Patient report

Alison M. Helfrich[a,*] and Katherine Q. Philla[b]

Late-onset hypercalcemia in Williams-Beuren syndrome: importance of early and frequent screening and intervention

Abstract: Williams-Beuren syndrome (WBS) affects multiple systems and has a known association with infantile hypercalcemia that is typically mild and transient. We report a 12-month-old female previously diagnosed with WBS by a chromosomal microarray, who was admitted for failure to thrive. Upon evaluation, serum calcium of 19.0 mg/dL (4.75 mmol/L) (normal 9–11 mg/dL, SI: 2.25–2.75 mmol/L) and serum ionized calcium of 2.33 mmol/L (normal 1.22–1.37 mmol/L) were revealed. Her hypercalcemia correlated with symptoms of irritability, poor feeding, mild hypotonia, and constipation, which were increasingly present for 6 months prior to admission. This calcium level is one of the highest reported in association with WBS. Additionally, while hypercalcemia associated with WBS typically resolves by the first year, this case represents a later presentation as compared to other reports. The patient initially responded to conservative treatment with intravenous fluids administration, loop diuretic therapy, and dietary calcium restriction. However, she subsequently had rebound hypercalcemia 5 weeks after treatment and received one dose of intravenous bisphosphonate with subsequent resolution of her hypercalcemia. Our report highlights the importance of screening, early management, and recognition of late presentation hypercalcemia in the setting of WBS.

[a]**Alison M. Helfrich**: She cared for the patient reported in this article while admitted to the inpatient pediatric service at Walter Reed National Military Medical Center. She also wrote the first draft of the case report submission.

[b]**Katherine Q. Philla**: She was the pediatric endocrine fellow consultant while the patient was admitted to the inpatient ward and outpatient follow-up care. She made management recommendations to rectify the associated hypercalcemia. She also provided guidance to Dr. Helfrich throughout her draft process. She completed final case report revisions.

***Corresponding author: Alison M. Helfrich,** Department of Pediatrics, Walter Reed National Military Medical Center, 8901 Wisconsin Avenue, Bethesda, MD 20889, USA, Phone +1-301-295-4900, E-mail: alison.m.helfrich.mil@mail.mil

Katherine Q. Philla: Department of Pediatric Endocrinology, Walter Reed National Military Medical Center, Bethesda, MD, USA

Keywords: bisphosphonate; constipation; failure to thrive; hypercalcemia; Williams-Beuren syndrome.

DOI 10.1515/jpem-2014-0266
Received June 20, 2014; accepted September 22, 2014; previously published online October 18, 2014

Introduction

Williams-Beuren syndrome (WBS) is a genetic disorder that occurs due to micro-deletion on chromosome 7q11.23, including the elastin gene, which affects multiple systems (1). Endocrine abnormalities classically include hypercalcemia, subclinical hypothyroidism, and diabetes mellitus. The incidence of infantile hypercalcemia in WBS is reported variably from 5% to 50% (2, 3). It is typically mild and transient. The moderate-severe forms most often occur within the first year of life and resolve by age 4 (3, 4). The exact mechanism that causes hypercalcemia remains unknown, but the proposed theories include vitamin D sensitivity (5), defective calcitonin synthesis or release (6), and calcitriol sensitivity (7). Symptomatic hypercalcemia, including irritability and poor feeding, can negatively affect growth; these may be the presenting symptoms prior to diagnosis of WBS (8). We report a 12-month-old female who presented with failure to thrive (FTT), as evident by no weight gain since her 9-month visit as well as plateau of her height and head circumference. Additionally, she had a 6-months' history of irritability with progressive difficulty feeding and constipation.

Case presentation

Our patient was a 12-month-old female who presented with several months' history of weight plateau and feeding

difficulties. Additionally, she was noted to have persistent decreased tone, increased irritability, and constipation. She was the product of a 39-week gestation complicated by maternal trigeminal neuralgia requiring the use of multiple medications to include methadone, lyrica, amitriptyline, and celexa throughout the pregnancy. The patient was small for gestational age with a birth weight of 2.2 kg. She was initially admitted to the neonatal intensive care unit for intermittent hypoglycemia, which self-resolved at 3 days of life. She was subsequently discharged, and at her 2-month well-baby follow-up, it was noted that she had a systolic murmur, which prompted cardiology evaluation. An echocardiogram confirmed the presence of mild pulmonary artery stenosis, a small ventricular septal defect, and hemodynamically insignificant long-segment hypoplasia of the aortic arch. She was also noted to have subtle phenotypic features of WBS, including mild dysmorphic features such as a prominent forehead with temporal narrowing, flat nasal bridge, mild hypertelorism, clinodactyly of the fifth digits bilaterally along with generalized hypotonia with mildly delayed developmental milestones. This subsequently prompted a genetics consultation; at 6 months of age, the whole genome oligonucleotide array revealed a deletion in chromosome 7q11.23, consistent with a diagnosis of WBS.

