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TYPES, MANIFESTATIONS, AND CAUSES OF HYPOPARATHYROIDISM

Amr Hasan Hemida [1] , Kholod Khalid Aljaberi [2] , Alaa Abdulhamid Alsammahi [3] , Hussam Muidh Althagafi [3] , Rawan Abdulhameed Alsamahi [3] , Wed Ziyad Alnajjar [3] , Rawabi Abdullah Alharbi [2] , Mouad Mohammed Alqadi [2] , Maryam Talal Abusalamah [2] , Rayan Ali Barakat [2] , Sumayah Ahmad Fallatah [2] , Shroq Abdulkreem Alghraibi [2]

[1]Consultant medicine, Al Noor Specialist Hospital, 0537104309 ahemida56@hotmail.com.,
[2]Umm Al-Qura University., [3]King Abdulaziz University

Abstract:

Introduction: *Hypoparathyroidism is considered uncommon problem that is described by decreased serum calcium, elevated serum phosphorus, and insufficient production of parathyroid hormone (PTH). The epidemiology of hypoparathyroidism has been studied very well, with many studies quantitating aspects of the disease not previously understood. Pseudohypoparathyroidism, a disorder of PTH resistance, is very uncommon disease described by similarly abnormal mineral biochemical abnormalities, however with elevated circulating levels of PTH. Surgically, hypoparathyroidism can be categorized into primary hypoparathyroidism because of intrinsic defects within the parathyroid glands primarily due to genetic causes, and the much more common secondary or acquired forms due to causes that ablate, weaken or destroy parathyroid gland function. Secondary causes of hypoparathyroidism are by far the most common causes. While the diagnosis of hypoparathyroidism is often uncomplicated once serum calcium, phosphorus, and PTH levels are well-known, determining the cause of nonsurgical hypoparathyroidism is considered difficult.****Aim of work:*** *In this review, we will discuss types, manifestations, and causes of hypo parathyroidism..****Methodology:*** *We did a systematic search for Types, manifestations, and causes of hypoparathyroidism using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.****Conclusions:*** *The recent developments have clarified some characteristics of the epidemiology and diagnosis of hypoparathyroidism. Postsurgical hypoparathyroidism is responsible for about 3/4 of all cases of known hypoparathyroidism. In patients undergoing anterior neck surgery, less than five percent will have permanent hypoparathyroidism, even though as many as fifty percent could develop transient hypoparathyroidism. The remaining cases of hypoparathyroidism are caused by autoimmune disease, metastatic disease, iron or copper overload, radiation therapy or radioactive iodine treatment, or a variety of rare genetic disorders. Complications of hypoparathyroidism are many including chronic kidney disease, kidney stones or nephrocalcinosis, seizures, posterior subcapsular cataracts, and intracerebral calcifications. The risk of infections may be higher in this disorder. Cardiovascular disease, fractures, and malignancy do not appear to be increased, except for increased upper extremity fractures in nonsurgical hypoparathyroidism. Gastrointestinal cancers could be reduced in hypoparathyroidism. The diagnosis of the genetic causes of hypoparathyroidism and pseudohypoparathyroidism has been significantly clarified in recent years, with recognition of an increasing variety of different genes affecting parathyroid gland differentiation and function. Evaluation for most of the recognized mutations can now be performed by research or commercially available genetic testing.*

Key words: *Types, manifestations, causes, hypoparathyroidism.*

Corresponding author:
Amr Hasan Hemida,
Consultant medicine, Al Noor Specialist Hospital,
0537104309 ahemida56@hotmail.com.

QR code

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INTRODUCTION:

Hypoparathyroidism is considered uncommon problem that is described by decreased serum calcium, elevated serum phosphorus, and insufficient production of parathyroid hormone (PTH) [1]. The epidemiology of hypoparathyroidism has been studied very well, with many studies quantitating aspects of the disease not previously understood. Pseudohypoparathyroidism, a disorder of PTH resistance, is very uncommon disease described by similarly abnormal mineral biochemical abnormalities, however with elevated circulating levels of PTH.

Surgically, hypoparathyroidism can be categorized into primary hypoparathyroidism because of intrinsic defects within the parathyroid glands primarily due to genetic causes, and the much more common secondary or acquired forms due to causes that ablate, weaken or destroy parathyroid gland function. Secondary causes of hypoparathyroidism are by far the most common causes [2]. While the diagnosis of hypoparathyroidism is often uncomplicated once serum calcium, phosphorus, and PTH levels are well-known, determining the cause of nonsurgical hypoparathyroidism is considered difficult.

