Parathyroid Adenomas in Adults and Adolescents. Critical Appraisal and Surgical Strategy in 18 Cases

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Rezumat

Adenoamele paratiroidiene la adulți și adolescenți. Evaluare clinică și strategie chirurgicală în 18 cazuri

Introducere: Studiul nostru subliniază raritatea cazurilor de adenoame paratiroidiene (AP) publicate în literatura medicală autohtonă, expresia clinică diferită în care predomină formele “istorice” ale bolii ca și dificultățile și întârzierile de diagnostic confirmând totodată chirurgia ca standardul de aur al tratamentului.

Pacienți și metodă: Sunt analizate retrospectiv demografia, datele clinice, de laborator și cele imagistice, procedurile chirurgicale și constatările anatomopatologice ca și rezultatele obținute în 18 cazuri documentate de AP tratate chirurgical.

Rezultate: Raportul m/f al cazurilor a fost de 1/5 iar vârsta acestora a variat între 16-58 (medie 46). Litiiza urinară (n=9) și leziunile osoase (n=6) au fost cele mai întâlnite manifestări menționate. Acestea li s-au adăugat tulburări psihiatrice și neuromusculare, cele digestive (pancreatita și ulcerul peptic), hipertensiune arterială ca și prezența unui nodul palpabil. Diagnosticul a fost confirmat prin dozările calciului și fosforului seric, fosfatazei alcaline și PTH, ecografia și scintigrafia cu tehneciu 99m. Au fost practicate 18 adenomectomii din care 16 după explorarea cervicală bilaterală și două prin abord minim invaziv. În 9 situații s-a recurs la exereze tiroidiene concomitente pentru leziuni asociate sau în scop tactic. Examenul microscopic a confirmat diagnosticul de AP cu celule principale și oxifile, într-un caz fiind identificat un adenom “atipic”. Într-o altă observație, la 3 ani după exereza unui AP benign, s-a constatat o recidivă clinică ipsilaterală care s-a dovedit a fi un carcinom (leziune nouă sau eroare a diagnosticului inițial?). Evoluția clinică și bioumorală postoperatorie imediată și la distanță a fost favorabilă în toate cazurile cu excepția cazului de carcinom care a decedat după 14 luni de la reintervenție.

Concluzii: În pofida rarității și dificultăților de diagnostic a cazurilor de AP, practicienii trebuie să fie conștienți de posibilitatea existenței acestor leziuni în vederea unui tratament cât mai precoce și adecvat în care chirurgia reprezintă standardul de aur.

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Cuvinte cheie: adenom paratiroidian, chirurgie, standard de aur

Abstract

Background: Our study underline scarcity of isolated case reports or small case series of parathyroid adenoma (PA) published in autochthonous medical literature, their variable clinical expression among the “historic” varieties but also the diagnostic difficulties and delays of diagnosis as well consecration of surgery as the golden therapeutic standard of this disorder.

Patients and Method: Demographic, clinical presentations, laboratory and imaging data, operative findings and procedures together with pathology account and outcome from the case reports of 18 patients with documented PHP were retrospectively analyzed.

Results: The male/female ratio was 1/5, with ages ranging from 16 to 58 (mean 46) years. Renal stones (n=9) and bone sufferings (n=6) were the most common modes of presentation. To these were added psychiatric and neuromuscular complaints, digestive disorders (pancreatitis and peptic ulcer) arterial hypertension and presence of a palpable nodule. Mean serum calcium and phosphorus, alkaline phosphatase and PTH dosage together with parathyroid ultrasound and 99m Tc sestamibi scintigraphy are the most useful parameters for diagnosis. Eighteen adenomectomies were performed of which bilateral neck exploration was done in 16 patients and minimally invasive approach in the remaining two cases. In 9 situations concomitant thyroid exeresis for associated lesions or tactical purpose were done. Pathology revealed single adenoma consisting of main and oxyphil cells in 17 cases. In one case an atypical adenoma was identified and in another case three years after removal of a benign adenoma the subject presented a clinical ipsilateral recurrence which provided to be a carcinoma. Postoperative clinical and humoral outcome was favorable in all situations less the case of carcinoma which died after 14 months.

Conclusions: Despite the rarity and difficulties of diagnosis in cases of PA, practitioners must be aware of potential existence of these lesions in order to apply as early and appropriate treatment where surgery is the gold standard.

Key words: parathyroid adenoma, surgery, gold standard

Introduction

Primary hyperparathyroidism (PHP) is the third most common endocrine disorder after diabetes mellitus and thyroid illnesses, the case studies showing an estimated prevalence in general population of 0,5-1% and an annual incidence of 28 cases per 100000 people (1,2,3). Single gland sporadic parathyroid adenoma (PA) represents the most frequent cause (85-90%) of PHP cases.

