Cystinosis: management of renal disease progression
from childhood to adulthood

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Overview of the lecture

• Introduction
  • biochemical and genetic basis of cystinosis

• Insights into pathogenesis of cystinosis
  • mechanisms of renal disease progression

• Treatment of cystinosis
  • cysteamine treatment
  • supportive therapies
  • novel therapies

• Take home messages
Introduction
Cystinosis

• An autosomal recessive disease caused by lysosomal accumulation of cystine due to defective exodus of cystine out of the lysosomes

• Incidence ~1:100,000 - 200,000 newborns (clustering in some populations)

• Most common cause of inherited generalized proximal tubular dysfunction (renal Fanconi syndrome) progressing to end stage renal disease (ESRD)
Cystinosis as a cause of ESRD

- ESPN/ERA-EDTA 2016: 255/14,366 1.8%
- NAPRTCS 2008: 104/7,037 1.5%
- ANZDATA 2009: 4/369 1.1%
Lysosomal cystinosin (CTNS, 17p13) is mutated in cystinosis

Most common mutation in North European population: 57 kb deletion

> 100 other mutations described
- Mutation detection rate > 95%:
  - Nonsense, missense, splice-site, promotor, micro-deletions, duplications
- Genotype – phenotype correlation: severe mutations → severe phenotype

Town et al. Nat Genet 1998
Attard et al. Hum Mol Genet 1999
Kalatzis et al. Hum Mol Genet 2004
Levtchenko et al. Eur J Hum Genet 2014
Cysteamine depletes intra-cellular cystine accumulation

Cysteine-cysteamine

PQLC2 transporter

INTERCELLULAR NONPROTEIN, CYSTINE nmol/mg PROTEIN

TIME (h)

1 mM
0.1 mM
0.01 mM
control

Thoene JG, Oshima RG, Crawhall JC, Olson DL, Schneider JA
Cystinosis. Intracellular cystine depletion by aminothiols in vitro and in vivo.
J Clin Invest. 1976, 58: 180
Kidney is the first organ affected by cystinosis
Pathogenesis of kidney disease in cystinosis

**Podocyte disease:**
glomerular proteinuria, FSGS

**Proximal tubule (PT) disease:**
renal Fanconi syndrome

**Renal interstitial inflammation and fibrosis:**
progressive CKD

**Involvement of other tubular segments?**
Proximal tubule (PT) dysfunction

- Loss of PT cells into urine (Ivanova et al. 2016)

- PT cell apoptosis (Park et al. 2002, 2006; Gaide Chevronnay et al. 2014)


- Loss of PT mass

- Renal Fanconi syndrome

- Dedifferentiation
- Reduced expression of PT transporters → Renal Fanconi syndrome

- Oxidative stress → Inflammation, fibrosis
Podocyte dysfunction

- Loss of podocytes into urine (Ivanova et al. 2016)
- Increased podocyte motility and decreased adhesion in vitro (Ivanova et al. 2016)
- Morphologic podocytes changes
  - Podocyte foot process effacement
  - Multi-nucleated podocytes (Ivanova et al. 2016; Elmonem et al. 2017)
- Glomerular proteinuria
- FSGS lesions
- Global collapse

Multi-nucleated podocytes (Lusco et al. 2017)
Renal interstitial inflammation and fibrosis

- Cystine crystals are mainly located in renal interstitium (free or in histiocytes), and rarely in PT cells or podocytes.

- Inflammasome activation by cystine crystals (increased expression of inflammasome-related genes Casp-1, Pycard, Il-18, Il18r1, Il1r1, Il1rl2):
  - Production of pro-inflammatory cytokines and chemokines
  - Renal interstitium inflammation and fibrosis

Prencipe et al. JASN 2014
Treatment of kidney disease in cystinosis
Treatment of kidney disease of cystinosis

• Cysteamine treatment

• Symptomatic treatment of renal Fanconi syndrome
  • replacement of losses
  • indomethacin

• Anti-proteinuric treatment

• Novel & experimental treatments
Cysteamine treatment improves kidney function survival

1.3 – 1.9 g/m²/day

Divided in:
4 daily doses (Cystagon®)
2 daily doses (Procysbi®)

