Calcium homeostasis is altered in patients with Williams syndrome. We report an infant in whom Williams syndrome was diagnosed at 4 weeks who presented with hypercalcemia, hypercalciuria, and medullary nephrocalcinosis. Fluorescence in situ hybridization demonstrated a deletion of the elastin gene on chromosome 7. This infant was treated with a low-calcium/vitamin D-deficient infant formula that resulted in the development of rickets. Replacement of the low-calcium/vitamin D-deficient formula with standard formula led to resolution of the rickets.

**Key words** Williams syndrome · Hypercalcemia · Hypercalciuria · Nephrocalcinosis · Rickets

**Introduction**

Williams syndrome is a developmental disorder involving connective tissue and the central nervous system characterized by common features that include a dysmorphic facial appearance, heart defects, growth retardation, premature aging of skin, mental retardation, an outgoing personality, and hypercalcemia [1]. The phenotypic expression of this syndrome is quite variable, and previously caused diagnostic difficulty in many patients. This changed in 1993 when Williams syndrome was discovered to be associated with a deletion of the elastin gene on chromosome 7 [2].

The hypercalcemia that is observed in patients with Williams syndrome is transient and typically found in infancy [3]. The hypercalcemia can be associated with hypercalciuria, dysregulation of calcitropic hormones, and nephrocalcinosis [3]. In addition to nephrocalcinosis, other renal abnormalities, including renal artery stenosis, renal dysplasia/hypoplasia, renal aplasia, or pelvic kidneys, have been observed in these patients [4]. Although the risk of developing renal dysfunction is rare in Williams syndrome, potential causes include hypertension and parenchymal renal disease resulting from either dysplasia or abnormal calcium metabolism [4].

We report an infant who presented with elevated levels of serum calcium, hypercalciuria, and nephrocalcinosis, whose clinical features and cytogenetic analysis were consistent with Williams syndrome. This infant was placed on a low-calcium/vitamin D-deficient formula that resulted in the development of rickets.

**Case report**

A premature male infant was delivered at 33 weeks and 5 days by cesarean section for fetal distress with Apgar scores of 8 and 9, and a birth weight of 1,015 g. Because of intrauterine growth retardation, mild respiratory distress, and hypoglycemia, the infant was admitted to the neonatal intensive care unit. His initial course was remarkable for transient respiratory distress and hyperbilirubinemia. At 4 weeks of age, the infant was noted to have dysmorphic features. Following a genetics consultation, the infant was thought to have Williams syndrome, based on clinical findings which included a high forehead, coarse facies, sparse eyebrows and eyelashes, short palpebral fissure, a short upturned nose, thick lips, and clinodactyly. Echocardiography revealed a patent foramen ovale and a small patent ductus arteriosus, the latter requiring three doses of indomethacin. The serum calcium level was 10.8 mg/dl (normal 8.4–10.2 mg/dl) and the ionized calcium 1.43 mmol/l (normal 1.0–1.30 mmol/l) while the infant was receiving maternal breast milk with a fortifier and supplemental multivitamins. Renal ultrasonography demonstrated moderate to marked bilateral medullary nephrocalcinosis (Fig. 1a). He continued to be fed on maternal breast milk but the multivitamins were discontinued. At 5 weeks of age, the serum calcium was 11.7 mg/dl and the ionized calcium 1.68 mmol/l. He was then changed to a formula (Calcilo XD, Ross Products Division, Columbus, Ohio, USA) containing low amounts of calcium (<50 mg/750 ml) and no vitamin D. Ten days later, his serum calcium was 9.6 mg/dl and the ionized calcium was 1.39 mmol/l. He was then switched to a 1:1 mixture of Calcilo XD and breast milk.

