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Original Research Article

Pediatric primary hyperparathyroidism: Surgical pathology and long-term outcomes in sporadic and familial cases

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ABSTRACT

Background: Primary Hyperparathyroidism (PHPT) is rare in pediatric patients. Data regarding surgical outcomes are scarce.
Methods: Single-center retrospective review (1994–2020) of patients ≤21 years undergoing surgery for PHPT.
Results: 66 patients were identified (61% female, 17 ± 3 years). 71% of patients were symptomatic at diagnosis. 32% of patients had known familial syndromes, most commonly MEN-1. 23% of patients without a known mutation had genetic testing, 22% positive. 56% of the total and 19% of the familial cohort underwent focused exploration. Single gland disease was found in 19% of familial vs 85% of sporadic cases, $p < 0.00001$. Persistence was 9%, all in the sporadic group, $p = 0.11$. Recurrence was 15%: 38% in the familial vs 2% in the sporadic groups, $p=0.0004$. Time to recurrence was 59 months (Q1-38, Q3-95), familial 61 vs 124 months sporadic, $p=0.001$.
Conclusion: Pediatric PHPT is frequently sporadic, although 5% of apparent sporadic cases are secondary to syndromes. Familial cases have higher rates of recurrence, requiring closer follow-up.

1. Introduction

Primary hyperparathyroidism (PHPT) is rare in the pediatric population, with an estimated incidence of 0.5–5 cases per 100,000 person-years in children, compared to 50–100 cases per 100,000 person-years in adults.[1–3] Clinical presentation differs between young and older patients, with children and young adults more often presenting with symptomatic disease and end-organ damage, which may be due to biologic differences and/or delays in diagnosis due to the rarity of the condition.[4–14] In both children and adults, most cases of PHPT are sporadic, but patients diagnosed at a young age are more likely to have an underlying hereditary syndrome, such as multiple endocrine neoplasia type 1 (MEN 1) or 2A (MEN 2A), familial isolated hyperparathyroidism (FIHP), or hyperparathyroidism-jaw tumor syndrome (HPT-JT), compared to older patients.[15,16]

Regardless of the etiology, surgery is the treatment of choice in children and young adults to alleviate symptoms and prevent development or progression of end-organ damage.[17] Several studies have shown that surgery is highly successful in lowering calcium in these patients, but due to the rarity of the disease, the majority of available data is derived from small series and little is known about long-term outcomes after surgery in this population.[4–9,11–14] Additionally, it has been debated whether diagnosis at a young age warrants routine bilateral cervical exploration due to a potential higher rate of multiglandular disease, but studies have shown conflicting results.[18,19]

In this study, we describe the clinical characteristics, management, and outcomes of pediatric and young adult patients who underwent surgery for PHPT over a 27-year period at our institution, with an emphasis on long-term outcomes and factors associated with disease persistence and recurrence.

2. Patients and methods

This was a single-center retrospective review of all patients aged 21

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or less undergoing surgery for primary hyperparathyroidism in our institution from 1994 to 2020. Once the Mayo Foundation Institutional Review Board approved this study, data was gathered from the electronic medical record system (EMR). Demographic information, pre-operative presentation, genetic associations, previous treatments, intra- and post-operative variables as well as pre- and post-operative laboratory values were retrieved from EMR. Data was recorded up to death or last follow-up available information in the electronic systems, specifically looking at disease persistence and disease recurrence. Persistence of primary hyperparathyroidism was defined as hypercalcemia detected within 6 months of surgery, and recurrence was defined as hypercalcemia present after 6 months from surgery. Categorical data is reported in descriptive statistics. Continuous data are reported as mean and standard deviation (SD) or median and interquartile range. Chi-squared test was used to assess differences for discrete variables and two sample *t*-test for continuous variables. The software JMP 14.1.0 (SAS, Cary, NC, 2018) was used for the statistical analysis. Study data were recorded and managed using the Research Electronic Data Capture system. Research Electronic Data Capture is a secure, web-based application designed to support data capture for research studies.[20]

3. Results

From 1994 to 2020, 66 patients ≤21 years of age underwent parathyroidectomy for PHPT. The majority of patients (n = 40, 61%) were female and mean age was 17 ± 3 years (range 6–21). Thirty one percent of diagnoses (n = 18) were made incidentally through laboratory evaluation performed for other reasons while 71% (n = 42) were symptomatic at diagnosis. The most common symptom was nephrolithiasis in 35% of the cohort (n = 20), followed by bone fractures in 22% (n = 13), Table 1.

The minority of the cohort (33%, n = 19) presented with family history of PHPT, of which 95% (n = 18) had known familial syndromes. Sixty-three percent of patients with family history had undergone genetic testing (n = 12). Twenty-three percent of patients without family history (n = 9) had genetic testing performed, two of which were positive (MEN 2A and MEN 1). In total, 32% (n = 21) of patients were carriers of genetic syndrome, MEN 1 being the most common (67%, n = 14), followed by FIHP (19%, n = 4), MEN-2A (10%, n = 2) and HPT-JT (5%, n = 1). Table 2 compares the sporadic and familial cohorts.

