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The European Rare Kidney Disease Reference Network

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Working Group on Inherited Kidney Disorders

WELCOME TO

ERKNet
Advanced Webinars on Rare Kidney Disorders

Date: 21 September 2021

Topic: Cystinosis – adult view

Speaker: Aude Servais (Paris, France)

Moderator: Tom Nijenhuis (Nijmegen, Netherlands)

Cystinosis: adult view

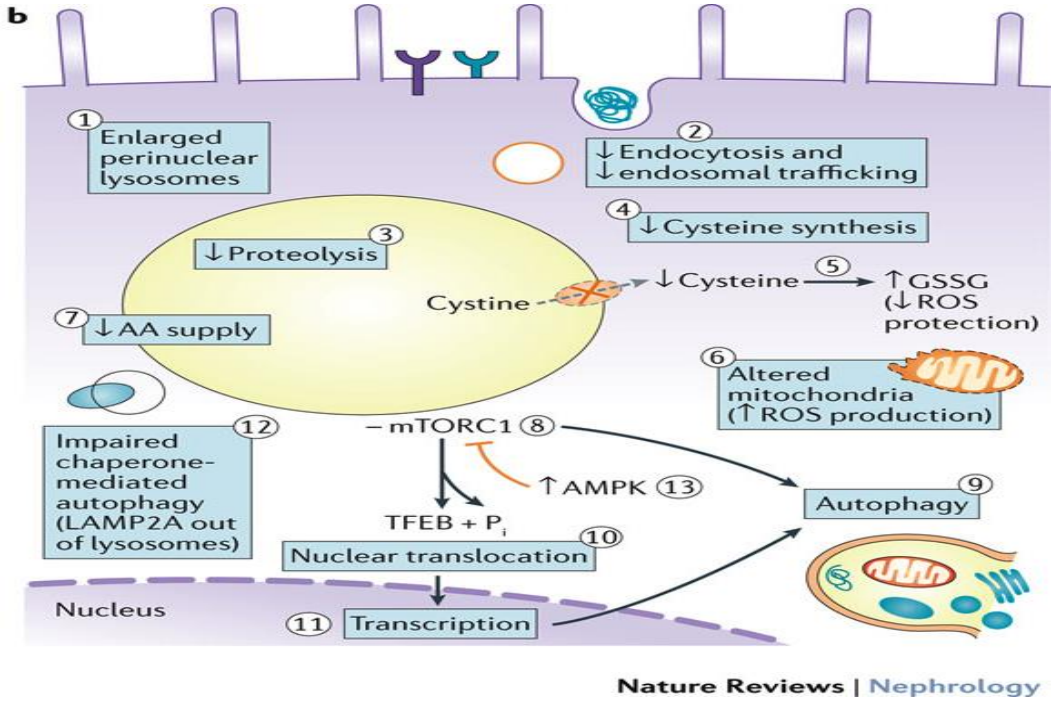
Dr Aude Servais
Adult Nephrology and Transplantation,
Reference Centre for child and adult hereditary renal diseases (MARHEA),
Necker-Enfants Malades University Hospital,
Paris, France

Introduction

- Cystinosis provides a good example of a “pediatric” disease with a spectrum extending into adult medicine
- In the European RaDiCo cystinosis cohort, 55% of patients living with cystinosis are adults
- These patients are likely to be followed up in adult units
- Adult services should ideally offer a model of care including both kidney & extra-renal manifestations of the disease

Cystinosis

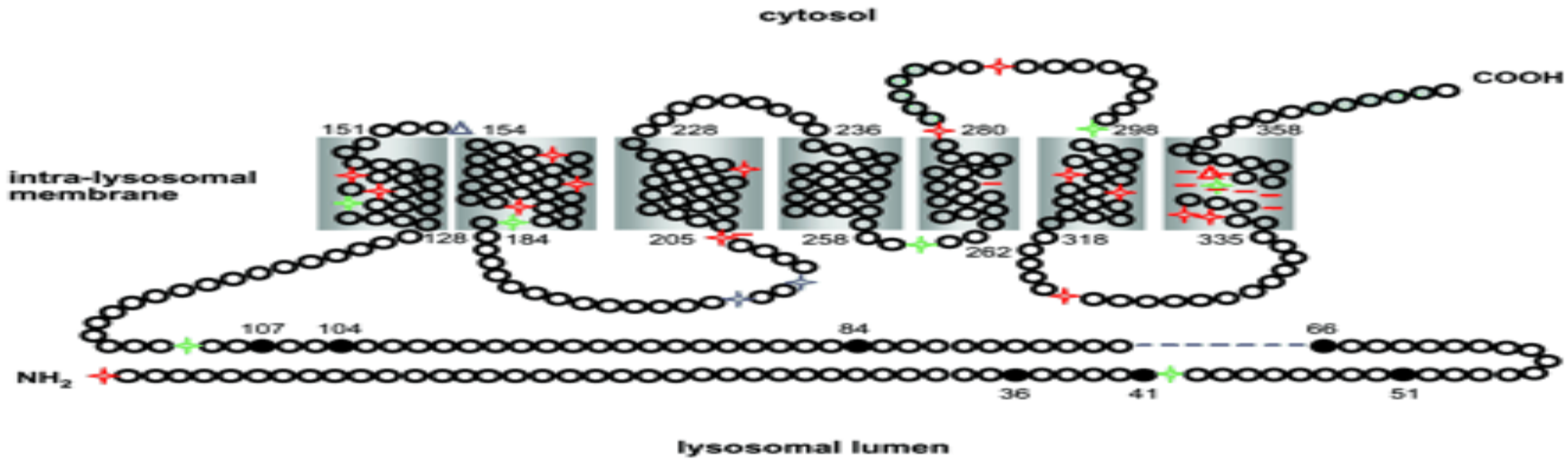
- Autosomal recessive disease
- Incidence: 1/100 000-200 000 births
- Mutation *CTNS* gene (chromosome 17p13): cystinosine
- Cystine transport defect
- Cystine accumulation in lysosomes and crystals formation



Cherqui & Courtoy, Nat. Rev. Nephrol. 2016

Genetic

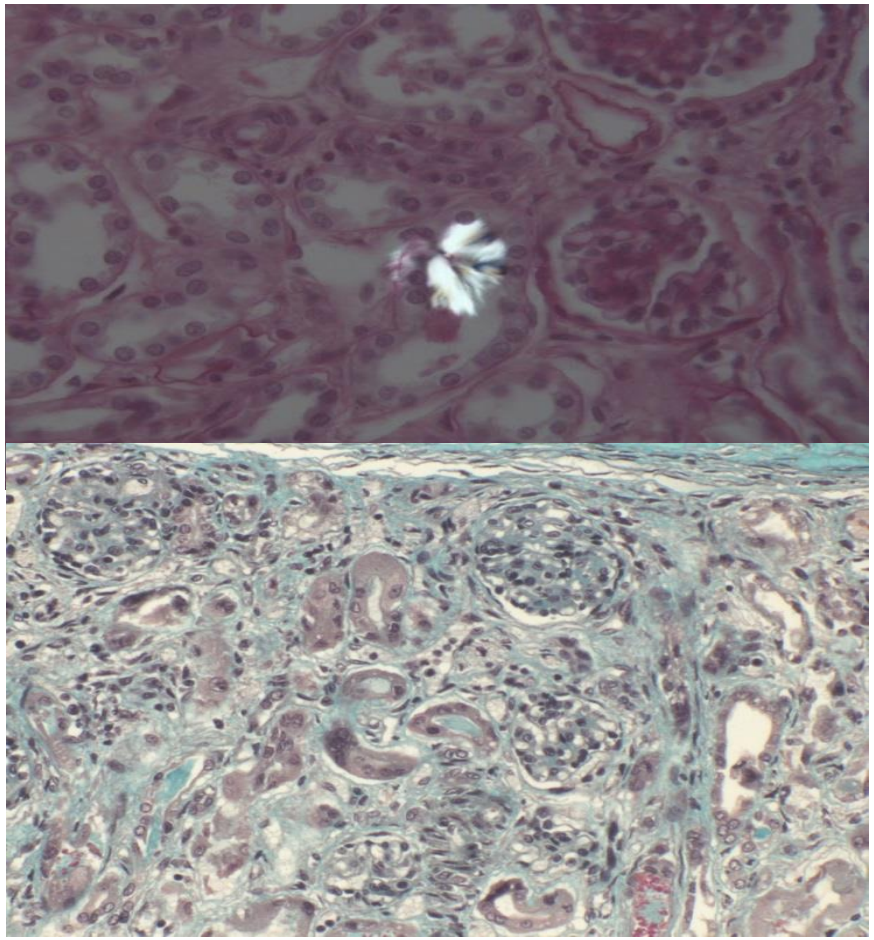
- > 140 different mutations
- « European » 57 kb deletion
  - >50%
- Infantile form (95%)
  - 2 severe mutations



Kalatzis et al, Hum Mol Genet, 2004

Clinical presentation

- First manifestation at 4-6 months
- Failure to thrive
- Rickets
- Fanconi syndrome or proximal tubule dysfunction: hypokalemia, low serum bicarbonate, hypophosphatemia, normoglycemic glucosuria
- Polyuria (2 to 6l/d): dehydration
- Renal function
  - Initially normal and then renal failure



Prencipe et al. JASN, 2014

How can you confirm the diagnosis?

