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ERKNet/ERA Educational Webinars on
Pediatric Nephrology & Rare Kidney Diseases

WEBINAR

07/03/2023

APRT deficiency: an undiagnosed cause of renal failure

Speaker: Aude Servais (Paris, France)

Moderator: Tom Nijenhuis (Nijemegen, Netherlands)

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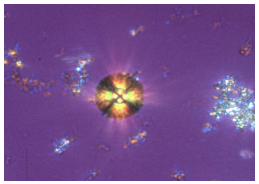

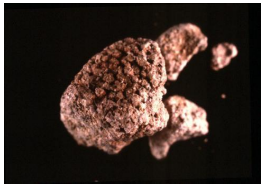

APRT deficiency: an underdiagnosed cause of renal failure

A Servais

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Reference Center for Rare Hereditary Kidney Diseases (MARHEA)

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Hereditary Nephrolithiasis

- 2% of adult stones
- 10%-20% of children stones
- Often overlooked
- Carry a high burden of :
  - stone recurrence
  - CKD , potentially leading to ESRD
- Awarness of nephrologists could decrease delay to diagnosis and improve outcome

Case

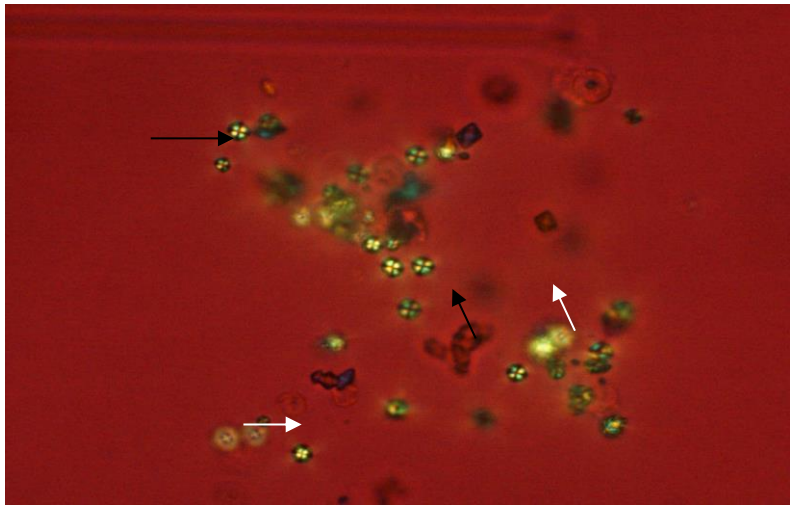
- Male pt
- 1st nephrology consult for CKD at 52 yrs
- Past history of stone disease:
  - Starting at 32 yrs
  - 3 extracorporeal shock wave lithotripsies, 1 lombotomy
  - Radiolucent stones by CT scan
  - No stone analysis
- Biochemistry:
  - Blood: Creatinine 180 µmol/l (eGFR 37 ml/mn); Uric Acid 380 µmol/l; normal ionogram
  - Urines:
    - pH 6.5
    - Uric acid 3,2 mmol/day
    - Normal calciuria, oxaluria

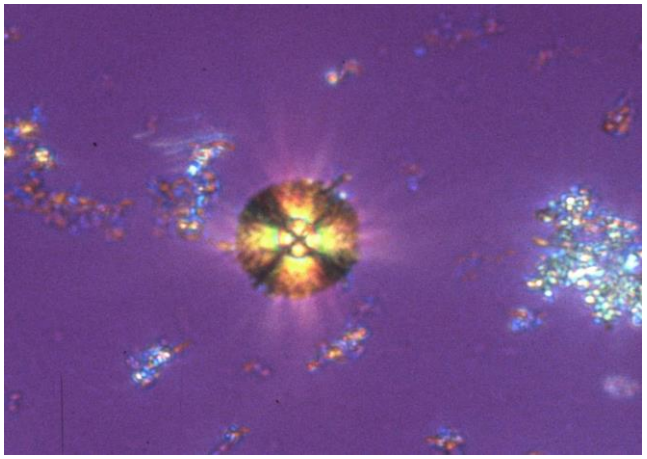
How to make the Diagnosis?

- Urine density
- Uric acid excretion
- Crystalluria
- Stone analysis
- Renal biopsy

How to make the Diagnosis?

Crystalluria !





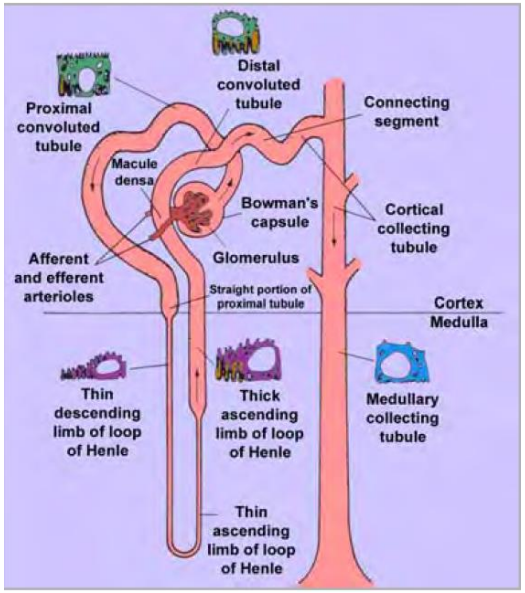
Numerous round and reddish-brown crystals

« Maltese cross » aspect by polarized light

= 2,8 DHA crystals

Main Causes of Hereditary Nephrolithiasis/ Crystalline Nephropathies

- **Inborn errors of Metabolism**
  - Oxalate — Primary Hyperoxaluria
  - Purines
    - Uric Acid — HGPRT deficiency
    - 2,8 DHA — APRT deficiency
    - Xanthine — XO deficiency
  - Pyrimidines
    - Orotic acid — UMP Synthase
  - Ca/Vit D : CYP24A1



- **Renal Tubular Transport Defects**

  Proximal Tubule
  - Dent disease (ClC5, OCRL)
  - Phosphate leakage (NpT2a, NpT2c, NHERF)
  - Hyperuricuria (URAT1, GLUT9)

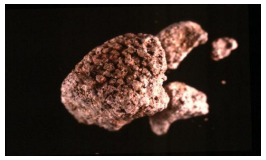
  Henle's Loop

  Bartter Syndrome (NKCC2, ROMK, CClkb)

  Familial Hypomagnesemia (Cld16/19)

  Familial Autosomal Dominant Hypocalcemia (CasR)

  Collecting Duct
  - Distal Renal Tubular Acidosis (H+ATPase, AE1)



