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Differences in primary hyperparathyroidism characteristics between children and adolescents

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ABSTRACT

Background: In children and adolescents, primary hyperparathyroidism (pHPT) is rare, associated with severe morbidity, and has different clinical characteristics than in adults. The aim of this study was to analyze differences in clinical and laboratory characteristics between children and adolescents with pHPT.
Methods: A retrospective cohort study was conducted to analyze pHPT characteristics in young patients, who have been operated at our institution. All patients were divided into two groups: group of patients ≤15 years (children) and group of patients >15 and ≤20 years (adolescents).
Results: Out of 1363 pHPT patients surgically treated during the study period, 14 patients (1%) were younger than 20 years: 6 children and 8 adolescents. Male-to-female ratio in children was 2:1, and in adolescents 1:1.7. Kidney stones were found in 62.5% of the adolescents and in none of the children patients. Bone form of the disease was the most frequent in children (in 83.1%), while in adolescents the kidney form was the most frequent (in 50%). Only 16.7% of children and 25% of adolescents did not have classical symptoms. All adolescent patients had single parathyroid adenoma, while 4 children patients had single parathyroid adenoma, one patient had hyperplasia, and one had parathyroid carcinoma. Both preoperative serum calcium and PTH levels were higher in children than in adolescents (3.87 mmol/L vs. 3.17 mmol/L; 812 ng/mL vs. 392 ng/mL, respectively). In all patients vitamin D level was low. All patients had normal postoperative values of serum calcium and PTH.
Conclusion: There is a significant difference in clinical and biochemical characteristics between children and adolescent pHPT patients. Therefore, these two groups should be analyzed and treated separately.
Type of Study: Retrospective comparative study.
Level of Evidence: Level III.

Primary hyperparathyroidism (pHPT) is rare and associated with severe morbidity in children and adolescents. Current knowledge about this topic is insufficient, since modern literature mostly offers case reports or case series of patients with pHPT in youths and only one meta-analysis dealing with comparison of biochemistry of pHPT between youths and the adults exists [1,2].

Still, it is clear that pHPT in younger age group has different clinical characteristics than in adults. In younger age group, almost all patients have severe symptoms (kidney stones, skeletal abnormalities, acute pancreatitis), as well as unspecific symptoms (nausea, fatigue, abdominal pain) [3]. Due to the small number of cases of pHPT in patients of this age, children and adolescents have been observed together [4–7]. Nevertheless, can we say that children and adolescents are the same regarding pHPT? Since the literature offers limited high quality data regarding this issue, the aim of our study was to analyze differences of clinical and laboratory characteristics between children and adolescents with pHPT.

1. Material and methods

Retrospective cohort study was conducted to analyze children and adolescent pHPT patients younger than 20. All patients have been operated due to pHPT from January 1st, 2004 to December 31st, 2017 at the Center for Endocrine Surgery, Clinical Center of Serbia, Belgrade. Data of interest were extracted from patients' charts and data base implemented in everyday work, and obtained by personal contact, as well.

All patients were divided into two groups: group of patients ≤15 years (children) and group of patients >15 and ≤20 years (adolescents). In our country, children are considered as not older than 15 years, and they are treated in children hospital.

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All patients were operated by experienced endocrine surgeons, with more than 10 years of practice. Open focused approach was used for all the patients, except for patients with possible multiglandular disease, when bilateral open exploration was performed. Open focused approach implies that if parathyroid adenoma is well located, direct preparation and extirpation will be performed, without additional dissection; bilateral open exploration implies exploration of both glands on each side. Standard practice at our institution is that every pHPT patient must have preoperative MIBI scan and neck ultrasound. If there is an undoubted single adenoma, open focused parathyroidectomy will be performed. If there is a suspicious multiglandular disease, both glands at the same side will at least be explored, and if the other parathyroid glands aren't enlarged, extirpation of single parathyroid adenoma will be performed.

There were no additional exclusion criteria. Study was approved by the Ethical Committee of School of Medicine, University of Belgrade.

The following data were collected: sex, age, preoperative PTH, calcium, phosphate and vitamin D serum level, concomitant thyroid disease, type of pHPT (bone form, kidney form, mixed form, asymptomatic), presence of familiar pHPT, concomitant thyroid pathology, number and weight of extirpated parathyroid glands, histopathology findings, postoperative PTH, calcium and phosphate serum level, surgical complications, postoperative follow up.

For statistical analysis software SPSS, version 20.0 (SPSS, Chicago, IL, USA) was used. Descriptive statistic methods were used for all variables in the study. Continuous variables are presented as means with standard deviation or medians with ranges, analyzed by Student t-test or the Wilcoxon sum rank test. Categorical variables are presented as numbers (n) with percentages (%) and were compared using the Pearson's chi-square test and Fisher exact test.

