Access to Orphan Drugs is a Challenge for Sustainable Management of Cystinosis in China

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As a rare autosomal-recessive metabolic disorder, cystinosis is caused by defective transport of cystine across the lysosomal membrane.[1] Once the diagnosis of cystinosis is confirmed, specific treatment with cysteamine, an aminothiol, should be applied to the patient as soon as possible in order to preserve renal function and improve growth in affected children.[2] Cysteamine is the only specific drug approved by the Food and Drug Administration for cystinosis. Although it cannot reverse the existing kidney damage, it was reported that 17 patients treated with cysteamine for 7 years recovered almost normal kidney function and, more importantly, they grew normally.[3] Another report suggested that cysteamine treatment could postpone end-stage kidney damage for 10–20 years.[4] However, the immediate challenge lies in the access to the necessary medication in China for the management of cystinosis. Here, we report the case of two sibling boys with cystinosis in order to raise awareness to the international community about the urgent need for worldwide policy and action for such rare diseases.

Nine years ago, a 4-year-old boy presented with joint deformities, weakness, disproportionate short stature, and bowing of the legs at 1 year old and proteinuria started when he was 2 years old. His parents were healthy, and he was born after a full-term pregnancy and normal delivery. Fanconi syndrome was considered initially. Although we could not measure his leukocyte cystine content at that time, direct sequencing of the polymerase chain reaction products was performed. A homozygous mutation (c.969 C>G) in exon 11 of the gene cystinosin (*CTNS*), which is the only known causative gene for cystinosis, was detected.[1] Subsequently, typical fine-cystine crystals were found in all layers of the corneal stroma in both eyes on slit-lamp examination at the 9th year of the follow-up after genetic diagnosis had been confirmed.

Unfortunately, cysteamine could not be accessed in China despite repeated attempts. Considering the development and immediate well-being of this child, citrate mixtures, phosphate supplements, and oral calcium were prescribed as supportive treatments to normalize both plasma electrolytes and acid levels as well as to prevent the development of renal rickets. In addition, recombinant growth hormone (rGH, 0.166 $U \cdot kg^{-1} \cdot d^{-1}$) was given due to the severe delay of growth when he was 6 years old.[5] The boy's height increased significantly after growth hormone administration for two years. The rGH therapy costs 10,000 USD per year, which accounts for 80% of the average income of a family in China. Moreover, rGH is a self-funded medicine which is not covered by Chinese medical insurance. Hence, after treating with rGH for 2 years, the child could no longer acquire rGH because his parents could not afford it. The clinical characteristics of his disorder, especially impaired renal function, had not improved after 9 years' follow-up although neither had they obviously worsened. However, the fear is that his kidney function will be constantly impaired and inevitably results in end-stage renal disease.

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The helpless state of the patient's family with cystinosis became even more critical when his brother, who was 9 years younger, was also diagnosed with cystinosis by clinical manifestation and genetic analysis at 4 months of the age. Although several courses of actions have been implemented to promote the advancement of rare disease healthcare in China, including newborn screening for hypothyroidism and the establishment of the China Rare Diseases Prevention and Treatment Alliance,[6,7] access to life-saving cysteamine is still impossible for Chinese patients because: (1) no orphan drugs have been successfully developed and marketed by the domestic pharmaceutical companies in China due to lack of financial incentive for their development;[8] (2) orphan drugs cannot be approved for marketing in a timely fashion in China despite the best effort to simplify the registration process of imported drugs; (3) a specific national healthcare system for rare disease patients has not been well established, which means that families, like the one in this report with two affected male siblings, have neither means to acquire the necessary drugs nor financial support to have sustained treatment; (4) the sourcing of medicine from developed countries is restricted by regulations on the importation of drugs. In this reported case, both the clinical doctors and the parents of the patients have tried various methods to purchase drugs abroad. However, these prescription medicines cannot be given by the United States doctors unless they diagnose the patients in person, which is very difficult for most Chinese patients and families.

Although the incidence of rare diseases is quite low, the actual number of patients is substantial in China with its immense population base. More importantly, rare diseases have a devastating effect on many patients and their families. We do need support from international organizations to get these effective drugs more readily and efficiently so that these patients can get continuous, effective therapy which is essential to sustain their normal growth, development, and, in many cases, survival.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patients have given their consent for their clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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