

Principles of Cystinosis Transition in Children: A Review

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Received: August, 2020
Revised: September, 2020
Accepted: October, 2020

Abstract

Children with chronic illness need special care during the transition to adolescence and adulthood. Cystinosis is a chronic childhood disease characterized by chronic renal failure and multi-organ involvement. With advances in treatment and kidney transplantation methods, the life expectancy of these patients has been prolonged. Renal transplantation is performed for most of the patients in childhood. These patients are at risk of non-adherence due to multiple drug usage and their chronic disease. As a child enters adulthood, parental care decreases and the patient should learn self-management. So the likelihood of non-compliance and loss of kidney transplant is high in transition time. This article gives a brief overview on transition of cystinosis patients from childhood to adolescence and adulthood.

Keywords: Cystinosis; Children; Adolescence; Chronic Renal Failure.

Conflict of interest: The authors declare no conflict of interest.

Please cite this article as: Saffari F, Arad B. Principles of Cystinosis Transition in Children: A Review. *J Ped Nephrol* 2020;8(4):1-6.
<https://doi.org/10.22037/jpn.v8i4.31802>

Introduction

Cystinosis is a rare autosomal recessive lysosomal storage disease, with an incidence of ~0.5–1.0 per 100,000 live births (1). Cystinosis Nephropathy (NC) is caused by cystinosine dysfunction. The CTNS gene consists of 12 exons, with the start and stops codons, and encodes a cystinosine protein with 367 amino acids (2). Cystinosine influx of a dimeric-amino acid, cysteine from lysosomes to cytosol, and in the absence of a functional protein, cystine accumulates in the lysosome lumen and crystallizes (3). The pathophysiology of renal injury in NC is unknown, but the hypotheses that have been proposed include decreased intracellular ATP, decreased glutathione synthesis, impaired mitochondrial respiratory chain complexes activity, and increased apoptosis (4, 5, 6). There are three clinical types of cystinosis. In nephropathic form, renal Fanconi syndrome usually develops at the age of 4 to 6 months with polyuria, polydipsia, failure to thrive, vomiting, constipation, dehydration, growth retardation and / or rickets with evidence of proximal tubular dysfunction. This includes significant loss of electrolytes, low molecular weight proteinuria, and severe acidosis. Hypophosphatemia and defect in 1- α hydroxylation

(calcitriol metabolism disorders) often cause severe rickets. Without cysteamine treatment, kidney function declines over time and causes ESRD at 10 to 12 years of age (7). Late-onset cystinosis is usually diagnosed later in childhood or adolescence, so these patients have milder Fanconi syndrome or isolated proteinuria. The ocular or adult form is characterized by symptoms associated with corneal cystine crystalline deposits and is rarely diagnosed before adulthood (1).

With early diagnosis of cystinosis, faster onset of cystine-depleting agents (8), and advanced kidney transplant programs (9), cystinosis changed from a fatal childhood disease to an illness with longer life expectancy. However, there will be problems in the transition to adolescent and adulthood, especially for patients that already received kidney transplantation.

The importance of the transition

Proper planning for the transition period will abate cystinosis complications and also prevent kidney rejection. Transition is a planned process that is progressively, timed, and continuous. Cystinotic patients who reached adolescence indicate receiving appropriate care of parents and caregivers, which

should continue exactly until adulthood. In transition time, a child under full care of his/her parents learns how to get personal autonomy.

Risk factors that may complicate the transition period can be categorized as; (1) Admission of cystinotic patients to adult wards, with insufficient information about the disease. (2) Noncompliant with treatment, one of common problems in adolescent and young adulthood. (3) Morbidities and mortalities due to cystine accumulation in extra-renal organs. (4) Lack of adequate information about patients care in her/his family and friends (10).

