Adult Issues and Management of Extra Renal Manifestations of Cystinosis

Neurological complication, ocular involvement, endocrinologic issues

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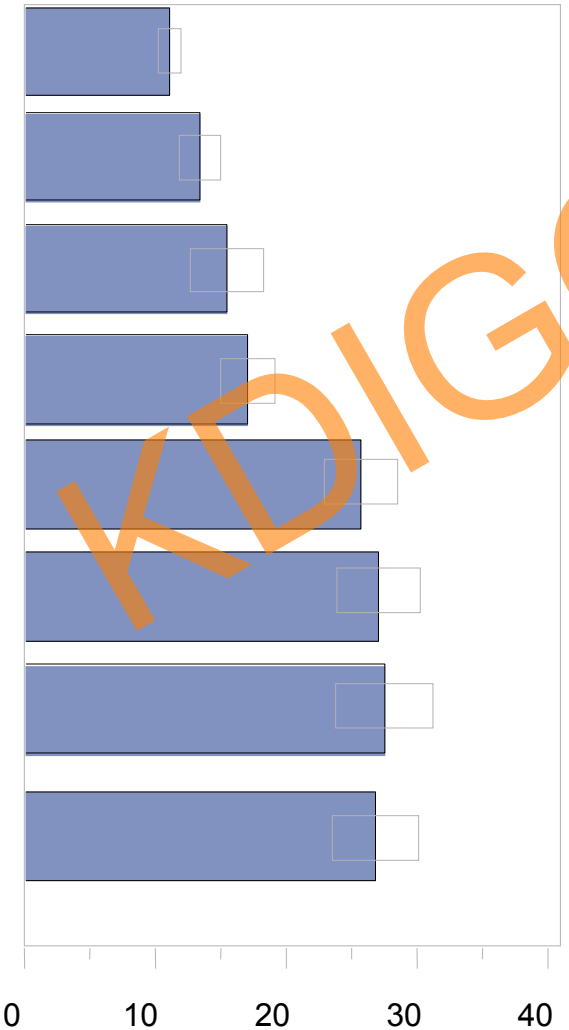
Disclosure of Interests

- Raptor pharmaceuticals France: consultancy
- Orphan Europe: research grant

Introduction

- Cystinosis provides a good example of a “pediatric” disease with a spectrum extending into adult medicine
- Specific treatment and kidney transplantation makes it possible for patients with infantile cystinosis to reach adulthood
- These patients are likely to be followed up in adult units and to suffer serious extrarenal complications of the disease

Chronology of complications



	Patients N=86	Age, mean (DS) (yrs)
ESRD	78 (91%)	11.1 (4.0)
Hypothyroidism	61 (72%)	13.4 (6.2)
Splenectomy	18 (21%)	15.5 (5.6)
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)

from Brodin Sartorius et al, Kidney Int , 2012

Chronology of complications

- Sequence of onset of complications: the first complication consisted in
  - ESRD (75.2%, median age 9.8 years),
  - hypothyroidism (19.8%, median age 8.7 years),
  - diabetes (2.5%, median age 4.8 years),
  - neuromuscular disorders (2.5%, median age 9.0 years)

- The most frequent complications were, in the chronological order, ESRD, hypothyroidism, and diabetes

Brodin Sartorius et al, Kidney Int , 2012

Hypothyroidism

- Cystine accumulation in thyroid follicular cells causes fibrosis, atrophy and dysfunction of the thyroid gland
- Thyroid impairment starts with a compensated hypothyroidism defined by a high TSH but a free T4 still in the normal range, followed by a confirmed hypothyroidism which may include clinical symptoms
  - Lucky et al, J Pediatr, 1977
- Thyroxine supplementation

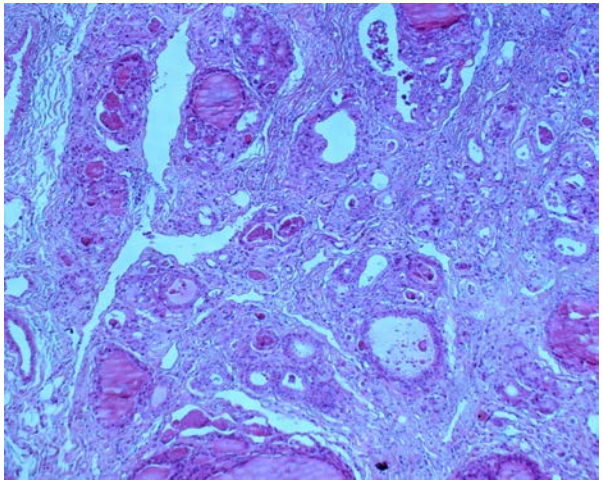
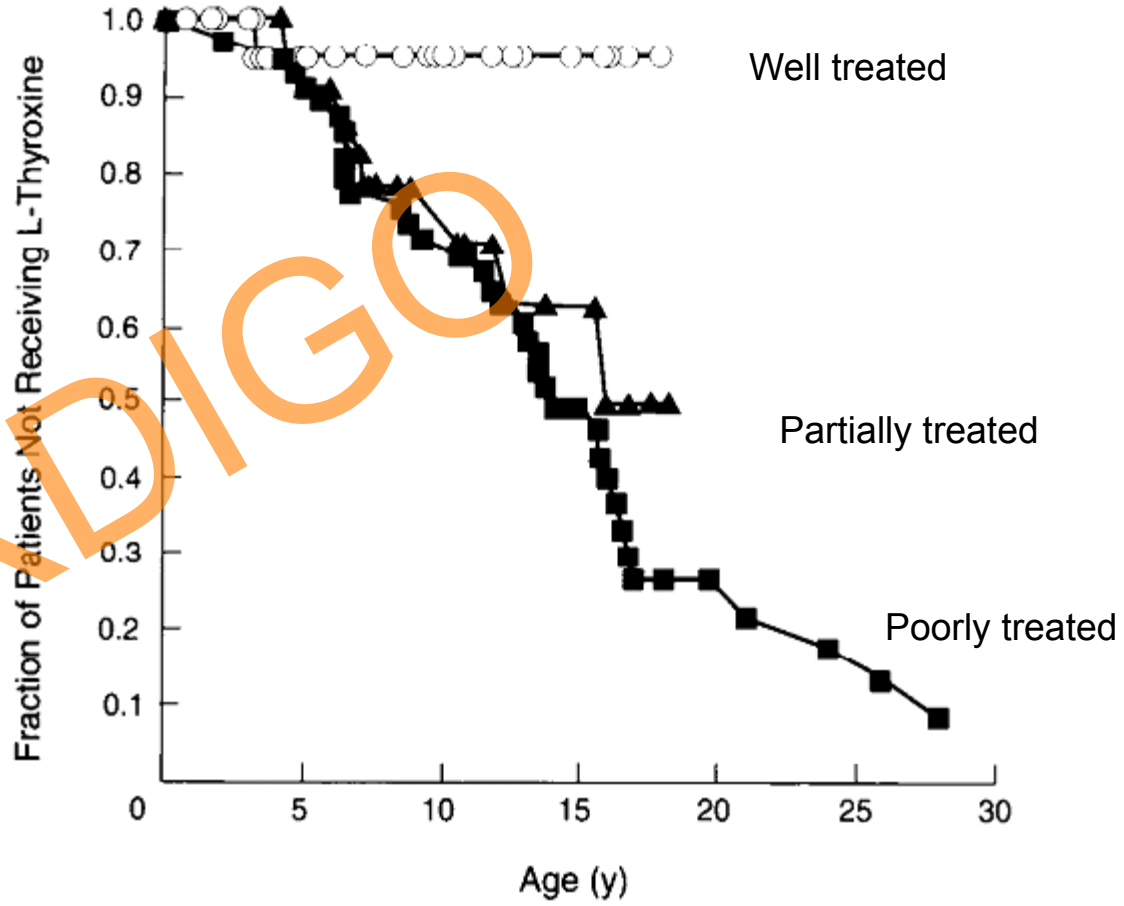


