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Clinical Research Article

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Basal Ganglia Calcification Is Associated With Local and Systemic Metabolic Mechanisms in Adult Hypoparathyroidism

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Abstract

Context: Hypoparathyroidism is characterized by low serum calcium, increased serum phosphorus, and inappropriately low or decreased serum parathyroid hormone, which may be associated with soft tissue calcification in the basal ganglia of the brain.
Objective: To assess the prevalence and factors involved in the pathophysiology of basal ganglia calcification (BGC) in the brain in chronic hypoparathyroidism and to evaluate proposed pathophysiologic mechanisms.
Design: Case-control study with retrospective review of medical records over 20 years.
Setting: Single academic medical center.
Patients: 142 patients with chronic hypoparathyroidism and computed tomography (CT) head scans followed between January 1, 2000 and July 9, 2020, and 426 age- and sex-matched controls with CT head scans over the same interval.
Interventions: None.
Main Outcome Measures: Demographic, biochemical, and CT head imaging findings, with semiquantitative assessment of volumetric BGC.
Results: The study found that 25.4% of 142 patients followed for a median of 17 years after diagnosis of chronic hypoparathyroidism had BGC, which developed at a younger age than in controls. BGC was 5.1-fold more common in nonsurgical patients and less common in postsurgical patients. Low serum calcium and low calcium/phosphate ratio correlated with BGC. Neither serum phosphorus nor calcium × phosphate product predicted BGC. Lower serum calcium was associated with greater volume of BGC. The extent of BGC varied widely, with nonsurgical patients generally having a greater volume and distribution of calcification.

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Conclusions: BGC is associated with low serum calcium and low serum calcium/phosphate ratio, which may be related to severity of the disease, its etiology, or duration of treatment.

Key Words: hypoparathyroidism, basal ganglia calcification, calcium, phosphate, parathyroid hormone, brain

Hypoparathyroidism is a rare disorder of mineral metabolism characterized by decreased serum calcium, increased serum phosphate, and absent or deficient production of parathyroid hormone (PTH) (1-4). Patients with hypoparathyroidism are at increased risk of soft tissue calcification (4,5), including calcification of the basal ganglia in the brain.

Soft tissue calcification is associated with alterations in the physiologic ratio between calcium and phosphate. An increased serum calcium × phosphate product is associated with vascular and visceral calcification in patients undergoing renal replacement therapy, with 60 mg^2/dL^2 initially reported as the threshold above which calcifications might develop. This threshold was later reduced to 55 mg^2/dL^2 due to recognition of additional risk of mitral valve calcification above the higher threshold (6). Since then, patients with chronic kidney disease (CKD) have been advised to keep their serum calcium × phosphate product below 55 mg^2/dL^2 (7). By extension, patients with chronic hypoparathyroidism have been advised to keep their calcium × phosphate product below 55 mg^2/dL^2 due to lack of data specific to this disorder.

The reasons why the basal ganglia have a greater likelihood of becoming calcified in patients with chronic hypoparathyroidism remain unclear. Physiology of calcium homeostasis is well understood, but less is known regarding phosphate metabolism. Interest in phosphate metabolism increased following the discovery of fibroblast growth factor 23, which is thought to be the main regulator of serum phosphate, along with parathyroid hormone. Novel mechanisms of phosphate sensing and transportation have recently been described, with dysregulation of these mechanisms possibly explaining in part the soft tissue calcification process (8-10). Increased serum phosphate may be necessary but insufficient to trigger soft tissue calcium phosphate deposition. While vascular calcification is not completely understood, despite increasing evidence in CKD, the pathophysiology of basal ganglia calcification (BGC) in hypoparathyroidism remains even less clear. Since chronic hypoparathyroidism was first associated with BGC in 1939 (11), a variety of hypotheses have been proposed to explain this phenomenon.

Almost 80 years after this association was first reported, a number of unresolved questions remain regarding the pathophysiology of BGC. It remains uncertain why calcification occurs most extensively in the basal ganglia, and occasionally in the cerebellum or other parts of the brain. It is not yet certain whether BGC is associated with seizures or neurocognitive dysfunction in chronic hypoparathyroidism (4). It remains unclear whether BGC is an active or passive process or whether BGC is reversible. BGC found in patients without chronic hypoparathyroidism or other pathological cause is classified as idiopathic BGC or Fahr's disease (12,13). It is not yet known whether Fahr's disease may share pathophysiological mechanisms with BGC in chronic hypoparathyroidism.

Recent advances in knowledge regarding phosphate regulation, advances in genetics of Fahr's disease and discoveries of genetic substrates in certain rare disorders of mineral metabolism have helped elucidate some of the possible mechanisms behind the onset, persistence, and progression of BGC. This case-control study focuses on the prevalence, anatomic distribution, risk factors, semiquantitation of BGC volume, density, and mass and possible pathophysiology of BGC in chronic hypoparathyroidism.

Materials and Methods

Patients

The Mayo Clinic Rochester patient database was searched for patients 18 years or older with a billing code diagnosis of hypoparathyroidism [International Classification of Diseases (ICD)-9 codes 252.1, 258.8; ICD-10 codes E20.0, E20.2-9, and E89.2; Hospital International Classification of Disease Adaptation codes 02521111, 02521120, 02521130, 02521140, 02521150, and 02521160; and SNOMED CT codes 125091015, 292681012, and 61678012] from January 1, 2000 to July 9, 2020. This database includes inpatient and outpatient medical encounters, emergency department visits, laboratory data, and pharmacy records.

A total of 2498 billing code diagnoses of hypoparathyroidism was identified during this interval. Subjects not providing authorization for use of their medical records for research were excluded. All patient records were reviewed using the electronic health record to confirm the diagnosis, date of diagnosis, and etiology of the hypoparathyroidism. After excluding patients without hypoparathyroidism for 6 months or longer and incorrect diagnosis

of hypoparathyroidism, we identified 1014 unique patients with chronic hypoparathyroidism and verified that their biochemistries were consistent with this diagnosis (Fig. 1). For patients with postsurgical hypoparathyroidism, the diagnosis was confirmed only if laboratory findings were consistent with hypoparathyroidism 6 months or more after neck surgery. If recorded in the clinical notes, external patient information and laboratory results from outside the Mayo Clinic Rochester patient database were used to confirm the diagnosis, but other information from external clinical databases was not included.

Of adult patients diagnosed with chronic hypoparathyroidism, we searched for those with at least 1 clinical head computed tomography (CT) exam performed between January 1, 2000 and July 9, 2020. This group constitutes the patient cohort used in this study. We carefully reviewed both the radiology records and electronic CT images of these patients to identify BGC. To evaluate imaging characteristics of these patients, we considered the date of recognition of BGC at the index head CT imaging during follow-up or the last follow-up head CT available in patients without BGC (index CT date). Clinical characteristics and comorbidities including hypertension, diabetes, or dyslipidemia were obtained through billing code diagnoses. Social habits were recorded. Medications taken at each patient's last recorded clinic or hospital visit before their head CT or at the time of their head CT were recorded.

This study was approved by the Mayo Clinic Institutional Review Board as exempt (IRB #20-004065).

Controls

To evaluate the prevalence and risk factors for BGC in patients without hypoparathyroidism, we identified a group of age- and sex-matched controls with head CT scans using the Mayo Clinic Rochester patient database. For each patient, 3 randomly matched controls were selected after matching by sex and age (±1 year) at the index head CT date. Control subjects were required to have had serum calcium measured within 90 days of their head CT scans. Head CT scans were performed over the same interval and at the same CT imaging facility as for patients. Electronic medical record data including biochemistries, comorbidities, and social habits were also recorded for controls.

Biochemistries

Biochemistries were retrieved from the Mayo Clinic Rochester database. Each patient had at least 1 measured biochemical value of each type during the follow-up period. For each patient, all biochemistries were retrieved within 10 years before the index head CT date and after the diagnosis of chronic hypoparathyroidism or the date of surgery causing chronic hypoparathyroidism. Time-weighted averages were calculated as the area under the curve using the trapezoidal rule divided by time between measurements, as reported in a prior publication (14). We excluded serum calcium and phosphate measurements in adult patients that were measured before age 12 years. The calcium × phosphate product or ratio were calculated only if both values were measured on the same day. In case multiple laboratory assessments of the same parameter were drawn on the same day, the mean was calculated and counted as a single value for the time-weighted average. For parathyroid hormone measurements, since different assays were used over the 20-year study interval, time-weighted Z-scores were used to standardize values. For each patient, the number of episodes in which laboratory values were above or below the normal range was determined.