Non-adherence to treatment

Treatment adherence should be a concern in adolescence and young adult cystinotic patients. Patients may miss the drug doses, change medication by themselves, and not take the recommended doses. Non-adherence was reported about 89% in cystinotic children younger than 11, and 56% of older than this age. The patients complain of unpleasant cysteamine odor, gastrointestinal upset, and numerous medications with multiple daily doses (11).

Therefore, it is suggested that management of each patients should be tailored to her/his condition:

1. Education about the consequences of not following the treatment regimen and adverse complications of cystine accumulation in different organs.
2. Applying behavioral techniques to remember the time for taking medications. For example, parents can remind him or he can use an alarm or a calendar.
3. Assessment of psychological problems such as depression, anxiety, and attention deficit disorder.
4. Engage family members, friends, and medical team to improve patient's adherence to treatment (12, 13).

Assessment the causes of non-adherence in patients with cystinosis

1. Measurement of immunosuppressive levels in kidney-transplanted patients, the limit below 2 standard deviation is acceptable (14).
2. Leukocyte cystine measurement: In most of cystinotic patients, leukocyte cystine level is 3.0-23.0 nmol half cystine/mg protein. Cystine measurement should be performed in a mixed leukocyte augmented with

polymorphonuclears with HPLC method, and evaluation has to be done in blood sample before taking the next cysteamine dosage. (15, 16) Normal leukocyte cystine value is below 0.2 nmol hemi cystine/mg proteins (17).

Lack of information about cystinosis in adult wards

The pediatric nephrologist is responsible for communication between other specialists, and refer the patients to adult-oriented system where they are experienced in cystinosis. The other effective protocols are exchange of information between pediatric and adult centers, and provide complete patients' record to other specialists.

The care-team can establish training classes for parents and children, so they will have enough information about their disease. In addition, medical team should provide facilities so the parents can easily contact health care providers during the transition time.

How to initiate the transition?

Most adults with chronic illness initiating from childhood acknowledge that sudden release from the pediatric team, with no prior preparation was huge concern for them and their parents (18). The child and his family should have the opportunity to discuss the transition stages with pediatric team and visit new health care team prior to transition. The transition steps should be carried out on a programmed guideline to avoid disease complication and kidney transplant rejection. In this protocol the task of each member of professional health-care team is determined beforehand. As chronic renal failure is the main presentation in cystinosis, a nephrologist has a key role in coordinating the care-team (19).

Mental health of children and adolescence with cystinosis in transition period

A person's physical health is often affected by the state of his mental and emotional health. More importantly, children with chronic diseases are more likely to suffer from mental health issues. That is why parents are concerned about adversity of their child's behavior and adjustment. Pre-school and school-aged children manifest temper tantrum or mood swing. The tantrum is expressed by crying, shouting, arguing and annoyance (20). The cystinosis individual often have frequent absences

from school that will worsen the learning performance and therefore peers communication. The parents should access to related services if they observe their child is making excuse for not participating in school activities, having no friends or little friends at school, depression, anxiety, sadness, low self-esteem, decreased appetite, or sleep difficulties (21).

The parents can help their children to be interested to participate in school activities. If the child is going to a new school, one of the ways to adapt to new environment is to meet child's teachers and administrators on the first day of academic year. When the child is missing school, he/she can stay connected by phone or email with his/her classmates, so he will have an easier return after a long absence. Parents also consider encouraging good behaviors and perfect school assignments, spend quality time for child's interests and favorite activities, and listening to their child and ask open-ended questions not just questions with yes/no answers. Parents have to teach their child or adolescent to be really independent in their life, and to be autonomous in solving their problems (22).

The proper age for transition

The time of emerging adulthood is variable in different cultures, but in most societies 18 to 29 years old is known as an individual enters adulthood. Adulthood is when individuals are responsible for their own lives and are able to decide independently. At this time, college education is completed, one is looking for suitable job, and one will get married and become parent (23).

