Autosomal recessive hypoparathyroidism with renal insufficiency and developmental delay

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Abstract

Four children (two boys and two girls) with hypoparathyroidism, renal insufficiency, and developmental delay are described. They were the products of consanguineous marriages in three related Asian families presenting over a six year period. All the children died within the first 15 months of life despite treatment. Postmortem examination on one child showed absent parathyroid glands. We believe these children represent a previously undescribed syndrome that appears to be inherited in an autosomal recessive manner.

Early onset idiopathic hypoparathyroidism is rare. It is usually a sporadic condition but familial forms have also been reported. It may occur in isolation or associated with other abnormalities. We report four children from three related families who presented in infancy with hypocalcaemia due to hypoparathyroidism. They also had evidence of renal insufficiency, failure to thrive, and developmental delay. This combination has not previously been described and appears to be inherited in an autosomal recessive manner.

Case reports

CASE 1

This boy was born in 1982 weighing 2100 g at 36 weeks' gestation (VI.1 in figure). He was the first child of Asian parents who were first cousins. He became lethargic on the ninth day of life and investigations showed evidence of a metabolic acidosis (pH 7.18, base excess -17 mmol/l), with hypocalcaemia (1.32 mmol/l), and hyponatraemia (115 mmol/l). He was treated with sodium bicarbonate, calcium gluconate, and the vitamin D analogue alfacalcidol. Further investigations gave normal results and included an infection screen, plasma 17 hydroxyprogesterone, serum amino acid and ammonia, and urinary organic acid concentrations. He had evidence of a distal renal tubular acidosis because he was unable to achieve a urinary pH below 5.5. Over the next few months he continued to have evidence of hypocalcaemia and failed to thrive. He was reassessed at the age of 5 months. At this time his weight was 3.4 kg (2.5 kg less than the third centile), height 61 cm, and head circumference 39 cm (both less than the third centile). He was generally hypotonic with poor head control. Investigations (see table) confirmed hypocalcaemia and hyperphosphataemia with a normal magnesium (0.93 mmol/l).

He had normal values for plasma albumin and alkaline phosphatase. He had evidence of renal insufficiency and a compensated metabolic acidosis. His calculated index of phosphate reabsorption (tubular maximum reabsorption of phosphate/glomerular filtration rate, TmPO_4/GFR)¹ was 3.6 mmol/l (normal range 1.15-2.26 mmol/l). Plain abdominal x ray films showed no evidence of renal calcification, and a renal ultrasound demonstrated a bright cortex and prominent pyramids. A renal biopsy specimen showed normal glomeruli and birefringent crystals in the tubules which appeared to be oxalate. He had raised values for oxalate: creatinine ratio at 105:1 (quoted normal less than 70:1) and a presumptive diagnosis of primary hyperoxaluria was made. He was initially discharged on alfacalcidol and pyridoxine but was readmitted one month later because of vomiting and weight loss. His metabolic abnormalities were unchanged and he subsequently died.

CASE 2

This girl was born in 1985 weighing 3400 g at term. She was born to Asian parents who were first cousins and she was a cousin to case 1 (VI.7 in figure). She was admitted at the age of 3 months because of poor feeding dating from birth and failure to thrive. Her weight, length, and head circumference were all below the third centile and she was generally hypotonic and developmentally delayed. Investigations (see table) showed a metabolic acidosis, hypocalcaemia, hyperphosphataemia, and renal insufficiency. There was evidence of a distal renal tubular acidosis because she was unable to lower the urinary pH below 6 when the bicarbonate was 13 mmol/l. She had normal values for plasma albumin and alkaline phosphatase. Her tubular maximum reabsorption of phosphate (TmPO_4/GFR) was 3.44 mmol/l (normal

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Family tree of affected children.

