

Spontaneous Remission of Primary Hyperparathyroidism in a Patient with Neurofibromatosis Type 1: Case Report

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Abstract

Neurofibromatosis type 1 (NF1) is an autosomal dominant multisystem disorder affecting approximately 1 in 3500 individuals. Patients with the disorder can develop carcinoid tumors, medullary thyroid carcinoma, pheochromocytoma and tumor of the hypothalamus. The association of NF1 with Primary Hyperparathyroidism (HPP) is very rare. We report a 56-year-old woman with NF1 who was referred to our service because of nephrolithiasis. Physical examination revealed the characteristic signs of NF1, and her laboratory calcium profile was compatible with HPP. The patient was referred for parathyroidectomy, but during the surgical work-up she underwent spontaneous remission of her HPP. This case is significant not only for the rarity of this presentation in NF1 patients, but also because of the spontaneous remission of HPP.

Keywords: Neurofibromatosis Type 1; Primary Hyperparathyroidism; Autosomal dominant disease

Introduction

Neurofibromatosis type 1 (NF1) or von Recklinghausen disease is an autosomal dominant disorder affecting approximately 1 in 3500 individuals, with 50% of the cases being familial and the others occurring by *de novo* mutation [1-3]. Affected individuals can develop a variety of benign and malignant tumors; the most common are neurofibromas which are a peripheral nervous system tumor.

The diagnostic criteria for NF1 are met in an individual who has two or more of the clinical features: 6 or more café-au-lait macules >5 mm in diameter in prepubertal and >15 mm in postpubertal individuals (the longest diameter of each lesion is measured); 2 or more neurofibromas of any type or 1 plexiform neurofibroma; freckling in the axillary or inguinal regions; optic glioma; 2 or more Lisch nodules (iris hamartomas); a distinctive bony lesion such as sphenoid dysplasia or thinning of the cortex of a long bone, with or without pseudoarthrosis; and a first-degree relative (parent, sibling, or offspring) with NF1 based on the previous criteria [4]. In addition to these findings, affected patients present an increased risk for neoplasias of the central nervous system, including, ependimomas, meningiomas, astrocytomas; and some endocrine tumors, including pheochromocytomas, parathyroid neoplasias, carcinoid tumors, and, most frequently, medullary carcinomas of the thyroid [5], which often occur in association with pheochromocytomas [6].

HPP results from hyper secretion of Parathyroid Hormone (PTH); in 85% to 90% of cases it is caused by an adenoma in 1 of the parathyroid glands [7]. It is the most common cause of hypercalcemia diagnosed in an ambulatory setting [7,8] and can occur at any age, but most frequently from 40 to 65 years, with a female:male predominance of 3:1. The incidence in Rochester-Minnesota during 1993–2001 was estimated to be 21.6 per 100,000 person-years [9]. Although the sporadic form is most common, about 10% of cases are familial and may be isolated or associated with other autosomal-dominant endocrine neoplasias such as Multiple Endocrine Neoplasia (MEN) types 1 and 2, and hyperparathyroidism-jaw tumor syndrome.

The association of NF1 with HPP has been reported, but is uncommon. We present a patient with both conditions, along with spontaneous remission of her hyperparathyroidism.

Case Report

A postmenopausal 56-year-old woman, who had been diagnosed with NF1 34 years previously and had a 3-year history of arterial hypertension, was referred to our service for investigation of nephrolithiasis. Two of her 4 children, whom she had with her first cousin, and 1 of her 4 grandchildren also had NF1 (Figure 1).

Her physical examination revealed numerous neurofibromas on the face, cervical region, trunk, and extremities; and café-au-lait spots larger than 1.5 cm on her back, abdomen, and thorax. Ophthalmologic examination showed numerous Lisch nodules, and she also had pulsatile exophthalmos of the left eye.

Results of laboratory investigations showed that the calcium profile was compatible with HPP (total serum calcium, 11.9 mg/dL [normal: 8.4-10.2 mg/dL]; PTH, 213 pg/dL [normal: 11-65 pg/dL]; 24-hour urinary calcium, 7.3 mg/kg; and serum phosphorus 2.2 mg/

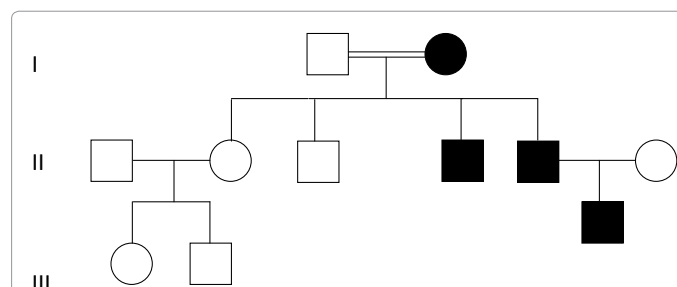


Figure 1: The patient had with her first cousin 4 children, two of them have Neurofibromatosis Type 1 and 1 of her 3 grandchildren also had the syndrome.

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dL [normal: 2.5-4.5 mg/dL]). Serum albumin and renal function were normal. Scintigraphy and ultrasonography of the parathyroids did not reveal abnormalities. Bone densitometry showed osteoporosis at the femoral neck (T-score, -2.87). Magnetic resonance imaging of the head demonstrated findings compatible with a plexiform neurofibroma originating in the left temporal region with infiltration of adjacent structures, gliosis in the left frontal lobe, probable arachnoid cyst in the left Sylvian fissure, and agenesis of the wing of the left sphenoid bone. Results of screening for pheochromocytoma, performed by testing for the presence of plasma catecholamines and urinary metanephrines, were negative.