The patient was subsequently followed in the pediatric clinic where the onset of significant constipation was noted at 7 months of age. She was treated with milk of magnesia with mild improvement. At 8 months of age, she was evaluated by pediatric gastroenterology and speech pathology for continued constipation and feeding intolerance. A modified barium enema swallow study showed small aspiration with thin liquids. Once feeds were thickened, she had less reflux but could only take a maximum of 2 ounces of infant formula per feed and did not gain weight over a 5-month period. She was not on any other supplements or medications.

With regard to her electrolyte status, a review of records showed serum calcium of 11.0 mg/dL (2.75 mmol/L) at 7 months of age. A renal ultrasound at that time showed bilateral medullary nephrocalcinosis. Despite this radiological finding which may have correlated with her slightly elevated serum calcium, no further laboratory data were obtained until hospitalization for FTT at 12 months of age. At the time of her admission, World Health Organization female growth curves placed her at <3rd percentile for all measurements (9); American Academy of Pediatrics (AAP) WBS growth curves placed her around (−)2 standard deviations (STD) for height and weight and above (−)2 STD for head circumference, with no significant change from 9 months to 12 months of age.

Upon admission, initial lab evaluation for FTT work-up revealed a total serum calcium of 19.0 mg/dL (4.75 mmol/L) corrected to 18.1 mg/dL (4.52 mmol/L) for an albumin of 5.1 g/dL, and a serum ionized calcium of 2.33 mmol/L (normal: 1.22–1.37 mmol/L). Other laboratory data included a phosphorus level of 4.0 mg/dL (normal for age 4.5–9.0 mg/dL), intact parathyroid hormone (PTH) 11.5 pg/mL (normal 10–65 pg/mL), 25-hydroxyvitamin D of 23.3 ng/dL, and urine calcium/creatinine ratio 0.84 (normal <0.2). She was started on intravenous fluid (IVF) therapy with a subsequent decrease in serum calcium, initially to 14.7 mg/dL (2.15 mmol/L) and then to 13.2 mg/dL (1.79 mmol/L) over 24 h. After one dose of intravenous (IV) furosemide, serum calcium further decreased to 11.9 mg/L (1.16 mmol/L). Her irritability, feeding difficulties, and constipation improved as her calcium normalized. She was transitioned to a vitamin D-free formula (Calcilo XD) to avoid excess vitamin D, which would further exacerbate her hypercalcemia. At discharge, she still had evidence of mild hypercalcemia with a serum calcium level of 12.6 mg/dL (3.15 mmol/L) that was followed with serial outpatient labs.

Five weeks after discharge from the hospital, her hypercalcemia worsened with a serum calcium level of 14.7 mg/dL (3.67 mmol/L) and symptoms of returned irritability and feeding intolerance. She was subsequently re-admitted and treated once again with IVF and also received one dose of IV bisphosphonate (pamidronate 0.5 mg/kg). Post-treatment serum calcium was 11.9 mg/dL (2.97 mmol/L), which further normalized at 10.9 mg/dL (2.72 mmol/L) 4 weeks post-bisphosphonate treatment. At 15 months of age, she has remained eucalcemic with dietary restrictions and no clinical signs of hypercalcemia.

Discussion

We report a 12-month-old female with WBS with a serum calcium level of 19 mg/dL (4.75 mmol/L) that normalized with IVF, a single dose of IV furosemide, dietary calcium and vitamin D restriction, and a single dose of IV pamidronate. To our knowledge, this case is among the highest serum calcium levels reported in an infant of this age. The highest reported serum calcium in an infant with WBS is 20 mg/dL at 10 months of age (10). Multiple case reports discuss the efficacy of bisphosphonate treatment for hypercalcemia, which we also report with our patient (4, 8, 10). Without laboratory evidence for confirmation, we postulate that our patient's serum calcium was already increasing after the initial screen at age 9 months based

on the presence of renal nephrocalcinosis. We also attribute her symptoms of feeding intolerance and constipation to her hypercalcemia, which may have contributed to her FTT. This case illustrates the importance of early and serial screening for hypercalcemia in patients with WBS and early intervention for abnormal levels.

Although the cause of hypercalcemia in WBS is unknown, many experts suggest an increased response to vitamin D as a plausible mechanism. A low PTH level and normal bone without demineralization suggest increased intestinal calcium absorption (7). The AAP Health Maintenance for WBS recommends low calcium diet and no supplemental vitamin D, and advocates for sunscreen use to prevent further vitamin D adsorption (3).

