Original Article

Primary Hyperparathyroidism in Young and Adolescents: Alike or Unlike Adult Hyperparathyroidism? - A Series from South India

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Abstract

Background: Primary hyperparathyroidism (PHPT) is a common endocrine condition but rare in the pediatric and adolescent populations. The presentations can be unique, accounting for significant morbidity in the case of untimely detection. **Aim:** To study surgically treated pediatric PHPT retrospectively. **Methods:** Surgically treated children of PHPT up to 20 years of age between 2010 to 2022 were analyzed. All of them were operated on by an endocrine surgeon and team. **Results:** There was a total of 712 parathyroidectomies over 12 years, out of which there were 52 children (7.3%) had PHPT at less than 20 years of age. This group included 32 male children. The mean age was 16.1 years, including 7 cases of neonatal severe HPT. Multiple Endocrine Neoplasia type 1 was confirmed in 12 children. Presentations were more severe like bone pain (35.13%), renal stones (27.02%), incidental asymptomatic detection (18.9%), failure to thrive (10.8%), and pancreatitis (8.1%) as compared to adults. Mean serum calcium was 12.9 mg/dl (highest-14.1, N-8.8-10.8 mg/dl), mean parathormone levels were 386.91 pg/ml (N-10-65) and vitamin D levels ranged from 2.9-22.8 ng/ml. Localization was done with ultrasound and ^{99m}Tc- SESTAMIBI scans. Mean serum calcium levels in NSPHPT were 28.6 mg/dl (N-8.8-10.8 mg/dl). There were a total of 45 cases (6.32%) of PHPT less than 20 years of age, excluding the cases of NSPHPT. All children underwent parathyroidectomy, with 14 cases having an additional thymectomy, 2 cases with thyroidectomy, and a single case of hemithyroidectomy. The cure rate was 97.3%, while one baby with NSPHPT had persistent disease (postop PTH-110 pg/ml). The uniglandular disease was seen in 54.05% and the rest had a multiglandular disease. Adults accounted for 559/660 cases with 80% uniglandular disease. All cases had a postoperative histopathological confirmation with an average follow-up of 1 year. **Conclusion:** Childhood PHPT has a few features same as the adult population. Symptomatic presentations like adults, though pancreatitis and fatigue were more commonly seen as compared to bone pain. Calcium, phosphorus, and parathormone levels were comparable. Uniglandular involvement was seen just like the adult population. There are a few others that make them a distinct subtype like their symptoms of bone pain and being more common among boys. One-fourth of them had MEN1. Fewer cases in this age group make them unique.

Keywords: Adolescent hyperparathyroidism, neonatal hyperparathyroidism, parathyroid adenoma, parathyroidectomy, pediatric hyperparathyroidism

Introduction

PHPT is a common disease in the middle age and elderly group.[1,2] The incidence of PHPT in children on the other hand is far lesser in children, contributing to 2-5 per 1 lakh children.[3] Symptoms in adolescents are usually atypical as compared to adults and may lead to delays in diagnosis.[4] The

Access this article online

Quick Response Code:

Website: https://journals.lww.com/indjem/

DOI: 10.4103/ijem.ijem_150_23

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Submitted: 31-Mar-2023 **Revised:** 24-May-2023
Accepted: 25-Jun-2023 **Published:** 26-Feb-2024

How to cite this article: Sadacharan D, Rao SS, Mahadevan S, Shanmugasundar G, Murthy S, Chandrashekaran S, *et al*. Primary hyperparathyroidism in young and adolescents: Alike or unlike adult hyperparathyroidism? - A series from South India. Indian J Endocr Metab 2024;28:22-8.

general perception is that the most common cause of PHPT in the younger age group is parathyroid hyperplasia and they are treated accordingly. Bone pain and unexplained failure to thrive may lead the pediatrician to evaluate for other systemic conditions before narrowing down to PHPT. Also, multiple endocrine neoplasias with four-gland hyperplasia and other rarer syndromic causes of PHPT like PHPT-jaw syndrome may need to be considered during evaluation in children, unlike single adenoma in most adults.[5] Hence, detailed evaluation from an etiological perspective is also warranted. From a management perspective, surgical exploration of all glands including ectopic locations may be required in most of the patients for optimal outcome implying the need for greater expertise. PHPT in children and adolescents is less often studied in India and hence we compile our clinical experience concerning pediatric PHPT in this study.