Photo MC Gubler

Hypothyroidism

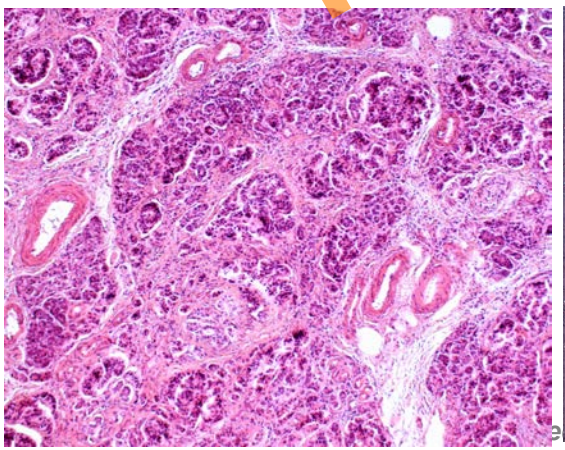
- Oral cysteamine therapy helps prevent hypothyroidism

Kimonis et al, JCEM, 1995



Diabetes

- Cystine accumulates in the bêta cells of the islets of Langerhans with massive cystal deposits in the pancreas and complete architectural disorganisation
  - Fivush et al, J Pediatr, 1988
- Glucose intolerance is characterized by a slow, progressive loss of insulin secretion and C-peptide production
  - There is no evidence of insulin resistance



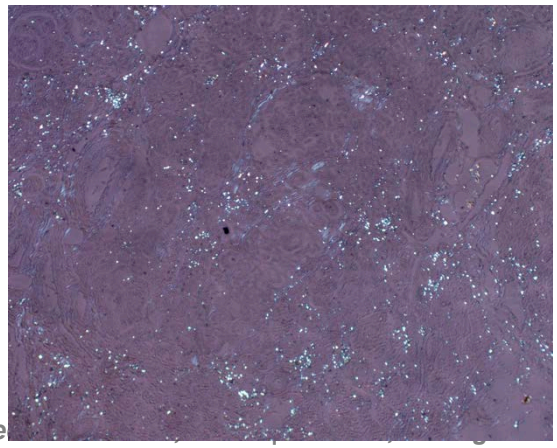
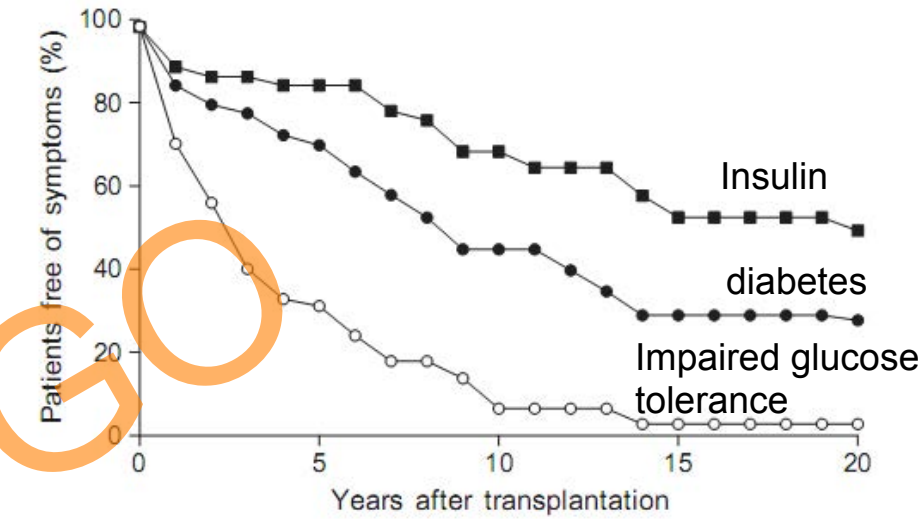


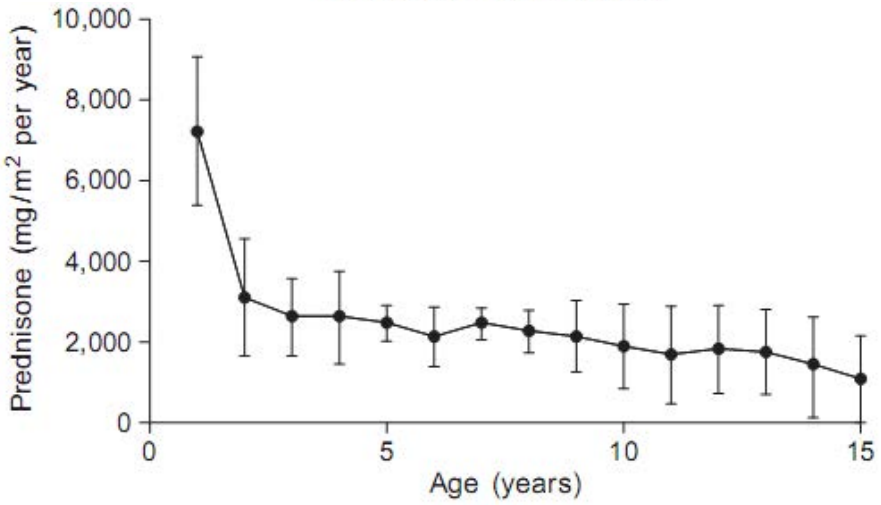
Photo MC Gubler

Diabetes

- After renal transplantation, the development of impaired glucose tolerance and diabetes depends mainly on the cystinotic process
  - Robert et al, Pediatr Nephrol, 1999
  - Filler et al, Eur J Pediatr, 1998

- The metabolic abnormalities gradually worsened over the years, while the mean doses of corticosteroids decreased





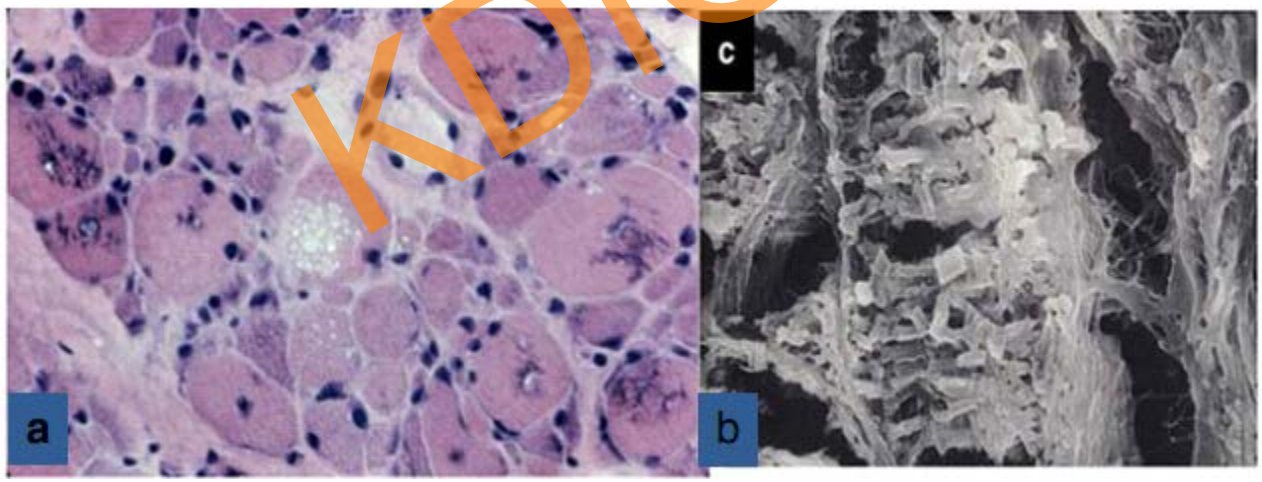
Robert et al,
Pediatr Nephrol, 1999

Questions

- How should glucose intolerance detected?
- Should repeated glucose tolerance tests be performed?

