Transient Neonatal Hypocalcemia: Presentation and Outcomes

OBJECTIVE: To determine the incidence of moderate-to-severe transient neonatal hypocalcemia in term neonates and to describe the characteristics of affected infants and the outcomes of their management.

METHODS: We reviewed medical records of all term infants <31 days of age who presented to Children's Medical Center Dallas from 2001 to 2009 with hypocalcemia (ionized calcium, 1.00 mmol/L [4.00 mg/dL]).

RESULTS: Seventy-eight infants met criteria. Median (interquartile range) age at admission was 8.0 (7.0–10.0) days, and median duration of admission was 3.0 (2.0–4.0) days. Most infants were male (71.8%) and Hispanic (62.8%). Neonates were generally severely hypocalcemic and hyperphosphatemic. Seventy-five of 78 were hypomagnesemic, and the majority had low or inappropriately normal parathyroid hormone responses. Levels of 25-hydroxyvitamin D were ≤62.4 nmol/L (25 ng/mL) in all 42 infants in whom they were determined. All infants responded to therapy of limited duration with 1 or more of the following: calcium supplements, calcitriol, low phosphorus formula, and magnesium supplementation. Neuroimaging did not affect management decisions in any neonate.

CONCLUSIONS: Moderate-to-severe late-onset neonatal hypocalcemia is more common in Hispanic and male infants, is often a sign of coexistent vitamin D deficiency or deficiency and hypomagnesemia, and is readily managed with therapy of limited duration. Neonates presenting with seizures who are found to be hypocalcemic are unlikely to benefit from neuroimaging evaluations. Pediatrics 2012;129:e1461–e1467
Neonatal hypocalcemia is a potentially life-threatening condition, with reported prevalence varying by gestational age, maternal and infant comorbidities, and perinatal factors. Because of the higher concentrations of calcium in neonates (up to 1.5 mmol/L, compared with 1.12–1.32 mmol/L in older children and adults), neonatal hypocalcemia is often defined as an ionized calcium <1.22 mmol/L. Although sometimes clinically silent, it may present with signs of neuromuscular irritability (ranging from myoclonic jerks to seizures), apnea, cyanosis, and/or cardiac rhythm disturbances.

Hypocalcemia in this age group has various causes, which are commonly differentiated by the time of onset. Early-onset neonatal hypocalcemia is defined as occurring within the first 4 days of life and is usually secondary to an exaggeration of the normal decline in serum calcium levels in the first 1 to 2 days of life. Late-onset neonatal hypocalcemia usually occurs 5 to 10 days after birth, and the differential includes transient hypoparathyroidism, transient parathyroid hormone (PTH) resistance, DiGeorge syndrome, maternal vitamin D deficiency, malabsorption, intake of formula high in phosphorus content, and hypomagnesemia.

There have been few reports regarding infants presenting in acute care settings with seizures or tetany, the etiology of which was later found to be hypocalcemia. In many of these reports, the infants received extensive workups that included cultures of blood, urine, and cerebrospinal fluid; complete blood cell counts; blood chemistries; EEGs; electrocardiograms; and/or neuroradiology imaging studies. To our knowledge, there have been no contemporary large-scale studies describing the diagnosis of hypocalcemia in the neonate, especially when limited to transient hypocalcemia. The largest modern case series of which we are aware described 21 Taiwanese infants diagnosed with late-onset hypocalcemia over the span of 12 years. This report limited detailed discussion to those 5 infants who had a final diagnosis of pseudohypoparathyroidism. In the current study, we aim to determine the incidence of moderate-to-severe neonatal hypocalcemia in term neonates without an identified syndromic, cardiac-associated, or iatrogenic etiology and to describe the characteristics of affected infants and the outcomes of their management at our institution.

METHODS
Charts were reviewed under a protocol approved by the Institutional Review Board at the University of Texas Southwestern Medical Center. To identify infants <31 days of age presenting to our institution between 2001 and 2009 (the beginning date marking the earliest availability of our electronic medical records) with moderate-to-severe hypocalcemia, we searched the billing databases of Children’s Medical Center, Dallas and University of Texas Southwestern Medical Center for the following diagnoses: hypocalcemia (International Classification of Diseases, Ninth Revision codes 275.40, 275.41, and 275.49), hypocalcemia of the newborn (775.4), tetany (781.7), vitamin D deficiency (268.0, 268.2, and 268.9), hypoparathyroidism (252.1), and DiGeorge syndrome (279.11). We defined moderate-to-severe hypocalcemia as ionized calcium <1.00 mmol/L (4 mg/dL) (potentiometric ion-selective electrode methodology, ABL800, radiometer [Westlake, OH]). We collected demographic information, results of biochemical data and investigative studies, and the types and durations of therapies. Levels of 25-hydroxyvitamin D (25(OH)D) were determined by ARUP Laboratories (Salt Lake City, UT) by quantitative chemiluminescent immunoassay (DiaSorin Liaison [DiaSorin Inc, Stillwater, MN]) coefficient of variation 2.9%–12.9%). We defined vitamin D deficiency as 25(OH)D <50 nmol/L (20 ng/mL) per the recent Endocrine Society Clinical Practice Guideline.