Numerous studies have concluded that the transition process should begin from preadolescence, after giving sufficient information to parents and patients and while the patient is in emotionally stable state (10, 19). This transition is normally performed in three stages:

Stage 1: Preadolescent (12-15 years)

At this stage, the child should be able to briefly explain the disease, know the names of medications and how to take them, and participate in preparing drugs under parental supervision. Patients can use alarm, phone, or notes for reminding medication time. In this stage parents should emphasize the benefits of regular drug use, and risk of non-adherence to treatment. Parents should start teaching the child what are the healthy foods, the

appropriate physical exercise, and the high risk behaviors.

They plan exactly how they're going to reach short and long term educational/vocational goals. Another goal is that children should meet with adult-medical team and learn to contact with health-care team. During visits, the pediatric team will encourage treatment adherence, promoting self-reliance, and start to have more autonomy.

Stage 2: Adolescence (16-18 years):

Adolescent should be able to explain cystinosis in details and effects of multi-systemic involvement. Also have more information about drugs' instruction and effects of non-adherence with having notes for drug schedule and dialysis program. The health-care system is supposed to describe the delay of puberty, reproductive health, high risk behaviors, and social relationships to the patients clearly.

An adolescent normally requests more independency, extensive social activity and may have problems with psychological exhaustion, high risk behaviors, and non-adherence to treatment. Therefore, being in constant contact with a psychologist and care-team, participating of parents and patients in cystinosis group, and meeting other cystinotic family help overcome these problems.

Stage 3: Adulthood (19-25 years):

At these ages the transition is completed and adult specialists take full responsibility for the disease management, nevertheless the pediatric team is ready to consult. The patient knows the disease and its complications in details, also the possibility of involvement of other organs.

The young adults learn the long-term effects of the disease on their lives, to be confident and self-reliant and try to achieve their life goals. The patient is completely independent in treatment process and is responsible for his own performance and its consequences. The family and friends can be supportive. Patients who had a successful transition can share their experiences with the transfer team, and help the transition team as mentors.

Recommended services to be involved during transition

Specialists (nephrologist, endocrinologist, ophthalmologist, neurologist), transplant team,

primary care physician, pharmacist, social workers, dietician.

Nephrology Service

Cystinosis patients and their family prefer to be in contact and visited by pediatric nephrologist even until young adulthood. It is preferable to refer the patient to an adult nephrologist who is well recognized for hereditary kidney diseases, with complete records and past medical history. In a renal transplanted patient the time and donor characteristics (deceased or alive, HLA typing, serologic results), recipient characteristics (HLA typing, serologic results, episodes of acute renal failure, immunosuppressive medications, type of cysteamine therapy, intra-granulocyte cystine level, hypertension, diabetes, bone disease) have to be informed to adult specialist (10).

If the patient is on dialysis, the record includes prescribed medications, type of cysteamine therapy, intra-granulocyte cystine level, type of dialysis (hemodialysis or peritoneal dialysis), vascular access, dialysis efficacy (KT/V), residual renal function, residual diuresis, Renal Fanconi Syndrome, hypertension, diabetes, bone disease, and if the patient is on waiting list.

In patients with chronic renal failure (CKD), medications and instructions, type of cysteamine therapy, intra-granulocyte cystine level, stage of CKD, episodes of acute renal failure, residual renal function, residual diuresis, renal fanconi syndrome, bone disease, and hypertension should be reported to adult nephrologist.

Endocrinology service

A child with cystinosis needs to be visited by pediatric endocrinologist at early childhood and then by adult endocrinologist after transition.

The major endocrine organs involved in cystinosis include thyroid, gonads, and pancreas. Hypothyroidism is an early complication of cystinosis that appears in the first decade of life and exacerbates growth retardation. Thyroid dysfunction occurs in about 50% of untreated children aged 5 to 10 years (24). Although the sexual activity and gonadal function in female patients with cystinosis are usually normal but hypogonadism may occur in about 70% of men who are not treated with cysteamine. (25)

Puberty is delayed for about one to two years and in untreated boys it causes primary hypogonadism.