Methods

The objective of the study was to study surgically treated pediatric PHPT retrospectively. We performed a retrospective review of PHPT less than 20 years of age with an average follow-up of 1 year. Out of the 712 PHPT patients over twelve years, 52 surgically treated children less than 20 years of age with PHPT were analyzed between 2010 to 2022. Seven babies with neonatal severe hyperparathyroidism (NSHPT) were also included. All of them were operated at a high-volume institution by a single endocrine surgeon and team. The study was approved by the Institutional review board and informed consent was taken. Serum calcium, serum parathormone, serum phosphorus, and vitamin D levels were done in all children by standard commercial assays to establish a diagnosis of PHPT. Serum parathormone was measured by Enzymatic chemilumniescent assay with different standardized values of individual labs. A range between 15 and 65 pg/ml was considered normal while Vitamin D levels of 10-30 ng/ml was considered insufficient. Serum calcium and phosphorus were repeated at a single institute and values of 8.5-10.5 mg/ml and 2.5-4.5 mg/ml were considered normal ranges. Corrected calcium levels were calculated using patient albumin levels. Preoperative localization was done in all cases with a Tc99 SESTAMIBI parathyroid scintigraphy and ultrasound. Some cases had the scintigraphy reports performed outside and hence were not repeated by us. All children underwent a bilateral neck exploration and parathyroidectomy with or without autotransplantation of the parathyroid. All cases had a postoperative histopathological confirmation of a diagnosis of adenoma and hyperplasia. Children with normal calcium levels of more than a 1-year postoperative period were considered cured, while those with persistent high postoperative calcium levels for more than 6 months were defined as having persistent hypercalcemia.[6] Recurrent hypercalcemia was those cases that recurred more than 6 months of normocalcemia.

Statistics: This data was compared with unpublished adult PHPT >20 years from our institution. Statistical analysis was done with SPSS23, and mean and standard deviation were calculated. Normal data was described as mean and standard deviation. Unpaired *t*-test was applied to normal data. Significant results were considered with a $P < 0.05$.

Ethical clearance statement

The study was approved by IEC, Madras Medical College, Chennai 600003 [EC Reg No (DHR).EC/NEW/INST/2021/1618] vide 02102023 on 27.10. 2023. Written informed consent was obtained for participation in the study and use of the patient data for research and educational purposes. The procedures follows the guidelines laid down in Declaration of Helsinki (2013).

Results

Out of the 52 children included in the study, 32 were males. The mean age of the study group was 16.1+/- 4 years, including 7 cases of neonatal severe HPT. Clinical presentations included bone pain (35.13%), renal stones (27.02%), incidental asymptomatic detection (18.9%), failure to thrive (10.8%), and pancreatitis (8.1%) [Figure 1]. Interestingly, 18 out of 52 children had chronic bone pain. The bone pain was noticed due to gait abnormalities and poor athletic performance in school in an otherwise healthy past. Most of the bone pain was noted in the legs and feet. None of the children in our series had any fractures. Renal stone disease on the other hand is not a common presentation in children. Those who had renal stone disease (4) had the abdominal colicky pain and incidental detection of renal stones on ultrasound after evaluation. Multiple Endocrine Neoplasia type 1 was genetically confirmed in 12 children. The comparison of various characteristics between the adult and adolescent population are described in Table 1. The comparative analysis between MEN 1 and Non-MEN 1 associated PHPT is detailed in Table 2.

Preoperative management and diagnosis: Hypercalcaemic crisis occurred in 4 babies who were treated medically with hydration, saline diuresis, bisphosphonates, calcimimetics, and prepared for surgery. All neonates in the study published by us earlier in addition to 3 more neonates operated, had hypotonia and failure to thrive [Figure 2]. Mean serum calcium was 12.9 mg/dl (highest-14.1, Normal-8.8-10.8 mg/dl), mean parathormone levels were 386.91 pg/ml (Normal-10-65) and vitamin D levels ranged from 2.9-22.8 ng/ml. Localization was done with ultrasound (81%) and ^{99m}Tc- SESTAMIBI scans (78.3%). Imaging was found to be concordant in 17 cases.