PRPP
AMP
IMP
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ADA
APRT
X
adenosine
inosine
HGPRT
PNP
adenine
hypoxanthine
XDH
XDH
Allopurinol
(or Febuxostat)
8-hydroxyadenine
xanthine
XDH
XDH
2,8-dihydroxyadenine
uric acid
2,8-DHA nephrolithiasis
2,8-DHA crystalline nephropathy

Bollée G et al. JASN 2010

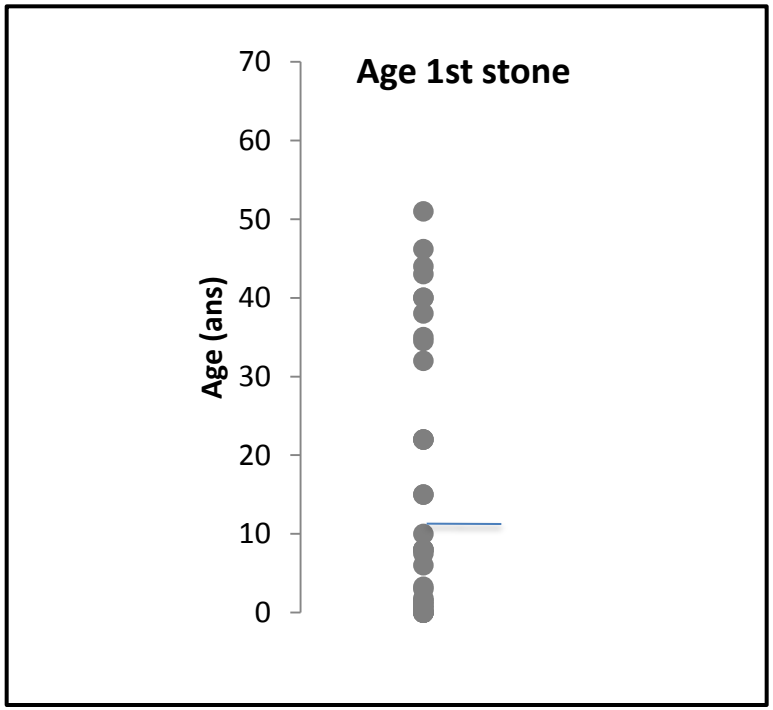
CLINICAL RESEARCH www.jasn.org

Phenotype and Genotype Characterization of Adenine Phosphoribosyltransferase Deficiency

Guillaume Bollée,* Cécile Dollinger,† Lucile Boutaud,† Delphine Guillemot,† Albert Bensman,‡ Jérôme Harambat,§ Patrice Deteix,‖ Michel Daudon,¶ Bertrand Knebelmann,* ** and Irène Ceballos-Picot†

53 cases /43 families
Origin: France and other countries

prevalence :1/50,000-1/100,000
less than 300 reported cases worldwide

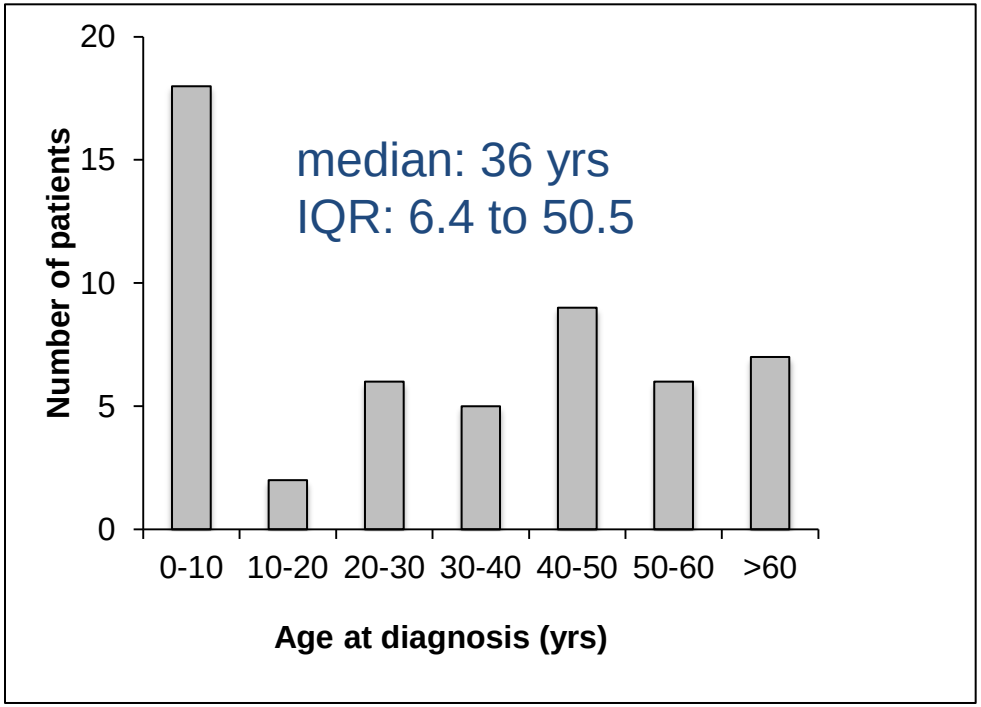


Median age at first stone:
12.5 yrs
IQR 3.1 to 35 yrs

Bollée et al, JASN, 2010

Age at Diagnosis: often delayed !

A



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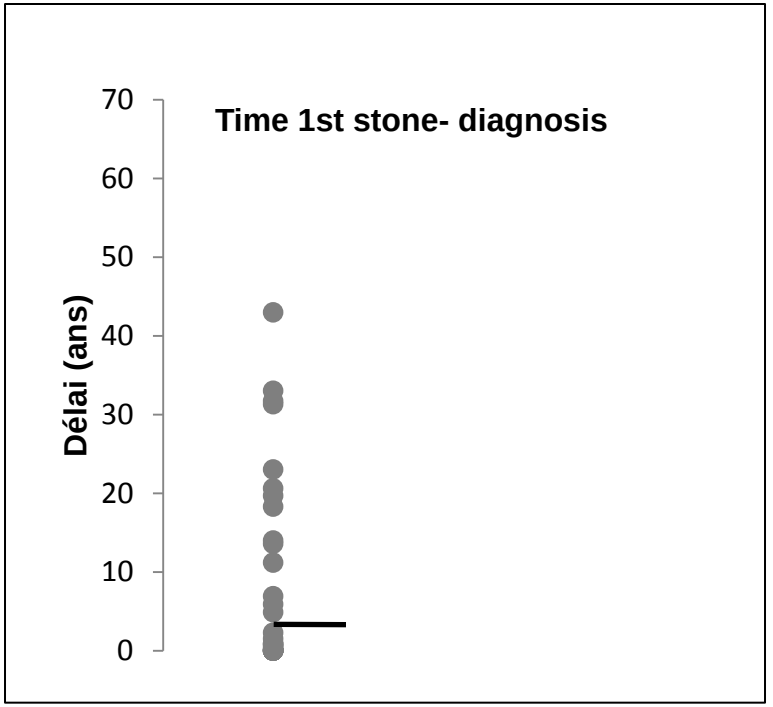