Biochemical abnormalities at presentation

Case No	Bicarbonate (mmol/l)	Calcium (mmol/l)	Phosphate (mmol/l)	Urea (mmol/l)	Creatinine (μ mol/l)	Potassium (mmol/l)
1	12.6	1.6	4.5	18.9	109	6.7
2	17.0	1.49	2.66	10.7	*	6.4
3	11.0	1.21	2.36	10.1	*	7.7
4	8.0	1.71	2.61	12.0	100	9.3

*Not done at presentation.

range 1.15–2.6 mmol/l).¹ She had a raised 24 hour urine oxalate excretion of 0.48 mmol/1.73 m²/day (normal range <0.46 mmol/1.73 m²/day).² A renal biopsy specimen showed mainly fetal type glomeruli with a prominent microcystic appearance and dilatation of the proximal tubules. A few oxalate crystals were seen in the tubules. She was initially treated for primary hyperoxaluria and commenced on pyridoxine. Subsequent results of her urinary oxalate excretion confirmed a raised oxalate:creatinine ratio of 159 mmol:mmol (normal range 14–25 mmol:mmol) but no increased excretion of glycolate or glycerate as would be expected in primary hyperoxaluria. She was readmitted at 11 months with deteriorating renal function (concentrations of urea 23.9 mmol/l and creatinine 187 μ mol/l). Her weight was less than 5 kg and she had profound developmental delay with very poor head control. After discussion with the parents it was decided she be offered palliative treatment only. She subsequently died a few weeks later.

CASE 3

This girl was born in 1988 weighing 1590 g at 35 weeks' gestation. She was a sibling of case 1 (VI.4 in figure). She made reasonable progress in the first week of life, but at 8 days developed a metabolic acidosis (see table) with renal insufficiency and hypocalcaemia. She was treated with sodium bicarbonate, calcium gluconate, and alfacalcidol. She subsequently had frequent convulsions over the next seven weeks. Because of the previous family history suggestive of primary hyperoxaluria, a liver biopsy was performed at 5 weeks of age. The biopsy specimen did not demonstrate any features of oxalosis and no evidence of deficiency of the specific enzyme hepatic alanine glyoxylate aminotransferase.³ She continued to have hypocalcaemia, convulsions, and poor weight gain and at the age of 3 months was transferred to another hospital for further investigation. At that time her weight was only 2.85 kg with head circumference and length also being well below the third centile. She had profound hypotonia and showed no obvious response to visual or auditory stimuli. The following problems were revealed on further investigation:

(1) *Hypoparathyroidism*—An initial parathyroid hormone concentration measured in the original hospital at age 24 days using an intact molecule assay (IncStar) gave a normal result of 88 pg/ml (normal range 20–80 pg/ml). However, a C-terminal assay gave a result of <250 pg/ml (normal range 250–600 pg/ml). A concentration measured in the second hospital at the age of 3 months using an intact molecule assay (Allegro)

gave a result of 4 ng/l (normal range 11–35 ng/l). This was when her calcium was only 1.21 mmol/l and therefore is very low for the degree of hypocalcaemia. Her tubular maximum reabsorption of phosphate (TmPO₄/GFR) was 3.36 mmol/l (normal range 1.48–3.3 mmol/l).¹ Further investigations into the aetiology of the hypoparathyroidism showed no evidence of parathyroid antibodies, normal immunoglobulins, low normal T lymphocyte numbers, but normal in vitro responses. She was treated with large doses of alfacalcidol and a dose of 0.75 μ g per day was found necessary to maintain her serum calcium in the normal range.

(2) *Renal insufficiency*—The serum creatinine concentration remained fairly static between 100–120 μ mol/l with a serum urea of 10–15 mmol/l. The hyperkalaemia settled from an initial potassium concentration of 6.9 to 4.3 mmol/l. There was evidence of a distal renal tubular acidosis requiring bicarbonate supplements. However, the acidosis resolved with correction of the hypocalcaemia. A renal ultrasound showed normal sized but echogenic kidneys. A renal biopsy was not performed because of her poor condition.

(3) *Convulsions and developmental delay*—She had numerous convulsions in the first few weeks of life which did not always respond to intravenous calcium. They were eventually controlled with a combination of clonazepam and sodium valproate. A computed tomogram showed mild generalised cerebral shrinkage and several small foci of low density parenchyma in the left hemisphere that had the appearance of infarcts. A urine metabolic screen for amino acids, organic acids, and mucopolysaccharides gave normal results. Visual evoked responses revealed intact visual pathways. Brain stem auditory evoked responses showed an absent response on the right. She remained severely developmentally delayed and hypotonic and did not achieve any developmental milestones.

(4) *Failure to thrive*—Despite an energy intake of at least 0.84 MJ/kg/day she showed negligible weight gain. There was no improvement on a diet free of cows' milk or an elemental peptide diet. Investigations showed excess split fats on stool microscopy, no reducing substances in her stool, and normal faecal chymotrypsins. Insufficient sweat was obtained for a sweat test. Chromosomes and thyroid function tests were normal. A barium meal showed appreciable oesophageal reflux, which showed no improvement with thickened feeds or the use of domperidone or cisapride. She remained in hospital and died at the age of 7 months. As in cases 1 and 2 parental consent was not obtained for a postmortem examination.