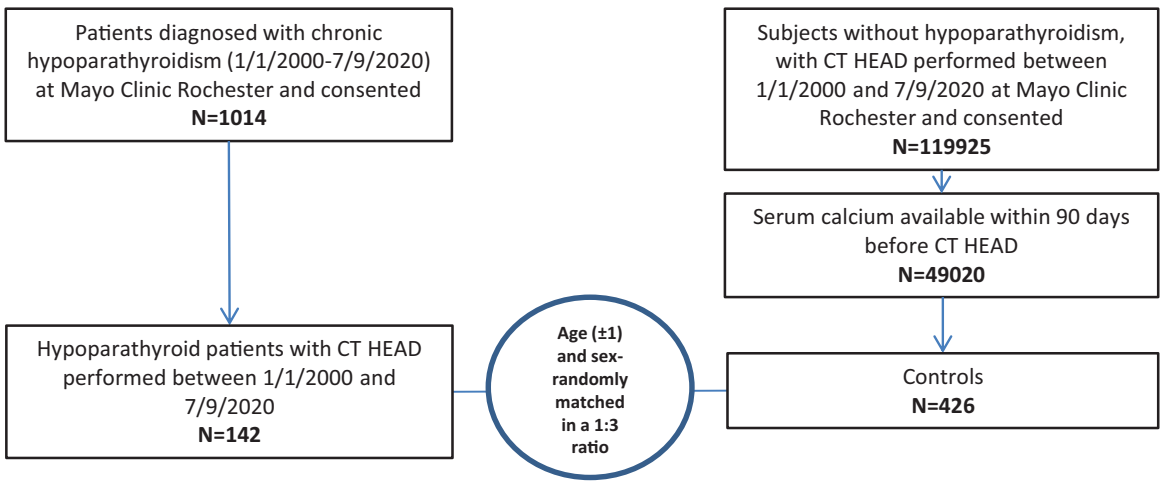

Figure 1. Flowchart showing design of the study.

Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation (15), if age at laboratory evaluation was 18 or older. Time-weighted creatinine values were then categorized by CKD stages 1 to 5.

Semiquantitative volumetric assessment of basal ganglia calcification

Electronic images from head CT exams were analyzed to quantify the total volume and mass of BCG. Exams were performed clinically on different CT scanner models over the study interval and were either contrast-enhanced or unenhanced. If the scanner model used to perform the exam was still available on campus, then calibration scans using calcium samples with known densities (50 mg/mL and 100 mg/mL) were performed to establish the relationship between CT Hounsfield unit (HU) values and calcium density. If the scanner model was no longer available on campus, the calibration curve established on a scanner with the closest X-ray spectrum and acquisition parameters was used. Images from each head CT exam were loaded onto a 3D segmentation and volume measurement research tool (Radiomics, Siemens Healthineers USA, Malvern, PA, USA) to determine the total volume of calcification based on a CT number threshold value. The CT HU number of the segmented volume was subsequently converted to density. Based on the volume and the density, the mass of BGC was calculated.

Neurologic complications

To assess the clinical significance of BGC within the cohort, billing code diagnoses (ICD-9 and ICD-10) of all neurological conditions were retrieved. Patients were counted as having a neurological condition if they had at least 1 diagnosis through the end of the follow-up period (July 9, 2020) or death.

Statistical analysis

Group characteristics were described using the median with SD or interquartile range \ and total ranges. Between-group differences were assessed by Chi-square test for categorical variables or Mann-Whitney U test for continuous variables. Crude odds ratios were reported with the 95% confidence interval. Spearman's correlations were used to correlate volume and density of calcification with clinical parameters. Spearman's Rho coefficient was reported as ρ. Two-tailed *P*-values were used in all analyses. All calculations were performed using SPSS software (IBM, SPSS 23.0).

Results

Demographics

A total of 142 adult patients with chronic hypoparathyroidism were identified with head CT scans performed between January 1, 2000 and July 9, 2020 (Table 1). Median age at diagnosis was 44.0 ± 21.1 years, with median disease duration at the time of the index head CT scan 11.0 ± 14.4 years. Median duration of follow-up after diagnosis was 17.0 ± 15.4 years. The majority of patients were female (66.2%), and 80.3% had postsurgical hypoparathyroidism. In 71.1% of cases, head CT scans were performed for acute or emergency medical conditions, with less frequent indications including cancer staging or nonurgent conditions (28.9%), or for hypoparathyroidism (3.5%). Of the 142 patients identified, 25.4% had BGC. Nonsurgical patients had a significantly higher prevalence of BGC (71.4%) compared to postsurgical patients (14.0%), with an odds ratio of having BGC of 15.4 (95% confidence interval, 5.8-40.0, $P < 0.001$) (Table 1).

These cases were compared to 426 age- and sex-matched controls without hypoparathyroidism with head CT scans during the same time period (Table 1). Median age at index head CT scan in the controls was 62 ± 20.5 years. Head CT scans were performed for acute or emergency conditions in 84.0%, and less frequently for cancer staging or nonurgent conditions in 16.0%. Imaging revealed that 7.3% had BGC. Controls more frequently drank alcohol than cases (70.0% *vs* 46.4%, $P < 0.001$) but did not differ in terms of diagnoses of diabetes mellitus, hypertension, or dyslipidemia.

Comparison of patients with or without BGC showed that those with BGC were younger at diagnosis of hypoparathyroidism (31 ± 26 years *vs* 46 ± 19 years, $P = 0.027$) and at the end of follow-up (50 ± 21.7 years *vs* 64.5 ± 17.7 years, $P = 0.025$) (Table 2). Duration of diagnosis at the time of the index head CT scan was the same in those with or without BGC (8 ± 18 years *vs* 11 ± 13 years). Patients with BGC more frequently had nonsurgical than postsurgical hypoparathyroidism (55.6% *vs* 7.5%). Patients with or without BGC had similar cardiovascular risk factors, including hypertension, diabetes mellitus, or dyslipidemia.

Controls with BGC had a median age of 70 ± 20.6 years at their index head CT scan, whereas those without BGC were 62 ± 20.3 years (Table 2). Controls with BGC had a median age at end of follow-up of 71 ± 18 years, whereas those without BGC were 61.5 ± 20.4 years. Controls were diagnosed with BGC at an older age than patients and were older at the end of follow-up.

Table 1. Characteristics of study population

	Hypoparathyroid patients	Controls	*P*-value
Patients, n	142	426	
Women, n (%)	94 (66.2)	282 (66.2)	1.000
Ethnicity			
White Caucasian, n (%)	128 (89.7)	375 (88.0)	0.418[a]
Asian, n	2	3	
African/African American, n	2	7	
American Indian/Alaskan Native, n	1	2	
Other, n	6	11	
Unknown/choose not to disclose, n	3	28	
Etiology		NA	
Postsurgical	114 (80.3)		
Thyroid surgery—malignant neoplasm	71 (62.3)		
Thyroid surgery—nonmalignant cause	30 (26.3)		
Parathyroid surgery	8 (7.0)		
MEN (1,2A)	2		
Other neck surgery (malignant causes)	3 (2.6)		
Nonsurgical	28 (19.7)		
Autoimmune or presumed autoimmune	9 (32.1)		
APS 1	2 (7.1)		
Genetic	13 (46.4)		
Di George	5 (17.9)		
Trisomy 21-associated	2 (7.1)		
Activating CaSR mutation	1 (3.6)		
Familial, gene unknown	5 (17.9)		
Idiopathic/unknown cause[b]	6 (21.4)		
Age at diagnosis (years)[§]	44.0 (21.1) (0-84)	NA	
Duration of disease (years) at CT scan[§]	11 (14.4) (0-71)	NA	
Age at CT HEAD scan[§]	62 (20.6) (11-97)	62 (20.5) (10-98)	0.974
Number of CTs per patient	1 (1-22)	NA	
Duration of whole follow-up[§]	17 (15.4) (1-71)	NA	
Postsurgical, median (SD)	17.0 (14.5)		
Nonsurgical, median (SD)	16.5 (19.4)		
Patients alive at follow-up, n (%)	94 (66.2)	247 (58.0)	0.093
Age at end of study period[§,c]	61.5 (19.3) (21-100)	63.0 (20.3) (16-105)	0.423
BMI (kg/m^2)[§]	27.9 (8.2) (14.6-58.4)	27.1 (9.1) (13.0–82.7) n = 201	0.644
Current or former smokers, n (%)	44/130 (33.8)	58/211 (27.5)	0.213
Unknown smoking status	12 (8.5)	215 (50.4)	
Alcohol use, n (%)	89/125 (71.2)	175/227 (77.1)	0.222
History of alcohol abuse	66/125 (52.8)	159/227 (70.0)	**0.001**
Unknown alcohol consumption	17 (12.0)	199 (46.7)	
Diabetes, n (%)	41 (28.9)	108 (25.4)	0.441
Hypertension, n (%)	77 (54.2)	255 (59.9)	0.240
Dyslipidemia, n (%)	75 (52.8)	190 (44.6)	0.099
Main reasons for CT head scan, n (%)			**0.001**[d]
Acute/emergency setting	101 (71.1)	358 (84.0)	
Other (cancer staging/nonurgent conditions)	41 (28.9)	68 (16.0)	
Hypoparathyroidism	5 (3.5)	NA	
Patients with basal ganglia calcification, n (%)	36 (25.4)	31 (7.3)	**0.001**
Postsurgical,[e] n (% of the postsurgical cohort)	16 (14.0)		
Nonsurgical,[e] n (% of the nonsurgical cohort)	20 (71.4)		

Values are expressed as n, total number (%), or median, (SD), and range (min-max) where appropriate. Significant correlations are in bold.
Abbreviation: CaSR, calcium-sensing receptor; NA, not applicable.
[§]Median (SD), (min-max), n
[a]White *vs* nonwhite.
[b]Hypoparathyroidism was classified as idiopathic/unknown if no genetic, familial or autoimmune history was present or if the nonsurgical etiology was not investigated further.
[c]Alive patients only, as of July 9, 2020.
[d]Acute setting *vs* other reasons.
[e]Odds ratio for nonsurgical *vs* postsurgical = 15.4 (5.8-40), $P < 0.001$.