Of the 78 neonates was 8.0 (7.0–10.0) days, and the median duration of admission was 3.0 (2.0–4.0) days. Fifty-six were male (71.8%, vs 58.1% of all neonates admitted to the hospital over the same period, P = .02 [χ2 with Yates correction]). Forty-nine (62.8%) were Hispanic (vs 50.8% of all neonates, P = .04 [Fig 1]). Eleven of the 78 neonates were infants of mothers with diabetes. All but 2 of the 78 presented with seizure-like activity that was deemed consistent with tetany in the context of low calcium levels. Of the 2 infants who did not present with tetany, 1 presented with decreased urine output (with normal renal function).
and the other with cold symptoms and a low-grade fever with a negative sepsis evaluation.

**Biochemical Characteristics**

Infants were generally severely hypocalcemic, hyperphosphatemic, and hypomagnesemic with low or inappropriately normal PTH responses (reported if checked before any calcium treatment) (Table 2). Levels of 25(OH)D were ≤62 nmol/L (25 ng/mL) in all 42 infants in whom they were determined, <50 nmol/L (20 ng/mL) in 35, and <30 nmol/L (12 ng/mL) in 10.

Sixty-seven infants were exclusively formula-fed, whereas 8 were both formula-fed and breastfed, and only 3 were exclusively breastfed. There were no associations between the type of feeding and any biochemical parameter, including levels of total calcium, ionized calcium, phosphorus, magnesium, or 25(OH)D (data not shown).

Total and ionized calcium levels were each significantly correlated with both magnesium and PTH levels, but there was no correlation between magnesium and PTH levels themselves (Table 2). There were also no correlations between vitamin D levels and any other biochemical parameters.

**Therapies**

Sixty-nine infants were initially treated with intravenous (IV) calcium. Other therapies prescribed per standard of care at our institution included oral calcium carbonate (in 76 subjects, median dose of 101 mg/kg per day elemental calcium), oral calcitriol (60 subjects, median duration of therapy 1.0 [0.6–1.5] months at a median dose of 0.25 mcg daily [56 of 60 subjects were treated with this dose]), and low-phosphorus formula (Similac PM 60/40, Abbott Nutrition, Columbus, OH) (71 subjects, median duration of therapy 1.8 [1.0–2.5] months). In addition, 55 subjects received treatment with IV, intramuscular, and/or oral magnesium. Infants receiving IV or intramuscular magnesium (42 subjects) were treated with a median dose of 4.9 (2.9–6.0) mg/kg elemental magnesium, divided in 1 or 2 doses in most cases. Twenty-five infants were treated with oral magnesium at a median initial treatment dose of 6.4 (3.3–33.8) mg/kg per day of elemental magnesium, of whom only 4 were discharged from the hospital on oral magnesium (at a median discharge dose of 8.0 [5.3–21.5] mg/kg per day with a median duration of therapy of 0.75 months). Neonates treated for hypomagnesemia did have significantly lower median magnesium levels on presentation (0.55 [0.45–0.60] mmol/L vs 0.62 [0.58–0.70] mmol/L, P < .001 [Mann–Whitney U test]), but the use of magnesium supplementation did not affect the duration of hospitalization (data not shown). All infants included in this report were followed until they were off all therapies.

**Investigative Procedures**

Blood and cerebrospinal fluid cultures and neuroimaging studies (head computed tomography scan and/or MRI) showed no clinically significant findings whenever performed (Fig 2). EEGs were abnormal in 5 of 23 infants. Four of the 5 were started on phenobarbital but rapidly weaned off after seizures were deemed more consistent with hypocalcemic tetany. None of the 5 had recurrent seizures after their hypocalcemia was corrected.