The median highest pre-operative serum total calcium was 11.5 mg/dL (Q1- 11.1, Q3- 12.5), without differences between familial and sporadic cases, p = 0.46. Similarly, there were no differences in pre-operative PTH between groups, with median value being 99 pg/mL (Q1- 7.15, Q3- 133), p = 0.58.

Pre-operative imaging was performed in 82% of patients (n = 54), T99/I123 dual isotope sestamibi scan being performed most commonly (76%, n = 50), followed by neck ultrasound (36%, n = 24). Fifty-six percent of the entire cohort (n = 37) underwent focused exploration: 19% of patients with familial disease (n = 4) vs 73% of patients with sporadic disease (n = 33). Sixty-five percent of patients had single gland disease, accounting for 19% of patients with familial syndromes vs 85% of the sporadic cohort, $p < 0.00001$. Fifty-three percent of patients were found to have parathyroid hyperplasia, with gland mean weight being 706 ± 638 mg. Seventy-seven percent of cases had intra-operative PTH measurements, with median PTH drop being 118 pg/ml from baseline (Q 1–57, Q3- 197). Eight patients developed surgical complication, accounting for 12% of the cohort. Transient hypocalcemia was the most common (n = 8) complication and there was one occurrence of recurrent laryngeal nerve injury.

Median initial post-operative serum calcium and PTH were 9.2 mg/dL (Q1- 8.9, Q3-9.6) and 13 pg/dL (Q1- 6.75, Q3-25) respectively. Disease persistence occurred in 9% (n = 6), all in the sporadic group (p = 0.11). All were treated surgically with 33% (n = 2) of persistences being due to mediastinal ectopic glands requiring thoracoscopic surgery, and 16% (n = 1) occurred due to hyperplasia. 33% of patients who presented with persistence had intra-operative PTH measured, with appropriate drop of serum PTH being identified in all patients whose values were available upon completion of this study. Sixty-six percent of the patients with persistent disease (n = 4) underwent bilateral cervical exploration at initial operation. Disease recurrence occurred in 15% (n = 10). 90% of recurrences occurred in patients with genetic syndromes (n = 9), of which 33% (n = 3) were in patients who underwent focused exploration. Thirty-three percent of recurrences were symptomatic. Thirty percent of recurrences occurred due to a newly identified adenoma. 50% of recurrences had intra-operative PTH measured, and all patients with available values had the appropriate drop of PTH of at least 50% and within normal serum limits. Eighty percent of recurrences required surgical re-intervention, with two patients requiring more than one surgery. Three patients underwent alcohol ablation of parathyroid remnants, two of which were genetic syndrome carriers. Median time to recurrence was 59 months (Q1 - 38, Q3 – 95). Sporadic patients had a longer disease-free period, 124 (Q1 – 11, Q3 – 237), vs 61 months (Q1 – 38, Q3 – 90) for familial cases, p=0.0012. Thirteen percent of the cohort lost follow-up immediately after surgery, of which 8% was part of the hereditary group. Mean follow-up time for patients who did not lose follow-up was 96 ± 89months.

Table 1
Primary hyperparathyroidism symptoms distribution.

Symptom	% (n)
Symptomatic nephrolithiasis	35% (22)
Fatigue	24% (16)
Bone fractures	22% (13)
Hypertension	9.8% (6)
Osteoporosis or Osteopenia	6% (4)
Other symptoms	56% (31)
- Abdominal pain	10% (7)
- Nausea	9% (6)
- Constipation	8% (5)
- Musculoskeletal pain	6% (4)
- Pancreatitis	3% (3)

Table 2
Sporadic vs Hereditary primary hyperparathyroidism patients'characteristic.

	Sporadic (n = 45)	Hereditary (n = 21)	*p*
Age (median, IQR)	18(Q1 = 16, Q3 = 19)	16 (Q1 = 12.5), Q3 = 19	*0.06*
Sex (M)	30%	37%	*0.23*
Pre-operative Calcium mg/dL	11.6 (Q1+11.1, Q3 = 12.15)	11.3 (Q1 = 10.95, Q3 = 12.65)	*0.56*
Pre-operative PTH pg/mL	99 (Q1 = 66, Q3+125)	98 (Q1 = 72, Q3 = 157.5)	*0.48*
Persistence	21%	0%	*0.11*
Recurrence	2%	37.5%	*0.0004*