Table 2. Characteristics of patients and controls with or without BGC

	Hypo		Controls		Hypo	Controls	BGC
	BGC n = 36	No BGC n = 106	BGC n = 31	No BGC n = 395	*P*-Value (BGC *vs* no BGC)	*P*-value (BGC *vs* no BGC)	*P*-value (hypo *vs* controls)
Women, n (%)	22 (61.1)	72 (67.9)	21 (67.7)	261 (66.1)	0.541	1.000	0.617
Age at hypoparathyroidism diagnosis[§,a]	31 (26) (11.5-63.0)	46 (19) (9-84)	NA	NA	**0.027**		
Nonsurgical hypoparathyroidism, n (%)	20 (55.6)	8 (7.5)	NA	NA	**<0.001**		
Age at CT head scan[§]	60.5 (23) (11-92)	62.5 (19) (15-97)	70 (20.6) (27-95)	62 (20.3) (10-98)	0.061	**0.011**	**0.006**
Duration of disease at head CT scan (years)[§]	8 (18) (3-36)	11 (13) (0-56)	NA	NA	0.478		
Age at end of follow-up[§]	50 (21.7) (21-95)	64.5 (17.7) (24-100)	71 (18) (67.5-89.5)	61.5 (20.4) (16-105)	**0.025**	**0.038**	**0.005**
Current or former smoker, n (%)	11 (30.6)	33 (31.1)	3/12 (25.0)	55/215 (25.6)	1.000	0.785	0.068
Unknown smoking status, n (%)	3 (8.3)	9 (8.5)	19 (61.3)	196 (49.6)			
Alcohol use, n (%)	24 (66.7)	65 (61.3)	9/13 (69.2)	166/215 (77.2)	0.668	0.501	1.000
Unknown alcohol consumption, n (%)	1 (2.8)	16 (15.1)	18 (58.1)	181 (45.8)			
BMI (kg/m^2)[§]	27.5 (8.5) (17.2-52.0)	28.6 (8.2) (14.6-58.4)	25.1 (7.3) (17.3–41.9) n = 15	27.3 (9.2) (13-82.7) n = 186	0.764	0.122	0.193
Diabetes, n (%)	11 (30.6)	30 (28.3)	7 (22.6)	101 (25.6)	0.833	0.832	0.583
Hypertension, n (%)	19 (52.8)	58 (54.7)	24 (77.4)	231 (58.5)	0.849	0.055	**0.044**
Dyslipidemia, n (%)	18 (50.0)	57 (53.8)	19 (61.3)	171 (43.3)	0.704	0.061	0.461

Values are n (%) unless otherwise noted. Significant correlations are in bold.

[§]Median (SD), (min-max).

[a]In 4 patients, the age of diagnosis is unknown.

Abbreviations: Hypo, hypoparathyroidism.

Patients with BGC were compared to controls with BGC. Median age of index head CT scan was 60.5 ± 23 years in patients and 70 ± 20.6 years in controls (Table 2). Median age at the end of follow-up was 50 ± 21.7 years in patients and 71 ± 18 years in controls. Patients were younger when they underwent their first head CT scan and were younger at the end of follow-up. Controls were more frequently hypertensive (77.4%) than patients (52.8%) ($P = 0.044$).

Biochemistries

Median time-weighted calcium (8.8 ± 0.8 mg/dL) and phosphate (4.2 ± 0.8 mg/dL) were lower and higher, respectively, in patients during the 10 years before their index head CT scan than in controls (Table 3), consistent with their diagnosis. Time-weighted eGFR was ≥30 mL/min in 93.3% of patients. Estimated GFR by the Modification of Diet in Renal Disease equation in patients was categorized as stage 1 CKD in 15.5%, stage 2 in 29.6%, stage 3 in 29.6%, stage 4 in 5.6%, and stage 5 in 3.5%. More patients had stage 3 CKD than controls, but the distribution of CKD was otherwise the same. Median time-weighted PTH Z-score was –2.6 ± 1.1 (range –2.9 to –1.8). Median time-weighted serum 25-hydroxyvitamin D was 34 ± 19 ng/mL (range 11-142). Median time-weighted serum 1,25-dihydroxyvitamin D was 30 ± 21 pg/mL (range 0-101). Median time-weighted 24-h urinary calcium was 191 ± 125 mg (range 13-584). A total of 22.2% of patients had a 24-h urinary calcium that exceeded 400 mg on at least 1 occasion.

Median time-weighted calcium × phosphorus product for patients was 36.4 ± 6.3mg^2/dL^2 (range 19-51), with the median time-weighted calcium/phosphate ratio 2.07 ± 0.50 (range 0.79-3.97) (Table 3). A total of 11.3% of patients had a calcium × phosphate product above 55 mg^2/dL^2 on at least 1 occasion.

Patients with BGC had significantly decreased time-weighted serum calcium over the 10 years preceding their index head CT scan compared to patients without BGC (8.4 ± 0.8 *vs* 8.8 ± 0.8 mg/dL, $P = 0.002$) (Table 3). Although the median time-weighted calcium × phosphate product did not differ between patients with or without BGC, median time-weighted calcium/phosphate ratio was significantly lower in patients with BGC (1.83 ± 0.52 *vs* 2.13 ± 0.47, $P = 0.004$). Median time-weighted serum phosphorus was not significantly increased in those with BGC, nor was median serum phosphorus closest to the index head CT scan date increased.

Controls without BGC had more stage 1 CKD (26.8%) and higher median eGFR closest to their index CT head scans than controls with BGC (Table 3). Patients with BGC had lower median time-weighted serum calcium and higher median time-weighted serum phosphorus than controls with BGC.

Supplements and medications

Table 4 summarizes the supplements and medications taken at the time of index head CT scans or the last documented encounter before these exams. Almost all patients took calcium supplements (96.5%), with 86.9% taking calcium carbonate and the majority of the remainder calcium citrate. Calcitriol was taken by 74.6% of patients, vitamin D3 by 23.9%, vitamin D2 by 9.9%, and high-dose vitamin D2 or D3 greater than 50 000 units each week by 6.3%. Magnesium supplements were taken by 13.4%, and a thiazide diuretic, by 21.1%. There were no differences in the types of supplements or doses taken between those with or without BGC. Patients may have taken a thiazide diuretic to treat hypertension or to reduce hypercalciuria.

Three patients were taking recombinant human PTH(1-84) [rhPTH(1-84)] at the time of their index head CT scan. Two took daily subcutaneous doses of 50 mcg, and 1 took 100 mcg each day. Two of the 3 patients had BGC on their head CT scans. These 2 patients had taken rhPTH(1-84) for 1 and 3 years, respectively. Head CT images were not available before they started rhPTH(1-84). One patient without BGC took rhPTH (1-34) for approximately 8 years before their index head CT scan.