Gonadal disorders in men include infertility due to azoospermia (26).

Cysteine deposition in the pancreas results in hyperglycemia after kidney transplantation, and some patients may need insulin for a long time (27). Short stature is more severe in patients with cystinosis than in other chronic kidney diseases. It may be due to the accumulation of cysteine in the bones, poor metabolic status (electrolyte imbalance, rickets, and metabolic acidosis) as a result of general fanconi syndrome, hypothyroidism, inadequate nutrition, bone disease and hypogonadism in male patients. Treatment with Cysteamine improves growth, but it is not enough to normalize growth even in cases with proper nutrition and good control of metabolic complications of the disease. Treatment with recombinant human GH (rhGH) is effective and safe in these patients and growth hormone is needed even with normal kidney function to accelerate growth rate (28). Growth hormone therapy can be started before development of renal insufficiency. Long-term treatment with growth hormone increases the final height.

Growth hormone is less effective in patients with pre- or post-pubertal disease who had kidney replacement therapy (29).

Diabetes Mellitus occurs in 5% of patients with cystinosis during adolescence or adulthood. In post-transplant patients after oral glucose tolerance test, impaired insulin response is seen in about 100% of patients. In approximately 30% of patients, 10 years after kidney transplantation, overt diabetes mellitus is reported to require insulin therapy. Administration of glucocorticoids and calcineurin inhibitors after renal transplantation may also increase blood glucose levels.

Due to these complications, it's recommended to record demographic characteristics (weight, height, height/weight charts), bone age, delayed puberty, and Tanner stage. The adult nephrologist is informed whether the patients prescribed hormone replacement therapy such as growth hormone, thyroxin, insulin, or testosterone. The last serum levels of thyroxin, TSH (thyroid stimulating hormone), glucose, HbA1C, growth hormone, IGF1, testosterone, LH, and FSH also reported.

Ophthalmology service

Cystinosis patients are examined regularly by an ophthalmologist from childhood. After transition,

the patient can be monitored by the same ophthalmologist. Adolescents aged 16 to 18 should be examined every 6 months and adults every year (10).

Examination of the cornea of the anterior chamber of the fundus and measurement of intra-ocular pressure is done in every visit. Corneal crystals dispersion in the periphery or diffused pattern, and the site of deposition in the parenchymal, stroma, or endothelium is reported. Adherence to cysteamine eye drops, and systemic cysteamine treatment is evaluated regularly. Photophobia, ocular discomfort, and blurred vision are the early signs of not receiving cysteamine eye drops (30, 31).

Neurology service

The cognition scale is generally normal in children with cystinosis (20). Although verbal IQ appears normal in these children, non-verbal IQ (functional IQ and verbal analysis index) are lower. Visual perception and visual memory deficit have been documented in cystinosis and leads to poor mathematical skill (32). In adults who have not received oral cysteamine regularly, distal myopathy results in restrictive lung disease and broncho-aspiration (33).

Idiopathic intracranial hypertension is also a neurological complication of cystinosis for which no factor has been found (34).

According to the neurological manifestations of cystinosis, the assessment of swallowing (35) and oropharyngeal movements and muscle strength, history of pneumonia and aspiration, neuro-imaging results are necessary.

Cardiology service

Vascular calcification including coronary arteries has correlation with duration of cysteamine therapy (36). Dilated coronary arteries and restrictive cardiomyopathy (37) are other cardiac complication that makes cardiology consult necessary in cystinosis.

Conclusion

Patients with cystinosis are at risk of non-adherence due to multiple drug usage and their chronic disease. As a child enters adulthood, parental care decreases and the patient should learn self-management. So the likelihood of non-compliance and loss of kidney transplant is high in transition time.

Acknowledgments

Not declared.

Conflict of Interest

The authors declare no conflicts of interest.

Financial Support

Not declared.

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