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Hypercalcemia in Patients with Williams-Beuren Syndrome

Sampat Sindhar, BS¹, Michael Lugo, BS¹, Mark D. Levin, MD², Joshua R. Danback, BS¹, Benjamin D. Brink, MS³, Eric Yu, BA³, Dennis J. Dietzen, PhD¹, Amy L. Clark, DO¹, Carolyn A. Purgert, MD, PhD¹, Jessica L. Waxler, MS⁴, Robert W. Elder, MD⁵, Barbara R. Pober, MD^{3,4,6}, and Beth A. Kozel, MD, PhD^{1,2}

¹Department of Pediatrics, Washington University School of Medicine, St. Louis, MO

²National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD

³Frank H. Netter School of Medicine, Quinnipiac University, North Haven, CT

⁴Massachusetts General Hospital, Boston, MA

⁵Section of Cardiology, Departments of Pediatrics and Internal Medicine, Yale University School of Medicine, New Haven, CT

⁶Harvard Medical School, Boston, MA

Abstract

Objective—To evaluate the timing, trajectory, and implications of hypercalcemia in Williams-Beuren syndrome (WBS) through a multicenter retrospective study.

Study design—Data on plasma calcium levels from 232 subjects with WBS aged 0–67.1 years were compared with that in controls and also with available normative data. Association testing was used to identify relevant comorbidities.

Results—On average, individuals with WBS had higher plasma calcium levels than controls, but 86.7% of values were normal. Nonpediatric laboratories overreport hypercalcemia in small children. When pediatric reference intervals were applied, the occurrence of hypercalcemia dropped by 51% in infants and by 38% in toddlers. Across all ages, 6.1% of the subjects had actionable hypercalcemia. In children, actionable hypercalcemia was seen in those aged 5–25 months. In older individuals, actionable hypercalcemia was often secondary to another disease process. Evidence of dehydration, hypercalciuria, and nephrocalcinosis were common in both groups. Future hypercalcemia could not be reliably predicted by screening calcium levels. A subgroup analysis of 91 subjects found no associations between hypercalcemia and cardiovascular disease, gastrointestinal complaints, or renal anomalies. Analyses of electrocardiography data showed an inverse correlation of calcium concentration with corrected QT interval, but no acute life-threatening events were reported.

Conclusions—Actionable hypercalcemia in patients with WBS occurs infrequently. Although irritability and lethargy were commonly reported, no mortality or acute life-threatening events

Reprint requests: Beth A. Kozel, MD, PhD, National Heart Lung Blood Institute, Building 10, 8N-110, Bethesda, MD 20892. beth.kozel@nih.gov.

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were associated with hypercalcemia and the only statistically associated morbidities were dehydration, hypercalciuria, and nephrocalcinosis.

Williams-Beuren syndrome (WBS; OMIM #194050) is a microdeletion disorder caused by the loss of 26–28 genes on the q arm of human chromosome 7. Its features include a characteristic facial appearance, specific neurocognitive profile, and cardiovascular disease.^{1,2} In addition, individuals with WBS are at increased risk for hypercalcemia.³ Reported hypercalcemia rates range between 0 and 43%.^{4–10} Published data provide insufficient information regarding the thresholds used to define hypercalcemia, making it difficult to interpret the true prevalence, timing, or contributing factors for hypercalcemia in these cohorts.

To date, no study has identified a definitive cause for hypercalcemia in individuals with WBS, although a combination of endocrine, gut, and renal abnormalities have been reported.^{11–14} Current health maintenance guidelines recommend avoidance of vitamin D supplementation in infants and children with WBS,^{2,15} and many parents feed their children with WBS calcium-reduced diets owing to the possibility that increased calcium intake may lead to high blood calcium levels. The degree to which such practices may explain the high incidence of decreased bone mineral density seen in adults with WBS is unclear,^{16–18} but in several cases, rickets have developed in children as a result of prolonged treatment for hypercalcemia.^{14,19}

The aim of this study was to assess the frequency, trajectory, triggers, and consequences of hypercalcemia in patients with WBS. Such data may serve as a rational starting point for the development of hypercalcemia screening and management guidelines.

Methods

Retrospective deidentified laboratory and demographic data were obtained on subjects with WBS recruited with Institutional Review Board approval through Massachusetts General Hospital (n = 102), Yale School of Medicine (n = 46), and Washington University School of Medicine (WUSM, n = 91). Additional medical record and parent-reported questionnaire data were available for the WUSM subset. Five duplicates and 1 triplicate, as well as 1 subject with a non-WBS-related electrolyte disturbance, were removed, yielding 232 subjects with WBS (123 females and 109 males; age range, 0–67 years).

