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Results of intraoperative gamma probe survey and frozen section in surgical treatment of parathyroid adenoma in children

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ABSTRACT

Aim: To evaluate the use of intraoperative gamma probe survey (IGPS) and frozen section (FS) in the surgical treatment of parathyroid adenoma (PA) in children.
Patients and methods: Children operated for PA between 2000 and 2015 were evaluated for age, sex, clinical features, presenting symptoms, diagnostic methods and results of surgical treatment retrospectively.
Results: Seven patients operated for PA were included in the study. The mean age of the patients was 14.58 years (11–17 years) and male to female ratio was 4:3. Presenting symptoms were non-specific such as fatigue, weakness and abdominal pain ($n = 4$). Six patients (85.8%) had adenoma of single parathyroid gland whereas remaining patient has involvement of two glands (14.2%). Localizations of adenomas were left inferior ($n = 3$, 42.8%), right inferior ($n = 2$, 28.3%), right superior ($n = 1$, 14.2%), left superior ($n = 1$, 14.2%) and intrathymic ($n = 1$, 14.2%). In case with involvement of more than one gland, adenomas were localized at right superior/left inferior glands. The mean longest diameter of the adenomas were 14.8 mm (4–23 mm) and all of the cases were underwent USG and Tc-99 m sestamibi scan. During surgical excision, FS were used in 5 cases, and 4 cases had IGPS after preoperative radioactive substance injection. In one patient, injection was performed directly into the adenoma and 3 patients had systemic injection. Patient who had injection directly into the involved gland had positive gamma counts in the adjacent tissues because of local spread of radioactive substance and diagnosis was also confirmed with FS. In two of the cases, adenoma excision was performed without FS with only IGPS. None of the patients had preoperative and postoperative complications.
Conclusion: PA is rare in children and appropriate gland excision can be obtained also by the help of IGPS after injection of radioactive substance, and frozen section examination as well as intraoperative parathormone (PTH) screening. IGPS is a helpful tool to define the target tissue during surgery in order to avoid extensive dissection. Since direct injection of involved gland may cause accumulation of radioactivity in the adjacent tissues, surgeons must be aware of advantages and disadvantages of different radiolabeling techniques.

Primary hyperparathyroidism (PHPTH) is a rare disorder caused by the hypersecretion of parathyroid hormone (PTH) usually from a single hyperfunctioning parathyroid gland [1]. Most of the cases are sporadic, benign and caused by a single parathyroid adenoma (PA) [2]. The incidence of PA is 2–5 in 100,000 in children and surgical removal of the abnormal parathyroid gland cures the disease [3]. Over the past years, the traditional treatment, bilateral neck exploration, has been replaced by localization radio-guided parathyroidectomy [4,5]. This minimally invasive procedure offers several advantages over bilateral neck exploration including shorter operative time, smaller scars, and fewer complications with similar prognosis [6].

Multiple adenomas, adenomas in ectopic locations, small glands (less than 500 mg) and anatomic variants may lead surgical failure and cause reoperation for persistent or recurrent PHPTH [7,8]. Therefore, reliable preoperative localization techniques should be performed to avoid unnecessary bilateral neck exploration in children. Although, parathyroid scintigraphy is effective in localizing enlarged glands, sestamibi scans in combination with single-photon emission computed tomography/computed tomography (Tc-MIBI-SPECT/CT) offer better information in smaller and/or ectopic glands. Despite the preoperative localization of affected glands, intraoperative methods such as detection of PTH levels, analysis of frozen sections (FS) of glands and radioguidance with Tc-99 m sestamibi scan can be used to improve the success of surgical treatments [9]. Intraoperative gamma probe survey (IGPS) has been used to detect adenomatous and hyperplastic

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glands in adults. Burke et al. pioneered in application of radioguided parathyroidectomy in pediatric patients with both adenomatous and hyperplastic glands [10]. Here, we present a case series of patients to evaluate the use of IGPS and FS in the surgical treatment of PA in children.

1. Patients and methods

Children operated for PA between 1st January 2000 and 31st June 2015 were retrospectively evaluated for age, sex, clinical features, presenting symptoms, laboratory tests, diagnostic methods and results of surgical treatment. Children who have hyperplastic glands were excluded and parathyroidectomies performed to treat PA were evaluated.

Neck ultrasonography (USG) and Tc-99 m sestamibi scanning were used for preoperative localization. The results of surgery were evaluated by serum calcium (Ca) levels six months after surgery and Ca levels less than 10.2 mg/dl were considered as surgical cure. Recurrent disease is defined as normalization of Ca level (<10.2 mg/dl) after surgery for at least 6 months followed by reappearance of hypercalcemia (Ca >10.2 mg/dl) [10].

