Cystinosis

An Introduction

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**OVERVIEW**

*Cystinosis* is a rare genetic disorder in which continuous cellular accumulation of the amino acid *cystine* rises to toxic levels, resulting in irreversible tissue and organ damage if left untreated even for a short time.\(^1,2\) Cellular organelles, lysosomes, break proteins down into constituent amino acids, including cystine, which is then removed via the lysosomal cystine transporter, cystinosin.\(^2-4\) A dysfunction in the transport of cystine out of the lysosome results in cystine accumulation that is diagnostic of cystinosis. Cystinosis is consequently described as a lysosomal storage disorder. Since cystine accumulation, which occurs at approximately 100-fold normal levels, takes place in all organs and tissues, nearly every part of the body is at potential risk for damage subsequent to the accretion of cystine to toxic levels. Commonly affected parts of the body include the kidneys (characteristically as Fanconi syndrome in children), eyes, mouth and throat, liver, thyroid, and other organs.\(^1,2\) Interventions to (continuously) deplete cystine from lysosomes may delay disease progression and improve long-term outcomes.\(^1\)
THE 3 TYPES OF CYSTINOSIS

- Nephropathic or classic infantile cystinosis constitutes approximately 95% of cystinosis cases and is the most severe form of the disease. “Infantile,” in this context, describes time of onset—most adults, as well as children, with cystinosis suffer from the nephropathic/infantile form of the disease.
- The intermediate form resembles nephropathic cystinosis, with typical onset at adolescence.
- Non-nephropathic ocular cystinosis is characterized by crystal formation in the cornea and photophobia.

CYSTINOSIS FACTS

<table>
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<th>Incidence</th>
<th>Estimated at 0.5-1 per 100,000 live births, or about 15 new cases per year in the US¹,²</th>
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<td>Prevalence</td>
<td>400-500 patients in the US, and approximately 2,000 worldwide²,⁵</td>
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<td>Ethnicity</td>
<td>Classically associated with blond-haired, blue-eyed children of European descent, but all races and ethnic backgrounds can be affected¹,²</td>
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<td>Male to Female Ratio</td>
<td>1.4:1²⁶</td>
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<td>Life Expectancy</td>
<td>• 10 years or less without treatment¹</td>
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<td>• With early diagnosis, diligent medical care, and successful kidney transplantation, extension into the 5th decade of life is possible¹</td>
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PATHOPHYSIOLOGY OF CYSTINOSIS

Cystinosis is caused by the continuous accumulation of the amino acid cystine in lysosomes, which frequently takes the form of crystal deposition due to the poor solubility of cystine. Left untreated, accumulation of cystine will rapidly reach toxic levels and may cause irreversible tissue and organ damage.\textsuperscript{1,7} Two credible pathophysiologic hypotheses of cystinosis include a) abnormal energy production and associated intracellular diminishment of adenosine triphosphate (ATP), and b) apoptosis, which is linked to dysfunction of the renal tubules.\textsuperscript{1}

Fanconi syndrome, a principal clinical manifestation of untreated cystinosis, results in insufficient renal tubule absorption of water, bicarbonate, calcium, glucose, electrolytes, phosphate, and other essential components. Reduced thresholds of bicarbonate reabsorption, and subsequent bicarbonate lowering, can cause metabolic acidosis, which is associated with hypovolemia, poor growth in children, and possible mortality.\textsuperscript{1,8} Among numerous other dysfunctions arising from toxic accumulation of cystine are end-stage renal disease, kidney failure, hypothyroidism, cardiopulmonary dysfunction, diabetes, stunted growth, muscle wasting, and premature death.\textsuperscript{1,7}
In healthy individuals, the protein cystinosin functions as the lysosomal cystine transporter to move cystine out of the lysosome, a cellular organelle where amino acids, including cystine, are stored. A dysfunction of the lysosomal cystine transporter in people with cystinosis results in rapid cystine accumulation that can reach toxic levels in a matter of hours. While other amino acids are able to pass through the lysosome membrane via their respective transporters, in individuals with cystinosis, cystine remains trapped in the lysosome. This is why cystinosis is called a lysosomal storage disorder.\(^7\)\(^9\)
In an untreated cystinotic lysosome, cystine is unable to exit the lysosome, and its accumulation leads to irreversible cell damage. As toxic cystine accumulation continues, crystals may form within the lysosome. Increased and sustained cystine levels eventually lead to cell destruction.

Amelioration of cystine accumulation is contingent upon continuous cystine depletion of the lysosome in order to slow disease progression and improve clinical outcomes.¹

**Cystinosis is a continuous and progressive condition in which toxic levels of cystine accumulate in every cell of the body, leading to cell death and eventual organ damage**.⁰,¹
Cystinosis is a multi-organ disease, potentially affecting any organ or tissue in the body. The diagram displays some of the most common clinical dysfunctions associated with cystinosis, from photophobia to childhood rickets.1,2
The prolongation of survival due to medical therapy and kidney transplantation has revealed numerous manifestations of tissue and organ damage caused by cystinosis. These manifestations have been seen to occur over a roughly predictable period of time.7

Adapted from Gahl et al, 2002.2

Cystinosis is a multi-organ disease that, without sustained medical therapy, will continue to cause significant organ and tissue damage even after kidney transplantation7

Besides the physical effects, there may be emotional or intellectual changes associated with cystinosis, which can happen alone or in combination, and can affect each person differently.8
Because cystinosis is a multi-organ disease, the range of clinical specialists required for treatment is large and diverse, and it is likely a given patient will require parallel treatment from more than one clinician at a time. However, the gradual emergence of comorbidities over a period of years—from infancy, to childhood, to adulthood—means that patients will engage with different specialists at different points of time over the course of their lives.
KEY POINTS

• Cystinosis is a rare genetic condition that, if left untreated, can lead to irreversible damage in multiple organs and tissues all over the body.

• Cystinosis occurs as a result of a lysosomal storage defect that causes rapid and toxic accumulation of the amino acid cystine.

• Cystinosis is a multi-organ disease that continues to progress even after kidney transplantation.

• Without treatment for cystinosis, life expectancy is 10 years or less, but with treatment patients may live into the 5th decade of life.

• Continuous depletion of cystine from lysosomes may delay disease progression and improve medical outcomes.
LEARN MORE ABOUT CYSTINOSIS

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The Cystinosis Foundation
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References: