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Preoperative multiple endocrine neoplasia type 1 diagnosis improves the surgical outcomes of pediatric patients with primary hyperparathyroidism ☆

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ABSTRACT

Background: Primary hyperparathyroidism (PHPT) is uncommon in children. The surgical management of PHPT in children has evolved over the past two decades.
Methods: A retrospective study of patients who underwent parathyroidectomy for PHPT diagnosed at age <18 years and managed at a tertiary referral center for endocrine and familial disorders.
Results: Thirty-eight patients met eligibility criteria (1981–2012). Median age at PHPT diagnosis was 15 years. Two-thirds of patients were symptomatic (68%, n = 26), most commonly from nephrolithiasis. Twenty-six (68%) patients underwent a standard cervical exploration while 32% underwent a focused unilateral parathyroidectomy. Multiple endocrine neoplasia type 1 (MEN1) was diagnosed preoperatively in 22/26 patients. Patients with a preoperative diagnosis of MEN1 were more likely to undergo a complete initial operation (≥3 gland parathyroidectomy with transcervical thymectomy, 13/22, 59% vs. 0/4, 0%; P = 0.03) and less likely to have recurrent disease (10/22, 45% vs. 3/4, 75%; P < 0.001) during follow up than patients diagnosed postoperatively.
Conclusions: Children with PHPT should raise suspicion for MEN1. Preoperative MEN1 evaluation helped guide the extent of initial parathyroidectomy and was associated with lower rates of recurrence in sporadic and familial PHPT in pediatric patients. Management should occur at a high volume center with experienced clinicians and genetic counseling services.

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1. Background

Primary hyperparathyroidism (PHPT) occurs at an incidence of 100,000 cases annually in the United States. Sporadic disease accounts for the majority of cases; it typically presents in the seventh to eighth decades of life, is caused by a single benign adenoma, and affects women more frequently than men (4:1 ratio) [1]. In children, PHPT is rare (1% of PHPT cases) [2], more evenly affects females and males [3–5], and is commonly associated with classic symptoms at diagnosis [3–6].

Regardless of age at presentation, approximately 3% to 5% of PHPT cases are hereditary and may represent the initial clinical manifestation of multiple endocrine neoplasia type 1 (MEN1) (OMIM 613733) [7]. Initially described in 1954 [8], MEN1 is the most common cause of hereditary PHPT [7]. Unlike sporadic disease, MEN1-associated PHPT manifests at a younger age (onset between 20 and 25 years with nearly 100% diagnosed by age 50), is associated with 4-gland parathyroid hyperplasia, frequently with supernumerary glands, and affects men and women equally [7]. Following parathyroidectomy, persistence and late recurrence are more common in MEN1 patients than in sporadic PHPT [9]. Modern genetic testing detects approximately 70%–95% of patients with MEN1 [9,10]; a clinical diagnosis of MEN1 in a patient presenting with PHPT requires a family history of MEN1 in a first degree relative and/or the occurrence of >2 MEN1-related tumors in the same individual [11].

Current guidelines for the treatment of PHPT in MEN1 patients call for standard cervical exploration (SCE) with resection of ≥3 parathyroid glands and transcervical thymectomy [11–13]. Thus, preoperative clinical or genetic diagnosis of MEN1 is essential to performing the appropriate operation and achieving cure.

This manuscript describes the clinical features, operative management, and outcomes of PHPT in a pediatric cohort referred for primary treatment or follow up to a tertiary referral center specializing in the treatment of sporadic and familial endocrine disorders. Due to the abundance of MEN1 patients in this cohort, we used this opportunity to evaluate the role of a preoperative MEN1 diagnosis on the surgical outcomes of parathyroidectomy in children with PHPT.

2. Methods

After obtaining institutional review board approval, we retrospectively analyzed the records of patients who underwent parathyroidectomy for PHPT diagnosed at age ≤18 years. Institutional and research databases were queried to identify pediatric patients treated with initial

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parathyroidectomy at The University of Texas MD Anderson Cancer Center as well as those referred for follow up, and/or evaluation of recurrent PHPT after initial parathyroidectomy off-site. The surgeons at our institution were high-volume surgeons with extensive experience in endocrine surgery. Clinical, pathological, operative, and genetic testing data were abstracted from the electronic medical records.

At our institution pediatric patients are defined as patients 18 years or younger. MEN1 was a clinical and/or genetic diagnosis. A clinical diagnosis of MEN1 was made if a patient had a family history of MEN1 in a first degree relative and/or the occurrence of ≥2 MEN1-related tumors in the same individual [11]. A genetic diagnosis was made based on identification of a pathogenic mutation using standard methodology [12,14,15]. While genetic testing is now a criterion for the clinical diagnosis of MEN1, for the purposes of this manuscript, a clinical diagnosis of MEN1 did not include genetic testing. Genetic testing was performed through federally certified Clinical Laboratory Improvement Amendments laboratories. At our institution, a research protocol established in 2002 allows for MEN1 genetic testing when clinical testing is unavailable to patients.

SCE refers to a bilateral neck exploration, but does not refer to the number of glands actually excised. Minimally invasive parathyroidectomy (MIP) refers to a focused, unilateral parathyroidectomy guided by preoperative imaging and intraoperative parathyroid hormone (PTH) monitoring. A complete operation for MEN1 patients was defined as SCE with ≥3 parathyroid glands excised and concomitant transcervical thymectomy [10,12,13]. Persistent PHPT was defined as hypercalcemia < 6 months postoperatively, while recurrent PHPT was defined as normocalcemia for at least 6 months, followed by recurrent hypercalcemia detected > 6 months. Cure was defined as eucalcemia for > 6 months without documented recurrence. Permanent hypoparathyroidism was defined as PTH < 10 pg/mL at more than 6 months postoperatively and continued daily calcium and/or calcitriol requirements.

Descriptive statistics were used to evaluate clinical and operative factors. Subgroup analyses were performed to evaluate for differences in outcomes based on a known MEN1 diagnosis preoperatively. Differences between groups were calculated using Pearson's χ^2 coefficient or Fisher's exact test, where appropriate. A p value of 0.05 or less was regarded as statistically significant. Analyses were carried out using IBM® SPSS© Statistics, Version 19.0.0, Armonk, NY: IBM Corp.

3. Results

3.1. Patient characteristics

Thirty-eight pediatric patients who underwent parathyroidectomy for PHPT from 1981 to 2012 were included in this study. The median age at initial diagnosis of PHPT was 15 years (range 11–18), and median age at initial operation was 18 years (range 12–34). The male to female ratio was 1:1.2. The majority of patients (n = 26, 68%) were symptomatic. Of those with symptoms, 73% had nephrolithiasis (n = 19). Other documented symptoms (n = 11) included difficulty concentrating, poor performance in school, and headaches; 7 patients exclusively reported this type of symptoms. One-third of patients (n = 12, 32%) had no objective symptoms documented. Nearly two-thirds (n = 24, 63%) of patients reported a family history of hypercalcemia and/or MEN1. The median follow-up after parathyroidectomy was 4.3 years (range 0–29 years).

3.2. Preoperative evaluation for MEN1

Three-fourths of patients in this study ultimately were diagnosed with a hereditary cause of PHPT (n = 28, 74%). The most common familial etiology of PHPT was MEN1 (26/28 patients with familial PHPT, 68% of total population) followed by hyperparathyroidism–jaw tumor

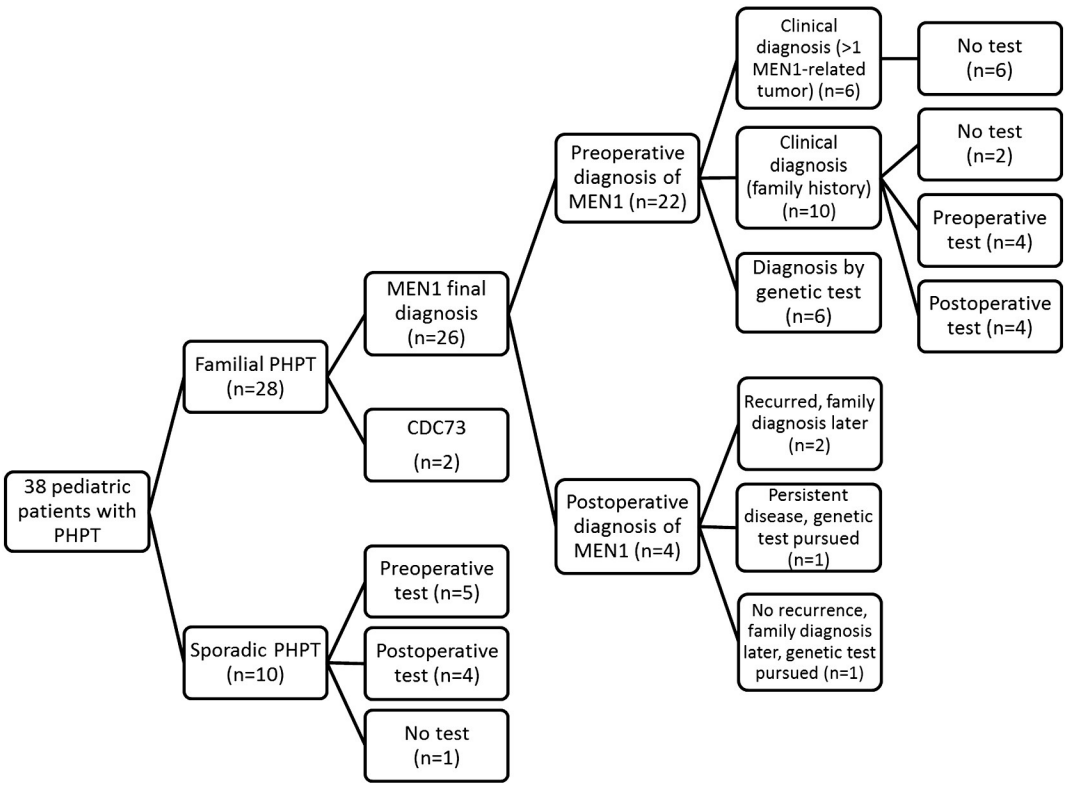

Fig. 1. Timing and method of diagnosis of familial primary hyperparathyroidism in 38 pediatric patients who underwent parathyroidectomy. Of the patients with known MEN1 preoperatively, 16/26 were diagnosed based on clinical guidelines. Six patients were diagnosed by genetic testing, of whom 3 underwent genetic testing based solely on age at diagnosis.

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