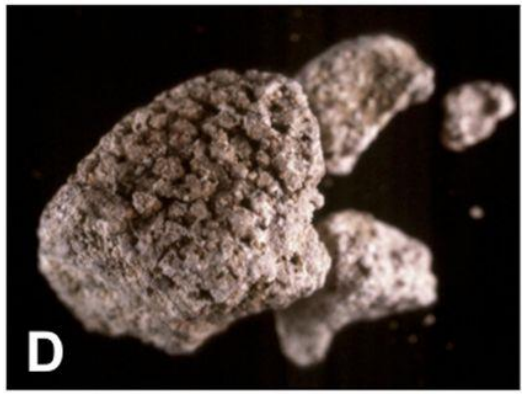
38% before 16 yrs
62% after 16 yrs

Médian 1,5 yrs
IQR: 0 to 17 yrs
extreme = 43 yrs!

Bollée et al, JASN, 2010

Means for Diagnosis

- Stone Analysis 58%
- Crystalluria 28%
- Kidney Biopsy 11%
  - native 4%
  - transplant 6%
- APRT activity 77%
- Asymptomatic 4%

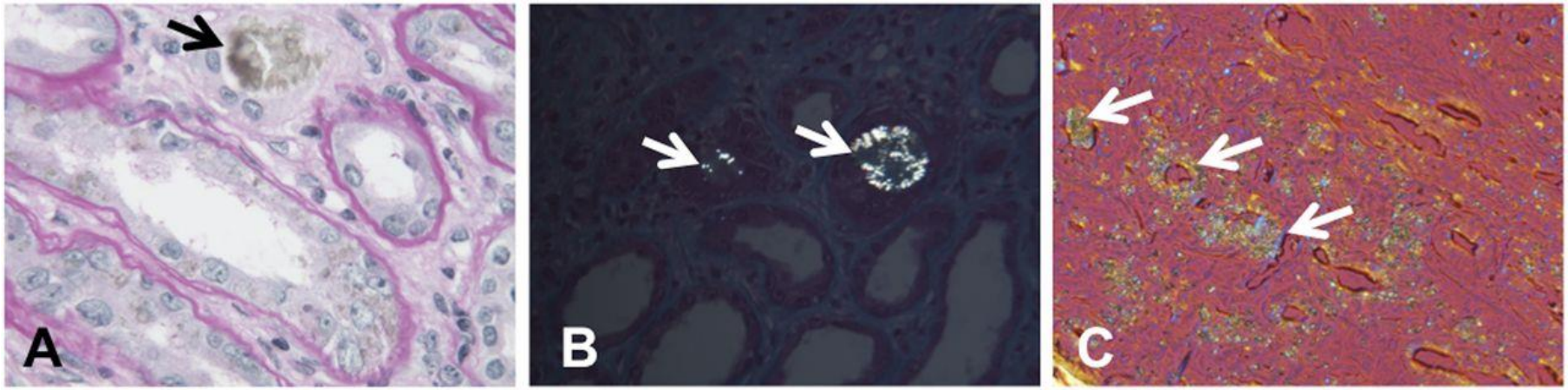


Reddish-brown turning gray when drying and friable stones
Composition confirmed by infrared spectroscopy

Reddish-brown diaper stain = 2,8 DHA crystals

Bollée et al, JASN, 2010

Renal biopsy



64-year-old woman with renal failure who had experienced only one stone episode 33 years earlier

- Tubulointerstitial injury secondary to precipitation of crystals
- Polarized light view allows better visualization of crystals
- Polarized microscopic view shows crystals in renal parenchyma
- Infrared analysis confirmed the DHA nature of crystals

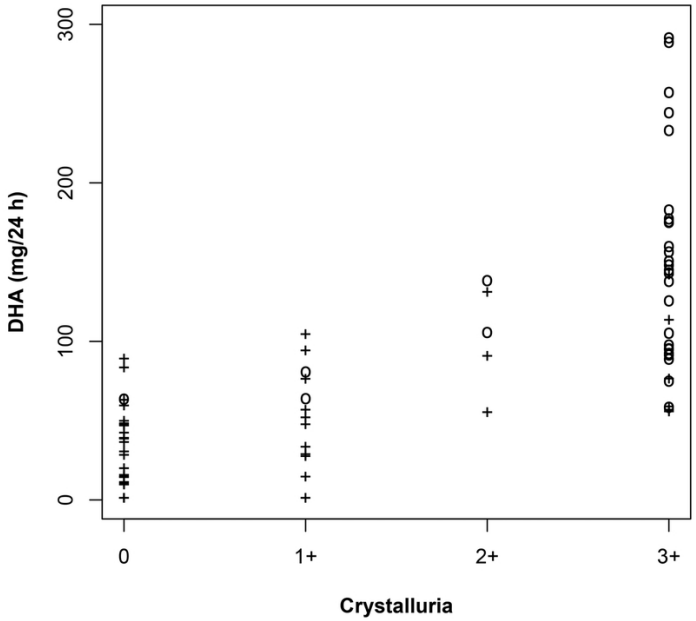
APRT activity

- APRT activity in erythrocytes lysates is not mandatory but is useful when available
- In type I APRT deficiency
  - nearly all cases in non-Japanese patients
  - activity is null in vitro
- In type II
  - APRT activity is usually 15%–30% of normal activity

Urinary 2,8-dihydroxyadenine excretion

- Several methods for quantifying DHA: HPLC coupled to tandem mass spectrometry and a multichannel ultraviolet detector, or capillary electrophoresis

- Ultra-performance liquid chromatography – electrospray tandem mass spectrometry (UPLC-MS/MS) assay for absolute urinary quantification of DHA
  - 100% sensitivity and specificity for the the diagnosis of APRT deficiency in patients who are not receiving treatment
  - urinary DHA not detected in samples from heterozygotes, healthy individuals and many treated patients



Runolfsdottir et al, Mol Genet Metab 2019

Genetics of APRT deficiency

- Autosomal recessive
- *APRT* gene located on chromosome 16q24
- Mutant alleles in type I classified as APRT*Q0
  – encompasses a heterogeneous collection of mutations distributed along the coding sequence
- Type II caused by a single mutant allele with a missense mutation referred to as APRT*J
  – reported exclusively in the Japanese population
- 10% of mutations remain unidentified

