MEDICAL GRAND ROUNDS

PARKLAND MEMORIAL HOSPITAL

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HYPERCALCIURIA AND STONES

The purpose of this manuscript is to review various aspects of nephrolithiasis with special emphasis on the clinical syndrome of "idiopathic hypercalciuria". Initial aspects of this paper will review the incidence of renal stone formers in the general population, develop a definition of normal urinary calcium excretion rates, and discuss the differential diagnosis of hypercalciuria. Next the general characteristics of renal stone formers will be reviewed and contrasted to those patients with idiopathic hypercalciuria. The final sections of this communication will be concerned with therapeutic approaches to patients with nephrolithiasis.

The frequency with which nephrolithiasis occurs in the general population is difficult to estimate. In 1952 Boyce et al. (1) reported the results based on a survey in which questionnaires were sent to all major hospitals of this country. From these results it was documented that definite "stone belts" existed, and also areas in which renal stones are quite rare. For the country as a whole it was estimated that approximately 1 person per 1000 was admitted annually with the diagnosis of nephrolithiasis. The estimated incidence for Texas was in keeping with the national average. At Parkland Memorial Hospital we have had 126 acute non-referral patients admitted during the past three years for evaluation and treatment of nephrolithiasis. I would estimate that the actual number of patients seen in our emergency room with a chief complaint referable to nephrolithiasis was twice to three times as high, but not all have required in-patient hospitalization. I am certain that most internists and general practitioners are frequently confronted with the difficult questions as to the nature and the extent of the work-up that a patient with renal stones should receive, and whether this patient should be admitted to the hospital for further diagnostic evaluation and therapeutic treatment.

In 1939 Flocks (2) was first to draw attention to the high incidence of increased 24 hour urinary calcium excretion rates in patients with renal stones. He was unable to determine the etiology of the high urinary calcium in most of his patients and used the expression "idiopathic high urine calcium" to describe this group. However, not until 1953 was the term "idiopathic hypercalciuria" coined by Albright and his co-workers (3) and it was largely from the works reported from his laboratory (4) that this syndrome of idiopathic hypercalciuria has become established as a distinct clinical entity.

It is impossible to set absolute limits on normal 24 hour urinary calcium excretion rates on world-wide basis. Our English counterparts generally consider a patient to have hypercalciuria, on a diet containing normal amounts of calcium, if the urinary calcium for males is over 300 mg/day while the upper limit of normal for females is 250 mg% (5). In this country the upper limit of urinary calcium level

seems to be much lower. Studies conducted on a large group of normals from Mayo Clinic (6) revealed that urinary calcium excretion rate for 24 hours on a low calcium diet (varying between 130-170 mg/day) was 83 ± 42 (SD) mg while on a normal 800 mg calcium diet, the urinary calcium excretion rate was 133 ± 55 (SD) mg per day. Expanding the mean by two standard deviations would indicate that 95% of the normal fell below 243 mg per day. Many investigators have chosen 250 mg per day as the upper limit of normal; I personally feel that levels above 225 mg are abnormal in most circumstances. There are two interesting points to make concerning the above "normal" values: 1) the amount of dietary calcium which the patients were taking when the urine samples were collected, and 2) the normal variation of urinary calcium excretion rates from day to day. It has been suggested that urinary calciums are meaningful only when obtained on low dietary calcium intakes. Seeming support for this concept would be the differential calcium excretion rates of normals in England as contrasted to patients in U.S.A. Since the water in England tends to have a much higher calcium concentration than in most areas of the United States, it was supposed that the increased intake of calcium in England was the cause of higher urinary calcium excretion rates and, therefore, it was logical to conclude that urinary calciums are significantly elevated on increased calcium intake. That this is not the case has been shown by a number of nice studies (7-9) in which the dietary calcium levels were increased by impressive amounts with only minimal increases in urinary calcium excretion rates. I feel these studies provide good experimental evidence to allow the initial evaluation of calcium excretion rates to be conducted on a regular diet without the necessity of the expense and inconvenience of resorting to specially prepared low calcium diets. The second point concerns the constancy of urinary calcium levels in normal, and patients with idiopathic hypercalciuria. In normal persons the daily output of calcium remains reasonably constant; however, the recent studies of Coe et al. (10) have shown that there is at least one subgroup of idiopathic hypercalciuria in which urinary calcium levels may be quite elevated for a while, only to return and remain at normal levels for a prolonged period of time. For this reason it appears advisable to check urinary calcium excretion rates periodically if one suspects of desires to document the syndrome of idiopathic hypercalciuria.

not related to intake

The number of disease processes must be ruled out which may be associated with increased urinary calcium excretion rates before hypercalciuria can be classified as idiopathic. These are listed in Table I.

