Summary of Chapter 37: Cystinosis

Introduction

Cystinosis is a rare, autosomal recessive lysosomal storage disorder caused by mutations in the *CTNS* gene. This results in defective cystinosin, a lysosomal cystine transporter, leading to the accumulation of cystine in lysosomes across tissues. The disease predominantly manifests as nephropathic infantile cystinosis, with early symptoms stemming from renal Fanconi syndrome. If untreated, cystinosis progresses to multiorgan involvement, including kidney failure, endocrine and neurological deficits and muscular disease. Early diagnosis and cystine-depleting therapy with cysteamine, have significantly improved outcomes, transforming the disease from fatal to chronic with a manageable quality of life.

Basic Defect and Pathophysiology

Cystine accumulation in lysosomes results from defective transport across the lysosomal membrane due to *CTNS* mutations. This disrupts multiple cellular functions, including endolysosomal dynamics, autophagy, mTOR signaling and oxidative stress responses leading to enhanced cell death.

Figure 1: Saturation kinetics of lysosomal cystine transport in normal and cystinotic cells demonstrates impaired cystine efflux in cystinosis (link to figure 1).

Figure 2: Birefringent cystine crystals under light microscopy highlight their characteristic shapes (link to figure 2).

Clinical Aspects

Cystinosis manifests in three clinical variants:
1. Nephropathic Infantile Cystinosis: early onset with Fanconi syndrome, growth failure, and kidney failure by 10 years, if left untreated (>95% of patients)
2. Intermediate (Juvenile) Cystinosis: later presentation during childhood, adolescence or adulthood with slower progression to kidney failure (<5% of patients)
3. Ocular Cystinosis: photophobia due to corneal cystine deposits without systemic involvement (very rare).

Key Clinical Features:

Infants and children:
- Renal: renal Fanconi syndrome presenting with polyuria, electrolyte imbalances, acidosis, episodes of dehydration
- Growth Impairment, failure to thrive and rickets
- Ocular: Photophobia due to corneal crystals cystine crystals

Adolescents
- Endocrine: hypothyroidism and delayed puberty
- Growth retardation

Adults
- Endoctine: hypothyroidism, hypohonadism, diabetes
- Male infertility
- Muscular weakness, swallowing dysfunction, diaphragm dysfunction
- Bone disease: factures
- Neurological: cognitive deficits, stroke-like episodes

Link to Table 2

Diagnosis
Diagnosis relies on biochemical and genetic testing:
- Leukocyte Cystine Levels: >1.5 nmol half-cystine/mg protein) confirm cystinosis
- Slit-Lamp Examination: detects corneal crystals by 18 months of age
- Genetic Testing: *CTNS* gene analysis at any age, inclusive prenatal diagnosis

Therapy
Treatment is divided into cystine-depleting therapy with cysteamine and symptomatic management:

1. *Cysteamine Therapy:*
   - Oral: cysteamine depletes lysosomal cystine, reducing systemic complications and delaying kidney failure. link to Figure 4, link to figure 5
Recommended cysteamine dosing schedules (link to Table 1)

   - Ocular: cysteamine eyedrops dissolve corneal crystals, improving photophobia (link to figure 6)

2. Renal Replacement and Transplantation:
   - Kidney transplantation resolves renal manifestations but not systemic complications
   - Post-transplant patients require standard immunosuppression
   - Post-transplant patients should continue cysteamine
   - No cysteamine dose adaptation on renal replacement therapy is required
   - Both hemodialysis and peritoneal dialysis are suitable
   - The disease doesn't recur in kidney graft

3. Symptomatic Management:
   - Electrolyte Replacement: sodium, potassium, and bicarbonate or citrate
   - Rickets: phosphate and active vitamin D
   - Growth Hormone Therapy: in children with severe short stature despite adequate metabolic control and cysteamine therapy
   - Nutritional Support: tube feeding when adequate caloric intake isn't achieved by oral feeding

Prognosis and Long-Term Management
With cysteamine therapy and supportive care, patients achieve improved survival and quality of life. Challenges remain in managing adherence, especially in adolescence, and addressing complications like hypothyroidism and myopathy. Emerging therapies, including gene and stem cell treatments, offer hope for further advancements.

Additional reading:

1. Nephropathic cystinosis: an international consensus document.
   Emma F, Nesterova G, Langman C, Labbé A, Cherqui S, Goodyer P, Janssen MC, Greco M, Topaloglu R, Elenberg E, Dohil R, Trauner D, Antignac C, Cochat P, Kaskel F, Servais A, Wühl E, Niaudet P, Van't Hoff W, Gahl W, Levtchenko E.
   Nephrol Dial Transplant. 2014 Sep;29 Suppl 4(Suppl 4):iv87-94. doi: 10.1093/ndt/gfu090.