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ORIGINAL ARTICLE

Primary hyperparathyroidism in adolescents: the same but different

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Abstract
Purpose Primary hyperparathyroidism has been studied more extensively in adults than in adolescents. The objective of this study is to define the similarities and differences that exist between these groups.
Methods A retrospective review of 1,000 primary hyperparathyroidism patients undergoing parathyroidectomy at a single tertiary-care university teaching hospital between 1990 and 2004. All patients 20 years of age or younger comprised our study cohort, and were compared to two historical adult groups.
Results Of 1,000 parathyroidectomies, 21 (2.1 %) were 20 years of age or younger (adolescent). The adolescents presented with higher serum calcium levels ($p < 0.01$) more severe symptoms ($p = 0.02$), more renal stones ($p = 0.048$), and a higher incidence of hypercalcemic crisis ($p = 0.02$), when compared with adults. We found that 67 % suffered from a triad of tiredness, weakness, and depression versus 39 % of adults ($p = 0.02$). Sestamibi scans were less helpful in the adolescents than in adults. Similar to the adults, 86 % of adolescent patients had single gland disease, and 95 % were cured at the first operation.
Conclusion Adolescents with primary hyperparathyroidism typically have more severe disease than adults. Contrary to popular belief, most adolescents have single gland disease and not hyperplasia associated with a genetic disorder.

Keywords Adolescent hyperparathyroidism · Pediatric hyperparathyroidism · Parathyroidectomy · Hypercalcemic crisis

Background

Primary hyperparathyroidism (PHPT) is usually a disease diagnosed in middle-aged or elderly individuals. In these age groups, females are 3–4 times more likely to be affected than are men [1, 2]. Far less is known about this disease in adolescents, for fewer studies have been done in this group [3–7]. A common perception is that most young patients have a genetic abnormality such as the multiple endocrine neoplasia, type I syndrome (MEN 1) and therefore have parathyroid hyperplasia at operation and require a subtotal parathyroidectomy or a total parathyroidectomy with autotransplantation for cure.

The purpose of this study is to clarify the similarities and differences between children and adults with primary hyperparathyroidism.

Methods and patients

We performed a retrospective review of all patients with PHPT who were operated upon at the University of Chicago Medical Center between 1990 and 2004 in order to identify a cohort of patients with primary hyperparathyroidism who

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were 20 years of age or younger at the time of operation. We compared these young patients to two series of historical adult controls published from our institution [1, 8]. The University of Chicago Institutional Review Board approved this study.

Serum calcium and parathyroid hormone determinations were used to establish the diagnosis in all patients. Normal serum calcium levels were 8.4–10.2 mg/dL and normal preoperative serum parathyroid hormone levels performed in the clinical laboratory were from 15 to 75 pg/mL. These patients also had preoperative localization studies. Ultrasound examinations were performed utilizing 7.5 or 10 MHz transducers. Most had sestamibi scans performed in our nuclear medicine department, however some sestamibi scans were done at other institutions and were not repeated at the University of Chicago.

At operation each patient who had not been previously explored received a four-gland exploration under general anesthesia by the same surgeon. Frozen section analyses were routinely performed during operation. Beginning in mid-1999 intraoperative parathyroid hormone determinations (IOPTH) were routinely performed using the Siemens Immulite® Turbo assay in the operating suite. Our criteria for cure has evolved and now requires a fall of IOPTH of greater than 50 % of the baseline values (usually greater than 75 %) with values clearly within the normal range for IOPTH (<50 pg/mL). Statistical analyses were performed using the GraphPad Prism Software Version 5. Student's *t* test was used to compare means. Fisher's exact test was used for nominal data. We considered a $p < 0.05$ to be statistically significant.

Results

Of 1,000 patients who underwent a parathyroidectomy at our medical center between 1990 and 2004, we found 21 individuals (2.1 %) with PHPT who were 20 years or younger at the time of operation. The youngest patient was 10 years of age, 5 others were between 11 and 15 years, and 15 were between 16 and 20 years (Fig. 1). Twelve patients were female and 9 were male (1.3:1), compared with a 3:1 female-to-male ratio in our adults [1]. At the time of diagnosis children had higher serum calcium levels compared with adults [12.1 ± 1.3 (SD) vs. 11.2 ± 1.08 mg/dL, $p < 0.01$] but lower parathyroid hormone concentrations [104.6 ± 36.57 (SD) vs. 137 ± 25.6 pg/dL, $p < 0.01$].