Although we intentionally left children with known syndromic diagnoses out of our analyses, fluorescence in situ hybridization to detect microdeletions of

<table>
<thead>
<tr>
<th>TABLE 1 Subject Acquisition Scheme</th>
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<tr>
<td><strong>Inclusion (n)</strong></td>
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<tr>
<td>Age &lt;31 days and met International Classification of Diseases, Ninth Revision criteria (425)</td>
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**FIGURE 1**

Demographic characteristics of all neonates with hypocalcemia compared with all neonatal admissions to the same hospital during the same study period. P = .02 for comparison of gender, and P = .04 for comparison of race.
chromosome band 22q11.2 was documented negative in 7 of the 78 infants in this study. Conversely, only 1 of 26 infants diagnosed with DiGeorge syndrome at <31 days of life at our institution over this period initially presented with hypocalcemia.

**DISCUSSION**

To our knowledge, this study represents the largest reported case series describing infants with late-onset moderate-to-severe transient neonatal hypocalcemia. Our data suggest a prevalence of this condition of ~0.02% in our population, recognizing that we may have missed infants who remained asymptomatic (unlikely at the calcium thresholds we report), that the 1 smaller children’s hospital in Dallas County may have treated some neonates with this condition, and conversely that our hospital’s catchment area is much larger than Dallas County.

Late maturation of the parathyroid axis is thought to be a predominant cause of transient neonatal hypocalcemia, as suggested by the inappropriately low or normal PTH levels and high phosphorus levels in these infants. These biochemical features may obscure the diagnosis of vitamin D deficiency, which was also common in our neonates, because vitamin D deficiency more commonly presents in older infants and children with low-to-normal phosphorus levels due to secondary hyperparathyroidism (and resultant phosphaturia). These observations extend previous case series of ~20 patients each in the United States and Qatar that suggested that hypovitaminosis D may coexist with relative hypoparathyroidism in the setting of symptomatic transient late-onset hypocalcemia. Ashraf et al found that 13 of 23 infants presenting with late neonatal hypocalcemia had 25(OH)D levels <32.5 nmol/L (13 ng/mL).

Lending credence to an etiologic role for hypovitaminosis D in late-onset neonatal hypocalcemia is that comparison with available data on the vitamin D status of healthy infants of comparable ethnic backgrounds suggests a higher prevalence of vitamin D deficiency and lower absolute 25(OH)D levels in our study population. In urban Massachusetts, Merewood et al found that in a predominantly Hispanic and African American population of 376 newborns, 58% were vitamin D deficient compared with 83% of available values in our patients ($P < .002, \chi^2$ with Yates correction). Moreover, median 25(OH)D levels were 43 nmol/L (no IQR reported) in the healthy newborns, compared with 35 (IQR 29–45) nmol/L in our patients. In a separate study of 111 healthy neonates in South Carolina, Hollis et al reported mean (SD) 25(OH)D levels of 46 (25) nmol/L, compared with 38 (17) nmol/L in our population ($P < .03, t$ test).

That no hypocalcemic infant had a 25(OH)D level >62 nmol/L (25 ng/mL) suggests that higher levels might be protective against hypocalcemia. This threshold differs from levels recommended by the recent Institute of Medicine report, which defined vitamin D deficiency as 25(OH)D <30 nmol/L (12 ng/mL) and inadequate vitamin D levels as 30 to 50 nmol/L (12–20 ng/mL). By using these definitions, 10 of our 42 infants with known 25(OH)D levels were vitamin D deficient, and an additional 25 infants had inadequate levels. However, the 2011 Endocrine Society Clinical Practice Guideline suggests that vitamin D sufficiency should be defined as 25(OH)D levels >75 nmol/L (30 ng/mL). At this level, calcium excretion in the urine appears to be normalized, and intestinal calcium transport appears to

### TABLE 2 Biochemical Data at Admission

<table>
<thead>
<tr>
<th>n</th>
<th>Median (IQR)</th>
<th>Units</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calculated, total</td>
<td>67</td>
<td>1.5 (1.4–1.7)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Calculated, ionized</td>
<td>78</td>
<td>0.81 (0.73–0.89)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Phosphorus</td>
<td>78</td>
<td>3.2 (2.9–3.5)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>Magnesium</td>
<td>78</td>
<td>0.58 (0.50–0.62)</td>
<td>mmol/L</td>
</tr>
<tr>
<td>PTH, intact</td>
<td>46</td>
<td>4.8 (3.6–7.9)</td>
<td>pmol/L</td>
</tr>
<tr>
<td>Vitamin D (25-OH)</td>
<td>42</td>
<td>35 (29–45)</td>
<td>nmol/L</td>
</tr>
</tbody>
</table>