Myopathy

- Cystine deposition in muscles causes progressive distal vacuolar myopathy
- Type 2 fiber atrophy and cystine accumulation in perimysial cells



Nesterova et al, Pediatr Nephrol, 2013

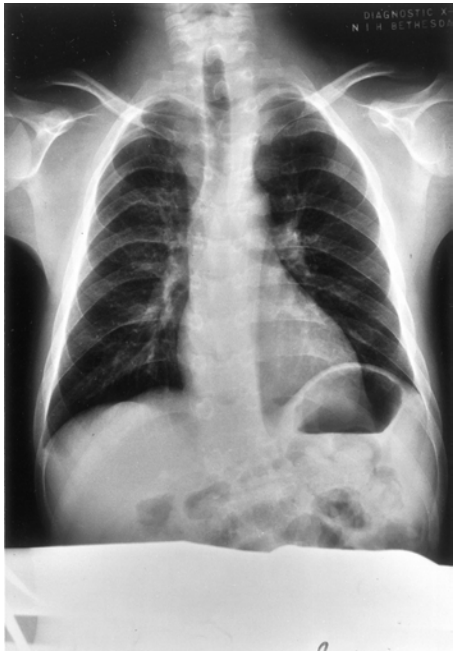
Myopathy

- Severe muscle atrophy and weakness
  - initially involving the distal extremities
- Distal myopathy can be detected even in the absence of clinically overt muscle weakness

Gahl et al, NEJM, 1988
Charnas, Ann Neurol, 1994
Vester et al, Pediatr Nephrol, 2000

Restrictive lung disease

- Thoracic muscle weakness results in an extraparenchymal pattern of restrictive lung disease with inspiratory and expiratory dysfunction
  - in adults who have not received long-term cystine depletion
- The severity of pulmonary disease correlates directly with the severity of myopathy
  - Anikster et al, Chest, 2001



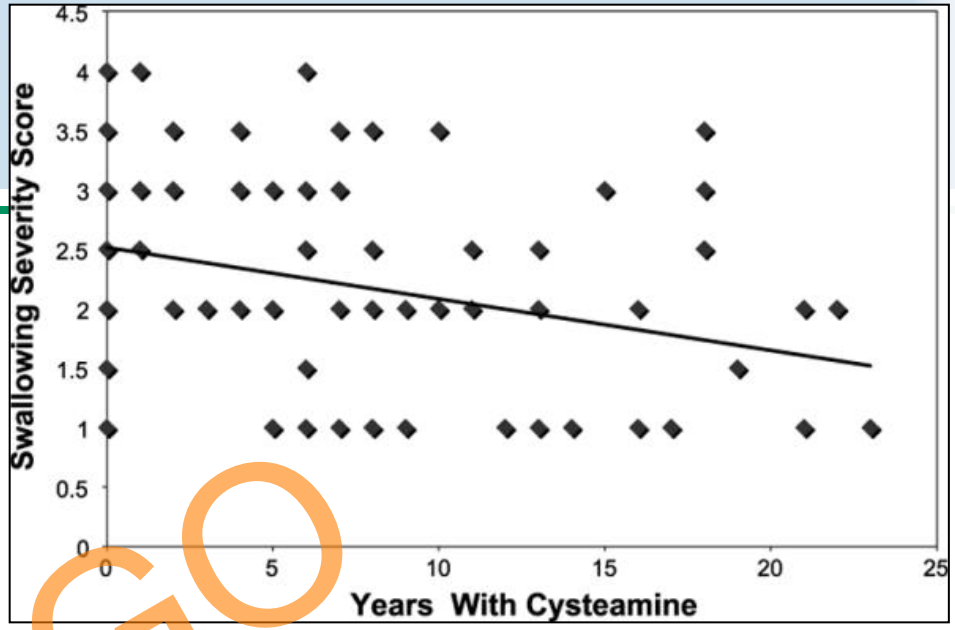
Chest radiograph of a patient showing conical thorax with normal parenchyma

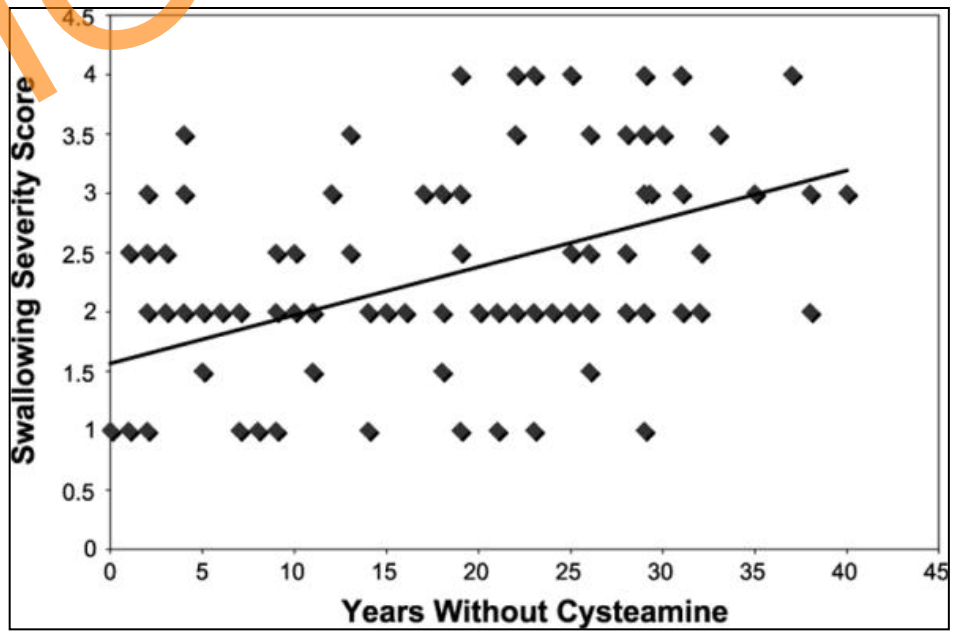
Swallowing dysfunction

- Most patients with myopathy develop swallowing dysfunction due to deterioration of oropharyngeal muscles
- Aspiration is a potentially fatal complication
- Correlates with the presence of muscle atrophy

Swallowing dysfunction

- Increases in frequency with age and number of years without cysteamine treatment
  - Sonies et al, Medicine, 2005





Central nervous system complications

- Rare
- Their frequency correlated directly with age
  - Broyer et al, JIMD, 1996
- Two forms are observed:
  - cystinosis encephalopathy
    - cerebellar signs and/or motor difficulties, mainly of the lower limbs
    - decrease of oral expression
    - development of pyramidal symptoms, somnolence, epileptic seizures, and mental deterioration finally resembling pseudo-bulbar palsy
    - motor coordination difficulties and muscular hypotonia
    - extrapyramidal symptoms
  - stroke-like episode with ischemic lesions
    - Broyer et al, JIMD, 1996
    - Fink et al, Arch Neurol, 1989
- Benign intracranial hypertension presents with headaches and papilledema Dogulu, J Pediatr, 2004

