

Molecular Diagnosis of Pseudohypoparathyroidism Type Ib in a Family With Presumed Paroxysmal Dyskinesia

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ABSTRACT. We describe 2 sisters diagnosed initially with paroxysmal kinesigenic choreoathetosis, a condition characterized by brief episodes of spasms precipitated by sudden movement. However, subsequent testing showed hypocalcemia, hyperphosphatemia, and elevated parathyroid hormone levels consistent with pseudohypoparathyroidism type Ib. This diagnosis was confirmed by genetic testing, which identified a 3-kilobase deletion on chromosome 20q13.3. Our report describes the neurologic presentation, metabolic derangement, and underlying genetic mutation in a family. It also reinforces the importance of metabolic testing in the evaluation of pediatric patients with movement disorders. *Pediatrics* 2005;115:e242–e244. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1878; *pseudohypoparathyroidism type Ib, paroxysmal dyskinesia, genetics (molecular)*.

ABBREVIATIONS. PHP, pseudohypoparathyroidism; PTH, parathyroid hormone; AHO, Albright's hereditary osteodystrophy; AD-PHP-Ib, autosomal dominant form of pseudohypoparathyroidism type Ib; PKC, paroxysmal kinesigenic choreoathetosis; G α_s , α subunit of the stimulatory G protein.

Pseudohypoparathyroidism (PHP) is a rare condition characterized by hypocalcemia, hyperphosphatemia, and elevated parathyroid hormone (PTH) levels caused by end-organ resistance to PTH. The main clinical types of PHP include PHP types Ia (PHP-Ia) and Ib (PHP-Ib). PHP-Ia is characterized by the classic laboratory findings and features of Albright's hereditary osteodystrophy (AHO), including short stature, developmental delay, brachydactyly, and heterotopic calcifications. Patients with PHP-Ib present with the typical laboratory findings but lack features of AHO. Recently, a microdeletion on chromosome 20q13.3 was identified as a plausible cause of an autosomal dominant form of PHP-Ib (AD-PHP-Ib).¹

Many individuals affected by PHP-Ib have no apparent clinical symptoms and may show only a mild

PTH elevation as evidence of PTH resistance.² However, some patients with this disorder may present with symptomatic hypocalcemia leading to abnormal movements suggestive of a primary neurologic etiology. This report describes the clinical presentation and molecular diagnosis of 2 siblings with AD-PHP-Ib who were initially diagnosed as having a paroxysmal movement disorder.

CASE REPORTS

The index patient (III-3) was an 11-year-old girl with a 3-month history of paroxysmal attacks during which her legs would stiffen, causing her to fall forward. These episodes occurred daily, lasted <1 minute, and resolved spontaneously. She also experienced facial spasms, tremors, and choreoathetotic movements of her hands and feet. The initial evaluation included a normal electroencephalogram and normal magnetic resonance imaging of the head, and she was thought to have paroxysmal kinesigenic choreoathetosis (PKC) because an elder sibling had been diagnosed with the same disorder 3 years earlier by a neurologist.

Her parents (II-1 and II-2) are healthy and not related. They have 9 children; 6 girls and 3 boys. The elder sibling (III-4) started experiencing similar events at 10 years of age. Investigations included a normal electroencephalogram and magnetic resonance imaging of the head. Based on the clinical features of these attacks, she was diagnosed with PKC and treated with carbamazepine

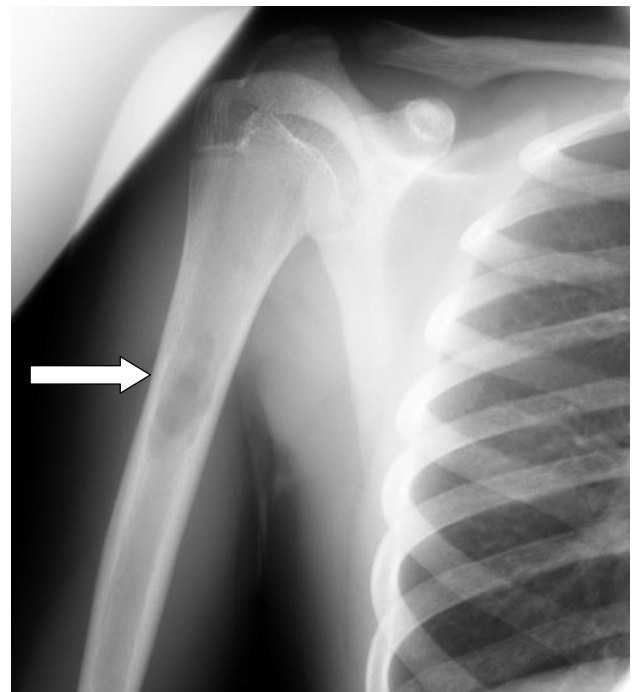


Fig 1. Skeletal evidence of hyperparathyroid bone disease indicated by a brown tumor in the right proximal humerus (arrow).

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(100 mg daily), which significantly reduced the frequency of these attacks. However, by 14 years old, symptoms were worsening progressively, and her dose of carbamazepine was increased (200 mg of sustained release daily). In addition, elemental calcium (600 mg daily) was added, which resulted in a mild improvement in her symptoms.

On examination, our index patient had a stature of 146.7 cm (40th percentile) and weighed 36 kg (50th percentile). She had discolored teeth with poor dental enamel. There were no features of AHO. Her neurologic examination revealed accentuated deep tendon reflexes and positive Chvostek's and Trousseau's signs.

Laboratory testing revealed low calcium (7.4 mg/dL; reference: 9.5–10.5 mg/dL) and elevated phosphorus (8.2 mg/dL; reference: 3.5–5.0 mg/dL) concentrations, with elevated intact PTH (37 pmol/L; reference: 1.5–2 pmol/L) indicative of PTH resistance and PHP.