Table I

Differential Diagnosis of Hypercalciuria

A. Increased bone resorption
   1. Hyperparathyroidism
   2. Immobilization
   3. Osteoporosis in the acute phase
   4. Cushing's syndrome
   5. Corticosteroid therapy
   6. Metastatic cancer
   7. Multiple myeloma
   8. Thyrotoxicosis

B. Increased GI absorption
   1. Vitamin D toxicity
   2. Sarcoidosis hypersensitive to Vit. D.
   3. Milk-alkali syndrome
   4. Idiopathic hypercalciuria initially hypercalcemia late ↓ Ca++ in urine

C. Increased renal leak
   1. Metabolic acidosis acid effect on kidney
   2. Renal tubular acidosis

By history, physical examination, and laboratory tests it is straight forward to rule out most of these diseases with the exception of primary hyperparathyroidism. Before considering this differential in detail, I would like to define the syndrome of idiopathic hypercalciuria more fully by contrasting it to the general group of stone formers regardless of the primary etiology. Table II summarizes the salient features of the

stone formers admitted to our hospital on acute basis during the past three years. These characteristics are somewhat skewed in that many of our ureteral stones are treated on outpatient basis.

Table II

3 Year Survey of Patients Admitted to

Parkland Memorial Hospital with Nephrolithiasis

Age	42.5 ± 14
Males	63.7%
Females	36.3%
Serum Ca	9.2 ± 0.6 mg% (6 over 10 mg%)
Serum P	3.6 ± 0.7 mg% (16 less than 3.0 mg%) tendency to Low Phos.
Uric Acid	5.7 ± 1.9 mg% (9 over 8 mg%)

66/117 (56.4%) required surgery (only 7 stones < 5 mm)

51/117 (43.6%) no surgery (only 3 reported stones > 5 mm)

3 patients with hyperparathyroidism

2 with pure uric acid stone

There are several interesting points. The patients generally are young with 12 of our patients being less than 25 years old. There is an obvious proponderance of males. Serum calciums are in the normal range, but the phosphorus levels tend to be decreased. A surprisingly large number of our patients had elevated uric acid levels in absence of azotemia. The significance of this is not clear. The majority of our patients required surgery, and in these, the stone was generally over 5 mm in size; whereas, only 3 of the spontaneously passed stones were reported to be over 5 mm in size. Obviously the group who were not admitted to the hospital had much smaller stones and presumably passed them spontaneously. In only a small percentage of cases was the primary etiology of stone formers determined. These findings are in general agreement with other

reported series (5,6). Not enough urinary calciums were measured in our patients for meaningful statistical analysis; however, other workers have estimated the incidence of hypercalciuria in stone formers to range from 22 to 65% (2,5,6). Compiling these numbers, it is estimated that some one fourth to one third of the patients having renal stones do in fact have hypercalciuria, with a great majority of these belonging to the syndrome of idiopathic hypercalciuria.

As stated earlier, the term "idiopathic hypercalciuria" was first coined in 1953 by Albright et al. (3) in a preliminary report of 23 patients. Five years later a further definition of this syndrome was made from this same laboratory (4). Though there were 35 patients in this second group, I would like to define the syndrome on the basis of 11 of their patients. All of the 11 were male, all appeared superficially quite similar to a group what Bartter's laboratory likes to call normocalcemia hyperparathyroidism in that their serum calcium levels were normal, serum phosphorus levels were low, and urinary calcium levels were distinctly elevated. They differ from Bartter's normocalcemic hyperparathyroidism in that when these patients underwent painstaking neck explorations with biopsies of the parathyroid gland in whom no adenoma or parathyroid hyperplasia was documented. On the basis of these patients the findings which have become accepted as characteristic of idiopathic hypercalciuria are: (1) normal serum calcium concentrations, (2) tendency to low serum phosphorus levels, (3) elevated urinary calcium excretion rates, (4) high GI absorption of calcium, (5) normal acid-base balance, (6) high preponderance towards male distribution, (7) normal parathyroid function and (8) no roentgenological evidence of bone disease.