Plasma calcium (Ca; n = 914), creatinine (Cr; n = 503), blood urea nitrogen (BUN; n = 775), and spot urine Ca and Cr (n = 406) levels over a collection period of August 1984 to July 2015 were obtained. Because individuals with WBS have shorter-than-typical stature, glomerular filtration rate (GFR) was calculated using the Schwartz equation $[0.413 \times (\text{height (cm)} / \text{Cr (mg/dL)})]^{20}$ for all ages (n = 194). Laboratory-specific reference levels were obtained from laboratory reports. Pediatric reference norms are available online from the St. Louis Children's Hospital (SLCH) laboratory test guide (<http://slchlabtestguide.bjc.org>). Control plasma calcium values from individuals aged 0 days to 80.4 years (n = 11 303) were obtained from SLCH.

Electrocardiography (ECG) analysis was performed by standard 12- or 15-lead ECG recorded within 24 hours of a plasma calcium measurement. Subjects with left² or right¹ right bundle branch block were excluded, as was the subject with a ventricular pacemaker. Corrected QT (QTc) interval was plotted as a function of the contemporaneous calcium level (n = 45).

Statistical Analyses

Statistical analyses were performed with GraphPad Prism version 6.0 for Mac (GraphPad Software, La Jolla, California). Plasma Ca, Cr, and BUN values were analyzed by the D'Agostino-Pearson test and found to have a nonnormal distribution. These values are presented as median (IQR). Categorical variables are presented as absolute and relative frequencies. Plasma calcium values were compared with SLCH control data using the Mann-Whitney *U* test. Univariate analyses were conducted using the χ^2 test. Two-tailed probability values of *P* < .05 were considered significant. Bonferroni correction was applied as appropriate.

Hypercalcemia and hypercalciuria definitions are as specified in Table I (available at www.jpeds.com). To calculate the proportion of subjects with hypercalcemia, plasma calcium values were stratified by age, and the percentage of subjects meeting our definitions of hypercalcemia were calculated for each group (0–12 months, 12.1–24 months, and >24 months) and for the total cohort. The McNemar change test was used to compute the difference in hypercalcemia calls between laboratory and pediatric-adjusted hypercalcemia.

To determine the extent to which screening calcium levels could predict subsequent actionable hypercalcemia, calcium values were analyzed from subjects with 2 calcium values measured 1–6 months apart (n = 180 pairs). Each value in the pair was categorized as normal, mild hypercalcemia, or actionable hypercalcemia. χ^2 analysis was used to compare the rate at which normal vs mild hypercalcemia initial values led to normal/mild hypercalcemia vs actionable hypercalcemia on the subsequent draw. Subanalysis was also done on pairs in which the first calcium value was measured before age 3 years (n = 71). Relative risk (RR) was calculated.

For GFR and BUN analyses, each value was binned according to whether it was drawn when the subject concurrently had actionable hypercalcemia, mild hypercalcemia, or normocalcemia based on pediatric-adjusted norms. For individuals with calcium levels in more than one bin, the average of the individual's GFR or BUN values in the highest calcium bin were used for analysis. Kruskal-Wallis testing was used to compare values among the calcium subgroups.

Individuals were stratified into groups with and without hypercalciuria according to spot Ca/Cr definitions (Table I). Hypercalciuria events were analyzed to determine whether they occurred within 1 week of actionable hypercalcemia or mild hypercalcemia, or during normocalcemia. χ^2 analysis was used to test for associations.

Spearman correlation testing was performed to evaluate for statistically significant correlations between calcium concentration and QTc interval.

Results

Subjects with WBS have plasma calcium values shifted toward the upper limit of normal (ULN; Figure 1, A). Compared with SLCH age-binned controls, subjects with WBS in all age groups had higher median plasma calcium levels ($P < .0001$ for all; Figure 1, B). The vast majority (86.7%) of all calcium values collected were normal for age, 7.9% were mildly elevated, at 0.1–0.5 mg/dL above the ULN, and 2.2% of values were more significantly elevated, at >0.5 mg/dL above the ULN. Hypocalcemia was noted in 3.2% of the specimens and was frequently seen in neonates and in individuals receiving intravenous fluids. This study covers a total of 721 patient-years. No deaths or acute life-threatening events occurred secondary to hypercalcemia. No cardiac (arrhythmia) or neurologic (seizures) morbidity was directly attributable to hypercalcemia.