Surgery: All children were operated on under general anesthesia with a small neck incision, Bilateral neck

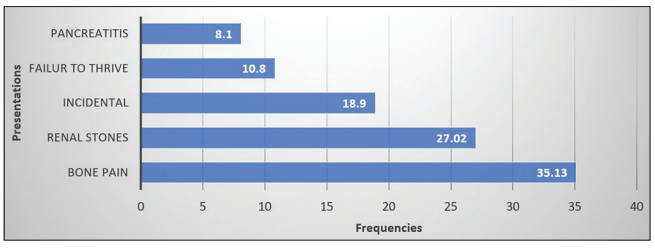

Figure 1: Various presentations of PHPT in our study group

Table 1: Comparison of clinical characteristics between adult and adolescent PHPT

Clinical	Characteristics	Adolescents (</=20 years)	Adults (>20 years)	*P*
	Number	52	660	
	Male: Female	32:20	1:1.6	
	Asymptomatic	7	5	
	Normocalcemia	0	8	0.28
Clinical features	Bone pain	18	689	0.42
	Pancreatitis	4	694	<0.001
	Failure to thrive	6	0	
	Incidental	10	5	
	Renal stones	14.05	187	0.18
	Pathological #	1	234	0.19
	Renal failure	9	32	
Postoperative complications	Transient hypercalcemia	11	187	0.28
	Permanent hypocalcemia	4	23	<0.01
Histopathology	Parathyroid adenoma	31	559	
	Parathyroid hyperplasia	20	102	
	Carcinoma	0	8	
	Atypia	1	0	

Table 2: Comparison between MEN 1 and Non-MEN 1 associated PHPT

	Characteristics	MEN-1 associated PHPT	Non MEN1 associated PHPT
Demographics	Female: Male	1:2	3:2
Clinical symptoms	Bone pain	4 (30%)	14 (27%)
	Renal stones	3 (25%)	11 (21.1%)
	Incidental	5 (41.6%)	5 (9.6%)
Biochemical parameters	Calcium (mean)	10.8 mg/dl +/- 1.2	12.9 mg/dl
	Parathormone (mean)	102.8 pg/ml	386.9 pg/ml
Imaging	Ultrasound	7 (58.3%)	42 (80.7%)
	Tc99 Scintigraphy	4 (33.3%)	40 (77%)
MEN 1 manifestations		Parathyroid adenoma-12 Pituitary prolactinoma -3	
Treatment	Surgery	Subtotal parathyroidectomy	Parathyroid adenoma excision

Figure 2: (a) Intraoperative picture showing right sided parathyroids, (b and d) intraoperative intubated pictures of children, (c) Postoperative picture showing 4 parathyroids and the thymus

exploration with parathyroidectomy was performed in all patients as per institution protocol. Abnormal-looking glands which were localized were removed in cases of uniglandular disease with inspection of other glands to confirm they were normal. NSPHPT was operated as described in the prior study published by us.[1] Parathyroids were approached laterally after mobilizing the sternocleidomastoid on either side. They were identified with the nerve, the position of the superior being more consistent and posterolateral to the nerve.[1,7,8] Inferior parathyroids are anteromedial to the nerve [Figure 2]. Parathyroids are identified as pink structures with no surrounding fat, unlike the adults, which it is more yellow with surrounding fat. Some might be significantly enlarged; others being minimally enlarged owing to hyperplasia. All four parathyroids with the thymus were separated, carefully preserving the RLNs on both sides. The thymus is traced till the innominate vein is ligated and removed to confirm the removal of supernumerary parathyroids if any.[8,9] Few cases had additional surgeries including an additional thymectomy

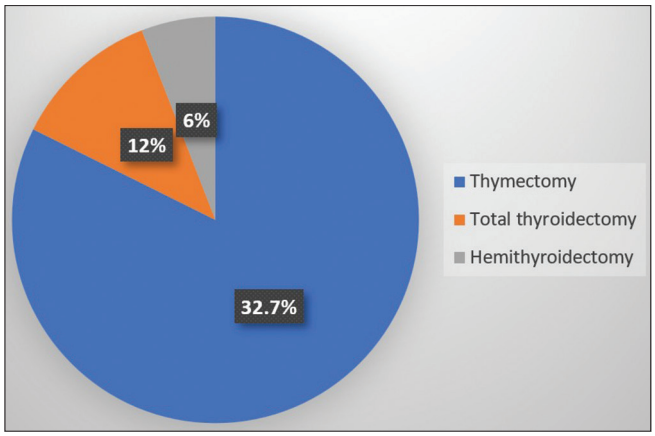

Figure 3: Additional surgeries performed in our study

in 17 cases because of supernumerary glands in MEN1 and NSPHPT [Figure 3]. There were 2 cases of thyroidectomy and a single case of hemithyroidectomy. Thyroidectomy was done for additional thyroid pathology (multinodular goiter) and hemithyroidectomy was done for an inadequate drop in parathormone intraoperatively due to the intracapsular location of the parathyroid.

