Birmingham Children's Hospital

Cystinosis: Endocrine and bone problems and their management

Dr Jeremy Kirk

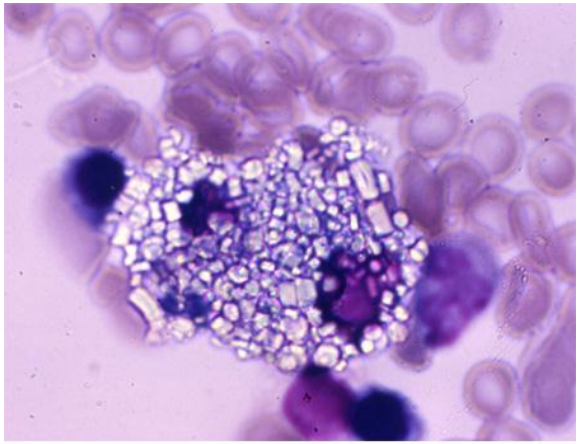
Consultant Paediatric Endocrinologist
Birmingham Children's Hospital

Cystinosis

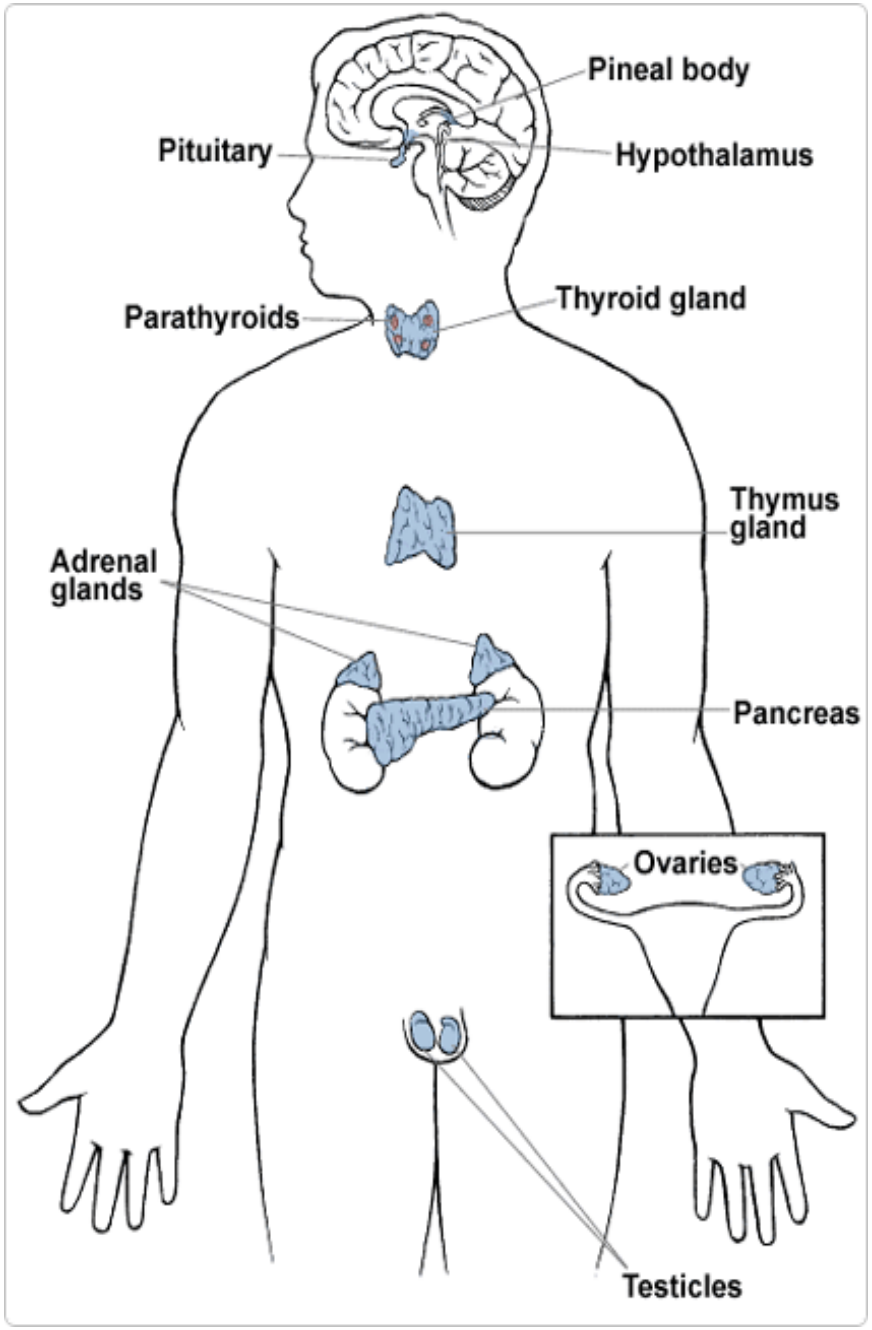
- A lysosomal storage disease characterized by abnormal accumulation of the amino acid cystine.
- Often inherited in an autosomal recessive (AR) pattern.