BGC semiquantitation

This study reports the first semiquantitation of BGC volume, density, and mass in patients with chronic hypoparathyroidism. Assessment showed a median volume of 0.075 ± 8.88 mL, with a range of <0.001 to 42.93 mL (Table 5). Median density of calcification was 73.15 ± 38.16 HU, with mean variance 199.2 ± 9487.2 HU. Postsurgical patients had a smaller median volume of calcification of 0.02 ± 15.42 mL, with nonsurgical patients having a greater volume of 2.15 ± 10.55 mL ($P = 0.011$), with 10 of 17 nonsurgical patients having volumes >2.0 mL (Table 5). In contrast, only 2/9 postsurgical patients had volumes above this level. No difference was seen between density and variance in BGC between postsurgical and nonsurgical patients. Estimated mass of calcification in postsurgical patients ranged between 0.077 and 450.6 mg and between 0.059 and 1613.3 mg in nonsurgical patients. Volume of BGC correlated with density ($P < 0.001$), age at diagnosis of hypoparathyroidism ($P = 0.009$), time-weighted serum calcium ($P = 0.025$), and time-weighted serum creatinine ($P = 0.018$) (Table 6). BGC density correlated with volume only ($P < 0.001$). Figure 2 shows the 3D

Table 3. Biochemistries in patients and controls, with or without BGC

	Hypo		Controls		Hypo	Controls	BGC
	BGC	No BGC	BGC	No BGC	*P*-value (BGC *vs* no BGC)	*P*-Value (BGC vs no BGC)	*P*-value (hypo *vs* controls)
Time-weighted serum total calcium[§]	8.4 (0.8) (6.3-10.3) n = 29	8.8 (0.8) (6.4-11.4) n = 98	9.3 (0.7) (7.5-10.1)	9.3 (0.7) (6.6-13.2)	**0.002**	0.763	**<0.001**
Serum calcium (single value closest to CT)[§]	8.6 (1.3) (6.8-14.1) n = 29	8.8 (0.8) (6.4-11.6) n = 98	9.3 (0.8) (7.1-10.1) n = 31	9.3 (0.9) (5.5-16.4) n = 391	**0.042**	0.811	**0.001**
Time-weighted serum phosphorus[§]	4.3 (1.1) (3.3-7.9) n = 30	4.2 (0.7) (2.7-6.7) n = 97	3.7 (0.6) (2.6-5.0)	3.6 (1.1) (1.7-11.5)	0.121	0.179	**0.009**
Serum phosphorus (single value closest to CT)[§]	4.5 (1.1) (1.8-7.7) n = 30	4.1 (0.9) (1.4-6.7) n = 97	3.7 (1.3) (1.6-7.9) n = 17	3.5 (1.2) (1.4-11.1) n = 199	0.102	0.212	**0.041**
eGFR (MDRD), n (%)	n = 26	n = 89	n = 18	n = 194			
Stage 1	4 (15.4)	18 (20.2)	0	52 (26.8)	0.778	**0.008**	0.133
Stage 2	10 (38.5)	32 (36.0)	9 (50)	67 (34.5)	0.821	0.207	0.542
Stage 3	9 (34.6)	33 (37.1)	6 (33.3)	47 (24.2)	1.000	0.400	1.000
Stage 4	2 (7.7)	6 (6.7)	2 (11.1)	14 (7.2)	1.000	0.632	1.000
Stage 5	2 (7.7)	3 (3.4)	1 (5.6)	14 (7.2)	0.316	1.000	1.000
eGFR (MDRD) closest to CT, median (SD)	59.4 (24.7)	60.6 (29.9)	57.4 (21.6)	69.4 (46.7)	0.374	**0.030**	0.364
Creatinine (mg/dL) (closest to CT), median (SD)	1.1 (0.9) (0.6-4.5)	1.0 (0.7) (0.4-4.3)	1.2 (1.3)	0.9 (1.8)	0.306	**0.024**	0.536
Time weighted creatinine[§]	1.1 (0.6) (0.5-4.2)	1.0 (0.6) (0.5-3.8)	1.1 (1.5) (0.6-7.4)	0.9 (1.8) (0.2-14.5)	0.803	0.180	0.919
Time-weighted Ca × P (mg^2/dL^2)[§]	38.1 (6.8) (28.0-50.8) n = 26	35.9 (6.1) (18.9-50.4) n = 89			0.403		
Time-weighted Ca/P[§]	1.83 (0.52) (0.79-3.16) n = 26	2.13 (0.47) (1.3-3.9) n = 89			**0.007**		
Ca × P > 55 mg^2/dL^2 (at least 1 episode), n (%)	5 (19.2) n = 26	8 (9.0) n = 89			0.166		
Time weighted serum magnesium[§]	1.84 (0.22) (1.5-2.2) n = 25	1.86 (0.27) (1.4-3.5) n = 81			0.911		
Serum magnesium (single value closest to CT)[§]	1.7 (0.2) (1.4-2.2) n = 25	1.9 (0.3) (1.3-3.5) n = 81			0.163		
PTH level	n = 28	n = 77					
Time-weighted *Z*-score for reference range, median (SD)	−2.5 (1.0)	−2.6 (1.1)			0.951		
Undetectable PTH (in at least one occasion), n (%)	14 (50)	43 (55.8)			0.661		

Table 3. Continued

	Hypo		Controls		Hypo	Controls	BGC
	BGC	No BGC	BGC	No BGC	*P*-value (BGC *vs* no BGC)	*P*-Value (BGC *vs* no BGC)	*P*-value (hypo *vs* controls)
Number of assessments per patient[$]	3 (1-20)	2 (1-19)			0.812		
Time-weighted average 25OH Vit.D[$]	37 (12) (13-54) n = 20	34 (22) (11-142) n = 60			0.777		
Time-weighted average $1,25(OH)_2$ Vit.D[$]	30 (24) (16-101) n = 12	30 (19) (undetect.-95) n = 32			0.536		
Time-weighted average urinary calcium (mg/die)[$]	185 (119) (56-286) n = 17	197 (127) (61-584) n = 37			0.268		
Time-weighted average urinary creatinine (mg/die)[$]	1138 (562) (304-2298) n = 14	1044 (557) (369-2757) n = 32			0.924		

Time-weighted average in the controls reflects all laboratory measurements within 90 days prior to CT head scan, if available. Significant correlations are in bold.
Abbreviation: Ca/P, calcium/phosphate; Hypo, hypoparathyroidism; MDRD, Modification of Diet in Renal Disease.
[$]Median (SD), (min-max).

volume and distribution of BGC in 4 representative patients. Figure 3 shows that the outer layers of calcification had lower density, explaining the higher variance in density in larger calcifications.

Neurological diagnoses and symptoms

No differences were found in the overall number or type of neurological diagnoses between patients with or without BGC, including Parkinsonism, tremor, seizure, ataxia, cognitive impairment, dementia, stroke, transient ischemic attack, headache, memory loss, sleep disorders, or musculoskeletal symptoms. Patients with BGC were younger than controls with BCG (Table 7).

The cause of chronic hypoparathyroidism did not appear to affect the prevalence of neurological complications or symptoms, except for tremor, which was more common in postsurgical than nonsurgical patients (15.8% *vs* 0%, $P = 0.024$). Review of the medical records showed that tremor in postsurgical patients was due to benign intention tremor or physiological tremor, but not Parkinsonism.

Imaging findings

Evaluation of distribution of BGC by brain region showed that 96% had calcification of the globus pallidus, 53.8% of the putamen and caudate nucleus, 42.3% of the thalamus, 46% of the grey-white matter junction, 30.8% of the cerebellar parenchyma, and 19.2% of the dentate nucleus. Figure 4 shows representative examples of BGC seen on head CT scans in patients and age- and sex-matched controls. Patients with nonsurgical hypoparathyroidism generally had more extensive BGC than postsurgical patients, but this varied with disease duration and by patient (Fig. 4A and B). Controls with BGC generally had less extensive and sometimes punctate BGC (Fig. 4C).

Most patients with BGC had BGC at the time of their index head CT scan and maintained this without progression or regression over up to 11 years (Fig. 5, top panels), whereas other patients with BGC had punctate and slowly progressive BGC (Fig. 5, bottom panels). These findings were observed in 10 patients had 2 or more head CT scans at least 1 year apart, with 1 patient having 2 head CT scans, and 2 patients having had 6 head CT scans during follow-up.

Discussion

This real-world case-control study found that 25.4% of 142 patients with chronic hypoparathyroidism with head CT scans obtained for clinical indications had BGC. Patients were followed for a median of 17 years after diagnosis of

Table 4. Medications in patients with chronic hypoparathyroidism

	N (%)	Dose[a]	
Calcium supplement (mg/day)[b]	137 (96.5)	1200 (1184) (200-6000)	
Calcium carbonate	119 (86.9)	1200 (375-6000)	
Calcium citrate	16 (11.7)	1260 (200-4725)	
Calcitriol[c]	106 (74.6)	0.5 (0.4) (0.25-3.0)	
Magnesium (mg/day)[d]	19 (13.4)	360 (125-964)	
Thiazide[e]	30 (21.1)	—	
Hydrochlorothiazide (mg/day)	26 (18.3)	25 (9) (12.5-50)	
Chlorthalidone (mg/day)	4 (2.8)	Range (25-50)	
Vitamin D3 (IU/day)	34 (23.9)	1000 (400-50 000)	
High-dose vitamin D3 (IU/wk)[f]	2 (1.4)	Range (50 000-350 000)	
Vitamin D2 (IU/day)	14 (9.9)	1200 (600-50 000)	
High-dose vitamin D2 (IU/wk)[f]	7 (4.9)	Range (50 000-350 000)	
	Hypo with BGC	**Hypo without BGC**	***P*-value**
Calcium supplement[§] (mg/day)[b]	1260 (1437) (400-6000), 31	1200 (1091) (200-5500), 101	0.287
Calcitriol (µg/day)[§]	0.5 (0.3) (0.25-1.25), 25	0.5 (0.250-3), 77	0.613
Magnesium (mg/day)[§]	482 (295) (241-964), 5	330 (241) (125-964), 14	0.666
Hydrochlorothiazide (mg/day)[§]	25 (12.3) (12.5-50), 6	25 (8.1) (12.5-50), 20	0.681

Three patients were on rhPTH(1-84) at the time of their CT (2 at 50 mcg per day, and 1 at 100 mcg per day). Two of them showed BGC at their head CT. These 2 patients had been taking rhPTH(1-84) for 1 and 3 years. No previous CT images were available for comparison. One patient had been taking twice-daily rhPTH (1-34) for approximately 8 years with no evidence of BGC at their head CT. Significant correlations are in bold.

