Endocrine Complications of Cystinosis

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Endocrine organs are frequently affected in cystinosis, especially in patients who are not treated adequately with cysteamine.

Hypothyroidism

Thyroid dysfunction chronologically follows kidney dysfunction and develops in about 50% of untreated children by 5-10 years of age.[1] In 1970, Chan et al[2] were the first to describe primary hypothyroidism in cystinosis and performed a histologic examination of the thyroid gland showing cystine crystal accumulation and fibrosis. Biochemically, hypothyroidism usually manifests with elevated thyroid stimulating hormone (TSH), but normal T4 levels (subclinical disease), and progresses toward overt hypothyroidism over subsequent years, requiring thyroxin supplementation.[3] In some patients, pituitary resistance to thyroxin has been reported and is characterized by elevated TSH levels despite absence of clinical or biochemical signs of hypo- or hyperthyroidism.[4] In such patients, TSH fails to normalize even if serum T4 concentrations are at the upper limit of normal because of adequate thyroxin therapy.

The pathogenesis of thyroid dysfunction appears to be more complex than merely thyroid gland destruction by lysosomal cystine. In early disease, accelerated thyrocyte turnover with increased cell proliferation plus enhanced apoptosis linked to endoplasmic reticulum stress yields impaired thyroglobulin production and altered endolysosomal trafficking and iodothyroglobulin processing as has been recently demonstrated in the knockout mouse model of cystinosis.[5] Importantly, cysteamine treatment prevents hypothyroidism in the majority of patients with cystinosis underscoring the essential role of cystine accumulation in the development of thyroid dysfunction (**Figure 1**).[6,7]