- 3 types, each with different onset and symptoms:
  - Infantile nephropathic cystinosis
  - Juvenile intermediate cystinosis
  - Non-nephropathic or ocular cystinosis.

Cystinosis and endocrine glands



- One mechanism of interference hormone metabolism is via disruption of the gland structure and function through progressive accumulation of toxic substances.
- Cystinosis (< 1-9/1000000, ORPHA213) appears to be one of these diseases.



Endocrine glands

A number of different hormonal systems are affected in patients with cystinosis.

Hormones and endocrine problems in cystinosis

- Growth failure/short stature
- Insulin-dependent diabetes
- Hypothyroidism
- Hypogonadism

- Bone problems and osteoporosis.

GROWTH

CRI

- “Chronic renal insufficiency (CRI), which may include end-stage renal disease, is defined as a persistent elevation of serum creatinine and/or urea. It can be caused by a variety of conditions, including congenital disorders, glomerular disorders and infections.
- Growth failure associated with CRI usually begins when the glomerular filtration rate falls to 50% of normal.”

NICE TA188, 2010

Growth and CRI

- “Children with congenital disorders leading to CRI (approximately 60% of children with CRI) are of normal length at birth, but are below the 3rd percentile for height within their first year and remain so throughout childhood
- Not all people with CRI in childhood are shorter than average; figures from the UK Renal Registry indicate that 29% of children who undergo renal transplantation and 41% of children on dialysis are below the 2nd percentile for height within their first year and remain so throughout childhood because of more pronounced deceleration in height velocity”.

NICE TA188, 2010

Cystinosis and growth

- Growth retardation is more pronounced in cystinosis than in other chronic kidney disease.

  Final height: 148cm (~4’10”) in males

  137cm (~4’5”) in females

- Growth retardation not corrected by cysteamine treatment, which may prevent further height loss, but not induce catch-up growth.

Growth retardation

Multifactorial in origin, due to a combination of:

- Decreased renal function
- Poor metabolic status secondary to renal Fanconi syndrome
- Feeding difficulties
- Cystine accumulation in the bone.

Growth retardation

Some data also indicates abnormalities in quantitative and qualitative secretion of growth hormone.

Nocturnal GH secretion was normal in all patients. Glucagon tests revealed GH deficiency in one patient; two of four patients had abnormal GH peak timing.

Martine et al., 2012

Chronic renal insufficiency (CRI): growth hormone

- 6 Randomised Controlled Trails (RCTs)
- 3 placebo controlled, 3 untreated controls
- Variable size: 11-203 patients.

- Trials lasted 12 months to 2 years.

CRI: growth hormone (GH) therapy

- GH-treated children in a 1-year study grew an average of 3.6 cm more than untreated children.
- Height SDS was statistically significantly higher in treated than in untreated children in two studies.

CRI and GH licence

- GH licensed and NICE approved to increase growth of prepubertal children with CRI.
- Treatment should be stopped after renal transplantation, and re-started after only 1 year if catch-up growth has not occurred.
- GH treatment can take place either before or after renal transplant, although allograft rejection can be a concern if GH treatment is given post transplant.