Abbreviation: Hypo, hypoparathyroidism.

[§]Median (SD), (min-max), n

[a]Median (SD) (min-max) dose for each patient's last recorded visit before or at CT head.

[b]Unknown type of calcium, n = 5 no calcium supplements. Elemental calcium.

[c]Four patients were on calcitriol at a dose of less than once a day: 2 patients on calcitriol 0.25 mcg every other day, 1 patient 0.25 mcg twice a week, 1 patient 0.25 mcg 3 times a week.

[d]Dose of elemental magnesium.

[e]Includes patients taking thiazides for any purpose.

[f]High-dose cholecalciferol or ergocalciferol was defined as greater than 50 000 IU per week. Vitamin D3: 1 patient was taking 50 000 IU twice a week, the other 50 000 IU once a week. Vitamin D2: 1 patient was taking 50 000 IU once a week; 1 patient, 50 000 IU every other day; 1 patient, 3 times a week; 1 patient, twice a week; and the remaining 3 patients, 50 000IU once a day.

hypoparathyroidism. BGC was 5.1 times more common in nonsurgical than postsurgical patients. Compared to age- and sex-matched controls with BGC, patients with BGC were younger. Patient serum and urine biochemistries were typical for conventionally treated patients with this disorder. Serum calcium and calcium/phosphate ratio correlated with BGC in patients, but not serum phosphorus or calcium × phosphate product. Patients with BGC seemed not to be at higher risk of neurological disorders or symptoms, but further data are needed. Finally, the volume and extent of BGC in patients with postsurgical and nonsurgical hypoparathyroidism varied widely, with nonsurgical patients having a greater burden of BGC. Volume of BGC correlated with lower serum calcium and worsened renal function.

Goswami et al (16) previously reported BGC prevalence of 73.8% in 93 patients with idiopathic hypoparathyroidism. An early small series of 16 patients with idiopathic hypoparathyroidism by Illum et al (17) showed the prevalence to be 69%. Sachs et al (18) reported that 11 of 12 (91.7%) patients with idiopathic hypoparathyroidism had BGC present on CT imaging. Determination of idiopathic BGC prevalence depends in part on imaging technique and diagnostic criteria. In the 1980s BGC was detected incidentally in 0.24% to 0.75% of head CT scans, while 2 decades later it was reported to be 12.5% (12). Mean age of onset of idiopathic BGC and whether prevalence may differ by sex are currently unknown (13).

Rubin et al (19) reported that 4 of 33 (12.1%) patients with chronic hypoparathyroidism had BGC, but brain imaging was carried out only in symptomatic patients. Mitchell et al (14) showed that 52% of 31 patients with head CT scans available for review in a large cohort of 120 patients with chronic hypoparathyroidism had BGC. The BGC prevalence of 25.4% found in our cohort is therefore in the range of what has previously been reported and may reflect conventional management of patients with chronic mostly postsurgical hypoparathyroidism over a median of 17 years during the interval studied.

In comparison, studies of BGC in the general population have shown prevalence rates as high as 15% to 20%,

Table 5. BGC volume semiquantitation in patients with chronic hypoparathyroidism

	Total cohort (n = 34)	Postsurgical	Nonsurgical	P-value[a]
Volume (mL)	0.075 (8.88), 0-42.93	0.02 (15.42), 0-20.86, N = 15	2.15 (10.55), 0-42.93, N = 19	0.011
Density (HU)	73.15 (38.16), 56.6-203.6	72.1 (15.42), 56.8-98.6, N = 9	85.7 (44.7), 56.6-203.6, N = 17	0.672
Variance (HU)	199.2 (9487.2), 1.6-42 772.2	91.2 (769), 3.2-2083, N = 9	1178 (11 260), 1.6-42 772, N = 17	0.339

	Baseline CT head					Follow-up CT head					
Patients	Volume (mL)	CT image density (HU)	HU variance	Mass density (mg/mL)	Mass estimate (mg)[b]	Volume (mL)	CT image density (HU)	HU variance	Mass density (mg/mL)	Mass estimate (mg)[b]	Interval (months)
1	0.01	63.1	39.7	7.71	0.077	0.02	61.3	33.5	7.17	0.143	92.6
2	0.02	74.2	287.0	13.04	0.260						
3	0.02	56.8	3.2	6.94	0.139						
4	0.02	69.2	91.2	9.51	0.190	0.02	93.1	541.2	6.59	0.132	74.4
5	0.02	72.1	7.2	12.31	0.246						
6	0.06	61.1	57.6	8.45	0.507						
7	0.76	85.5	1311.5	14.32	10.883	1.00	80.5	1242.3	15.25	15.25	14.3
8	3.57	98.0	1205.5	18.0	64.26						
9	20.86	98.6	2083.7	21.6	450.576	21.21	100.1	2016.3	22.12	469.165	42.1
10	0.01	59.4	2.2	6.61	0.066	<0.01	57 (equivalent to 7.01 mg/mL)	0	NA	NA	102.7
11	0.01	57.0	1.6	5.91	0.059	0.19	59.9	20.8	6.76	1.284	81.6
12	0.02	56.6	3.6	6.87	0.137						
13	0.09	59.2	22.7	9.51	0.856	0.31	63.8	59.1	9.40	2.914	30.9
14	0.21	60.6	111.4	8.27	1.737						
15	0.28	59.6	17.0	7.92	2.218						
16	0.31	61.5	28.9	7.23	2.241						
17	2.15	67.4	98.5	10.66	22.919						
18	2.45	90.7	3700.7	18.83	46.134						
19	4.02	111.3	4257.5	26.05	104.721						
20	6.95	85.7	1178.8	17.07	118.637						
21	8.36	120.4	10 435.3	29.24	244.446						
22	8.9	92.8	3656.3	19.56	174.084						
23	14.2	132.7	8737.7	33.55	476.41						
24	16.43	169.7	20 197.4	46.52	764.324						
25	16.46	203.6	42 772.2	49.18	809.503						
26	42.93	144.2	17 533.8	37.58	1613.309						

This table shows the values of measurable BGC with volume ≥0.01mL. Values are median, SD (range). Patients 1-9 are postsurgical cases, while patients 10-26 are nonsurgical cases. Of the total 34 patients with BGC, 8 (6 in the postsurgical group) had a volume less than 0.01mL, and in these patients density could not be assessed. In 2/34 patients the volume or density of BGC could not be measured due to technical issues. Significant correlations are in bold.

[a]Postsurgical vs nonsurgical.

[b]Mass estimate (mg) = Volume (mL) × mass density (mg/mL).