In the other affected patients hyperplasia, carcinoma and familial forms can occur (4,5). Demographics and clinical characteristics of PA underwent a dramatic change in the 1970s with the widespread availability of serum calcium screening by the multichannel autoanalyzer (6,7). Therefore the rare classical observations of PA diagnosed by consecrated clinical tetrad “painful bones, renal stones, abdominal groans and psychic moans” and objectification of hypercalcemia, become actually a common endocrine disease, 80% of cases appearing asymptomatic at diagnosis and often having mild hypercalcemia (8,9). However in our country the number of operated cases and publications about this pathology is still limited to few practitioners in some specialized units (10-20).

Patients and Method

Eighteen cases with confirmed clinical, biological and histological diagnosis of PA operated on within a period of three decades in our clinic were retrospectively analysed. In our series we registered 15 females and 3 males with a female/male ratio of 5/1, and an average age of 46 years (range 16-58) years. There was no statistically significant difference in the frequency of clinical manifestations between males and females.

Demographic data, clinical presentation, pre-operative biochemical and hormonal findings, localization imaging, operative findings and techniques, postoperative outcome, histopathological reports, immediate and long-term status were also assessed. All the patients underwent surgery. Bilateral neck exploration was performed in 16 cases and two minimally invasive adenomectomy were also done.

Statistical analysis was performed with Student's t test and with Mann Whitney U test. The mean results and standard deviation was given. A P value less than 0,05 was considered to be significant.

Results

Except one case appearing as familial PHP (a sister operated on for PA) all our observations were considered as sporadic. We encountered only cases of solitary adenoma even if in our experience we also founded two cases of parathyroid carcinoma. Outside only one asymptomatic observation incidentally discovered during thyroidectomy for a simple multinodular goiter, the rest of the 17 cases of PA presented a polymorphic "florid" symptomatology interesting many of body systems and apparatus sometimes difficult to interpret which has led to some delays or errors in diagnosis and hesitations of treatment.

The analysis and hierarchy of different anatomic or functional features led them together in major syndromes that dominated clinical scene.

Neuropsychiatric troubles (n=5) were present as depressive phenomena of psychasthenic type, mental slowness and also one case of sudden confusion syndrome appearing after urologic surgery. Varying degrees of asthenia, somnolence or fronto-occipital cephalalgia added in some cases. In 8 patients myasthenia intricate with osteoarticular pains.

Main clinical circumstances and surgical selection in our cases occurred through bone manifestations (n=6), those of urolithiasis (n=9) or pancreatic acute sufferings (n=2).

Bone and joint disorders demonstrated by current clinical and radiological examinations included joint pains, subperiosteal resorption, systemic osteopenia, osteitis fibrosa cystica, bone calcifications, cyst or geodes and sequels of pathological fractures fracture sequelae (Fig. 1).

Urolithiasis was the most common feature encountered in PA often being the alarm signal of disease presenting itself as multiple or bilateral (n=4) and recurrent (n=5) forms, associated with

hematuria and infection produced by *E coli*, proteus with often tenacious resistance to chemotherapy and renal dysfunction. Urinary stones were diagnosed, sometimes incidentally, by ultrasound, standard X-ray exams or urography (Fig. 2).

Before or rarely after PA surgery specific urolithiasis treatment was done performing urethero- or pyelotomies in 8 cases, one observation benefiting from a lithotripsy. In six patients iterative urologic surgery was necessary: A 52-year old man underwent in 1966 a gastrectomy for perforated duodenal peptic ulcer and 5 years later surgical debridement and drainage for acute necrotizing pancreatitis was done. After ward he experienced a numberless advents of multiple, bilaterally recurrent urinary tract stones resorting to 10(!) pyelo- and/or uretherolithotomies. Finally a huge left coral form stone imposed a nephrectomy. Twenty years then addressing to our unit he presented a 2 cm Ø irregular calculus in the remaining right kidney associated with chronic renal failure (BUN=75-138 mg/dL, creatinine= 2,8 -4,3 mg/dL) also accusing asthenia, osteoarticular pains, edema and pruritus. Serum calcium was 12 mg/dL, AF=49IU and iPTH =290 pg/mL. Ultrasound revealed a 1,8 cm Ø round, hypoechoic, well-circumscribed left cervical nodule. At cervicotomy we discovered a left sided adenoma of 1,7x1,0x0,7 cm weighting 6 gm. Pathology confirmed the diagnosis of parathyroid cell adenoma. Postoperative evolution was normal the patient being directed for a qualified lithotripsy. At 1-5 years follow-up he was in good clinical and humoral condition. We noted retrospectively in his sagacious medical history two sisters with urolithiasis one of them also operated for PA (18).