1. Urine cystine dosage
2. Ophtalmological exam
3. Leucocyte cystine dosage
4. Cristalluria
5. Genetic exam

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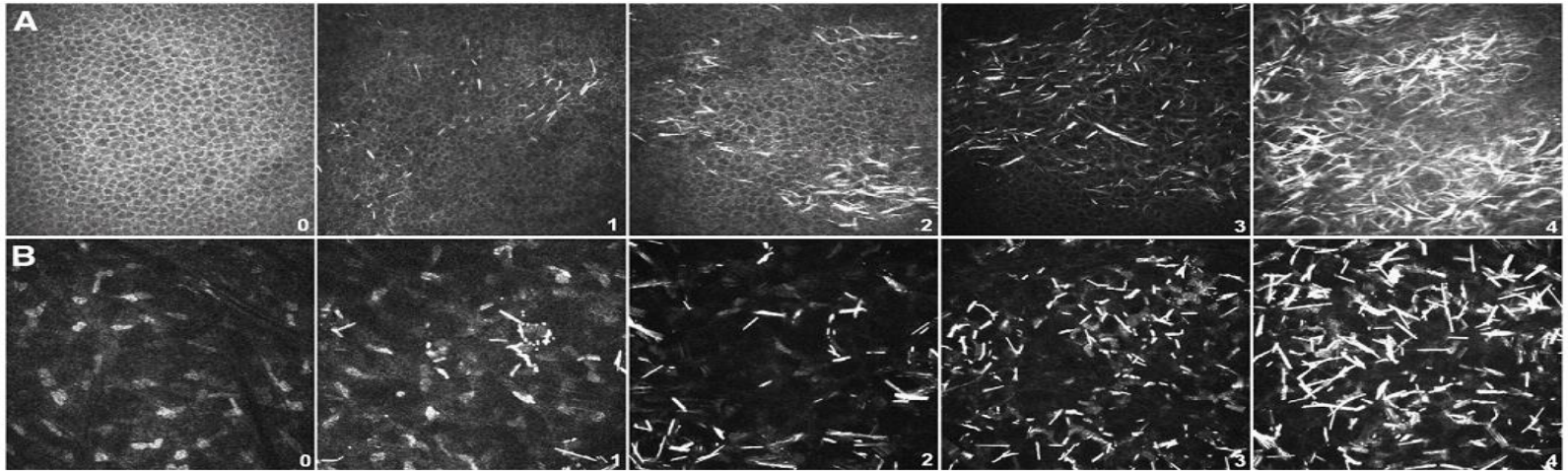
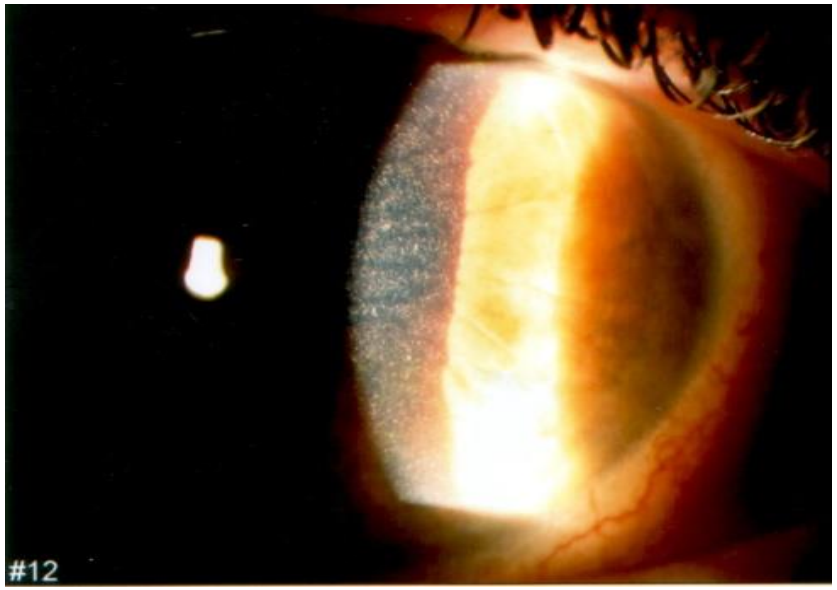
Diagnosis

- White blood cell cystine dosage
- Slit lamp examination: corneal crystals
  - Always present after 18 months
- Genetic study





- Confocal microscopy

Labbe et al, Mol Genet Metab, 2014

Symptomatic treatment

- Hydratation/electrolytes
  - Potassium, phosphate
  - Bicarbonates, citrate, sodium
  - Vitamin D

Is there any specific treatment?

1. D-Penicillamine
2. Cysteamine
3. Cystamine
4. Tiopronine

Is there any specific treatment?

1. D-Penicillamine
2. Cysteamine
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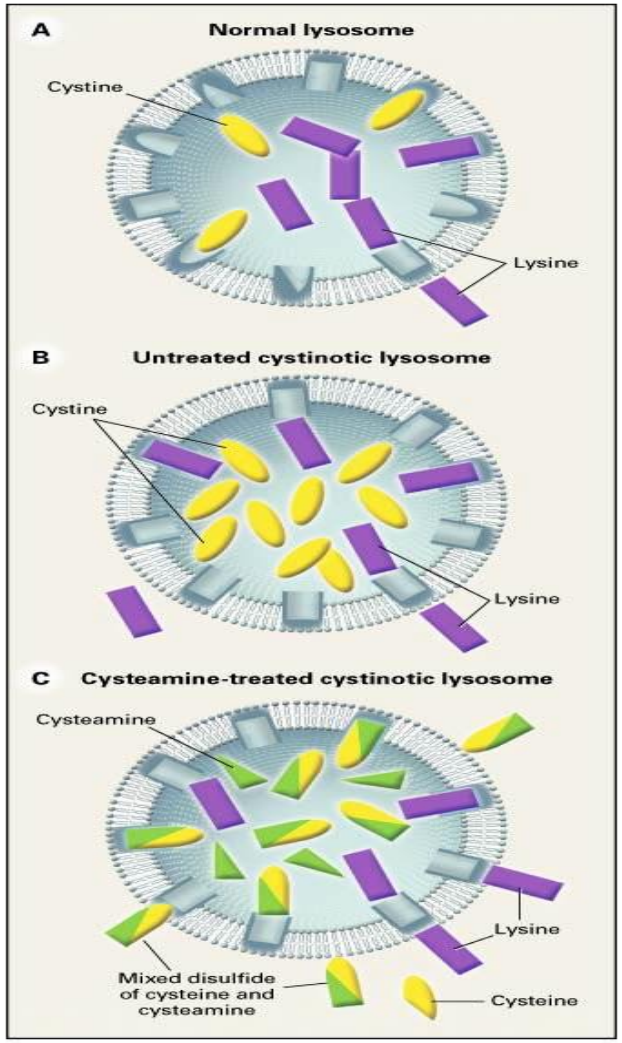
4. Tiopronine

Specific treatment: cysteamine bitartrate

- Cystagon®
  - Dose/6 hours
- Procysbi®
  - Micro-spheronized enteric-coated, allowing twice daily dosing
  - Non-inferiority of the delayed release formulation compared to immediate-release cysteamine on WBC cystine levels
- Dose: 1.3 g/m², max 2 g/d or max 1.95 g/m²/d
- Objective: cystine <1 nmol ½ cystine /mg protein
- Side effects
  - Gastro-intestinal complaints
  - Disagreeable breath and sweat odor due to the conversion of cysteamine to methanethiol and dimethylsulphide

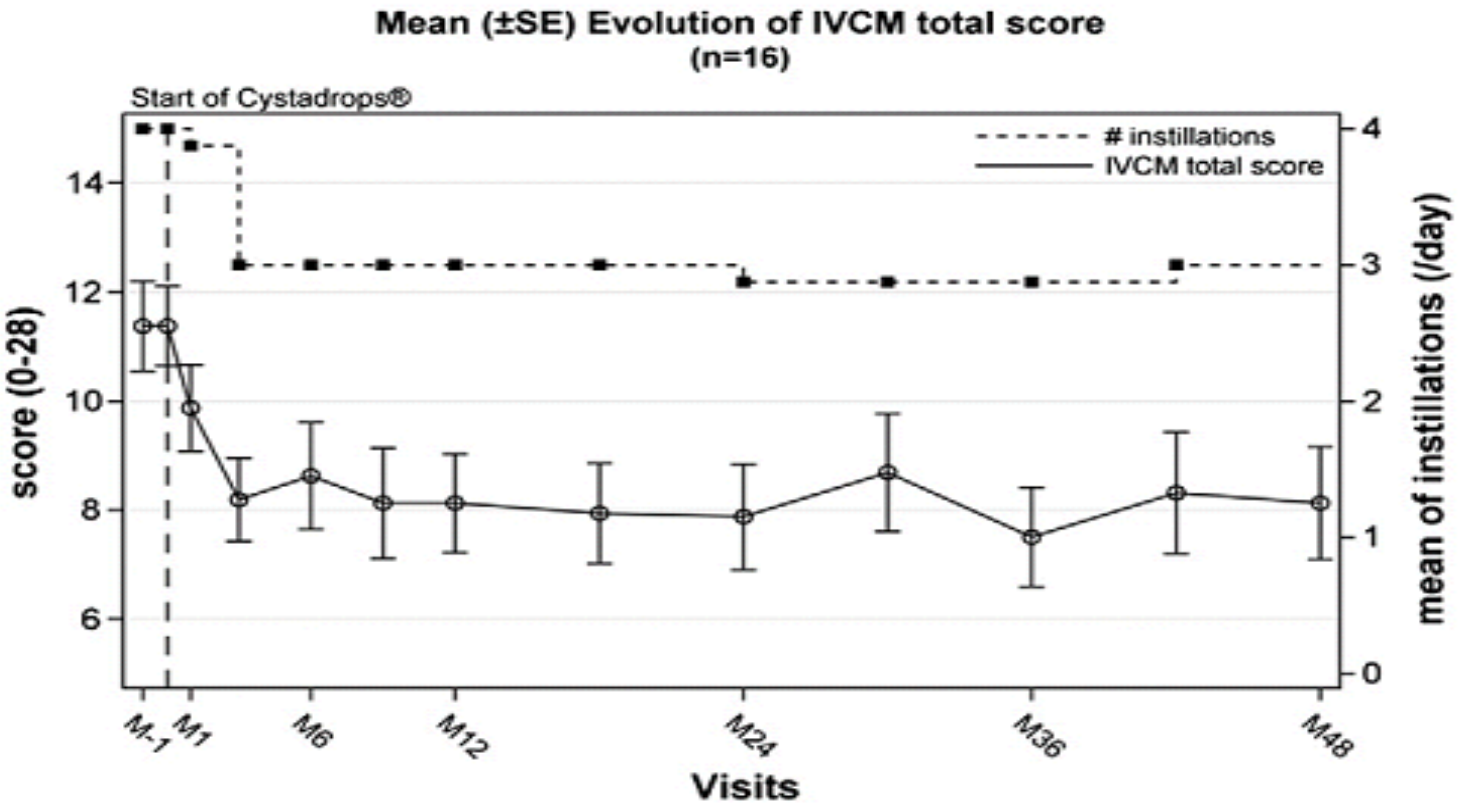


Gahl W et al. N Engl J Med 2000;
Langman et al, CJASN, 2012

Ophtalmological treatment

- Local treatment: gel formulation 0.55% (Cystadrops®)