This diagnosis prompted reevaluation of her elder sibling, who was found also to be hypocalcemic and hyperphosphatemic, with elevated PTH levels (Ca: 5.7 mg/dL; P: 7.4 mg/dL; intact PTH: 34 pmol/L). Her skeletal survey showed a brown tumor in the proximal humerus consistent with hyperparathyroid bone disease (Fig 1). Both siblings also had elevated thyroid-stimulating hormone levels (6.3 and 5.3 mIU/L, respectively; reference: 0.3–5.0 mIU/L), with normal free thyroxine levels and undetectable thyroperoxidase antibodies.

Both sisters were diagnosed with PHP-Ib and therefore were evaluated for the presence of the 3-kilobase (kb) deletion upstream of *GNAS* on chromosome 20q13.3; this deletion was identified recently as a molecular cause of this disorder.¹ Analysis of genomic DNA revealed this deletion in both affected siblings but not in 3 of the remaining 7 siblings who were available for testing. The mother and maternal grandfather also possess the deletion; both are asymptomatic with normal calcium and phosphorus levels (Fig 2).

Both sisters started treatment with calcium (3000 mg daily) and 1,25-vitamin D3 (0.5 μg daily), which resolved their symptoms.

DISCUSSION

Both siblings described in this report possessed an identical 3-kb deletion centromeric of the *GNAS* locus on chromosome 20q13.3. *GNAS* encodes, besides several other transcripts, the α subunit of the stimulatory G protein (*Gsα*), an essential signaling protein that couples a large variety of cell-surface receptors, including the PTH/PTHrP receptor, to the stimulation of adenylyl cyclase.³ Defects in this signaling pathway result in renal PTH resistance and thus hypocalcemia, hyperphosphatemia, and elevated PTH concentrations despite otherwise normal renal function. However, the skeleton remains sensitive to the calcemic actions of PTH, maintaining blood calcium concentrations at the expense of bone. Because of the prolonged PTH-dependent bone resorption,

changes in bone that are characteristic of long-standing hyperparathyroidism were observed in the elder sister.

The PHP-Ib variant is different from other PHP types, because mutations in *Gsα*-encoding *GNAS* exons have not been found in most cases.^{2,4} Our patients carry the same 3-kb deletion upstream of *GNAS*, which has been found in numerous other unrelated kindreds with AD-PHP-Ib.^{1,5,6} It is currently postulated that this deletion affects, in *cis*, directly or indirectly, the establishment or maintenance of exon A/B methylation on the maternal *GNAS* allele, which then silences *Gsα* expression in the proximal renal tubules and possibly few other tissues.¹ Thus, the genetic defect leads to resistance to PTH only if the deletion is inherited by a female carrier. In our case, the mother shared the same deletion as her 2 affected daughters, but she is an asymptomatic carrier, because she inherited her deletion from her father, who presumably inherited the mutation paternally as well.

Our patients also had elevated thyroid-stimulating hormone levels, which is consistent with recent reports indicating that *Gsα* expression is also paternally imprinted in the thyroid.⁷

The elder sister described in this report was treated initially for presumed PKC with carbamazepine, which partially masked her symptoms putatively through sodium-channel inhibition and neuronal membrane stabilization.⁸ PKC is a rare condition characterized by brief episodes of chorea or dystonic spasms precipitated by sudden movement and can be sporadic or familial.⁹ A favorable response to antiepileptic medications is often a diagnostic criterion for PKC; thus, no other investigations were pursued after treatment was initiated.^{8,9}

Although reports of PKC caused by hypocalcemia and hypoparathyroidism have been described in adults,^{10–13} our review of the literature found only 2 cases involving children with PHP.^{14,15} These 2 patients had intracranial calcifications on computerized tomographic imaging and features more consistent with a hypocalcemic disorder.^{14,15}

Our cases describe a unique diagnosis of AD-PHP-Ib in 2 siblings with a neurologic presentation of a metabolic derangement illustrative of a specific

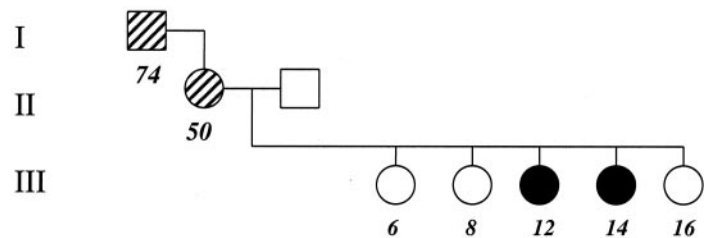


Fig 2. Laboratory findings and pedigree of family with a 3-kb deletion centromeric of *GNAS* on chromosome 20q13.3 associated with AD-PHP-Ib. Affected siblings (filled circles) and unaffected carriers (hatched symbols) are shown. (Reference values: Ca, 9.5–10.5 mg/dL; P, 3.5–5.0 mg/dL; PTH, 1.0–5.2 pmol/L.)

Calcium (9.5–10.5)	9.8	9.8	9.7	7.4	5.7	9.8
Phosphorus Adult (2.5–4.5) Child (3.5–5.0)	3.5	4.9	4.0	8.2	7.4	4.2
PTH (1.0–5.2)	**	1.2	2.4	37	34	4.1

genetic defect: a 3-kb microdeletion centromeric of *GNAS*, which seems to be directly or indirectly involved in silencing *Gs α* expression from the maternal allele. This case also reinforces that metabolic evaluations should be conducted in all patients with dystonia and choreoathetotic movements, which may be mimicked by symptomatic hypocalcemia.

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