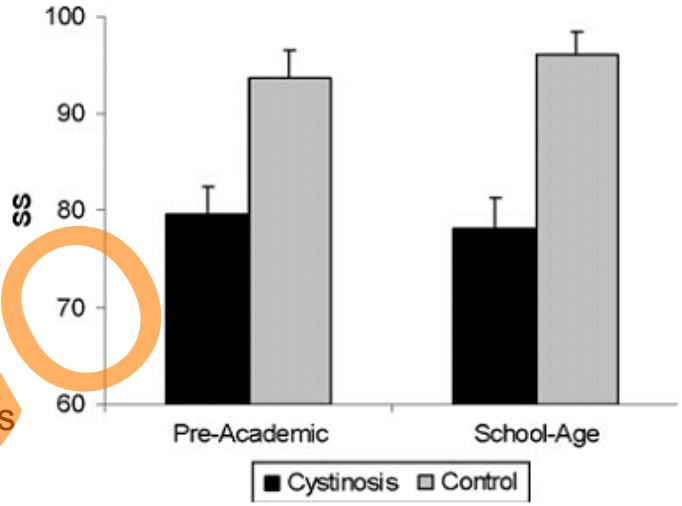
Neurocognitive abnormalities

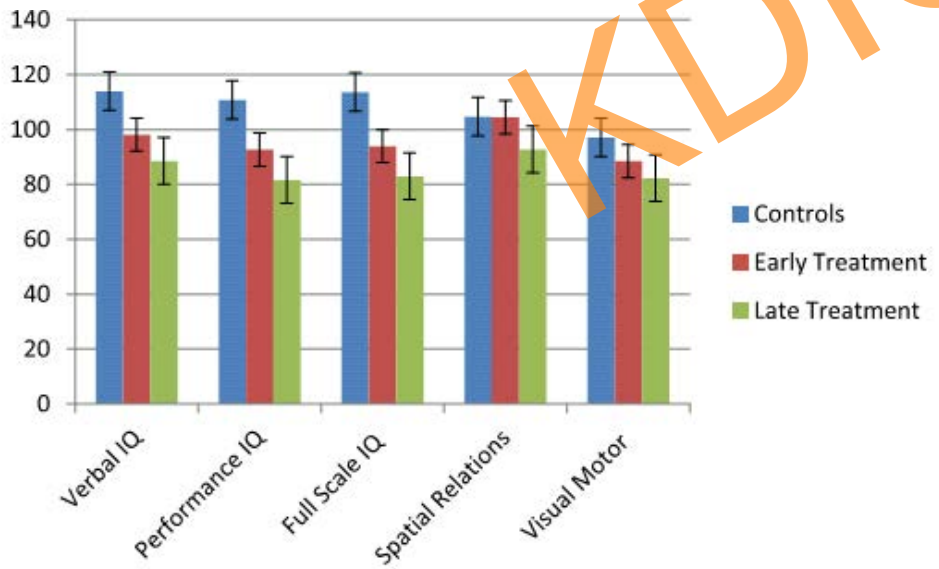
- Patients have generally normal intelligence but may have mild neurocognitive abnormalities
  - Trauner et al, J Pediatr, 1988
  - Viltz et al, J Pediatr, 2013
  - Scarvie et al, Percept Mot Skills, 1996
- Specific impairments in the processing of visual information: relative weakness is found in visual motor, visual spatial and visual memory skills, and may be associated with academic difficulties, primarily in arithmetic

Neurocognitive abnormalities

- A fine-motor coordination deficit has also been documented
  - Trauner et al, Pediatr Nephrol, 2010

Mean standard scores on the Motor Coordination Test for the cystinosis and control preacademic and school-age groups





- Early treatment appears to improve intellectual function

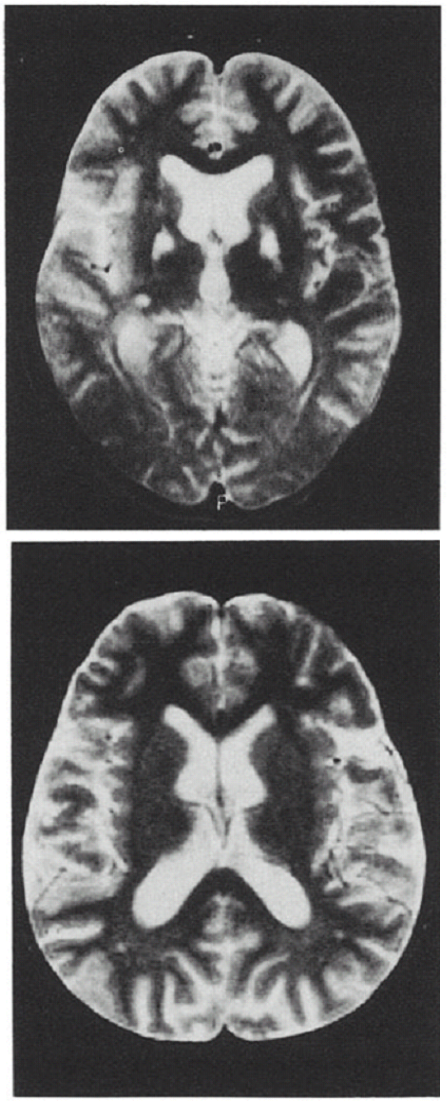
Viltz et al, J Pediatr, 2013

Brain imaging

- Cerebral atrophy: observed in all patients with central nervous system symptoms, but also in patients without gross central nervous system clinical abnormality
  - Broyer, JIMD, 1996
  - Nichols et al, Pediatr Neurol, 1990
- Calcifications may be detected
  - Gahl et al, Ann Int Med, 2007
- Mineralization of the basal ganglia
  - specific to severe encephalopathy
- By magnetic resonance imaging, children with cystinosis evidence selective changes in cerebral white matter in areas of the dorsal visual pathway
  - Bava et al, Cortex, 2010

Brain imaging

- Cysteamine may stop the progression of encephalopathy and in some cases could improve neurological deficits



T2-weighed axial MRI. Moderate atrophy. Bilaterally hyperintense signal is seen in the region of the internal capsule.

Moderate atrophy is stable but the internal capsules are of normal signal. The hyperintensity has disappeared.

Broyer et al, JIMD, 1996

Questions

- How effective is the exercise to avoid the myopathy?
- What is the role of carnitine or growth hormone in patients with cystinosis myopathy?
- Are pulmonary function tests recommended to monitor progression of extraparenchymal lung dysfunction?
- Should specialized ORL and orthophonists be involved in the treatment of swallowing dysfunction?

Fertility status in male patients

- Primary hypogonadism
- Testosterone replacement therapy allows pubertal development, but does not prevent infertility
  - Germinal dysplasia, increased fibrosis and Leydig cell hyperplasia

Chik et al, Ann Int med, 1993

Fertility status in male patients

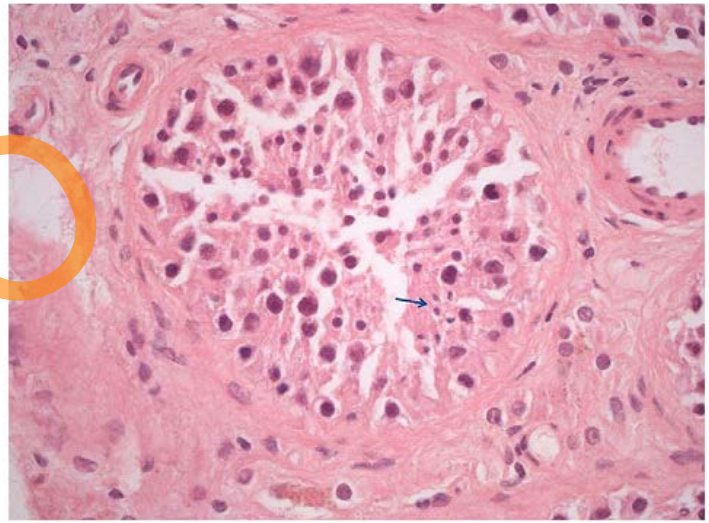
- Study of 7 patients between 19 and 43 years
  - Treated with cysteamine starting from 1,5 to 23 years (median 4)
  - 5 transplanted, one on hemodialysis, one preterminal renal failure
- Dysfunction of the pituitary-testicular axis seems to be related to the metabolic disease and not to the degree of renal failure
- Azoospermia even in patients with normal hormonal status
- Testicular ultrasound showed mild interstitial fibrosis

Besouw et al, Fertil Steril, 2010

Fertility status in male patients

- Testicular biopsy showed marked fibrosis with no germinal dysplasia and sufficient spermatogenesis

Besouw et al, Fertil Steril, 2010



Normal spermatogenesis and presence of the different stages of maturation. The arrow indicates secondary spermatids (spermatozoa).

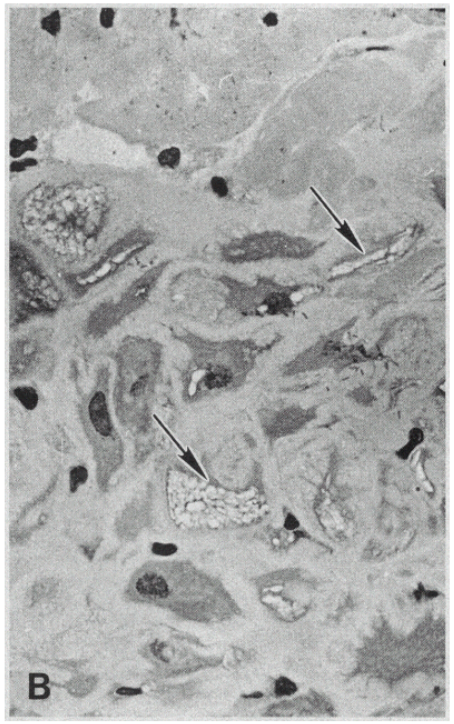
Questions

- Can cysteamine penetrate the blood-testes barrier and deplete testicular cystine accumulation?
- May cysteamine itself decrease somatostatin levels, inhibit ghrelin release, diminish testosterone production and spematogenesis?
- Might viable semen be obtained by testicular sperm extraction?