Unadjusted laboratory hypercalcemia, defined as plasma calcium above the ULN as reported by the laboratory running each sample (Table I), was noted at least once in 26.7% of all subjects. Stratified by age, 35% of infants aged 0–12 months, 41% of toddlers aged 12.1–24 months, and 17.9% of those aged >24 months had laboratory hypercalcemia (Table II). However, plasma Ca levels have a broader normal range in young infants and toddlers,²¹ and not all laboratories account for this in their reports. Using pediatric-adjusted hypercalcemia norms (Table I), the prevalence of hypercalcemia fell to 17% of infants and 26% of toddlers (Table II), a drop of 51% and 38%, respectively, relative to unadjusted laboratory hypercalcemia ($P < .05$ for both). Because normal values are established statistically rather than physiologically, up to 2.5% of healthy individuals may have levels above the ULN. Consequently, we defined actionable hypercalcemia as a plasma Ca level 0.5 mg/dL above pediatric-adjusted norms. By these criteria, we found that 5% of infants, 10% of toddlers, and 3.4% of those aged >2 years had actionable hypercalcemia, most commonly in those aged 5–25 months. Cumulatively, 6.1% of the total cohort with WBS had a history of actionable hypercalcemia (Table II).

To evaluate whether screening blood Ca values were predictive of actionable hypercalcemia in the subsequent 6 months, we evaluated temporally paired Ca levels from the same individual. When the first Ca level in a period was normal, actionable hypercalcemia developed 1.3% of the time, and initial mild elevations in Ca led to actionable hypercalcemia 7.7% of the time (RR, 5.9; 95% CI, 0.9–40.2; $P = .10$). In children aged <3 years, actionable hypercalcemia develops in 3.3% with a normal Ca level and in 9.1% with a mildly elevated Ca level (RR, 2.8; 95% CI, 0.3–27.6; $P = .40$). This finding is consistent with the natural history of increased Ca levels in children with actionable hypercalcemia (Figure 1, C), in whom elevations in Ca were acute and transient.

Clinical characteristics, treatment, and pertinent history for all patients with actionable hypercalcemia are reported in Table III (available at www.jpeds.com). The children were often described as dehydrated or irritable at the time of actionable hypercalcemia. Of the 6 subjects aged >3 years with actionable hypercalcemia, 2 had parathyroid disease and 1 had significant malnutrition and gut dysmotility. Two subjects were on multivitamins at the time of hypercalcemia diagnosis. In one of these subjects, the multivitamin was discontinued, but in both subjects the hypercalcemia resolved.

To assess the role for renal dysfunction in hypercalcemia of WBS, we reviewed GFR and BUN data from the tri-institutional cohort. At the time of actionable hypercalcemia, affected subjects had a median GFR of 61.3 mL/min/1.73 m² (IQR, 49.2–73.3 mL/min/1.73 m²), compared with 98.3 mL/min/1.73 m² (IQR, 86.0–114.3 mL/min/1.73 m²) in those with mild hypercalcemia and 90.3 mL/min/1.73 m² (IQR, 78.6–111.1 mL/min/1.73 m²) in those with no history of hypercalcemia ($P = .004$; Figure 2, A). Decreased GFR during episodes of hypercalcemia indicated the potential for decreased extracellular volume. BUN levels showed similar findings. The median (IQR) BUN value was 19 (15.7–24.5) mg/dL in subjects with actionable hypercalcemia, 12 (10.4–15.8) mg/dL in those with mild hypercalcemia, and 13 (11–15.3) mg/dL in those with no history of hypercalcemia ($P < .001$; Figure 2, B).

Of note, 33% of subjects with actionable hypercalcemia also had nephrocalcinosis, compared with only 3% of patients with no recorded history of hypercalcemia ($P < .001$). Subjects with actionable hypercalcemia also were more likely to have concurrent hypercalciuria compared with those with mild hypercalcemia or no history of hypercalcemia ($P = .006$).

Using questionnaire data from the 91 subjects enrolled through WUSM, we tested for associations between hypercalcemia and various WBS-related phenotypes (sex, low birth weight, failure to thrive, constipation, colic, congenital renal abnormalities, 1 functional kidney, supraaortic stenosis [SVAS], and hypertension). No statistical associations were identified (Table IV; available at www.jpeds.com).