2. Results

Within study period, a total of 1363 patients have been operated due to pHPT, out of which 14 patents (1%) were younger than 20: 6 patients were children and 8 were adolescents. Average age at the time of surgery was 16.3 ± 2.8. The youngest patient was 10 years old.

Male-to-female ratio in the children group was 2:1. On the other hand, the adolescent group had more girls, with male-to-female ratio 1:1.7 (Table 1). This difference was not statistically significant. There was only one 10-year-old boy with familiar pHPT (MEN 1 syndrome).

These two groups were significantly different according to the type of the disease. The most common type of pHPT in children was bone form (in 83.1%) and kidney form in adolescents (in 50%), ($p = 0.048$). Kidney stones were found in 62.5% of adolescents, and none of them were found in the children's group ($p = 0.015$). On the other hand, half of the patients in the children's group had bone fractures, while those were present in only 25% of adolescents ($p = 0.334$). Asymptomatic form of pHPT was noted in only one child (16.7%) and in two adolescents (25%) ($p = 0.048$).

Extirpation of a single parathyroid adenoma was performed in all adolescent patients and in 66% of children. A subtotal parathyroidectomy has been made in a child with parathyroid hyperplasia (MEN I syndrome), and en-bloc resection in one case of parathyroid carcinoma. Mean total weight of extirpated parathyroid tissue was 3520 ± 1776.8 mg in children's group and 2375 ± 3326.8 mg in adolescents' group ($p = 0.497$).

Mean preoperative serum calcium level in children and adolescents' groups were 3.87 ± 0.96 mmol/L and 3.17 ± 0.36 mmol/L, respectively, but this difference was not statistically significant. The highest value of preoperative serum calcium was 5.28 mmol/L in children's group. Also, there was no statistically significant difference in preoperative phosphate level (Table 1). Although mean preoperative value of PTH was more than twofold higher in children's group than in adolescents (812.6 ± 689.6 ng/L and 392.5 ± 319.6 ng/L, respectively), this difference was not statistically significant due to the small number of patients. In all patients vitamin D level was low.

Table 1
Demographic and clinical characteristics of children and adolescent pHPT patients.

	Children [6]	Adolescents [8]	p Value
Sex, male, n (%)	4 (66.7%)	3 (37.5%)	0.287
Form of the disease			
Familiar, n (%)	1 (16.7%)	0	0.238
Sporadic, n (%)	5 (83.3%)	8 (100%)	
Type of the disease			
Kidney, n (%)	0	4 (50%)	
Bone, n (%)	5 (83.3%)	1 (12.5%)	0.048
Mixed, n (%)	0	1 (12.5%)	
Asymptomatic, n (%)	1 (16.7%)	2 (25%)	
Kidney stones, n (%)	0	5 (62.5%)	0.015
Fractures, n (%)	3 (50%)	2 (25%)	0.334
Surgery			
Parathyroidectomy No 1, n (%)	4 (66.6%)	8	
Subtotal parathyroidectomy, n (%)	1 (16.7%)	0	0.211
En bloc resection, n (%)	1 (16.7%)	0	
Histology findings			
Adenoma, n (%)	4 (66.7%)	8 (100%)	
Hyperplasia, n (%)	1 (16.7%)	0	0.211
Carcinoma, n (%)	1 (16.7%)	0	
Weight of parathyroid tissue, mg ± SD (min-max)	3520 ± 1776.8 (2000–6000)	2375 ± 3326.8 (200–10,000)	0.497
Concomitant thyroid pathology			
Yes, n (%)	0	1 (12.5%)	0.369
No, n (%)	6 (100%)	7 (88.5%)	
Serum calcium level, mmol/L ± SD (min-max)	3.87 ± 0.96 (2.52–5.28)	3.17 ± 0.36 (2.80–3.80)	0.079
Serum phosphate level, mmol/L ± SD (min-max)	0.95 ± 0.08 (0.88–1.04)	0.73 ± 0.18 (0.38–0.99)	0.090
PTH level, ng/L ± SD (min-max)	812.6 ± 689.6 (130–2000)	392.5 ± 319.6 (150–1000)	0.151
Vitamin D ng/mL ± SD (min-max)	39.5 ± 30.8 (14.3–73.8)	23.0 ± 14.9 (4.01–40.5)	0.334
Serum calcium 1st POD, mmol/L ± SD, (min-max)	2.54 ± 0.55 (1.94–3.14)	2.35 ± 0.13 (2.25–2.60)	0.554
Serum phosphate 1st POD, mmol/L ± SD, (min-max)	0.86 ± 0.29 (0.58–1.04)	0.95 ± 0.33 (0.47–1.56)	0.679
PTH level 1st POD, ng/L ± SD (min-max)	11.4 ± 11.1 (4.85–28)	29.3 ± 39.8 (4–117)	0.411

POD, postoperative day.

