Ischemic Stroke as the Presenting Symptom of Primary Hyperparathyroidism Due to Multiple Endocrine Neoplasia Type 1

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We report a 14-year-old boy whose initial presentation of primary hyperparathyroidism was ischemic stroke in the absence of hypertension. We propose measurement of serum calcium and parathyroid hormone in all children with stroke symptoms or unexplained cranial infarcts. ***(J Pediatr 2008;153:582-5)***

The diagnosis of primary hyperparathyroidism (PHP) is frequently delayed in children, and 79% of patients already have significant morbidity at diagnosis.[1] Most patients present between age 15 and 18 years, with the most common symptoms including fatigue, lethargy, headache, nephrolithiasis, nausea, abdominal pain, vomiting, and polydipsia.[1] A rare initial presentation with brown tumors also has been described in children.[2] The main causes of PHP in children are parathyroid adenoma and parathyroid hyperplasia, as in multiple endocrine neoplasia syndrome (MEN) or familial non-MEN hyperparathyroidism. Parathyroid adenoma is the most common cause of hyperparathyroidism in children.[3] Atherosclerosis and myocardial infarction have been associated with untreated PHP in adults, and stroke has been reported in up to 7% of adults with PHP.[4,5]

CASE REPORT

A 14-year-old male, previously healthy, experienced a generalized seizure during football practice. Physical examination was unremarkable, with a heart rate of 80 beats/minute and blood pressure of 120/65 mmHg. There was no evidence of dehydration. The patient was 183.3 cm tall (97th percentile), weighed 89.6 kg (> 97th percentile), and had a BMI of 26.6 kg/m^2 (95th percentile). Complete blood count, electrolytes, transaminases, blood urea nitrogen, and creatinine values were normal. Total calcium was elevated at 11.3 mg/dL (reference range, 9.6 to 10.6 mg/dL), with an ionized calcium level of 6 mg/dL (reference range, 5.1 to 5.9 mg/dL). Phosphorus was normal at 4.7 mg/dL (reference range, 3.5 to 5.3 mg/dL), and parathyroid hormone (PTH) was elevated at 98 pg/mL (reference range, 11 to 67 pg/mL), consistent with PHP. The 24-hour urine calcium was normal at 232 mg/specimen (reference range, 25 to 300 mg/specimen).

Magnetic resonance imaging (MRI) of the brain revealed a mass with increased T2 signal starting in the right orbital frontal lobe and extending into the insular cortex, producing a mass effect. No pituitary lesion was identified. A subsequent head MRI performed 10 days after the initial examination showed an increased T2 hyperintensity and mass effect, suggesting an evolving infarct rather than a tumor (Figure 1). Magnetic resonance angiography (MRA) of the brain and echocardiography results were unremarkable. Carotid ultrasound was normal. A workup for hypercoagulability, including protein C and protein S, was unremarkable. The differential diagnosis of the patient's PHP was parathyroid adenoma, MEN, or non–MEN-related parathyroid hyperplasia.

Ultrasonography of the neck revealed a 0.4 × 0.8 cm, well-defined hypoechoic nodule posterior to the mid-portion of the left lobe of the thyroid gland, along with a 0.6 × 1.6 cm hypoechoic mass posterior to the mid-portion of the right lobe of the thyroid gland, consistent with enlarged parathyroid glands. Nuclear medicine scanning of the parathyroid glands revealed a focus of increased sestamibi activity posterior to the mid-portion of the right lobe of the thyroid gland, suspicious for parathyroid adenoma (Figures 2 and 3). No nephrocalcinosis was noted.

The patient's family history was notable for PHP in the mother, maternal grandfather, and maternal uncle, all of whom had undergone parathyroidectomy. The maternal

MEN	Multiple endocrine neoplasia	PHP	Primary hyperparathyroidism
MRA	Magnetic resonance angiography	PTH	Parathyroid hormone
MRI	Magnetic resonance imaging		

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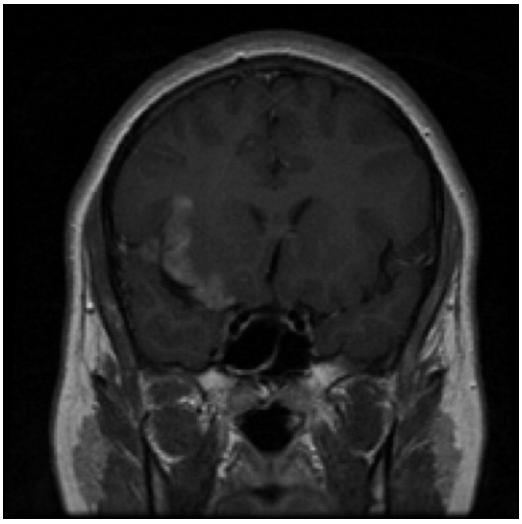

Figure 1. Brain MRI showing an evolving infarct.

grandfather also had gastric ulcers, for which he had undergone partial gastrectomy. Endocrine studies for evidence of underlying MEN, including prolactin, insulin-like growth factor-1, insulin-like growth factor binding protein-3, thyroid hormones, glucose, gastrin, urine free cortisol, metanephrines, and catecholamines, were normal.

