CASE REPORT

Dent's disease complicated by an acute Budd-Chiari syndrome

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cazardron@doctors.org.uk**SUMMARY**

We present the case of a young boy with Dent's disease, identified as having a mutation in the kidney-specific chloride-proton antitransporter CLCN5 during investigation for nephrotic-range proteinuria. He went on to develop growth hormone deficiency and was treated with recombinant growth hormone. He later presented acutely with hepatorenal failure and thrombotic occlusion of the middle and right hepatic veins consistent with a diagnosis of Budd-Chiari syndrome, which required a prolonged period of intensive care. The diagnosis of Dent's disease should be considered early in boys with nephrotic-range proteinuria in the absence of clinical oedema and hypoalbuminaemia to allow for the timely introduction of strategies, such as a high-citrate diet, to preserve renal function. The measurement of urinary β -2 microglobulin has been shown by this case to be a more reliable and specific marker of tubular dysfunction than the urinary retinol-binding protein.

BACKGROUND

This report focuses on two rare conditions that have not been described in association with each other previously. The measurement of the urinary low molecular weight protein, β -2 microglobulin, was shown to be a reliable and specific marker for renal tubular dysfunction in this case.

Dent's disease is an X linked recessive renal tubulopathy encompassing features of proximal tubular dysfunction such as low molecular weight (<70 kDa) proteinuria (thought to be due to the defective tubular resorption of α -1 and β -2 microglobulin, retinol-binding protein and vitamin D-binding protein), glycosuria, aminoaciduria, acidification abnormalities, hypercalciuria, nephrolithiasis and nephrocalcinosis, hypophosphataemia and rickets. The renal insufficiency progresses and leads to end-stage renal disease between the third and fifth decades of life in two-thirds of affected men.¹ Low molecular weight proteinuria is the most consistent feature of the condition, occurring in 99% of affected men.^{1 2}

The treatment is predominantly supportive and focuses on the prevention of nephrocalcinosis/nephrolithiasis and the management of deteriorating renal disease (hypertension/vitamin D deficiency).

Increased awareness of the diagnosis of Dent's disease in young men with nephrotic-range proteinuria in the absence of clinical oedema and hypoalbuminaemia will allow the earlier introduction of a high-citrate diet, the only treatment currently known to have an influence on the progression of the disease towards end-stage renal failure.³

The Budd-Chiari syndrome describes the disorders resulting from obstruction of hepatic venous outflow. The condition is very rare in children. Management involves anticoagulants, thrombolytics and interventional radiological procedures such as the transjugular intrahepatic portosystemic shunt (TIPSS).⁴

CASE PRESENTATION

A 4-year-old boy presented with a 10-day history of 'frothy urine'. His antenatal history included a transient mild bilateral hydronephrosis along with a 'dumb bell' appearance of the cerebellum on ultrasound at 20 weeks gestation.

Investigation revealed nephrotic-range proteinuria (early morning urine protein: creatinine 326 mg/mmol) without coexistent haematuria (see table 1). He was normotensive and of average height and weight (50th centile for both). Further investigation revealed a normal creatinine (32 μ mol/L) and estimated glomerular filtration rate as well as a normal total protein, serum albumin and auto-immune profile including C3 and C4 complements. His serum phosphate was low at 1.0 mmol/L with a mildly elevated alkaline phosphatase of 379 IU/L and a borderline 25 (OH) vitamin D level of 29.7 μ g/L (see table 1).

At this stage, he was started on 60 mg/m² of prednisolone for 4 weeks followed by a dose of 40 mg/m² for a subsequent 4 weeks after which the treatment was discontinued. His heavy proteinuria continued for 3 months. Further analysis showed a raised urinary albumin: creatinine ratio of 71.2 mg/mmol and a mildly elevated urinary retinol-binding protein of 66 mg/L (see table 1).

Subsequent renal biopsy showed global sclerosis of one out of the five glomeruli within the tissue core obtained. The remainder were of normal architecture and cellularity and showed no evidence of immune complex deposition. The angiotensin enzyme converter inhibitor enalapril was started at a dose of 5 mg once daily (0.2 mg/kg). A dimercaptosuccinic acid (DMSA) renal scan was organised to exclude parenchymal scarring as an explanation for the heavy proteinuria. The findings supported the presence of renal disease showing massive leakage of the tracer substance through the tubules directly into the collecting system without evidence of renal scarring.