Diabetes Mellitus

This complication of cystinosis usually develops during adolescence or adulthood in about 5% of the patients.[1] However, longitudinal systematic evaluation of the endocrine pancreas by oral glucose tolerance test in post-transplant patients in the
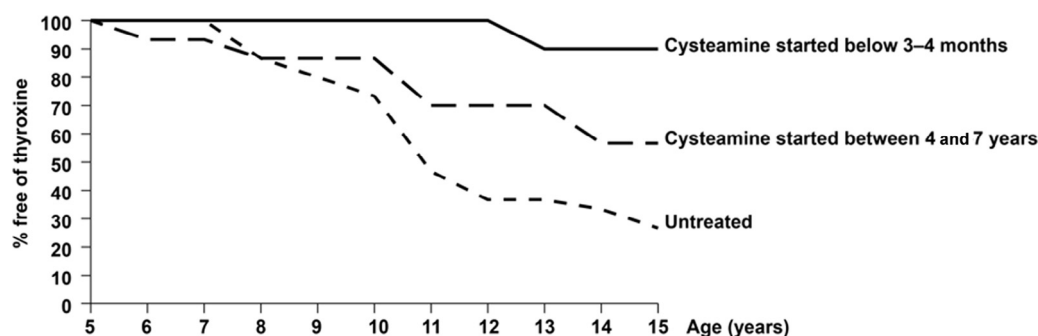
Figure 1. Actuarial survival of patients with cystinosis free of thyroxin treatment according to the age at start of cysteamine treatment. Adapted from Tete et al.[6]
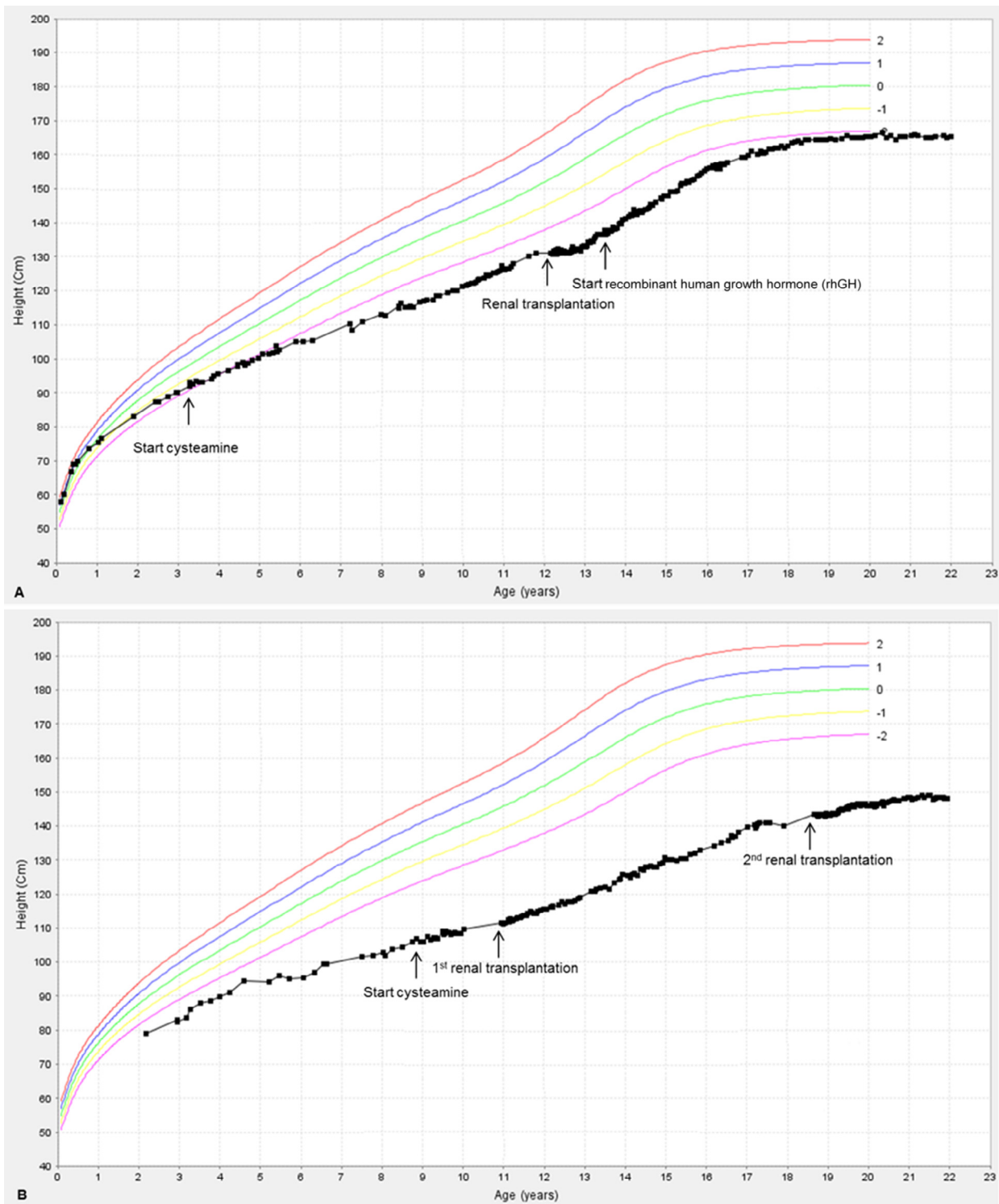
CKD	Chronic kidney disease	rhGH	Recombinant human GH
GH	Growth hormone	TSH	Thyroid stimulating hormone

Figure 2. Growth curves of 2 siblings with cystinosis. **A,** Growth curve of the younger sibling. Diagnosis of cystinosis was made at the age of 5 months and confirmed by molecular analysis of the CTNS gene showing common homozygous 57 kb deletion. Note the initial normal growth after birth, with decreased growth velocity during the first months of life. A temporary improvement in longitudinal growth occurred after initiation of cysteamine therapy at the age of 3 years. Initiation of recombinant human growth hormone (rhGH) therapy after renal transplantation resulted in catch-up growth after a period of stunting; **B,** Growth curve of the older sibling, who was diagnosed at the age of 3 years and cysteamine initiated at age 9 years. Note the severe growth retardation at diagnosis, which worsened in the years thereafter. Cysteamine administration did not improve longitudinal growth. Renal transplantation did improve longitudinal growth, resulting in growth paralleling the normal growth curves, but there was no catch-up growth. Adapted from Besouw et al.[17]