In this review, we will discuss the most recent evidence regarding Types, manifestations, and causes of hypoparathyroidism.

METHODOLOGY:

We did a systematic search for Types, manifestations, and causes of hypoparathyroidism using PubMed search engine (http://www.ncbi.nlm.nih.gov/) and Google Scholar search engine (https://scholar.google.com). All relevant studies were retrieved and discussed. We only included full articles.

The terms used in the search were: Types, manifestations, causes, hypoparathyroidism.

Epidemiology of Hypoparathyroidism

Anterior neck surgery is considered the most common cause of acquired hypoparathyroidism and is estimated to be responsible for more than seventy five percent of cases. The following most common acquired etiology in adult population is believed to be autoimmune disease, both affecting only the parathyroid glands, or multiple endocrinal glands. The remaining cases of acquired hypoparathyroidism are due to secondary causes which compose a variety of rare infiltrative disorders in which the parathyroid glands are affected by metastatic disease or iron or copper overload, or ionizing radiation exposure. Some genetic disorders although rare could also cause hypoparathyroidism. [3]

Prevalence

One of the best prevalence calculations of hypoparathyroidism in the U.S. is based on data of a large health plan database, which estimates that more than 77 000 cases [4]. This diagnostic estimation was based on the number of recent diagnoses of hypoparathyroidism in the database over the interval studied. On the contrary, a surgical incidence estimate is based on calculation of the proportion of total neck operations resulting in transient or chronic hypoparathyroidism.

Incidence

The acquired hypoparathyroidism usually occurs following the removal of, irreversible damage to, or to vascular compromise of the parathyroid glands. The incidence of postsurgical hypoparathyroidism is dependent on the center, type of intervention, and surgical expertise. Transient postsurgical hypoparathyroidism lasting less than six months is believed to occur in twenty-five to eighty percent of patients worldwide after performing neck surgery [5], while permanent postsurgical hypoparathyroidism, which is defined as lasting more than six months, has been believed to affect about less than five percent of cases [6].

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Cost and Hospitalization

The population-based study by Leibson et al [7] calculated overall cost of medical care for patients with hypoparathyroidism in Olmsted County, Minnesota, USA.

The annual cost of medical care for patients with hypoparathyroidism
in 2007–2009 was calculated to be approximately 3 times that for healthy adults.

Morbidities
Different morbidities are associated with hypoparathyroidism. They are linked to directly to hypocalcemia and/or to hyperphosphatemia, or indirectly due to treatment, the latter due to excessive or insufficient amounts of calcium and active vitamin D. When patients are not sufficiently managed, symptoms and signs of neuromuscular excitability (tetany) because of hypocalcemia which is common. If the patients get high amounts of calcium and vitamin D, hypercalcemia and/or hypercalciuria can occur. [8]

Mortality
The side effects of chronic hypocalcemia, intermittent hypercalcemia, hypercalciuria, and many comorbidities on mortality in patients with hypoparathyroidism have not been ascertained yet. No recent studies have estimated overall or cause specific mortality yet. Analyses of mortality and comorbidities in patients with postsurgical hypoparathyroidism in the Danish historical cohort study [9] had limitations to patients who developed hypoparathyroidism only after neck surgery for nonmalignant diseases, it also did not include patients with postsurgical hypoparathyroidism after parathyroidectomy due to renal insufficiency.

DIAGNOSIS:

Hypoparathyroidism is known by hypocalcaemia, defined as a total serum calcium below the lower limit of normal and hyperphosphatemia, both of which result from deficiency in circulating PTH [10]. In contrast to, pseudohypoparathyroidism (PHP) is characterized by hypocalcemia and higher levels of PTH [11].

Hypoparathyroidism
Hypoparathyroidism is characterized by low serum concentrations of PTH, but in very rare situations higher concentration of a mutant form of PTH can be seen with certain assays [12]. The level of 1,25-dihydroxyvitamin D and bone turnover markers including alkaline phosphatase activity are often in the low normal to low range [13]. The daily urinary excretion of calcium is decreased when patients are hypocalcemic, though the fractional excretion of calcium is elevated. Nephrogenous cyclic adenosine monophosphate (cAMP) excretion is low and renal tubular reabsorption of phosphate is elevated. Urinary cAMP, plasma cAMP,and urinary phosphate excretion increase markedly following giving of exogenous bioactive PTH. [14]

Pseudohypoparathyroidism
The main feature of PHP is the resistance to PTH, which could occur because of a variety of defects. Recently it is defined post receptor defects that lead to PTH resistance and the biochemical hallmarks of hypocalcemia, hyperphosphatemia, and elevated serum levels of PTH include PHP type 1a, PHP type 1b (PHP1B) (*GNAS* methylation abnormalities), PHP type 2 (PHP2), acrodysostosis type I and type II.