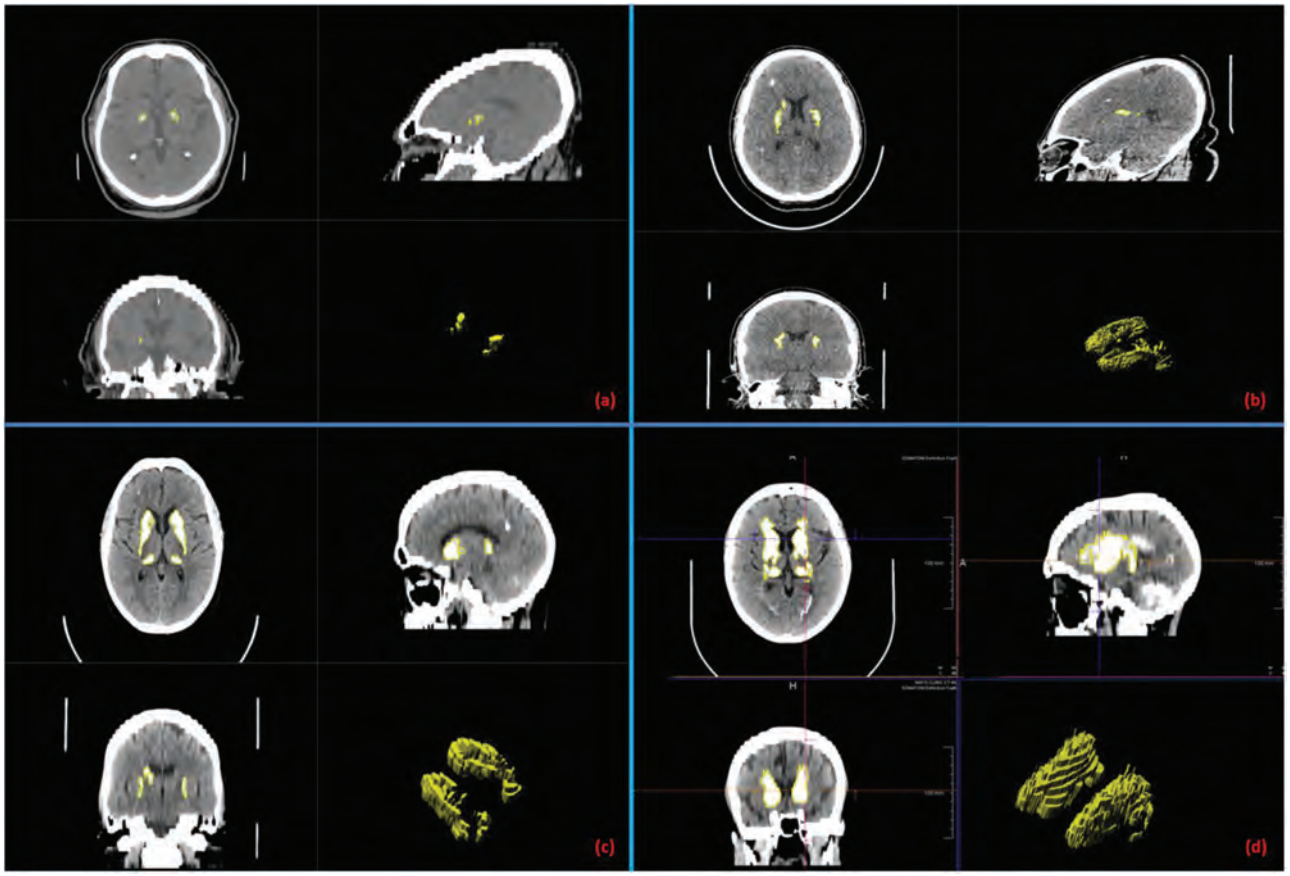

Figure 2. Examples of BGC volume semiquantitation in 4 representative patients with chronic hypoparathyroidism. Different volumes of calcification are shown; 3D reconstruction images are illustrated in each bottom right quadrant. (A) Postsurgical patient with BGC volume 0.76 mL. (B) Postsurgical patient with volume 3.57 mL. (C) Nonsurgical patient with volume 16.43 mL. (D) Nonsurgical patient with volume 42.93 mL.

Table 6. Correlations of BGC volume and density with clinical parameters in hypoparathyroidism patients

	Volume of calcification	Density of calcification (HU value)
Volume of calcification	—	**ρ = 0.842, *P* < 0.001, n = 26**
Density of calcification (HU value)	**ρ = 0.842, *P* < 0.001, n = 26**	—
Age at head CT	ρ = –0.320, *P* = 0.065, n = 34	ρ = 0.201, *P* = 0.325, n = 26
Age of diagnosis of hypoparathyroidism	**ρ = –0.463, *P* = 0.009, n = 31**	ρ = –0.105, *P* = 0.626, n = 24
Disease duration at head CT	ρ = 0.348, *P* = 0.055, n = 31	ρ = 0.267, *P* = 0.208, n = 24
Serum calcium	**ρ = -0.431, *P* = 0.025, n = 27**	ρ = –0.165, *P* = 0.500, n = 19
Serum phosphate	ρ = 0.324, *P* = 0.093, n = 28	ρ = 0.335, *P* = 0.148, n = 20
Serum creatinine	**ρ = 0.416, *P* = 0.018, n = 26**	ρ = 0.393, *P* = 0.078, n = 21
Calcium × phosphate product	ρ = 0.290, *P* = 0.169, n = 24	ρ = 0.289, *P* = 0.260, n = 17
Calcium/phosphate ratio	ρ = –0.389, *P* = 0.060, n = 24	ρ = -0.319, *P* = 0.213, n = 17
25-OH Vit. D	ρ = –0.040, *P* = 0.872, n = 19	ρ = 0.114, *P* = 0.685, n = 15
1.25 (OH)2 Vit. D	ρ = –0.137, *P* = 0.689, n = 11	ρ = 0.479, *P* = 0.162, n = 10
PTH Z-score	ρ = 0.033, *P* = 0.879, n = 24	ρ = –0.124, *P* = 0.574, n = 20
PTH closest to CT, Z-score	ρ = –0.368, *P* = 0.077, n = 24	ρ = –0.290, *P* = 0.215, n = 20

All biochemistries are time-weighted averages. ρ = Spearman's coefficient. Significant correlations are in bold.

with rates twice as high in patients over 65 years (12). In a population-based sample of 466 women with mean age of 74 years, BGC was detected in up to 38.7% of the participants by head CT imaging and associated with a variety of age-related vascular abnormalities (20). Controls in our cohort matched for cardiovascular risk factors to patients with chronic hypoparathyroidism developed BGC, but about a third as often as the patients. BGC in these controls

Table 7. Neurologic complications in patients[a] and controls, with or without BGC

	Hypo		Controls		*P*-Value		
	With BGC (n = 36)	Without BGC (n = 106)	With BGC (n = 31)	Without BGC (n = 395)	Hypo (BGC *vs* no BGC)	Controls (BGC *vs* no BGC)	BGC (Hypo vs Controls)
Age at end of study period[b,§]	50 (21.7) (21-95)	64.5 (17.7) (24-100)	71 (18.0) (27-95)	61.5 (20.4) (16-105)	**0.025**	**0.038**	**0.005**
Neurologic diagnoses, n (%)	31 (86.1)	99 (93.4)	27 (87.1)	368 (93.2)	0.181	0.267	1.000
Parkinsonism, n (%)	2 (5.6)	4 (3.8)	1 (3.2)	18 (4.6)	0.643	1.000	1.000
Tremor, n (%)	3 (8.3)	15 (14.2)	1 (3.2)	46 (11.6)	0.563	0.231	0.618
Seizures, n (%)	6 (16.7)	14 (13.2)	4 (12.9)	47 (11.9)	0.589	0.777	0.742
Ataxia/lack of coordination, n (%)	12 (33.3)	25 (23.6)	9 (29.0)	118 (29.9)	0.276	1.000	0.795
Cognitive impairment or dementia, n (%)	8 (22.2)	15 (14.2)	9 (29.0)	70 (17.7)	0.297	0.147	0.581
Cerebrovascular disease (stroke or TIA), n (%)	11 (30.6)	33 (31.1)	11 (35.5)	115 (29.1)	1.000	0.540	0.795
Headache, n (%)	13 (36.1)	52 (49.1)	12 (38.7)	201 (50.9)	0.245	0.263	1.000
Memory loss, n (%)	2 (5.6)	14 (13.2)	1 (3.2)	43 (10.9)	0.359	0.232	1.000
Sleep disorders, n (%)	15 (41.6)	47 (44.3)	10 (32.3)	143 (36.2)	0.847	0.703	0.459
Musculoskeletal symptoms, n (%)	12 (33.3)	35 (33.0)	10 (32.3)	114 (28.9)	1.000	0.685	1.000

Significant correlations are in bold.

[§]Median (SD), (min-max).

Abbreviations: Hypo, hypoparathyroidism; TIA, transient ischemic attack.

[a]Number of patients receiving the neurological diagnosis at least once by the end of follow-up (July 9, 2020 or death).

[b]Alive patients only.

was mostly in a punctate distribution rather than involving the globus pallidus and the remainder of the bilateral basal ganglia. Our control group was not necessarily representative of the general population, as it may have included patients with more pronounced neurological symptoms, increased cardiovascular risk factors, or greater alcohol intake than the general population. These conditions and their complications are frequent reasons for performing head CT scans in clinical practice. We also selected hypoparathyroidism patients with a head CT scan, and this may have introduced bias because these patients might have been more prone to develop neurologic symptoms and may have had less-well controlled disease than other patients.

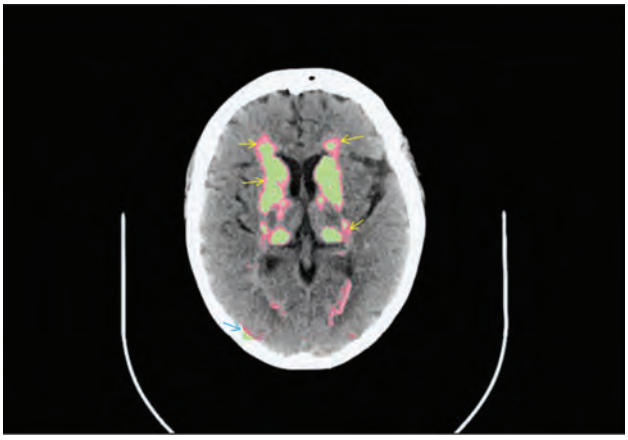

Figure 3. Different densities of calcification. The outer rim corresponds to a range of HU densities between 55 and 100 HU, while the inner background corresponds to densities greater than 100 HU, similar to bone, as shown in the small triangle in the bottom left.

