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Journal of Parathyroid Disease

Journal of Parathyroid Disease 2013,1(2),21–23

Hypothesis

Current concepts on normocalcemic primary hyperparathyroidism

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Primary hyperparathyroidism is described by high plasma levels of calcium associated with high or inappropriately normal plasma value of parathyroid hormone and is usually associated with hypophosphatemia (1). Primary hyperparathyroidism is thought to be the principal cause of hypercalcemia encountered in many studies (1,2). While, there was various etiology for hypercalcemia such as vitamin D intoxication, cancer, and use of lithium and thiazide diuretic, however, the diagnosis, of primary hyperparathyroidism is generally simple. For many years, primary hyperparathyroidism, used to be clinically known as a symptomatic disease, which presented clinical signs of renal stones, severe bone disease, or acute neuropsychiatric syndrome, which is accompanied by hypercalcemia (1-4). However, after the presentation of routine serum calcium assessment in ambulatory care in the 1970s, the clinical presentation of primary hyperparathyroidism altered, and a period of asymptomatic primary hyperparathyroidism began with a 4- to 5-fold increase in occurrence. According to a better understanding of primary hyperparathyroidism and the amended techniques for measuring serum calcium, primary hyperparathyroidism became asymptomatic (2-8). It is defined by normal total and ionized serum calcium values and consistently elevated PTH levels. These individuals have no obvious causes for secondary elevations of PTH, like renal disease or vitamin D insufficiency. Detection of this new phenotype of primary hyperparathyroidism provides a concept, in which a biphasic chronology of its clinical development (1-6). During the first phase, PTH levels are elevated but the serum calcium is normal. Till just, this first phase was a subclinical one, while PTH levels were seldom measured when the serum calcium value was normal. The second phase is the one that has traditionally been documented because hypercalcemia appears. The incidence of primary hyperparathyroidism increases with age and is more prevalent in women, particularly postmenopausal women. To find the impact of age and gender on presentation of symptomatic primary hyperparathyroidism, Shah et al, analyzed of 184 histopathologically proven primary hyperparathyroidism patients (9-14). They found, age and sex have substantial impact on presentation of primary hyperparathyroidism. Bone pain and rickets were common in children and adolescents while kidney stones in adults. Women had more severe illness, like musculoskeletal manifestations and higher value for parathormone levels compared to men. Many reports of normocalcemic primary hyperparathyroidism have main published from referral centers in which patients were evaluated for a metabolic bone disease (3-10). Various studies, revealed fatigue and muscle weakness are amongst the most common complaints presented by patients with asymptomatic primary hyperparathyroidism and are often associated with various degrees of behavioral, constitutional and psychiatric symptoms (5-12). It was suggested that normocalcemic primary hyperparathyroidism may be due to target organ resistance to the actions of parathormone. In fact, normocalcemic subjects with primary hyperparathyroidism, had revealed inadequate

Implication for health policy/practice/research/medical education

Primary hyperparathyroidism, the most common cause of hypercalcemia due to extreme secretion of parathormone, is frequently associated with hypophosphatemia and elevated serum chloride. Though primary hyperparathyroidism was frequently complicated by kidney stone disease and osteitis fibrosa in the past, however routine screening of serum calcium and development of high-level assay of parathyroid hormone have donated to earlier detection of primary hyperparathyroidism.

Received: 10 February 2013, **Accepted**: 30 March 2013, **ePublished**: 1 September 2013

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suppression of parathormone in response to the oral calcium load, in comparison to hypercalcemic subjects with regard to age, gender, and plasma parathormone concentration (3-15).

Moreover, secondary causes of an elevated parathyroid hormone level must be ruled out. In order to make a diagnosis of normocalcemic primary hyperparathyroidism, the following circumstances should be excluded:

A; vitamin D insufficiency, while there is an inverse association between parathormone and 25-hydroxyvitamin D, in the case of reduced level of 25-hydroxyvitamin D, the parathyroid glands are signaled to increase parathormone secretion. Hence to be assured in the diagnosis of normocalcemic primary hyperparathyroidism, it would appear advisable to ensure that the 25-hydroxyvitamin D level is greater than 30 ng/ml (4-14).

In the conditions of reduced creatinine clearance, it was found that parathormone commences to rise with a GFR <60 cc/min. It is also important that, in hypercalcemic primary hyperparathyroidism, the reduction in creatinine clearance to <60 cc/min is associated with increased parameters of bone resorption. Hence, it appears reasonable to require that GFR be greater than 60 cc/min if the diagnosis of normocalcemic primary hyperparathyroidism is to be confirmed (4-13).

B; some lithium and hydrochlorothiazide have both been associated with increased parathormone levels and thus should be believed as an etiological cause for increased parathormone levels in individuals on these medications. If the abnormality continues after these medications are withdrawn for several months, the diagnosis can once again be entertained (8-16).

In summary, the historical observation of primary hyperparathyroidism defines two distinct entities marked by two periods. Preceding to the advent of the multichannel autoanalyzer in four decades ago, classical primary hyperparathyroidism frequently presented with marked hypercalcemia and symptomatic stone and bone disease (11-17). Then the presentation shifted four decades ago to a disorder considered by mild hypercalcemia without classical symptomatic characteristics. Interestingly, it seems, we have entered a third period in the history of this disease in which patients are being noticed with normal total and ionized serum calcium concentrations but with parathormone levels that are consistently elevated (14-19). In fact, the result of these data, highlighting the importance of a suitable laboratory diagnosis, assessing possible signs or symptoms associated such as renal stones or osteoporosis, which can help the clinician to diagnosis of normocalcemic primary hyperparathyroidism, however, larger investigations are necessary to define the true prevalence and natural history of these parathyroid disorders (15-19).

Authors' contributions

All authors wrote the paper equally.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the author.

Conflict of interests

The authors declared no competing interests.

Funding/Support

None.

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Please cite this paper as: Sanadgol H, Ardalan MR, Tamadon MR, Mardani S, Nasri H. Current concepts on normocalcemic primary hyperparathyroidism. J Parathyr Dis 2013; 1(2): 21-23.