Primary hyperparathyroidism in a child with tuberous sclerosis

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ABSTRACT

Primary hyperparathyroidism in patients with tuberous sclerosis (TS) is extremely rare: only three cases have been reported previously, two of them in pediatric patients.

An 11-year-old male patient with a clinical and molecular diagnosis of TS presented with mild symptomatic hypercalcemia in routine laboratory tests. Biochemical evaluation confirmed hypercalcemia with hypophosphatemia and inadequate parathyroid hormone levels, with radiological signs of hyperparathyroidism. Ultrasound demostrated hyperplasia of the left superior parathyroid gland, and a sestamibi and technetium-99m scintigram showed hyperfunctioning parathyroid tissue in both superior parathyroid glands.

Patient underwent surgical excision of the affected parathyroid glands He presented with transient postoperative hypoparathyroidism.

Although the presentation of hyperparathyroidism in TS is infrequent, we recommend evaluating symptoms associated with hypercalcemia and eventually obtaining serum calcium and phophorus measurements early diagnosis and timely treatment may prevent renal and bone complications.

Keywords: *primary hyperparathyroidism; tuberous sclerosis.*

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INTRODUCTION

Tuberous sclerosis (TS) is a rare, multisystemic disease characterized by the development of hamartomas in multiple organs. It has an estimated prevalence of 1:6000-10 000;[1,2] most cases are sporadic, although there are also hereditary forms of autosomal dominant transmission.

The disease is caused by variants in one of two associated genes: *TSC1*, which encodes hamartin, or *TSC2*, which encodes tuberin. Both are tumor suppressors that inhibit the TOR pathway. When they are inactive, the TOR pathway remains active, triggering a cascade of intracellular signaling that promotes angiogenesis, growth, and cell proliferation.[2]

Clinical manifestations include typical skin lesions (hypomelanotic macules, angiofibromas, shagreen plaques), hamartomas in the central nervous system (CNS) or retina, renal tumors (angiomyolipoma), and cardiac rhabdomyomas, among others. There are major and minor criteria for confirming the diagnosis.[1]

There are a few reports of endocrine tumors,[3] such as pituitary adenomas, insulinomas, gastrinomas, pheochromocytoma, or bronchial carcinoid tumors. Their association with primary hyperparathyroidism is exceptional: only 3 cases have been reported in the literature, 2 of which involved pediatric patients.[4-6]

The objective was to describe a clinical case of primary hyperparathyroidism in a patient with TS, its therapeutic management and evolution, and to compare it with previously described cases.

CLINICAL CASE

An 11-year-old boy with TS, diagnosed at 3 years of age based on clinical criteria (hypochromic macules, facial angiofibromas, subependymal nodule) and a family history of the same diagnosis in his mother and sister.

A molecular study was performed using an NGS panel of genes associated with hereditary tumors available at our hospital. This study identified a heterozygous nonsense variant in exon 2 of the *TSC2* gene NM_000548.5:c.40A>T-p.(Lys14Ter), subsequently confirmed by Sanger sequencing. It had not been previously reported and was classified as pathogenic (PVS1_vs, PM2_supp, PP1_supp) according to the criteria established by the American College of Medical Genetics and Genomics (ACMG). The family segregation study showed the same variant in the mother and sister.

He was referred to Endocrinology due to hypercalcemia detected in a routine laboratory test. Upon further questioning, he reported headache, nocturia, and behavioral changes with self- and other-directed agression. Physical examination showed weight and height in the 25-50th percentile, blood pressure in the 90th percentile, and a normal electrocardiogram, with no other positive findings.

Biochemical profile was requested: calcemia 11.3 mg/dl (normal range [NR]: 8.5-10.5), phosphatemia 3.3 mg/dl (NR 3.8-5.2), parathyroide hormone levels (PTH) 49 pg/mL (RR 12-95), 25(OH) vitamin D 12.8 ng/mL (RR 20-80), alkaline phosphatase (ALP) 296 IU/L (NR 91-291), 24-hour urine with calciuria 436 mg/day (NR <250) and 13 mg/kg/day (NR <4), tubular reabsorption of phosphate (TPR) 86% (NR >85), with creatinine 0.52 mg/dl (NR up to 0.7) and urea 17 mg/dl (NR 15-42).

We interpreted that the patient had hypercalcemia with hypercalciuria, hypophosphatemia, PTH inappropriately elevated for calcemia, TRP inappropriately decreased for phosphatemia (since in this case it should be close to 100%), with normal renal function, results consistent with symptomatic primary hyperparathyroidism. Renal protection measures were indicated, including increased fluid intake, increased consumption of fruits and vegetables, and reduced dietary sodium intake.

