Hypercalcemia in Patients with Williams-Beuren Syndrome

Sampat Sindhar, BS[1], Michael Lugo, BS[1], Mark D. Levin, MD[2], Joshua R. Danback, BS[1], Benjamin D. Brink, MS[3], Eric Yu, BA[3], Dennis J. Dietzen, PhD[1], Amy L. Clark, DO[1], Carolyn A. Purgert, MD, PhD[1], Jessica L. Waxler, MS[4], Robert W. Elder, MD[5], Barbara R. Pober, MD[3,4,6], and Beth A. Kozel, MD, PhD[1,2]

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 electrogradiography 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 were associated with hypercalcemia and the only statistically associated morbidities were dehydration, hypercalciuria, and nephrocalcinosis. *(J Pediatr 2016;178:254-60).*

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.

BUN	Blood urea nitrogen
Ca	Calcium
Cr	Creatinine
ECG	Ekectrocardiography
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

From the [1]Department of Pediatrics, Washington University School of Medicine, St. Louis, MO; [2]National Institutes of Health, National Heart, Lung, and Blood Institute, Bethesda, MD; [3]Frank H. Netter School of Medicine, Quinnipiac University, North Haven, CT; [4]Massachusetts General Hospital, Boston, MA; [5]Section of Cardiology, Departments of Pediatrics and Internal Medicine, Yale University School of Medicine, New Haven, CT; and [6]Harvard Medical School, Boston, MA

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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*(height (cm)/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 left[2] or right[1] 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. Bonferonni 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