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Infants With Congenital Adrenal Hyperplasia Are at Risk for Hypercalcemia, Hypercalciuria, and Nephrocalcinosis

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Context: Hypercalcemia is reported as a rare finding in adrenal insufficiency, but is not well described in congenital adrenal hyperplasia (CAH).

Methods: A retrospective chart review was conducted of patients with CAH diagnosed before the age of 2 years who had at least one recorded serum calcium measurement. Data from birth to 6 years of age were reviewed.

Results: Of the 40 patients who met inclusion criteria, 33 (82.5%) had at least one elevated calcium concentration and 21 (53%) had two or more elevated calcium concentrations. Of the 126 elevated serum calcium concentrations, the median was 10.9 mg/dL (range, 10.6 to 14.2 mg/dL). Median age at the last elevated calcium measurement was 5 months (range, 0.3 to 46 months). Serum calcium concentration was inversely related to age ($r = -0.124$; $P = 0.004$). Overall, calcium level positively correlated with 17-hydroxyprogesterone (17OHP) concentration ($r = 0.170$; $P = 0.003$), and this remained significant after adjusting for age ($P < 0.05$). However, patients had hypercalcemia with both high and low 17OHP concentrations. Serum calcium concentration also was positively related to glucocorticoid ($r = 0.196$; $P = 0.012$) and fludrocortisone ($r = 0.229$; $P = 0.003$) doses, and remained significant after age adjustment. Only seven patients were evaluated for hypercalciuria. Of these, six had at least one period of documented hypercalciuria. Three patients had nephrocalcinosis on renal ultrasound.

Conclusion: Children with CAH are at risk for developing hypercalcemia, hypercalciuria, and nephrocalcinosis. Further studies are needed to determine the broader prevalence and the etiology of hypercalcemia in CAH.

Freeform/Key Words: congenital adrenal hyperplasia, adrenal insufficiency, hypercalcemia, hypercalciuria, nephrocalcinosis

Congenital adrenal hyperplasia (CAH) describes a group of rare, autosomal recessive disorders of impaired cortisol synthesis. Approximately 95% of CAH occurs because mutations in the *CYP21A2* gene, in turn, cause reduced 21-hydroxylase enzymatic activity and impaired adrenal cortisol production [1]. These defects ultimately lead to increased adrenal androgen synthesis and female virilization. Infants with the classic form of CAH can also have mineralocorticoid deficiency and may present with a life-threatening, salt-wasting crisis and hypovolemia. Hyponatremia and hyperkalemia are typically seen at presentation or during adrenal crises and resolve with treatment.

Abbreviations: 17OHP, 17-hydroxyprogesterone; AI, adrenal insufficiency; CAH, congenital adrenal hyperplasia.

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Hypercalcemia is relatively uncommon in children but can have serious clinical consequences, including development of nephrocalcinosis and acute kidney injury [2]. Adrenal insufficiency (AI) is a rare cause of hypercalcemia, although the mechanism for hypercalcemia is uncertain and a number of case reports describe resolution of hypercalcemia after steroid replacement [3–8]. The most common cause of AI in infancy is CAH [9]. We have observed the anecdotal occurrence of hypercalcemia in children with CAH; however, its prevalence has not been established. To our knowledge, only one study reported classic CAH as a cause of hypercalcemia in two children [2] and no studies describe hypercalciuria or nephrocalcinosis.

The aim of this study was to determine the prevalence of hypercalcemia, hypercalciuria, and nephrocalcinosis among infants and young children with CAH at our tertiary children's hospital. We also sought to explore the pathogenesis of these comorbidities in CAH.

1. Subjects and Methods

This retrospective cohort study was approved by the Indiana University School of Medicine Institutional Review Board. Patient records at Riley Hospital for Children, a tertiary care hospital in Indianapolis, Indiana, were reviewed for all patients who were billed by the endocrine section using the International Classification of Diseases, Ninth Revision, code for adrenogenital disorders (255.2) from January 1994 to March 2014. Patients were included in the study if they were diagnosed with CAH before the age of 2 years. Data were extracted from patient records up to 6 years of age based on observations of high calcium concentrations only during this time. Patients were excluded after initial chart review if they did not have CAH, if they had nonclassic CAH, if they did not have any records in the hospital system from the first 2 years of life, if they did not have at least one calcium measurement documented, and if their records were completely unavailable. Because our hospital is a national referral center for genitoplasty procedures, some patients with CAH only had data available from their hospitalization for surgery and were excluded.