NICE TA188, 2010

GH and NICE: economic benefits in CRI

- £7,048 to £11,345 per cm gained for CRI.
- £39,273 per QALY (quality added life years) gained for CRI; £28,296 using cheapest growth hormone

NICE TA188, 2010

Cystinosis and GH therapy

- 74 children with cystinosis (age 3.0 to 18 years) were treated with GH for an average of 3.1 years (range 1 to 10 years).
- 52 patients were receiving conservative treatment (mean age 7.1 years), 7 were receiving dialysis (12.5 years), and 15 had received a renal transplant (14.8 years).
- The mean standardized height (SD score) was -4.0 in the conservative treatment group, -4.4 in the dialysis group, and -4.9 in the renal transplant group.

Wuhl et al., 2001

Cystinosis and GH therapy

- During the first year of GH, height velocity doubled in the conservative treatment group, increased by 80% in the dialysis group, and increased by 45% in renal transplant group.
- Within 3 years the height SD score increased by +1.6 ($P < .001$) in prepubertal patients receiving conservative treatment, and percentile parallel growth was maintained thereafter.
- Effects of GH were less expressed in peripubertal patients receiving renal replacement therapy.
- No major side effects were observed.

Wuhl et al., 2001

Cysteamine

- Cystinosis is usually treated with cysteamine: this reduces the intracellular cystine content.
- When administered regularly, cysteamine decreases the amount of cystine stored in lysosomes and correlates with conservation of renal function and improved growth.