Prevalence of BGC in chronic hypoparathyroidism may vary with the etiology of the hypoparathyroidism. Series of postsurgical hypoparathyroidism cases are usually small and have shorter disease duration and follow-up and therefore may miss BGC development and, consequently, give lower prevalence estimates. Raue et al (21) reported a case series of 25 patients with autosomal dominant hypocalcemia caused by activating mutations of the calcium-sensing receptor with BGC prevalence of 36%. Forman et al (22) reported one of the first series of postsurgical hypoparathyroidism that evaluated brain morphology by CT imaging and found that 5 of 9 (55.6%) patients had BGC. Patients in this series had hypoparathyroidism for a minimum of 8 years prior to detection of BGC. Lorente-Poch et al (23) recently demonstrated a 4-fold increase in BGC in a small cohort of 29 patients with postsurgical chronic hypoparathyroidism.

Patients with BGC in our cohort had biochemistries similar to those without BGC, except that serum calcium and the serum calcium/phosphate ratio were lower compared to patients without BGC or controls. We did not find BGC to correlate with serum phosphate or increased calcium × phosphate product. Patients with BGC had a median time-weighted calcium × phosphate product of 38.1 ± 6.8 mg^2/dL^2, with a range of 28 to 50.8 mg^2/dL^2, well below the threshold of 55 mg^2/dL^2 recommended for prevention of vascular and soft tissue calcification in patients with CKD. At least 1 episode of calcium × phosphate product >55 mg^2/dL^2 occurred in 11.3% of patients with available biochemistries during the preceding 10-year interval, but there was no difference in prevalence of BGC between those with or without such episodes (5/13 *vs*

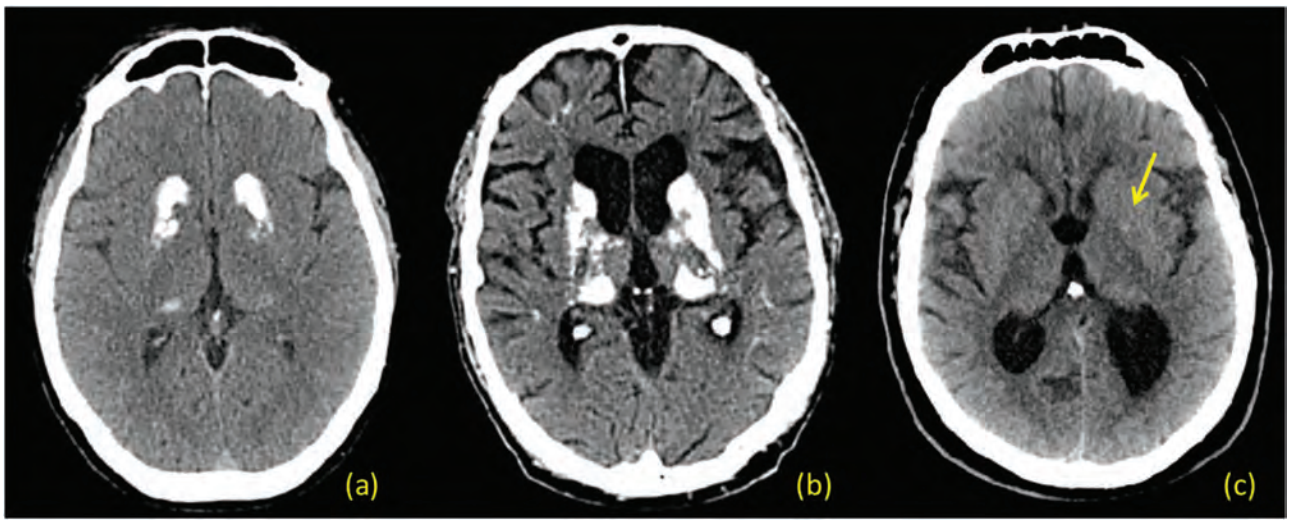

Figure 4. BGC on head CT scans. (A) Male, 53 years old, with familial hypoparathyroidism diagnosed at 7 years of age. (B) Male, 69 years old, with postthyroidectomy hypoparathyroidism since age 26. (C) 68-year-old male with hypertension, diabetes, and dyslipidemia with benign mineralization of the basal ganglia bilaterally, greater on the left (arrow).

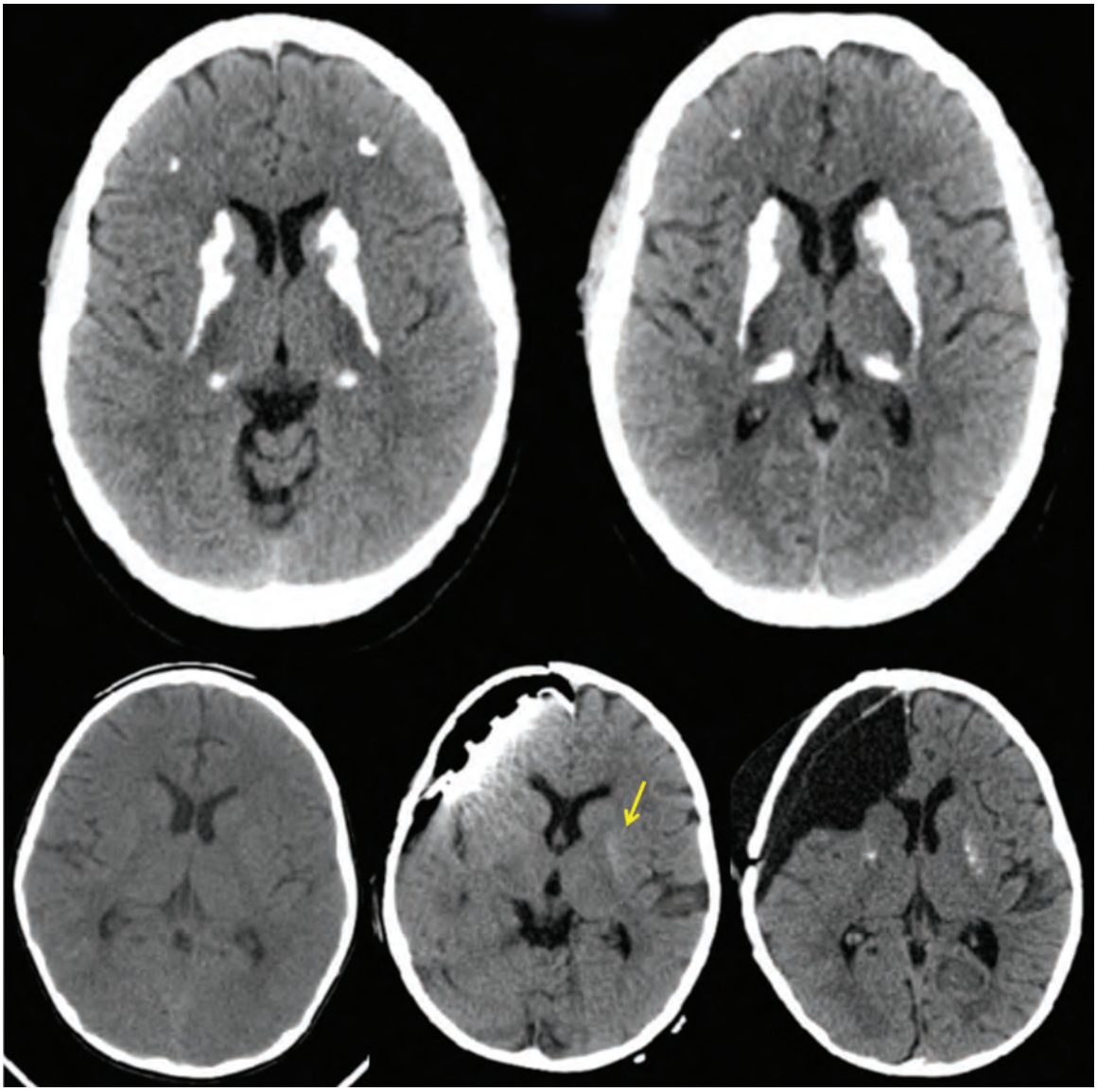

Figure 5. The upper 2 panels show apparent stability of BGC over 11 years in a 59-year-old patient with familial hypoparathyroidism. The 3 bottom panels show the onset of basal ganglia calcification in a 25-year-old patient with autoimmune hypoparathyroidism and lobectomy due to a brain tumor who had three head CT scans performed over 13 years.