Stone Activity

36 pts (90%) had stones

Nb of stone episodes before diagnosis

O	10%
1 - 2	42.5%
3 -5	25%
>5	22.5%

Nb Surgical procedures before diagnosis

0	57,5%
1- 2	30%
3-5	10%
>5	2,5%

Shock waves lithotripsy	30%
Ureteroscopy	12,5%
Percutaneous nephrolithotomy	7,5%
Surgery	12,5%
Nephrectomy	2,5%

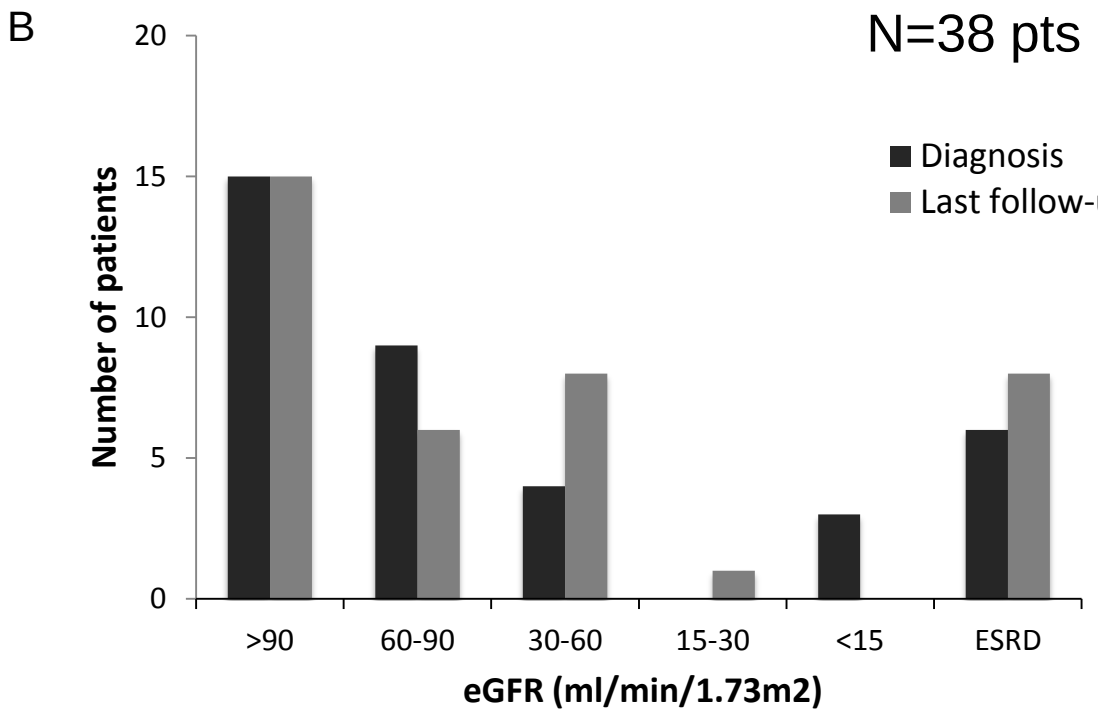
Bollée et al, JASN, 2010

Renal function at diagnosis

AKF	1 pt (2,5%)
CKD	13 pts (32.5%)
ESRD	6 pts (15%)
transplantation	4 pts (10%)
back to dialysis	2 pts (5%)

Bollée et al, JASN, 2010

Renal Function at last follow up

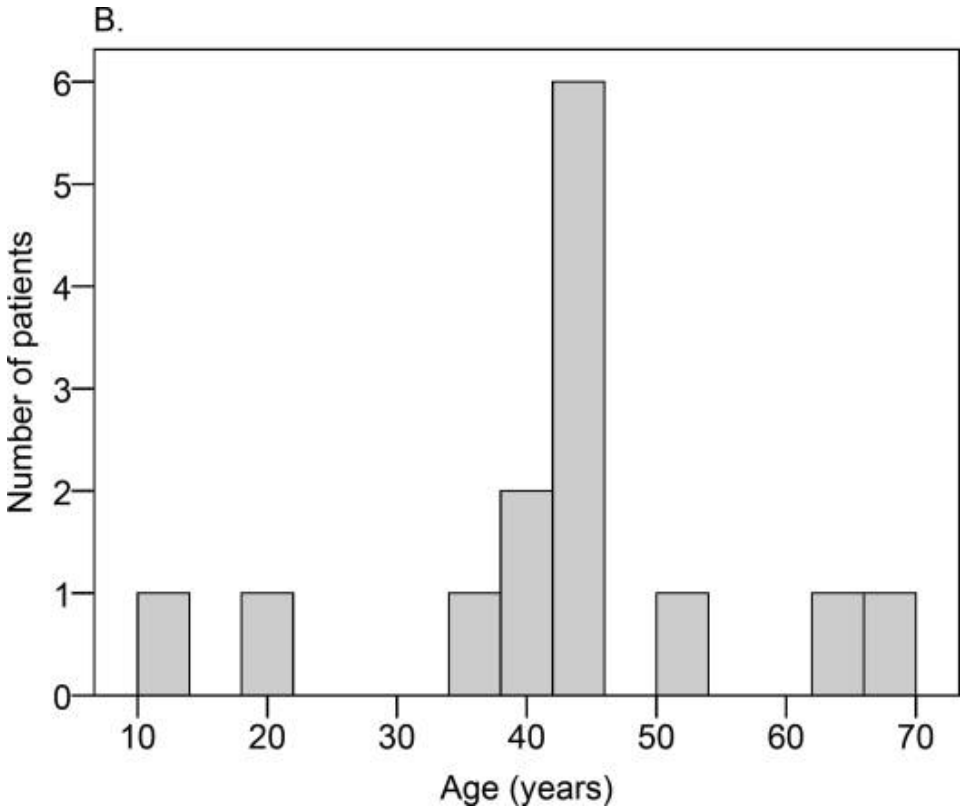


8 pts ESRD (20%)

40% have CKD 3 or more

Bollée et al, JASN, 2010

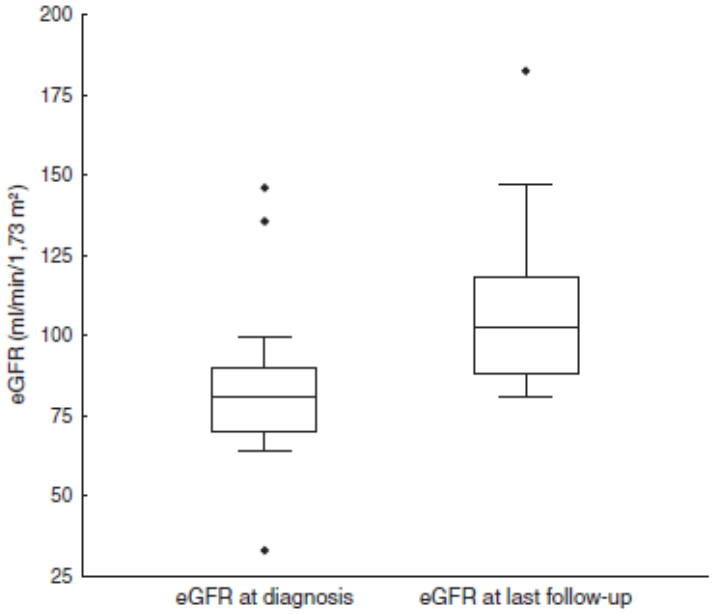
Age at ESRD



14/53 (26%) pts reached ESRD

Runolfsdottir at al, AJKD, 2016

Outcome in children



19 patients with childhood onset APRT deficiency

At latest follow-up, eGFR was 114 (70–163) and 62 (10–103) mL/min/1.73 m2 in patients who initiated treatment as children and adults, respectively.
All 3 patients with CKD stages 3–5 at last follow-up were adults when pharmacotherapy was initiated.