Presenting symptomatology differed in the two groups (Table 1). While fatigue and depression were found in about one-third of adults, the combination of fatigue, weakness, and/or depression were prominent symptoms in two-thirds of adolescent patients ($p = 0.02$). Renal stones were found in 52 % of the adolescents and 29 % of adults

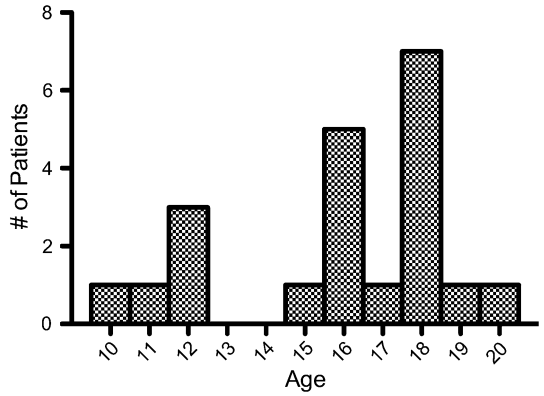

Fig. 1 Age distribution of adolescent patients with primary hyperparathyroidism. Note that the youngest patient was 10 years of age, and the majority were between ages 16 and 20

Table 1 Presenting symptoms of adolescents versus adults with PHPT

Symptoms	Adolescents, % (*n*)	Adults[a], % (*n*)	*p*
Fatigue, depression and/or weakness	67 (14)	39 (120)	0.02
Renal stones	52 (11)	29 (89)	0.048
Polyuria/nocturia	33 (7)	19 (59)	0.16
Bone pain	29 (6)	22 (68)	0.59
Abdominal pain	19 (4)	NA	NA
Nausea	14 (3)	NA	NA
Pancreatitis	5 (1)	NA	NA
Hypertension	5 (1)	NA	NA
Hypoglycemia (part of MEN-1)	5 (1)	NA	NA
Asymptomatic	5 (1)	23 (71)	0.055
Hypercalcemic crisis	5 (1)	1 (3)	0.02

NA data not available

[a] From reference [1]

($p = 0.048$). Likewise, abdominal pain was also very common in the adolescents. Osteopenia and osteoporosis, while common in adults, was not diagnosed in the younger cohort. Twenty-three percent of our adult patients were considered asymptomatic compared to only one asymptomatic adolescent patient (5 %). This patient was found to have hypercalcemia during a workup following an automobile accident.

Hypercalcemic crisis occurred more frequently in adolescents than in adults (5 vs. 1 %, $p < 0.02$). One 12-year-old female developed severe nausea, vomiting, weakness, and mental status changes following arthroscopic knee surgery. Her serum calcium level was found to be 15.7 mg/dL with a PTH level of 128 pg/mL and subsequently a diagnosis of dehydration with hyperparathyroid crisis was made. She was treated with saline and Lasix. An urgent

parathyroidectomy was performed, and an 800 mg parathyroid adenoma was removed with resolution of her symptoms and cure of the hyperparathyroidism.

Single gland disease was found in a similar proportion in both the adolescents and the adults. Eighteen of 21 adolescent patients (86 %) were found to have single gland disease. Multiglandular parathyroid disease was found in three adolescent patients. One of these patients had MEN-1 syndrome, the second one had a failed operation previously at another institution and was cured by a repeat operation at our institution, and the third one had a recurrence of hypercalcemia after removal of an enlarged gland at our initial operation. The rate of single-gland disease in the adult population was 85 % and thus the rate of single-gland disease in the adolescent population was similar to our adult population.

Even though the adolescent patients presented with higher serum calcium levels and more significant symptoms, the median weight of adenomas was smaller in adolescents than in adults [350 (range 30–1,900) vs. 1,000 (38–9,000) mg]. The smallest adenoma was found in a 10-year-old child and weighed only 30 mg. Preoperatively her serum calcium and PTH values were 13.1 mg/dL and 79 pg/mL; after removal of the adenoma the postop values were 9.9 mg/dL and 18 pg/mL, respectively. Thus the removal of this small adenoma resulted in a return to normocalcemia in this young patient. The finding of smaller glands also correlates with the fact that sestamibi scans were less sensitive in children 50 % than in adults 75 %. Ultrasound was performed in all 21 adolescent patients and had a sensitivity of 76 versus 63 % in adults.

Each of the 21 adolescent patients appeared to be cured. However, one patient recurred several years postoperatively, resulting in a 95 % success rate in the adolescents. Among the adult patients, 98.6 % had a resolution of hypercalcemia [1]. None of the younger patients had an infection, bleeding, or a recurrent nerve injury. No adolescent individual developed permanent hypoparathyroidism. Symptoms of temporary hypocalcemia were treated with intravenous and oral calcium with vitamin D.