Pregnancy

- Pubertal delay in female cystinotic patients
  Protective effect on gonads of an early cysteamine treatment
  Tête and Broyer, in Cystinosis, 1999

- 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
  Reiss et al, NEJM, 1988



Pregnancy

- Cysteamine produced dose-dependent developmental toxicity
  - apparent no adverse effect observed level of 75 mg/kg/day
  - Specific malformations were associated with this effect (cleft palate, kyphosis), as well as intrauterine growth retardation and fetal death

    Beckman et al, Teratology, 1998
- Pregnancies may be complicated by infections, hypertension, diabetes, growth retardation, proteinuria or pre-eclampsia
  - In some patients cesarean section may also be indicated because of cephalopelvic disproportion

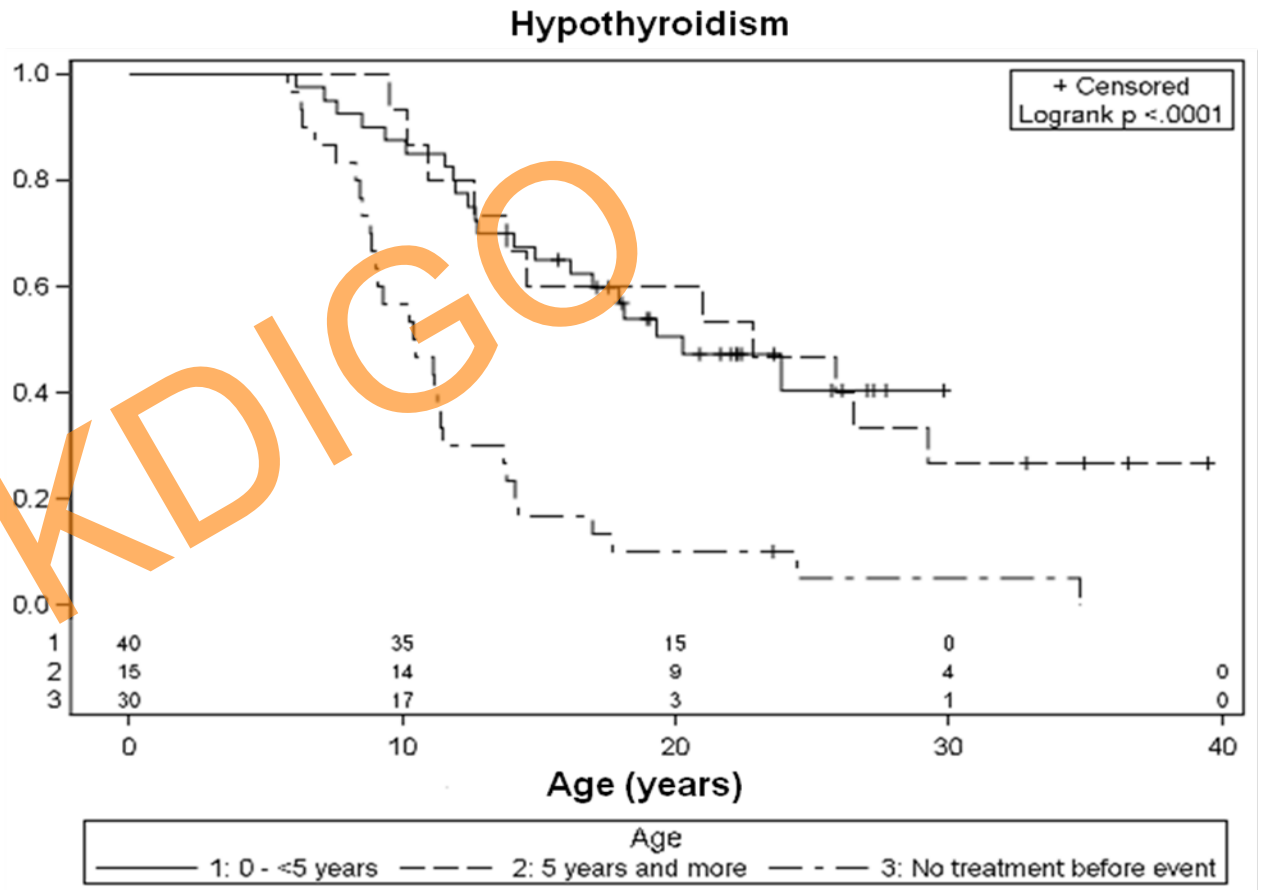
Effects of cysteamine therapy

- The incidence of hypothyroidism, diabetes, and neuromuscular disorders is significantly reduced when cysteamine is started before 5 years of age in comparison with the absence of treatment
  - Starting therapy after 5 years still decreases the incidence of hypothyroidism and diabetes when compared with no treatment
- The total number of events among ESRD, hypothyroidism, diabetes, neuromuscular events, and death is significantly lower in the group treated before 5 years than in the other groups

Brodin-Sartorius et al, Kidney Int, 2011

Hypothyroidism

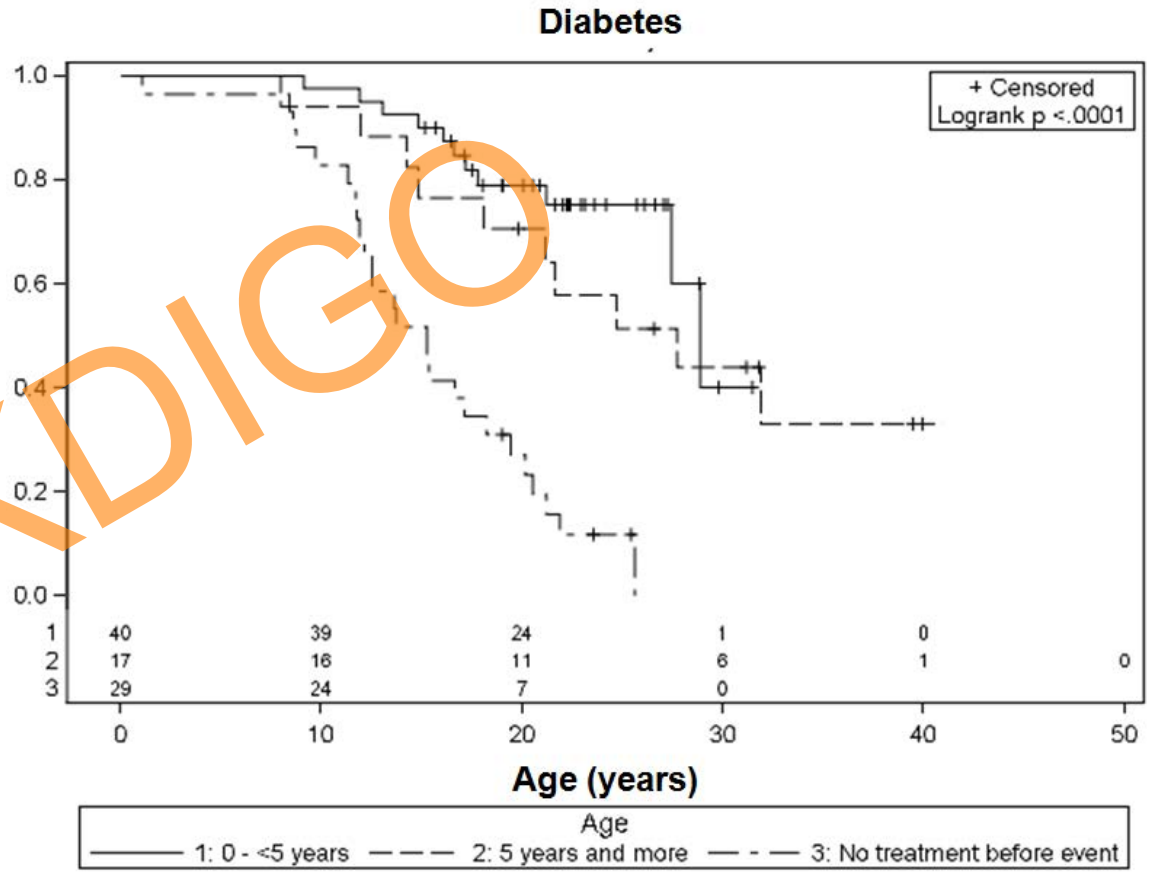
- Treatment started before 5 years of age is associated with significant delay in the occurrence of hypothyroidism
- A significant delay is still noticed between patients who started treatment after the age of 5 years compared with the absence of treatment



