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Case 17-2017: A 14-Year-Old Boy with Acute Fear of Choking while Swallowing

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PRESENTATION OF CASE

Dr. Juliana Mariani (Pediatrics): A 14-year-old boy was seen in the emergency department of this hospital because of fear of choking while swallowing.

The patient had been well until 2 days before admission, when he choked while eating a piece of chicken during dinner. He became fearful of swallowing and was unable to finish the meal despite cutting his food into small pieces. The next day, he vomited after trying to eat ice cream, and his daily fluid intake decreased to only 710 ml (24 oz) of water. He reportedly needed his mother near him throughout the day and had an "irrational fear" of choking. He had not had recent fevers, rhinorrhea, cough, or sore throat. Nine days earlier, during a routine annual examination at the clinic of the patient's primary care pediatrician, the patient's mother reported that he had had several episodes of inspiratory stridor while he was sleeping during the past few weeks; the patient was referred to an otolaryngologist, but this visit had not yet occurred. On the day of this presentation, the patient consumed only small sips of water, reported feeling hungry, and slept most of the day. His mother noted that, in addition to the inspiratory stridor during sleep, the patient had some gasping for air that was associated with deep involuntary burping. She contacted a physician at this hospital and was advised to bring the patient to the emergency department for evaluation.

The patient had been delivered at full term. He had a nuchal cord at birth, and the birth weight was 3.6 kg. Apgar scores at 1, 5, and 10 minutes were 2, 6, and 9, respectively, and initial resuscitation efforts were provided. Subsequent growth and development were reportedly normal. As an infant, the patient had had gastroesophageal reflux and a milk-protein allergy, and he had received some training on sensory-integration skills during childhood. Immunizations had been administered through 2.5 years of age; after that age, the recommended routine vaccinations were refused by the patient's parents. The patient had keratosis pilaris and eczema. He took no medications and had no known allergies. He lived with his

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family in a suburb and was a student who received writing support. His younger brother had moderate autism spectrum disorder, with verbal (but not conversational) skills, and had received diagnoses of PANDAS (pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections) and vitamin D deficiency. Both parents were healthy. The patient's maternal grandfather had heart disease and non–insulin-dependent diabetes mellitus, his maternal grandmother had had psoriasis and had died from breast cancer, an aunt had hypoglycemia, and his paternal grandmother had hypertension, hypoglycemia, and congestive heart failure.

On examination in the emergency department, the patient was alert and appeared to be anxious. He had persistent involuntary burping, with evidence of drooling on his shirt. The temperature was 36.1°C, the blood pressure 127/64 mm Hg, the pulse 67 beats per minute, the respiratory rate 18 breaths per minute, the weight 54.1 kg (60th percentile for his age), and the height 160 cm (32nd percentile for his age). The oral mucosal membranes were dry. Sexual development was classified as Tanner stage 4 (with stages ranging from 1 to 5 and higher stages indicating more advanced pubertal development). Results of examinations of cranial nerves II through XII were normal. The patient spoke clearly, and his gait, strength, sensation, and deep-tendon reflexes in the arms and legs were normal. The remainder of the examination was also normal. His initial laboratory studies revealed profound hypocalcemia and hyperphosphatemia, but other laboratory test results were normal, including blood levels of alanine aminotransferase, aspartate aminotransferase, amylase, and lipase, as well as titers of antistreptolysin O and anti-DNase B; other test results are shown in Table 1. An electrocardiogram showed a normal sinus rhythm with no acute ischemic changes. The corrected QT interval was reportedly mildly prolonged, at 471 msec.

Because the patient had severe, symptomatic hypocalcemia, he was admitted to the pediatric intensive care unit (ICU) for cardiovascular and respiratory monitoring and supportive care. On examination, he refused to swallow, had persistent burping, and stated, "I don't want to die." The leg muscles were hypertonic. On examination performed by a pediatric endocrinology consultant, a mildly positive Chvostek's sign (twitching of the facial muscles) was elicited on the left side in response to tapping on the region of the facial nerve anterior to the external auditory canal.

Additional diagnostic tests were performed.