All of the adolescent patients were operated upon using general anesthesia, with a small neck incision and a four-gland exploration. All but one were found to have parathyroid adenomas in the usual locations in the neck. One 17-year-old girl had an adenoma in the mediastinum near the heart (Fig. 2) that was removed through a small neck incision using a mediastinoscope and was cured. This was the only ectopic gland among the adolescents.

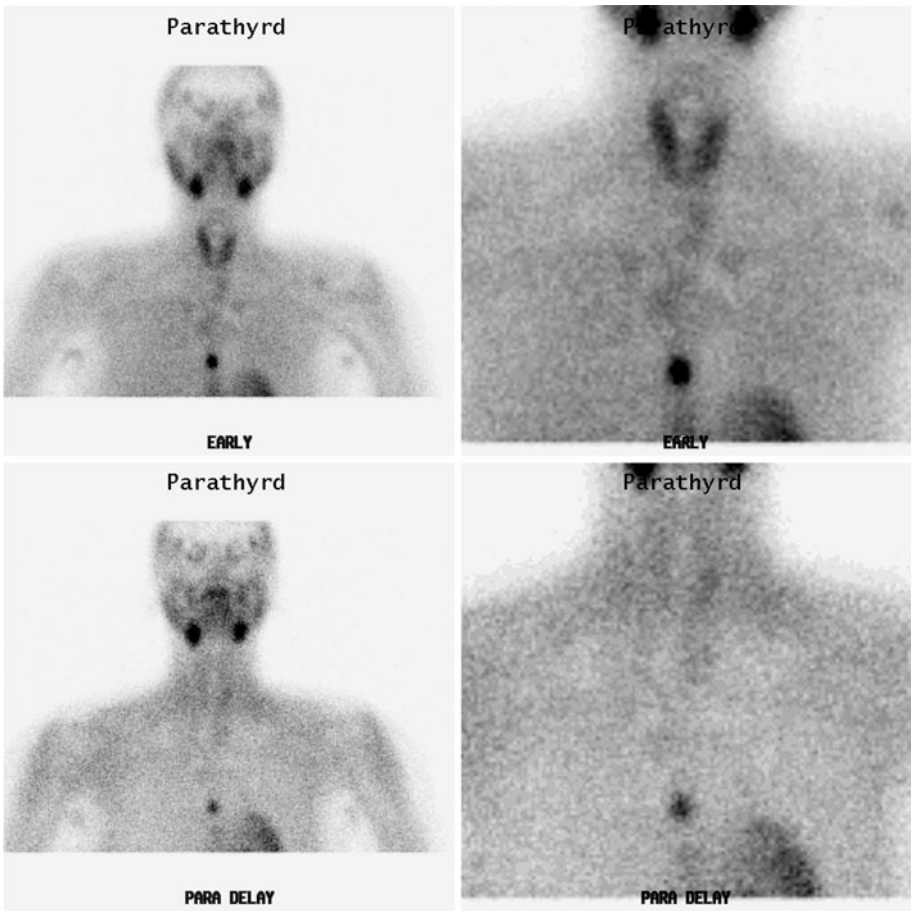

Fig. 2 Mediastinal parathyroid adenoma in a 17-year-old patient with primary hyperparathyroidism. While most abnormal parathyroid glands in the adolescent patients were in the usual anatomic locations, this gland was localized preoperatively to the mediastinum near the heart. The gland was able to be removed through a neck incision. This case illustrates the importance of good preoperative localization studies

Discussion

Although there are some similarities, primary hyperparathyroidism in adolescents is different from the disease in adults in a number of ways. First, it is an uncommon disease in patients less than 20 years. Miller et al. [2] analyzed patients from the Nationwide Inpatient Sample (NIS) that represents approximately 20 % of all hospital stays in the United States. Their tally surveyed over 10,000 patients who had a parathyroidectomy for PHPT during a 5-year period from 2000 to 2004. They identified only 41 males and 47 females who were 20 years of age or younger who were operated upon. This group represented only 1.53 % of all males and 0.62 % of all females who were operated upon. In our study, the adolescent patients represent 2.1 % of all parathyroidectomies done at our institution. Because this percentage is higher than the findings from the NIS data, we believe that this represents a referral bias. No patient in the NIS group was less than 5 years of age and only 3 were 10 years or less. Eighty-three percent of the adolescent patients in the NIS group were between 16 and 20 years. This distribution is similar to our findings. Overall, the demographics of our study cohort appear to be quite similar to and representative of the larger NIS study cohort.