To explore a potential link between Ca abnormalities and rhythm disturbances, we evaluated ECG contemporaneous with plasma Ca levels. Previous work by others has suggested that individuals with WBS display prolonged QTc intervals on ECG²²; however, increased extracellular Ca levels would be predicted to increase the repolarizing Ca current, shorten action potential duration, and shorten the QTc interval. Consistent with this predicted effect, correlation analysis showed inverse correlation of QTc interval and plasma Ca level ($r = -0.35$; $P = .02$) (Figure 3). Short QTc intervals (<370 ms) were seen in subjects with the highest Ca levels and some normocalcemic subjects, but no subject had tachyarrhythmias or was diagnosed with a channelopathy. Abnormal QTc intervals were transient in all subjects, and no acute life-threatening events were reported.

Discussion

Hypercalcemia has been reported in individuals with WBS, with frequencies between 0 and 43% in studies of 8–110 subjects,^{4–10} with a combined prevalence of 14.9%. Data from our study show that on average, individuals with WBS have higher plasma Ca levels than the general population, but the majority of values are normal. When Ca levels are elevated, only 6.1% of individuals with WBS have actionable hypercalcemia, and the remainder have elevations just above the ULN. Consequently, clinically actionable hypercalcemia appears to be uncommon and may be overestimated, owing to the use of nonpediatric norms at some laboratories.

Actionable hypercalcemia occurred in a bimodal distribution: during infancy and again in adolescence/adulthood. The infancy group included those aged 5–25 months. Dehydration, irritability, and decreasing oral intake were common. In the adolescent/adult group, actionable hypercalcemia was commonly secondary to another medical condition, such as hyperparathyroidism, but other conditions, such as poor gut motility, have been reported as well. Multivitamin intake, although generally not recommended in individuals with WBS, was also noted in some, but hypercalcemia resolved at times, even if the multivitamin was continued. In all pediatric subjects in this cohort, the actionable hypercalcemia was transient and responsive to standard treatments. This finding is in line with what is typically reported in the literature, although case reports of recurrent infantile hypercalcemia exist.²³ Interestingly, hypocalcemia occurred in our cohort as well, largely in the neonatal period but also in some adults, as has been reported previously.^{16,17}

The 2001 health supervision guidelines for WBS recommends measuring Ca levels at diagnosis, age 2 years, age 5 years, and then annually in adolescence and adulthood.¹⁵ In our study, screening Ca values did not reliably predict which subjects would go on to develop actionable hypercalcemia. The *P* value for the full cohort comparison was .10, which may suggest that the study was simply underpowered. However, when only infants and toddlers aged <3 years (the age group in which hypercalcemia most commonly occurs) were investigated, the potential association between initial slight elevations of Ca and later actionable hypercalcemia was further minimized (RR, 2.8), and the *P* value increased to .40. These data suggest that actionable hypercalcemia of infancy in WBS is more poorly predicted by screening than actionable hypercalcemia in adults, in whom the primary disease process, such as hyperparathyroidism, may be responsible for a more gradual rise. A larger prospective study is needed to assess the true benefit of screening at each age.

Patients with WBS frequently demonstrate dehydration at the time of actionable hypercalcemia. Hypercalcemia directly affects renal distal tubular function, impairing concentrating ability and causing polyuria and nausea/vomiting, which may further exacerbate dehydration. The increased BUN during hypercalcemia also supports an association with dehydration, but current data are insufficient to suggest that primary differences in GFR are responsible. Nonetheless, physicians should order Ca measurements in infants and children with WBS and signs of dehydration. Concurrent hypercalciuria and nephrocalcinosis were common; thus, renal studies should be performed in patients with recent hypercalcemia.

Previous studies have highlighted an association between SVAS and hypercalcemia during pregnancy.^{24,25} Although this study did not specifically assess the prenatal period, we did not find any association between hypercalcemia and a history of hypertension or SVAS. Our data show a weak negative correlation between plasma Ca concentration and QTc interval. Multiple subjects had short QTc intervals. Importantly, no acute cardiac events were reported, and no subject exhibited features of short QT syndrome.²⁶

Based on our findings in this study and our clinical experience, we suggest the following practical management strategies for monitoring Ca in patients with WBS:

