PSEUDOHYPOPARATHYROIDISM

1. Introduction – Definitions

Parathyroid hormone (PTH): This is a hormone produced by the parathyroid glands. When blood calcium levels fall too low, PTH brings them back to normal by i) breaking down the bone (where most of the body's calcium is stored) and causing calcium release ii) increasing calcium absorption from food in the intestine iii) increasing the kidney's ability to retain calcium that would otherwise be lost in the urine.

Calcium: A mineral stored in the bones where it builds and maintains bone strength. It is also found in every part of the body. It helps muscles contract, helps nerves and the brain function properly, and helps regulate the heart rhythm and blood pressure.

Phosphate: A mineral found in all cells but stored mostly in the bones. It is an essential element for energy production. It also aids in proper function of the kidneys, muscles, heart, and nerves.

Vitamin D: A hormone that helps the body absorb calcium from food and keep blood calcium levels in the normal range, improves muscle strength and promotes bone growth.

2. What are the parathyroid glands, and what do they do?

The parathyroid glands are four tiny glands, located in the neck, just behind the thyroid gland that control the body's calcium levels. Each gland is about the size of a grain of rice (weighs approximately 30 milligrams and is 3-4 millimeters in diameter). The parathyroids produce a hormone called parathyroid hormone (PTH). When the blood calcium levels is too low, PTH is released to bring the calcium level back up to normal. When the calcium level is normal or high, normal parathyroids stop releasing PTH. Proper calcium balance is crucial for the normal function of the heart, nervous system, kidneys, and bones.

3. What is Pseudohypoparathyroidism (PHP)?

Pseudohypoparathyroidism (PHP) is a genetic disorder in which the body fails to respond to PTH, although the hormone is present in normal amounts. Those with the condition have a low serum calcium and high phosphate, but PTH levels are appropriately high (due to the low level of calcium in the blood). This disorder is extremely rare, with an estimated overall prevalence of 7.2/1,000,000 or approximately 1/140,000.

4. What are the symptoms of PHP?

The symptoms are very similar to hypoparathyroidism (when PTH levels are too low). Levels of calcium in the blood are usually low, while phosphate and PTH are elevated. These laboratory findings indicate resistance to PTH action. Symptoms are generally first seen during childhood. Affected individuals may experience headaches, weakness, easy fatigue, lack of energy, blurred vision, and/or abnormal sensitivity (hypersensitivity) to light. Additional symptoms and findings may include stiffness, cramps, numbness and tetany (muscle twitches, hand and foot spasms), palpitations, and/or abdominal pain. Teeth with underdeveloped enamel tend to erupt later than normal during infancy. During childhood, seizures may occur.

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People with this disorder may be also resistant to other hormones such as thyroid-stimulating hormone (TSH) and gonadotropins (hormones that regulate the function of the thyroid and testes/ovaries, respectively). Thus, patients may develop hypothyroidism, hypogonadism, growth hormone (GH) deficiency and rarely cortisol deficiency.

Specific subtypes of PHP (Types Ia and Ic) are also associated with a group of physical features referred to as **Albright's hereditary osteodystrophy**, which includes short stature, a round face, obesity, and short hand and feet bones. Subcutaneous ossification, which is bone formation outside the skeleton, in the soft tissues and under the skin, may also be present. Intelligence usually ranges from low normal to mentally retarded. Symptoms may vary among patients with this condition. People with the same disease may not have all the symptoms mentioned above. Patients with PHP can lead a normal life.

5. What are the causes of PHP and what are the various subtypes of PHP?

PHP is caused by changes (mutations) in a number of different genes including the GNAS1 gene. A mutation in this gene is most often inherited from the affected person's mother, although it can sometimes be inherited from the father. GNAS1 protein is involved in signal transduction following binding of PTH and other hormones to their receptors on cell surface.

There are two different types of PHP, **type I and type II**. Type I can be further divided into three subtypes.

PHP type Ia is inherited in an autosomal dominant manner that means only one parent needs to pass the faulty gene to the child for the condition to develop. The risk of transmitting the disorder from affected parent to offspring is 50% for each pregnancy regardless of the sex of the child. PHP type Ia occurs in a child only when the mutation is inherited from the mother. PHP type Ia patients show a 50% reduction in GNAS1 protein activity.People with this disorder have normal or low calcium and high phosphate and PTH in the blood, resulting in cataracts, dental problems, seizures, numbness, and tetany. They also develop symptoms of Albright hereditary osteodystrophy and resistance to other hormones, as previously described.

PHP type Ib involves resistance to PTH only in the kidneys. Less is known about type Ib than type Ia but changes in the GNAS gene are also involved. Calcium in the blood is low, phosphate and PTH are elevated, but there are no features of Albright hereditary osteodystrophy. Some people with PHP type Ib also have elevated TSH levels due to TSH resistance. PHP type Ib is usually sporadic (not inherited), but familial cases with autosomal dominant inheritance, from the mother only, have been reported.

PHP type Ic is very similar to type Ia. However, people with PHP type Ic do not have abnormal activity of the GNAS1 protein.

PHP type II also involves low blood calcium and high blood phosphate and PTH levels. People with this form do not have the physical traits common to people with Type Ia. The genetic abnormality that causes it is not known.

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Pseudopseudohypoparathyroidism (PPHP) is genetically related to PHP type Ia. Signs and symptoms are similar (Albright's hereditary osteodystrophy), however people with PPHP do not show resistance to PTH, while people with PHP type Ia do. Obesity is characteristic for PHP type Ia and may be severe, while obesity is less prominent and may be absent among people with PPHP. Both PHP type Ia and PPHP are caused by mutations that affect the function of the GNAS gene. Patients who carry the mutation from their mother develop PHP type Ia, whereas those who carry the mutation from their father develop PPHP.

6. How is a PHP diagnosis made?

Pseudohypoparathyroidism can be diagnosed by blood or urine tests to measure the levels of calcium, phosphate, and PTH. If the levels of PTH and phosphate are high and if the levels of calcium are normal or low, this indicates the possibility of PHP. A doctor may wish to confirm the diagnosis through genetic testing for a mutation in the GNAS1 gene.

7. How is PHP treated?

The goal of treatment for PHP is to restore the levels of calcium and phosphate to normal and, when possible, bring PTH levels near the upper limit of the normal range. This can be achieved by receiving calcium supplements to increase the level of calcium in the body. Vitamin D supplements also act indirectly to increase calcium levels in the body because vitamin D improves the absorption of calcium. PHP patients are treated with the biologically active forms of Vitamin D, alfacalcidol or calcitriol.

Resistance to additional hormones should be treated when present. Levothyroxine replaces deficient thyroid hormone levels caused by resistance to TSH. Corticosteroids and sex hormones may be needed, albeit less frequently.

People affected with certain types of PHP may be shorter than others. If a diagnosis of growth hormone deficiency is made, growth hormone may also be given as replacement therapy.

There is no treatment for the physical traits of Albright hereditary osteodystrophy. Subcutaneous ossifications may be surgically removed when particularly large or causing pain/discomfort.