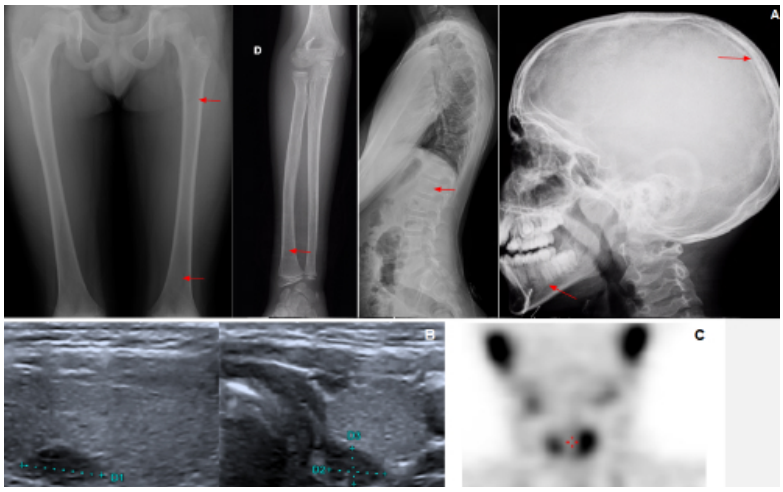
Imaging studies were performed, revealing skeletal signs of hyperparathyroidism, including mild generalized osteopenia, absence of periodontal lamina dura, thickening of the diploe on radiographs (*Figure 1*), with bone mineral density (BMD) of 0.578 g/cm² and a pathological z-score of -2.2 on total body densitometry excluding the head. Renal ultrasound was normal.

For topographic localization of the lesion, a cervical ultrasound was requested and showed hyperplasia of the left superior parathyroid gland; and a technetium-99m sestamibi scan with delayed imaging and thyroid suppression revealed hyperfunctioning tissue in both superior parathyroid glands.

Excisional surgery was indicated, during which enlarged superior parathyroid glands were identified and resected.

The pathological study was consistent with hyperplasia of both parathyroids. In the immediate postoperative period, he presented with a decrease in calcemia to 7.2 mg/dl despite preventive calcium carbonate and calcitriol,

Figure 1. Imaging studies at diagnosis



A. X-rays of the lower limbs (front), right forearm (front), spine (profile), and skull (profile): report mild generalized osteopenia in long bones and vertebrae, absence of periodontal lamina dura, and thickening of the diploe.
B. Cervical ultrasound: shows an 8 mm hypoechoic image behind the left thyroid lobe consistent with hyperplasia of the upper left parathyroid gland.
C. Technetium-99m sestamibi scan with delayed imaging and thyroid suppression reports hyperfunctioning parathyroid tissue in both upper parathyroid glands.

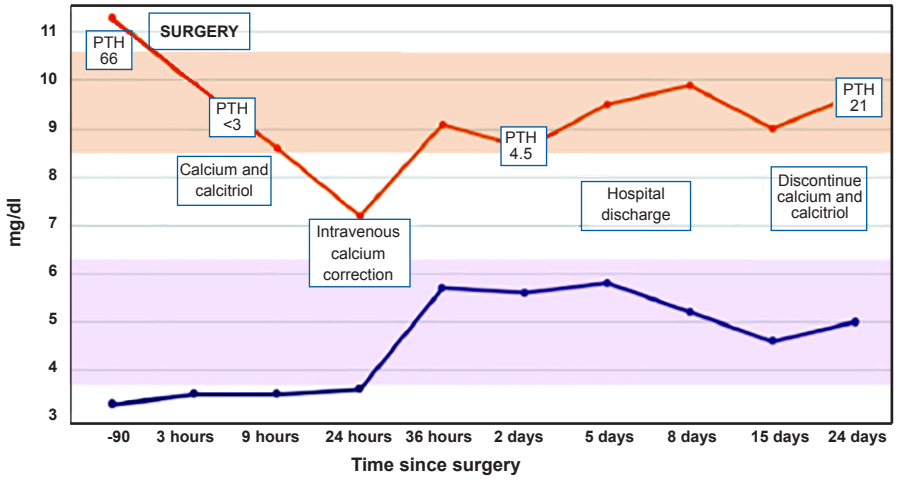
and an increase in phosphatemia to 5.8 mg/dl, with normal ALP. He required a single intravenous calcium correction and increased oral intake. Calcemia progressively increased, phosphatemia progressively decreased, and PTH normalized, leading to the diagnosis of transient hypoparathyroidism (*Figure 2*).

More than two years after surgery, he remains with normal calcemia and phosphatemia levels in periodic outpatient follow-up.

