

Urolithiasis : Screening for Hyperparathyroidism is Essential

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Abstract

Thirty two patients having complex renal stones in the age group of 10-60 years were studied to detect hyperparathyroidism (HPT). The clinical diagnosis varied from bilateral renal stones in 20 (62.5%), 2 (6.22%) had large unilateral stone, 2 (6.622%) had recurrent bilateral renal calculi and 4 (12.5%) had unilateral recurrent calculi. Serum calcium was raised (>10.5 mg%) in 9 (20%) cases. Parathyroid hormone (PTH) was found raised, ranging from 80-1330 pg/ml (N : 16-65 pg/ml) in 9 (28%) cases out of 32. Hypercalcemia (>10.5 gm %) was found in 7 out of 9 cases of HPT whereas in other 2 cases it was normal (8.9 mg %) and upper normal (10.3mg %) respectively. Hypercalciuria (>250 mg/24 hrs) was found in 5 patient of HPT and rest 3 patients had normal levels. Serum phosphate was found in the range of 1.4-7.1mg% (N : 2.5-6.8mg %) in 30 cases, on patient had <2.5 mg % and one patient had >6.8 mg %. One patient with hypercalcemia had both urinary calcium as well as PTH normal. Dual subtraction scan (thallium and technetium) was done in all 9 patients with raised PTH. Scan was positive with adenoma in 4 (12.5%) cases. One patient 15 years old girl with a positive scan had both serum calcium and 24 hrs. urinary calcium levels normal with raised PTH (90-100 pg/ml). Scan reported doubtful hyperplasia in one (3.12%) patient out of 32. This patient, a multiple stone passer had normal serum calcium as well as 24 hrs. urinary calcium with raised PTH (99.60) pg/ml). 4 cases (12.5%) had a normal scan. Four (12.5%) cases with positive scan underwent parathyroidectomy (PTX). Serum calcium and PTH concentration dropped to normal levels in the postoperative period. Rest of the cases of HPT with normal and doubtful scans are under follow up.

Key words

Renal stones, Urolithiasis, Hyperparathyroidism.

Introduction

Recent advances in minimally invasive procedures, such as extra corporeal shockwave lithotripsy and endourologic intervention, have improved the surgical morbidity associated with kidney stone disease. However, the prevalence of urolithiasis and the rate of stone recurrence still remain high (1). It has been estimated that 5-15% of the population will develop

kidney stones during their lifetime (2). The recurrence rate is high ranging from 10-23% per year (3).

Multiple characteristics of patients with kidney stones have been identified that predisposes them to early recurrence. Male gender, multiple stones, stone location, residual fragments and some anatomic or functional urinary tract abnormalities are known major risk factors

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for recurrence (1). In addition, urinary metabolic abnormalities such as low volume, hypercalciuria, hyperoxalurea, hyperuricosurea and hypocitrations also predispose the patient to early stone recurrence if left untreated (1). 89.2% of renal stone cases usually present with metabolic disturbances of different types. As such metabolic evaluation and prevention of recurrent urolithiasis remain important elements in the management of this disease.

Hypercalciuria has been reported to be the most common metabolic abnormality for stone formation and recurrence (1). In a patient with kidney stones, an elevated serum calcium level is accepted to be suggestive of HPT or, much less frequently, sarcoidosis (4). HPT has been reported to account for as many as 8% of all calcium stone formers (4).

Evaluation of biochemical milieu in stone formers though a well accepted in principle is not widely practised. This is a preliminary report of a study for identification of metabolic derangements in cases of renal stones. Association of HPT with renal stone disease using estimation of parathormone as a screening test is a major focus of this study.

Material and Methods

The patients of urolithiasis with features consistent with complex behaviour of stone disease were surveyed for metabolic profile. Thirty-two patients of different age groups ranging from 10-60 years belonging to both sexes were studied. A simple ambulatory protocol was followed for this study. After the initial diagnosis of urolithiasis the blood analysis was done for calcium, phosphate, uric acid, kidney function tests, serum proteins, serum electrolytes and serum alkaline phosphates. 24 hrs. urine was tested for volume, pH, calcium, phosphorus and uric acid. A routine urine test for microscopy and culture was carried out. PTH

estimation test was done in all patients. The patients showing raised PTH were investigated with a dual subtraction thallium technetium parathyroid scan. The patient who had a positive scan underwent parathyroidectomy (PTX) followed by renal stone surgery.