Recorded data included sex, race, CAH subtype (salt wasting or simple virilizing), age at diagnosis of CAH, height, weight, body surface area, medications and doses, clinical laboratory testing [*i.e.*, basic metabolic profile and blood concentrations of calcium, phosphorus, alkaline phosphorus, vitamin D, parathyroid hormone, 17-hydroxyprogesterone (17OHP), androstenedione, and testosterone; plasma renin activity; and urine concentrations of calcium and creatinine], and renal imaging studies, if available. Other comorbidities, such as documented hypertension, were also recorded. Hypercalcemia was defined as serum calcium concentration >10.5 mg/dL (>2.63 mmol/L), and hypercalciuria was defined according to published normative data for children based on age [10].

The values of 17OHP and age were logarithmically transformed (log10) for analysis. The relationships between variables were tested using Pearson correlations and linear regression. This was adjusted for age and for multiple measurements in individual subjects. Statistical significance was set at $P < 0.05$. Analysis used SPSS statistics version 24 (IBM).

2. Results

A diagnosis code search identified 248 patients having the International Classification of Diseases, Ninth Revision code 255.2 from January 1994 through March 2014 who were evaluated by a pediatric endocrinologist at Riley Hospital for Children or at a satellite clinic. Of these, paper or electronic records were unavailable for 35 patients. An additional 173 patient charts were reviewed and excluded, leaving 40 patients who met the inclusion criteria (Fig 1). The largest groups excluded comprised infants with classic CAH seen at our institution for genitoplasty only (not followed longitudinally) and patients who were found not to have CAH based on chart review.

Patient characteristics are outlined in Table 1. Most patients were white (73%) or Hispanic (23%). All patients were diagnosed with classic (*i.e.*, 21-hydroxylase deficiency) CAH based on clinical presentation. Genetic testing results were available to confirm the diagnosis of 21-hydroxylase deficiency in eight patients. Most (90%) were reported to have salt-wasting CAH