Harambat et al, Pediatr Nephrol, 2012
Runolfsdottir et al, Pediatr Nephrol, 2019

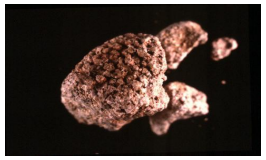
Treatment?

- Hyperdiuresis
- Alcalinisation
- Allopurinol
- Tiopronine
- Febuxostat

Treatment is efficient ….

- Hyperdiuresis
  - > 3l /day
  - Density on morning urines < 1010
- Limit Purines intake
- XO inhibitor: Allopurinol or Febuxostat

Edvardsson et al, Eur J Intern Med, 2018



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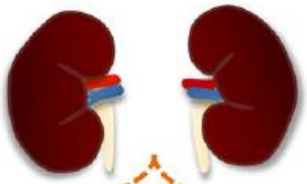
uric acid



2,8-DHA nephrolithiasis
2,8-DHA crystalline nephropathy

Bollée G et al. CJASN 2012

Treatment is efficient ….

- Hyperdiuresis
  - > 3l /dy
  - Density on morning urines < 1010
- Limit Purines intake
- XO inhibitor: Allopurinol or **Febuxostat**
  - ✓ 200-300 mg/dy or 5-10 mg/kg
  - ✓Adjust dose on crystalluria (negative)
  - ✓Adjust on Urine 2,8 DHA ?
  - ✓No use of alcalinisation

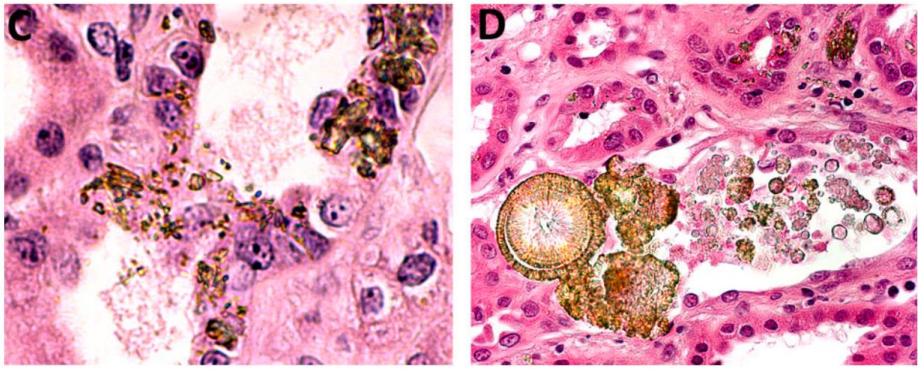
Creatinine decreased and stabilized around 150 µmol/l

Edvardsson et al, Eur J Intern Med, 2018

…But interruption can be dramatic

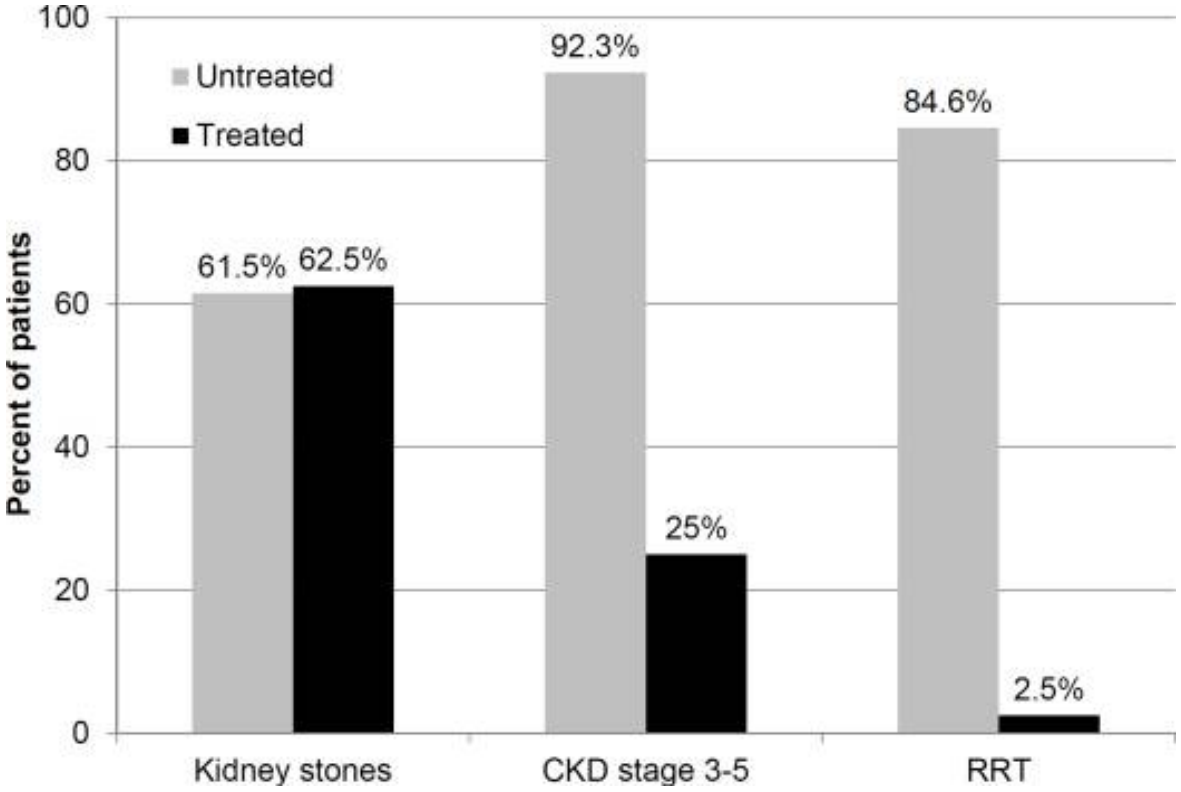
Lost of follow up for 2 yrs (lumbar surgical procedures) and Allopurinol discontinued