1.1. Intraoperative gamma probe survey (IGPS)

All patients underwent ultrasonography and parathyroid scintigraphy. Thirty minutes (early phase) and hundred twenty minutes (late phase) after i.v. injection of 10 MBq/kg Tc-99m sestamibi, planar scintigraphic images were obtained by gamma camera (GE Healthcare, Milwaukee, WI, USA) equipped with a parallel hole collimator. SPECT-CT was also performed in two patients for better anatomical correlation. In three out of four patients preoperative labeling of PA was performed by i.v. injection of 10 MBq/kg Tc-99m sestamibi 2–3 h before surgery. In one patient with negative scintigraphic findings, PA was labeled with ultrasound guided intralesional injection of 11 MBq Tc-99m macroaggregate [radio-guided occult lesion localization (ROLL) method].

Intraoperative gamma counting was performed with gamma probe (Europrobe, France) for the detection of focal radioactivity retention that was observed with scintigraphic imaging or the detection of intralesional radio-isotope activity. Gamma probe counting was used for adenomatous parathyroid gland localization. PA is confirmed with ex vivo counts of excised glands. Also background counts were obtained in vivo after excision of effected gland. The 20% rule; lesions having ex vivo counts more than 20% of the background counts at the operative basin were accepted as parathyroid adenoma as suggested by European Association of Nuclear Medicine (EANM) guidelines [11].

1.2. Frozen sections (FS)

FS were taken from the tissues embedded in OCT compound and rapidly frozen. 6 μm sections were cut, fixed in 95% alcohol for 30 s, and subsequently stained with hematoxylin-eosin.

2. Results

Seven patients operated for PA were included in the study with the mean age of 14.58 years (11–17 years) and a male to female ratio of 4:3. Demographic features and clinical findings of patients are listed in Table 1. Presenting symptoms were non-specific such as fatigue, weakness and abdominal pain ($n = 4$) and three of the patients were diagnosed during assessments for other causes. In one patient, more than one gland was involved (14.2%) and in six patients (85.8%) single gland adenoma was observed. Localizations of adenomas are listed in Table 1. In case of the involvement of more than one gland, adenomas were localized at right superior/left inferior glands. In one case, the involved gland was localized in the thymus. The mean of the longest diameters of the adenomas was 14.8 mm (4–23 mm) and all of the cases underwent USG and Tc-99m sestamibi scanning.

Preoperative and postoperative laboratory findings including serum Ca, phosphorus (P) and PTH levels are listed in Table 2.

The surgical removal of glands was performed through a 3 cm collar incision. According to preoperative localization, glands were removed without bilateral neck exploration. During surgical excision, results of FS were considered in five cases, and IGPS localization was applied in four cases following preoperative radiotracer injection.

In one patient, the injection was performed directly into the adenoma whereas three patients had systemic injections. The ex vivo counts were more than 20% in all patients (200%, 100%, 80% respectively) and in two of the cases, adenoma excisions were performed only in combination with IGPS. The patient who had injection directly into the involved gland had positive gamma counts in the adjacent tissues and still higher background counts (500 cps before excision and 200 cps after excision) after parathyroidectomy. Therefore the diagnosis was also confirmed with FS. Also, histopathological analyses of permanent sections confirmed the diagnosis of PA in all patients. None of the patients had intraoperative PTH monitoring in our series of patients and there was no preoperative or postoperative complications.

The mean follow-up duration of the patients was 77 months (13–180 months) and none of the patients had surgical failure and/or recurrent disease as further supported by the postoperative Ca levels after 6 months (Table 2).

3. Discussion

HPTH is an extremely rare endocrine disease requiring surgical treatment in children. Only 1–2% of all primary HPTH are encountered in childhood. Although 80% of adult cases are asymptomatic, children usually present with symptoms including urinary and bone tissue impairment [12]. The diagnosis of primary HPTH is frequently delayed in children with higher levels of serum calcium compared to normal levels [13]. In older children, polyuria, polydipsia and constipation are among the presenting clinical features of the primary HPHT and non-specific symptoms account to 36–64% of the cases [14]. In our study, all of the patients were diagnosed with PA and most of them showed non-specific symptoms. Some of the patients were diagnosed upon consideration of other

Table 1
Demographic and clinical features of patients.

Case	Age (year)	Sex	Clinical finding	Localization	Size (mm)	USG	Scintigraphy	IGPS	FS
1	15	M	Abdominal pain,	Right superior Left inferior (intratimic)	13 × 9 23 × 7	+	+	−	+
2	17	F	Fatigue, weakness	Left superior	10 × 5	+	+	+	−
3	16	M	Abdominal pain	Left inferior	10 × 5	+	+	+	+
4	14	M	Fatigue, artralgia	Right inferior	10 × 8	+	+	+	+
5	14	F	Fatigue, type I diabetes	Left superior	19 × 10	+	+	−	+
6	15	F	Abdominal pain, vomitting	Right inferior	20 × 15	+	+	+	−
7	11	M	Urolithiasis, pathologic fracture	Left inferior	18 × 11	+	+	−	+

Abbrevations: M: male, F: female, USG: ultrasonography, IGPS: intraoperative gama probe scan, FS: frozen section.