CASE 4

This boy was born in 1988 weighing 2800 g at term. He was born to Asian parents who were second cousins and he was a cousin to the other three cases (VI.10 in figure). At birth other than bilateral talipes equinovarus he was well. He was admitted at the age of 3 weeks with a history of poor feeding, irritability, vomiting, and poor weight gain. He was 5% dehydrated, wasted, and hypotonic. He had a profound metabolic acidosis (see table) hyperkalaemia, hypocalcaemia, renal insufficiency, and hyperphosphataemia. He was rehydrated and commenced on bicarbonate and calcium supplements. A parathyroid hormone concentration at the age of 3 weeks using an intact molecule assay (IncStar) was normal at 95 pg/ml (normal range 20–80 pg/ml) but a value of less than 250 pg/ml was obtained using a C-terminal assay (normal range 250–600 pg/ml). This was at a time when his serum calcium was only 1.4 mmol/l. He had evidence of excess faecal fat excretion of 56% (normal less than 25%) and a normal sweat test. Despite correction of his hypocalcaemia with a dose of alfacalcidol of 0.75 µg/day he continued to have feeding difficulty with failure to thrive. At the age of 4 months he was 1.3 kg less than the third centile and he was developmentally delayed by at least two months. He was subsequently investigated at the Hospital for Sick Children in London. The following abnormalities were shown:

(1) *Hypoparathyroidism*—An intact parathyroid hormone measurement (IncStar) gave a concentration of <16 ng/l (quoted normal range 20–80 ng/l). A subsequent concentration using the intact molecule assay (Allegro) was low (8 ng/l) at the age of 9 months. His immune status was also investigated revealing normal immunoglobulins, low T cell numbers, but normal in vitro lymphocyte responses.

(2) *Renal insufficiency*—He had a raised creatinine concentration of 99 µmol/l. A renal ultrasound showed increased echogenicity of the renal cortex. Micturating cystogram showed no evidence of reflux and a technetium labelled dimercaptosuccinic acid scan no evidence of scarring. A renal biopsy was not performed.

(3) *Developmental delay*—He had generalised hypotonia with a persistent asymmetric tonic neck reflex. He had hypertonic legs with hyperreflexia. He had a persistent grasp reflex and showed signs of scissoring when held upright. He was unable to sit and had no parachute reflexes at the age of 7 months. An electroencephalogram was normal for his age. Visual evoked responses were normal. Brain stem auditory responses showed no responses bilaterally. A computed tomogram showed a single focus of dense calcification in the right corona radiata and minimal generalised cerebral atrophy.

(4) *Failure to thrive*—His weight was 5.4 kg at age 7 months. Length and head circumference were between the third and tenth centiles. Other investigations performed and found to be normal were plasma amino and organic acids, barium swallow, chromosomes, and thyroid function tests.

Despite being maintained on alfacalcidol,

sodium bicarbonate, and calcium supplements his condition continued to deteriorate and he subsequently died at the age of 14 months. Permission for a postmortem examination was obtained and showed the following features. Detailed histological sections through the neck failed to detect any parathyroid glands but a normal thymus gland. There was evidence of nephrocalcinosis and microcalcification in the brain with ischaemic necrosis of the hippocampal gyri. No other anatomical or developmental malformations were found.

Discussion

The four children presented in a very similar manner and had the following features in common: hypoparathyroidism, renal insufficiency with a renal tubular acidosis, failure to thrive, and developmental delay. In addition, cases 3 and 4 had evidence of nerve deafness. Although parathyroid hormone concentrations were not obtained in cases 1 and 2, the hyperphosphataemia, hypocalcaemia, and values for tubular maximum reabsorption of phosphate are consistent with hypoparathyroidism. The presentation of these four children in three related Asian families is consistent with autosomal recessive inheritance.

