Pseudohypoparathyroidism Type 1A

Pseudohypoparathyroidism Type 1A is a disorder that occurs due to a defect in PTH receptors, resulting in increased PTH, hypocalcemia, and hyperphosphatemia. It is characterized by autosomal dominant inheritance, a mutation in the GNAS gene, and maternal imprinting. Patients can present with short stature, shortened 4th fingers, developmental delay, subcutaneous calcifications, tetany, and seizures. Treatment may include calcium and vitamin D supplements.

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Characteristics

Defect in PTH Receptor

Broken Receptor of Hippo-para-thigh-droid

The primary pathophysiologic feature of pseudohypoparathyroidism is a defect in the Parathyroid Hormone (PTH) receptor. This will lead to impairment of parathyroid hormone (PTH)-dependent signaling.

Increased PTH

Up-arrow Parachute-thigh-droid

The main pathogenesis of pseudohypoparathyroidism type 1A is the resistance of parathyroid hormone's target organ to respond to parathyroid hormone. This will trigger the body to produce more parathyroid hormone in an effort to overcome the resistance.

Hypocalcemia and Hyperphosphatemia

Hippo-calcium-cow and Hiker-phosphate-P

Hypocalcemia is seen in patients with pseudohypoparathyroidism type 1A due to the impaired function of parathyroid hormone. Hyperphosphatemia is also present due to the impaired regulation of renal phosphate reabsorption.

Autosomal Dominant

Domino

Pseudohypoparathyroidism Type 1A is inherited in an autosomal dominant fashion. Therefore, information about family history is essential in these patients. On average, 50% of children of heterozygous parents (one affected) will inherit this disease.

Mutation in GNAS Gene

Mutant in G-NASA Jeans

A mutation in the GNAS gene is seen in Pseudohypoparathyroidism Type 1A. The GNAS gene encodes the G stimulatory alpha-subunit (Gs□) of guanine nucleotide-binding protein, which contributes to the transmission of stimulatory signals to adenylate cyclase, resulting in the production of cyclic AMP (cAMP). In the presence of a GNAS gene mutation, resistance to parathyroid hormone will occur.

Maternal Imprinting

Mother Imprinting a Stamp

Pseudohypoparathyroidism Type 1A occurs when an imprinted GNAS gene is maternally inherited.

Clinical Features

Short Stature

Shorts Statue

The inadequate response of chondrocytes to parathyroid hormone impacts bone growth resulting in short stature (shortening of the skeleton), shortening of the bones in the hands and feet, and a shortened neck.

Shortened 4th Fingers

Shortened 4th Fingers

Patients can present with shortening of the metacarpals of the 4th/5th digits, resulting in short fingers. It can be one or both hands. During physical examination, dimpling over the knuckles of a grasped fist can be present. This is known as the Archibald sign. It can also be recognized as a sign in other disorders that cause hypoparathyroidism.

Developmental Delay

Developmental-bus

Developmental delay can be seen in patients. Its severity is variable among patients. However, around 30% of patients have normal cognitive development.

Subcutaneous Calcifications

Submarine-Q-tip Calcium-cows

Gs deficiency in mesenchymal stem cells as a result of this disease can result in the development of ectopic ossifications. Subcutaneous calcifications is one of the manifestations of this disease and can present as a small asymptomatic nodule or large, coalescent plaques of bone that evolve deeply into muscles and around joints.

Tetany

Titanic

Tetany can occur due to severe hypocalcemia with serum calcium levels < 7 mg/dL. Symptoms can begin with muscle cramps then advance to tetany or carpal spasm.

Seizures

Caesar

The presence of hypocalcemia in patients can lower the excitation threshold for seizures.

Management

Calcium and Vitamin D Supplementation

Calcium-cow and Viking-Daisy Pills

Oral calcium and vitamin D supplementation are recommended for these patients. The goal of managing this disorder is to maintain normal calcium and phosphorus, prevent hypercalciuria, and normalize PTH levels.

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