3-4 daily adminstration

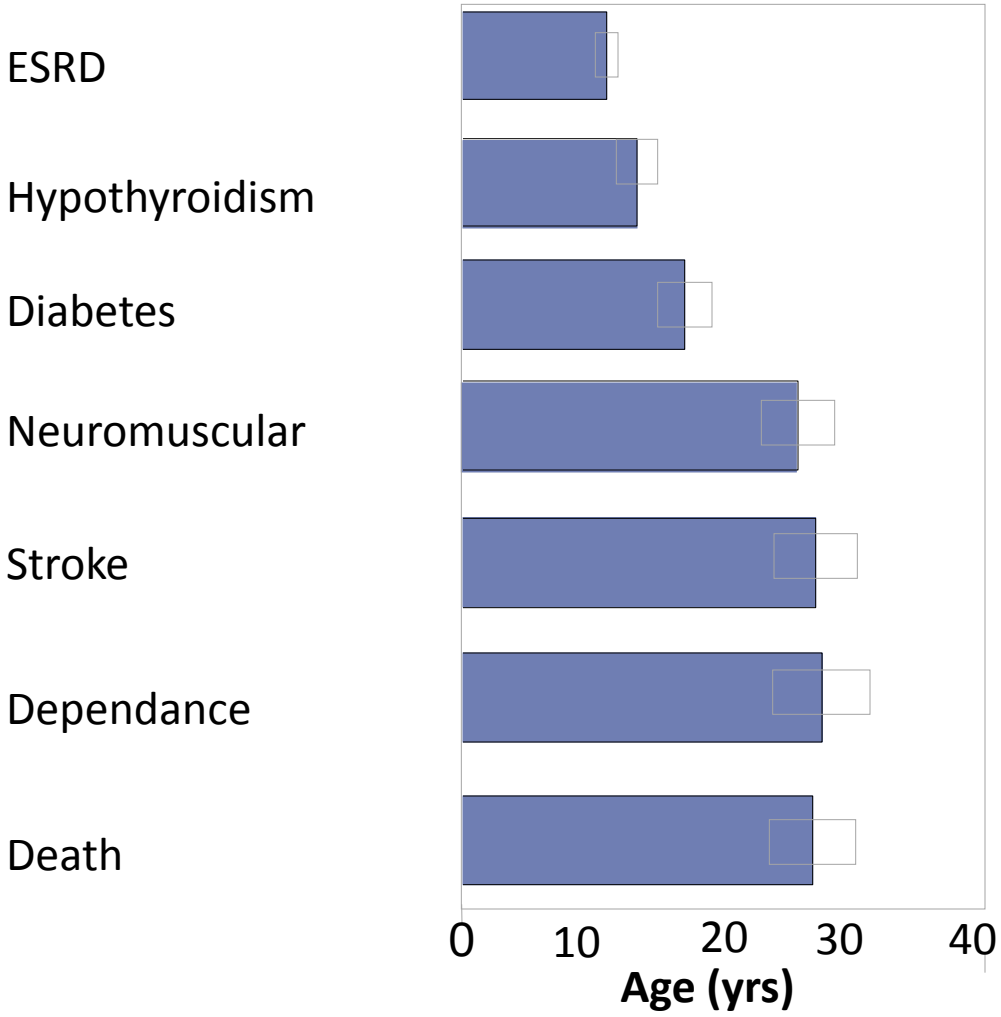


Labbe et al, Mol Genet Metab, 2014

Case presentation. Miss A.

- Diagnosis of cystinosis at 13 months
  - Failure to thrive, polyuria, rickets
- Cysteamine treatment at 15 months
- Proximal tubulopathy and rickets, corneal cystine cristals
- Poor adhesion to treatment
- 18 years: transition to adult department
  - Creatininemia 188 µmol/l, eGFR 31 ml/min/1.73m²
  - Cystine level 3 nmol hemicystine/mg protein
  - Has stopped studies, no formation

Chronology of complications in historical cohorts

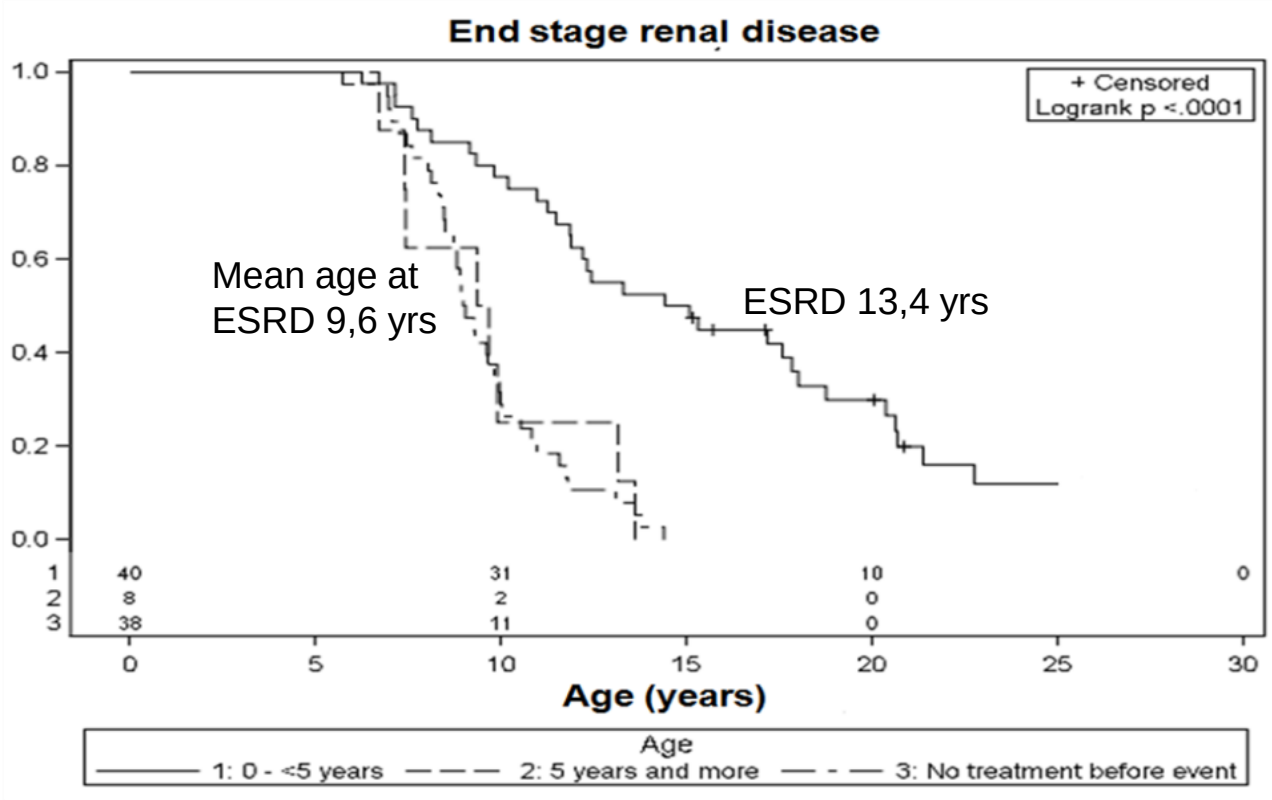


	Patients (N=86)	Age, mean (SD)(yrs)
ESRD	78 (91%)	11.1 (4.0)
Hypothyroidism	61 (72%)	13.4 (6.2)
Diabetes	48 (56%)	17.1 (7.2)
Neuromuscular	32 (37%)	23.3 (6.3)
Stroke	12 (14%)	27.1 (4.9)
Dependance	18 (21%)	27.5 (7.5)
Death	24 (28%)	26.8 (7.8)

Brodin Sartorius et al *Kidney Int* 2012; 81:179-189

End Stage Renal Disease

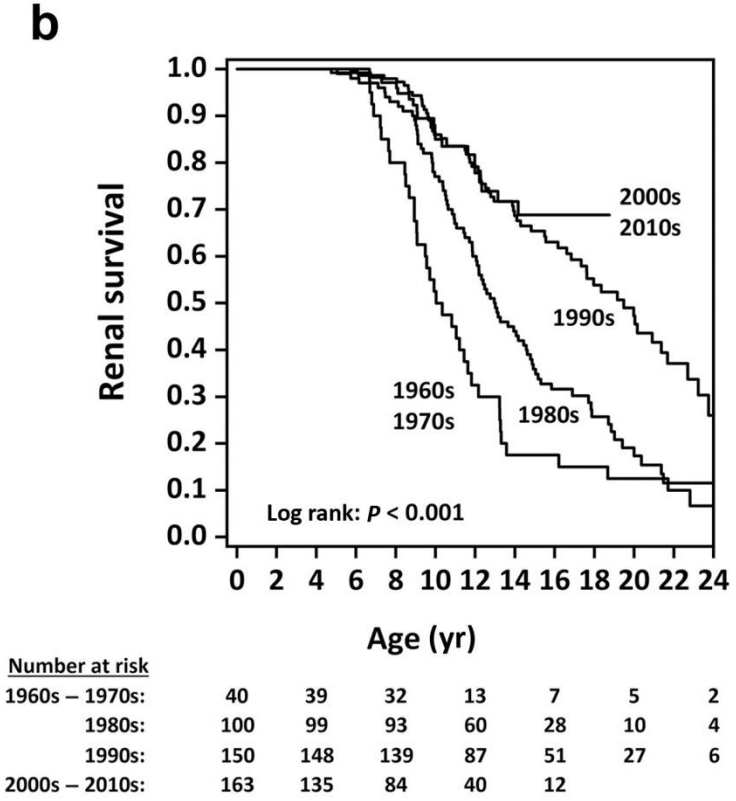
- Historical cohort:
  - ✓ 86 patients
  - ✓ Mean age at ESRD 11,1 years
  - ✓ 8/86 (9%) patients functioning native kidney at adult age



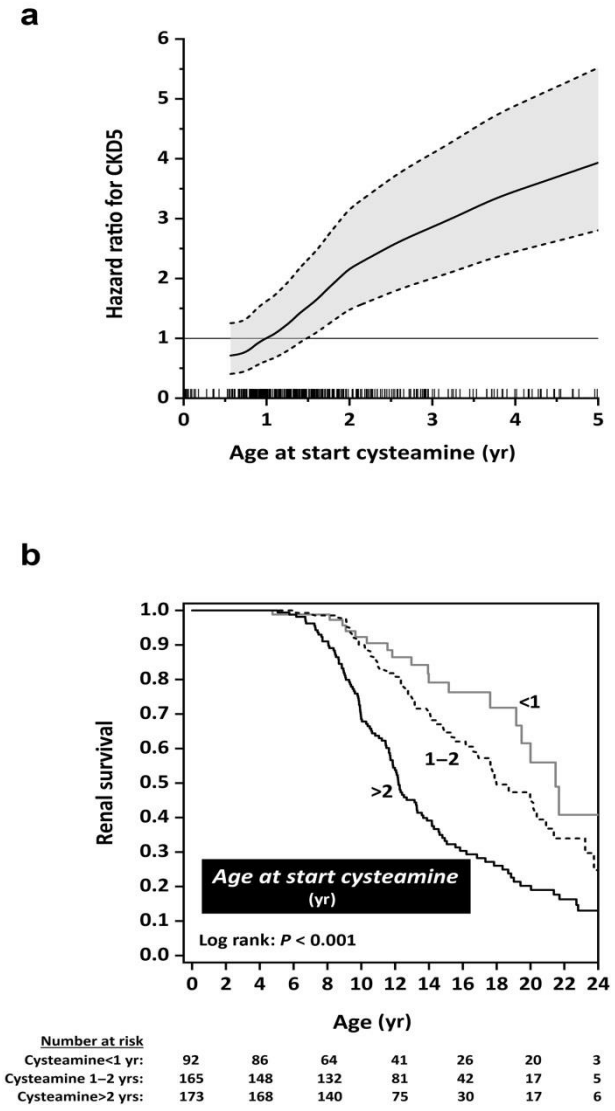
Brodin-Sartorius et al *Kidney Int* 2012;81:179-189

Age at ESRD

- The prognosis of kidney function has improved steadily between the 1970s and 1990s
- The median gain in renal survival was 9.1 years