A significant body of controversial literature has arisen concerning the basic defect in this syndrome following Albright's initial description. One school believes that the syndrome is entirely a consequence of a renal leak of calcium with a compensatory increase in GI absorption, whereas another group feels the hypercalciuria is secondary to primary increase in GI reabsorption of calcium. There is still a third etiology which has been put forth which argues that the primary abnormality in idiopathic hypercalciuria is neither of the above, but a more fundamental disturbance in calcium metabolism of as yet unknown cause, leading to a high calcium turnover rate (11). The last hypothesis has been put forth on the basis of kinetic data obtained from disappearance rates of radioactive calcium pools with extrapolation of information to bone accretion and reabsorptive rates. I personally feel that these methods are not accurate estimations of bone turnover data and will not discuss the latter hypothesis further, but will try to put the controversy of primary renal versus primary GI theory in perspective.

On the basis of increased incidence of pyelonephritis in original group of patients reported from Albright's (3,4) laboratory, they postulated renal leak of calcium as the primary defect in this syndrome; however, 4 of their patients had low fecal calciums making them somewhat suspicious that their primary renal theory may not be correct in each case. The primary renal theory was soon supported by Jackson and Dancaster (12) who also postulated a primary increase in urinary calcium leading to secondary stimulation of intestinal absorption. However, it soon became evident that antecedent history of pyelonephritis was not usual, and that most of the patients in fact has sterile urines (13,15). This latter point has been repeatedly documented thereafter. Nassim (15) was the first to clearly point out in a 1963 lecture given at the Royal College of Physicians meeting in London that perhaps this entire syndrome could be explained on the basis of primary increase in the intestinal absorption of calcium with excess calcium being cleared by the kidneys. Since these studies (13-15), the issue as to which theory is correct has not been resolved. In my mind it is quite noteworthy that none of the reported cases with idiopathic hypercalciuria have had osteoporosis of other bone disease suggestive of long-term negative calcium balance. If the syndrome was secondary to primary renal leak, then it would be reasonable to postulate that the GI compensation is not 100% complete and that the patients should be in negative calcium balance. Pak and associates (16) now have elegant data in this group of patients to suggest that they actually are in positive calcium balance lending support to the primary GI theory. They also have a group of patients which are in somewhat a negative balance and feel that this group is secondary to primary hyperparathyroidism with grossly normal serum calcium levels. However, it is quite conceivable that the ionized calcium might be elevated in this last group or that the thermostat regulating PTH secretion rates in this last group is set at lower levels than normal. Unfortunately our measurements of ionized calcium levels are so crude that this question cannot be resolved at present.

A recent case history by Finn, Cerilli and Ferris (17) gives clear cut evidence that at least a fraction of idiopathic hypercalciuria patients is secondary to primary increase in GI absorption of calcium. This case involves a renal transplantation of a 16 year old boy with a kidney from a father with well documented idiopathic hypercalciuria. Before nephrectomy, urinary calcium in the father was 393 $\pm$ 23 mg per day on a standard 1 gram calcium diet - clearly in the abnormal range. A year after nephrectomy of the father, his urinary calcium excretion had returned to a level of 300-400 mg per day without hypercalcemia or evidence of hyperparathyroidism. In the son the transplanted kidney functioned immediately with creatinine clearance of 83 cc/min on the

second post-operative day. On similar diets of 1 gm calcium and 150 mEq of sodium the son and father were studied one year after transplantation. Father's urinary calcium was 375 ± 48 mg/24 hrs while the son's urinary calcium was in the normal range of 150 ± 18 mg/24 hrs despite identical creatinine clearances. Therefore, in the father hypercalciuria was not an intrinsic defect in the kidney. This case and other data from the literature makes me strongly lean towards the view that the primary defect in the majority of the cases of idiopathic hypercalciuria is increased absorption of calcium from the GI tract, and perhaps the syndrome should be renamed as such. I fully realize that many investigators now feel that the syndrome of idiopathic hypercalciuria is not a homogeneous one, but made up of disease processes of differing etiologies. Certainly one fraction is secondary to primary increase in GI absorption of calcium. It remains to be seen whether those patients who are in mild negative calcium balance end up having hyperparathyroidism as the primary etiology, or whether they will be included as another fraction of the idiopathic hypercalciuria syndrome with primary renal tubular leak of calcium. The current methods for determining increased ionized calcium levels are too crude to establish levels which are physiologically elevated for this group of patients.