Postoperative status: There were no complications like nerve injury, bleeding, or postoperative infection. The cure rate was 97.3%, while one baby with NSPHPT had persistent disease (postoperative PTH-110 pg/ml). The uniglandular disease was seen in 59.6% and the rest had the multiglandular disease. The histopathology included 31 cases of parathyroid adenoma, 20 cases with hyperplasia, and one case showing atypia. Figure 4 is our management protocol in a case of NSPHPT.

How is it different compared to the adult PHPT?

Firstly, it is uncommon to see PHPT in this particular adolescent age group. Childhood PHPT was more common among male children. Nearly one-fourth of them have associated MEN1. In contrast to adults with more asymptomatic manifestation, bone disease followed by renal stones was the most common mode of presentation. Uniglandular involvement was more common than the multi glandular disease in our series as compared to the rest of the world's data where the multiglandular disease was seen in 14% of cases.

Discussion

In our study, 52 children out of 712 patients, (7.3%) were below 20 years or in other words, if the NSPHPT cases were excluded (given the neonatal and pathophysiological difference in condition) then it would still amount to 6.3% of adolescent PHPT out of PHPTs over a 12-year period, which was comparable to Miller *et al*.[10] and Pashtan *et al*.[11] This could be attributed to referral bias to a tertiary care center. Vitamin D and calcium deficiency could be other reasons for a higher incidence in the Indian population.[5] Our study group included four babies with NSPHPT unlike other published studies [Table 2] with an updated series of a total of 7 babies to

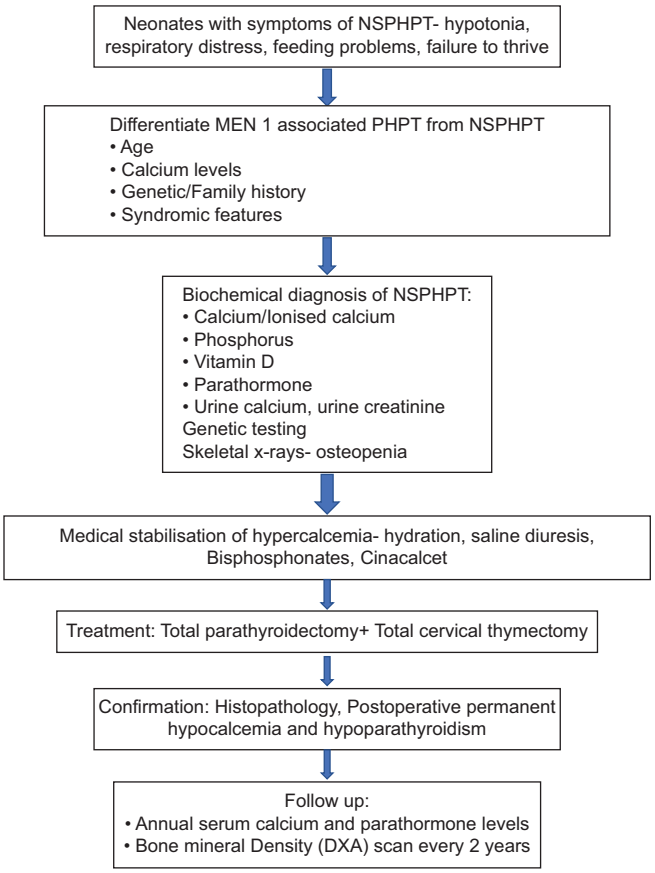

Figure 4: Management algorithm for neonatal severe PHPT

date. The age distribution is very similar to the adult population since the younger and middle-aged clusters of PHPT are more common in the adult PHPT as well.