Side effects:
GI complaints
Bad breath and skin smell

Markello TC, Bernardini IM, Gahl WA.
Improved renal function in children with cystinosis treated with cysteamine
N Engl J Med. 1993, 1157
Age at start RRT

Data from ESPN/ERA-EDTA Registry

n = 245 (1-19 years old)

Overall improvement of kidney survival in cystinosis 1985 – 2008: 4 years

Van Stralen et al. CJASN 2011
Probability of ESRD depending on cysteamine treatment

Brodin-Sartorius et al. KI 2012
Cysteamine attenuates chronic CKD progression in non-cystinotic kidney disease

Unilateral uteter obstruction model (mice)

↓ interstitial matrix deposition

Day 14 UUO

Control

Cysteamine

Day 7

Day 14

A

B

C

D

Interstitial macrophage infiltration

↓

Control

Cysteamine

↓ Interstitial myofibroblast accumulation

↓ TGF-β pathway

↓ Reactive oxygen species generation

→ attenuates progression chronic kidney injury

Akai et al. JASN 2014

AKI model (mice)

A

B

C

D

E

↓

Control

Cysteamine
Indomethacin treatment reduces urinary losses due to renal Fanconi syndrome

- Rational: increased urinary PGE + successful use of indomethacin in one child (Bétend et al. 1979)
- 3 children with cystinosis
- Dose: 3 mg/kg/day, 9-18 months
- Increased sodium reabsorption, reduced free water clearance, improved plasma concentrations of Na, K, bicarbonate, P
- No acceleration of kidney function deterioration

Fig. 3 Effects of 2 weeks’ treatment with indomethacin on plasma electrolyte concentrations.

Haycock et al. Arch Dis Child 1982
Anti-proteinuric treatment: use of ACE inhibitors

Wilmer et al et al. AJKD 2008

Greco et al. Pediatr Nephrol 2010: use of ACE inhibitors decreased risk of chronic renal failure in cystinosis (H.R. 0.15 (95% C.I. 0.03-0.68))
Novel pharmacologic therapies
Cysteamine action at cellular level

Adapted from Settembre et al. Nat Rev Mol Cell Biol. 2013

Cysteamine has no effect on renal Fanconi syndrome

Cysteamine

- **Upregulated apoptosis**
- **Enhanced exocytosis**
- **Cystine**
  - Degradation and recycling of intracellular substrates
  - Degradation and recycling of extracellular substrates
  - Altered vesicle trafficking
  - Altered lysosomal morphology and dynamics
- **Oxidative stress, inflammation**

- **Altered endosome**
- **Late endosome**
- **Autophagosome**
- **Plasma membrane**

Adapted from Settembre et al. Nat Rev Mol Cell Biol. 2013
Targeting ROS and ZONAB signaling improves PT dysfunction in cystinosis

The administration of Mito-TEMPO and blockage of ZONAB signaling ameliorated PT dysfunction in the Ctns-/- mouse model.

Festa et al. Nat Commun 2018
Transcription factor EB

Sardiello et al, Science 2009

Rega et al. Kidney Int 2016
Activation of TFEB with genistein in cystinosis

The phytoestrogen genistein modulates lysosomal metabolism and Transcription Factor EB (TFEB) activation.

Marta Moskot, Sandro Montefusco, Joanna Jakóbkiewicz-Banecka, Paweł Mozolewski, Alicja Węgrzyń, Diego Di Bernardo, Grzegorz Węgrzyń, Diego L. Medina, Andrea Ballabio, and Magdalena Gabig-Cimińska

CTNS fibroblasts

CTNS -/- ciPTEC

Rega et al. Kidney Int 2016
Take home messages

• Pathogenesis of kidney disease in cystinosis is complex and involves PT and podocyte damage resulting in renal Fanconi syndrome, glomerulosclerosis, chronic tubulo-interstitial inflammation and fibrosis

• Treatment with cysteamine remains the basis of the therapy
  • Early administration improves kidney function prognosis

• Indomethacin treatment improves kidney function survival and can be recommended

• Novel therapies targeting oxidative stress and vesicle trafficking are underway
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