Results

Thirty two patients with renal stones were studied, age ranging from 10-60 years. 9 (28%) out of 32 patients were found in age group of 41-50 years. Male and female numbers were 18 and 14 (ratio 1.29:1). The clinical diagnosis of renal stones varied from bilateral renal stones 20 (62.5%) had large unilateral stone, 2 (6.22%) had recurrent bilateral renal calculi and 4 (12.5%) had unilateral recurrent calculi. Serum calcium was raised more than 10.5 mg% in 9 (28%) cases. PTH was found raised in 9 (28.2%) out of cases ranging from 80-1330pg/ml (normal : 16-65pg/ml). Out of these 9 cases with raised PTH, serum calcium was found elevated in 7 patients, whereas in other two cases it was towards upper normal (10.3 mg%) in one and normal (8.9mg%) in another. Hypercalciuria (>250mg/24 hrs.) was found in 5 patients of this raised PTH group and 3 patients had upper normal was found to be in range of 1.4-1.1 mg% values. One patient with hypercalcemia had both 24 hrs. urinary calcium and PTH within normal range.

Dual subtraction scan thallium and technetium was done in all 9 patients with raised PTH. Scan was positive with adenoma in 4 (12.5%) cases. One patient, a 15 year old girl with a positive scan had both serum calcium and 24 hrs. urinary calcium levels normal with raised PTH (90-100 pg/ml). Scan was reported of doubtful hyperplasia in one (3.12%) patient out of 32. This patient a multiple stone passer had normal serum calcium as well as 24 hrs. urinary calcium with raised PTH (99.60 pg/ml). 4 cases (12.5%) had a normal scan. 4 (12.5%)

cases with positive scan underwent parathyroidectomy (PTX). Serum calcium and PTH concentration dropped to normal levels in the postoperative period. Rest of the cases of HPT with normal and doubtful scans are under follow up.

Four (12.5%) cases with positive scan underwent PTX. Single parathyroid adenoma was found in each of these 4 cases confirmed on histopathological examination. Serum calcium and PTH levels dropped to normal level in the post operative period.

Discussion

Urolithiasis is a common disorder known to have multifactorial etiology. The occurrence of disease exhibits geographical distribution. The incidence is reported high in areas of deserts, mountains and topical areas. Northern India where the centre of the present study is situated is located in the high incidence zone for urinary stone disease (5). It is generally well appreciated that an approach to a patient with urinary stone disease requires to go beyond care of stone episode.

Evaluation of these patients should include the assessment of their comorbidities and underlying medical conditions. It is reported that a cause can be indentified in more than 90% of these patients. Stone-recurrence rates can be decreased by 85% for calcium oxalate stone formation with medical treatment (4).

There is a good place for medical therapy in the overall management of calculus disease. Introduction of nonspecific medical therapy in uncomplicated calcium stone disease has been described to improve the quality of life of these patients. However, patients with identified underlying medical conditions require disease-specific therapy (6).

Nephrolithiasis is known to be a recurrent condition that carries significant morbidity. The life time

prevalence of kidney stones in North America is estimated at 8% to 20% with an annual incidence exceeding 1 per 1000 persons (2). Characteristically patients presenting with their first stone are between 20 and 50 years of age and 80% are men. The recurrence rate is high at 10% to 23% per year and 50% within 5 years of presentation (2).

A study conducted on 32 North Indian children with nephrolithiasis and the underlying disorder was detected in 50% of the cases (7). An underlying disorder is present in a large proportion of children with nephrolithiasis where appropriate treatment may be beneficial. More than 26% of cases had hypercalciuria (7).