1. Physicians should advocate for the use of pediatric normative data by the laboratories with which they work closely, to avoid inappropriate diagnosis of hypercalcemia in infants and toddlers with WBS. In addition to the SLCH norms, age-based reference Ca data can be found in such resources as the *Harriet Lane Handbook*.²⁷ Interestingly, the ULN for Ca in this reference is even higher than the SLCH norms.
2. Our data suggest that routine blood Ca screening is of limited value for predicting subsequent actionable hypercalcemia, especially in the young. Consequently, we recommend blood Ca measurements at the time of WBS diagnosis and then moving to symptom-based testing in infants and children. Parents should be counseled to inform their provider about changes in their child's behavior, including increasing irritability, changes in feeding pattern, new nausea/vomiting, and/or signs of dehydration. These findings should prompt laboratory investigation (blood Ca, BUN, and Cr). For teens and adults, Ca and vitamin D levels can be incorporated into the annual well-adult evaluations already recommended for this population.^{15,16} Testing for a primary cause of hypercalcemia (eg, hyperparathyroidism, cancer, renal failure, gastrointestinal dysmotility) is indicated in all adults with actionable hypercalcemia and in pediatric patients with recurrent or refractory actionable hypercalcemia.
3. Given the association of WBS with decreased bone density in adults, Ca and vitamin D restriction below the recommended daily intake (RDI) levels²⁸ should be avoided for those with a normal plasma Ca level. For the majority of individuals with WBS, adequate Ca and vitamin D intake can be achieved through a healthy diet. Consultation with a dietician is recommended for children and adults with overly restrictive diets. Selective supplementation with foods designed to meet but not exceed the RDI for Ca and vitamin D may be attempted. If unsuccessful, the selection of multivitamin preparations that in combination with diet similarly approach, but do not exceed, the RDI for these nutrients can be used. Ca and 25-OH vitamin D levels can be monitored at 1 month after implementation of diet/multivitamin changes.
4. Patients with mild hypercalcemia should be monitored symptomatically and with repeat Ca levels. A 1-month follow-up level is reasonable unless the patient becomes symptomatic. If no further rise in Ca level is detected, then subsequent testing should be symptom-based. Reduction of extreme dietary intakes of Ca and vitamin D to closer to the RDI²⁸ can be considered. Increased free water may be of benefit in patients aged >9 months.
5. Endocrinology should be consulted on an outpatient basis for patients with a Ca level >0.5 mg/dL higher than the ULN but <13 mg/dL. Symptomatic individuals may require inpatient management. Transient reductions in Ca and vitamin D intake to below the RDI²⁸ can be considered, but intake

should be normalized over the next several months after normalization of Ca level. Coincident dehydration should be evaluated and treated, and Cr level should be followed until it normalizes. Renal ultrasound should be evaluated for nephrocalcinosis, and urine Ca and Cr levels should be monitored for hypercalciuria. Abnormalities in either value may necessitate more aggressive monitoring and involvement of nephrology services (Table V; available at www.jpeds.com).

6. Patients with a markedly elevated blood Ca level should be admitted for inpatient intravenous hydration (Table V). If the Ca level remains >14 mg/dL after 24 hours or >12 mg/dL after 48 hours of intravenous hydration, loop diuretics can be initiated in suitable patients. When Ca level fails to drop with these 2 interventions, steroids, calcitonin, and bisphosphonates may be used.^{30,33} Treatment with pamidronate is cited most frequently, but this should be avoided in those with renal failure. Dialysis may be used in extreme situations or when other life-threatening events occur.^{21,34} A reduction of dietary Ca and vitamin D intake is often required but should be carefully monitored with a gradual return to RDI over the several months after Ca level normalizes. Renal studies should be performed, and an ECG should be considered.

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Glossary

BUN	Blood urea nitrogen
Ca	Calcium
Cr	Creatinine
ECG	Electrocardiography
GFR	Glomerular filtration rate
QTc	Corrected QT interval
RDI	Recommended daily intake
RR	Relative risk
SLCH	St. Louis Children's Hospital
SVAS	Supravalvar aortic stenosis

ULN	Upper limit of normal
WBS	Williams-Beuren syndrome
WUSM	Washington University School of Medicine

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Figure 1.

A, Plasma Ca plotted against subject age. Solid lines indicate upper and lower limits of normal. Pediatric-adjusted norms. Points above the dotted line are clinically actionable. **B,** Plasma Ca plotted by age in the cohort with WBS against controls. **C,** Plasma Ca plotted for subjects with actionable hypercalcemia with more than 1 Ca value.

Figure 2.

A, GFR is reduced and B, BUN is increased in subjects with actionable hypercalcemia compared with those with mild hypercalcemia or no history of hypercalcemia. Plots are shown with mean (IQR) in the box and maximum to minimum depicted in the whiskers. ** $P < .01$; *** $P < .001$.

Figure 3. Plasma Ca levels plotted against the QTc interval for the contemporaneous ECG. The regression line is shown in black. Gray bars highlight QTc intervals of ≤ 370 ms and >470 ms.