precysteamine era demonstrated impaired insulin response in almost 100%, and overt diabetes mellitus requiring insulin treatment was present in approximately 30% of the patients 10 years after kidney transplantation.[8] Post-transplant use of glucocorticoids and calcineurin inhibitors is likely to exacerbate glucose intolerance. Thus, a steroid-free post-transplant immunosuppressive regimen might be advocated in patients with cystinosis after renal transplantation; however, potential benefits of such regimens should be weighed against hazards in patients at risk for acute or chronic graft rejection.[9]

Hypogonadism

Although gonadal function and sexual development are usually normal in female patients with cystinosis, with several successful pregnancies and births reported,[10] male hypogonadism is a frequent complication reported in up to 70% of patients untreated with cysteamine.[1] This complication was first described in 1993 by Chik et al,[11] who reported that most male patients with cystinosis had delayed and incomplete puberty, decreased testes volume, and low testosterone levels. Histologic examination of the testes showed cystine crystal accumulation, fibrosis, and Leydig cell hyperplasia.[11]

More recently, Besouw et al[12] showed that hypogonadism was also present in all studied patients treated with cysteamine, having incomplete pubertal development and decreased testes volumes. Although sexual hormones (testosterone, inhibin B, luteinizing hormone, and follicle stimulating hormone) were in the normal range in the majority of these patients, all of them had azoospermia despite normal erectile function. Biopsy of the testes in a male patient with cystinosis, well-treated with cysteamine, demonstrated preserved spermatogenesis, suggesting the possibility of in vitro fertilization.[12] At present, there are no publications in which a male patient with nephropathic cystinosis has fathered a child. The mechanism of azoospermia in cystinosis requires further investigation.

Female fertility is not affected per se by cystinosis, however, underlying chronic kidney disease (CKD) decreases fertility depending on its stage, and poses risks for the mother and child.[13] Moreover, different classes of drugs used in CKD, including antihypertensive and immunosuppressive treatments, decrease fertility and increase risks of fetal malformations and premature delivery.[14]

Growth Retardation

Growth retardation is more pronounced in cystinosis compared with other CKDs and has a multifactorial etiology.[15,16] At early disease stages, renal Fanconi syndrome leading to electrolyte imbalance, rickets, metabolic acidosis, and dehydration cause severe growth delay. Inadequate nutrition, hypothyroidism, bone disease, and, at later stages, hypogonadism in male patients further impair growth, resulting in a final height of 156 cm in male patients and 147 cm in female patients, between 1974 and 2009 as registered in the European Society for Pediatric Nephrology/European Renal Association-European Dialysis and Transplant registry.[16] Thus far, growth hormone (GH) deficiency has been reported in only 1 patient with cystinosis, however, 2 of 4 other patients demonstrated altered timing of GH peak after glucagon stimulation, which might indicate subclinical alterations in GH secretion.

Cysteamine treatment improves growth, probably because of the inhibition of somatostatin; however, in many patients, it is still insufficient to normalize growth, even in patients having adequate nutrition and good metabolic control of the disease, in the absence of rickets or hypothyroidism (**Figure 2**).[17,18] In contrast, treatment with the recombinant human GH (rhGH) in cystinosis is safe and effective, and should be initiated early, and it is approved for use in CKD in the US. rhGH may be given even prior to the development of renal insufficiency, as young children before starting renal replacement therapy show the best response to the rhGH.[19] Long-term rhGH treatment improves final height, which ranges on average from −2.6 to −2.0 SDS.[20] ∎