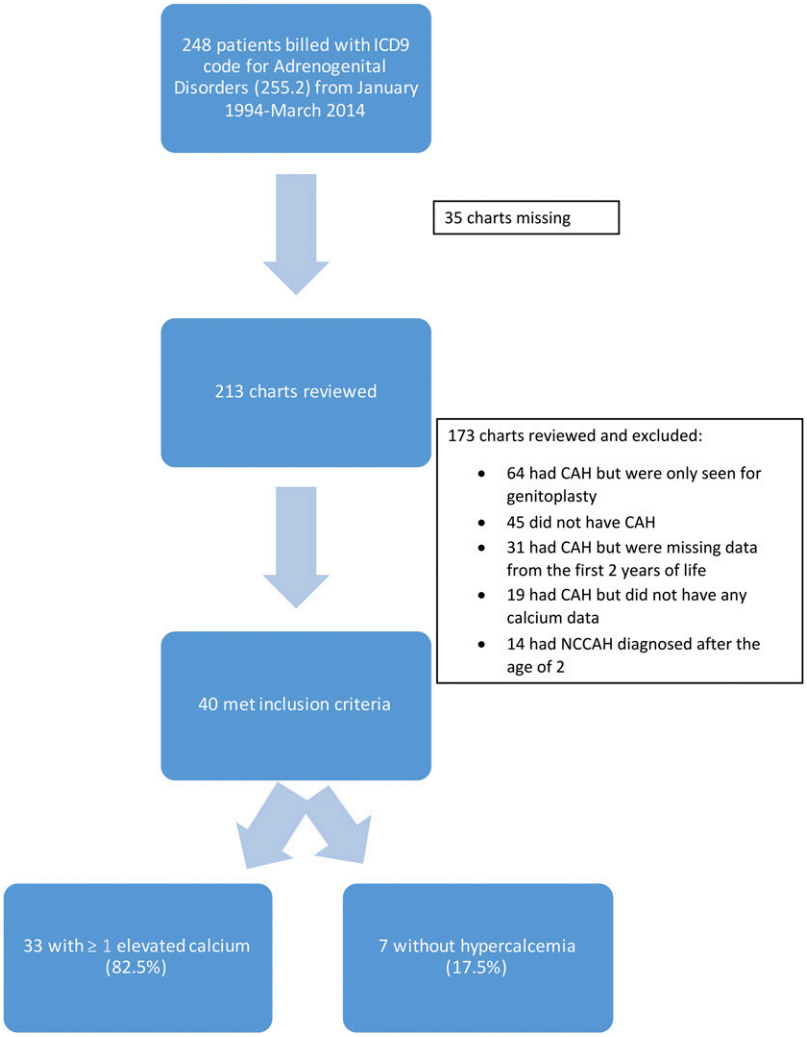

Figure 1. Flow diagram of patient selection. ICD9, International Classification of Diseases, Ninth Revision; NCCAH, nonclassic congenital adrenal hyperplasia.

in their clinical records. Thirty-three patients (82.5%) had at least one elevated serum calcium concentration. Of those, 12 had only one elevated serum calcium measurement recorded and the remaining 21 had more than one recorded high serum calcium level. For patients with calcium assessments, serum calcium was measured a median of 13 times (range, 1 to 48) during the first 6 years of life, most often as part of a standard basic metabolic profile either with routine screening laboratories or during hospitalization. Of the 126 elevated calcium measurements, the median calcium concentration was 10.9 mg/dL (2.73 mmol/L) with a range of 10.6 to 14.2 mg/dL (2.65 to 3.55 mmol/L). Median age at the last elevated calcium concentration was 5 months (range, 0.3 to 46 months). Overall, serum calcium concentration was inversely related to age ($r = -0.124$; $P = 0.004$).

Table 1. Patient Characteristics

	All Patients	Hypercalcemia	Hypercalciuria	Nephrocalcinosis
No. (% of total)	40 (100)	33 (84)	6 (15)	3 (8)[a]
Male sex, %	50	52	50	100
Salt-wasting CAH subtype, %	90	91	83	100

[a]Twelve of the total of 40 patients had at least one renal ultrasound assessment.

Patients were being treated with glucocorticoids at the time of measurement in 83% of the instances of hypercalcemia and with mineralocorticoid in 79%. The median 17OHP concentration was 2775 ng/dL (84 nmol/L) with range of 35 to 229,000 ng/dL at the time of hypercalcemia. As seen in Fig 2, there was a slight positive correlation between the 17OHP concentration and simultaneous serum calcium concentration (r = 0.170; P = 0.003), which decreased but remained significant after adjusting for age (r = 0.132; $P < 0.05$). However, the patient with the highest serum calcium level had hypercalcemia both with very elevated [8201 ng/dL (248 nmol/L)] and very low [41 ng/dL (1.2 nmol/L)] 17OHP concentration [calcium concentrations of of 12.4 and 14.2 mg/dL (3.1 and 3.6 mmol/L), respectively]. In addition, the patient with very low serum calcium [6.9 mg/dL (1.7 mmol/L)] had elevated 17OHP concentration [12,300 ng/dL (373 nmol/L)].

Serum calcium concentration also was positively related to doses of glucocorticoid (r = 0.196; P = 0.012) and fludrocortisone (r = 0.229; P = 0.003). After age adjustment, calcium concentration remained significantly related to glucocorticoid (r = 0.185; P = 0.018) and fludrocortisone (r = 0.204; P = 0.009) doses.

Urine calcium was assessed only in seven patients (Table 2). Of these, at least one period of hypercalciuria was documented by urine calcium to creatinine ratio on a random urine sample in six patients. Parathyroid hormone was measured in only five of the 40 patients, all of whom had hypercalciuria, and ranged from undetectable (with a simultaneous calcium concentration of 13.9 mg/dL) to 46 pg/mL (with a simultaneous normal calcium concentration of 10.4 mg/dL). Vitamin D levels measured in three patients ranged from 29 to 43.9 ng/mL. Two of these patients had hypercalciuria, and one had normal serum calcium measurements but demonstrated poor growth. Four patients (12%) with hypercalcemia also had hypertension. Twelve patients had renal ultrasound scans performed. Of those, three (25%) had documented nephrocalcinosis, all of whom had hypertension. One patient had hypertension with a normal renal ultrasound. Two patients had transient mild elevations in creatinine at the time of diagnosis of CAH associated with hypercalcemia. However, no patient developed chronic kidney failure. Details of the patients with hypercalciuria and/or nephrocalcinosis are outlined in Table 2.