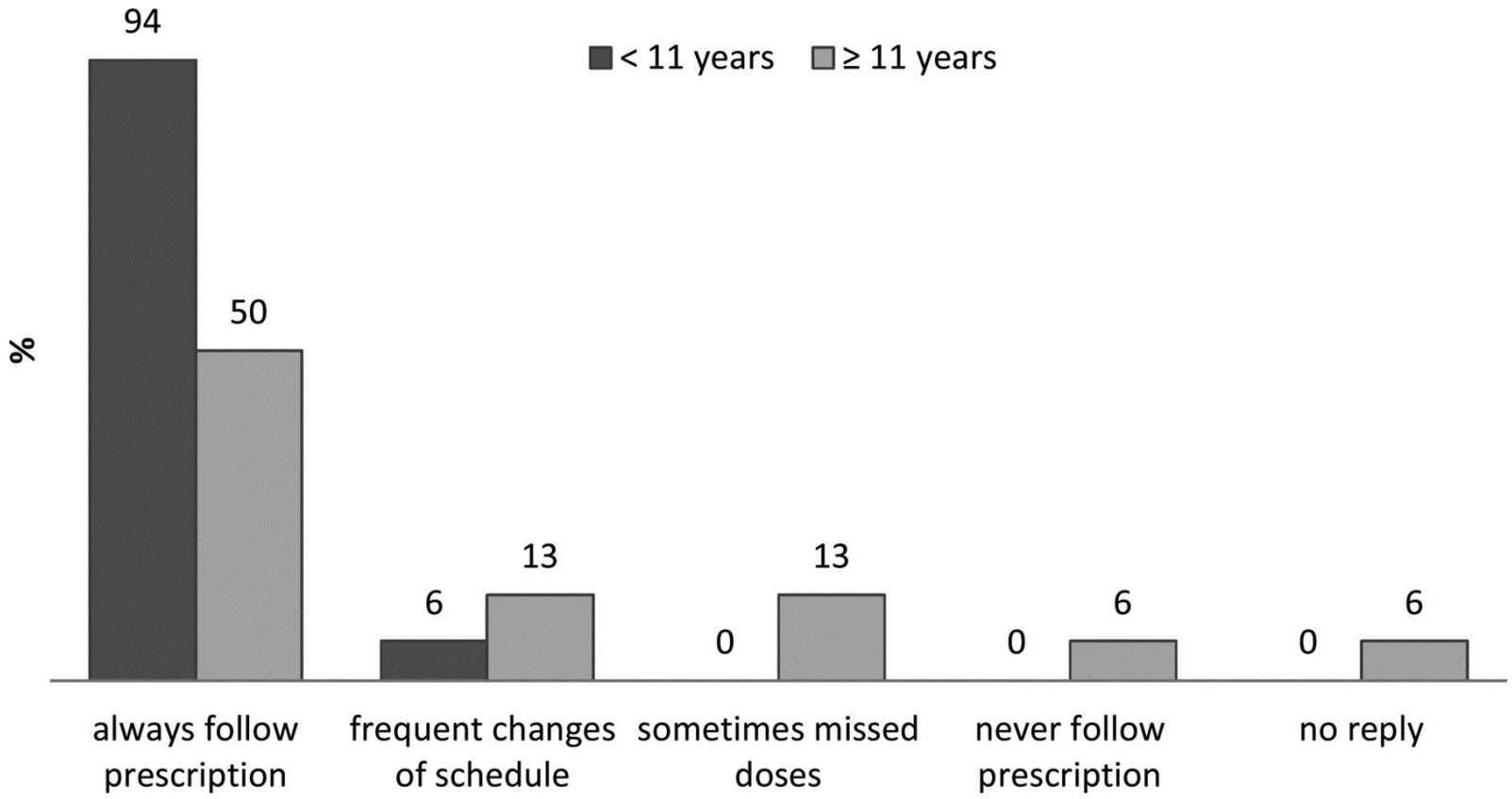


By multivariable analysis, the age when cysteamine was started was associated with delayed development of ESRD