Table I**Definitions**

Laboratory hypercalcemia	Plasma Ca above the ULN at the reporting laboratory
Pediatric-adjusted hypercalcemia	Plasma Ca above the SLCH ULN for infants and children (>11.0 mg/dL for 0–12 mo and >10.7 mg/dL for 12.1–24 mo) and above the house laboratory norms for older individuals.
Mild hypercalcemia	Plasma Ca 0.1–0.5 mg/dL above pediatric-adjusted hypercalcemia norms
Actionable hypercalcemia	Plasma Ca >0.5 mg/dL above pediatric-adjusted hypercalcemia norms
Hypocalcemia	Plasma Ca <8.6 mg/dL (all ages)
Hypercalciuria	Spot urine Ca/Cr ratio ³⁵ >0.86 mg/mg for 0–7 mo, >0.60 mg/mg for 7.01–18 mo, >0.42 mg/mg for 18.01 mo to 6 y, and >0.22 mg/mg for >6.01 y

Table II

Frequency of hypercalcemia in patients with WBS

Age group	n/N (%)
0–12 mo	
Laboratory hypercalcemia	14/40 (35)
Pediatric-adjusted hypercalcemia	7/41 (17)
Actionable hypercalcemia	2/41 (5)
12–24 mo	
Laboratory hypercalcemia	19/45 (42)
Pediatric-adjusted hypercalcemia	13/50 (26)
Actionable hypercalcemia	5/50 (10)
Above 24 mo	
Laboratory hypercalcemia	37/207 (17.9)
Actionable hypercalcemia	7/207 (3.4)
Actionable hypercalcemia in WBS cohort	14/229 (6.1)

Table III

Chart review for patients with significant hypercalcemia (sorted by age)

Patient ID	Elevated blood Ca level	Relevant laboratory results	Treatment plan	Medications	Relevant history
WBS_123	12.8 mg/dL at age 0.83 y on admission, rose to 13.8 mg/dL in hospital; 11.3 mg/dL at age 1.28 y	Cr 2.3 mg/dL, later stabilized to 0.6 mg/dL at age 0.83 y	Calcilo for 18 mo	None listed	FTT (0.83 y) plus gastrostomy tube; small echogenic kidneys and loss of corticomedullary differentiation; stage II chronic kidney disease; long QT syndrome due to familial KCN mutation (maternally inherited)
WBS_191	12.1 mg/dL at age 0.86 y	Not available	Calcilo for approximately 24 mo	Atenolol, Synthroid, Xopenex, Pulmicort	Atypical WBS deletion (8 Mb) and fibrillin 1 mutation; history of hypothyroidism, seizures, microcephaly, spasticity, and constipation
WBS_181	11.4 mg/dL at age 0.91 y; 12.9 mg/dL at age 1.08 y; 11.7 mg/dL at age 1.08 y (repeated measurement)	Increased oxalate in urine	Primary hyperoxaluria type II was the presumptive diagnosis. Treated with K citrate at age 0.91 y. No change in diet until WS diagnosis, then dietary Ca restriction.	None listed	Diagnosed with WBS at 1.17 y; history of FTT; undescended testes, and anterior anus; bilateral nephrocalcinosis (0.83 y); remains on K citrate, Ca intake is normalized, and Ca level is currently normal
WBS_120	12.1 mg/dL at age 1.04 y, stabilized to 9.8 mg/dL by the end of hospitalization; 10.8 mg/dL at age 1.04 y initially after surgery	Not available	Iatrogenic. Reduced Ca gluconate infusion rate	Zyrtec	Branch pulmonary arterioplasty and repair of SVAS; following surgery, epinephrine infusion of 0.03 mg/kg/min and Ca gluconate infusion of 40 mg/kg/min; history of hypercalciuria
WBS_164	17.7 mg/dL at age 1.05 y	Not available	Acute treatment: IV hydration, Lasix, and calcitonin. Placed on Calcilo, 30 oz/d.	Prevacid	Presented to emergency department with complaints of fussiness and irritability; constipation and hypercalciuria were concurrent complaints; history of hypothyroidism, GERD, FTT; nephrocalcinosis at age 1.33 y
WBS_163	11.2 mg/dL at age 1.05 y; 11.2 mg/dL at age 2.05 y	Not available	No treatment	None listed	High Ca on routine test; irritability and constipation; history of pulmonary valvular stenosis and SVAS
WBS_109	11.3 mg/dL at age 1.25 y	Not available	Discontinue multivitamin preparation; limit dairy intake to <24 oz/d	Multivitamin use before hypercalcemia	Birth at 32 weeks gestation; history of FTT; asymptomatic, but history of gagging with occasional vomiting; bilateral mild/moderate nephrocalcinosis at age 2.84 y
WBS_146	12.2 mg/dL initially, then 14.9 mg/dL at age 1.47 y	25-OH vitamin D level: 17 mg/dL at age 3.01 y	Acute treatment: IV hydration, Lasix, and pamidronate. Low-Ca diet and Calcilo for 20 mo (until age 3.01 y)	400 IU vitamin D for 10 mo due to low 25-hydroxy vitamin D levels at age 3.01 y; switched to multivitamin after.	History of FTT, colic, and constipation; atypical deletion (>2 Mb) and autism spectrum disorder; SVAS; nephrocalcinosis at age 2.97 y

