Nephrogenic diabetes insipidus, cystinosis, and vitamin D

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SUMMARY We describe a patient with early diagnosed cystinosis who presented with nephrogenic diabetes insipidus in addition to proximal tubular dysfunction. Another feature in this patient was abnormally low serum concentration of 24,25 dihydroxy vitamin D₃ (24,25(OH)₂D₃) with normal 25 hydroxy vitamin D₃ (25(OH)D₃) and relatively low 1,25 dihydroxy vitamin D₃ (1,25(OH)₂D₃).

Cystinosis is a disorder of cystine metabolism with autosomal recessive inheritance. In this disease cystine is stored intracellularly in the lysosomes. There are three known clinical forms of cystinosis: nephropathic-infantile, intermediate-juvenile, and the adult onset type, which is the only form where the kidneys are unaffected.¹

The nephropathic form has been described with a variety of clinical manifestations. Almost all patients present with polydipsia, polyuria, anorexia, failure to thrive, growth retardation, typical brown yellowish skin and hair, rickets, hepatosplenomegaly, and corneal and retinal involvement. The laboratory findings reflect the biochemical abnormalities of Fanconi syndrome, hypothyroidism, and somatomedin C deficiency.^{2,3}

In this report we describe unusual tubular dysfunctions and an interesting abnormality in vitamin D metabolism in an early diagnosed case of cystinosis.

Case report

A girl aged 25 months was admitted because of polydipsia, polyuria, and failure to thrive; the symptoms had begun at 8 months of age. Pregnancy and delivery were uneventful. Birth weight was 4500 g. Family history showed that three of the child's siblings had died: two boys and one girl. One boy had suffered from polydipsia and polyuria and died at the age of 2½ years. Another boy had died after intractable vomiting and diarrhoea at 6 months of age, and one girl died from an unknown cause at the age of 4 months. The other members of the family and two parents were healthy. Developmental milestones were normal in our patient.

On admission the child's weight was 7900 g and

the height was 71 cm, both below the third percentile. Heart rate was 116 beats/minute and blood pressure was 100/70 mm Hg. Physical examination was otherwise normal.

Laboratory investigations showed hyponatraemia with serum sodium concentration of 129 mmol/l (normal range 135–145 mmol/l) and hypokalaemia with serum potassium concentration of 2.9 mmol/l (normal range 3.5–5.0 mmol/l), serum urea concentration of 9.3 mmol/l (normal range 1.5–7 mmol/l), and creatinine concentration of 119 µmol/l (normal 80 µmol/l). Serum alkaline phosphatase activity was 822 IU/l (a normal result for this age is less than 300 IU/l), serum phosphorus concentration ranged between 0.96 and 1.43 mmol/l (normal range for this age 1.4–2.0 mmol/l), and calcium concentration was 2.4 mmol/l (normal range 2.0–2.6 mmol/l). Glucose, total protein, albumin, and liver enzymes were within normal limits. Capillary pH was 7.4 (normal range 7.38–7.42), serum bicarbonate was 20 mmol/l (normal range 20–23 mmol/l). Urinalysis showed traces of albumin and glucose on several occasions. Tubular reabsorption of phosphorus was 67% (normal 85%). A random urine osmolarity measurement was 114 mmol/kg H₂O. Urinary output was 2000 ml/24 hours.

An x ray film showed that her bone age was in the lower range for her chronological age. There was no radiological evidence of rickets.

A seven hour water deprivation test terminated by an intranasal deamino-8-D-arginine vasopressin (DDAVP) test was performed.⁴ Urine osmolarity increased from 121 mmol/kg H₂O to 148 mmol/kg H₂O only. Therefore the diagnosis of nephrogenic diabetes insipidus was made. Treatment by hydrochlorothiazide and indomethacin caused a reduction in urinary output to 1000–1400 ml/24 hours, cessation of polydipsia, improvement in appetite, and a weight gain of 500 g within one week.

At the age of 32 months she had grown only 3 cm during the previous seven months. Hepatosplenomegaly and clinical signs of rickets were first detected. Her growth retardation became more pronounced than the lag in weight gain and was appreciably below the third percentile (74 cm). A brown yellowish colour of her skin and hair was noticed.