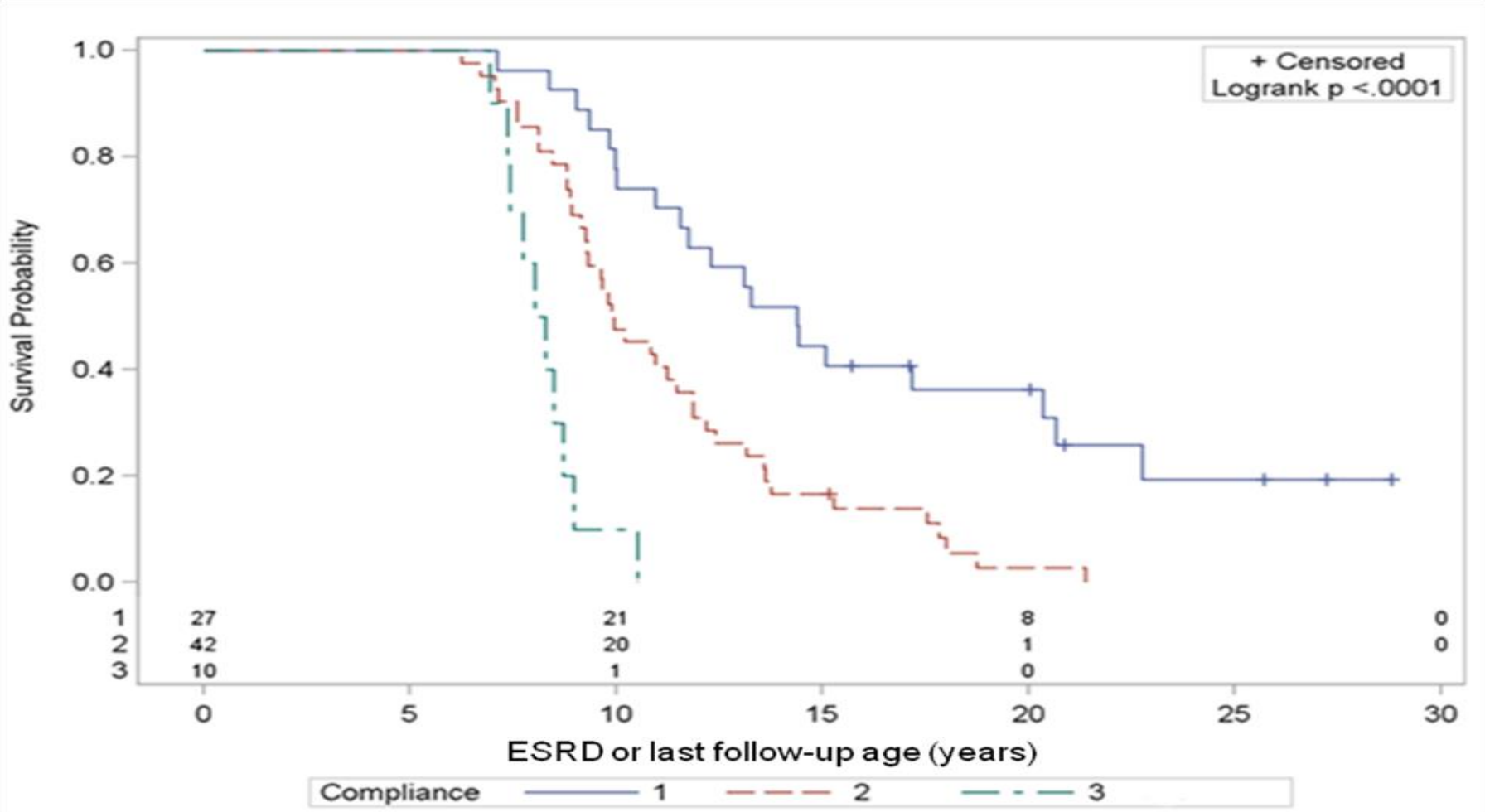
Emma et al, *Kidney Int*, 2021

Self-reported adherence to cysteamine by patient age



Ariceta et al, *Nephrol Dial Transplant* 2015;30:457-480

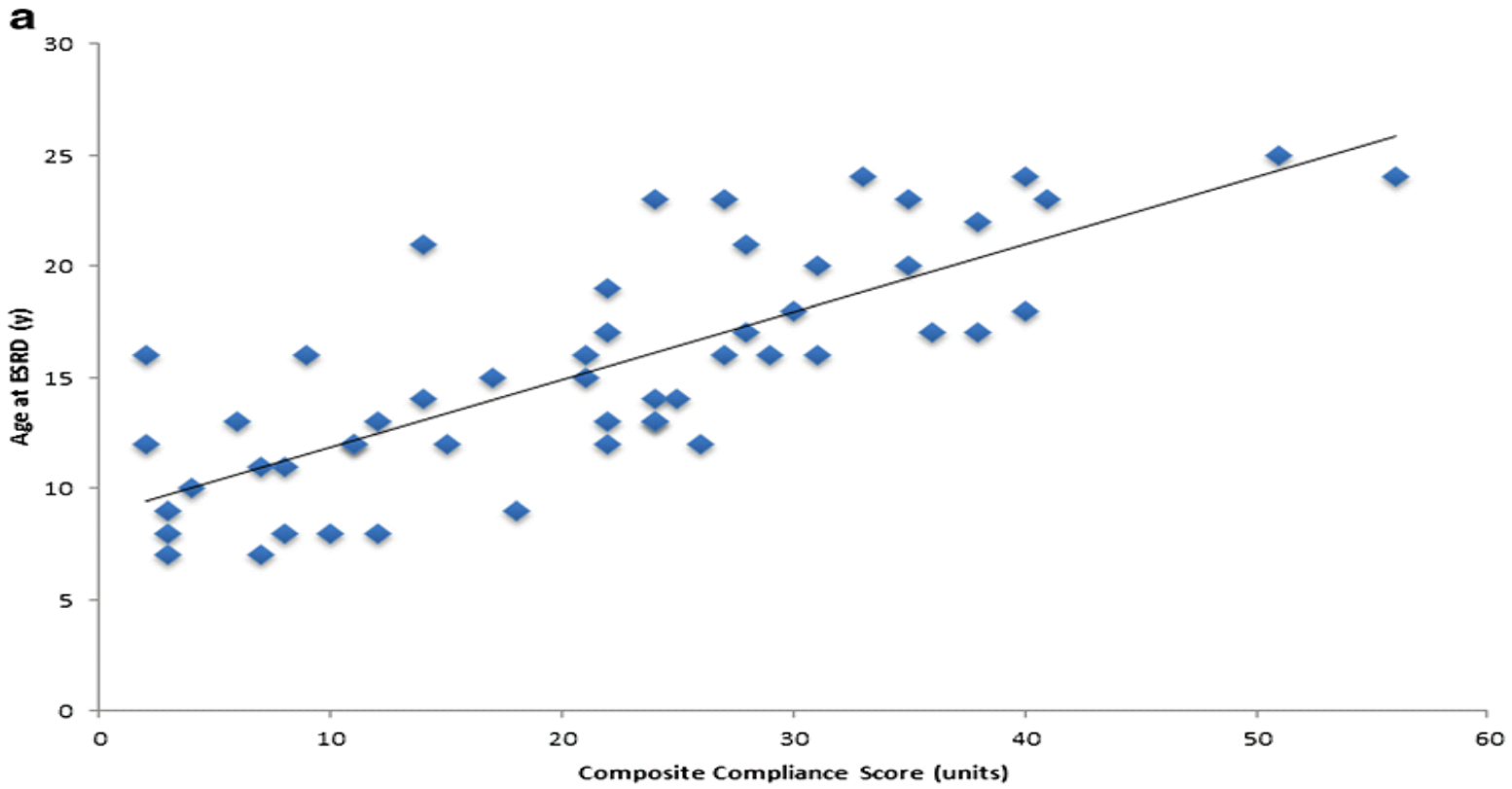
Compliance and ESRD



Brodin-Sartorius et al, *Kidney Int*, 2012

Compliance and ESRD

For each year of good cystine depletion, one year of preserved renal function



Nesterova et al, *Pediatr Nephrol*, 2015

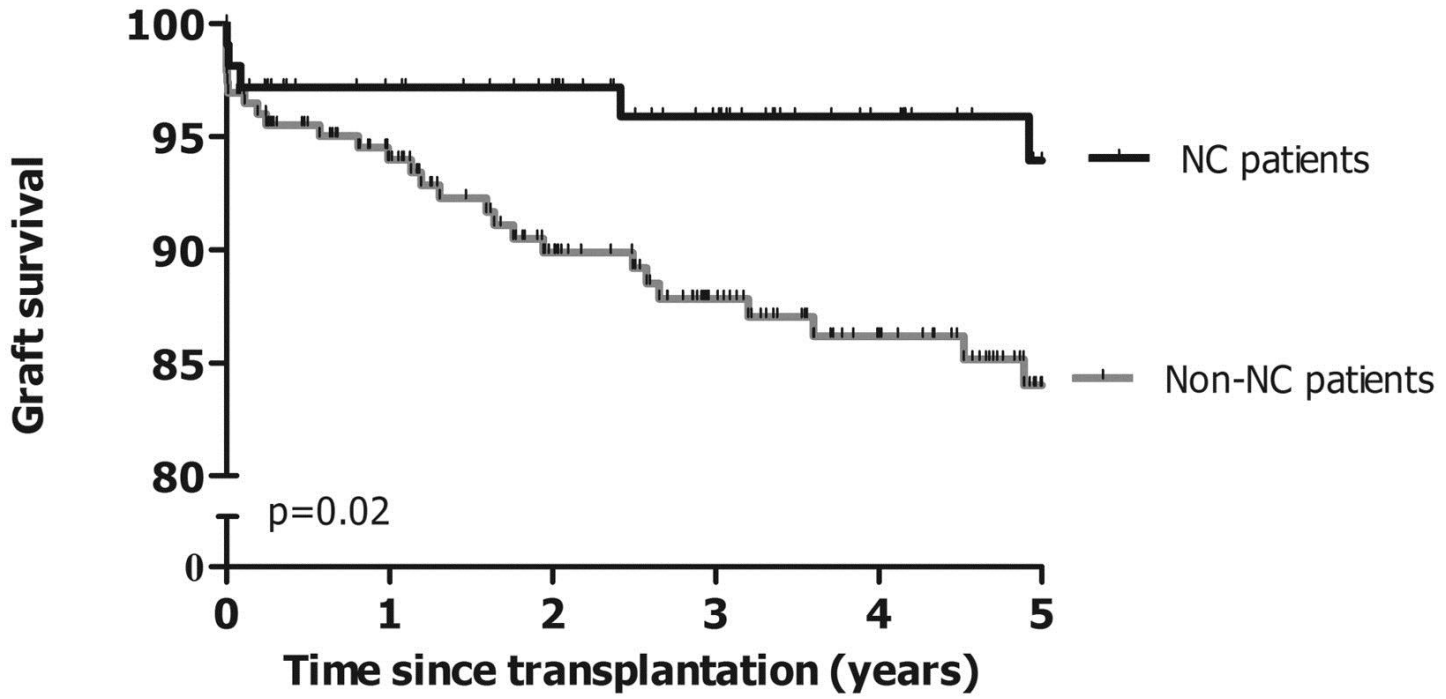
Renal transplantation

- Renal transplantation is the treatment of choice of end-stage renal disease in cystinosis
- Both living donor kidneys and cadaveric kidneys perform well

Renal transplantation

Results of kidney transplantation in cystinosis patients are better than in other patients undergoing transplantation

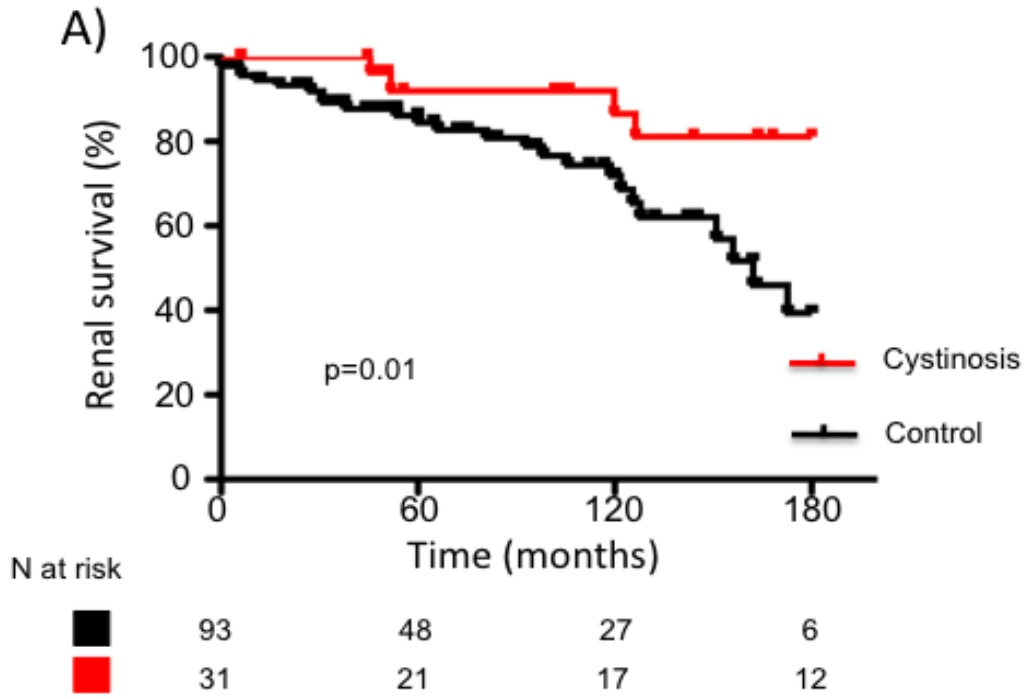
Five-year graft survival of patients with nephropathic cystinosis (NC) and non-NC patients

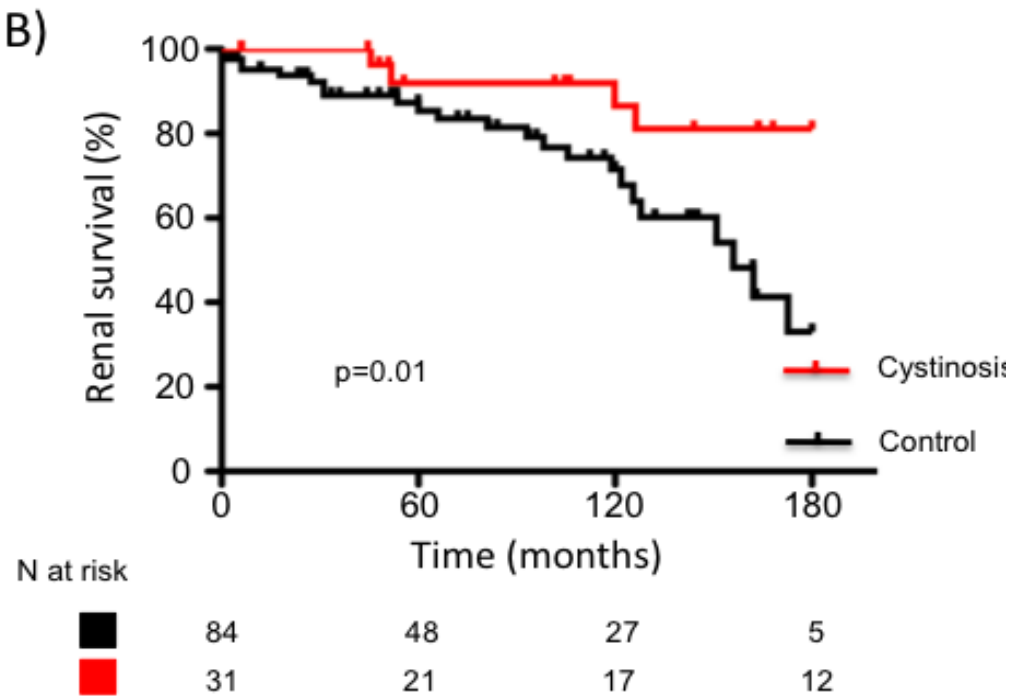


NC patients	122	92	85	71	56	47
Non-NC patients	235	175	144	117	94	67

Van Stralen et al *Clin J Am Soc Nephrol* 2011;10:2485-2491

Long term graft survival





Cohen et al *Orphanet J Rare Dis* 2015;10(90):1-8

Immunosuppressive regimen

- Patients with cystinosis can experience rejection episodes if they are not appropriately treated with immunosuppressive medications
- Immunosuppressive therapies (mainly corticosteroids and tacrolimus) may increase the risk of developing diabetes mellitus
  - However, the benefits of these medication exceed their risks
  - Post-transplant diabetes mellitus occurs as frequently in cystinosis than in control patients

Cohen et al *Orphanet J Rare Dis* 2015;10(90):1-8

Should cysteamine be stopped after end stage renal disease?

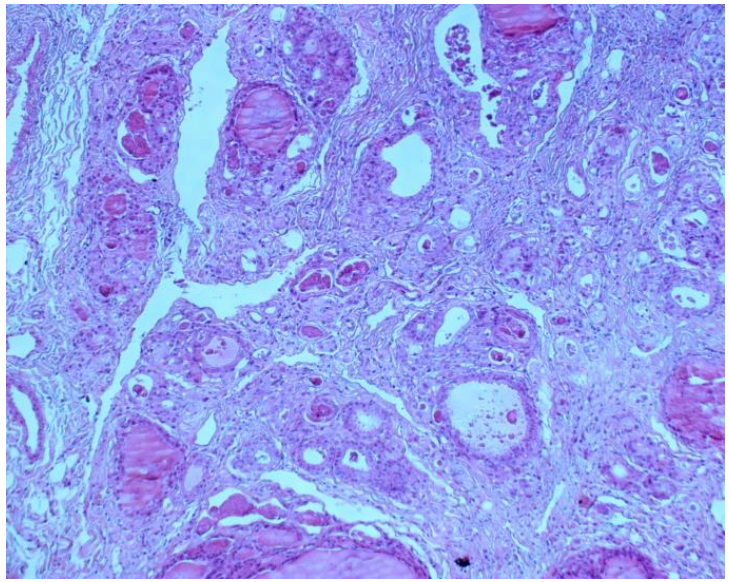
- Yes
- No

Should cysteamine be stopped after end stage renal disease?