4. Discussion

This retrospective study analyzed short- and long-term surgical outcomes of parathyroidectomy in a pediatric population over a period of almost three decades. Most of the current literature shows that PHPT in the pediatric population is slightly more prevalent in female patients (54–65%),[4,8,11,13,21–25] with some series documenting similar prevalence between sexes.[12,26] Mean age at diagnosis was 17 ± 3 years in our study, somewhat older than other series.[1,4,8,11,22–24,27] We attribute this difference to two factors: no neonatal cases were added to our series; and different series have used different ages as pediatric age cut off, with our series being conservative accruing patients up to 21 years of age. Most pediatric patients were symptomatic at diagnosis, 71% in our series. This is a well-established phenomenon in the literature, with the rate of symptoms ranging from 30 to 94% of patients[1,8,23,24,27,27] and a minority of cases incidentally discovered on laboratory evaluation. The

rate of end-organ dysfunction (nephrocalcinosis, osteopenia, osteoporosis) at diagnosis has been reported to be as high as 44%.[28] Non-specific symptoms, such as fatigue, abdominal pain and nausea, have been reported in up to 39%[4,24,26] and neurocognitive symptoms being reported as high as 64% of patients.[11] Most asymptomatic patients are usually discovered during screening in patients with known hereditary disorders.[25] These findings echo our experience, with a high percentage of symptomatic patients at diagnosis both with specific and non-specific symptoms. In view of the wide array of clinical spectrum these patients may present, and the relative rarity of this disorder, diagnosis delay has been described to range from 7.2 month to 32 months.[4,8,21]

Family history was present in 33% of our cohort, of which the vast majority was aware of their carrier status of a genetic syndrome. Thirty-six percent of cases were familial, MEN 1 being the most prevalent (67%), which is similar to other studies.[15,23] It is estimated that genetic syndromes are present in 11–74% of pediatric PHPT.[12,15,22,23,26–29] This wide range of prevalence is likely a result from the different referral patterns and patient population characteristics in different institutions, with the true prevalence of familial PHPT being around 10–30%. Interestingly, similar to our study, 10–31% of patients in other series appeared to have some family history of PHPT,[4,11,21] with 38% of positive family history patients undergoing genetic testing. In our study, approximately two-thirds of patients with positive family history and 23% of patients without family history had genetic testing performed. Other series also did not do routine genetic testing,[8,23] in some cases in view of clinical diagnosis of genetic syndromes, or low suspicion for familial disease. Iacobone et al. suggest that 5–10% of apparent sporadic cases have a germ line genetic cause,[29] similar to our study, 5%. This is one of the crucial discussions of pediatric PHPT, as the presence of a genetic syndrome can have an important impact with regards to treatment and screening for other associated conditions. Given the relative rare nature of pediatric PHPT, there are no official recommendations or guidelines to guide evaluation and management, but clinicians should have high suspicion for familial disease with PHPT in the pediatric population.

Traditionally, pediatric PHPT was treated with bilateral neck explorations in view of the higher prevalence of genetic predisposition and therefore, higher rates of multiglandular disease. Overall, 56% of our overall cohort underwent focused exploration, but only 19% of familial cases. Single gland disease was identified in 65% of our cohort, 85% and 19% of sporadic and familial cohorts respectively.[21,22,24,27] In the literature, focused exploration is described to be performed in 32–87%,[8,9,11,22,23] with rates varying with percentage of familial disease in any given series. A focused, unilateral approach may have less operative time, lower hospital costs, shorter hospital length and fewer post-operative complications.[1] Disease persistence is described to vary between 2.9 and 5%,[26,27] often associated to ectopic gland locations such as the mediastinum, and this was similar in our series. In our study, 66% of disease persistence occurred in patients who underwent bilateral cervical exploration in sporadic disease. Disease recurrence occurred in 15%, 90% of which were in familial cases, similar to findings in other studies.[1,21,23,26] Most recurrences required re-operation, with two MEN 1 patients eventually requiring more than one operation. Familial cases tended to recur more frequently and earlier, 124 vs 61 months for sporadic cases. This highlights the need for a more structured follow-up and surveillance of familial cases, as they are more commonly caused by multigland disease, which due to the pathobiology of the disease present with higher and earlier recurrences.

Our study describes a large cohort of pediatric PHPT with a long period of follow-up. However, it does have some limitations. Firstly, in view of the low disease prevalence, despite this being a large cohort, it may not be adequately powered to capture significantly all the data and differences. Secondly, this is a retrospective study, and so it is subject to data gathering and interpretation biases. Lastly, there is a lack of uniformity on the work-up, diagnosis, treatment, and follow-up protocols, which can partly be attributed to changes in practice during the long study period, but also to the paucity of standardized protocol in world literature.

5. Conclusion

PHPT is a rare diagnosis in the pediatric population. Pediatric PHPT is frequently sporadic and often single gland. However, approximately 5% of seemingly sporadic cases in our series had a genetic predisposition identified. Therefore, an appropriate familial screen should be performed clinically and if relevant, tested genetically. Most cases are seemingly due to isolated adenomas. While focused single gland parathyroidectomy may result in resolution of hyperparathyroidism, this approach should be utilized with caution given the possibility of multigland disease in this population. In view of the intricate clinical minutiae and rarity of the disease, these patients should be treated in specialized centers that offer care by an experienced multidisciplinary team. More prospective and randomized data is needed for further understanding of this disease process.

Data statement

Due to the sensitive nature of the questions asked in this study, patients were assured raw data would remain confidential and would not be shared.

Declaration of competing interest

Authors report no proprietary or commercial interest in any product mentioned or concept discussed in this article.

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