**Selected Correlations (No Correlations With Vitamin D Levels Were Significant)**

<table>
<thead>
<tr>
<th>Spearman $\rho$</th>
<th>$\rho$</th>
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</thead>
<tbody>
<tr>
<td>Calcium, total versus magnesium</td>
<td>0.39</td>
</tr>
<tr>
<td>Calcium, ionized versus magnesium</td>
<td>0.35</td>
</tr>
<tr>
<td>Calcium, total versus PTH</td>
<td>0.33</td>
</tr>
<tr>
<td>Calcium, ionized versus PTH</td>
<td>0.33</td>
</tr>
<tr>
<td>Magnesium versus PTH</td>
<td>0.14</td>
</tr>
</tbody>
</table>

**FIGURE 2**

The 78 neonates had various combinations of investigative studies performed, with blood culture as the most commonly performed study.
be optimal.22,24 By this recent guideline, all of the hypocalcemic infants in our study who had a 25(OH)D level drawn were vitamin D insufficient or worse. These data provide a rationale for the investigation of the vitamin D status of all neonates presenting with moderate-to-severe late-onset neonatal hypocalcemia.

The predominance of formula feeding in our vitamin D–deficient infants (similar to that described in the study by Ashraf et al20) suggests that maternal vitamin D status is the dominant determinant of the infant’s vitamin D status at this age. Indeed, maternal and infant 25(OH)D levels are known to be correlated.15,20 It would have been interesting to also know the vitamin D status of the mothers of our patients, but these data were unavailable. Standard practice in our population of pregnant mothers is daily supplementation with a prenatal vitamin that provides 400 IU of vitamin D.25 There is evidence that this dose is inadequate to maintain vitamin D sufficiency during pregnancy. Hollis et al22 found that pregnant women supplemented daily with 4000 IU of vitamin D were more likely to achieve a 25(OH)D level >80 nmol/L (32 ng/mL) than women supplemented daily with 2000 or 400 IU of vitamin D. The magnitude of the disparity between the recommendations by Hollis et al22 and our current practice suggests a high likelihood of vitamin D deficiency in our mothers and their offspring. It would be worthwhile to investigate whether higher doses of maternal vitamin D supplementation in our population might achieve vitamin D sufficiency and thereby play a role in decreasing the prevalence of late-onset neonatal hypocalcemia.

Whereas the relatively high frequency of Hispanic infants in our series might be explained by a greater prevalence of vitamin D deficiency in that population, the predominance of males has not been previously reported, and an explanation for this observation is not obvious. Available data do not allow us to distinguish between gender-specific differences (at least in our population) in such factors as neonatal vitamin D levels, PTH secretion, or dietary calcium absorption or an ascertainment bias due to increased susceptibility of males to hypocalcemic seizures. We found no differences in the vitamin D levels of males versus females (data not shown). Population-based studies might be able to address some of these possibilities. Although a seasonal variation in the incidence of neonatal hypocalcemia (ie, decreased incidence in summer months) would support an etiologic role for vitamin D deficiency in the pathogenesis of late-onset neonatal hypocalcemia, our data did not show seasonal variations in either vitamin D levels or incidence of hypocalcemia (not shown). This is consistent with the observed lack of seasonal variation in vitamin D levels in our obesity clinic population, particularly among Hispanic and African American patients, which may reflect lifestyle choices in our locale that limit sun exposure.26

In addition to the high prevalence of vitamin D deficiency, 75 of 78 infants were also hypomagnesemic, a well-recognized risk factor for hypocalcemia.27 It is noteworthy but not surprising that magnesium and PTH levels were not correlated in our patients. Magnesium is necessary for both PTH secretion and peripheral responsiveness to PTH.27 and decreased PTH secretion due to hypomagnesemia may have been partially counterbalanced by compensatory increases in PTH secretion in response to hypocalcemia caused by alterations in responsiveness to PTH. The coexistence of multiple biochemical abnormalities in this population suggests a synergistic role for hypoparathyroidism, vitamin D deficiency, and hypomagnesemia in causing severe late-onset neonatal hypocalcemia.