Brodin-Sartorius et al, Kidney Int, 2011

Diabetes

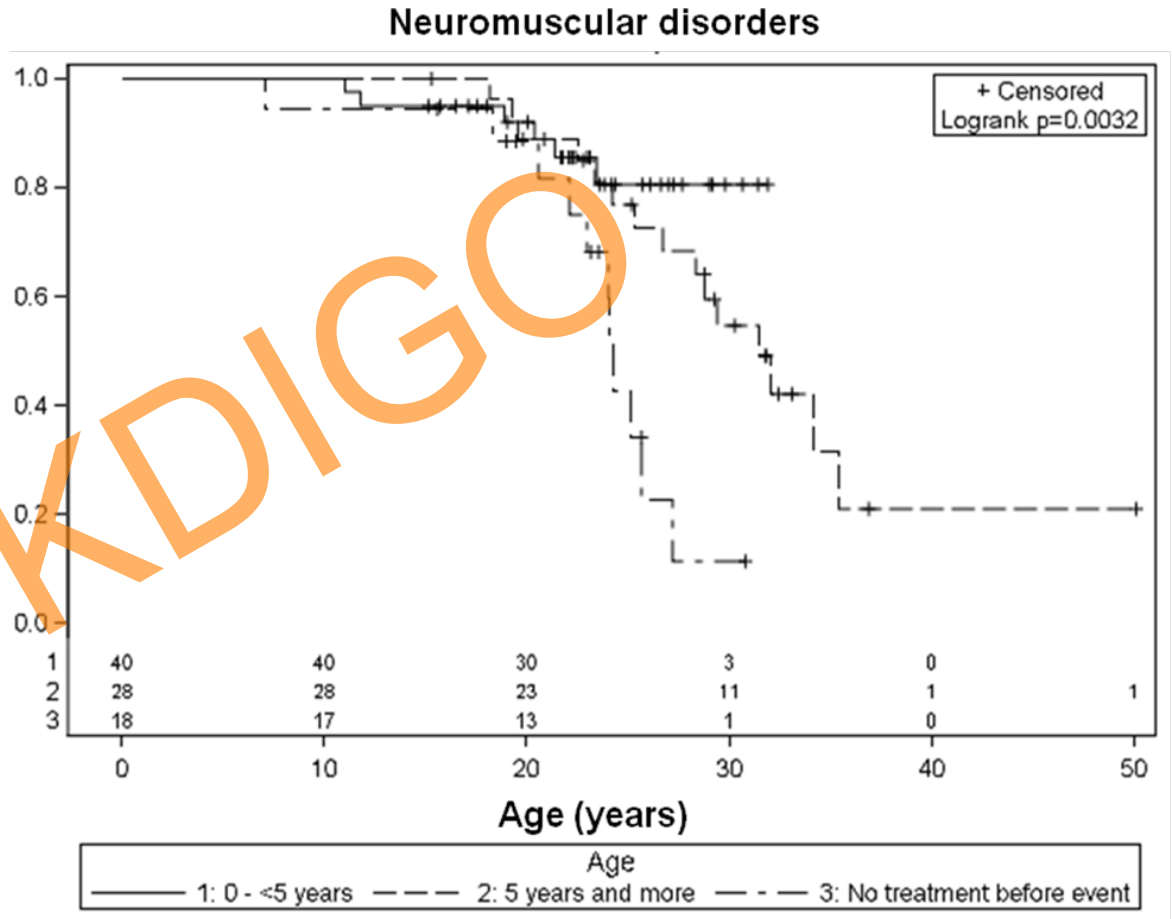
- Treatment started before 5 years of age is associated with significant delay in the occurrence of diabetes
- A significant delay is still noticed between patients who started treatment after the age of 5 years compared with the absence of treatment



Brodin-Sartorius et al, Kidney Int, 2011

Neuromuscular disorders

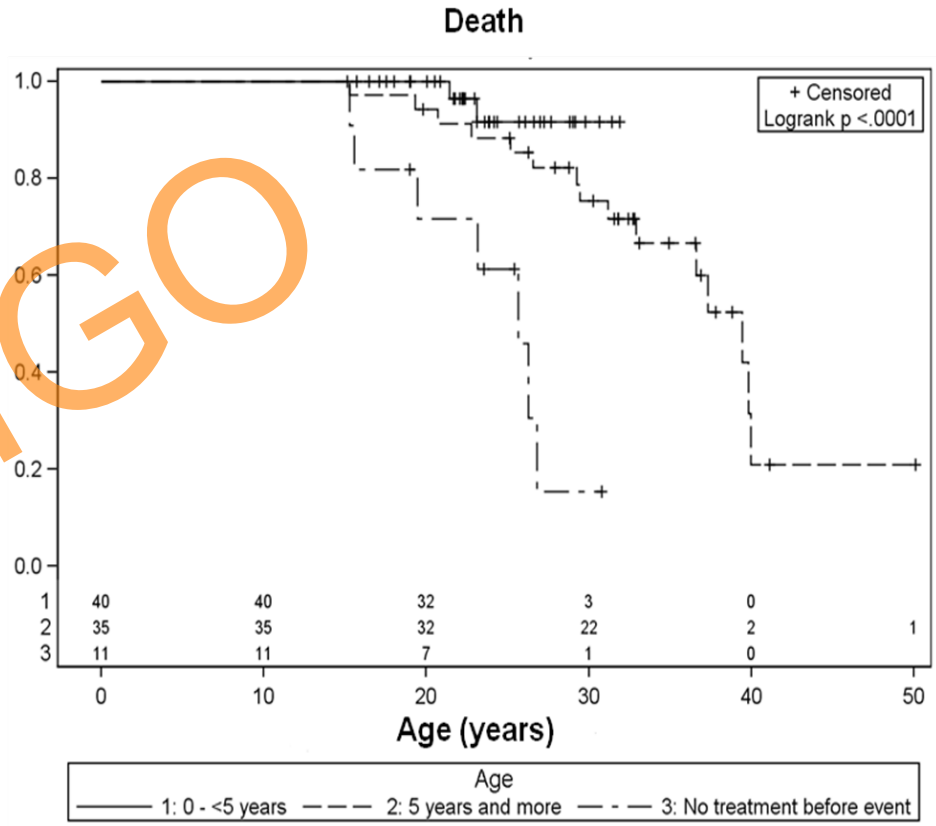
- Treatment started before 5 years of age is associated with significant delay in the occurrence of neuromuscular disorders