Owing to the rising proteinuria (reaching a peak urinary protein: creatinine ratio of 460 mg/mmol), the angiotensin 2-receptor antagonist losartan was started as a once daily dose of 12.5 mg (0.5 mg/kg) as an additional therapy. This produced a transient but unsustained improvement in the proteinuria, which

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Table 1 Summary of relevant investigations

Test	Result	Normal range
Early morning urine protein: creatinine	326 mg/mmol	<30 mg/mmol
Urinary retinol-binding protein	66 mg/L	<15 mg/L
Urinary albumin: creatinine	71.2 mg/mmol	<30 mg/mmol
Urinary calcium: creatinine	1.2 mmol/L	<0.74 mmol/L
Urinary beta-2 microglobulin	58.8 mg/L	1.2–2.4 mg/L
Serum creatinine	32 µmol/L	30–70 µmol/L
Serum phosphate	1.0 mmol/L	1.2–1.8 mmol/L
Serum alkaline phosphatase	379 IU/L	130–260 IU/L

persisted over a total period of 2 years despite optimisation of drug doses and the addition of the calcineurin inhibitor tacrolimus at a dose of 2 mg twice daily (0.2 mg/kg/day) for 9 months.

Further urinalysis provided supporting evidence of a low molecular weight (tubular) proteinuria with a significantly elevated β -2 microglobulin (58.8 mg/L, see table 1).

A second renal biopsy at the age of 7 years showed changes consistent with a diagnosis of focal global glomerulosclerosis. Urinalysis at this time indicated hypercalciuria with a urinary calcium: creatinine ratio of 1.2 mmol/L (see table 1). Mutation screening confirmed a heterozygote mutation of the *CLCN5* gene on chromosome Xp11.22 confirming a diagnosis of Dent's disease type 1. His mother was subsequently identified as a carrier for the Dent's mutation.

Over the 4 years from presentation, growth parameters became a concern with a slowing of linear growth and an absolute height below the mid-parental height range. His bone age was shown to be delayed by 2 years and an insulin-like growth factor-1 level was at the lower end of the normal range at 8 nmol/L (normal range 7–40 nmol/L). An insulin tolerance test revealed a suboptimal response to growth hormone and alongside a normal MRI scan of the pituitary gland; a diagnosis of isolated growth hormone deficiency was made. Growth hormone replacement therapy was started when he was 9 years and 5 months. He was also started on desmopressin due to problematic secondary enuresis around this time.

At 9 years and 8 months of age, he presented acutely with a 24 h history of vomiting, right upper quadrant pain and an altered conscious level. He was found to be hypertensive with hepatomegaly on admission with a significant derangement of liver and renal function tests indicating acute hepatorenal failure. His alanine aminotransferase and aspartate aminotransferase levels were both >2600 IU/L; urea and creatinine levels are 42.8 mmol/L and 303 µmol/L, respectively. He was coagulopathic with a prothrombin time of 27 s and an activated partial thromboplastin time of 54 s. Liver ultrasonography and abdominal CT scan identified thrombus in the middle and right hepatic veins with absence of portal venous blood flow, leading to a diagnosis of acute Budd-Chiari syndrome.

Haemofiltration was started. He underwent a TIPSS procedure. Subsequently, his hepatic and renal function returned to normal and venography after 6 months demonstrated a patent stent. His thrombophilia screen was negative and there was no family history of thrombotic disease.

OUTCOME AND FOLLOW-UP

At present, his renal and liver function tests are within the normal range and his current management includes warfarin,

and potassium citrate for the control of his hypercalciuria. He attends mainstream school and has been diagnosed with dyslexia.

DISCUSSION

Three case reports have alluded to an association of growth hormone deficiency in Dent's disease as well as showing evidence of improved linear growth with the use of recombinant growth hormone in such cases.^{5 6}

The origins of the Budd-Chiari syndrome remain elusive. Growth hormone and desmopressin are potentially implicated, as both treatments predated the acute illness by only a short time period. Growth hormone excess or deficiency has been shown to have an effect on markers of coagulation and fibrinolysis⁷ and as such may be a risk factor for thrombotic events.

It is interesting to speculate a role for the low-density lipoprotein endocytic receptor, megalin, in the neurocognitive aspect of this case (the diagnosis of dyslexia). Megalin is expressed at the brush border of proximal tubular cells. The endocytosis and processing of low molecular weight proteins that is defective in Dent's disease involves this receptor. In Dent's patients, megalin is absent at the brush border, which may indicate that the defect is in part due to the deficiency of this protein.⁸ Recently, megalin has also been demonstrated in neurons throughout the brain where it is suggested to have a role in neural regeneration.⁹

Learning points

- The diagnosis of Dent's disease should be considered early in males with nephrotic-range proteinuria in the absence of clinical oedema and hypoalbuminaemia.
- In cases where proteinuria is identified, an albumin: creatinine ratio should be defined early and a urinary β -2 microglobulin result is obtained as a reliable and specific marker of renal tubular function in place of the retinol-binding protein: creatinine ratio.
- The association of Dent's disease with an acute thrombotic event and subtle neurocognitive abnormality has not previously been described and potentially widens the phenotype of this multifaceted condition.

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Competing interests None.

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