INITIAL MANAGEMENT

Dr. Ryan W. Carroll: My colleagues will address the differential diagnosis of this patient's overall presentation. However, I would like to highlight the aspects of this case that were potentially life-threatening.

This patient's fear of swallowing suggested the possibility of airway compromise, which can lead to respiratory insufficiency. We were immediately concerned about mechanical obstruction due to a neoplasm that involved the tissue of the neck (e.g., sarcoma, rhabdomyosarcoma, or lymphoma), an infectious process (e.g., a retropharyngeal or tonsillar abscess), a cystic lesion, or subglottic stenosis or web. We also considered the possibility of neuromuscular dysfunction due to rabies, increased intracranial pressure or mass effect of the posterior fossa (both of which can lead to vocal-cord dysfunction), the Miller Fisher variant of the Guillain–Barré syndrome, a variant of Bell's palsy, or severely altered electrolyte levels. In this case, the patient did not have frank stridor or respiratory distress, and the sensation of being at risk for choking was most likely caused by profound hypocalcemia.

In the ICU, we considered the potential life-threatening effects of severe hypocalcemia. Hypocalcemia has the potential to lead to seizures, tetany that results in respiratory insufficiency or failure, rhabdomyolysis, acute kidney injury, electrocardiographic alterations (e.g., a prolonged QT interval), bradycardia, and myocardial dysfunction. We also considered underlying illnesses that result in profound hypocalcemia, which can lead to or reflect other grave complications. These include phosphorus overdose, hyperphosphatemia due to rhabdomyolysis or tumor lysis, chronic kidney disease, recent use of an extracorporeal circuit (i.e., plasmapheresis or renal-replacement therapy) that required citrate anticoagulation, infusion of EDTA, massive transfusion of blood products anticoagulated with citrate, genetic syndromes that harbor additional complications (e.g., the DiGeorge syndrome), sepsis, hepatic dysfunction, the use of medications that

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Table 1. Laboratory Data.

Variable	Reference Range, Adults*	On Presentation, Emergency Department	1 Hr after Initial Testing	3 Hr after Initial Testing	5–9 Hr after Initial Testing
Blood†					
Sodium (mmol/liter)	135–145	136	139		
Potassium (mmol/liter)	3.4–4.8	4.0	3.4		
Chloride (mmol/liter)	100–108	94	98		
Carbon dioxide (mmol/liter)	23.0–31.9	25.9	24.4		
Plasma anion gap (mmol/liter)	3–15	16	17		
Urea nitrogen (mg/dl)	8–25	10	10		
Creatinine (mg/dl)	0.60–1.50	0.70	0.65		
Glucose (mg/dl)	70–110	82	81		
Calcium (mg/dl)	8.5–10.5	5.4	5.1		
Ionic calcium (mmol/liter)	1.14–1.30		0.57		
Phosphorus (mg/dl)	3.0–4.5	10.6	10.0		
Magnesium (mg/dl)	1.7–2.4	1.9	1.8		
Protein (g/dl)					
Total	6.0–8.3		6.5		
Albumin	3.3–5.0		4.4		
Globulin	1.9–4.1		2.1		
Alkaline phosphatase (U/liter)	15–350		325		
Bilirubin (mg/dl)					
Total	0.0–1.0		1.2		
Direct	0.0–0.4		0.2		
Parathyroid hormone (pg/ml)	10–60				310
Thyrotropin (μU/ml)	0.40–5.00				7.69
Free thyroxine (ng/dl)	0.9–1.8				1.4
Urine					
Sodium (mmol/liter)	Not defined			161	
Creatinine (mg/ml)	Not defined			2.15	
Calcium (mg/dl)	Not defined			0.9	
Phosphorus (mg/dl)	Not defined			63.0	

* Reference values are affected by many variables, including the patient population and the laboratory methods used. The ranges used at Massachusetts General Hospital are for adults who are not pregnant and do not have medical conditions that could affect the results. They may therefore not be appropriate for all patients.