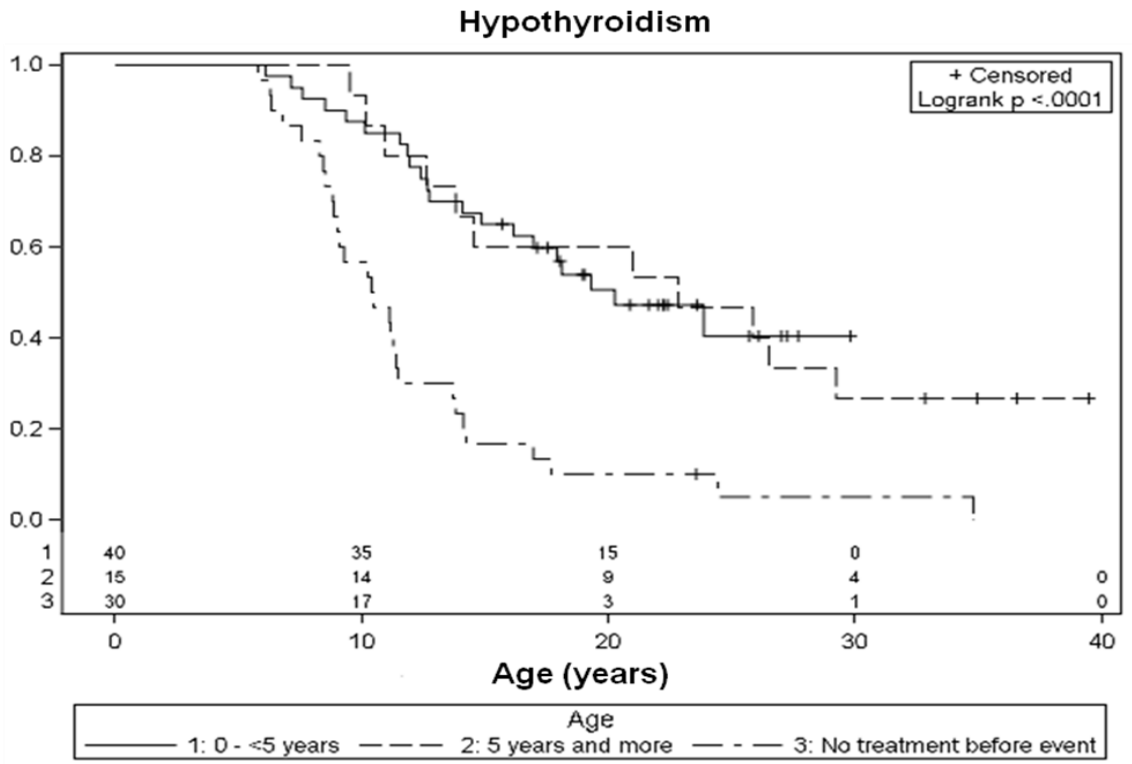
- Yes
- No

Hypothyroidism

- Cystine accumulation in thyroid follicular cells causes fibrosis, atrophy and dysfunction
- Thyroxine supplementation



Lucky et al, *J Pediatr*, 1977 Photo MC Gubler

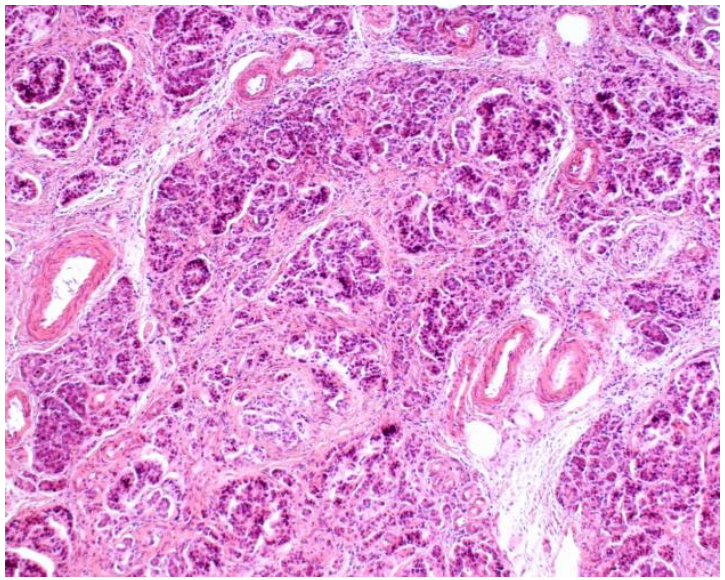


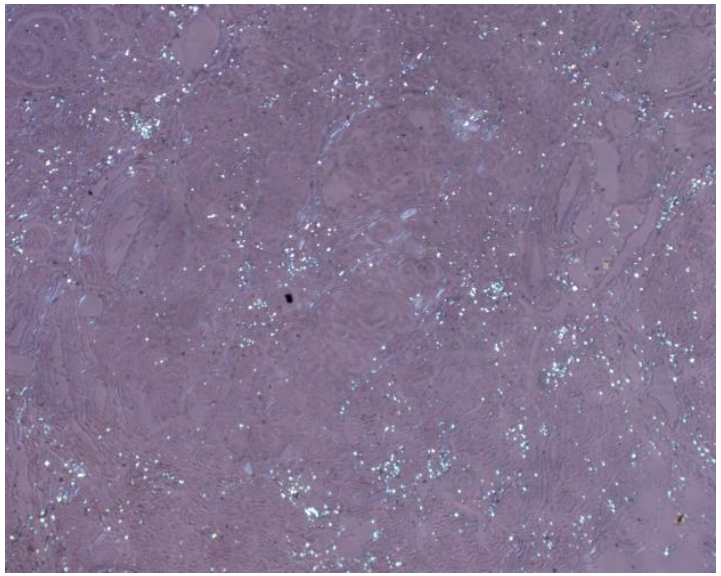
Treatment started before 5 years of age is associated with a significant delay in the occurrence of hypothyroidism

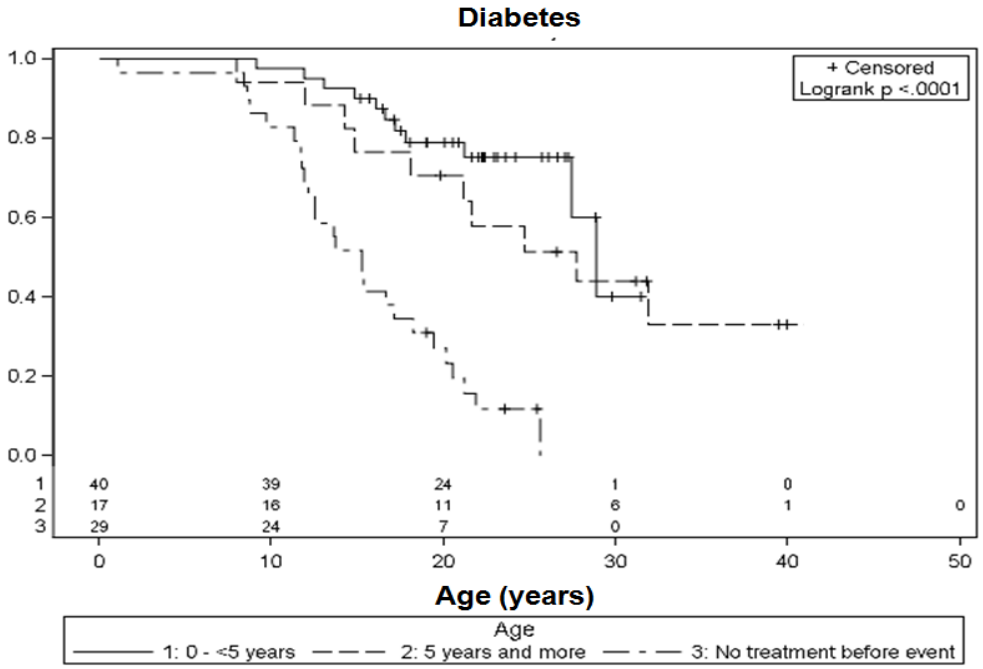
Brodin-Sartorius et al *Kidney Int* 2012;81:179-189

Diabetes

- Cystine accumulates in the bêta cells of the islets of Langerhans with massive crystal deposits in the pancreas and complete architectural disorganisation







Treatment started before 5 years of age is associated with significant delay in the occurrence of diabetes