DISCUSSION

Hypercalcemia is a rare condition in pediatrics, with both congenital or acquired etiologies. Unlike

Figure 2. Pre- and post-surgical evolution of calcemia, phosphatemia, and parathyroid hormone levels



PTH: parathyroid hormone.
Calcemia (mg/dl).
Phosphatemia (mg/dl).

in the adults, PTH-independent mechanisms predominate over PTH-dependent mechanisms in children and adolescents, as previously reported by our group.[7]

Although children with hypercalcemia may be asymptomatic,[7-9] sudden onset or values greater than 14 mg/dL can result in a medical emergency. At the same time, chronic forms can cause irreversible kidney damage, increasing patient morbidity and mortality.[10] If the origin of hypercalcemia is due to excess PTH, bone damage is also added. In our case, the diagnosis was made early based on laboratory findings, preventing serious acute or chronic complications.

The finding of a parathyroid adenoma in pediatric patients should raise suspicion of a predisposing genetic cause, given its low frequency in children.[11]

When parathyroid hyperfunction is strongly suspected, cervical ultrasound is the initial study, which, together with a technetium-99m sestamibi scan with delayed imaging and thyroid suppression, usually allows topographic localization.

Although our patient had mild hypercalcemia, long-term hyperparathyroidism can lead to the complications mentioned above. For this reason, the recommended treatment in pediatric patients is surgical excision of the affected parathyroid glands. Postoperatively, this procedure can cause transient or persistent hypoparathyroidism or hungry bone syndrome. In our case, transient hypoparathyroidism occurred secondary to inhibition of healthy glands due to previous hypercalcemia and a rapid decrease in PTH during surgery. It differs from hungry bone syndrome in that it presents with inhibited PTH and normal to high phosphatemia.

Three similar cases (*Table 1*) are described; our case is the youngest reported to date. The clinical presentation was variable, often with a family history, with no gender predominance. The two cases with molecular confirmation presented different variants, reflecting the high genetic variability, lack

Table 1. Comparison with previously described cases

	Case 1[4]	Case 2[5]	Case 3[6]	Our case
Date and location	1984, England	1991, Denmark	2015, Japan	2022, Argentina
Clinical presentation of TS	Sebaceous adenoma, cortical tubercles, lymphangioleiomyomatosis, renal polycystosis, liver and lung lesions	Sebaceous adenoma, hypomelanotic macules, and subependymal calcifications	Cortical tubercles, subependymal nodules, renal hamartoma, cardiac rhabdomyoma, hypomelanotic macules, and chagrin plaques	Hypomelanotic macules, hamartoma in the CNS
Family history	Mother	Mother and sister	ND	Mother and sister
Age at diagnosis of hyperparathyroidism (years)	20	15	23	11
Gender	Female	Male	Female	Male
Genetic testing	Not performed	Not performed	Variant in *TSC1* that causes abnormal splicing	Nonsense variant in *TSC2*
Reason for consultation	Laboratory findings	Abdominal pain	Laboratory findings	Laboratory findings
Symptoms	High blood pressure, impaired renal function	Pancreatitis	Asymptomatic	Headache, nocturia, behavioral changes
Maximum calcemia (mg/dl)	NA	NA	11.5	11.3
Minimum phosphate (mg/dl)	NA	NA	1.9	3.3
Maximum PTH (pg/mL)	NA	NA	147	49
Cervical ultrasound	Increase in all parathyroid glands	Lower right parathyroid enlargement	Lower right parathyroid enlargement	Upper left parathyroid enlargement
Parathyroid scintigram	NA	Increase uptake of the lower right parathyroid glands	Increase uptake of the lower right parathyroid	Increase uptake of both upper parathyroid glands
Treatment	Total parathyroidectomy	Lower right parathyroidectomy	Lower right parathyroidectomy	Both upper parathyroid glands parathyroidectomy

CNS: central nervous system, NA: not available, TS: tuberous sclerosis.

of genotype-phenotype correlation, and clinical heterogeneity previously described in TS.[2]

It is noteworthy that most were consulted due to laboratory findings of hypercalcemia, but upon further review of medical history and complementary studies, three presented with associated symptoms. Regarding treatment, all patients require a parathyroidectomy to manage the condition.

There may be an association between TS and hyperparathyroidism, and even with different types of neuroendocrine tumors.[3] However, given the low frequency of both entities, this relationship has not yet been conclusively demonstrated. The primary mechanism supporting the possible association is the lack of TOR pathway inhibition by genetic variants that inactivate the hamartin-tuberin complex. Sustained activation of this pathway stimulates the synthesis of proteins that promote cell growth, which could explain the abnormal proliferation of different cell types, such as parathyroid cells.[2,3]

In conclusion, although the presentation of hyperparathyroidism in TS is infrequent, we suggest systematically evaluating the presence of symptoms associated with hypercalcemia and eventually obtaining serum calcium and phophorus measurements, as early diagnosis and timely treatment could prevent long-term complications. ■

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