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References

1. Gahl WA, Thoene JG, Schneider JA. Cystinosis. N Engl J Med 2002;347:111-21.
2. Chan AM, Lynch MJ, Bailey JD, Ezrin C, Fraser D. Hypothyroidism in cystinosis. A clinical, endocrinologic and histologic study involving sixteen patients with cystinosis. Am J Med 1970;48:678-92.
3. Lucky AW, Howley PM, Megyesi K, Spielberg SP, Schulman JD. Endocrine studies in cystinosis: compensated primary hypothyroidism. J Pediatr 1977;91:204-10.
4. Bercu BB, Orloff S, Schulman JD. Pituitary resistance to thyroid hormone in cystinosis. J Clin Endocrinol Metab 1980;51:1262-8.
5. Gaide Chevronnay HP, Janssens V, Van Der Smissen P, Liao XH, Abid Y, Nevo N, et al. A mouse model suggests two mechanisms for thyroid alterations in infantile cystinosis: decreased thyroglobulin synthesis due to endoplasmic reticulum stress/unfolded protein response and impaired lysosomal processing. Endocrinology 2015;156:2349-64.
6. Tete MJ, Broyer M. Thyroid and gonads involvement in cystinosis. In: Broyer M, ed. Cystinosis. Paris; New York: Elsevier; 1999. p. 63-9.
7. Kimonis VE, Troendle J, Rose SR, Yang ML, Markello TC, Gahl WA. Effects of early cysteamine therapy on thyroid function and growth in nephropathic cystinosis. J Clin Endocrinol Metab 1995;80:3257-61.
8. Robert JJ, Tete MJ, Guest G, Gagnadoux MF, Niaudet P, Broyer M. Diabetes mellitus in patients with infantile cystinosis after renal transplantation. Pediatr Nephrol 1999;13:524-9.
9. 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.

10. Andrews PA, Sacks SH, van't Hoff W. Successful pregnancy in cystinosis. JAMA 1994;272:1327-8.
11. Chik CL, Friedman A, Merriam GR, Gahl WA. Pituitary-testicular function in nephropathic cystinosis. Ann Intern Med 1993;119:568-75.
12. Besouw MT, Kremer JA, Janssen MC, Levtchenko EN. Fertility status in male cystinosis patients treated with cysteamine. Fertil Steril 2010;93:1880-3.
13. Tong A, Jesudason S, Craig JC, Winkelmayer WC. Perspectives on pregnancy in women with chronic kidney disease: systematic review of qualitative studies. Nephrol Dial Transplant 2015;30:652-61.
14. Piccoli GB, Cabiddu G, Attini R, Vigotti F, Fassio F, Rolfo A, et al. Pregnancy in Chronic Kidney Disease: questions and answers in a changing panorama. Best Pract Res Clin Obstet Gynaecol 2015;29:625-42.
15. Elmonem MA, Veys KR, Soliman NA, van Dyck M, van den Heuvel LP, Levtchenko E. Cystinosis: a review. Orphanet J Rare Dis 2016; 11:47.
16. Van Stralen KJ, Emma F, Jager KJ, Verrina E, Schaefer F, Laube GF, et al. Improvement in the renal prognosis in nephropathic cystinosis. Clin J Am Soc Nephrol 2011;6:2485-91.
17. Besouw MT, Van Dyck M, Francois I, Van Hoyweghen E, Levtchenko EN. Detailed studies of growth hormone secretion in cystinosis patients. Pediatr Nephrol 2012;27:2123-7.
18. Greco M, Brugnara M, Zaffanello M, Taranta A, Pastore A, Emma F. Long-term outcome of nephropathic cystinosis: a 20-year single-center experience. Pediatr Nephrol 2010;25:2459-67.
19. Wühl E, Haffner D, Gretz N, Offner G, van't Hoff WG, Broyer M, et al. Treatment with recombinant human growth hormone in short children with nephropathic cystinosis: no evidence for increased deterioration rate of renal function. The European Study Group on Growth Hormone Treatment in Short Children with Nephropathic Cystinosis. Pediatr Res 1998;43:484-8.
20. Wühl E, Haffner D, Offner G, Broyer M, van't Hoff W, Mehls O, et al. Long-term treatment with growth hormone in short children with nephropathic cystinosis. J Pediatr 2001;138:880-7.