FACULTY OF MEDICINE AND HEALTH SCIENCES

AN UNUSUAL GENETIC DIAGNOSIS IN A CHILD PRESENTING WITH END-STAGE KIDNEY DISEASE

Snauwaert Evelien, Dehoorne Joke, Dendooven Amélie, Dossche Lien, Prytula Agnieszka, Raes Ann, Van Damme Tim, en Vande Walle Johan

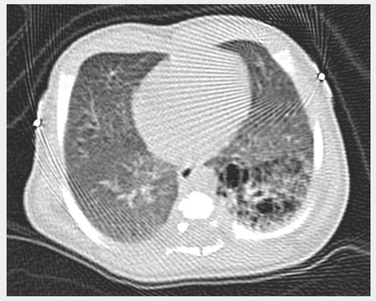
DEPARTMENT OF PEDIATRIC NEPHROLOGY GHENT

11 years

Short stature (SD -2,0)

Prenataly diagnosed congenital cystic adenomatoid malformation for which left lower lobe lobectomy (at age of 1)

Development coordination disorder



Vomiting, fatigue and pale appearance

Malignant hypertension

Oliguria

Pediatric intensive care

PROBLEMLIST @ PRESENTATION

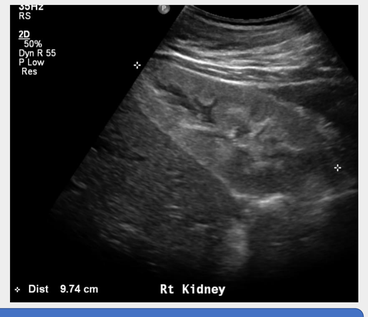
End-stage kidney disease with signs of chronicity

Serum creatinine	Serum urea	Serum PTH	Hemoglobin	Reticulocytes (relative)	Urine Red blood cells	Urine protein
11,93 mg/dL	302 mg/dL	273 ng/L	8,5 g/dL	11.80 /1000	58/µL	11 g/g creatinine

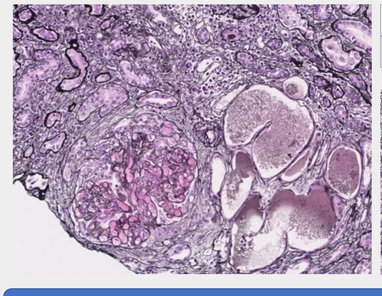
Renal US: two normal sized kidneys (50th percentile) with hyperechogenic cortex bilaterally and no hydronephrosis.

Kidney biopsy: significant signs of chronicity (IFTA 9) with thrombotic micro-angiopathy, without arguments for immune complex etiology.

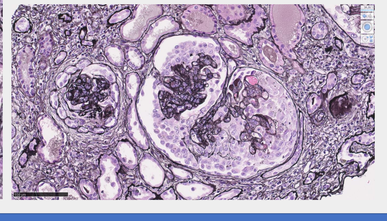
Course: No recovery of kidney function occurred, and patient was transferred to chronic dialysis, initial peritoneal dialysis, subsequently to intensive nocturnal hemodialysis



Thrombotic micro-angiopathy



Hemoglobin	Haptoglobin	LDH	Trombocytes	Coombs	ADMAST-13	Verotoxin	C3 level
8,5 g/dL	<0.09 g/L	745 U/L	146,000/µL	negative	88 IU/dL	negative	0,9 g/L



Genetic analysis of *ADAMST-13*, *C3*, *C5*, *CD46*, *CFH*, *CFHR5*, *CFI*, *DGKE*, *MMACHC*, *PLG*, *THBD* genes and MLPA-analysis of *CFH*, *CFHR1-5* came back negative.

Signs of thrombotic micro-angiopathy resolved after correction of blood pressure.

Hypertension

At 8 years: one blood pressure registered >p99

At presentation:

Left ventricle hypertrophy on echocardiography

Bilateral cotton wool spots on eye exam

During dialysis: Hypertension remained difficult to treat, even in extended hemodialysis schedule with good dry weight control she remained dependent on triple antihypertensive therapy

age	1 month	1 year	2 years	11 years
Serum creatinine (mg/dL)	0,33	0,33	0,23	11,93
Serum potassium (mmoL/L)	5,30	4,30	4,50	4,20
Serum chloride (mmol/L)	105,00	105,00	103,00	106,00
Serum bicarbonate (mmoL/L)			25,30	15,60
Serum renine (pg/mL)				4,40
Serum aldosteron (ng/dL)				5,20

DIAGNOSIS

Genetic analysis (panel) revealed a novel *de novo* heterozygous (class 5) mutation in Cullin 3 (*CUL3*) (exon 9; c.1349del,p.(Ser450LeufsTer5)), diagnostic for **pseudohypoaldosteronism type IIe**.

→ Gordon syndrome due to de novo *CUL3* mutation

Gordon syndrome is a rare inherited disease characterized by **hypertension**, **hyperkalemia**, **hyperchloremic metabolic acidosis**, normal glomerular filtration rate, and **sensitivity to thiazide diuretics.** The mutations in *CUL3* cause the most severe Gordon Syndrome phenotype, with early onset of severe hypertension in childhood. All mutations in *CUL3* described are distributed in sites involved in splicing of exon 9.

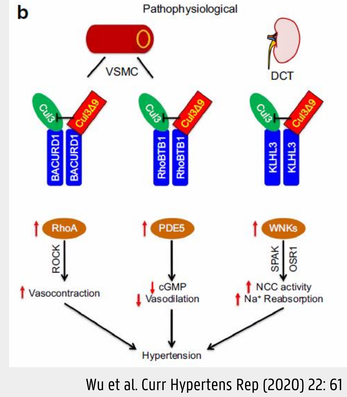
Cullin 3 (*CUL3*) is part of the **ubiquitin proteasomal system** and controls several cellular processes critical for normal organ function including the cell cycle, and Keap1/Nrf2 signaling.

Mutations in *CUL3* cause hypertension by

- impairing the ability of *CUL3* to degrade WNK kinases, leading to **increased activity of the renal sodium chloride co-transporter**.
- impairing vascular smooth muscle function

Adult mice with an induced tubule-specific *CUL3* deletion presented with sustained proximal tubule injury, followed by interstitial inflammation, progressive fibrotic renal disease and death.

While previously published patients with a *CUL3* mutation have normal kidney function, this case presented with a **severely impacted kidney function**. The involvement of CUL3 in kidney injury and fibrosis might – next to malignant hypertension related TMA – also explain the severity of renal impairment in our patient and needs to be addressed in future research.



Wu et al. Curr Hypertens Rep (2020) 22: 61

GHENT UNIVERSITY

UZ GENT

Contact Evelien Snauwaert, M.D., PhD

evelien.snauwaert@uzgent.be

orcid.org/0000-0003-2660-7460

www.linkedin.com/in/esnauwaert

@esnauwae