- Creat 823 µmol/l
- Kidney Biopsy:
  - Crystalline Nephropathy
    - FTIR: 2,8 DHA crystals
  - IF 60%



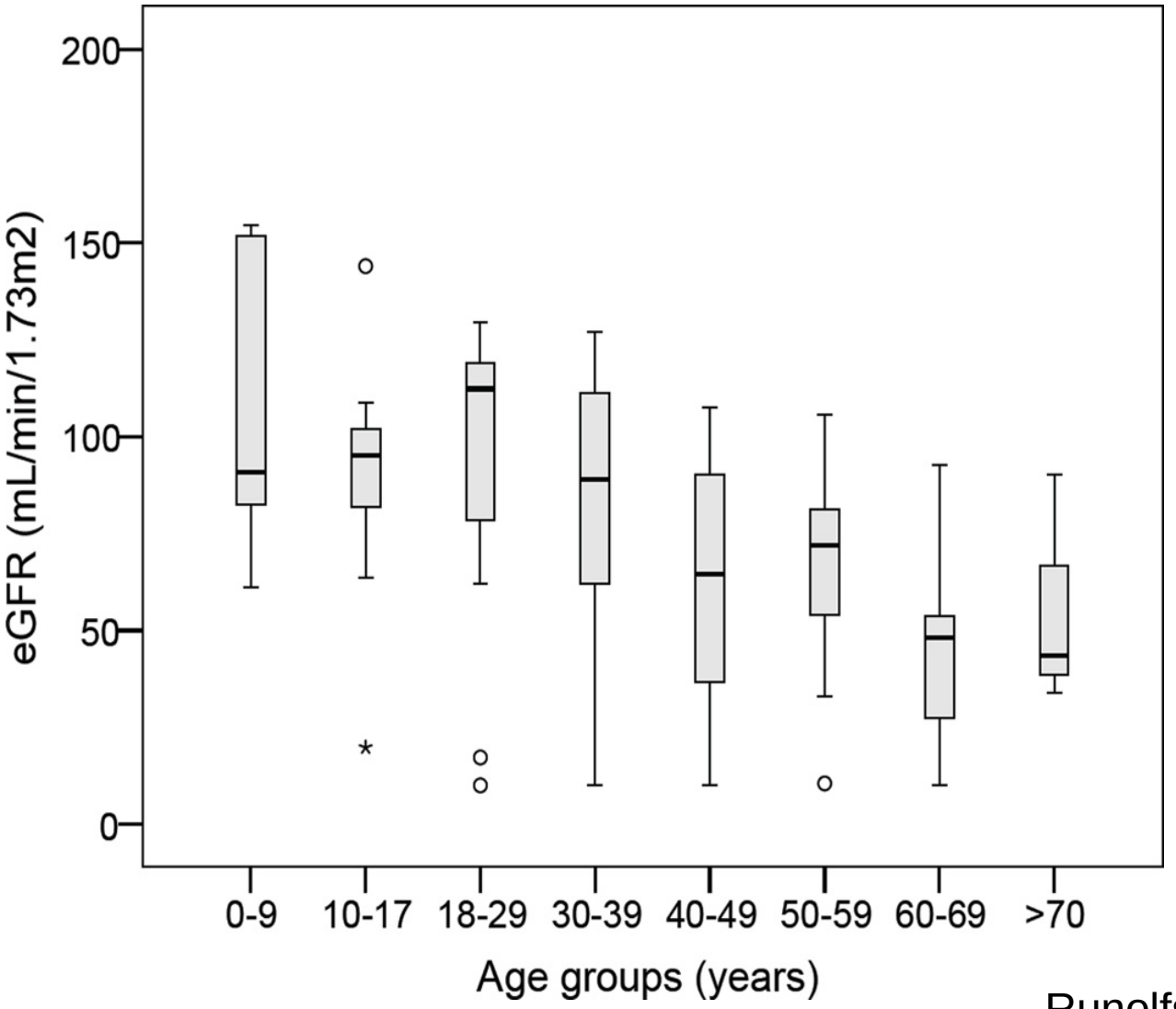
- TRT : Hyperhydratation + Allopurinol+ Steroids
- Follow up:
  - Creatinine initially decreased # 340 µmol/l; eGFR 18 ml/mn
  - CKD 5 and kidney graft 2 years later

Effect of treatment on renal function



Runolfsdottir at al, AJKD, 2016

Effect of treatment on renal function



Boxplot of eGFR
in different age groups

Median eGFR slope:
-0.38 ml/min/yr if treated
-5.75 ml/min/yr if not treated

Runolfsdottir at al, AJKD, 2016

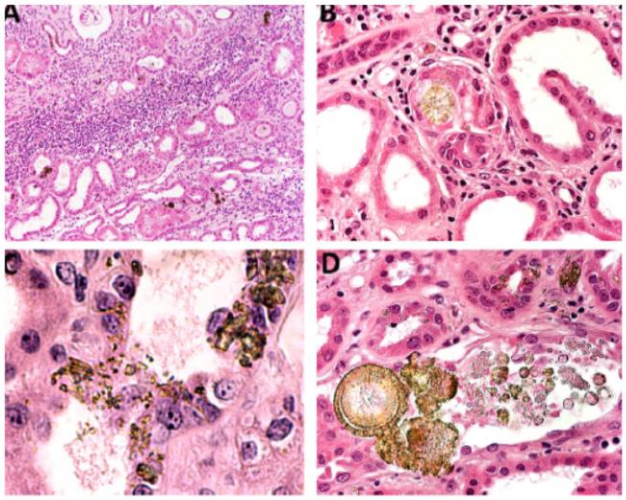
Recurrent 2,8 DHA nephropathy on allograft

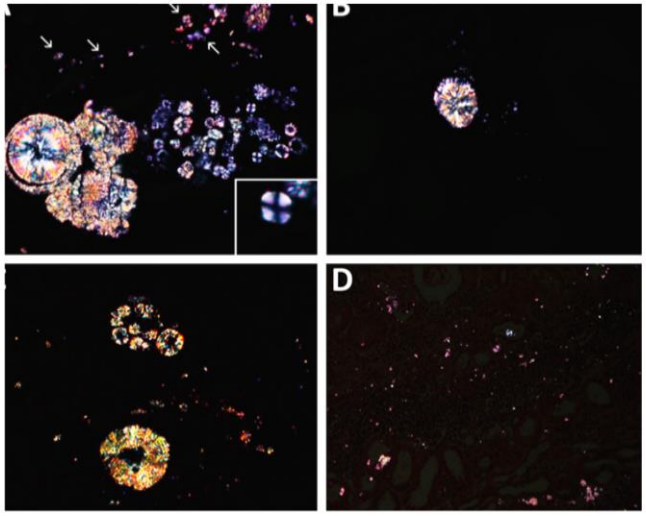
Age at ESRD	43 yrs (25-65)
Order of Renal Tx:	1st: 7
	2nd: 2
History of nephrolithiasis:	5/9 (55%)
Suspected cause of CKD:	Chronic tubulointerstitial nephropathy/NL: 2
	Oxalate Nephropathy 1 !!
	Nephroangiosclerosis 1
	Unknown 5
Time to Diagnosis (Post Tx)	Median 5 weeks (1.5 to 312)
Delay between 1st stone and diagnosis: Median 30 yrs (11-52)	
Serum creat at Diagnosis:	6/9 not on dialysis: mean 264 µmol/l (109-430)
	3/9 on dialysis