Furthermore, the AAP's Health Maintenance Guidelines for WBS, published in 2001, give recommendations for medical evaluation for every well-child visit. Recommended evaluation includes serum calcium, urine calcium/creatinine ratio, and renal ultrasound to be obtained in the neonatal period, or upon diagnosis, then not again until 12 months of age (3). However, because WBS is not a routine genetic test on amniocentesis or newborn metabolic screening, it may not be detected until later in life. Even when diagnosis is made with fluorescence in situ hybridization analysis, hypercalcemia may not be present on initial work-up. Additionally, symptoms of hypercalcemia are often present in WBS and may not be related to hypercalcemia. These patients are known to have feeding issues (reflux, refusal) and constipation at baseline. Given the tendency to appear smaller and have an increased risk for poor weight gain, there is a WBS-specific growth chart. While these patients have been identified as at risk for FTT, this case emphasizes the importance of hypercalcemia as a cause of poor weight gain potentially beyond neonatal or infancy period. Morris recommends screening serum calcium levels every 4 to 6 months from diagnosis until age 2 (11). A recent case report described a toddler with FTT from feeding intolerance related to hypercalcemia that developed rapidly over a 2-month period (12). As primary care managers of these patients, it is important to closely monitor these symptoms with a low threshold to obtain laboratory studies if suspicious for hypercalcemia.

Following the guidelines from the AAP, primary care managers also need to anticipate the future for these patients. Cardiovascular screening, early intervention, family support, and dietary/nutritional interventions are important. Due to the risk of hypercalcemia and its possible vitamin D relationship, supplements with vitamin D are not recommended (3). However, one case report discussed a 4-week-old male with WBS who was placed on a low-calcium/vitamin D-deficient diet due to his hypercalcemia, hypercalciuria, and medullary nephrocalcinosis that resulted in development of rickets. The rickets resolved after dietary change to the standard formula (13). Of the case reports of hypercalcemia treated with bisphosphonate, all addressed the dietary restrictions once hypercalcemia resolved. All these patients returned to a normal diet without additional supplementations (4, 7, 8, 10, 13, 14). Currently there are no published large-scale studies that support a specific treatment for WBS-associated hypercalcemia, and the mechanism remains unknown. However, hypercalcemia in WBS resolves with age (4). It is important to know the signs of hypercalcemia, confirm with laboratory studies, and follow serial levels after interventions until the serum calcium remains within the normal range with the understanding that the manifestations of WBS can have variable presentations and penetrance.

Acknowledgments: We wish to acknowledge the assistance of Drs Vogt, Emerick, and Loprieato in the preparation of this case report. We also would like to acknowledge the active duty family members who have provided valuable contributions to our medical education.

Conflict of interest statement: The authors have no conflicts of interest to disclose. The views expressed in this article are those of the authors and do not reflect the official policy or position of the United States Armed Forces, Department of Defense, or the U.S. Government.

References

1. Morris CA. Introduction: Williams syndrome. Am J Med Genet C Semin Med Cenet 2010;154:203–8.
2. Pober BR. Williams-Beuren syndrome. N Engl J Med 2010;362:239–52.
3. American Academy of Pediatrics. Health care supervision for children with Williams syndrome. Pediatrics 2001;107:1192–204.
4. Cagle AP, Waguespack SG, Buckingham BA, Shankar RR, Dimeglio LA. Severe infantile hypercalcemia associated with Williams syndrome successfully treated with intravenously administered pamidronate. Pediatrics 2004;114:1091–5.
5. Forfar JO, Balf CL, Maxwell GM, Tompsett SL. Idiopathic hypercalcaemia of infancy: clinical and metabolic studies with special reference to the aetiological role of vitamin D. Lancet 1956;267:981–8.
6. Culler FL, Jones KL, Deftos LJ. Impaired calcitonin secretion in patients with Williams syndrome. J Pediatr 1985;107:720–3.
7. Kruse K, Pankau R, Gosch A, Wohlfahrt K. Calcium metabolism in Williams-Beuren syndrome. J Pediatr 1992;121:902–7.
8. Sangun O, Dundar BN, Erdogan E. Severe hypercalcemia associated with Williams syndrome successfully treated with

pamidronate infusion therapy. J Pediatr Endocrinol Metab 2011;24:69–70.
9. Centers for Disease Control and Prevention. WHO Child Growth Standards, 2009. http://www.cdc.gov.
10. Clark BC, Fleming R, Spaeder MC, Tuchman S. Severe hypercalcemia without hypercalciuria in a previously healthy infant. J Pediatr Endocrinol Metab 2012;25:187–90.
11. Morris CA. Williams syndrome. In: Pagon RA, Adam MP, Ardinger HH, Bird TD, Dolan CR, et al., editors. GeneReviews, 9 April 1999. http://www.ncbi.nlm.nih.gov/books/NBK1249/ (updated 13 June 2013).
12. Lameris AL, Geesing CL, Hoenderpo JG, Schreduer MF. Importance of dietary calcium and vitamin D in the treatment of hypercalcemia in Williams-Beuren syndrome. J Pediatr Endocrinol Metab 2014;27:757–61.
13. Mathias RS. Rickets in an infant with Williams syndrome. Pediatr Nephrol 2000;14:489–92.
14. Oliveri B, Mastaglia SR, Mautalen C, Gravano JC, Argerich LP. Long-term control of hypercalcemia in an infant with Williams-Beuren syndrome after a single infusion of biphosphonate (pamidronate). Acta Paediatr 2004;93:1002–3.