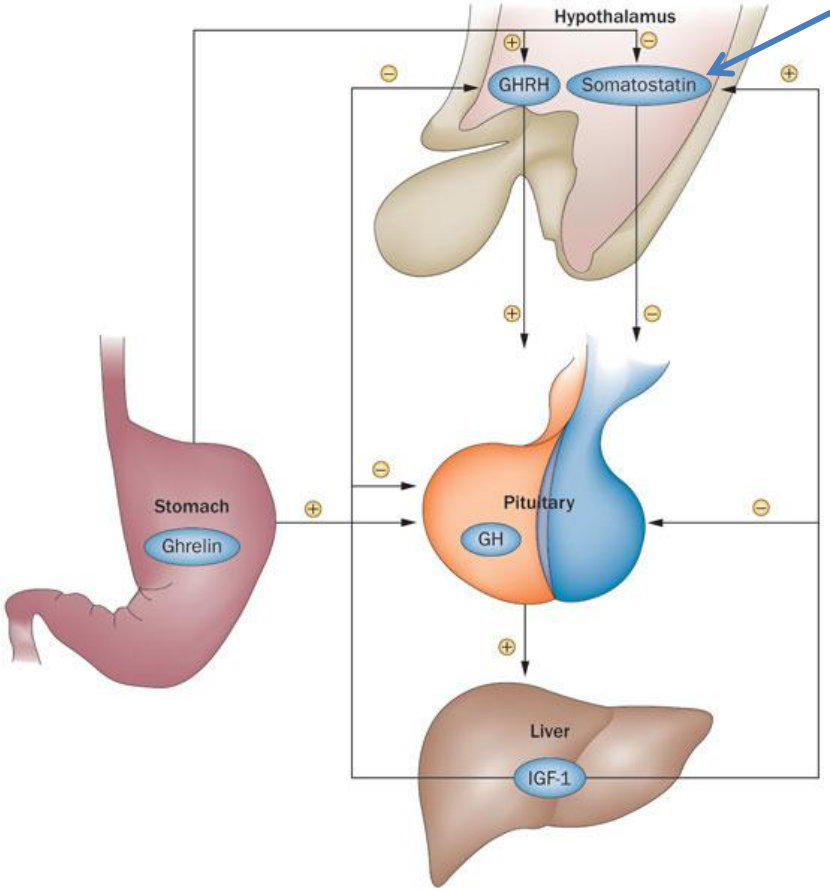
Cysteamine

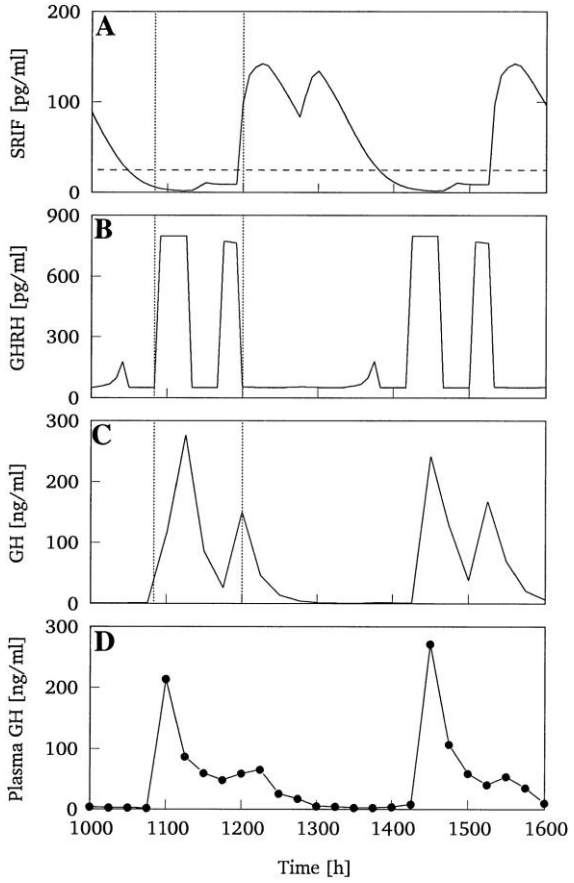
Improved growth in cysteamine-treated children with cystinosis may be explained by:

1. Cystine depletion in bones and cartilage
2. Somatostatin inhibition by cysteamine.

Hypothalamo-pituitary-growth axis

cysteamine





Cysteamine

- Cysteamine therapy also improved mean height z-scores: -2.17 in well-treated, -3.04 in poorly treated, and -4.07 in untreated and reduced the bone age deficit (ie. chronological age minus bone age) by 1.5 yr. for every 10 yr. of previous cysteamine therapy.

Kimonis et al., 1995

Other endocrine disorders

- Cystine crystal accumulation also leads to other endocrinopathies, including primary hypogonadism, diabetes and thyroid dysfunction. These complications are only partially prevented or improved with cysteamine treatment.

DIABETES

Infantile cystinosis and diabetes

- Unlike type I diabetes mellitus, glucose intolerance is characterized by a slow, progressive loss of insulin secretion and C-peptide production.
- There appears to be a 50% risk of developing glucose intolerance by the age of 18 years of age.
- Authors recommended performing intravenous glucose tolerance tests (ivGTT) at 5-year intervals.

Filler et al., 1998

Cystinosis and diabetes

- Twenty-four percent of a cohort of 100 patients had diabetes, with a quarter of those needing insulin therapy (*Gahi et al., 2007*).
- The cause is mainly due to decreased insulin secretion associated with pancreatic fibrosis. Microarray studies have shown that some of the differentially regulated genes in cystinosis were involved in mitochondrial dysfunction, endoplasmic reticulum and oxidative stress, as well as immune function.

HYPOGONADISM

Hypogonadism

Of 53 adult males, 39 (74%) were receiving testosterone replacement

- Of the 44 adult patients who were evaluated for sexual development
  - 1 was Tanner stage I
  - 2 were stage II
  - 6 were stage III
  - 21 were stage IV
  - 14 were stage V.

Gahi et al., 2007

THYROID

Hypothyroidism

- One hundred patients (58 males) aged 18-45 years (mean age 26.2 years) with cystinosis.
- 92% had had renal transplant.

- 75% of patients were receiving thyroxine therapy.

Gahi et al., 2007

Cysteamine

- To determine whether cysteamine also prevents hypothyroidism. Lifetable analysis indicated a significantly higher probability of remaining free of L-T4 replacement in well treated vs. partially treated ($P = 0.09$) or non-treated ($P = 0.004$).

Kimonis et al., 1995

BONE

Cystinosis and bone

Most end-organ effects of cystinosis are also known to be risk factors for osteopenia;

- Deposition of cystine crystals in bone
- Hypothyroidism
- Diabetes mellitus
- Primary hypogonadism
- Urinary phosphate wasting
- Chronic renal failure.

Cystinosis and bone

- Bone density (DEXA) scanning often does not reveal any evidence of reduced bone mineral density, despite an apparent increased fracture risk.

Thank you!

The Birmingham Children's Hospital NHS Trust