Zaidan et al, AJT, 2014

Biopsy Findings and Diagnosis Methods in post transplant 2,8 DHA Recurrence

- Initial diagnosis on the current graft biopsy
  - Oxalate CN 4/9
  - Urate CN 1/9
  - Undetermined 3/9
  - 2,8 DHA 1/9 !!
- Maltese Cross aspect on biopsy: 2/9
- Diagnosis Method
  - Infrared spectroscopy 9/9
  - Crystalluria 4/4
  - APRT activity 0% 7/7
  - Genetic analysis 6/6



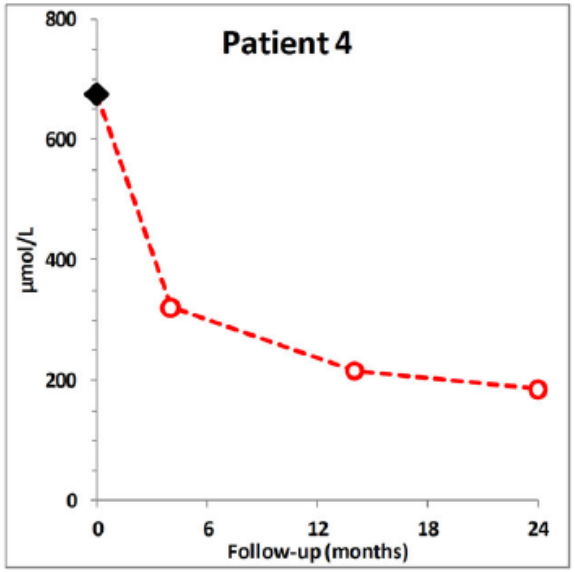


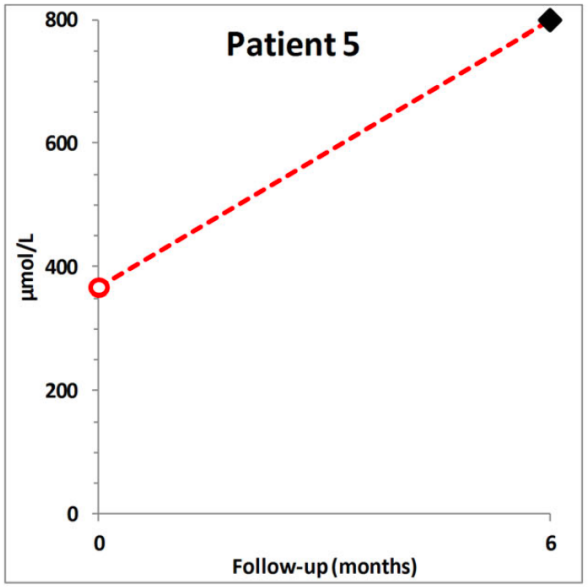
Zaidan et al, AJT, 2014

Treatment can be efficient

- Hyperdiuresis
  - > 2 ,5 to 3l /d
  - Urine Density < 1010
- Limit purines intake

- XO inhibitors +++

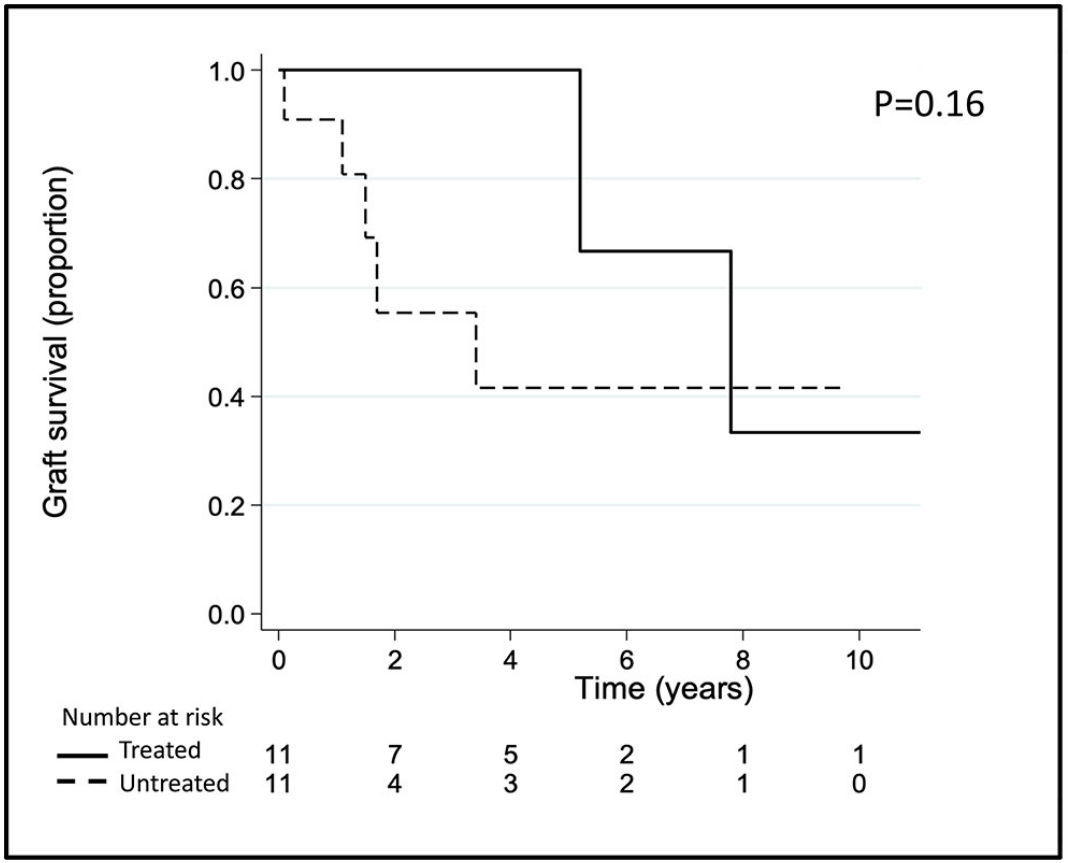




Outcome

- Follow up: median 24 months (6-32)
- Stable 1/ Worsened 1/ Initially improved 7
- Creatinine at last follow up (if not on HD): median 168 µmol/l (105-220)
- Renal outcome
  - Chronic graft dysfunction 5/9
  - Normal graft function 2/9
  - Graft loss 2/9