It is interesting that as a group, young individuals have a much more serious form of PHPT than most adults do. Their serum calcium levels are higher despite the fact that their parathyroid hormone levels are lower and their abnormal glands are smaller. Perhaps this is due to more active bone turnover in young individuals. However, it is quite possible that there is a substantial delay in diagnosis in these adolescent patients that leads to the severity of their disease. It is striking that in the youthful group, 67 % presented with fatigue, weakness, and depression. This triad has not been previously emphasized in young patients. Knowledge of these findings should lead pediatricians to consider hyperparathyroidism in an adolescent patient who presents with this triad. Certainly, kidney stone disease should also lead to a prompt evaluation for hyperparathyroidism in adolescents. Abdominal pain and bone pain make up the remaining major symptoms in the adolescent group. Any child who presents in such a way should be studied for PHPT.

While many physicians and surgeons believe that most young patients have a genetic syndrome such as MEN-1, it is important to note that only 1 of 21 of our patients was diagnosed with this disease when she presented with hypoglycemia. No one in her family had any symptoms suggestive of this entity and hence she was the index case. At operation, she and two other patients had either hyperplasia or multiglandular disease. All other patients had a single adenoma and were cured by removal of one enlarged parathyroid gland. The findings from our series as well as those of other studies demonstrate that in an unselected group of young PHPT patients with no family history of MEN-1 syndrome, most will have single gland disease and can be cured by removal of this single adenoma. In the absence of a family history the finding of the MEN-1 syndrome is rare. Familial hypocalciuric hypercalcemia is another very rare disease that could be confused with primary hyperparathyroidism [9]. This disease entity can be ruled-out with a preoperative 24-h urinary calcium collection demonstrating low calcium clearance and a careful family history. No patients in our series were found to have this disorder.

Both ultrasound and sestamibi scans were helpful as localization procedures and we recommend them as part of the preoperative workup. Sestamibi scanning may not be so useful in these adolescent patients as in adults, however. This may be because the adenomas in the young are usually smaller in size and weigh less than those found in adults. Larger adenomas are known to be imaged more successfully with nuclear imaging techniques [10]. Another possibility is that there are fewer mitochondria rich oxyphil cells in the parathyroid adenomas of adolescent patients. Oxyphil cells and their mitochondria are thought to be cells that lead to sestamibi accumulation [11].

Our study also shows that the rise in incidence of primary hyperparathyroidism begins during adolescence and increases most rapidly between ages 20 and 30 years. In our data as well as the NIS data, the male to female ratio of patients with PHPT is close to 1:1 in adolescents and then rises to a ratio of 3–4 females to every male patient by middle age (Fig. 3). A possible theory to explain this phenomenon is that since hyperparathyroidism occurs almost equally in young males and females, it may be due to an unknown genetic abnormality in both sexes. Then a growth factor occurs during adolescence, particularly in

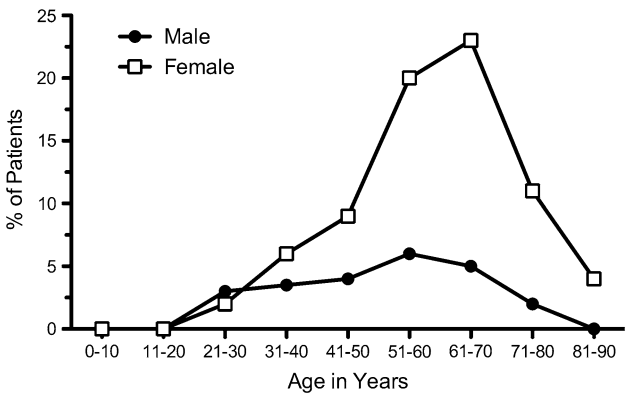

Fig. 3 Age and sex distribution of adult patients with primary hyperparathyroidism. Note that in this adult control group the female-to-male ratio is 3:1 by the fifth decade of life, and began to increase between 20 and 30 years of age

females. This growth factor causes changes in the parathyroid glands, leading to PHPT. This process probably takes years to manifest, resulting in the higher incidence in females later in life. While estrogen receptors have not been found on human parathyroid adenomas, perhaps another factor associated with puberty plays a role [12]. This should prove to be an excellent area for research in the future.

Finally, it is clear that although they are similar in certain ways, many differences do occur in the presentation, diagnosis, and treatment of PHPT between adolescent and adult individuals. It is important for physicians who care for young patients to be aware of these differences so that the diagnosis is made early to prevent significant future complications in these young patients.

Conflict of interest None.

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