The incidence of PHPT begins with neonates, progressing into adolescence and eventually peaking from 20-30 years. It is generally equal in both genders in the adolescent population as studied in other series but our study had a slight male preponderance. The cause of gender neutrality or reversal in adolescent PHPT is possible genetic predisposition. In the adult PHPT, predominance in females is known to occur due to the release of growth factors during adolescence. Estrogen receptors during puberty may also play a role.[9,10]

Presentations were considerably more severe with younger age despite lower parathormone levels compared to the adult population. However, the calcium levels are higher with lower parathormone levels. The mean PTH was 386.91 pg/ml and the mean calcium levels were 12.6 mg/dl. The reason could be the delayed diagnosis in this age group. There is a trend towards milder hypercalcemia and asymptomatic manifestation in recent times due to early diagnosis. Bone pain, deformities, and fatigue formed the major symptoms in our series with the adolescent population which was similar to other series. Peripheral X-rays demonstrated deformities and fractures in our series. We noted pancreatitis as a presentation in 8.1% of our patients due to an increase in pancreatic protease with hypercalcemia.[12]

Table 3: Comparison of our series with other series of Adolescent PHPT

Comparison	Our study	Sadacharan *et al*.[1]	Kreetapirom P *et al*.[12]	George J *et al*.[13]	Nicholson *et al*.[14]	Mukherjee S *et al*.[15]
Total number	52	4	3	15	39	47
Male: Female	20:32	3:1	2:1	3:12	15:24	1.24:1
Study duration (years)	12	10	12	13	38	6
Mean Age (Years)	16.1	28.7 days	13.3	17.73	16.1	19
MEN1	12	0	0	0	9	0
Mean PTH (pg/ml)	386.91	1963 SD270.4	1077.6	801.87 SD660.89	237	392
Presentation M/C	Bone pain-34%	Failure to thrive Hypotonia Respiratory distress	Bone pain and deformities- 66.6%	Bone pain- 86.67%	Fatigue/ Depression- 56.3%	Bone pain-57%
Localisation	USG- 81% Tc99 SESTAMIBI- 78.3%	USG-0 Tc99 SESTAMIBI-0	Tc99 SESTAMIBI	USG-95% CT neck-83.3% Tc99 SESTAMIBI-66.7%	USG- 53.8% Tc99 SESTAMIBI-23%	USG-91% Tc99 SESTAMIBI- 72%
Postoperative Histology	Hyperplasia-20 Adenoma-31 Atypia-1	Hyperplasia-4	Hyperplasia-1 Adenoma-2	Hyperplasia-0 Adenoma-15	Hyperplasia-11 Adenoma-28 Atypia-0	Hyperplasia-2 Adenoma-45 Atypia-0

It is presumed that the younger patients with PHPT have associated MEN1 but our series had 12 cases of MEN1 (23.07%). We had a significantly higher number of diagnosed MEN1 cases as compared to Pashtan *et al.* (4.7%). A series from King Edward Memorial, Mumbai had no cases of MEN 1 as compared to ours.[13] [Table 2] Contrary to popular belief, our patients had a higher number of single gland adenomas (59.6%) than multiglandular involvement similar to adults (after exclusion of MEN 1 and NSPHPT). In the absence of MEN1, younger patients with PHPT tend to have single-gland disease and the disease is cured with the removal of the gland. However, the treating team especially the surgeon should be diligent to not be complacent in examining the other glands and excluding a multiglandular involvement during surgery. We had no documented cases of Familial hypocalciuric hypercalcemia.[13]

Preoperative localization is done with USG and Tc99 SESTAMIBI scintigraphy as standard protocol just like adults. Scintigraphy could miss lesions in the adolescent population due to smaller adenomas and lesser oxyphil cells in the mitochondria.[13,14] This explains the high discordance rate between the two imaging methods in our study. The cases with NSPHPT however will have no localization on scintigraphy due to multiglandular involvement.

We had no cases of parathyroid carcinoma but had one case of atypia. There was no history of Hyperparathyroidism-jaw tumor syndrome.[14,15]

Roizen *et al.*[2] published a meta-analysis with 268 patients who had higher hypercalcemia in young PHPT as compared to adults. This has been seen in the literature from the West with no particular identified reason. Our series had very comparable calcium and PTH levels similar to adult PHPT. A possible reason could be screening for hypercalcemia in the West as compared to us to identify asymptomatic cases. Our series had a 13% of asymptomatic cases too, owing to improved awareness among physicians for detection. Asymptomatic cases were detected by the evaluation of hypercalcemia by endocrinologists.