The patient was diagnosed with an ischemic stroke and PHP secondary to MEN-related parathyroid hyperplasia. He underwent subtotal parathyroidectomy with transcervical thymectomy and autotransplantation. The pathology of all glands was consistent with hypercellular parathyroid tissue. Postoperatively, he had transient hypocalcemia and hyperphosphatemia, requiring treatment with oral calcium, calcitriol, and phosphate binders.

Genetic testing for MEN type 1 disclosed 2 heterozygous sequence changes in exon 10 of the MEN 1 gene. The first was deletion of 79 bp and insertion of 2 bp (c.1643_1721del79insTG) on the cDNA level. This mutation occurs in glycine codon 548 and results in a frameshift and premature stop codon 22 residues downstream of the mutation site (p.Gly548fsX22) on the protein level. The second variant was a G>A nucleotide substitution that leads to replacement of the normal valine codon with the methionine codon at position 537 (V537M) of the resultant protein. Genetic testing for MEN type 2 was negative.

One year postsurgery, the patient had normal calcium and PTH levels. He remains seizure-free on phenytoin therapy. Brain MRI has shown evidence of a resolving infarct with structural scarring but with no evidence of a sellar lesion. The Table gives pertinent laboratory values at presentation and at follow-up.

DISCUSSION

We have described a child with MEN-related hyperparathyroidism who experienced an ischemic stroke. No other cause of vascular occlusion or vasoconstriction was found in this patient. His coagulation studies were normal, making stroke secondary to clotting disorders unlikely. Vascular causes also were suspected, but brain MRA revealed normal vascular anatomy. The diagnosis of PHP secondary to MEN was suggested in this patient because of the family history of hyperparathyroidism in multiple family members and of gastric ulcer in a grandparent.

PHP is a rare but treatable cause of vascular occlusion and stroke. The presentation of PHP described here has been reported previously only in adults.[4-6] The rare occurrence of PHP in children (2 to 5 in 100,000, compared with 1 in 1000 in adults) is the most likely reason for the lack of similar reports in pediatric patients.[7,8]

In patients with PHP, hypertension secondary to calcium-induced vasoconstriction and renal insufficiency may cause strokes.[9] Our patient did not have hypertension at the time of presentation, however. We propose that his stroke resulted from vasoconstriction, because no obvious vascular lesions could be identified on imaging studies. It is difficult to ascertain whether his stroke was a result of hypercalcemia or due to the effect of elevated PTH independent of calcium level. Hypercalcemia is known to produce vasoconstriction, and angiography-verified hypercalcemia-induced reversible cerebrovascular vasoconstriction and MRI abnormalities have been reported previously. Vasospasm may involve a hypercalcemia-induced actin–myosin coupling with activation of vascular smooth muscle contraction in the arteriolar circulation. Furthermore, cerebral vasospasm secondary to hypercalcemia has been reported to play a role in the pathogenesis of epileptic discharges, with subsequent focal or generalized seizures.[10-12] The vascular endothelium also has been demonstrated to be a target tissue of PTH action.[13,14] Elevated PTH level has been proposed to be active in accelerating vascular atherosclerosis and/or calcification secondary to an increased production of collagen by the vascular smooth muscle cells.[15] Recently, PTH was shown to stimulate mRNA expression on the receptor of advance glycation end products and interleukin-6, both of which are associated with atherosclerotic disease.[16] This effect may account for the atherosclerosis, myocardial infarction, and stroke reported in adults with PHP.[4]

Our patient had a significant family history of PHP, but the diagnosis of MEN had not been established. The complex deletion/insertion mutation c.1643_1721del79insTG, which has not been published previously, is predicted to result in nonsense-mediated mRNA decay or, if translation proceeds, in protein truncation. Therefore, the finding of this novel frameshift mutation supports a diagnosis of MEN type 1. Another missense variant, V537M, has not been described previously in the context of MEN 1 and is not known as a common polymorphism. Thus, the significance of this finding is unknown, and further family studies are underway to investigate its importance.[17,18] We do not know whether the MEN mutations detected in this patient predispose to a greater risk of an ischemic event.

Evaluation of both calcium and PTH values is recommended in PHP screening. Screening involving measurement