Inherited metabolic renal disorders in children

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Abstract

Inherited metabolic conditions of the kidney are uncommon but require consideration as diagnostic clarity informs specific treatment which improves outcomes considerably and allows children with life limiting disorders to experience greater longevity. This article focuses on four conditions, cystinosis, methylmalonic aciduria (MMA), primary hyperoxaluria and Fabry's disease. These conditions often present with renal impairment, predominantly in childhood, but with appropriate treatments survival well into adult life is becoming more common. Recognition of the genetic mutations, phenotypic variability and specific treatment options can improve long term prognosis.

Keywords cysteamine; cystinosis; Fabry's disease; Fanconi's syndrome; kidney failure; kidney transplantation; methylmalonic aciduria; primary hyperoxaluria

Inheritable metabolic conditions cause considerable morbidity and mortality, but each individual disease is seldom encountered. This article focuses on four conditions: cystinosis, methylmalonic aciduria (MMA), primary hyperoxaluria and Fabry's disease. These conditions provide a diagnostic challenge to the clinician as the initial symptoms may be non-specific or show great genetic heterogeneity. The development of treatments that can delay multi-system involvement and death, increases pressure for early identification and institution of medical management plans. Extensive communication is required with the families of children with these conditions to ensure they receive genetic counselling and the necessary knowledge to maximize compliance with treatment regimens. All these conditions are chronic and lead ultimately to multi-system involvement, making multidisciplinary and interdisciplinary working essential.

Any child with chronic illness must be compliant with treatment, and management strategies should maximize the educational, social and psychological development of these young individuals. Increasing numbers of children with rare inherited metabolic conditions are reaching adulthood and effective smooth transfer to adult care is essential. Transition to adult care is always complex, but these young adults present an additional challenge as their conditions will previously have been seen rarely in adult practice and will require ongoing multidisciplinary management.

A summary of inherited metabolic conditions affecting the kidney is provided in Table 1. This article focuses on conditions that present with renal impairment, predominantly in childhood (Table 2).

Cystinosis

Cystinosis is an autosomal recessive multi-system disease, in which cystine crystals accumulate in the tissues of the body as a result of a defective cystine transporter in the lysosomal membrane. The kidney and cornea are very sensitive to this accumulation. The condition affects 1:150,000 births with both sexes affected equally. Over 100 mutations have been described in the cystinosis gene, *CTNS*, located on chromosome 17p13; the gene encodes a protein 'cystinosin'. At birth, the infant appears normal and develops appropriately until 3–6 months of age, before presenting with polyuria and polydipsia, unexplained fever, anorexia, constipation, vomiting causing dehydration, and failure to thrive. Signs of rickets may be present. Caucasian infants typically have blonde hair and blue eyes. At presentation, the glomerular filtration rate (GFR) is normal.

In the kidney, cystine accumulation impairs oxidative phosphorylation in proximal tubular cells and decreases the activity of Na^+-K^+-ATPase, reducing the gradient for sodium entry into the cells and thereby decreasing the sodium-coupled transport of other solutes, manifesting as 'Fanconi's syndrome'. Blood and urine tests reveal a Fanconi's syndrome pattern that includes:

- hypokalaemia
- hyponatraemia
- hypophosphataemia
- acidosis
- generalized aminoaciduria
- glycosuria.

In adolescence, the multi-system effects of cystine accumulation, including growth failure, delayed puberty, hypothyroidism, insulin-dependent diabetes and mild hepatomegaly, may be present. In adulthood, additional features may include muscle weakness, increased risk of fracture, oromotor dysfunction and central nervous system (CNS) involvement (cerebellar dysfunction, cerebral atrophy, stroke), with survival expected into the fifth decade.[1]

The diagnosis is made by assaying white cell cystine concentration (which is typically 10–100 times above the normal range), identifying corneal crystals on slit-lamp examination and genetic analysis of the *CTNS* gene[2] Antenatal diagnosis is possible by examining DNA from amniotic fluid or chorionic villi.

Management involves the continuing correction of dehydration and electrolyte losses with high doses of potassium, sodium, bicarbonate, phosphate, large fluid volumes and active vitamin D. Indometacin and an angiotensin converting-enzyme inhibitor may be used with care to reduce losses. To maintain nutritional intake, nasogastric or gastrostomy feeding is often required. Thyroid supplements and growth hormone are considered beneficial.