Fivush et al, *J Pediatr*, 1988

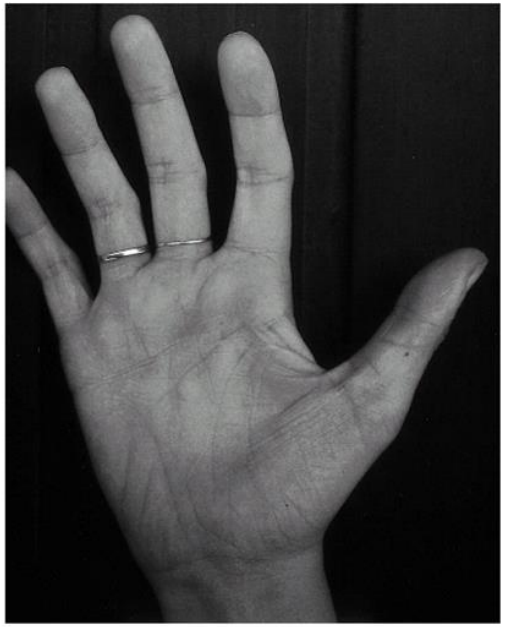
Photo MC Gubler

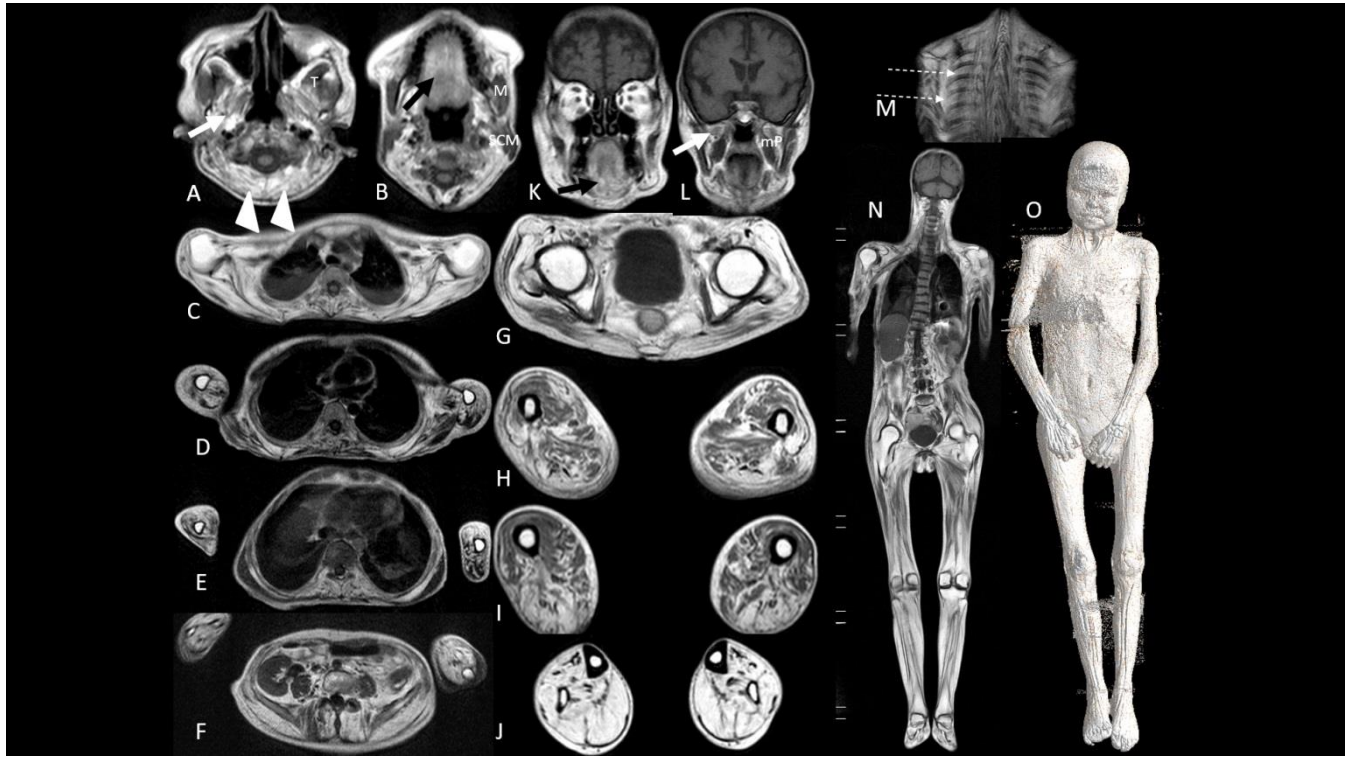
Brodin-Sartorius et al *Kidney Int* 2012;81:179-189

Myopathy

Cystine deposition in muscles may cause progressive distal myopathy

Muscle weakness initially involves the distal extremities





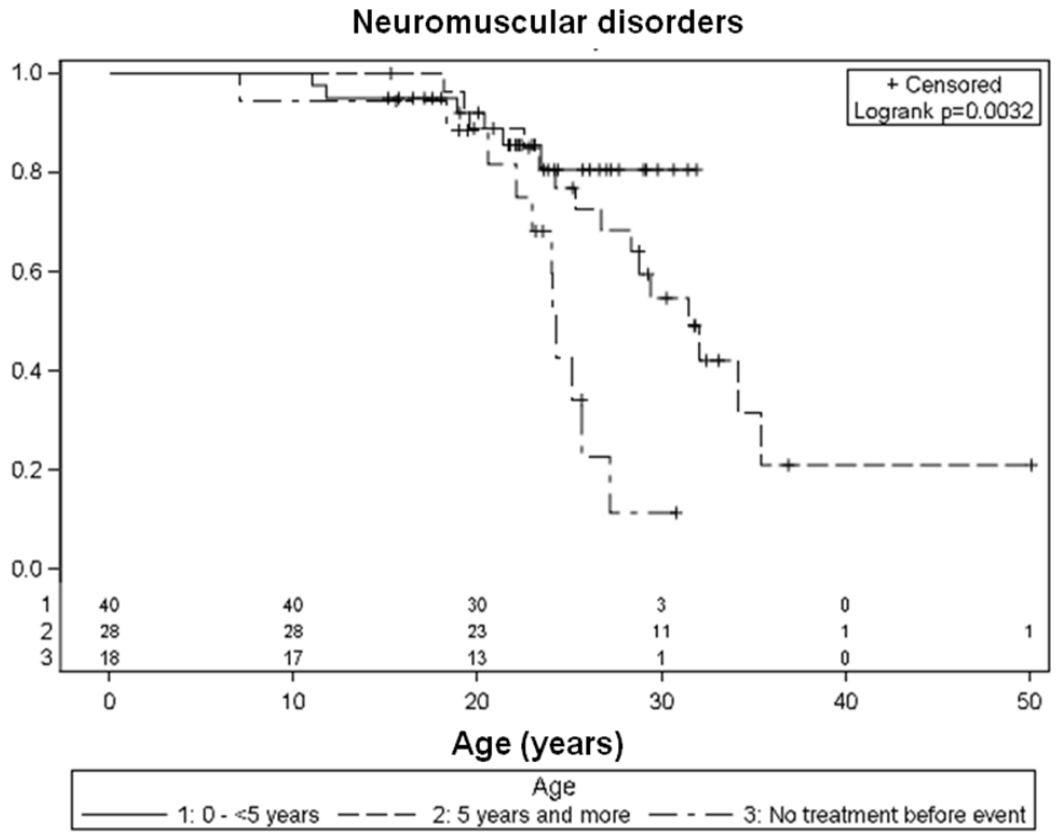
Muscle imaging performed with whole-body magnetic resonance imaging showing the pattern of muscle involvement in a 37 year old man with axial, proximal and distal muscle weakness: muscles are atrophied and fatty replaced

Figure, Pr Carlier , radiology, Raymond Poincarré Hospital, Garches, France

Gahl et al *NEJM 1988*;319(22):1461-1464,
Charnas et al *Ann Neurol* 1994;35(2):181-188,
Vester et al *Pediatr Nephrol* 2000;14:36-38

Neuromuscular disorders

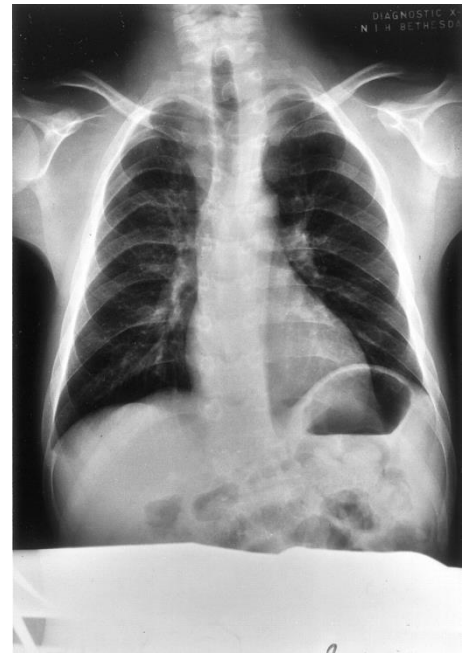
- Treatment started before 5 years of age is associated with a significant delay in the occurrence of neuromuscular disorders



Brodin-Sartorius et al *Kidney Int* 2012;81:179-189

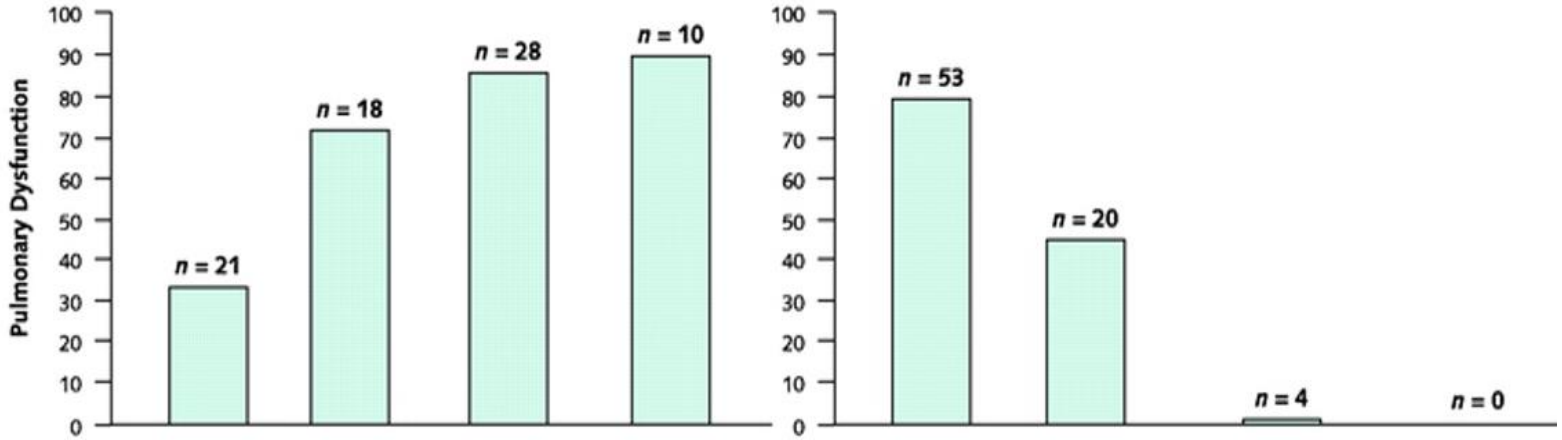
Restrictive lung disease

- Thoracic muscle weakness may result in a restrictive lung disease
- The severity of pulmonary disease correlates directly with the severity of myopathy



Chest radiograph: conical thorax

Frequency of pulmonary dysfunction, by duration of oral cysteamine therapy



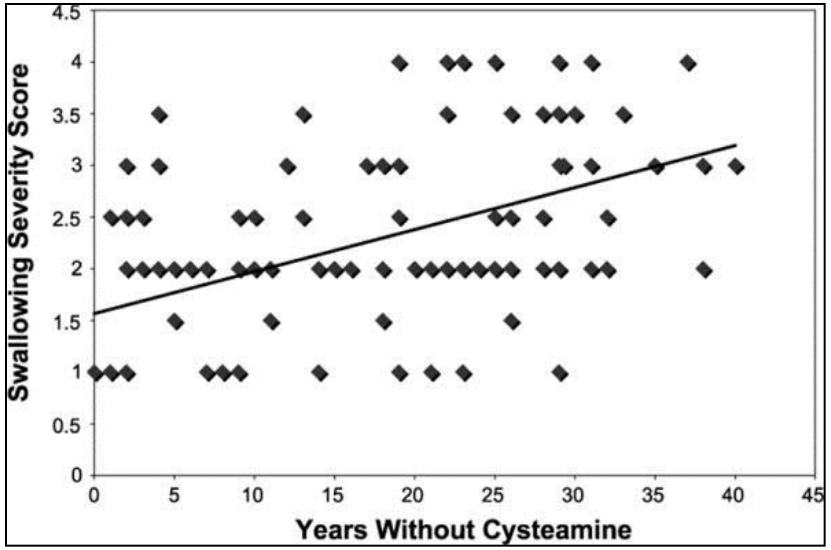
Anikster et al *Chest* 2001;119(2):394-401; Gahl et al *Ann Intrn Med* 2007;147(4):242-250;

Swallowing dysfunction

- Patients with myopathy may develop swallowing dysfunction due to deterioration of oropharyngeal muscles
- Adult patients with cystinosis have significant dysphagia for solid food
- Aspiration is a potentially severe complication
- Correlates with the presence of muscle atrophy

TOMASS results of the healthy adults, cystinosis patients and MD1 patients. The *p*-values indicate the difference between the patient group and healthy adults.