† To convert the values for urea nitrogen to millimoles per liter, multiply by 0.357. To convert the values for creatinine to micromoles per liter, multiply by 88.4. To convert the values for glucose to millimoles per liter, multiply by 0.05551. To convert the values for calcium to millimoles per liter, multiply by 0.250. To convert the values for ionic calcium to milligrams per deciliter, divide by 0.250. To convert the values for phosphorus to millimoles per liter, multiply by 0.3229. To convert the values for magnesium to millimoles per liter, multiply by 0.4114. To convert the values for bilirubin to micromoles per liter, multiply by 17.1.

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increase the activity of cytochrome P-450, and pancreatic dysfunction or frank pancreatitis.

The initial treatment of this patient included respiratory and cardiovascular monitoring and calcium repletion. Although his blood pressure was elevated at the time of admission, it returned to normal on the third hospital day, which suggests that the elevation might have been due to anxiety. The patient did not ultimately need respiratory assistance, and his symptoms dramatically improved as his blood calcium level increased.

DIFFERENTIAL DIAGNOSIS

Dr. Michelle L. Katz: The differential diagnosis of severe hypocalcemia in this patient's age group can be broadly categorized as primary disorders of calcium, vitamin D, or parathyroid hormone (PTH). Because of the patient's age, we did not consider the possibility of neonatal hypocalcemia.

PRIMARY DISORDERS OF CALCIUM OR VITAMIN D

Various conditions and medications can lead to diminished calcium availability. Hypocalcemia can be caused by the precipitation of calcium into insoluble salts, which can occur in acute pancreatitis, rhabdomyolysis, or the tumor lysis syndrome.[1] Hypocalcemia can also be caused by several medications, such as bisphosphonates, calcitonin,[2] and trisodium phosphonoformate (foscarnet).[3] These causes of hypocalcemia can be ruled out in this patient on the basis of medical history.

Disorders of vitamin D metabolism or action also commonly cause hypocalcemia. Vitamin D is synthesized in the dermis or absorbed from dietary sources. It is then converted to 25-hydroxyvitamin D in the liver. The conversion from 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, the active form of vitamin D, is catalyzed in the renal tubules by 1α-hydroxylase, which is stimulated by PTH. Disorders of vitamin D include diminished substrate due to limited dietary intake or limited sun exposure, severe liver disease that interferes with 25-hydroxylation of vitamin D, and chronic kidney disease that leads to a diminished level of 1,25-dihydroxyvitamin D. Conditions caused by a genetic mutation of 1α-hydroxylase (vitamin D–dependent rickets type 1) or a genetic mutation of the vitamin D receptor (vitamin D–dependent rickets type 2 or hereditary vitamin D–resistant rickets) can also lead to hypocalcemia, although the onset of these conditions most commonly occurs in infancy.[4] The vitamin D levels in this patient were not sufficiently low to cause hypocalcemia: the 25-hydroxyvitamin D level was 19 ng per milliliter (47 nmol per liter; reference range, 33 to 100 ng per milliliter [82 to 250 nmol per liter]), and the 1,25-dihydroxyvitamin D level was 49 pg per milliliter (127 nmol per liter; reference range, 19 to 83 pg per milliliter [49 to 216 nmol per liter]). Furthermore, phosphorus levels are typically low in patients with vitamin D deficiency or resistance, but this patient had an elevated inorganic phosphorus level of 10.6 mg per deciliter (3.42 mmol per liter), a finding consistent with impaired PTH secretion or action.

HYPOPARATHYROIDISM

Hypoparathyroidism can lead to severe hypocalcemia and hyperphosphatemia, which were seen in this patient. Hypoparathyroidism occurs most commonly after thyroidectomy or other surgical procedures of the neck and can be transient or permanent. Genetic causes of hypoparathyroidism include the DiGeorge syndrome (22q11 microdeletion), activating mutations of the calcium-sensing receptor or of Gα11 (one of the signaling proteins at this receptor), mutations in the *PTH* gene, mutations in transcription factors that regulate the development of the parathyroid gland, and mutations in mitochondrial genes.[5] Autoimmune hypoparathyroidism may be a component of autoimmune polyglandular syndrome type 1 — which is characterized by the triad of candidiasis, hypoparathyroidism, and adrenal insufficiency, with or without other autoimmune disorders — or it may be an isolated autoimmune condition.[5] Hypomagnesemia and hypermagnesemia impair PTH secretion, and hypomagnesemia also impairs the skeletal and renal response to PTH.[5] Damage to the parathyroid gland caused by the accumulation of heavy metals, which occurs in Wilson's disease or hemochromatosis, or infiltration by a malignant tumor can also lead to hypoparathyroidism.[5]