All patients had PTH and serum calcium levels within the referent range on the first postoperative day, with no difference between groups. There were no surgical complications.

Only one patient from the adolescents' group had thyroid pathology that required surgery (benign colloid adenoma). Also, one patient from children's group with parathyroid carcinoma had ipsilateral thyroid lobectomy, but without thyroid pathology.

3. Discussion

Nowadays, parathyroid pathology is more common and more often diagnosed in adults. Although it is still rare in children and adolescents (2–5 cases in 100,000), there is an increasing trend of diagnosed and treated patients in these age groups [1]. The chances are that due to the unspecific symptomatology children and adolescent pHPT patients are being misdiagnosed, so the symptoms are revealed and treated later in life, when children become adults.

We have explored differences between children and adolescent pHPT patients who have undergone parathyroidectomy.

As well as with other endocrine diseases, pHPT in adults is far more often in females than in males, with female-to-male ratio 3–4:1 [8]. However, results of studies which have dealt with pHPT in youths are not consistent regarding sex predominance. Some of the studies found that pHPT in this age group is more common in females [3,9,10], while other authors stated the opposite [11,12]. Still, the results of meta-analysis conducted by Roizen et al. found no significant difference

regarding gender in youth pHPT patients [1,13]. Therefore, it seems that there is a changing trend of female-to-male ratio in pHPT patients with younger age, so that females are less affected. This trend is proven by our study: female-to-male ratio in adolescents was 1.7:1, and in children was 1:2.

Results of our study reveal that children had higher levels of PTH and serum calcium preoperatively. Levels of serum calcium and phosphorus are higher in healthy children than in healthy adults, therefore different referent ranges should be established [14]. Additionally, the level of 24-h urinary calcium is higher in healthy children. The most probable explanation for this might be increased bone development and calcium turnover in this age. Meta-analysis of Roizen et al. found higher values of serum and urinary calcium in children and adolescents compared to adults with similar PTH level. Also, similar to our study, in this meta-analysis there was no significant difference in parathyroid adenoma weight. Possible reason for this might be that target organs (kidney, bones and intestines) are more sensitive to PTH action in younger age, with less efficient negative feedback of calcium to parathyroid adenoma in pHPT [1,3,15].

The presence of symptoms in our study is significantly different between the groups: the most predominant type of the disease in children was bone and in adolescents' kidney type. Furthermore, only one patient from children's group and two patients from adolescents' group were asymptomatic. Literature findings are in concordance with our study: most of the children and adolescents with pHPT are symptomatic at the time of the diagnosis contrary to adults, who are mostly asymptomatic, according to nowadays cohorts [9,14]. Greater morbidity and end-organ damage are present in children and adolescents than in adults with pHPT. This might be due to the lack of routine biochemical analyses in juvenile age. Therefore, the diagnosis of pHPT in children and adolescents is usually made during examination of symptoms or end-organ damage. Prior to 1970s, when routine calcium screening was introduced, almost all adult pHPT patients were also symptomatic. On the other hand, the decrease in percentage of symptomatic pHPT in adults is not just due to the earlier diagnosis, but because there is also an increasing number of diagnosed pHPT patients discovered in asymptomatic phase, by routine calcium screening [16]. Symptoms of pHPT (bone pain, polydipsia, polyuria, fatigue, nausea, weight loss, etc.) are very unspecific, especially in children, and can be the only manifestation of pHPT. This delay of diagnosis leads to organ damage and juvenile pHPT patients are usually seriously ill. According to our previous study, kidney stones are present in 45.1% of adult pHPT patients, similar to 62.5% of adolescent patients from this paper [17]. Also, PTH and calcium levels of adolescent pHPT patients are closer to adults than to children.

Thyroid pathology that requires surgery is uncommon in youth and becomes more frequent with age. Only one adolescent pHPT patient (12.5%) had concomitant thyroid pathology, while none was found in children. As we reported in our previous paper regarding concomitant thyroid and parathyroid diseases, pHPT patients had concomitant thyroid disorders that required surgery in 26.4%. Therefore, when it comes to thyroid pathology, adolescent pHPT patients are more like adults than children [17].

The biggest single center study which analyzed pHPT in youths was from Mayo Clinic in Rochester, USA [9]. In this study, Kollars et al. found 52 patients younger than 19, during a 30 years period (1970–2000), who have undergone parathyroid resection for pHPT. Female-to-male ratio was 3:2, 79% of patients were symptomatic and 44% had end-organ damage. As well as in our study, very high percentage of symptomatic pHPT patients was reported. Solving of hypercalcemia was accomplished in 94% of cases. They have concluded that diagnosis of pediatric pHPT is usually delayed, with severe morbidity. Therefore, parathyroid surgery is effective and represents a treatment of choice for pHPT in young patients.