Brodin-Sartorius et al, Kidney Int, 2011

Death

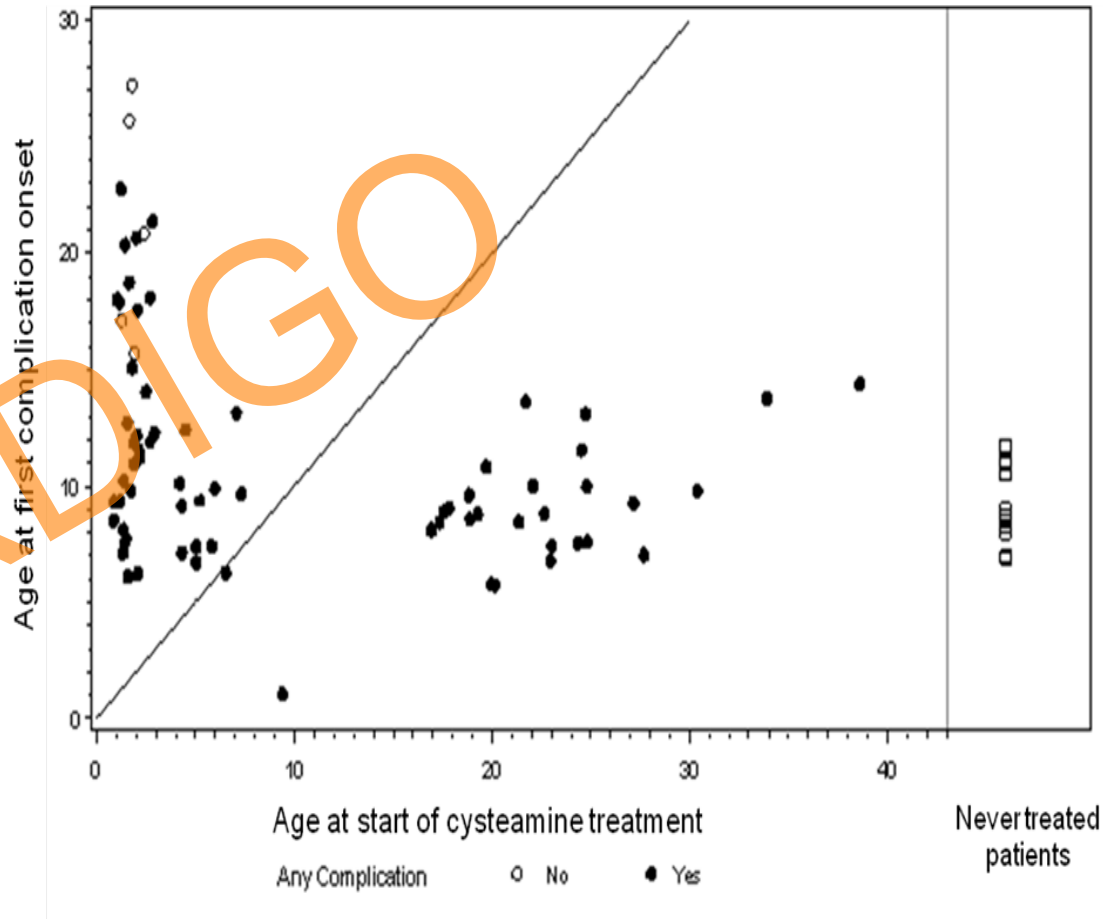
- Life expectancy is significantly improved in the before 5 years treated patients versus the absence of treatment
- Starting cysteamine after 5 years still significantly improves the life expectancy in comparison with the untreated patients



Brodin-Sartorius et al, Kidney Int, 2011

Age at the first complication onset according to the age at the start of cysteamine treatment

- All patients who had the first complication after 15 years of age were treated with cysteamine before 3 years of age
- Only five percent of patients, with a median age of 20.9 years (15.7–27.2), all treated before 2.5 years of age, did not develop any complications



Brodin-Sartorius et al, Kidney Int, 2011

Clinical Characteristics of Patients Who Received Long-Term Oral Cysteamine Therapy

Characteristic	Duration of Cysteamine Therapy	
	<8 Years (*n* = 61)	≥8 Years (*n* = 39)
Age, *y*	26.4 (6.0)	25.8 (7.3)
Time on cysteamine therapy, *y*	2.0 (2.4)	15.1 (5.4)
Time off cysteamine therapy, *y*	24.3 (5.9)	10.7 (10.1)
Height, *cm*	143.6 (11.2)†	154.7 (10.8)
Weight, *kg*	45.3 (10.7)	53.2 (10.4)
Age at transplantation, *y*	11.0 (3.2)	14.8 (4.6)‡
Serum cholesterol level§		
mmol/L	5.05 (1.48)	4.40 (1.06)
mg/dL	195 (57)	170 (41)
Complications per patient, *n*	4.0 (2.0)	2.2 (2.2)
Hypothyroidism, *n/n (%)*	53/61 (87)	22/39 (56)
Deaths, *n/n (%)*	30/61 (49)	3/39 (8)

Gahl et al, Ann Int Med, 2007

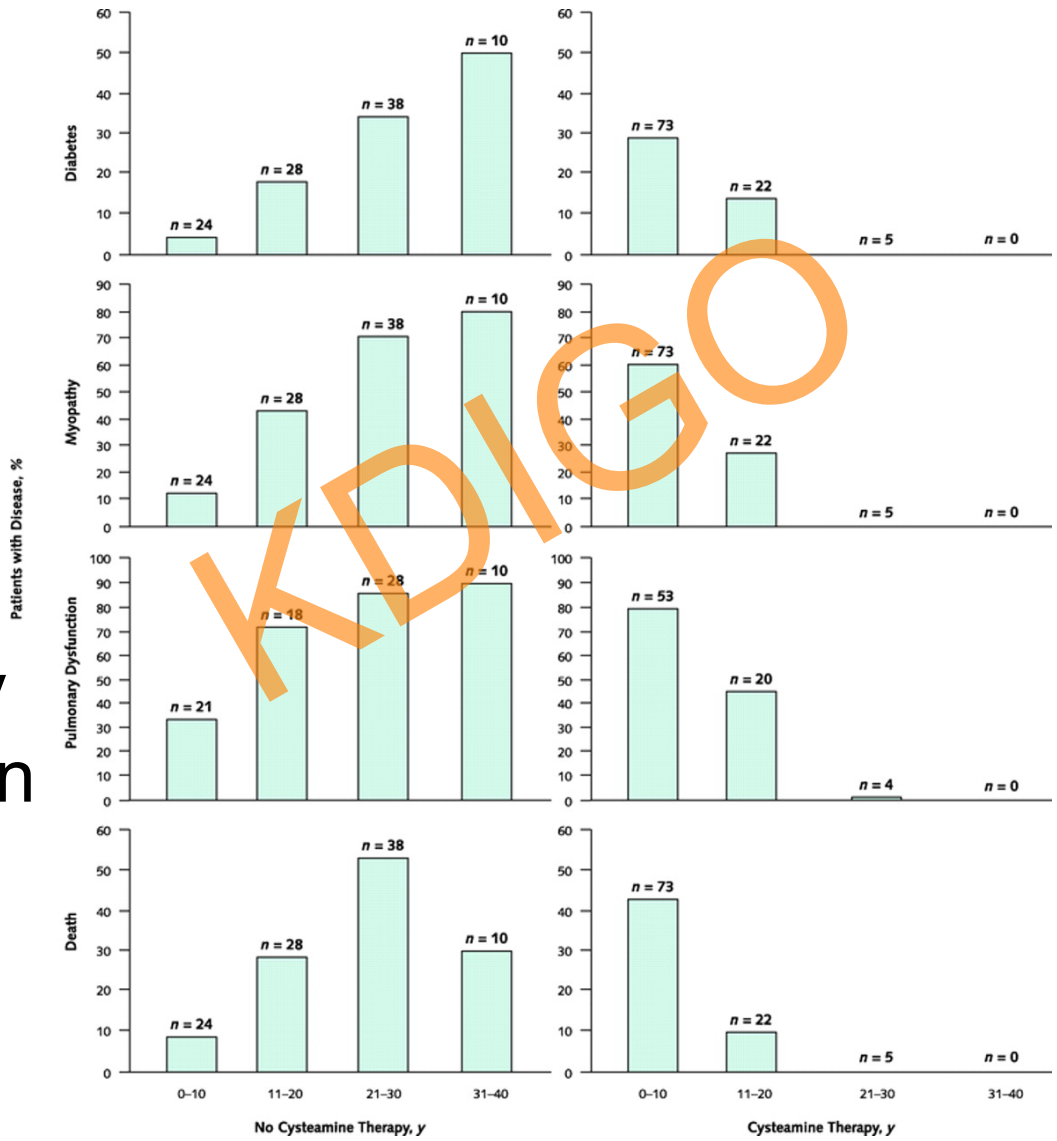
Frequency of cystinosis complications, by duration of oral cysteamine therapy

diabetes

myopathy

pulmonary dysfunction

death



Gahl et al, Ann Intern Med, 2007

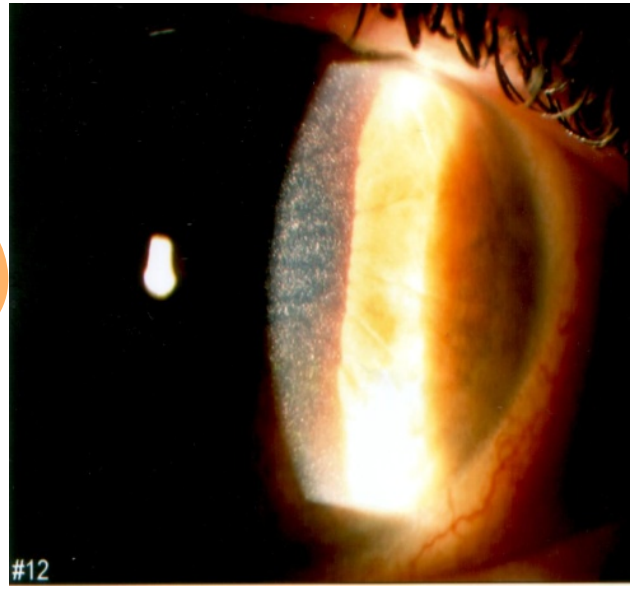
Questions

- Which will be the incidence of extrarenal complications in a cohort of patients with early treatment and good compliance?
- What is the optimal cysteamine dose in adult cystinosis patients?
- Is there evidence for life-time therapy with substrate-depleting agents?
- What are the adherence issues for cysteamine treatment?