Other than intravenous fluids for admitted patients, along with appropriate glucocorticoid and mineralocorticoid treatment, patients did not undergo specific medical treatment of

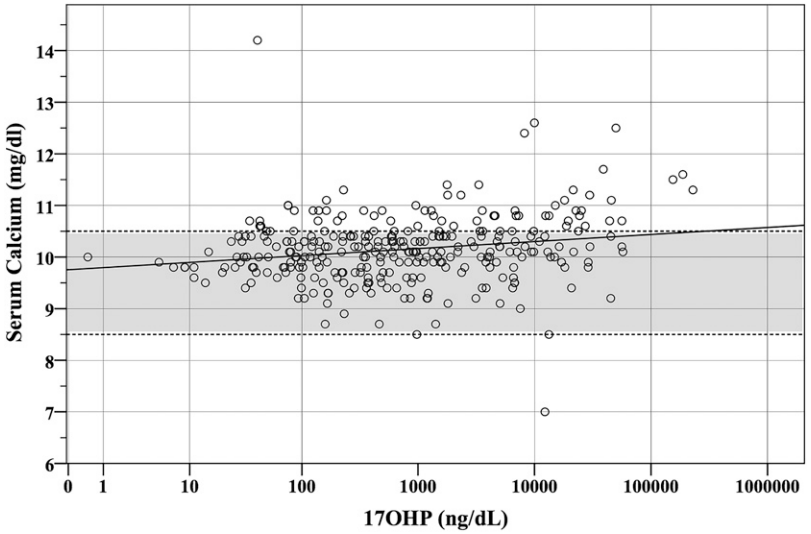

Figure 2. Comparison of 304 simultaneous measurements of 17OHP (log-scale) and serum calcium concentrations. Multiple data points are plotted for each patient (range, 0 to 25 per patient). Normal calcium range is highlighted in the gray box. There was a positive correlation (r = 0.170; P = 0.003), which remained significant after adjusting for age (r = 0.132; P = 0.024). To convert calcium mg/dL to mmol/L, multiply by 0.25. To convert 17OHP ng/dL to nmol/L, multiply by 0.0303.

Table 2. Patients With Hypercalciuria and/or Nephrocalcinosis

	Patient No.						
	1	**2**	**3**	**4**	**5**	**6[a]**	**7[a]**
Sex	F	M	M	M	M	F	F
Highest Ca level, mg/dL[b]	11.0	14.2	10.9	11.3	12.5	11.5	11.6
Mean Ca level, mg/dL[b]	10.2	12.2	10.3	10.1	10.4	10.5	10.3
Total no. of Ca measurements	26	15	26	48	22	15	14
Ca range (min–max)[b]	9.5–11	10.6–14.2	9.2–10.9	9.5–11.3	9.5–12.5	9.7–11.5	9.8–11.6
Age at first elevated Ca measurement, d	15	11	17	7	8	16	16
Age at last elevated Ca measurement, mo	22	Unresolved at 5	0.3	1	1	26	21
Hypercalciuria	Yes	Yes	Yes	Yes	No	Yes	Yes
Laboratory testing performed[c]							
Ca, mg/dL[b]	10	13.9	—	—	11.2	10.6	10.4
Phos, mg/dL[b]	5.2	4.4	—	—	9	—	—
PTH, pg/mL[b]	25	<1	—	—	—	31	46
25D, ng/mL[b]	29	43.9	—	—	—	—	—
1,25D, pg/mL[b]	69	58	—	—	—	—	—
Ur Ca/Cr	0.8 at 9 mo	2 at 5 mo	0.55 at 11 mo	0.83 at 2 mo	0.56 at 5 mo[d]	0.73 at 2 y	0.81 at 2 y
Nephrocalcinosis	No	Yes	No imaging	Yes	Yes	No imaging	No imaging
HTN	No	Yes	No	Yes	Yes	No	No

Abbreviations: —, no data; 1,25D, calcitriol; 25D: calcidiol; Ca, calcium; HTN, hypertension; max, maximum; min, minimum; Phos, phosphorus; PTH, parathyroid hormone; Ur Ca/Cr, urine calcium to creatinine ratio.
[a]Patients are twin sisters.
[b]Conversion factors for SI units: Ca, multiply by 0.25 to get mmol/L; Phos, multiply by 0.323 to get mmol/L; PTH, multiply by 1 to get ng/L; 25D, multiply by 2.496 to get nmol/L; 1,25D, multiply by 2.6 to get pmol/L.
[c]Serum samples drawn simultaneously, not at the time of hypercalcemia, for patients 1 and 7.
[d]Patient was treated for presumed hypercalciuria based on nephrocalcinosis and Ur Ca/Cr ratio >75th percentile for age before treatment.

hypercalcemia. No patient received bisphosphonates or calcitonin. One patient (patient 2 in Table 2) started a low-calcium diet but remained hypercalcemic at the end of the study period.