The main limitation of our study is a relatively small sample size, so many differences between children and adolescents could not be statistically proven. Still, since pHPT in youths is very rare and there is no single center with great experience, only a larger multicentric study can provide more information.

4. Conclusions

There is a significant difference in clinical and biochemical characteristics between children pHPT patients (≤15 years of age) and adolescent pHPT patients (between 16 and 20 years of age), and hence they should be analyzed and treated separately. Clinical characteristics of adolescent pHPT patients are more likely than in adults, and children pHPT is a distinct clinical entity. Almost all pHPT patients at this age are seriously ill and this should be kept in mind, even in patients with unspecific symptoms. Parathyroid surgery is effective, with few complications, if it is performed by the experienced endocrine surgeon.

Declarations of interest

None.

References

[1] Roizen J. Levine MA. A meta-analysis comparing the biochemistry of primary hyperparathyroidism in youths to the biochemistry of primary hyperparathyroidism in adults. J Clin Endocrinol Metab 2014;99(12):4555–64. https://doi.org/10.1210/jc.2014-2268.
[2] Alagaratnam S, Aetiology Kurzawinski TR. Diagnosis and surgical treatment of primary hyperparathyroidism in children: new trends. Horm Res Paediatr 2015;15:101–4.
[3] Roizen J, Levine MA. Primary hyperparathyroidism in children and adolescents. J Chin Med Assoc 2012 Sep;75(9):425–34. https://doi.org/10.1016/j.jcma.2012.06.012.
[4] Nicholson KJ, McCoy KL, Witchel SF, et al. Comparative characteristics of primary hyperparathyroidism in pediatric and young adult patients. Surgery 2016 Oct;160(4):1008–16. https://doi.org/10.1016/j.surg.2016.06.028.
[5] Mukherjee S, Bhadada SK, Arya AK, et al. Primary hyperparathyroidism in the young: comparison with adult primary hyperparathyroidism. Endocr Pract 2018 Dec;24(12):1051–6. https://doi.org/10.4158/EP-2018-0268.
[6] Paunovic I1, Zivaljevic V, Stojanic R, Kalezic N, Kazic M, Diklic A. Primary hyperparathyroidism in children and young adults:–a single institution experience. Acta Chir Belg. 2013 Jan-Feb;113(1):35–9.
[7] Cronin CS, Reeve TS, Robinson B, et al. Primary hyperparathyroidism in childhood and adolescence. J Paediatr Child Health 1996 Oct;32(5):397–9.
[8] Bilezikian JP, Bandeira L, Khan A, et al. Hyperparathyroidism Lancet 2018 Jan 13;391(10116):168–78. https://doi.org/10.1016/S0140-6736(17)31430-7.
[9] Kollars J, Zarroug AE, van Heerden J, et al. Primary hyperparathyroidism in pediatric patients. Pediatrics 2005;115(4):974–80.
[10] George J, Acharya SV, Bandgar TR, et al. Primary hyperparathyroidism in children and adolescents. Indian J Pediatr 2010;77:175–8. https://doi.org/10.1007/s12098-009-0289-5.
[11] Hsu SC, Levine MA. Primary hyperparathyroidism in children and adolescents: the Johns Hopkins Children's Center experience 1984–2001. J Bone Mineral Res: Off J Am Soc Bone Mineral Res 2002;17:N44–50.
[12] Loh KC, Duh QY, Shoback D, et al. Clinical profile of primary hyperparathyroidism in adolescents and young adults. Clin Endocrinol (Oxf) 1998;48(4):435–43.
[13] Alagaratnam S, Brain C, Spoudeas H, et al. Van't Hoff W, Kurzawinski TR. Surgical treatment of children with hyperparathyroidism: single Centre experience. J Pediatr Surg 2014;49:1539–43. https://doi.org/10.1016/j.jpedsurg.2014.05.032.
[14] Stokes VJ, Nielsen MF, Hannan FM, et al. Hypercalcemic disorders in children. J Bone Miner Res 2017;32(11):2157–70. https://doi.org/10.1002/jbmr.3296.
[15] Lietman SA, Germain-Lee EL, Levine MA. Hypercalcemia in children and adolescents. Curr Opin Pediatr 2010 Aug;22(4):508–15. https://doi.org/10.1097/MOP.0b013e32833b7c23.
[16] Lo CY, Chan WF, Kung AW, et al. Surgical treatment for primary hyperparathyroidism in Hong Kong: changes in clinical pattern over 3 decades. Arch Surg 2004;139:77–82.
[17] Jovanovic MD, Zivaljevic VR, Diklic AD, Rovcanin BR, V Zoric G, Paunovic IR. Surgical treatment of concomitant thyroid and parathyroid disorders: analysis of 4882 cases. Eur Arch Otorhinolaryngol 2017;274(2):997–1004, DOI:https://doi.org/10.1007/s00405-016-4303-z