Eye complications

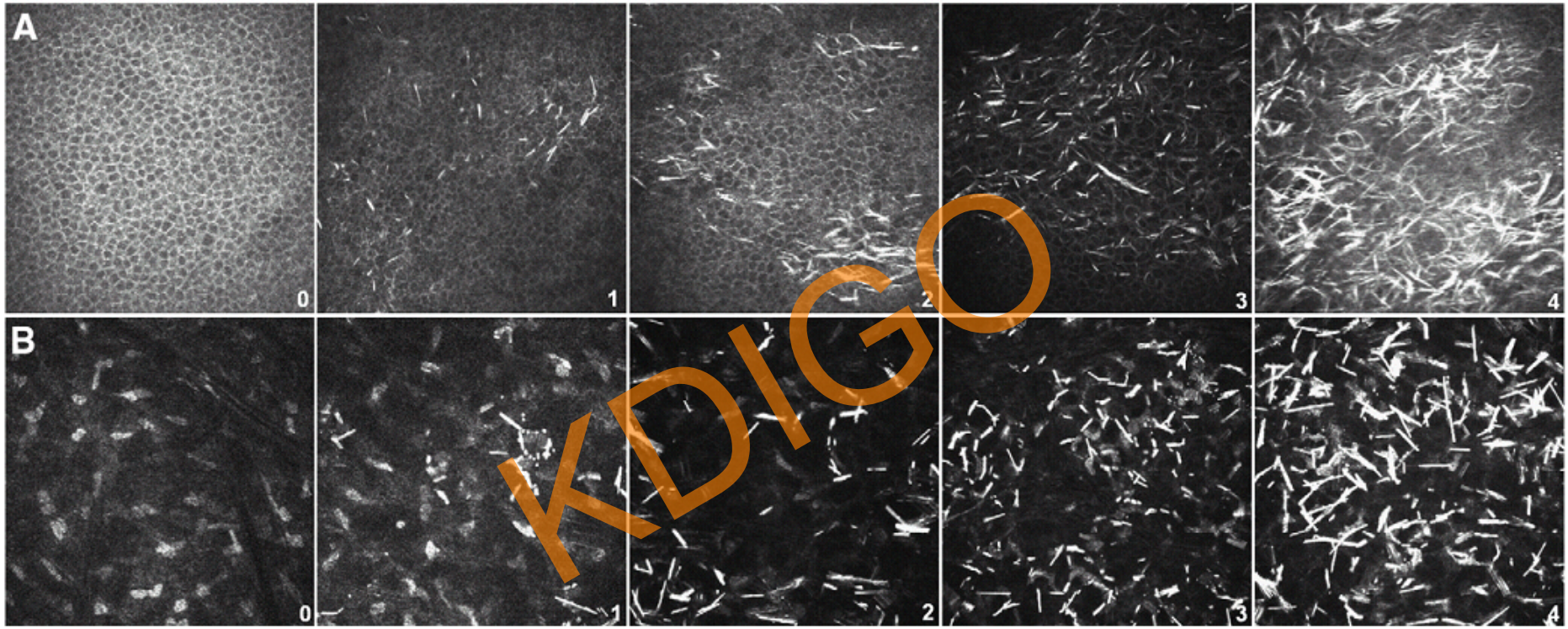
- The most frequently described ocular manifestation is crystal deposition in the conjunctiva and cornea
- Increase with age and gradually leads to photophobia, blepharospasm, superficial punctate keratopathy and recurrent corneal erosions
- In older patients, filamentous keratopathy, band keratopathy and peripheral corneal neovascularization may also be observed

- Gahl et al, Mol Genet Metab, 2000



Corneal crystals typically appear as needle-shaped and highly reflective crystals by a slit lamp biomicroscopy

Eye complications



- In vivo confocal microscopy images of corneal crystal deposits in the epithelium (A) and stroma (B).
- Percent of deposits in the field of each image: 0: no crystal; 1: b25%; 2: 25–50%; 3: 50–75%; 4: N75%.
  - Labbe et al, Mol Genet Metab, 2014

Eye complications

- Oral cysteamine has no effect on cystine corneal crystals
- Topical treatment with cysteamine hydrochloride eye drops is effective in reducing corneal crystal density and alleviating symptoms regardless of age
- However, results have been obtained with a 0.55% collyrium taken 6 to 10 times a day
  - Such a high number of administrations is difficult to maintain on a regular basis in adults
  - Eye drops should be kept refrigerated to prevent oxidation
  - In clinical practice eye drops are eventually used 3 to 6 times daily
- Very rarely, not treated patients develop corneal lesions severe enough to require a corneal transplant

Eye complications

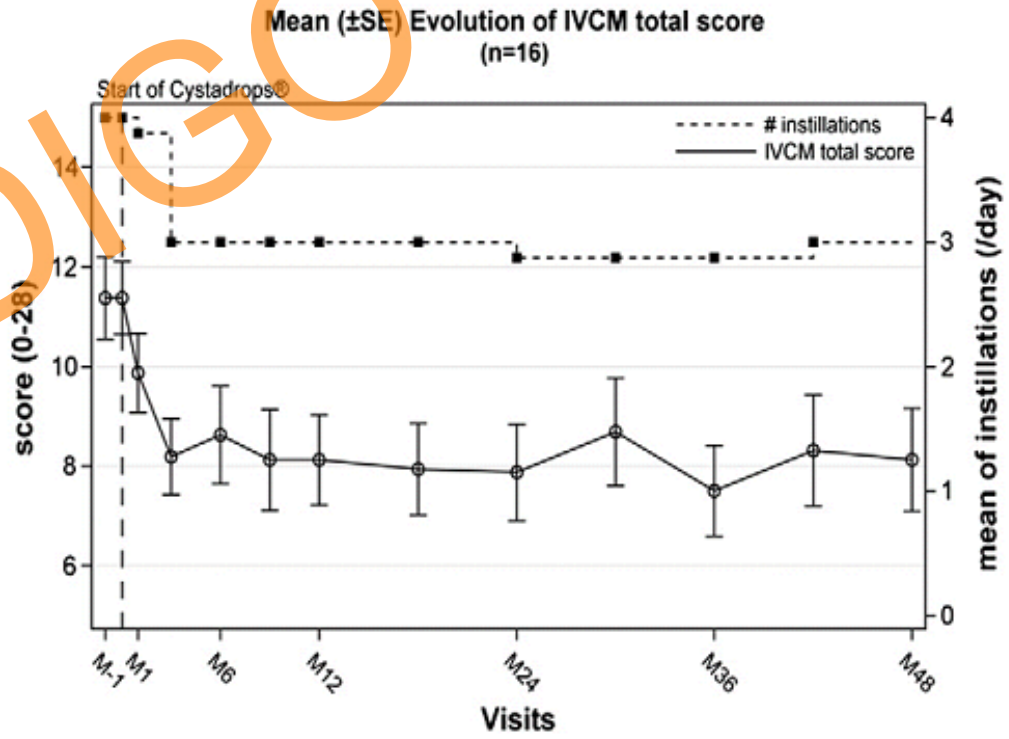
- A commercial 0.44% cysteamine ophthalmic solution (Cystaran®) has recently been approved for clinical use in the USA

Eye complications

- A 0.55% gel formulation (Cystadrops®) has been developed

Good efficacy and safety profile with a decrease nubber of instillations (3+/-1)

Labbe et al, Mol Genet Metab, 2014



Conclusion

- Management of systemic disease involvement is a new challenge
- What is the optimal multi-disciplinary follow-up of cystinosis patients?
- Who are the relevant physicians-specialists to participate in cystinosis clinics?