Conclusions to the Supplement, "Extra-Renal Complications of Cystinosis"

Jess G. Thoene, MD

One of the founders of the field of inborn errors of metabolism, J. Edwin Seegmiller, once said, "Cystinosis is a durable, but perhaps not doable, problem." Since he said that more than 50 years ago, great progress has been made in understanding this complex multiorgan, systemic disease.

Now with genotyping readily available, a host of new questions can be asked, such as, why are some late complications (eg, myopathy), so severe in some patients? Does the incidence and severity of myopathy and vascular calcifications correlate with a specific genotype? Are linked genes involved in the overall severity of the condition, accounting for the spectrum currently known as ocular, intermediate, and nephropathic cystinosis?

Some questions may be amenable to study of recently described additional defects in cystinosis beyond cystine transport that have to do with apoptosis,[1] cellular trafficking, and the mammalian target of rapamycin complex 1 pathway.[2,3] This might explain features of the condition such as why the order of affected tissues: retina before proximal tubule, tubule before glomerulus, glomerulus before muscle, and thyroid. Why does the myopathy presents distally and then progress centrally? Why do male patients with cystinosis suffer hypogonadism, but female patients do not? Why do some children achieve normal stature without recombinant human growth hormone therapy? Why is the lung parenchyma spared when the somewhat similar tissue (eg, renal tubule) is seriously affected?

In this brief supplement, we hope to assist clinicians, and primarily pediatricians, to recognize that cystinosis, although seen as a renal and ophthalmologic disease in childhood, also displays a number of serious side effects in late childhood through adulthood that affect many other tissues and organ systems. Prompt recognition and treatment is essential to ensure the best quality of life for these patients, and early and continued treatment with cysteamine has a major positive impact (**Figure**). ■

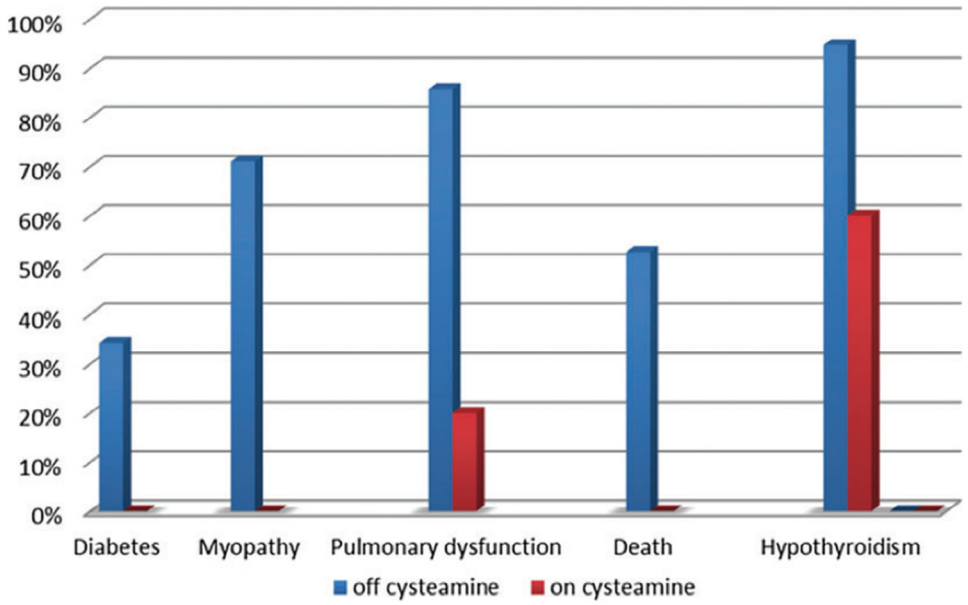

Figure. Reduction in the incidence of severe non-renal complications in cystinosis by cysteamine therapy. Reprinted with permission from Emma et al.[4]

From the University of Michigan School of Medicine, Ann Arbor, MI

Please see the author disclosures at the end of the article.

0022-3476/$ - see front matter. © 2016 Published by Elsevier Inc.
http://dx.doi.org10.1016/j.jpeds.2016.12.057

Author Disclosures

The author declares no conflicts of interest, real or perceived.

Reprint requests: Jess G. Thoene, MD, University of Michigan School of Medicine, 1500 E Medical Center Drive #1, Ann Arbor, MI 48109. E-mail: jthoene@med.umich.edu

References

1. Park MA, Pejovic V, Kerisit KG, Junius S, Thoene JG. Increased apoptosis in cystinotic fibroblasts and renal proximal tubule epithelial cells results from cysteinylation of protein kinase Cdelta. J Am Soc Nephrol 2006;17:3167-75.
2. Andrzejewska Z, Nevo N, Thomas L, Chhuon C, Bailleux A, Chauvet V, et al. Cystinosin is a component of the vacuolar H+-ATPase-ragulator-rag complex controlling mammalian target of rapamycin complex 1 signaling. J Am Soc Nephrol 2016;27:1678-88.
3. Ivanova EA, van den Heuvel LP, Elmonem MA, De Smedt H, Missiaen L, Pastore A, et al. Altered mTOR signalling in nephropathic cystinosis. J Inherit Metab Dis 2016;39:457-64.
4. Emma F, Nesterova G, Langman C, Labbé A, Cherqui S, Goodyer P, et al. Nephropathic cystinosis: an international consensus document. Nephrol Dial Transplant 2014;29(Suppl 4):iv87-94.