Another large series has been published in India[15] with 47 patients. They had a higher number of female patients very similar to our series. Bone pain and fatigue were noted as the most common symptoms not very different from adults. The symptoms were similar in our series seen in 38% of our patients as the most common one. This series did not have patients with significant family history while our series had 12 cases of MEN 1. Biochemical workup was comparable between the adult and young patients. Localization was done with standard imaging including both ultrasound and SESTAMIBI in most cases. 91% of the patients in this series had unilateral neck exploration of excision of adenomas while all our patients underwent bilateral neck exploration as standard protocol in young patients. Adenomas were more common in this series while we had more hyperplasia [Table 2]. Table 3 shows comparison of various characteristics between our series with a few other similar ones.

Preoperative stabilization was done in all cases of NSPHPT and 6 other cases of adolescent PHPT. Preoperative stabilization was done with hydration, saline diuretics, and calcimimetics like cinacalcet and bisphosphonates. Another study published by Gafar *et al.*[16] also mentioned preoperative hydration, saline diuresis, and cinacalcet to treat severe hypercalcemia before surgery.

Few case reports have been published in the recent past, one from Sudan where a 12-year-old boy was treated with adenoma excision. Generalized bone pain was noted with high calcium and PTH levels.[16] Another case report from Sri Lanka published in 2017 also had a 12-year-old girl with difficulty in walking and bilateral genu valgum.[17] Another

report of 2 adolescent boys from South Africa also noted bone pain involving lower limbs resembling rickets.[18] A French multicenter experience suggested the use of long-term cinacalcet in hypercalcemia identified in these 18 young patients with an average age of 10 years.[19]

Another small series of 3 cases published by Oh *et al.*[20] who were of 8 and 14 years of age?. They came with classical symptoms of PHPT with hypercalcemia. All 3 had parathyroid adenomas treated surgically. One case was preoperatively treated with cinacalcet before surgery. Another case report published in 2020[21] had a 10-year-old boy who presented with abdominal pain and hypercalcemia. He had a RET mutation of unknown significance. He is said to have undergone partial parathyroidectomy which revealed hyperplasia.

Tuli *et al.*[22] published a series of 2 cases with an average age of 15 years. They presented with symptoms of hypercalcemia including pain in the foot. They were initially treated medical to alleviate the symptoms followed by definitive management with surgery.

Postoperatively, the hungry bone syndrome was noted with symptoms of perioral tingling, numbness, and tetany. Eight of them excluding NSPHPT had severe hypocalcemia needing intravenous calcium for 48 hours followed by oral calcium and calcitriol supplementation. Postoperatively calcium and phosphorus levels were estimated and hypocalcemia was treated accordingly. All cases of NSPHPT had permanent hypocalcemia requiring lifelong supplementation. Both Oh *et al.* and Tuli *et al.* reported postoperative hungry bone syndrome which was symptomatically treated.[20,22]

The need for thymectomy to ensure the removal of supernumerary parathyroids and the occasional requirement for hemithyroidectomy emphasizes the need for experienced parathyroid/endocrine surgeons in the management of these patients. In the hands of an expert surgeon, the success rate is more than 95% in normalizing hypercalcemia and surgical complications remain negligible.

We would need to study this further to understand the minute differences and their advantages in earlier identification and management. Screening for genetic mutations needs to be more standardized to identify cases of MEN1 as well, which is not standard practice in most Institutions.

Limitations: CASR mutation was positive in six infants (a novel mutation in three).

Genetic testing was done to confirm MEN 1 in 12 children. However, 34 children did not have any form of genetic testing due o financial constraints. Few of them did agree to the testing in the due course of treatment.

Conclusion

It is important to understand that adolescent PHPT is similar to and different from adult PHPT in certain ways. Few features are the same as the adult population. Symptomatic presentations were commonly seen, though pancreatitis and fatigue were more common than bone pain. Calcium, phosphorus, and parathormone levels were comparable. Uniglandular involvement was seen just like the adult population. There are a few others that make them a distinct subtype like their symptoms of bone pain and being more common among boys. One-fourth of them had MEN1. Fewer cases in this age group make them unique. Identifying the differences in diagnosis and management would help us treat these cases better, leading to the prevention of end-organ damage and cure. Expertise with higher volumes has proven beneficial in the treatment of NSPHPT, adolescent, and adult PHPT in our experience. However, the inherent limitations of any retrospective study cannot be ignored. Age should not be a deterrent to parathyroid surgery and has to be managed by a multidisciplinary team of an endocrinologist, endocrine surgeons, pediatricians, and pediatric surgery.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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