Hypoparathyroidism is characterized by either a low PTH level or an inappropriately normal PTH level in the presence of a low calcium level. This patient had an elevated PTH level of 310 pg

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Table 2. Laboratory Test Results Associated with Vitamin D Deficiency, Hypoparathyroidism, and Variants of Pseudohypoparathyroidism.*

Condition	Blood PTH	Blood Calcium	Blood Phosphorus	Urinary cAMP	Urinary Phosphorus	$G_s\alpha$ Activity
Vitamin D deficiency or resistance	↑	↓ or normal	↓ or normal	NA	NA	Normal
Hypoparathyroidism	↓	↓	↑	↑	↑	Normal
Pseudohypoparathyroidism						
Type 1a	↑	↓	↑	↓	↓	↓ (by 50%)
Type 1b	↑	↓	↑	↓	↓	Normal
Type 1c	↑	↓	↑	↓	↓	Normal
Type 2	↑	↓	↑	↑	↓	Normal

* An up arrow indicates that the level is increased, and a down arrow that the level is decreased. Urinary cyclic adenosine monophosphate (cAMP) and phosphorus levels are measured after an infusion of parathyroid hormone (PTH). $G_s\alpha$ denotes the α subunit of the stimulatory G protein, and NA not applicable.

per milliliter (reference range, 10 to 60), a finding that rules out hypoparathyroidism as the cause of his hypocalcemia, unless a mutant, less active form of PTH were being secreted.

PSEUDOHYPOPARATHYROIDISM

Pseudohypoparathyroidism is defined as resistance to PTH that is caused by defects in the G-protein receptor signaling cascade. Laboratory testing reveals hypocalcemia, hyperphosphatemia, and an elevated PTH level, findings that were seen in this case. Pseudohypoparathyroidism can occur in the presence or absence of Albright's hereditary osteodystrophy. The features of Albright's hereditary osteodystrophy include short stature, round facies, brachydactyly, obesity, subcutaneous ossifications, and various degrees of neurocognitive impairment.

In healthy persons, PTH binds to the PTH receptor, which triggers a signal-transduction cascade involving the α subunit of the stimulatory G protein ($G_s\alpha$). This leads to increased production of cyclic adenosine monophosphate (cAMP), increased calcium reabsorption in the distal renal tubules, decreased phosphorus reabsorption in the proximal renal tubules, and increased calcium mobilization due to bone resorption. These processes may be impaired in various ways, depending on the variant of pseudohypoparathyroidism.

The variants of pseudohypoparathyroidism can be distinguished to some extent according to whether features of Albright's hereditary osteodystrophy are present or absent, whether other hormones that are mediated by the $G_s\alpha$ signaling cascade are affected, and whether impairment of the signal-transduction cascade is complete.[6] Some overlap can occur among the variants (Table 2).

In pseudohypoparathyroidism type 1a, the kidneys are resistant to PTH, and thus the urinary cAMP and phosphorus levels do not increase appropriately in response to an infusion of PTH; resistance to other hormones, particularly thyrotropin, may also be present, and Albright's hereditary osteodystrophy is present. In pseudohypoparathyroidism type 1b, the kidneys are resistant to PTH, and mild resistance to thyrotropin is possible; however, evidence of Albright's hereditary osteodystrophy is absent in most cases.[6] Pseudohypoparathyroidism type 1c is similar to type 1a, with the exception that receptor-independent cAMP production remains intact in vitro.[7] There are probably several variants of pseudohypoparathyroidism type 2. In one of these variants, the urinary phosphorus level does not increase appropriately in response to PTH infusion, but the cAMP level does; Albright's hereditary osteodystrophy is absent.[6]

At the time of admission, this patient's thyrotropin level was 7.69 μU per milliliter (reference range, 0.40 to 5.00). Because the patient had hypocalcemia, hyperphosphatemia, an elevated PTH level, and a mildly increased thyrotropin

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level but had no evidence of Albright's hereditary osteodystrophy, a presumptive diagnosis of pseudohypoparathyroidism type 1b was made, and genetic confirmation was sought.