3. Discussion

In this study, most children <6 years of age with CAH had at least one episode of hypercalcemia and approximately half of CAH patients (21 of 40 with calcium measurements) had persistent elevations of serum calcium across at least two measurements. Hypercalcemia was transient in most children and resolved over time without requiring specific intervention. However, one patient remained hypercalcemic at the end the study period despite starting a low-calcium diet. Our results suggest that children with CAH who are noted to have hypercalcemia are also at risk for developing hypercalciuria, nephrocalcinosis, and hypertension. Unfortunately, hypercalcemia on laboratory testing was frequently unrecognized and most patients did not receive further testing for causes or complications of hypercalcemia. Thus, the frequencies of hypercalciuria and nephrocalcinosis are uncertain because they may have been undetected in some patients.

Patients with CAH had more hypercalcemia than the children between 0 and 5 years of age undergoing laboratory testing in our children's hospital (approximately 8.2% over a recent 1 month time period). However, because healthy children do not routinely undergo laboratory testing, this would not represent a true healthy control group.

The mechanism of hypercalcemia in AI is uncertain. Proposed mechanisms have included increased bone resorption (though a bone biopsy study actually demonstrated low bone turnover despite elevated bone resorption markers) [11]; increased gut absorption (which some authors have suggested also does not explain the hypercalcemia in AI); or decreased

glomerular filtration rate during adrenal crisis, leading to enhanced reabsorption of calcium [8, 12–14]. Although AI may be a contributing factor for developing hypercalcemia, most instances of elevated calcium levels occurred during glucocorticoid therapy. Interestingly, serum calcium concentration was found to positively correlate with 17OHP concentration. 17OHP is often used as a marker of adrenal control in children with CAH. However, hypercalcemia was also noted to occur during both high and low 17OHP concentrations (sometimes in the same patient), suggesting that perhaps mechanisms other than AI are also involved. Our finding that higher doses of glucocorticoid were also associated with higher calcium concentrations is unexpected, though this might be reflective of higher doses prescribed in the setting of acute adrenal crisis or medication noncompliance.

Hypercalcemia in children with CAH has been anecdotally recognized, but to date, only one other retrospective study, to our knowledge, has described hypercalcemia in two children with CAH [2]. This study of >61,000 children was conducted to determine the frequency and causes of childhood hypercalcemia. The authors reported hypercalcemia in only 203 children (0.33%) with an overall frequency of sustained hypercalcemia (on two or more measurements) of one per 500 children. Two of these cases of sustained hypercalcemia occurred in children with CAH and were attributed to AI [2].

Interestingly, in our study, hypercalcemia associated with CAH appeared to occur primarily in infancy and toddlerhood. This observation is consistent with the previous finding that 66% of all sustained hypercalcemia occurred in children <1 year of age vs 13.7% in children ages 1 to 5 years and 7.6% in adolescents [2]. In addition, children with CAH have the most admissions for medical problems, including adrenal crisis, during the first year of life [15]. Consequently, infants and young children with CAH may be at greater risk for hypercalcemia. This may be due, in part, to increased difficulties during phlebotomy in children, resulting in prolonged tourniquet time. Prolonged tourniquet time has been shown in other studies to cause mild hypercalcemia due to artifact from hemoconcentration [16, 17]. This may be the reason some laboratories generate slightly higher normal ranges for serum calcium in very young children. Although this effect might explain some of the mild hypercalcemia seen in our study, two-thirds of the hypercalcemic patients had at least one serum calcium measurement ≥11 mg/dL (≥2.75 mmol/L).