It is recommended that patients with recurrent nephrolithiasis undergo investigation for metabolic abnormalities (2,8). A simplified approach to biochemical evaluation has been used in this study including serum concentrations of creatinine, electrolytes, (sodium, potassium, chloride, bicarbonate), calcium, phosphorus and uric acid, random urine samples for pH analysis, and a 24 hour urine collection for volume, calcium, creatinine, oxalate and urate concentrations. The panel of tests has been selected on the basis of evidence that specific treatment for the abnormalities identified by this panel of tests reduces the risk of stone recurrence.

It is recommended that the serum calcium level should be measured in all patients with stones (4). Although the vast majority have a normal value, those who have elevated serum calcium levels must be identified not only to prevent further urolithiasis also because of the implications for other organ systems.

In a patient with kidney stones, an elevated serum calcium level usually means hyperparathyroidism or, much less frequently, sarcoidosis (4). HPT has been reported to account for as many as 8% of all calcium

stone formers (4). A few centres have reported that 2-3% of patients with calcium nephrolithiasis have HPT (4). In the present study association of HPT with stone disease has been the main focus. HPT has been encountered in 9 of the cases of stone disease. Stones are about 3 times commoner in men than women (9). Hence a woman with stones should be suspected to have HPT more than in a man (4).

Derangement in the parathyroid hormone axis can lead to elevation in serum calcium. Most often, the cause is excess secretion of PTH by the parathyroid gland, resulting from adenomatous enlargement. The incidence of renal calculi in a contemporary study of patients with HPT is 10% (6). Hypercalciuria has been reported to be the most common metabolic abnormality for stone formation and recurrence (1).

PTH acts at the renal level to decrease calcium and decrease phosphate resorption through the release of cyclic adenosine monophosphate. In addition, PTH activates 25-cholecalciferol to 1-25-dihydrocholecalciferol, therapy leading to increase intestinal absorption of calcium. In bone, PTH stimulates osteoclasts to demineralize bone and release calcium and phosphorous. Hypercalciuria results from increase in serum calcium levels, which overwhelm the kidney's ability to resorb the filtered calcium.

Diagnosis of HPT is made on demonstration of hypercalcemia and elevated PTH. Patients with total serum calcium level close to the upper limit of normal, however, also should be suspected to have HPT (6). Elevation of ionized calcium may be present with high normal total serum calcium levels. Radioimmunoassay techniques directed towards the intact PTH molecule can detect PTH and are more sensitive than tests directed towards the aminoterminal end (10). Broadus (11) suggested that whether increased level of circulating 1, 25-dihydroxy vitamin D level influences stone formation level in HPT.

The parathyroid function should always be evaluated in the patient of renal stones. About 7% of patients with calcium urolithiasis suffer from primary HPT (12). A systemic search for this diagnosis is therefore mandatory in such cases. Because hypercalcemia is often discrete or intermittent, determinations of calcium levels may be misleading and should be repeated at least thrice. Measurement of ionized calcium levels improves the detection of hypercalcemia together with an increased plasma level of 1-84 intact PTH. Availability of improved laboratory techniques for direct estimation of PTH is likely to identify the patients of HPT more easily.

Muldowney FP et. al. 1976 (13) in their study found that serum ionized calcium was shown to be significantly elevated in a group of patients with idiopathic hypercalciuria in whom the mean total serum calcium concentration was within normal limits. Measurement of PTH levels confirmed that elevated values are suppressible by infusion of calcium are indicative of HPT.

In 1989, Chang *et. al.* reminded that 17% of parathyroid adenoma has renal calculi in Levin's report. The association of parathyroid adenoma is often overlooked in the patients of renal calculi (14).

The intact PTH assay is the test of choice for the differential diagnosis of hypercalcemia. Usually, the diagnosis of HPT is apparent. A patient with a history of kidney stones, a serum calcium level of 11.5mg/dl, and an elevated serum PTH level obviously has HPT.

There are occasional patients, however, in whom the data are borderline. The serum calcium may be at or just above the upper limit of normal and the PTH level may be high normal or slightly elevated. This situation has been given several names, including subtle hyperparathyroidism and normocalcemic hyperparathyroidism.