PTH assays
Low, near normal, concentration of serum PTH with hypocalcemia is the main feature of hypoparathyroidism and can help differentiate this disease from other disorders which also occur with hypocalcemia such as vitamin D deficiency.Therefore, an accurate assay for measuring serum PTH is important to make the right diagnosis. PTH is produced by the parathyroid glands as preproPTH, [15]. PTH is then secreted from secretory granules that fuse with the parathyroid cell membranes in response to a decrease in extracellular ionized calcium. Circulating PTH has of the full-length PTH peptide and several carboxyl-terminal fragments, most which being PTH(34–84) and PTH(37– 84).

The initial first generation PTH assays were radioimmunoassays (RIA), it used antibodies that were developed using parathyroid extracts from several different species. Epitopes were found to identify mid and C-terminal parts of the PTH. While this assay for the first time let us measure PTH, it recognized not only intact PTH, but also the bio-inactive C-terminal PTH fragments that represented the preponderance of PTH immunoactivity, so its usage was limited. To enhance the clinical utilization, a two-site immunoradiometric (IRMA) assay was invented [15].

This PTH assays can detect the full-length PTH (1–84), but not intended to detect the large, amino-terminally truncated fragments, like PTH (7– 84), that lack bioactivity. The 3rd generation assays, while theoretically better, have not been proven to be better than the 2nd generation assays in clinical practice. This has been frustrating for the evaluation of patients with chronic kidney disease (38–40) in which such large inactive fragments accumulate. Moreover, 3rd generation assays detect an insufficiently characterized form of PTH, which is thought to be phosphorylated at serine 17. [16]

Gene Testing in Clinical Practice

Genetic testing could be done using DNA obtained from leukocytes, salivary cells, skin cells or hair follicles. It is critical to mention that best clinical practice for such genetic testing should include informed consent from the patient and access to genetic counselors.

Hypoparathyroidism

Genetic testing for mutations in patients with hypoparathyroidism is useful in clinical practice in many methods that involve: 1) confirming the diagnosis so that appropriate screening for associated endocrinopathies is done; 2) implementing appropriate management plan. 3) identifying of family members who may be asymptomatic but has the mutation and therefore require screening for development of endocrinopathies or other disorders and early/appropriate treatment; and 4) identification of the fifty percent of family members who do not have the familial germline mutation in order to reassure them.

Pseudohypoparathyroidism

Analysis of genetic and epigenetic of *GNAS* and mutation analysis of *PPKAR1A* and *PDE4D* can aid the diagnosis through differentiating between the different variants of PHP and its related disorders. Patients affected by PHP1B require testing for *GNAS* methylation modifications; some laboratories will analyze exon A/B only as a screen, as loss of methylation of this DMR on the maternally derived *GNAS* allele is present in all reported cases of both inherited and sporadic forms of PHP1B.

CONCLUSIONS:

The recent developments have clarified some characteristics of the epidemiology and diagnosis of hypoparathyroidism. Postsurgical hypoparathyroidism is responsible for about 3/4 of all cases of known hypoparathyroidism. In patients undergoing anterior neck surgery, less than five percent will have permanent hypoparathyroidism, even though as many as fifty percent could develop transient hypoparathyroidism. The remaining cases of hypoparathyroidism are caused by autoimmune disease, metastatic disease, iron or copper overload, radiation therapy or radioactive iodine treatment, or a variety of rare genetic disorders. Complications of hypoparathyroidism are many including chronic kidney disease, kidney stones or nephrocalcinosis, seizures, posterior subcapsular cataracts, and intracerebral calcifications. The risk of infections may be higher in this disorder. Cardiovascular disease, fractures, and malignancy do not appear to be increased, except for increased upper extremity fractures in nonsurgical hypoparathyroidism. Gastrointestinal cancers could be reduced in hypoparathyroidism. The diagnosis of the genetic causes of hypoparathyroidism and pseudohypoparathyroidism has been significantly clarified in recent years, with recognition of an increasing variety of different genes affecting parathyroid gland differentiation and function. Evaluation for most of the recognized mutations can now be performed by research or commercially available genetic testing.

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