DR. MICHELLE L. KATZ'S DIAGNOSIS

Pseudohypoparathyroidism type 1b.

PATHOLOGICAL DISCUSSION

Dr. Harald Jüppner: Pseudohypoparathyroidism type 1a, a long-known disease variant, is caused by heterozygous loss-of-function mutations involving the maternal exons 1 through 13 of *GNAS*, a complex genetic locus on chromosome 20q. These *GNAS* exons encode $G_s\alpha$. Through the use of alternative first exons, additional transcripts are generated that are spliced onto $G_s\alpha$ exons 2 through 13; through the use of yet another first exon, a noncoding antisense transcript is derived (Fig. 1A). In healthy persons, the promoters of these alternative first exons are methylated on either the maternal or the paternal *GNAS* allele.[8,9] Patients affected by pseudohypoparathyroidism type 1b, such as this patient, typically have abnormal *GNAS* methylation[10-13]; such an epigenetic change can be detected by means of a DNA amplification method called methylation-specific multiplex ligation-dependent probe amplification (MLPA), a sensitive tool that can help to establish the diagnosis. Most cases of pseudohypoparathyroidism type 1b are sporadic. The underlying genetic defect of this disease variant is unknown, except in the case of patients who have two paternal copies and no maternal copies of chromosome 20q (which is known as paternal uniparental disomy involving chromosome 20q).[14,15] Such an epigenetic event disrupts parent-specific *GNAS* methylation and thus allows expression of most *GNAS*-derived transcripts exclusively from the nonmethylated DNA. Familial forms of pseudohypoparathyroidism type 1b can be caused by maternal deletions in *GNAS*[13,16-20] or, more frequently, by maternal deletions in syntaxin 16 (*STX16*), a gene located centromeric to *GNAS*.[16,17,21]

In this case, the symptomatic PTH-resistant hypocalcemia, the hyperphosphatemia, the mildly elevated thyrotropin level, and the absence of features of Albright's hereditary osteodystrophy raised the possibility that the patient was affected by pseudohypoparathyroidism type 1b, rather than type 1a. There was no family history of PTH-resistant hypocalcemia, and the patient's genomic DNA showed no evidence of the most frequent *STX16* deletion (not shown). We used MLPA to rule out deletions involving other regions of *GNAS* or *STX16*[13] (Fig. 1B) and then used methylation-specific MLPA to search for epigenetic changes at the *GNAS* locus (Fig. 1C). These studies revealed abnormalities in the patient's DNA at four differentially methylated *GNAS* regions[10-13] and thus confirmed the diagnosis of pseudohypoparathyroidism type 1b. The mother's DNA showed a normal pattern of *GNAS* methylation, a finding consistent with the possibility that the patient carries either a recessive or a new mutation in an unknown gene.

The absence of a family history of PTH-resistant hypocalcemia combined with broad changes in *GNAS* methylation made it likely that this patient had the sporadic form of pseudohypoparathyroidism type 1b. We therefore considered the possibility that his disease was caused by paternal uniparental disomy involving chromosome 20q. However, when his genomic DNA was analyzed for microsatellite markers across the *STX16–GNAS* region, we observed heterozygosity for four markers (D20S86, 261P9-CA, 806M20-CA, and 543J19-TTA) (Fig. 1D). Furthermore, comparison of the haplotypes seen across the *STX16–GNAS* region in the patient with those in each parent ruled out the possibility of paternal uniparental disomy involving a large region on chromosome 20q.