Outcome according to pretransplant XOR inhibitor treatment

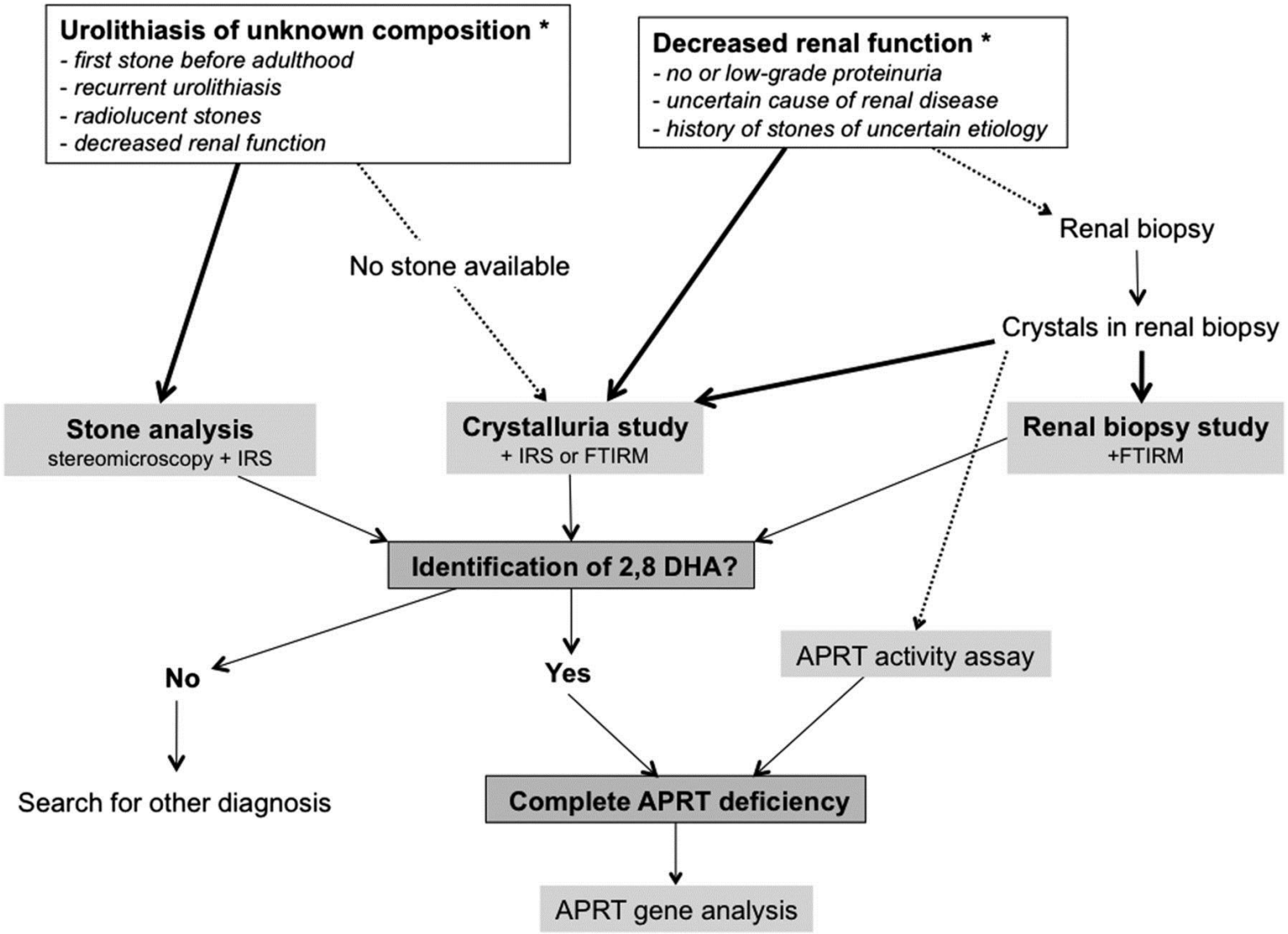


Graft function superior in the XOR inhibitor-treated group at 2 years posttransplant: median eGFR of 61.3 mL/min/1.73 m2 vs 16.2 (p=0.009)

2-year allograft survival 91% and 55%

Runolfsdottir et al, Transplantation 2020

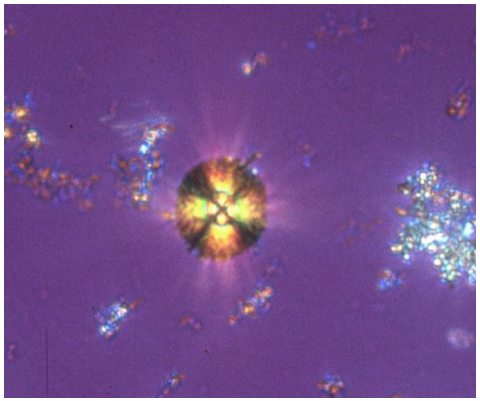
Recommended diagnostic algorithm for APRT deficiency

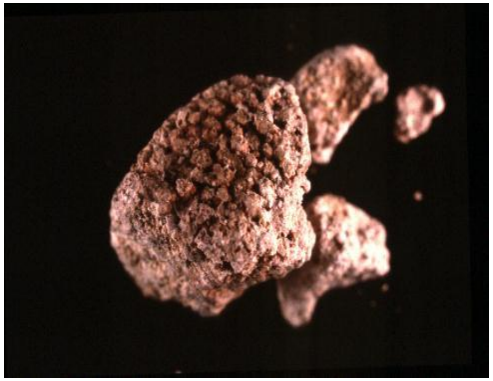


Bollée G et al. CJASN 2012

Conclusion

- 2,8-DHA crystalline nephropathy is a rare and underrecognized cause of CKD that can lead to renal failure, ESRD and recurrence in the renal allograft
- The presence of crystals in the renal parenchyma and urine sediment should not be overlooked
- Prompt pharmacologic inhibition of xanthine dehydrogenase may allow the improvement of renal function





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21/03/23

Glycogen storage disease Ib and XI, disease mecahnisms and novel treatment
Francesco Trepiccione (Naples)

25/04/23

Disorders of renal calcium handling
Pascal Houillier (Paris)

16/05/23

Syndromic Ciliopathies (Bardet Biedel)
Jens König (ERKNet) & Hélèn Dollfus (ERN-Eye)

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