Arterial hypertension observed In 5 patients as minor EKG changes had rather an essential character (18).

Paramedian cervical swelling with small volume

Figure 1. Subperiosteal phalangeal resorption

Figure 2. Multiple, bilateral urinary stones

of 1-1,5 cm Ø suggesting a parathyroid adenoma was found in only 5 cases while coexistence with an uni- or multinodular goiter was present in 6 patients (four of them coming from endemic areas). We also mention various other symptoms as palpebral congestion, ectopic calcifications or pseudogout.

Laboratory tests and complimentary imaging localization tools was the major elements that defined functional diagnosis of PA.

Biochemical parameters in our series documented hypercalcemia (mean values = $3,08 \pm 0,25$ mmol/L) in all patients even the asymptomatic one.

Hypophosphatemia (mean values $1 \pm 0,2$ mmol/L) was present in 13 patients. Also mean value serum alkaline phosphatase was higher than normal values in 12 patients (mean values 230 ± 40 UI/L). Serum iPTH was elevate in all 12 cases in whom it was available ranging between 127-778 pg/mL Therefore second- and third-generation PTH assays also becomes compulsory of diagnostic algorithm.

The initial preoperative evaluation of the hyperfunctioning culprit was considered vitally important prior to definite its surgical management of. High resolution ultrasound and 99m Tc sestamibi scan was practiced objectifying the presence, topography and dimensions of PA together with any associate thyroid pathology. US also accurately inventoried the presence of coexistent thyroid processes. Single photon emission computed scintigraphy (SPECT), CT and MRI recommended by many authors as current imaging techniques for preoperative localization were not utilized.

Management

Literature data as well as our modest personal experience attest surgery as the gold standard in the management of these lesions. Formal indica-

tions of the method include cases that manifest overt bone or urinary symptoms, severe morbid associations and important biochemical markers (elevated serum calcium and/or PTH) but for some authors surgery was also indicated in so-called “chemical” and/ or asymptomatic forms. In these conditions in 17 of our cases surgery was formally recommended by coexistence of clinical data, laboratory findings (sometimes incomplete) and finally elements provided by ultrasound and in last years 99m Tc sestamibi scintigraphy (*Figs. 3 and 4*).

All patients had preoperative and postoperative vocal cord assessment. Of the 18 patients the procedure was accomplished under cervical blockade in 5 but in the rest 13 cases general anesthesia was preferred.

Sixteen cases underwent classical approach with collar incision more or less stretched depending clinical or imaging data. To these added two video-assisted minimally-assisted surgeries (*Figs. 5 and 6*).

Both techniques proceeded to a first assessment of preoperative ascertainments concerning location items providing more or less facile identification of the lesion by topographical and macroscopic criteria of color and volume.

In 9 cases with associated macroscopic thyroid pathology or lack of concordance between preoperative imaging and surgical findings encountering difficulties in the recognition of culprit lesion a wide exploration of bilateral entire parathyroid system was necessary. Thus three patients each underwent subtotal thyroidectomy respectively lobectomy for multinodular benign goiter. In another two cases atypical excision of thyroid tissue was done together with PA located more or less deeply in a small crater or even inside of the thyroid lobe, removal growth also requiring sacrifice of host parenchymal tissue. Finally for tactical purpose one PA located retropharyngeal impose deliberated thyroid sacrifice.

Figure 3. Ultrasound of al left parathyroid adenoma

Figure 4. 99m Tc sestamibi scan of parathyroid adenoma

Figure 5. Simple open excision of PA

Figure 6. Minimally invasive removal of PA

A particular situation we faced in a 45 year-old female presented with a clinical and biological recurrence after removal of a right sided PA performed elsewhere 3 1/2 years ago. Beside reappearance of functional features 6 months ago she present a round, irregular hypoechogenic lesion of 1,5 cm Ø situated in the same location. Reoperation identified a well-constituted odd firm mass which was en block resected together with ipsilateral thyroid lobe. Paraffin section surprisingly allowed the diagnosis of parathyroid carcinoma (initial histological error or a new lesion ?) but postoperatively the hypercalcemic syndrome recured more severely and she died 14 months later after iterative surgery (17).

In other 9 patients only single adenomectomy (minimally-invasive in two cases) was practiced. After adenoma acknowledgment, lateral retraction of jugular vein and carotid artery, ligation and division of middle thyroid vein with systematic identification of recurrent laryngeal nerve was carried out. Thyroid lobe can then be displaced up

and out of its bed, the prominent lesion, being gradually delivered of lax surrounding tissues by gently blunt dissection avoiding rough handling as well as few cutting and hemostatic gestures which can cause capsule breaking and glandular seeding resulting the rare parathyromatosis appearance. Thus complete enucleation preserving the integrity of adenoma capsule was preferred to excision and was possible in all such lesions. Postoperative histopathology showed in 17 patients unique, well circumscribed, homogenous nodules of 0,4-2 cm Ø mainly composed of chief cells and some oxyphil cells with minimal mitotic activity. In one case examination revealed an “atypical” structure of PA with either excess mitotic cells and tumor capsule invasion without trespassing its boundaries and no spontaneous necrosis nor vascular invasion was described. The case had a uneventful postoperative course (*Figs. 7 and 8*).