Mechanisms for hypercalciuria and nephrocalcinosis in CAH are also unclear because AI has not been reported to be a specific cause of renal pathology. It is possible that excessive salt intake or mineralocorticoid treatment may play a role. High dietary salt ingestion has been found to be associated with hypercalciuria and stone formation [18–21]. Calcium handling is highly dependent on sodium in the renal proximal tubule. When presented with a salt load, the reabsorption of sodium is diminished, as well as that of calcium, which is passively coupled with sodium and water [18]. It has been estimated that for every 100 mEq/dL increment of sodium excretion in the urine, there is a 40 mg/dL rise in calcium excretion [22].

Sodium chloride supplementation is part of the standard therapy for children with classic CAH and salt wasting, with a recommended total dose of 17 to 34 mEq/d divided throughout the day [1]. Interestingly, one patient in our study who developed hypercalciuria had simple virilizing CAH and was never treated with sodium chloride (but was receiving fludrocortisone). Doses of sodium chloride in the remaining five patients with hypercalciuria in our study were within the recommended range for all but one patient, who was recorded as taking 15 mEq four times daily (60 mEq/d). However, it is possible that this dose was recorded incorrectly in the chart, because it is far outside the range of what is typically prescribed. Although excessive salt load could explain hypercalciuria in these patients with CAH, it does not explain hypercalcemia. An alternate explanation would be that the hypercalciuria may be secondary to hypercalcemia and an increased filtered load of serum calcium.

Nephrocalcinosis refers to calcium deposits in the tubules, tubular epithelium, and/or the interstitial tissue of the kidney, and can result in deterioration of renal function [23]. The biggest known risk factor for developing nephrocalcinosis is hypercalciuria. Of the three patients in our study who had nephrocalcinosis, two had confirmed hypercalciuria with a urine calcium to creatinine ratio >95th percentile for age and one patient had a high-normal urine calcium to creatinine ratio (>75th percentile for age).

Although hypercalciuria likely contributes to the development of nephrocalcinosis in children with CAH, excess mineralocorticoid supplementation might also play a role. There are three case reports of nephrocalcinosis thought to be due to hyperaldosteronism in young men (ages 15, 17, and 22 years) with CAH due to 11β-hydroxylase deficiency [22, 24]. All three cases were undiagnosed in childhood and presented with significant hypertension and hypokalemia. Likewise, nephrocalcinosis and renal cysts have been reported in the setting of apparent mineralocorticoid excess syndrome, which is caused by 11β-hydroxysteroid dehydrogenase deficiency in the kidney [25]. The pathogenesis of nephrocalcinosis due to hyperaldosteronism is unclear; however, chronic hypokalemia resulting in ammonia-mediated renal scarring has been postulated as a prime causal factor [22, 25]. None of the patients in our study were noted to have long-standing hypokalemia and the three who developed nephrocalcinosis were all prescribed fludrocortisone within the recommended dose range of 0.05 to 0.2 mg/d [1]. However, two of these patients did require higher fludrocortisone doses in infancy (up to 0.3 mg/d and 0.4 mg/d) to maintain normal sodium, potassium, and renin concentration, though this was ultimately weaned down to the standard range. Of note, it is not uncommon for infants with CAH to require higher doses of fludrocortisone in infancy; approximately 30% of the patients in this study were taking doses >0.2 mg daily. In addition, anti-inflammatory doses of glucocorticoids have also been associated with the development of nephrocalcinosis, which may be due to increasing the urine calcium and phosphorus excretion [26–28]. However, again, these explanations do not account for the increased serum calcium observed in our study.

There are a number of limitations to our retrospective study, particularly that only a relatively small cohort of patients met our inclusion criteria. A large number of patients were excluded owing to missing data or lack of calcium data. Similarly, few patients had renal imaging or urine studies performed as part of their clinical evaluation. There are also several confounding factors at play that cannot be controlled for in a retrospective study, such as patient compliance with medication. Patients had laboratory data from laboratories all over the state adding laboratory variability, thus our definition of >10.5 mg/dL may have overestimated or underestimated the true frequency of hypercalcemia.

5. Conclusion

This study demonstrates that hypercalcemia is a common finding in young children with classic CAH and may place children at risk for serious renal complications such as hypercalciuria and nephrocalcinosis. Calcium monitoring during routine CAH laboratory testing may be worthwhile in children with CAH, particularly during the first year of life. Recognition of hypercalcemia should be followed by appropriate evaluation to determine etiology and to detect possible hypercalciuria and nephrocalcinosis. Further studies are needed to determine the broader prevalence, etiology, and consequences of hypercalcemia in CAH.

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