Pseudo- and Pseudo-pseudohypoPARAthyroidism

PseudohypoPARAthyroidism is characterized by an inability of some portions of the kidney to respond to parathyroid hormone (PTH), which is termed resistance to PTH. This condition is associated with low serum levels of calcium and high serum levels of phosphorus but unlike other forms of hypoparathyroidism the PTH level is high rather than low. There are several different types of pseudohypoPARAthyroidism, types 1A and 1B, type 1B, and type 2.

PseudohypoPARAthyroidism type 1A and type 1C are associated with resistance to multiple hormones in addition to PTH, including TSH resistance with mild hypothyroidism, resistance to LH and FSH with pubertal and reproductive problems, and GHRH with decreased secretion of growth hormone that contributes to poor growth and short stature. In addition, pseudohypoPARAthyroidism is associated with other features, termed Albright Hereditary Osteodystrophy (AHO), that include short fingers and toes and development of bone fragments under the skin and sometimes in the muscles. AHO is also associated with mild to moderate developmental delays.

Patients with pseudohypoPARAthyroidism type 1B have a more limited condition with PTH resistance as the primary manifestation. A few patients may also have mild shortening of a few fingers and very modest hypothyroidism. These patients have imprinting defects that affect methylation of the GNAS gene, which reduces expression of the stimulatory G protein, and for most patients a genetic defect has not been defined.

The type 2 form of pseudohypoPARAthyroidism is limited to PTH resistance with low serum calcium levels and elevated serum phosphate levels, and usually occurs in patients with severe vitamin D deficiency. This form of pseudohypoPARAthyroidism is reversible with vitamin D replacement.

Pseudo-pseudohypoPARAthyroidism is related to type 1A and type 1B**,** but patients have only AHO and respond normally to their hormones. These patients have normal serum levels of calcium, phosphate and PTH i.e. no resistance to PTH and other hormones. Patients with these disorders usually have mutations in those portions of the GNAS gene that code for the stimulatory G protein , but inheritance follows an unusual pattern. If the GNAS mutation occurs on the gene inherited from the mother the child will have pseudohypoparathyroidism type 1A but if the GNAS mutation occurs on the gene copy inherited from the father the child will have pseudopseudohypoPARAthyroidism

Condition		AHO	PTH levels	Calcium	Phosphates	Urinary Calcium*	Molecular Defect
Hypoparathyroidism		NO	Low	Low	High	High	variable
Pseudohypoparathyroidism	Type 1A	YES	High	Low	High	Low	*GNAS* defect on the maternal allele
	Type 1B	No or Mild	High	Low	High	Low	Imprinting defect on maternal *GNAS* allele
	Type 2	NO	High	Low	High	Low	NIL
Pseudopseudohypoparathyroidism		YES	Normal	Normal	Normal	Normal	*GNAS* defect on paternal allele

*** With treatment consisting of oral calcium and activated forms of vitamin D (e.g., calcitriol)**

Treatment

Goals of treatment are to achieve normal serum calcium and phosphate levels while avoiding increased urinary calcium levels. Treatment consists of oral calcium supplements plus active forms of vitamin D such as calcitriol. PTH levels should be monitored and maintained at levels near or slightly above the upper limits of normal.

References

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