Cysteamine is a treatment but not a cure for cystinosis; it acts by circumventing the defective lysosomal cystine-carrier system,

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Glomerulus	Fabry's disease
	Congenital disorders of glycosylation
	Familial lecithin-cholesterol acyltransferase deficiency
Fanconi	Cystinosis
	Fanconi–Bickel syndrome
	Purine transport and metabolism disorders
	Lowe's syndrome
	Tyrosinaemia
	Wilson's disease
	Glycogen storage disorder type 1
Tubular	Nephrogenic diabetes insipidus
	Pyruvate carboxylase deficiency
	Methylmalonic acidaemia
	Carbonic anhydrase deficiency type II
	Lesch–Nyhan syndrome
Any part of kidney	Mitochondrial cytopathies
Renal calculi	Primary hyperoxaluria
	Cystinuria
	Dent's disease

Table 1

thereby reducing the cystine content of lysosomes. Effectiveness is measured by monitoring white cell cystine. For greatest efficacy, it should be started as early in infancy as possible and administered every 6 hours. Unfortunately, it is unpleasant to take, as the sulphur component causes the breath to smell of rotten eggs and it can cause gastrointestinal upset, which reduces compliance. Cysteamine may delay the onset of renal failure and some of the other systemic effects of cystinosis by several years, but has no effect upon proximal tubular dysfunction.[3] A modified-release cysteamine preparation given twice daily has recently been developed and may lead to improved compliance. Cysteamine eye drops are effective in the short-term reduction of corneal cystine accumulation. Before the advent of cysteamine treatment, children typically reached end-stage renal failure (ESRF) by 10 years of age; this is now delayed to late adolescence. Cystinosis accounts for around 5% of chronic renal failure in children. Kidney transplantation is successful in these patients, but cystine continues to accumulate in all tissues of the body and cysteamine treatment is required indefinitely. There is ongoing research into autologous gene-modified haematopoietic stem cell transplants, which may offer a potential cure for this disease in the future.

Overview of inheritance, incidence and age at presentation

Condition	Inheritance	Incidence	Presentation
Cystinosis	AR	1:150,000	Infancy
Methylmalonic aciduria	AR	1:50,000–100,000	Infancy
Primary hyperoxaluria	AR	1:60,000–120,000	Any age
Fabry's disease	X-L	1:40,000–117,000	Childhood

Table 2

Methylmalonic aciduria (vitamin B_{12} non-responsive)

Methylmalonic aciduria (MMA) is an autosomal recessive defect in organic acid metabolism, leading to the accumulation of methylmalonic acid and its by-products in biological fluids. MMA is a heterogeneous group of disorders (ranging from fatal to asymptomatic) with an incidence of 1:50,000–100,000. It is caused by many different genetic defects including deficiency of the enzyme, methylmalonyl-coA mutase, and disorders of intracellular cobalamin metabolism. The gene for methylmalonyl co-A mutase is located at 6p12–q21.2. MMA usually presents in the first year of life, 80% presenting within the first week after birth with metabolic decompensation following the introduction of protein or illness. The infant presents with recurrent vomiting, lethargy, dehydration leading to profound metabolic acidosis, respiratory distress and failure to thrive, leading acutely to seizures, stroke or encephalopathy and, if left untreated, death. The mortality in the first year of life is 10% with a median survival of 6.4 years. Of those surviving, 40% have impaired development; the younger the child is at presentation, the worse the prognosis. Progressive renal failure, secondary to tubulo-interstitial disease, occurs in 20–60% of adolescents with MMA. The mechanism of the renal impairment is unknown but is thought to be secondary to dysfunction of the respiratory chain and the tricarboxylic acid cycle, secondary to the intramitochondrial accumulation of methylmalonic acid and its metabolites.[4]

Elevated serum glycine with raised methylmalonic acid, methylcitrate and propionic acid in urine suggests the diagnosis, which is confirmed by enzymology of fibroblasts and DNA analysis. Prenatal testing using enzyme assay on chorionic villus (CVS) and DNA analysis is available.

Management aims to control methylmalonate and propionate production by limiting dietary intake of precursors (methionine, threonine, valine, isoleucine, odd chain fatty acids and cholesterol), carnitine supplementation to replete intra- and extracellular stores of free carnitine, and oral antibiotic therapy, which can be useful in decreasing gut production of propionate. During times of increased catabolism, prompt discontinuation of protein-containing feeds and generous administration of glucose-containing fluid to avoid decompensation leads to greater survival.

Liver or combined liver/kidney transplantation are options for metabolic control. The benefit of any transplant is limited because of the ongoing systemic metabolic defect and transplantation does not normalize the concentration of methylmalonic acid in the cerebrospinal fluid and brain.[5] With early diagnosis and careful medical management, these children now survive and the longer-term complications of the condition need to be considered. These include neurological impairment (secondary to deposition in the basal ganglia), mental retardation and cardiomyopathy.

Primary hyperoxaluria

Oxalate has no known useful function in man. It is derived principally from the diet and produced endogenously by the