The primary goal of the physician caring for a patient with increased urinary calcium levels is first to rule out all the known causes. This generally is quite simple except the differential diagnosis between primary hyperparathyroidism and idiopathic hypercalciuria may prove to be difficult. Statistics would indicate that hyperparathyroidism is rare. If the serum calcium level is clearly elevated with low serum phosphorus, this would be strong evidence favoring primary hyperparathyroidism, especially if there is roentgenological evidence of bone disease. However, this usually is not the case, and the differential diagnosis frequently involves a patient with serum calcium around 10 mg%, low serum phosphorus, and increased urinary calcium excretion rates. The determination of serum parathyroid hormone may not be of help. If it were normal or low, this would be evidence against idiopathic hypercalciuria secondary to primary GI hyperabsorption, however, if it is elevated, then this could be on the basis of primary hyperparathyroidism or compensatory increase in parathyroid hormone if part of the syndrome of idiopathic hypercalciuria is secondary to primary renal leak of calcium. Under these circumstances there would be an increase in parathyroid hormone which would cause increased gut reabsorption of calcium, and perhaps mobilize calcium from the bone. Coe and associates (10) feel strongly that patients with idiopathic hypercalciuria have primary renal leak of calcium with secondary elevated parathyroid hormone. They have been able to suppress this measured parathyroid hormone level with oral thiazides which act to increase reabsorption of calcium from the

kidney and therefore would increase the serum calcium levels, thus acting in a negative feedback sense to inhibit parathyroid hormone secretion. I find these studies interesting, but difficult to reconcile with since efforts to demonstrate a primary tubular defect in patients with idiopathic hypercalciuria, as compared to normals, have shown no differences. Peacock and Nordim (18) have intravenously infused both normals and patients with idiopathic hypercalciuria with calcium glucomate and then determined the excretion and reabsorption of calcium at different levels of filtered load. The results were virtually identical in the two groups suggesting that a renal tubular defect does not exist in idiopathic hypercalciuria. Thus if in fact there is no renal leak, then perhaps increased serum parathyroid hormone levels would be of diagnostic significance. This, however, becomes an academic argument since most places do not have parathyroid hormone assays available to them, and if they were, it is currently difficult to evaluate the significance of these values in view of poor reproducibility of parathyroid hormone assays between various laboratories. When adequate assay methods for human parathyroid hormone become available, then perhaps this controversy can be resolved. Probably the single best test to diagnose hyperparathyroidism in most hospitals is the measurement of urinary phosphorus levels in response to IV infusions of calcium. This test was originally devised by Howard, Hopkins and Comer (19), and modified by Pak and associates (20) to give less overlap between normal and hyperparathyroid patients. The test basically requires a patient to be on a constant phosphorus diet for two days. Urine is collected for phosphorus and calcium for a 12 hour period between 9 P.M. and 9 A.M. for control period. Next morning, starting at 9 A.M., a 4 hour infusion of calcium gluconate is started. The total amount of calcium that a patient receives is calculated by giving 15 mg of elemental calcium per kilogram of body weight. (Equivalent amount of $CaCl_2$ is a local irritant.) This generally elevates the plasma calcium level to approximately 13 mg%. Urine is then collected from 9 P.M. to 9 A.M. for phosphorus and creatinine. A decrease of greater than 20% in the urinary phosphorus/creatinine ratio is considered normal, whereas a decrease of less than this would suggest autonomous hyperparathyroidism. This delayed 12 hour urinary collection seems to be more specific than a 24 hour collection started immediately after the calcium infusion (20).

A number of considerations come up when the nature of therapy is contemplated: 1) should these patients be treated at all, and 2) if treatment is indicated, what are the specific aims of this treatment, and what are the most ideal therapeutic approaches to the individual patient. If a patient has a single stone and the recurrence incidence is low, then therapy probably is not indicated; however, if the recurrence rate is high, then some form of treatment should be considered. Good statistics to indicate recurrence rate of stone formation in patients

with idiopathic hypercalciuria are not available. All of us are aware of a single patient who comes in with repeated renal stones each year, however, this patient would be at the opposite extreme from a patient with a single renal stone without a repeat occurrence. In our own hospital admissions a positive history of previous stones was obtained in 81.2% of the cases. Since our admission policies are such that they may not reflect the recurrence rate of the entire renal stone population at large, this figure should not be taken as representative of all patients with renal stones. However, our figures are so high that they are suggestive of a significant recurrence rate, and therefore, some form of therapy is indicated. A possible exception might be a patient who presents with a calcium oxalate stone in a setting with severe volume depletion. If the renal stone follows a clinical circumstance with associated serum volume contraction, and other causes of nephrolithiasis have been ruled out, then I would just advise forcing fluids and cutting down on milk and cheese products, especially at times when volume depletion might be expected as in cases of prolonged exposure to heat, severe diarrhea, etc.