Laboratory investigations showed metabolic acidosis (pH 7.28, serum bicarbonate concentration 15 mmol/l), persistence of high serum urea and creatinine concentrations, low serum phosphorus, high alkaline phosphatase activity and normal calcium concentration. Serum sodium and potassium concentrations were normal.

Vitamin D metabolites concentrations were: 1,25(OH)₂D₃ 59.76 pmol/l, 25(OH)D₃ 67.6 nmol/l, both in the normal range (>46.8 pmol/l, >39 nmol/l, respectively). Concentrations of 24,25(OH)₂D₃ 1.42 nmol/l, 1.15 nmol/l, and 1.17 nmol/l were found in three separate samples (normal 2.5–10 nmol/l by high performance liquid chromatography depending on 25(OH)vitamin D concentration).⁵ Concentrations of thyroid hormones were triiodothyronine (T₃) 3.06 nmol/l (normal range 1.25–3.14 nmol/l) and thyroxine (T₄) 130.8 nmol/l (normal 59–158 nmol/l).

Results of urine examinations were: pH 6.5–7 and the glucose and protein traces intermittently persisted. Tubular reabsorption of phosphorus was 63%, nephrogenous cyclic adenosine 5 monophosphate (cAMP) was 1438 pmol/ml glomerular filtration rate (GFR) (normal 1000–2000 pmol/ml GFR). Chromatography of the urine did not show aminoaciduria.

Bone x ray films showed severe rachitic changes. Bone age corresponded to 1½ years. Intravenous pyelography and kidney ultrasonography gave normal results.

Bone marrow aspiration showed cystine crystals. There was a high free cystine content of peripheral leukocytes: 4.14 µmol ½ cystine/g of protein (50 times results from normal controls). Both findings were consistent with cystinosis. Slit lamp microscopy did not visualise corneal cystine crystals. Treatment with 1 mmol/kg/day sodium bicarbonate corrected the metabolic acidosis and her appetite improved. Indomethacin was stopped because of high serum creatinine and urea concentrations but no improvement was noticed. During a follow up of one year, tubular disturbances continued. Tubular reabsorption of phosphorus was 64% and glycosuria appeared more often. Urine osmolality was 162 mmol/kg H₂O after 10 hours of water deprivation. Treatment included bicarbonate, hydrochlorothiazide, and cysteamine.

Discussion

Nephrogenic diabetes insipidus as the initial presentation of cystinosis has been described in only a few cases.² It is possible that some patients with cystinosis with polyuria and polydipsia who are not routinely subjected to an antidiuretic hormone

(ADH) test escape the diagnosis of nephrogenic diabetes insipidus. This specific test has not been performed in almost all the previously reported cases. We can assume, therefore, that the tubular defect in cystinosis may also affect the distal nephron. It is noteworthy that the proximal tubular abnormalities in this patient did not include aminoaciduria but the phosphaturia and occasional glycosuria were prominent findings. The former led to the clinical bone disease. In previous reports describing early diagnosed cases of cystinosis there were some patients showing an incomplete form of tubular defects referred to as 'partial Fanconi syndrome'.²

The possibility of nephropathic cystinosis in this girl was raised because of the presence of 'nephrogenic diabetes insipidus', which as an isolated defect is inherited as a sex linked disease rarely found in such severity in female patients.

Analysis of serum vitamin D metabolites concentrations showed that the 24,25(OH)₂D₃ concentrations in our patient were much lower than those described in patients with vitamin D resistant rickets from other etiologies. Their fraction of total serum 25(OH)D₃ was 2% in our patient, in comparison with 10% in normal children (figure).⁵ Serum 1,25(OH)₂D₃ and 25(OH)D₃ concentrations were normal, but in view of low serum phosphate the concentration of 1,25(OH)₂D₃ can be considered as relatively low.

Figure Relation between serum 24,25 dihydroxy vitamin D₃ (24,25(OH)₂D₃) and serum 25 hydroxy vitamin D₃ (25(OH)D₃) concentrations in 16 normal children (●)⁵ and in our patient (○).

It is possible that 24-hydroxylase activity in the kidney is much more sensitive to the specific metabolic changes of cystinosis than that of α -1-hydroxylase.

