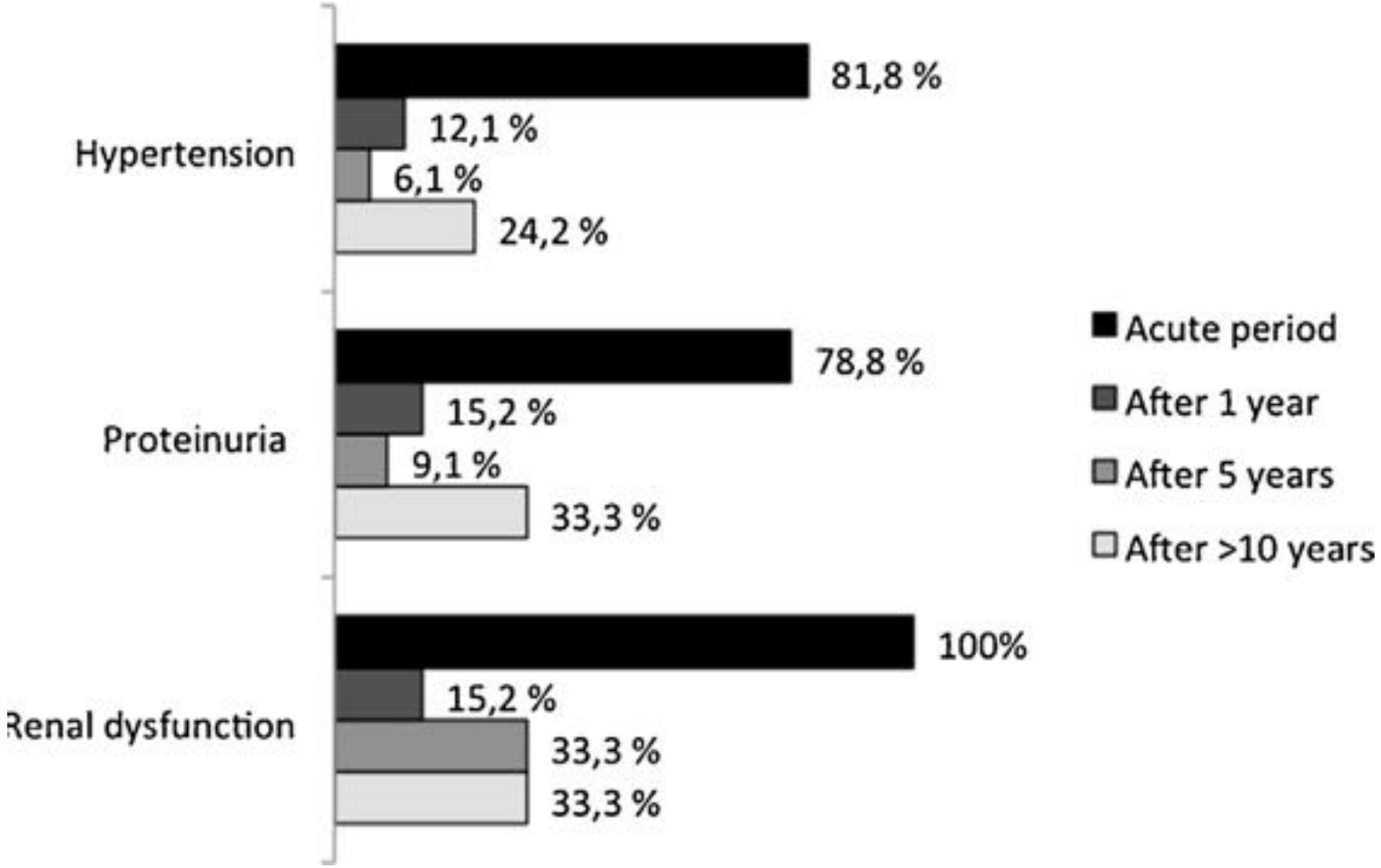
Proteinuria as a Sequelae of HUS

STEC-HUS: kidney outcome at 1-year and at long-term follow-up



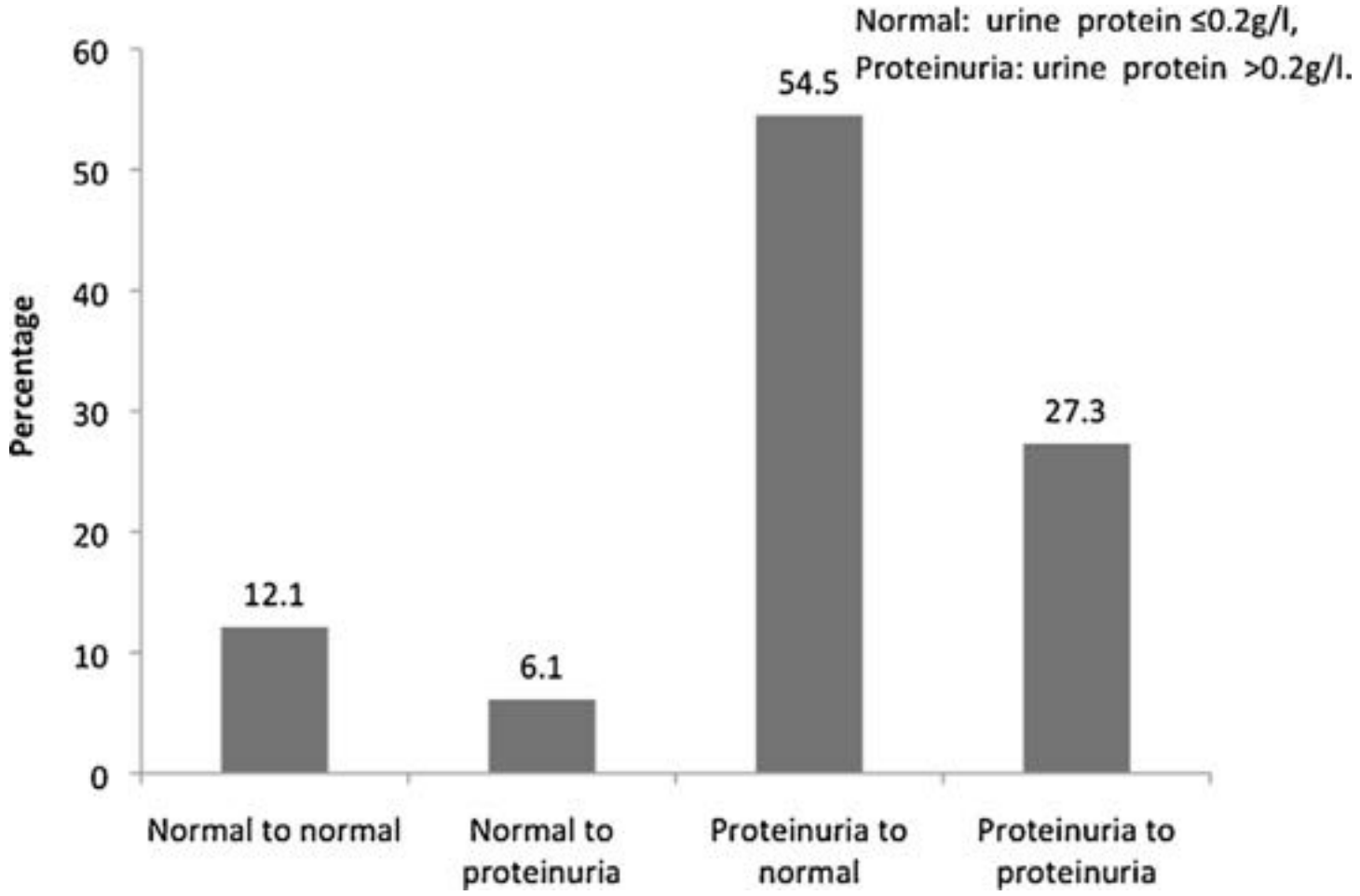
Monet-Didailler C et-al Pediatr Nephrol (2019) 34:657–662

Dynamics of residual symptoms of HUS in group of children after 10-year follow-up (n = 33).



Pundzienė B et-al, M e d i c i n a 5 1 (2 0 1 5) 1 4 6 – 1 5 1

Changes of proteinuria at 10-year follow-up after onset (n = 33).



Pundzienė B et-al, M e d i c i n a 5 1 (2 0 1 5) 1 4 6 – 1 5 1

THANK YOU

FOR YOUR EXTRA ATTENTION