The basic goal of therapy in a patient with nephrolithiasis is to decrease state of supersaturation of urine with respect to activity product of calcium and phosphorus. Pak et al. (21) have previously shown that patients with idiopathic hypercalciuria have urines which are supersaturated with respect to brushite ($CaHPO_4 \cdot 2H_2O$) as measured by concentrations and activity coefficients of calcium and phosphate in the urine. Thus a decrease in either the calcium or phosphorus concentration in the urine would lead to a state where the formation of a renal stone would be less likely; whereas, an increase in the concentration of either of these urinary constituents would have the reverse effect.

There are a number of possible approaches by which urinary calcium concentration could be decreased. One such method would be to put the patient on a low calcium diet of less than 300 mg per day coupled with large intakes of oral fluids. This approach is not feasible since most of the time a patient will not stay on this regime. Another approach is to tie up the calcium in the gastrointestinal tract by oral administration of phosphates. This was the approach initially taken (4), and indeed, if patients are given 1.5 grams of phosphorus per day, the urinary levels of calcium can be decreased significantly. However, despite decreases in urinary calcium excretion rates, there is a significant increase in urinary phosphorus levels resulting in an increase in the activity product of calcium and phosphorus (21). Thus, exactly an opposite effect from the desired is achieved by use of oral phosphate.

Nassim and Higgins (15) were first to point out the use of oral thiazides for treatment of hypercalciuria. They were able to determine

that administration of 5 mg bendrofluazide per day reduced the urinary calcium excretion rate in a stepwise fall reaching a plateau after three to four days. They also were able to show that use of thiazide did not increase urinary concentrations of phosphorus and that these changes persisted as long as the drug was given. The reduction in urinary calcium excretion rates that Nassim and Higgins (15) noted ranged between 12 and 50%. Thus thiazides do have a role in the therapy of idiopathic hypercalciuria, but the patients will be subjected to all the complications associated with this form of therapy.

In 1963, Dart and his associates (13) were first to use cellulose phosphate in treatment of idiopathic hypercalciuria with good results. The rationale for its use is the following. Cellulose phosphate has been developed as a laboratory ion exchange substance which has a particular affinity for divalent cations because of the steric configuration of the phosphate radicals attached to the cellulose molecule. It thus binds calcium in the gut without increasing urinary phosphorus output to nearly the same degree as with sodium phytate. Since Dent's original description of its use, a number of laboratories in England have used it with impressive results (14,15). The side effects have been very few, if any. Serum magnesium levels tend to decrease, but if supplemental for magnesium is given, this side effect can be overcome. Some phosphate hydrolysis has been reported by use of this drug (13,14,21); however, the increase in urinary phosphate excretion rates has been much less than with use of oral sodium phosphates.

The drug appears as the ideal manner by which to decrease urinary calcium excretion rates, but unfortunately, it is not available for general use in this country. It has been used on an experimental basis at NIH (21), and their results, like the British, are quite impressive. Currently negotiations are underway with one of the drug manufacturing houses and the FDA to release this drug for general use. Until it is released, obviously we cannot use it.

If a patient is seen with his first stone secondary to idiopathic hypercalciuria, I would just recommend forcing fluids and reducing the dietary intake of calcium. If this is not successful and they return with a second or more frequent occurrences while on the above diet, then judicial use of thiazides is indicated. Currently I would stay away from the use of oral phosphates in that these may increase nephrocalcinosis even in the face of decreased urinary calcium concentrations.

In summary, idiopathic hypercalcinuria is characterized by: male preponderance; normal serum calcium; normal to decreased serum phosphorus;

increased urine calcium; high GI absorption of calcium; normal acid-base balance normal parathyroid function; and no roentgenological evidence of bone disease. Evidence was put forth to suggest that the majority of these patients have hypercalciuria as a compensatory mechanism secondary to a primary increase in reabsorption of calcium from the gastrointestinal tract. The preventive treatment of choice is to decrease intestinal calcium absorption. If stone is over 5 mm in size, surgical intervention often becomes necessary. Approximately 1/1000 persons are admitted annually to hospitals with renal stones, and one fourth to one third of these are secondary to idiopathic hypercalciuria. It is suggested that the recurrence rate of renal stones after the initial occurrence is high.

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