Patient ID	Elevated blood Ca level	Relevant laboratory results	Treatment plan	Medications	Relevant history
WBS_115	10.8 mg/dL at age 15.66 y	25-OH vitamin D levels: 15 mg/dL and 25 mg/dL at age 15.66 y Urine Ca: low	Observation	Amlodipine Labetalol	No hypercalcemia as an infant; long-standing hypertension; very limited dairy intake
WBS_167	11.1 mg/dL at age 19.33 y	BUN: 22 mg/dL Cr: 0.74 mg/dL (high for the patient's size) GFR: 77 mL/min/1.73 m ²	Discontinue multivitamins; calcium stabilized on improved pureed food diet	Multivitamins and special milkshakes (to meet caloric needs)	Gastrointestinal dysmotility and esophageal bezoar; malnutrition, dehydration, and right pelvic kidney
WBS_158	11.5 mg/dL at age 20.51 y	Not available.	Recommendation to decrease milk intake and multivitamin use	Multivitamins and DDAVP use at time of hypercalcemia	Subject was consuming cheese, but not milk at time of hypercalcemia.
WBS_186	11.4 mg/dL at age 26.47 y	Urine Ca (24 h): 390 mg at age 26.21 y PTH: 79 pg/mL at age 26.21 y; 108 pg/mL at age 26.77 y 25-OH vitamin D: 22 mg/dL at age 26.46 y	Parathyroidectomy	None listed	Parathyroid adenoma contributing to hypercalcemia; history of Burkitt lymphoma, protein calorie malnutrition, and renal calculi
WBS_153	11.4 mg/dL at age 30.66 y; 12.1 mg/dL at age 30.82 y	PTH level: 78 pg/mL at age 30.66 y; 90 pg/mL at age 30.82 mg/dL at age 25-hydroxy vitamin D level: 43.4 mg/dL at age 31.21 y; 38.6 mg/dL at age 30.61 y	Parathyroidectomy at age 31.08 y	Multivitamin; 600 mg Ca and 400 IU vitamin D after parathyroidectomy	Hyperparathyroidism contributing to hypercalcemia at age 30.82 y; hypercalcemia noted on routine testing; history of GERD and hypertension
WBS_199	10.9 mg/dL at age 39 y	25-OH vitamin D level: 15.1 mg/dL at age 36 y; 32.3 mg/dL at 1 mo after hypercalcemia	No treatment; no change in multivitamin use	500 IU vitamin D at age 36 yo; 400 IU + Theropec, a reduced vitamin D multivitamin at age 38 y; Centrum multivitamin at age 39 y to present; oral contraceptive for menstrual control	Mild osteopenia

DDAVP, desmopressin; FTT, failure to thrive; GERD, gastroesophageal reflux disease; IV, intravenous.

Table IV

Association of symptoms with hypercalcemia

Factor/symptom	Actionable hypercalcemia, n/N (%)	Mild hypercalcemia, n/N (%)	No history of hypercalcemia, n/N (%)	<i>P</i> value
Female sex	5/13 (39)	20/35 (57)	98/182 (54)	.50
Low birth weight	2/6 (33)	7/17 (41)	18/57 (32)	.76
Difficulty gaining weight	6/6 (100)	9/16 (56)	32/56 (57)	.12
Constipation	4/5 (80)	10/16 (63)	41/57 (72)	.68
Infantile “colic”	6/6 (100)	14/16 (89)	47/53 (89)	.67
Congenital renal abnormalities	1/9 (11)	0/20 (0)	9/81 (11)	.29
One functioning kidney	1/9 (11)	0/20 (0)	4/81 (5)	.39
SVAS (all)	5/8 (63)	7/18 (29)	19/65 (29)	.15
SVAS (requiring catheterization or surgery)	2/8 (25)	3/18 (17)	4/65 (6)	.14
Hypertension (all)	5/8 (63)	10/18 (56)	23/65 (35)	.14
Hypertension (requiring medication)	2/8 (25)	7/18 (39)	8/65 (12)	.03*

* Bonferroni correction requires $P < .005$ for significance.