In summary, we observed a loss of all maternal *GNAS* methylation imprints, but there was no evidence for either a deletion in this locus or for paternal uniparental disomy. The epigenetic changes that were present in this patient, which were used to establish the diagnosis of pseudohypoparathyroidism type 1b, result in decreased or abolished $G_s\alpha$ expression from the maternal *GNAS* allele. Since the paternal *GNAS* allele does not substantially contribute to the total $G_s\alpha$ expression in the proximal renal tubules (and in a few other tissues, such as the thyroid and pituitary glands), this patient had a deficiency in $G_s\alpha$ protein levels in this portion of the kidney, which explains his PTH-resistant hypocalcemia.[8,9]

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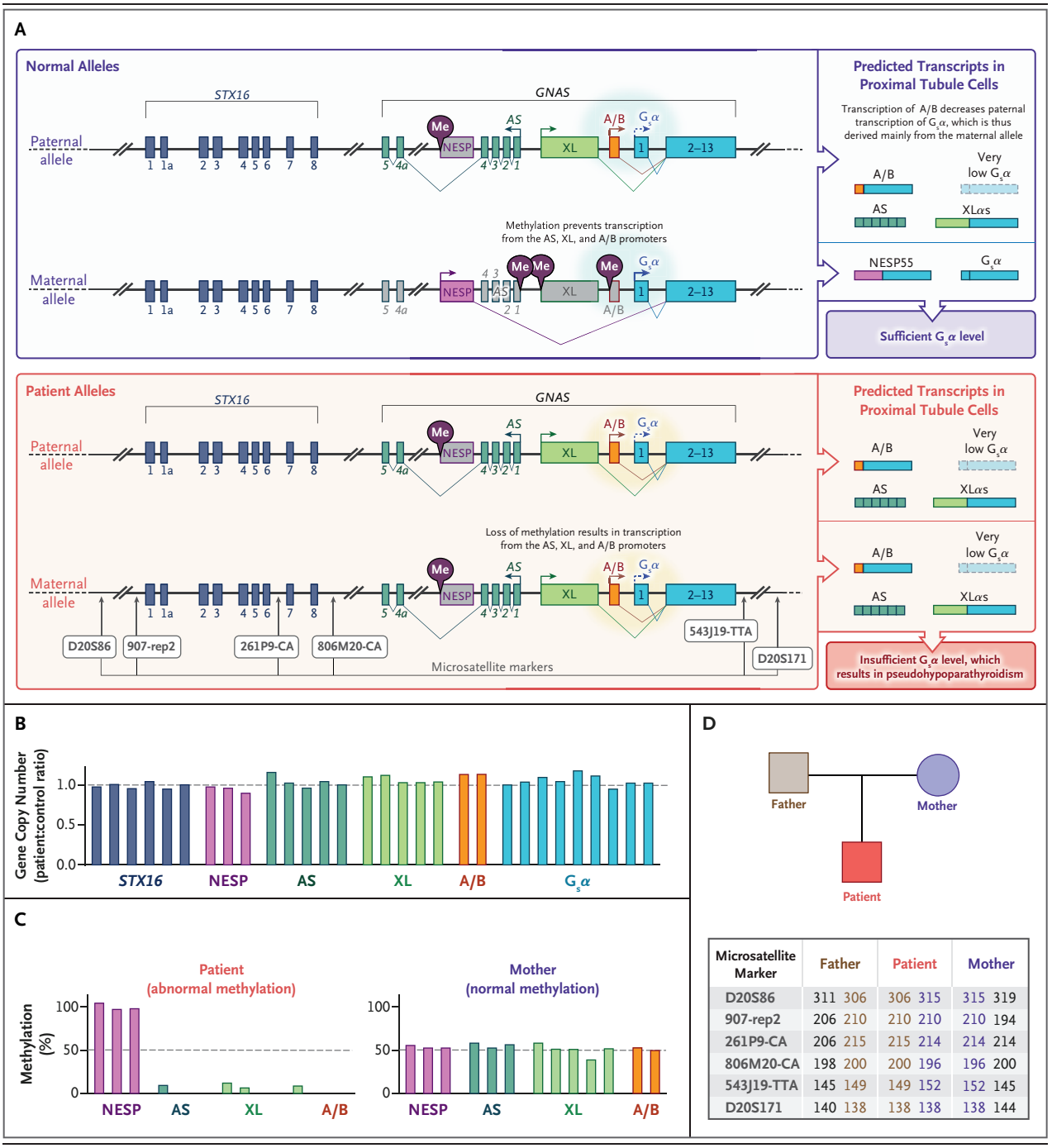