Although the phosphate leak, per se, could account for the pathogenesis of rickets, one cannot rule out that the low concentration of $24,25(\text{OH})_2\text{D}_3$ could also contribute to the bone disease in this patient.⁶

References

¹ Schneider JA, Schulman JD. Cystinosis and the Fanconi syndrome. In: Stanbury JB, Wyngaarden JB, Fredrickson DS, eds. *The metabolic basis of inherited disease*. 5th ed. New York: McGraw-Hill, 1982:1844.

² Lemire J, Kaplan BS. The various renal manifestations of the nephropathic form of cystinosis. *Am J Nephrol* 1984;**4**:81-5.

³ Bercu BB, Corden BJ, Schulman JD, et al. Circulating somatomedin-C levels in nephropathic cystinosis. *Isr J Med Sci* 1984;**20**:236-9.

⁴ Hendricks SA, Lippe B, Kaplan SA, et al. Differential diagnosis of diabetes insipidus: use of DDAVP to terminate the seven hour water deprivation test. *J Pediatr* 1981;**98**:244-6.

⁵ Nguyen TM, Giuliozo H, Garabedian M, et al. Serum concentrations of $24,25$ dihydroxyvitamin D in normal children and in children with rickets. *Pediatr Res* 1979;**13**:973-6.

⁶ Malluche HH, Henry H, Meyer-Sabellek W, et al. Effect and interactions of $24\text{R},25(\text{OH})\text{D}$ and $1,25(\text{OH})\text{D}$ on bone. *Am J Physiol* 1980;**238**:E494-8.

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Ophthalmitis in meningococcal disease

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SUMMARY We report an infant with meningococcal septicaemia and meningitis who had panophthalmitis at presentation that was unresponsive to standard systemic antibiotic treatment but which responded to topical steroid and mydriatic treatment. The pathogenesis may have been immune mediated.

Case report

The patient, a 7 month old boy in whom there was no important family or perinatal medical history, had been unwell for three days before admission with cough, poor feeding, and diarrhoea. (On questioning later his mother recalled noting that his eyes were 'blood shot' two days before admission.) On the day of admission he deteriorated and developed a widespread rash. On admission he was ill but not shocked or hypotensive. Axillary temperature was 39°C and he had a widespread purpuric rash but no conjunctival petechiae, although both bulbar conjunctivae were injected. He was very irritable, noticeably photophobic, and had meningism. A clinical diagnosis of meningococcal meningitis was made and the following initial investigations performed: cerebrospinal fluid was turbid with $4.56 \times 10^9/\text{l}$ leucocytes, glucose 0.1 mmol/l , total protein 2.6 g/l with raised globulins; Gram staining showed Gram negative diplococci, and both cerebrospinal fluid and blood culture subsequently

confirmed *Neisseria meningitidis* (later reported as Group C) sensitive to benzylpenicillin and chloramphenicol. Peripheral blood count showed: haemoglobin 110 g/l , white blood count $22.8 \times 10^9/\text{l}$ with 57% neutrophils and platelets $312 \times 10^9/\text{l}$.

Treatment was started with intravenous benzylpenicillin 300 mg/kg/day and his general condition gradually improved. Photophobia persisted as well as low grade fever, however, although his meningism resolved and there were no localising neurological signs. On the seventh day of treatment a repeat examination of the cerebrospinal fluid gave normal results, and a computed tomogram was normal with no evidence of abscess or subdural collection. Antibiotic treatment was stopped on the eighth day.

An ophthalmological opinion was obtained 12 days after admission as his eyes continued to be red, and he was photophobic with a low grade temperature. The appearances were suggestive of uveitis with limbal injection; and he had miosis non-reactive pupils, fibrinous exudates in the anterior chamber, and a dull red reflex. Topical treatment with prednisolone 0.5% drops and cyclopentolate 1% was started and within two days he had considerably improved, he was not feverish and had minimal photophobia.

An examination under general anaesthetic later confirmed the diagnosis of anterior uveitis; dilated iris vessels and posterior synechia were found in both eyes. The pupils continued to be poorly dilated and phenylephrine 2.5% drops were added to the