Cytogenetic analysis by fluorescence in situ hybridization demonstrated a deletion of the elastin region on chromosome 7. Biochemical analysis of serum revealed a phosphorus level of 7.7 mg/dl (normal 4.5–7.1 mg/dl), alkaline phosphatase of 440 U/l (normal 145–320 U/l), intact parathyroid hormone (PTH) of 24 pg/ml (normal 20–65 pg/ml), 1,25-dihydroxyvitamin D
[1,25(OH)₂ D] of 115 pg/ml (For reference values, see footnote 1), serum 25-hydroxyvitamin D of 50 mg/l (normal 9–52 mg/l), and osteocalcin of 95 µg/l (normal 8–52 mg/l). The spot urine calcium to creatinine ratio was 3.17.

He was discharged home at 8 weeks of age on a 1:1 mixture of breast milk and Calcilo XD without supplemental vitamin D. At 3 months of age, he was switched to a 1:2 mixture of breast milk and Calcilo XD because of persistent hypercalcemia. However, his serum alkaline phosphatase continued to remain elevated at 598 U/l and his urine calcium to creatinine ratio decreased to 0.09 (Table 1). At approximately 4 months of age, his alkaline phosphatase level peaked at 737 U/l. At the same time, the breast milk was replaced by regular formula (Goodstart, Carnation Nestle, Glendale, Calif., USA) and his calcium intake increased by changing his feeding regimen to a 1:1 mixture of Goodstart and Calcilo XD. Two weeks later, he was placed on 100% Goodstart formula because his serum alkaline phosphatase continued to be elevated at 720 U/l and isoenzyme fractionation demonstrated 92% was of bone origin. Table 1 shows the results of biochemical analysis of serum and urine and his formula prescriptions over the 1st year of life. Follow-up renal ultrasonography at 8.5 months of age demonstrated a significant reduction in the degree of medullary calcinosis (Fig. 1b).

**Discussion**

The presentation of Williams syndrome is quite variable. The diagnosis of this disorder is usually made in infancy by characteristic dysmorphic facial features associated with feeding disorders and irritability, cardiac disease, or disturbed calcium homeostasis [3]. Our patient was thought to have Williams syndrome at 4–6 weeks of age based on both clinical and laboratory findings. The diagnosis was confirmed by cytogenetic analysis of peripheral blood lymphocytes that revealed a deletion of the elastin gene on chromosome 7 [1].

The calcium homeostatic system is disturbed in patients with Williams syndrome [3]. Our patient manifested hypercalcaemia, hypercalciuria, and medullary nephrocalcinosis. In contrast to another report in infants with Williams syndrome in which the serum levels of 1,25(OH)₂ D were elevated in infancy [7], the serum level of 1,25(OH)₂ D in our patient was within the normal range [5, 6]. Although the mechanism(s) leading to these disturbances is unclear, potential possibilities have included altered regulation of 1,25(OH)₂ D synthesis [8], elevated levels of 1,25(OH)₂ D [7], deficient calcitonin secretion [9], or a defect in the maturation of the calcium homeostatic system [10]. The latter theory is supported by Kruse et al. [3] who observed normalization of the abnormal serum calcium and vitamin D levels with time in patients with Williams syndrome.

Renal abnormalities have been observed in patients with Williams syndrome [4, 11]. They include intrinsic renal anomalies, such as renal artery stenosis, cystic disease, and structural malformations, including hypoplasia/aplasia, and secondary disorders such as nephrocalcinosis [11]. The disturbed calcium homeostasis observed in patients with Williams syndrome has been associated with renal dysfunction [11]. This suggests that the management of hypercalcaemia and hypercalciuria in infants with Williams syndrome may have an impact on the development of renal disease. However, guidelines for the treatment of the hypercalcaemic phase of Williams syndrome are lacking. A common approach is to place the infant on a restricted calcium and vitamin D diet [7]. A low-calcium/vitamin D-deficient infant formula (Calcilo XD) is available for infants with Williams syndrome and hypercalcaemia. The calcium content of Calcilo XD is <50 mg/750 ml, which is quite low compared with hu-