Several different maneuvers have been used to suppress PTH in these borderline situations, including thiazides, 25-hydroxy-vitamin D, calcium infusions and oral calcium loading. Modern PTH assays with their increased accuracy have eliminated for the most part, the need for oral calcium-load suppression test (4).

A diagnosis of HPT in patients with urolithiasis raises a few issues and concerns.

Untreated patients of primary HPT were followed up for an average of 2.45 years with several determinations of serum ionized and intact parathyroid hormone (PTH). Despite the greater precision of serum ionized calcium, measurements of intact PTH are evidently more sensitive than measurements of serum ionized calcium for the detection of progression of PHPT (15).

The only therapy for PHPT is total surgical removal of all parathyroid tissue responsible for hypersecretion. Treatment of HPT is directed towards the primary disease and is reported to have a greater than 90% success rate (6). If the patients with asymptomatic hypercalcemia and renal calculi, then PTX is performed as the initial intervention. Symptomatic obstructive renal calculi or hypercalcemia may require immediate treatment prior to PTX (5). A preoperative differential diagnosis between simple parathyroid adenoma and diffuse gland hyperplasia is essential. Total removal of all parathyroid tissue is not necessary, minimizing the risk of hypoparathyroidism.

There are advantages of knowing preoperative diagnosis and localization of parathyroid gland. In 1991, Consensus Development Conference, it was opined that preoperative imaging was not necessary in view of the fact that non-invasive techniques yielded only 60% positive results and 15% false positives (4). However, there has been a change in the perspective. In a patient

with simple adenoma it is possible to obtain the exact localization of the eventually responsible adenoma with all modern diagnostic tools (17).

Ultrasound and scintigraphy are used most frequently of all the available imaging techniques for the preoperative evaluation of patients with possible HPT disease. The sensitivity and specificity of scintigraphy is reported as 84.4% and 95.9% respectively and ultrasound is 66.6% and 98.6% respectively (18).

Parathyroid imaging with sestamibi appears to be superior to T_1 -201/ T_c -99m pertechnetate subtraction based on the reported results of both techniques at various institutions. Dual phase sestamibi imaging appears to be useful and cost effective for presurgical localization of hyperfunctioning parathyroid tissue. In addition, sestamibi imaging in conjunction with an intra-operative probe is a promising technique that has the potential to provide both localization information of a suspected parathyroid adenoma and to facilitate its surgical removal by reducing operation time. The overall sensitivity and specificity were 83% and 75% respectively (19).

Radionuclide parathyroid scans are especially valuable for identifying ectopic glands, including those in the mediastinum. Ranits PC et. al. in 1995 found in their study that radionuclide parathyroid scan limited to the neck is an incomplete study. Scans that do not include the thorax will miss mediastinal glands that occurred in 5% of the patients in their series (20).

Average surgical time was reduced by 50% with preoperative localization and there was a decrease in the number of non-parathyroid tissue biopsies (21).

MRI of the parathyroid glands presented a sensitive imaging modality, thus demonstrating its high potential to preoperatively detect abnormal glands with sensitivity of 82%. All ectopic glands were correctly identified (22).

For the patient who has had calcium nephrolithiasis, the consensus conference guidelines suggested that PTX is almost always indicated. The experts agree that the patient who has had a stone and who then is discovered to have HPT should undergo neck exploration in the absence of a reason not to operate.

The traditional surgical treatment for PHPT is bilateral neck exploration with identification of all parathyroid glands. Multiple investigators who recommend initial unilateral neck exploration based on more advanced localization studies have recently challenged this approach. Unilateral neck exploration based on the results of a T99ms scan can be used as an initial approach for PHPT if the scan identifies a solitary lesion. The second gland on the same side of the lesion should be biopsied, and if it is normal, the opposite side of the neck may be left undisturbed. If the second gland is not normal, or if the T99ms scan shows multiple lesions, bilateral neck exploration should be performed (23).

In patients with PHPT, PTX results in the normalization of biochemical values and increased bone density (24).

