A DIAGNOSIS OF CYSTINOSIS

Clinical History

A 9 month old boy was admitted to hospital with a 3 month history of reduced feeding and failure to thrive, with severe weight loss more evident in the previous 3-4 weeks. On examination, he appeared skinny, pale and fragile, with loose skin folds over his abdomen. His weight on admission was 5.36 kg (less than 0.4th centile). It was noted that his weight had been on the 75th centile at birth. He was of European origin, with thin white hair and very prominent blue eyes. His parents were blonde and blue-eyed but these features were much more pronounced in the child. There was no other medical or family history of note.

Preliminary Laboratory Investigations

His initial biochemistry was as follows:

Sodium	134 mmol/L	(133-143)	Bicarbonate	12 mmol/L	(21-34)
Potassium	2.3 mmol/L	(3.7-5.2)	Chloride	111 mmol/L	(95-105)
Urea	3.6 mmol/L	(3.0-7.0)	Anion gap	11 mmol/L	(6-14)
Creatinine	82 μmol/L	(30-50)	Phosphate	1.04 mmol/L	(1.3-2.0)
Uric acid	0.05 mmol/L	(0.06-0.24)			

These results are typical features of a proximal renal tubular acidosis. The patient was immediately commenced on potassium citrate, sodium bicarbonate and phosphate supplementation.

Liver function appeared normal:	Bilirubin	9 μmol/L	(<22)
	Alkaline phosphatase	113 IU/L	(160-460)
	ALT	15 IU/L	(5-65)
	Albumin	36 g/L	(29-55)
	Total protein	62 g/L	(62-80)

Further biochemistry tests showed persistent glycosuria and proteinuria, generalised aminoaciduria and a reduced tubular reabsorption of phosphate (TmP/GFR=0.59 mmol/L glomerular filtrate, normal age-related range is 1.15-2.6). These findings were consistent with a Fanconi's proximal renal tubular acidosis, although atypically, the patient had no polyuria or polydipsia.

Differential diagnoses

- The causes of proximal renal tubular acidosis in children:

Cystinosis	Tyrosinaemia	Fructose bisphosphatase deficiency
Wilson's disease	Toxicity (lead)	Hereditary fructose intolerance
Lowe's syndrome	Galactosaemia	Respiratory chain disorders
Idiopathic		

- Possible causes of failure to thrive:

  Cystic fibrosis
  Chronic malnutrition

There was now rising concern about the patient's nutritional status. Social history showed that the patient had not received his 2nd and 3rd immunisations, and that the health visitor had made 15 failed attempts to visit the family.

Recommended further investigations

Evidence of liver disease would be expected in tyrosinaemia, galactosaemia and Wilson's disease, although it should be noted that Wilson's disease is has never been reported this early in childhood. The absence of hypoglycaemia makes fructose bisphosphatase deficiency and hereditary fructose intolerance unlikely.

Tests were prioritised and the following investigations were requested:
Sweat Test – to exclude cystic fibrosis
Ophthalmological examination – to check for Lowe's syndrome and cystinosis
Further biochemistry: Urinary reducing substances
Plasma PTH & vitamin D
Plasma copper & caeruloplasmin
Urine toxicology screen
Autoimmune screen
Trace elements (selenium, zinc)
White cell cystine

Results of further tests

Ophthalmological examination: - no abnormality detected
Sweat Test: - insufficient sweat was collected (23mg)
Urinary reducing substances: negative (despite the early evidence of glycosuria)
PTH = 1.5 pmol/L (0.8-7.7) 25-OH Vitamin D = 56.8 µg/L (19.0-57.0)
Copper = 5.1 µmol/L (13.0-24.0) Caeruloplasmin = 0.87 g/L (0.12-0.35)
Selenium = 0.24 µmol/L (0.32-0.63) Zinc = 9.5 µmol/L (8-17)
These trace element results were suggestive of nutritional deficiency.
Urine toxicology screen: - negative
Autoimmune screen: - negative
White cell cystine = **2.3** nmol ½ cys/mg protein (ref range <0.3)
The elevated white cell cystine level confirmed the diagnosis of cystinosis.

The patient was commenced on mercaptamine (cysteamine), initially on a dose of 2-3mg/kg QDS, to increase weekly to a maintenance dose of 12.5mg/kg/day. The patient was now clinically well, his electrolytes had stabilised and he was gaining weight. He was discharged with close follow-up in the renal clinic.

It was advised that carnitine levels should be checked, because of the risk of urinary losses, and these were found to be low:
Plasma carnitine, total 11 µmol/L (23-60)
Plasma carnitine, free 8 µmol/L (15-53)
However it was not clear whether carnitine supplementation was commenced.

Summary

This is the case of a baby boy who presented with severe failure to thrive and proximal renal tubular acidosis. A diagnosis of cystinosis was made. A decreased ability to sweat and loss of pigmentation (causing the child to have marked blonde hair and blue eyes) can be clues to the diagnosis An ophthalmological examination may also be useful, although corneal crystals may be absent before one year of age, as in this case.

CYSTINOSIS

Cystinosis is an autosomal recessive lysosomal storage disorder, with an estimated incidence of 1 in 100,000-200,000 live births. It is caused by a defect in the cystine transporter protein, cystinosin, encoded by the *CTNS* gene. More than 50 mutations in the gene have been identified, but approximately 50% of Northern European patients are homozygous for a 57,257-bp deletion. Accumulation of free cystine in lysosomes affects almost all cells and tissues, with most severe effects in the kidney.

Patients with nephropathic cystinosis usually present between 6-12 months after birth with symptoms of renal Fanconi's syndrome (polyuria, polydipsia, electrolyte imbalance, dehydration, and hypophosphataemic rickets) due to failure of the renal tubules to reabsorb water and low-molecular weight molecules. Non-renal complications such as hypothyroidism and photophobia may develop later in life, due to the formation of cystine crystals in the thyroid tissue and cornea, respectively.

Diagnosis of cystinosis is made by measuring the leukocyte cystine content (reference range is <0.3nmol of half-cystine per mg protein), by amino acid analysis or using a binding protein assay. The presence of typical corneal crystals on slit-lamp examination is also diagnostic, although crystals may be absent before one year of age.

Treatment involves:-
1 Supportive therapy to replace the enormous loss of fluids and solutes due to impaired renal tubular reabsorption.
2 Specific therapy with oral cysteamine. This is an aminothiol which brings about long-term depletion of lysosomal cystine. The target leukocyte cystine content is less than 1.0 nmol of half-cystine per mg protein, and regular biochemical monitoring is required. Clinical trials have demonstrated that commencement of cysteamine therapy early in life retards renal glomerular deterioration and improves linear growth.

Summary
Cysteamine therapy has dramatically changed the course of cystinosis, with particular improvement in prognosis of the renal disease although other problems may emerge later in life. Early diagnosis and treatment is therefore imperative, through increased awareness of the disorder and, eventually perhaps, neonatal screening. The characteristic features of fair skin and very blue eyes, and their inability to sweat normally can give clues towards the diagnosis.

References

- Gahl WA, Thoene JG, Schneider JA. Cystinosis. *N Engl J Med* 2002; **347**: 111-121
- Gahl WA. Early oral cysteamine therapy for nephropathic cystinosis. *Eur J Pediatr* 2003; **162**: S38-S41

Patient Confidentiality

The patient’s parents have given permission for this case report to appear on the MetBioNet website.