Three main forms of persistent idiopathic hypoparathyroidism have been described in children. Familial isolated hypoparathyroidism which may present in the neonatal period is an isolated defect with no other abnormalities. In addition to sporadic occurrence sex linked recessive⁴ and autosomal dominant⁵ forms have been reported. The second form of hypoparathyroidism recognised is that which occurs in association with developmental abnormalities of the third and fourth pharyngeal pouches (DiGeorge's syndrome). These individuals have congenital heart defects, usually of the aortic arch, impaired cell mediated immunity, and may have characteristic dysmorphic features. Inheritance is usually sporadic, but autosomal dominant and recessive inheritance has been reported. The third form of hypoparathyroidism seen in children is felt to be autoimmune in nature. Other autoimmune disorders occur in association, notably Addison's disease, but also alopecia areata, hypothyroidism, ovarian failure, and diabetes. Chronic mucocutaneous candidiasis is usually present. Circulating antibodies to parathyroid glands and other endocrine tissues may be detected. Steatorrhoea has also been reported as a feature in this form.⁶

The children described in this paper do not readily fit into any of these three categories. They certainly do not have an isolated hypoparathyroidism and they also lack features consistent with a partial or complete DiGeorge's syndrome. Although there was no evidence of other autoimmune disorders, it is reported that features of these may not occur for several years after the onset of hypoparathyroidism.⁷ Parathyroid autoantibodies were not found in case 3, but these may only be present in 38% of cases.⁷ There was also some evidence of steatorrhoea in cases 3 and 4, so it is possible they belong to the autoimmune group. The absence

of parathyroid gland tissue seen at postmortem examination in case 4 may be due to one of two mechanisms. It may represent atrophy of the parathyroid glands as has been reported in autoimmune hypoparathyroidism or may be due to agenesis of parathyroid tissue due to a defect in embryogenesis.

Familial hypoparathyroidism has also been reported in association with some diverse developmental abnormalities. Dahlberg *et al* reported two brothers who also had lymphoedema, pulmonary lymphangiectasia, renal insufficiency, and prolapsing mitral valves.⁸ Barakat *et al* reported two brothers who had hypoparathyroidism, nerve deafness, and steroid resistant nephrotic syndrome.⁹ A renal biopsy specimen taken from one of the boys revealed fetal like glomeruli. There are some similarities between these children and those reported here in that two of the children in our series had documented nerve deafness and fetal like glomeruli was seen at biopsy in case 2. However, none of our cases had hypoalbuminaemia or a level of proteinuria consistent with nephrotic syndrome.

There are some similarities between our cases and those recently described by Richardson and Kirk¹⁰ and Sanjad *et al*.¹¹ Richardson and Kirk described four children with failure to thrive, dysmorphic features, developmental delay, and hypoparathyroidism. They all had medullary stenosis of the long bones on skeletal survey. They were the products of consanguineous marriages of Middle Eastern parents. Sanjad *et al* described 12 children from Saudi Arabia, 10 of whom were products of consanguineous marriages. They all had hypoparathyroidism, severe growth failure, psychomotor retardation, and dysmorphic features similar to those described by Richardson and Kirk. Our cases differ in that all had renal insufficiency as a prominent feature, had no obvious dysmorphic features, and no abnormalities on skeletal survey. In addition two of our cases had absent auditory evoked responses whereas hearing was normal in the patients described by Richardson and Kirk. Although there are many similarities, we believe our cases represent a separate unique syndrome. It is likely that the genetic basis for these conditions will be similar.

Several features of the cases merit further discussion. The presence of apparently normal values for parathyroid hormone (using an intact molecule assay) in the first month of life in cases 3 and 4 is unusual. However, there are very few data available on parathyroid hormone concentrations in the newborn and it may well be that the assay was also measuring parathyroid hormone related peptide thus giving the

erroneous impression that parathyroid function was normal. It appears clear that the developmental delay seen in these children was not a consequence of untreated hypoparathyroidism as case 4 was commenced on treatment early, but still had developmental delay despite normocalcaemia. Finally, the first two cases reported illustrate the diagnostic difficulty that can occur as a result of the finding of oxalate crystals on renal biopsy and raised urinary oxalate excretion. It appears clear in retrospect that these children had secondary hyperoxaluria possibly as a consequence of malabsorption. It is important that raised concentrations of the oxalate metabolites or absence of the specific enzyme hepatic alanine glyoxalate aminotransferase⁴ are demonstrated before a diagnosis of primary hyperoxaluria is made. The existence of reliable parathyroid hormone assays in recent years that are specific for the intact molecule also aided the investigation of these children. Inheritance of this disorder would appear to be autosomal recessive in nature and currently attempts are being made to isolate the gene defect in this extended family which may provide a means of antenatal diagnosis.

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