Only fourteen observations could be subjected to watchful postoperative follow-up from three months

Figure 7. Chief cell parathyroid adenoma Hex200

Figure 8. Atypical parathyroid adenoma Hex400

to three years. We have no mortality or recurrences but morbidity show only two patients with transitory postsurgical symptomatic hypocalcemia requiring intravenous calcium infusion.

All these cases however recovered well after operation. Effects of successful surgery materialized in stable endocrine equilibrium, control of hypercalcemic features through disappearance or at least enhancing of most clinical features and normalization of biological constants, firstly improving of psychic and neuromuscular symptoms i.e. fatigue, depression, lack of concentration or sleep disturbances but also increasing bone density and significant reduction of urolithiasis, resulting for everyone a meaningful improvement in patients QOL. Preexisting arterial hypertension generally not improved.

Discussions and Conclusions

Current clinical practice guidelines recommend surgery as the main curative approach for most primary hyperparathyroidism patients due in 80% to a single parathyroid adenoma. Its removal is strongly sustained to correct hypercalcemia and decrease the risk of lesion's complications, especially in patients under 50 years, those with history of osteoporosis or even fractures, urinary stones and low glomerular filtration rate (21,22).

Diagnosis of PHP remain essentially based on laboratory findings of persistent hypercalcemia associated with plasma levels of PTH that are elevated or inappropriately normal together with pre and intraoperative cervical ultrasonography and parathyroid scintigraphy acknowledged as the first-line method used to located pathological parathyroid tissues (23,24).

The number of parathyroidectomies performed worldwide for PA has grown exponentially over the last decades since the advent especially in developed countries of routine testing of blood calcium levels, the greater accuracy and earlier diagnosis of clinically evident but also of asymptomatic or smaller, profound or ectopic located lesions by broad use of well-established modern preoperative imaging and finally by sustained development of less invasive surgical procedures (25,26).

Thereby from classical bilateral four gland exploration of PA an increasing number of unilateral focused minimally invasive techniques have been introduced in numerous centers including open minimal parathyroidectomy but also video-guided, radio-guided and endoscopic removal of PA with or without rapid intraoperative PTH assay reducing

the cost and morbidity while maintaining cure rates (27,28,29).

On the contrary the paucity of patients diagnosed and treated for PA in our country, most of them presenting with delayed, severe metabolic bone and renal disease complaints, is related to lack of systematically calcium screening and therefore the default of awareness of this conditions.

At the same time even if casuistry is reduced, encouraging satisfactory results continuously obtained in our growing experience due to personal concern to endocrine cervical surgery and constantly increasing number of cases operated in time.

By far the most consistent successes were achieved after surgery applied in symptomatic cases – which are majoritarian in Romania as in developing countries - providing most number of patients undergoing parathyroidectomy (17 observations in our series).

Natural history and features of the asymptomatic PA counting only one case in our series revealing modified BMD and bone affecting, mainly neurocognitive complaints and functional cardiovascular abnormalities all improving after parathyroid adenomectomy. However regarding the increasing proportion of unknown asymptomatic patients and the impossibility to predict their evolution the firm indication of parathyroidectomy in these cases must be formulated with more courage (29).

Overall in both symptomatic and asymptomatic cases surgery of PA was safe and effective without mortality but minimal and transient morbidity. Follow-up to three years revealed disappearance or improving of majority of symptoms and clinical signs and normalization of PTH and serum calcium levels.

Our modest experience as main international statistics fail to prove that surgery remain the current definitely gold standard of PA treatment, contributing to an often spectacular remission of most clinical sufferings concomitant with prompt normalization of serum calcium and PTH levels otherwise equivalent to their real healing in great majority of cases.

Our work recognized some limitations. Thus the former observations had a random character and were incompletely explored. Also the number of patients, even notable for our country is however reduced and our report includes the shortcomings and biases inherent in a retrospective research. Moreover we did not looked for intervention of avitaminosis D in these conditions.

Further institutional research with larger series

of cases are desirable.

On the whole numerous studies as our own activity show that surgical treatment shared the same subjective and objective clinical benefits contributing significantly to improve the quality of life (QOL). Concentration in high-volume centers in which this exquisite surgery will be performed only by fully trained practitioners will increase the number and the quality of management of these patients.

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