Microsatellite Marker	Father	Patient	Mother
D20S86	311 306	306 315	315 319
907-rep2	206 210	210 210	210 194
261P9-CA	206 215	215 214	214 214
806M20-CA	198 200	200 196	196 200
543J19-TTA	145 149	149 152	152 145
D20S171	140 138	138 138	138 144

DISCUSSION OF MANAGEMENT

Dr. Elahna Paul: Initial treatment was administered in the emergency department of this hospital. Intravenous infusion of calcium gluconate abrogated the patient's acute symptoms, but it had only a minor effect on the hypocalcemia itself.

The presence of high blood phosphorus levels limited our ability to continue aggressive intravenous calcium repletion, since the risk of intravascular precipitation of calcium phosphorus increases when there is an increase in the calcium phosphorus product (calcium level × phosphorus level). Therefore, during calcium repletion, it was

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Figure 1 (facing page). Genetic Analysis of the *STX16–GNAS* Region.

Panel A shows a schematic depiction of the region extending from the syntaxin 16 (*STX16*) gene to the *GNAS* complex locus, which is located approximately 250 kb telomeric to *STX16*. The maternal and paternal alleles are shown for a healthy person and for this patient. The boxes represent different exons. *GNAS* exons 1 through 13 encode the α subunit of the stimulatory G protein ($G_s\alpha$). Through the use of alternative first exons, additional transcripts are derived that are spliced onto $G_s\alpha$ exons 2 through 13. These include the A/B transcript, which is associated with exon A/B; the XLαs transcript, which is associated with exon XL; and the NESP55 transcript, which is associated with exon NESP. A noncoding antisense mRNA transcript is derived from antisense (AS) exons 1 through 5. The abbreviation Me indicates the location of a differentially methylated region. In most tissues, $G_s\alpha$ is expressed from both parental alleles; however, in the proximal renal tubules (and a few other tissues), it is derived mainly from the maternal allele. Panel B shows multiplex ligation-dependent probe amplification (MLPA; MRC-Holland) of the *STX16–GNAS* region. The dashed line shows the normal ratio (1.0); in a patient with a deletion that affects one parental allele, the ratio is 0.5. In this patient, there is no evidence of allelic loss at the *GNAS* and *STX16* exons. Panel C shows methylation-specific MLPA for the patient and his mother. The probes are specific for exons NESP, AS, XL, and A/B; the dashed line shows normal methylation (50%). Analysis of DNA from the patient shows loss of methylation at *GNAS* exons AS, XL, and A/B and shows gain of methylation at *GNAS* exon NESP. In contrast, analysis of DNA from the patient's mother, who was healthy, shows normal methylation at all four differentially methylated regions. Panel D shows the results of microsatellite-marker analysis for the patient and his parents. Each number indicates the size of a polymerase-chain-reaction amplicon that is derived from a parental allele; the presence of two different numbers at one marker indicates that the patient has two distinct repeats. Brown numbers indicate paternally inherited haplotypes, and purple numbers maternally inherited haplotypes.

imperative to lower the blood phosphorus levels to normal. On presentation, the patient's calcium phosphorus product was approximately 47; levels higher than 55 are associated with a risk of subacute or acute calcification of vascular, cardiac, and other soft tissues.

Calcium repletion requires not only intravenous and oral calcium but also an activated vitamin D analogue for the gastrointestinal absorption of enteric calcium. Therefore, as we transitioned from intravenous to oral calcium supplementation, we administered calcitriol, an activated vitamin D analogue that improves gastrointestinal absorption of enteric calcium and suppresses PTH secretion. Suppression of PTH slows bone turnover and resorption and decreases the amount of phosphorus (and calcium) that is released from bone into the blood; it thus helps to lower blood phosphorus levels and mitigates the risk of progressive osteopenia. In this patient, the alkaline phosphatase level, which was initially elevated, progressively normalized with therapy.

Vitamin D in the form of ergocalciferol was also administered, because the patient had a low vitamin D level. It is possible that the gradual progression of vitamin D deficiency is what destabilized the patient and led to his initial symptomatic presentation. This vitamin D depletion may have begun during the previous year, when the family moved from southern California to the northeast United States, because the patient had diminished exposure to ambient sunshine.