A retrospective determination of the necessary duration of therapy for a purportedly transient condition, without prospectively defining the criteria for adjusting and eventually stopping treatment, might be confounded by variations in practice between physicians. Nevertheless, our study suggests that only 1 to 2 months of individualized treatment is necessary for neonates with transient hypocalcemia, aside from ongoing routine vitamin D supplementation. Recommendations for the management of neonatal hypocalcemia in widely used pediatric texts (Table 3) are inconsistent in their recommendations for the use of infant formulas with low phosphorus content and are often nonspecific in their recommendations of particular forms of vitamin D to treat these infants. Our data suggest a role for calcium and magnesium supplementation, low-phosphorus formula, and supplementation with both the activated form of vitamin D (calcitriol, ie, 1,25-dihydroxyvitamin D) and 1 of its inactive parent compounds (vitamin D2 [ergocalciferol] or vitamin D3 [cholecalciferol]). Calcitriol supplementation compensates for the body’s inability to efficiently convert 25-hydroxylated forms of vitamin D to 1,25-dihydroxylated forms due to decreased 1α-hydroxylase activity in the setting of hypoparathyroidism.

Our data suggest that electrophysiologic, genetic, and radiographic studies should not play a role in the initial evaluation of neonates with moderate-to-severe hypocalcemia. The 1 infant with DiGeorge syndrome who presented with hypocalcemia (not included in the analyses) had dysmorphic facies, and whereas the hypocalcemia was transient, this infant was diagnosed with congenital heart disease soon afterward. It is also noteworthy that this infant had an initial 25(OH)D level of 147 nmol/L (59 ng/mL), which was ∼4 times higher than the mean 25(OH)D level of
TABLE 3 Highlights of Recommendations for Management of Neonatal Hypocalcemia From Standard Pediatric Texts

<table>
<thead>
<tr>
<th>Source</th>
<th>Vitamin D</th>
<th>Low-Phosphorus Formula</th>
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<tbody>
<tr>
<td>Nelson Textbook of Pediatrics&lt;sup&gt;39&lt;/sup&gt;</td>
<td>Yes, emphasis on calcitriol</td>
<td>No specific mention</td>
</tr>
<tr>
<td>Rudolph's Pediatrics&lt;sup&gt;40&lt;/sup&gt;</td>
<td>Suggests role for both vitamin D supplements</td>
<td>Yes</td>
</tr>
<tr>
<td>Current Diagnosis and Treatment: Pediatrics&lt;sup&gt;31&lt;/sup&gt;</td>
<td>Nonspecific allusion to role of vitamin D supplementation</td>
<td>No specific mention</td>
</tr>
<tr>
<td>Oski’s Pediatrics&lt;sup&gt;22&lt;/sup&gt;</td>
<td>Nonspecific allusion to role of vitamin D supplementation</td>
<td>Yes</td>
</tr>
<tr>
<td>Principles and Practice of Pediatric Endocrinology&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Yes, emphasis on calcitriol</td>
<td>Inferred in recommendation to aim for 4:1 molar ratio of calcium to phosphorus in formula</td>
</tr>
<tr>
<td>The Merck Manual of Diagnosis and Therapy&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Yes, emphasis on calcitriol</td>
<td>Inferred in recommendation to aim for 3–4:1 molar ratio of calcium to phosphorus in formula</td>
</tr>
<tr>
<td>Endocrinology&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Yes, emphasis on calcitriol</td>
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All texts advocate treatment with calcium in oral and/or IV formulations.

diagnosis of a serious neonatal infection is delayed.

In summary, we recommend that the evaluation of neonates presenting with late-onset hypocalcemia should include an initial assessment of calcium, phosphorus, magnesium, intact PTH, and 25 (OH)D levels. Neuroimaging and genetic studies can be deferred in the absence of focal neurologic findings or features of dysmorphism or cardiac abnormalities, respectively. Although management should be individualized, therapy with calcium supplements, vitamin D in the form of 1,25-dihydroxyvitamin D and D$_2$ or D$_3$, magnesium (IV and/or oral), and a formula low in phosphorus for a short duration of 1 to 2 months appears to be effective in treating neonates presenting with late-onset hypocalcemia.

CONCLUSIONS

Moderate-to-severe late-onset neonatal hypocalcemia is more common in Hispanic and male infants, is usually a sign of coexistent vitamin D deficiency and hypomagnesemia, and is readily managed with therapy of limited duration. Neonates presenting with seizures who have moderate-to-severe hypocalcemia but no other causes for concern are unlikely to benefit from studies to screen for DiGeorge syndrome or from neuroimaging studies.

REFERENCES


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Teena C. Thomas, Joshua M. Smith, Perrin C. White and Soumya Adhikari
Pediatrics 2012;129:e1461; originally published online May 21, 2012;
DOI: 10.1542/peds.2011-2659

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