21/102, $P = 0.147$). Goswami et al (16) found the mean calcium × phosphate product in patients with progression of BGC was 39.9 mg^2/dL^2, compared to 34.5 mg^2/dL^2 in those who remained stable.

Goswami et al (16) reported that baseline serum calcium was lower in patients with idiopathic hypoparathyroidism with BGC compared to those without ($P = 0.04$) but not associated with progression, whereas serum phosphate was higher in patients with BGC progression. Multiple logistic regression analysis showed that a decreased calcium/phosphorus ratio, but not serum phosphate, was independently associated with BGC progression, as found in our cohort. Even though serum phosphate was increased in our patients with BGC compared to controls with BGC, we found no correlation between serum phosphate and BGC. The median time-weighted calcium/phosphate ratio in our patients with BGC was lower at 1.83 ± 0.52, compared to 2.13 ± 0.47 in patients without BGC, similar to what Goswami et al (16) reported. Nevertheless, the calcium/phosphate ratio did not correlate with BGC volume by semi-quantitative analysis. Instead, low serum calcium correlated with both the presence and volume of calcification.

Absolute or relative absence of PTH may have important effects on development of BGC in the setting of low serum calcium level. Both PTH receptor 1 and 2 (PTHR2) messenger RNA have been detected in human caudate nuclei and the gray matter, with PTHR2 protein confirmed by Western blot (24), supporting a possible role

for physiological action of PTH in the brain. PTHR2 is less expressed in the caudate nucleus compared to the gray matter. However, it has not yet been demonstrated that PTH can easily cross the blood-brain barrier (25); therefore, the magnitude of PTH effect on these receptors is still unknown. PTHR2 might be protective against calcification. PTH stimulated calcium uptake in cultured rat striatal cells in both resting and depolarized states (26), and carbonic anhydrase II was responsive to PTH signaling in the basal ganglia (16,27). These observations suggest that PTH might prevent BGC by different mechanisms, possibly acting through variable expression of PTH receptors.

It has been observed that patients with late-stage CKD and markedly increased PTH levels typically do not develop BGC, whereas patients with chronic hypoparathyroidism on renal replacement therapy may develop extensive basal ganglia and cortical calcification (28). In the small cohort of 25 subjects with autosomal dominant hypocalcemia type 1 previously mentioned, it was observed that only 4 patients with normal PTH levels had BGC, compared to about half the patients with reduced PTH (21). We did not find lower time-weighted PTH levels in our patients with BGC than in those without.

The expression of osteogenic molecules in caudate nuclei suggests that BGC may develop in some cases by mechanisms similar to those of bone mineralization. Goswami et al (24) showed that the caudate nuclei are able to express messenger RNA of RUNX2, bone morphogenetic proteins 2 and 4, osteonectin, osteopontin, osteocalcin, vitamin D receptor, and carbonic anhydrase II. These findings and the previous report of lamellar deposition of hydroxyapatite in basal ganglia (11) suggest that an active osteogenic process may occur in basal ganglia.

Patients with chronic hypoparathyroidism with BGC typically have symmetric bilateral dense calcification affecting much if not all of the basal ganglia. In comparison, BGC due to normal aging is usually small, faint, asymmetric, and limited to the globus pallidus (12). Goswami et al (16) assessed the extent of calcification within the basal ganglia of patients with idiopathic hypoparathyroidism. The globus pallidus (69%), putamen (56%), and caudate nucleus (55%) were found to be most commonly affected, with calcification of the gray-white matter junction (40%), cerebellar parenchyma (32%), dentate nucleus (24%), and thalamus (24%) also present. Choroid plexus calcification (57%) was more common in those with baseline BGC and in those with progression. Our study showed a similar pattern of distribution.

It remains unclear as to why the globus pallidus appears to be the most commonly affected site in patients with BGC, but several hypotheses have been proposed to explain this. The globus pallidus apparently has greater vascularity and a higher metabolic rate than other basal ganglia, and it develops calcifications more frequently during carbon monoxide poisoning or anoxia (29,30). However, in these circumstances, calcification develops rapidly over several days to weeks. Other proposed causes include higher neuronal excitability, shorter distance from the ventricular space, or expression of RUNX2 (16).

Periventricular spaces may calcify due to alterations in exchange of calcium and phosphate between the cerebrospinal fluid (CSF) and cerebral parenchyma. Physiologically low calcium may inhibit the choroid plexus calcium-ATPase pump to prevent CSF calcium from leaving the ventricles and diffusing into the cerebral capillaries, thus maintaining stable CSF calcium that favors calcium retention within neural tissue (31). Although phosphate transporters typically remove phosphate from the CSF, these may not be fully functioning in chronic hypoparathyroidism as they are at least partly dependent on PTH (16). The calcium × phosphate product in CSF may therefore be higher than in peripheral blood, resulting in calcification preferentially in periventricular sites like the basal ganglia, which are in close proximity to the choroid plexus (16).

A population-based study of hospitalized postsurgical patients showed increased risk of seizures (32). Our patients may have been less severely affected than hospitalized postsurgical patients, as we did not find increased seizures or Parkinsonism. It is not yet clear whether BGC directly impacts quality of life or symptoms commonly experienced by patients with chronic hypoparathyroidism, such as fatigue, "brain fog," or muscle weakness (33). Head CT scans in our study were obtained for the usual clinical indications. Because neurological symptoms such as Parkinsonism or cerebellar ataxia are relatively uncommon in chronic hypoparathyroidism (5), it is difficult to obtain an accurate clinical understanding of development of BGC and to determine whether symptoms precede onset of BGC, rather than developing as a manifestation of BGC. Goswami et al (16) concluded that duration of hypocalcemic symptoms or seizures was independently associated with development of BGC in idiopathic hypoparathyroidism. As yet, there are no prospective studies that have investigated quality of life in hypoparathyroid patients with or without BGC. Cognitive dysfunction may be worsened by hypoparathyroidism (34) and directly associated with longer duration of disease or higher calcium × phosphate product or serum calcium due to high-dose calcium supplementation (35).

Ten patients in our cohort had serial head CT scans over up to 13 years, and BGC volume semiquantitation showed mild progression in some but not others. Most patients presented with fully developed BGC on their index head CT

scan and did not progress over time. This may indicate that BGC develops fairly rapidly in nonsurgical hypoparathyroidism, especially in those with low serum calcium or low calcium/phosphate ratio. Persistence of BGC after diagnosis, despite conventional medical management, appears to be common in chronic hypoparathyroidism. By contrast, patients without chronic hypoparathyroidism who developed mostly punctate BCG seemed to progress more slowly over years and to be diagnosed most commonly later in life, suggesting a different underlying pathophysiology, possibly associated with aging or ischemia.

Patients and controls surprisingly had similar frequencies of neurological diagnoses. The ages of the patients with or without BGC were significantly different, suggesting that neurological complications may develop at a younger age in patients with BGC. These findings also imply that patients might be less likely to develop these complications as they become older. Most patients with chronic hypoparathyroidism were postsurgical, with significantly lower volume of calcification compared to those with nonsurgical hypoparathyroidism. The clinical impact of BGC on neurological diagnoses in patients with nonsurgical hypoparathyroidism remains to be fully elucidated.

Strengths of this study include a relatively large cohort of 142 patients with chronic hypoparathyroidism of different etiologies who had head CT scans for clinical indications available over 20 years of follow-up to assess the prevalence of BGC. All outpatient and inpatient medical records, biochemistries, radiological images, and pharmacy records for both patients and age- and sex-matched controls were available for review in a single institutional electronic health record. Limitations of the study include the retrospective nature of the study, real-world data collection in patients followed clinically, relatively small numbers of subsets of patients, and single institutional referral bias.

Summary and Conclusions

Chronic hypoparathyroidism was associated with BGC in 25.4% of 142 adult patients, compared to 7% of healthy controls, when followed over a median of 17 years after diagnosis. Nonsurgical patients were about 5 times more frequently affected with BGC than postsurgical patients. Compared to age- and sex-matched controls with BGC, BGC developed in patients at a younger age. Serum and urine biochemistries were as expected for conventionally managed patients with this disorder. Low serum calcium and low serum calcium/phosphate ratio correlated with BGC in patients but not serum phosphate or calcium × phosphate product. Patients with BGC were not diagnosed more frequently with neurological diagnoses than age- and sex-matched controls, but further studies are needed to investigate neurological diagnoses as primary endpoints. Semiquantitative imaging analysis showed that volume, distribution, and mass of BGC in patients with postsurgical and nonsurgical hypoparathyroidism varied widely, with nonsurgical patients having a greater burden of BGC. Low serum calcium and decreased renal function were associated with volume of calcification. Prospective studies are needed regarding the mechanism(s) of causation of BGC and whether adjunctive treatment with PTH or PTH analogues may prevent or slow development of BGC.

Additional Information

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Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repositories listed in references.

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