Because of the findings and because her hypercalcemia (serum calcium >11 mg/dL) had been present at least 1 year, the patient was referred for parathyroidectomy. However, spontaneous HPP remission occurred during preoperative programming (total serum calcium, 9.7 mg/dL; PTH, 59.2 pg/dL; 24 hour urinary calcium and phosphorus, 138 mg/dL and 3.8 mg/dL, respectively). Normal serum calcium and PTH levels have been maintained for 2 years.

The patient's children were also screened for the disease. They were provided with information regarding the hereditary nature of NF1 and the need for regular specialized medical follow-ups. Because of the uncommon association of NF1 with HPP, the calcium profiles of all the NF1-affected children and grandchild were determined. The results of the HPP screening examinations were negative.

Discussion

The *NF1* gene, located at chromosome 17q11.2, has been mapped and cloned [10] it codes for neurofibromin, which is a protein expressed in tissues such as brain, kidney, spleen, and thymus [11]. Mutations in *NF1* lead to a functional loss of this protein, thereby provoking a wide array of clinical findings, including the association of NF1 with diverse benign and malignant tumors. A study of a defined Swedish population found that neuroendocrine tumors such as, pheochromocytoma, and C-cell hyperplasia of the thyroid, represented 10% of all tumors that appeared in patients with NF1 [11].

Approximately 13 patients with NF1 and HPP have been described, but the pathogenesis of this association has not yet been well elucidated [12]. Dayle et al. [6] reported the first cases in the literature, and presented the hypothesis that there could be a genetic link between parathyroid adenoma (originating in endoderm) and NF1 (originating in neuroectoderm). However, Chakrabarti et al. [13] interpreted the association as another variant of MEN type 2B.

There is great variety of expression in NF1 patients, and there is also a series of characteristics that only occur in a minority of cases [2,14]. Some of these variations can reflect different mutations in *NF1*, while others might be associated with environmental or other external factors [15]. However, genetic evaluations of the association between NF1 and HPP have never been reported; thus, to ascertain the mechanism of this association further, new studies are necessary.

In the last few decades, along with the increase in the number of diagnosed HPP cases, the profiles of clinical and laboratory presentations and therapeutic interventions have undergone changes. In general, familial HPP presents with severe hypercalcemia; and the management of these patients differs from sporadic HPP due to the variability of the presentations including: penetrance, delay in the onset of symptoms, severity of hypercalcemia, propensity for parathyroid cancer (hyperparathyroidism jaw-tumor syndrome), viability and

precision in the evaluation of the status of the mutation carrier, and elevated post-parathyroidectomy relapse rate [16].

There have been a few reported cases of spontaneous remission of HPP [17]. Remissions in these cases were generally attributed to hemorrhage and/or infarct of the adenoma [18-23]. This phenomenon has been termed "autoparathyroidectomy" or "parathyroid apoplexia" because of similarities with pituitary apoplexia [24]. Elangovan et al. [24] also proposed that the rapid growth of an adenoma might lead to a vascular event that is insufficient for producing an infarct but sufficient for reducing the supply of oxygen, leading to reduced production of PTH.

Regarding clinical presentation the patients can have hypocalcemia with or without tetania, followed by a period of normocalcemia or/and recurrence of the disease. In rare cases, patients can present with signs and symptoms of cervical mass or mediastinal hemorrhage due to extra capsular hemorrhage of the adenoma. Although most patients are symptomatic, this phenomenon can be mild and the patients can have no clinical disorders [25]. In the majority of the cases reported in the literature, surgical treatment was ultimately performed, while only a few patients were treated conservatively, under periodical clinical and biochemical follow-up [24].

Nylen et al. [22] proposed a classification scheme for parathyroid apoplexy based on the extent of hemorrhage and clinical characteristics. The same patient can present with acute symptoms of hypocalcemia, or even with acute hypercalcemia caused by copious release of excess PTH, followed by a period of normocalcemia and, finally, recurrence of the disease. The same patient can also present with asymptomatic reductions of calcium and PTH levels [25].

The routine use of one or more localizing studies commonly identifies the parathyroid tumor in patients with single-gland disease; but in some cases the localizing studies can be negative or discordant and these patients should have intra-operative PTH levels monitored or have a bilateral neck exploration to ensure a high rate of biochemical cure [22]. Comparisons of different imaging methods have demonstrated the superiority of parathyroid scintigraphy for preoperative localization [26]. One systematic review of the medical literature showed that the overall sensitivity of dual-phase ^{99m}Tc sestamibi scintigraphy in comparison with high-resolution Ultrasonography (US) was 88% versus 78% for single adenomas, 30% versus 16% for double adenomas, and 44% versus 35% for multiple-gland hyperplasia [27].

In conclusion, we described a patient with a clinical picture typical of NF1, in whom associated HPP was diagnosed during investigation of nephrolithiasis. Despite being a classical association, it is very rare. This patient manifested criteria for surgical intervention; however, she underwent spontaneous clinical remission of HPP during preoperative evaluation. Despite the rarity of HPP and, in this case, spontaneous remission, HPP can be associated with NF1, which should be remembered for this group of patients.

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