Renal tubular leakage complicating microcephalic osteodysplastic primordial dwarfism

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Abstract

We describe a male infant with phenotypic and radiological features of microcephalic osteodysplastic primordial dwarfism type I/III. He showed severe osteoporosis and biochemical derangement owing to renal tubular leakage, which has not previously been reported in this condition. He died aged 5 months.

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We describe a male infant with microcephalic osteodysplastic primordial dwarfism. The purpose of this paper is to report the previously unrecognised complication of renal tubular leakage.

Case report

Our patient was the second child born to healthy, non-consanguineous parents. The mother, aged 39 years, had no history of miscarriages. She was a non-smoker and on no medication during pregnancy. Increasingly severe intrauterine growth retardation was noted on antenatal ultrasound scanning from 17 weeks onwards and maternal alpha-fetoprotein level was raised. Cordocentesis showed a normal karyotype. Labour was induced at 36 weeks owing to the growth retardation and normal vaginal delivery ensued.

Birth weight was 1260 g, length 40 cm, and occipitofrontal circumference 27 cm (all parameters well below the 3rd centile). He had large and protruding eyes and nose, micrognathia, low set, simple ears, and a short neck (fig 1). The hands were relatively broad with

short fingers (all of similar length) (fig 2) and bilateral single palmar creases. He showed a lack of subcutaneous fat and sparse eyebrows and lashes, but normal growth of scalp hair.

The neonatal course was complicated by recurrent apnoea, hyperbilirubinaemia, hyperglycaemia, and hyponatraemia. Aged 9 weeks he had recurrent seizures which responded to phenobarbitone. EEG showed no focal abnormality. He showed developmental delay with no social smile detected and dependence on tube feeding throughout his life. His postnatal weight gain was satisfactory but length and head circumference deviated further below the 3rd centile.

Radiographs showed several skeletal abnormalities. The iliac wings were short and the acetabular roofs horizontal and irregular (fig 3). There was an increase in the intervertebral spaces with mild flattening of the vertebral bodies. The upper femora were broad. The clavicles were long. The metacarpals and phalanges were short and broad with pronounced cupping of the proximal ends. The metaphyses were flared and showed some irregularity. The anterior fontanelle was patent but extremely small. Absence of ossification of the epiphyses at the knee and foot suggested severe growth retardation. There was generalised osteoporosis (fig 3).

Blood and urine tests for intrauterine infection were negative. Karyotype confirmed 46,XY (including skin fibroblasts to exclude mosaicism). Random growth hormone level was 7.9 mU/l, insulin level <25 pmol/l, and C peptide <75 pmol/l. He also showed normal thyroid function, plasma cortisol, blood amino acids, lactate and pyruvate, immunoglobulins, urinary organic acids, urine culture, and renal

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Figure 1 Profile at 5 weeks showing protuberant eyes, prominent occiput, and micrognathia. Note also the sparse eyebrows and lashes but normal scalp hair.

Figure 2 Dorsal aspect of both hands showing the broad appearance with short fingers, each of similar length.

Figure 3 Radiograph showing short iliac wings and horizontal, irregular acetabular roofs. The upper femora are broad. Note the severe generalised osteoporosis.

tract ultrasound. Early cranial ultrasound was normal but aged 10 weeks showed cerebral atrophy.

He developed persistent hyponatraemia, hypokalaemia, hypocalcaemia, and hypophosphataemia. He was not acidotic. Investigations showed a renal tubular leak of amino acids (generalised), protein, glucose, sodium, potassium, calcium, and phosphate. Large doses of supplements (potassium dihydrogen phosphate, sodium hydrogen phosphate, and potassium chloride) were required.

He eventually died of a chest infection aged 5 months. Permission for necropsy was declined.

Discussion

In a series of papers Majewski *et al*¹⁻³ defined three main groups of microcephalic osteodysplastic primordial dwarfism distinct from Seckel syndrome. Winter *et al*⁴ suggested that types I and III were very similar and the x ray differences may be age dependent. Meinecke and Passarge⁵ suggested that the term "type III" should be abandoned altogether leaving only the two types. As well as extreme growth retardation and microcephaly our patient showed characteristic facial features of microcephalic osteodysplastic primordial

dwarfism type I/III (protuberant eyes, micrognathia, prominent occiput, and low set ears). The radiological changes were typical apart from the marked osteoporosis. Our infant displayed the previously unreported feature of a generalised renal tubular leak. He showed persistent hypokalaemia despite supplements and needed a very high level of sodium input to maintain a normal serum level. The calcium and phosphate loss probably caused his osteoporosis. The two cases reported by Meinecke and Passarge⁵ showed normal urinary amino acids. Our infant showed early hyperglycaemia like that reported by Van Maldergem *et al*.⁶ Glucose intolerance with glycosuria is a recognised feature of certain dwarfing syndromes such as leprechaunism. However, our case showed persistent glycosuria after the blood sugar level normalised, suggesting renal tubular leakage. Unilateral hydronephrosis has been reported⁷ but our baby had a normal renal tract ultrasound. Unfortunately our patient did not undergo necropsy. Winter *et al*⁴ reported microscopic abnormalities of the kidney with focal dilatation of the proximal tubules and fibrin deposits occluding the capillaries of a few glomeruli.

We cannot explain this new finding but the knowledge of its existence adds to the complex list of problems this syndrome entails. Its recognition carries important therapeutic implications.

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