There has been some controversy regarding the influence of PTX on the recurrence of stone. Mollrup and Linodewald reported 151 cases of renal stones with PHPT and had undergone PTX, 107 patients remained normocalcaemic and were followed up for 5 years (25). 30% patients formed one to four new stones within 5 years. This recurrence rate is comparable to the expected recurrence rate in idiopathic stone formers. As all renal stone formers are screened for PHPT by serum calcium analysis, the two disease renal stone and PHPT might by coincidence be found in the same patients.

But in contrast to above, in another study conducted by Jabbour *et al.* studied the natural history of renal stone disease after parathyroidectomy for PHPT. The frequency of renal colics, 0.66% per patient per year

before parathyroidectomy decreased to 0.002 per patient per year after the first postoperative year (26). In 1987, Deaconson *et al.* studied the effect of parathyroidectomy on the recurrence of nephrolithiasis. The rate of stone formation per patient per year was 0.36 before and 0.22 after 5 year ($p < 0.001$). Surgical correction of PHPT significantly reduces the rate of stone formation (27).

Although conflicting findings have been reported, bone loss has been noted in patients with PHPT, especially at cortical skeletal sites. Most densitometry studies support the concept that the parathyroid hormone appears to be catabolic at cortical sites and may have anabolic effects at cancellous bone sites. PHPT is now increasingly being detected during the asymptomatic phase. The need for PTX has been questioned in such patients because there may be no disease progression in the absence of surgery (28).

Bone densitometry is advised, particularly for monitoring of bone mass at the midradius or femoral neck, in patients with PHPT (29).

Rothmund in 2000 (30) observed several cases of patients who believed they were free of symptoms or signs of PHPT pre-operatively, reported a change of clinical state following PTX. Many apparently asymptomatic patients with PHPT will only realise that they did in fact have preoperative symptoms in retrospect, following PTX. This study suggests that using an up to date definition of asymptomatic PHPT, there are only a small number of truly asymptomatic patients and that these cannot be predicted preoperatively as their symptoms may become apparent only after PTX. Asymptomatic patients with PHPT may share the same objective and subjective benefits from PTX as symptomatic patients. They should be operated as soon as diagnosis is established.

Preoperative PHPT patients showed decreased bone density, bone loss in symptomatic cases was especially prominent compared to asymptomatic cases. Most PHPT patients had not completed the bone mineral density

(BMD) recovery after surgery. So even asymptomatic and mild PHPT patients should undergo PTX to minimize irreversible bone loss (31).

Medical management does not seem to be associated with increased morbidity or mortality in patients with asymptomatic PHPT.

PTX provides effective treatment for primary and secondary HPT with a predictable response of symptoms related to hypercalcemia and elevated parathyroid hormone. Calcium and Vit D supplementation has reduced the need for PTX in dialysis patients with secondary HPT. However, surgery continues to be only effective treatment of PHPT. Potential nonoperative treatments for HPT have included the use of estrogen replacement, bisphosphonates, and a new class of drugs known as calcimimetics. Hormone replacement therapy with estrogen has been reported to improve cortical bone density in post menopausal women with asymptomatic or mildly symptomatic PHPT. Calcimimetic agents are a new class of drugs that increase the sensitivity of the calcium receptor to ionized calcium. Initial studies have shown that calcimimetics can acutely lower PTH levels in patients with primary and secondary HPT. These drugs are currently being evaluated in phase II clinical trials. Ultimately, these medical modalities will need to be compared to PTX in randomized controlled clinical trials (32).

Vitamin D supplementation, when given with calcium, has shown to increase BMD and reduce the incidence of hip fracture in elderly subjects. Hunter *et. al.* conducted a study in 2000 (33) and on the basis of these results, vitamin D supplementation, on its own, cannot be recommended routinely as an osteoporosis prevention for healthy post menopausal women with normal vitamin D levels under age of 70 years.

Conclusion

Scrutiny for HPT in cases of complex urolithiasis with or without associated secondary problems is recommended. Hypercalciuria has been reported to be

the most common metabolic abnormality. We suggest parathormone test in all such cases. Primary hyperparathyroidism can be managed by surgery where patients have well documented parathyroid abnormality on parathyroid scanning.

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