Table V

Treatment of hypercalcemia in WBS

Treatment	Indications	Response time	Monitoring*	Other considerations
Restriction of Ca and vitamin D to RDI	•	Ca >0.5 mg/dL above age-adjusted ULN Days	Weekly Ca, phosphorus until at goal	In more severe cases (Ca >12 mg/dL or in patients admitted for treatment), restrict Ca to below RDI, using 25% below RDI as a starting point. Modest restriction of Ca intake that corrects hypercalcemia can be continued for several months as long as close clinical and laboratory monitoring are maintained. Long-term Ca restriction cautioned against.
Increase oral fluid intake, 2–2.5 L/m ² /d	•	Ca >0.5 mg/dL above age-adjusted ULN Days	Weekly Ca, phosphorus until at goal	
IV hydration with normal saline bolus as needed, then continued fluids at 3 L/m ² /d (typically D5 1/2 NS + 20 mEq/L KCl)	•	Ca >13 mg/dL or symptomatic 12–24 h	Telemetry, electrolytes	Reduce fluid rate in patients with congestive heart failure, renal failure, or hypertension. May be contraindicated in some. Consider further reduction in Ca/vitamin D intake at this time using medical formula.
Loop diuretics; furosemide 1 mg/kg up to every 12 h ²⁹	•	Continued elevated Ca following IV hydration within 24 h if Ca >14 mg/dL 12–24 h	Monitor blood pressure Monitor potassium level	Volume expansion is required before and during diuretic therapy. Use with caution in renal/heart failure or nephrocalcinosis. Monitor closely for hypokalemia and hypotension, especially in patients with cardiovascular disease.
	•	OR after 48 h of hydration if Ca remains >12 mg/dL		
Bisphosphonates; pamidronate 1 mg/kg ^{30–32}	•	Continued Ca elevation >14 mg/dL following IV hydration and 24 h of diuretics 24–72 h; duration 2–4 wk	Renal function panel, magnesium, phosphorus and Ca before and after infusion	Most commonly published treatment for persistent hypercalcemia in WS other than dietary restriction of Ca and hydration therapy. Nephrotoxic (use with caution in patients with renal failure). Risk of acute-phase reaction (low-grade fever, headache, nausea, emesis, rash, tachycardia, myalgia, bone pain). Hypocalcemia and hypophosphatemia may develop, so Ca and phosphorus should be checked before and after treatment. In most cases, a single dose is adequate, but the dose may need to be repeated in 1 mo if hypercalcemia recurs on a Ca-restricted diet.
	•	OR after IV hydration and 48 h of diuretics if Ca still >12 mg/dL at that time		
	•	OR if above treatments are contraindicated		

Treatment	Indications	Response time	Monitoring*	Other considerations
Glucocorticoids; methylprednisolone 2 mg/kg/d ²⁹	<ul style="list-style-type: none"> Continued Ca elevation >14 mg/dL following IV hydration and 24 h of diuretics OR after IV hydration and 48 h of diuretics if Ca still > 12 mg/dL at that time OR if above treatments are contraindicated 	2–5 d; duration days-weeks		A short course of glucocorticoids could be considered prior to bisphosphonates. Glucocorticoids are most effective in treatment of hypercalcemia related to inflammation but has been used in patients with WS. Prolonged therapy should be avoided as it may cause cushingoid features, osteoporosis and iatrogenic adrenal suppression.
Calcitonin 2–4 U/kg up to every 12 h ³⁰	<ul style="list-style-type: none"> Continued Ca elevation >14 mg/dL following IV hydration and 24 h of diuretics OR after IV hydration and 48 h of diuretics if Ca still >12 mg/dL at that time OR if above treatments are contraindicated 	4–6 h; duration 48 h		Tachyphylaxis develops after 48 hours so response to therapy is short lived.
Dialysis	<ul style="list-style-type: none"> Only consider in patients refractory to above therapies with life-threatening hypercalcemia 	Hours		May be needed in extreme cases where patients have contraindications to all above medical/fluid therapy or severe symptomatic levels of hypercalcemia.

* Blood Ca levels should be followed in all patients, the frequency of which determined by the severity of hypercalcemia and expected rate of change with treatment. Ionized Ca, renal function panel, intact parathyroid hormone, 25-OH vitamin D, spot urine Ca/Cr and renal ultrasound should be obtained as part of an initial evaluation in patients with persistent or refractory to treatment mild hypercalcemia (Ca >0.5 mg/dL over normal limit but <12 mg/dL) and all patients with moderate to severe hypercalcemia (Ca >12 mg/dL).