	Healthy adults	Cystinosis	MD1
	Mean (SD)	Mean (SD)	Mean (SD)
		p-value	*p*-value
Bites (n)	1.97 (1.11)	2.74 (1.20) $p < .01$	2.10 (0.99) $p = .73$
Masticatory cycles (n)	34.39 (11.78)	57.53 (28.11) $p < .01$	49.30 (15.69) $p < .01$
Swallows (n)	1.65 (0.87)	3.26 (1.59) $p < .01$	2.60 (0.84) $p < .01$
Total time (sec)	28.53 (10.80)	58.77 (28.89) $p < .01$	53.10 (15.85) $p < .01$



Sonies et al *Medicine (Baltimore)* 2005;84(3):137-146;
Van Rijssel et al, Mol Genet Metab, 2019

Neurocognitive abnormalities

- Patients may have mild neurocognitive abnormalities
- Specific impairments in the processing of visual information
- Relative weakness in visual motor, visual spatial and visual memory skills
  - may be associated with academic difficulties, primarily in arithmetic

Trauner et al, *J Pediatr*, 1988; Viltz et al, *J Pediatr*, 2013
Scarvie et al, *Perceptual and motor skills*, 1996; Trauner et al, *J Pediatr*, 2017

Central nervous system complications

18 adult cystinosis patients

At least 1 CNS complication	7 (38.9%)
Cognitive defect	5 (27.8%)
Memory defect	3 (16.7%)
Seizures	2 (11.1%)
Transient Stroke	1 (5.5%)

Mini Mental State examination was assessed in 12 patients

-median score was 27 (20-30)

Servais et al, JIMD, 2019

Neuroimaging study

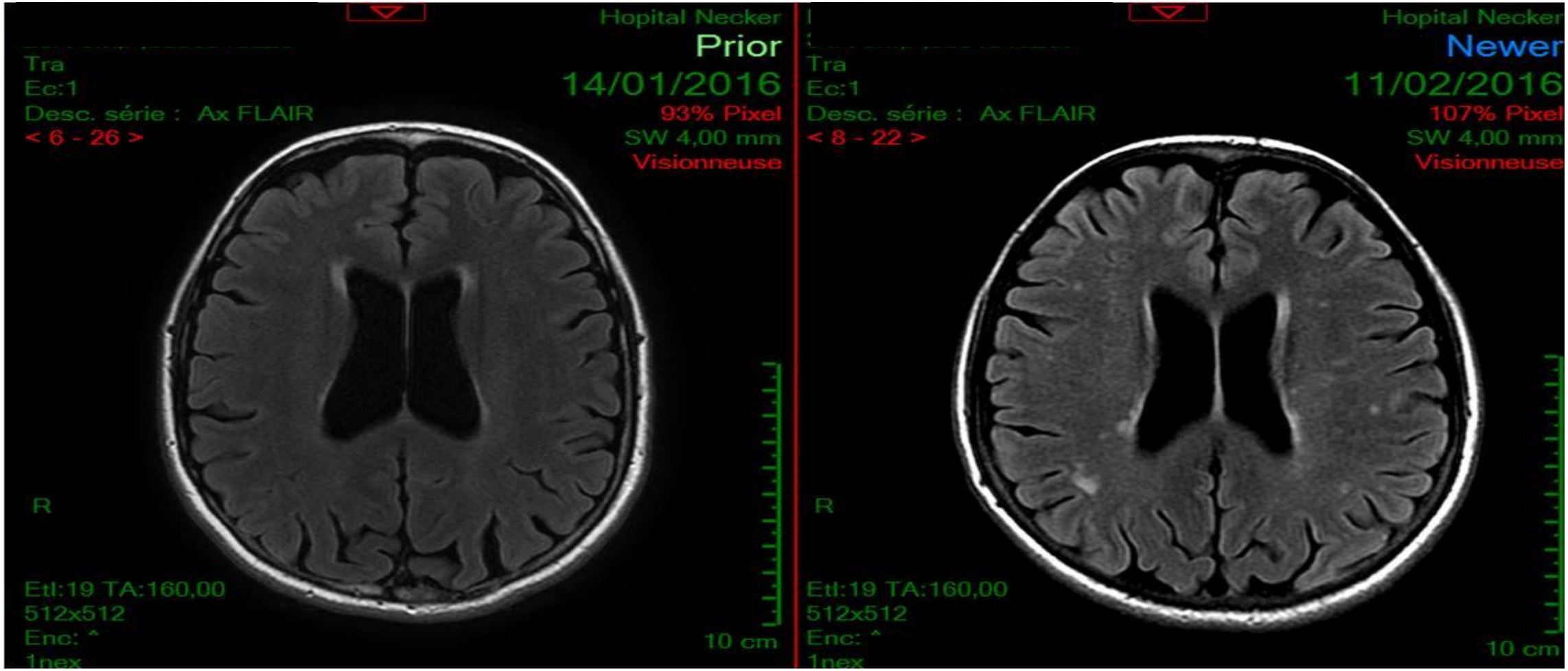
- Cohort of 21 patients
- High prevalence of clinical and radiological central nervous system defects in adult cystinosis patients:

  - 39% of adult patients have at least one clinical central nervous system complication

  - 89% have a radiological abnormality

- Cortical or central atrophy are observed in more than 70% of patients
  - but are not correlated with symptoms
- Leucocyte cystine levels are associated with decreased rest cerebral blood flow in the frontal cortex
- Compliance to cysteamine treatment could be one of the determinants of cognitive and neurological complications

Servais et al, *JIMD*, 2019

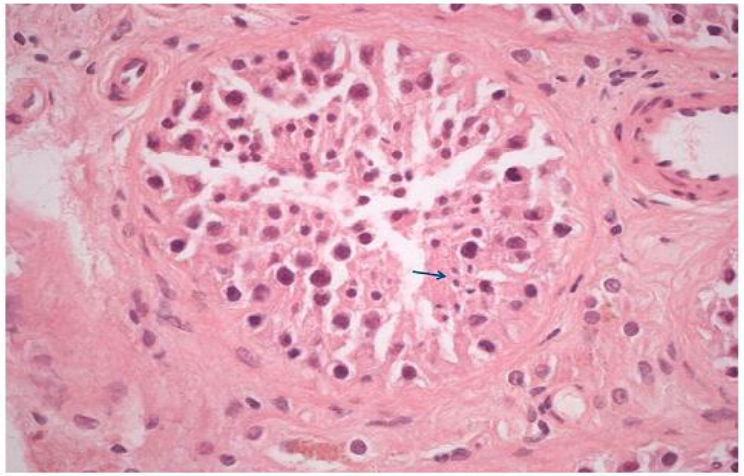


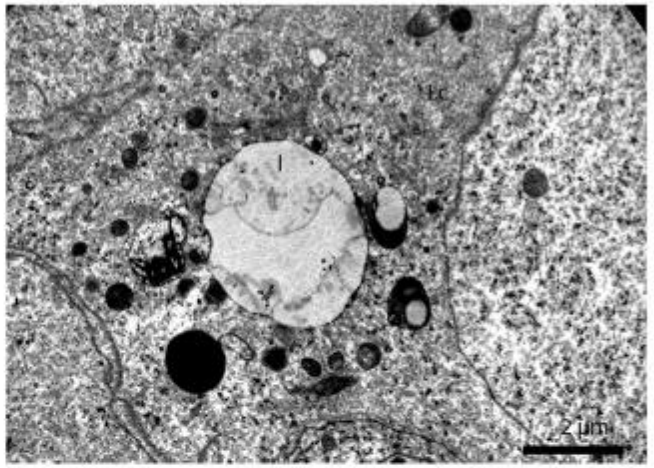
Isolated ventricular dilatation

Cortical atrophy, ventricular dilatation, diffuse white matter anomalies

Male fertility

- Hypergonadotropic hypogonadism in men>20 years
  - Testicular volumes and testosterone levels in the normal ranges
- Azoospermia or oligospermia in 80%
  - even if normal hormonal tests
- Fibrosis without germinal dysplasia and with sufficient spermatogenesis
  - Atrophy appears to be associated with lysosomal cystine overload of both somatic Sertoli cells within seminiferous tubules and Leydig cells in the testicular interstitium
- Cryostorage of semen could be an option
  - for 20% of young males with surgical sperm retrieval
- 1 successful conception reported through assisted reproductive technology



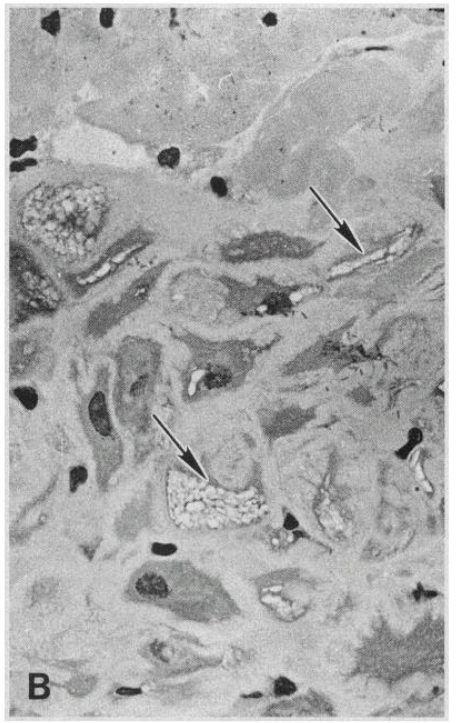


Lysosomes (l) within Leydig cells (Lc) in the testicular interstitium

Chik et coll, Ann Int med, 1993; Besouw et coll, Fertil Steril, 2010; Veys K et al, JIMD, 2017; Rohayem at al, Hum Reprod, 2021

Pregnancy

- The first successful pregnancy was reported in 1988 in a transplanted patient with unusual histopathological finding of cystine crystals packed in the maternal portion of the placenta
- Pregnancy should be planned
- Multidisciplinary follow up: renal obstetric clinic with expertise in complex pregnancies
- Treatment adaptation before pregnancy
  - stop cysteamine at diagnosis of pregnancy
- Increased risk of hypertension, diabetes, pre eclampsia
  - depend on renal function
  - cesarean section may be indicated because of cephalopelvic disproportion



Reiss et al, *NEJM*, 1988

Conclusion

- The spectrum of the disease has extended from a renal disease of childhood to a multisystem adult disease
- Management of systemic disease involvement is a new challenge
- There are substantial risks of non-adherence at adult age
- Psychosocial issues have to be adressed

ERKNet

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RaDiCo Rare Disease Cohorts

PARIS DESCARTES

Thank you for your attention!

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Next Webinars

IPNA Clinical Practice Webinars

Date: **23 Sept 21**

Speaker: **Francesco Emma**

Topic**: Approach to Tubular disorders: Salt-losing nephropathies**

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

Date: **05 Oct 2021**

Speaker: **Martin Konrad**

Topic: **Bartter and Gitelmann syndromes**

IPNA Clinical Practice Webinars

Date: **14 Oct 2021**

Speaker: **Detlef Bockenhauer**

Topic**: Distal Renal Tubular acidosis guideline**