EDITORIAL

Cystinosis: a rare multisystem disease

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Cystinosis is a rare autosomal recessive disease due to variants in the *CTNS* gene coding cystinosin, a cystine transporter in lysosome membranes. In this issue of *Polish Archives of Internal Medicine*, Sikora et al[1] report on the long-term follow-up of a national cohort of cystinosis patients in Poland. Interestingly, the authors show that the 57 kb deletion, which is the most common variant affecting about 76% of northern European alleles,[2] is rare in Poland, and only identified in 2 patients in the study. However, the clinical course of the disease was very severe in this cohort, as specific treatment with cysteamine became available in Poland only in 2014, and all but 2 patients did not receive early and continuous treatment. Cysteamine depletes lysosomal cystine by cleaving cystine into free cysteine and cysteamine-cysteine mixed disulfide, which is exported from the lysosomes by a cationic amino acid transporter, PQLC2.[3]

As initial manifestation of the disease, more than 90% of patients failed to thrive: this confirms that a urinary dip stick should be performed in all children with growth retardation. Then, diagnosis was made based on clinical manifestations, that is, the association of the Fanconi syndrome and corneal cystine crystals. In most patients, the diagnosis was reached rather early after the occurrence of the first symptoms.

However, the patients presented with the severe disease and renal failure at a median age of 11 years, similar to that found in nontreated patients in other historical cohorts.[4,5] These young patients received a kidney allograft with good allograft survival in two-thirds of them. Indeed, it has been shown that the allograft prognosis is excellent in these patients.[6,7] Only 2 patients could be treated early with cysteamine as currently recommended, since the age at the treatment onset directly affects renal survival, extra-renal complications, and life expectancy.[5,8]

White blood cell cystine level could be assessed in the majority of patients for diagnosis but was not routinely available for regular follow-up. It could help with monitoring a specific treatment.

The patients developed severe ocular complications including keratopathy, and even unilateral blindness in 1 case due to the absence of specific ocular drops with cysteamine. A very high prevalence of hypothyroidism was observed, as all patients showed this complication, easily treated with L-thyroxine supplementation. Another endocrine complication, diabetes, was also frequent, diagnosed in two-thirds of the patients. It has been demonstrated that the use of early or even delayed cysteamine treatment is associated with a decrease in the incidence of these 2 extrarenal complications.[5]

The patients had a short stature despite receiving a recombinant growth hormone in 4 cases. The role of early cysteamine treatment in body growth has also been shown.[5,8] Distal myopathy may occur in young adults and it is a severe complication, observed here in 3 patients. It may be associated with dysphagia, which is related to increased mortality. It was detected in 4 patients, including a pediatric patient with a very severe form of the disease. For this complication, the positive preventive impact of cysteamine treatment has been documented in the past.[9]

Central nervous system complications are less frequent. Two forms may be observed, that is, a cystinosis encephalopathy or stroke-like episodes as described in 1 patient at 24 years of age in this series.[10-12] Cerebral atrophy on systematic brain imaging is frequent but not always associated with clinical manifestations.[12]

Successful pregnancies were observed in 2 patients. Indeed, women with cystinosis are fertile and the progress in kidney transplantation and specific treatment with cysteamine have increased the number of patients with cystinosis who get pregnant. The European series of pregnancies in cystinosis patients has shown that the majority of pregnancies were successful, but severe complications were also observed, in particular pre-eclampsia and fetal loss.[13]

Two patients presented with a late-onset form of cystinosis. Its diagnosis is more difficult, as the clinical presentation is less characteristic,

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with usually a mild form of proximal tubulopathy, isolated proteinuria due to focal segmental glomerulosclerosis, as in 1 of the 2 patients, and corneal crystals.[14]

Better access to diagnostic procedures and early cysteamine treatment will improve the care for cystinosis patients in the future. However, studies have identified a role for cystinosin beyond cystine transport, in endolysosomal trafficking and proteolysis, lysosomal clearance, autophagy, mTOR pathway, and regulation of energy balance. This could lead to new therapeutic options. In particular, stem cell therapy is a very promising approach for cystinosis and a phase 1/2 clinical trial is on-going in the United States.[3] *CTNS* gene-modified hematopoietic stem and progenitor cells, upon autologous transplantation, are intended to engraft into the bone marrow, divide, and differentiate, thus providing a population of corrected cells that can supply functional cystinosin in the diseased organs for the life of the patient.[15] This would represent a life-long therapy that has the potential to prevent renal failure and extrarenal complications of the disease.

ARTICLE INFORMATION

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