Administration of intravenous calcium supplementation and then oral calcium supplementation combined with oral calcitriol led to improvement in the blood calcium and phosphorus levels during the first several days. Thereafter, much higher doses of both agents were needed to achieve normal calcium levels; the total daily dose of calcitriol peaked at 5 μg, and the total daily dose of calcium carbonate supplementation peaked at 20 g. During this time period, the phosphorus level continued to be elevated; dietary phosphorus was therefore restricted and the phosphorus binder sevelamer carbonate was added to the patient's regimen, and his condition improved. He was discharged on the eighth hospital day.

The patient's medications were tapered after discharge. The phosphorus binder was discontinued within 6 weeks after discharge, and the restrictions were removed from his diet. Calcium carbonate supplementation was stabilized at a dose of 3 g three times a day, and calcitriol was gradually tapered from 5 μg daily to 0.25 or 0.5 μg daily (on alternating days). Further medication adjustments were made to maintain normal blood levels of calcium, phosphorus, and 25-hydroxyvitamin D and normal urinary calcium excretion. The calcitriol dose was adjusted on the basis of the PTH level; the goal was to maintain the PTH level at the upper end of the normal range, which would presumably ensure normal bone

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turnover (as indicated by a normal alkaline phosphatase level) while avoiding excess urinary calcium excretion.

Dr. Virginia M. Pierce (Pathology): Are there questions or comments for any of our discussants?

Dr. John T. Truman (Pediatrics): Since the days of Dr. Jüppner's predecessor, Dr. Crawford, pediatric residents at this institution have been taught that a subtle sign of pseudohypoparathyroidism type 1a in a pediatric patient is a problem with the fourth metacarpal bone. When the patient makes a fist, you can see a little dimple in there. Was that observed in this case?

Dr. Jüppner: I do not think that hand films were obtained in this case, but when we looked at the patient's fist, no shortening of the fourth metacarpal bone or any of the metacarpal bones was observed, so it is unlikely that he had this sign of pseudohypoparathyroidism type 1a. Even patients with pseudohypoparathyroidism type 1b sometimes have shortening of the metacarpal or metatarsal bones.

Dr. Ronald E. Kleinman (Pediatrics): Have you taken the methylation studies a step further, to look at the genes responsible for methylation? Are the methylation defects seen in this patient specific to those particular genes or are they generalized issues?

Dr. Jüppner: The absence of methyltransferases leads to a lethal or much more severe phenotype than that of pseudohypoparathyroidism type 1b; it is therefore not surprising that whole-exome sequencing has not revealed mutations in these genes. Changes in methylation in pseudohypoparathyroidism type 1b are typically restricted to the *GNAS* locus, and therefore, we usually limit our analysis to this particular locus. However, in approximately 10% of cases of pseudohypoparathyroidism type 1b, changes in methylation have been observed at other genetic loci, such as the Prader–Willi locus or the Angelman locus. There may be an unknown mutation that does not allow methyltransferase to interact with the *GNAS* locus.

Dr. Lynne Levitsky (Pediatrics): Did the elevation in the patient's thyrotropin level resolve?

Dr. Paul: The patient's thyrotropin level improved slightly. His free thyroxine level is normal, so we will check the thyrotropin level every 6 months.

Dr. Sonia Lewin (Emergency Medicine): As this patient's pediatric attending physician in the emergency department, I would like to thank the panel for this presentation and to thank Dr. Mariani for being my resident when the patient arrived during one incredibly busy shift. I think this child is lucky to have received the diagnosis of profound hypocalcemia so promptly, given that he was referred to the emergency department by one of my colleagues who monitors his brother for PANDAS and thought this might be another case of PANDAS. I think we sometimes put on blinders when we get a referral for a specific disorder. This patient's presentation was not the result of PANDAS, and it was the quick thinking and broad workup in the emergency department that facilitated the diagnosis.

ANATOMICAL DIAGNOSIS

Pseudohypoparathyroidism type 1b.

This case was presented at Pediatric Grand Rounds.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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