CASE REPORT

Williams syndrome with severe hypercalcaemia

Vishal Gupta, Aakash Pandita, Astha Panghal, Venkat Reddy Kallem

SUMMARY
We present an 11-month-old girl child with complaints of constipation, cough, fever, vomiting and growth retardation. On examination, she had facial dysmorphism, hypertension and murmur. The genetic evaluation showed 7q microdeletion specific to Williams syndrome. Abdominal imaging was suggestive of nephrocalcinosis which is rare for this age group. The baby was managed symptomatically and specific treatment like pamidronate, calcitonin and steroid therapy were also administered to reduce hypercalcaemia. Severe hypercalcaemia with associated hypertension and nephrocalcinosis is very rare. Hence, we emphasise here the importance of early detection of these features and their appropriate management for a better outcome of the patient.

BACKGROUND
Williams syndrome also known as Williams-Beuren syndrome (WBS) is a rare familial multisystem disorder caused by microdeletion of 26–28 genes on the q arm of human chromosome 7, leading to suppression of elastin gene. This microdeletion is seen approximately in 90% of cases. This disorder was first identified in 1961 by Williams. It occurs in 1 per 20,000 live births and is usually sporadic in most families. Williams syndrome has often been associated with congenital heart disease, characteristic facial features, mental retardation with a specific cognitive and behavioural profile, growth retardation, renal and skeletal anomalies, inguinal hernia and infantile hypocalcaemia. Various studies in past have reported the frequency of renal and urinary tract anomalies to be variable, ranging from 3% to 86%. Hypercalcaemia has been observed in 0%–43% of cases. A combination of endocrine, gut and renal anomalies have been reported in some studies to be the cause for hypercalcaemia.

CASE PRESENTATION
An 11-month-old girl child presented with complaints of constipation for 5 months; vomiting, cough and fever for 2 days. The baby also had one episode of seizures at 6 months of age. On examination, growth retardation with weight for height below third percentile as per WHO charts was present. She also had hypertension with a blood pressure of 160/57 mmHg and had dysmorphic facial features such as flat nasal bridge, long philtrum and wide mouth. She had a systolic murmur with evidence of aortic stenosis. Abdominal ultrasound showed calcium deposits in bilateral renal pyramids. Urine spot calcium and creatinine ratio was 1.39 (normal <0.2). The 24 hours urine calcium was 7.2 mg/kg (normal <4 mg/kg). On developmental assessment, the baby was found to have global developmental delay.

INVESTIGATIONS
- Investigations revealed haemoglobin 11.3 g/dL, leucocyte count 19.3×10⁹/L, platelet count 482×10⁹/L.
- Urea 41 mg/dL, creatinine 0.7 mg/dL, uric acid 4.6 mg/dL.
- Calcium 13.9 mg/dL, ionised calcium 7 mg/dL, phosphorous 4.6 mg/dL.
- Sodium 140 meq/L, potassium 4.6 meq/L, magnesium 2.4 meq/L, serum albumin 4.2 g/dL.
- Thyroid profile was normal.
- Urine spot calcium and creatinine ratio was high (1.39); 24 hours urine calcium was high (7.2 mg/kg). Parathyroid hormone level was 12.23 pg/mL; 25 hydroxy (OH) vitamin D was 12 ng/mL.
- Fluorescent in situ hybridisation revealed 7q micro deletion.
- MRI brain showed arachnoid cyst in the right anterior temporal region.
- 25 OH vitamin D was 12 ng/mL.

DIFFERENTIAL DIAGNOSIS
Conditions causing hypercalcaemia in children were kept as differential diagnosis. These include:
- Hyperparathyroidism.
- Vitamin D intoxication: iatrogenic, ectopic production, sarcoidosis, tuberculosis, granulomatous lesions, subcutaneous fat necrosis.
- Thyrotoxicosis.

TREATMENT
- For hypercalcaemia, the baby was managed with intravenous fluids, loop diuretic (furosemide), corticosteroids, calcitonin infusion and bisphosphonates (pamidronate) infusion at a dose of 1 mg/kg/day (maximum 60 mg). Citrate and magnesium supplements were added to manage hypercalciuria, and constipation was treated with oral laxatives.

OUTCOME AND FOLLOW-UP
On follow-up after 6 months of treatment, hypercalcaemia resolved and the baby was thriving well. Calcium levels on follow-up were 8.2 mg/dL. Her blood pressure was normal and did not require any further intervention.
any antihypertensive medication. Her renal ultrasound was also normal.

**DISCUSSION**

We report an 11-month-old female infant with WBS with a serum calcium level of 13.9 mg/dL presenting with hypertension, growth retardation, stenosis, nephrocalcinosis and general developmental delay. The hypercalcaemia, normalised with intravenous fluids, corticosteroids, a single dose of intravenous furosemide, dietary calcium and vitamin D restriction, calcitomin and a single dose of intravenous pamidronate. Children with Williams syndrome are prone to develop hypercalcaemia. The incidence of hypercalcaemia in WBS is variable and has been reported to occur in 0%-43% of the patients. A recent study by Sampat et al reported hypercalcaemia in 13% of their 232 patients. Out of these, only 6.1% of patients had actionable hypercalcaemia. Usually, the hypercalcaemia is mild and transient, but in approximately 5% of patients, it may be severe enough to cause medullary nephrocalcinosis. The 2001 health supervision guidelines for WBS recommends regular monitoring of serum calcium levels at diagnosis, age 2 years, age 5 years and then annually in adolescence and adulthood. They also recommend low-calcium diet and no supplemental vitamin D and advocates for sunscreen use to prevent further vitamin D adsorption. The moderate–severe forms most often occur within the first year of life and resolve by age 4. Nephrocalcinosis is detected in approximately 5%-10% of patients undergoing renal ultrasonography. Hypercalcaemia causes dehydration by directly affecting renal distal tubular function, impairing concentrating ability leading to polyuria. Nausea and vomiting may further exacerbate the dehydration. Hypercalcaemia may also present with hypotonia, irritability, poor feeding, failure to thrive, hyperventilation and abdominal pain. Mechanisms explaining hypercalcaemia in WBS are still not clearly known. It may be due to increased absorption and/or decreased clearance of calcium. Increased absorption may be explained by high serum levels of 1,25-dihydroxy vitamin. An Indian case series of 11 patients from North India did not observe hypercalcaemia in any of their cases. Hypocalcaemia is also observed in Williams syndrome, which may be due to decreased basal and calcium-stimulated calcitonin serum levels. Hypocalcaemic episodes are commonly seen during first year of life and most of them resolve by 4 years of age. Reported incidence of hypocalcaemia ranges from 5% to 50%. Hypocalcaemia is usually mild, but can be moderate or severe, particularly during infancy. Hypercalcauria may be accompanied by hypocalcaemia, but isolated hypercalciuria usually occurs after infancy. In our patient, there was symptomatic hypercalcaemia and hypercalciuria with nephrocalcinosis. There has been one case report in past reporting nephrocalcinosis and single kidney in Williams syndrome in a 20-month-old child, thus emphasising the importance of radiological imaging in these patients. The other prominent manifestation of Williams syndrome include cardiovascular manifestations which are present in 75% of the cases, the most common being supravalvular aortic stenosis which is seen in approximately 70% of patients. Other cardiovascular defects include aortic stenosis, pulmonary stenosis and pulmonary artery stenosis, ventricular or atrial septal defects and myxomatous degeneration of aortic or mitral valve leaflets. Stenosis or coronary ostial occlusion and aortic collateral branch stenosis may also occur (coronary, cerebral or renal arteries), leading to cerebral or cardiac ischaemia. However, these manifestations are not always present or may be present in a milder form in patients with Williams syndrome. Hence, the absence of any of them does not exclude diagnosis of Williams syndrome. Furthermore, there is smooth muscle cells migration in the arterial wall and neointimal hyperplasia. Onset of hypertension occasionally starts in childhood and develops in approximately 50% of patients as a result of stenosis of the renal arteries. Our patient developed hypertension at an early stage. In a retrospective study of 41 children with Williams syndrome, mean age of developing hypertension was reported to be 4.7 years. American Academy of Pediatrics recommends series of evaluation for children with WBS. However, annual evaluation of every child should include:

- Growth and developmental assessment.
- Blood pressure monitoring.
- Auditory and vision screening.
- Cardiovascular evaluation: to look for progressive vascular stenosis, including supravalvular aortic stenosis, which is generally seen in the first 5 years of life.

**Learning points**

- Williams syndrome should be kept as a differential diagnosis in children presenting with facial dysmorphic features with cardiovascular and altered calcium metabolism.
- Early identification of hypercalcaemia in these patients may avoid risk of severe manifestations like nephrocalcinosis.
- Patients with Williams syndrome should be screened for cardiovascular anomalies and hypertension.

**REFERENCES**

Unusual presentation of more common disease/injury


