Pseudohypoparathyroidism with Diabetes Mellitus and Hypothyroidism

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We report a12-year-old child with pseudohypoparathyroidism (PHP) whose mother had pseudopseudohypoparathyroidism. The child had low serum calcium, high phosphorous and high parathormone (PTH) levels. PHP occurs due to a defect in the guanine nucleotide binding protein (G protein). She also had hypothyroidism which is known to utilize the G protein pathway. She developed T 1 diabetes mellitus (T1DM) while under follow-up. This is arguably the first time T1DM has been reported associated with PHP.

Key words: *Albright's Hereditary Osteodystrophy, Hypothyroidism, Parathyroid hormone, Pseudopseudohypoparathyroidism, Type 1 Diabetes Mellitus.*

Insensitivity to parathormone (PTH) in pseudohypoparathyroidism (PHP) results from a defect in the stimulatory G protein needed for activation of cyclic adenosine monophosphate (c-AMP). G protein is also needed for activity of a number of other peptide hormones. PHP associated with poor responsiveness to thyroid stimulating hormone, gonadotrophin, glucagon, corticotropin and vasopressin have been reported previously [1]. Although insulin is another peptide hormone, association of PHP with diabetes mellitus has not been reported previously. We report a child with PHP with hypothyroidism and diabetes mellitus. This child also had vitamin D deficiency. Maternal imprinting of the defective gene is suggested by the fact that she inherited the disorder from her mother who has pseudopseudohypoparathyroidism (PPHP).

CASE REPORT

A 12 year old girl born of a non-consanguineous marriage presented with one year history of multiple episodes of generalized seizures and tetany. She had history of poor scholastic performance and gradual development of subcutaneous nodules over abdomen. On examination, she was noted to have round chubby face, short neck, short stubby hands and feet. Her height was 136 cm (<3rd percentile) and weight was 37 kg (25th percentile) for age) and body mass index (BMI) was 20 kg/m^2 (75th centile) Four hard subcutaneous nodules were palpable over the abdomen (0.7-1.8 cm in size). Chvostek and Trousseau's signs were positive. Sexual maturity rating was Stage 2.

Table* I** shows the results of her laboratory investigations. Radiograph of hands and feet showed marked shortening of the metacarpals and metatarsals (Fig.* 1 and 2**). Neuroimaging of brain revealed intracranial striopellidodentate calcification (***Fig.* 3**). Histopathologic examination of abdominal nodules revealed small spicules to large masses of mature bone in the dermis suggestive of primary subcutaneous calcification.

TABLE I LABORATORY RESULTS OF THE INDEX CASE AND HER MOTHER ALONG WITH THE REFERENCE LEVELS OF LABORATORY PARAMETERS

Parameters	*Index Case*
Serum calcium	3.0 mg/dL
Serum phosphorous	11.2 mg/dL
Serum alkaline phophatase	565.0 U/L
Serum albumin	3.7 g/dL
Serum magnesium	1.4 mg/dL
Serum intact parathyroid hormone	468.0 pg/mL
Serum 25 – OH Vitamin D	9.0 ng/mL
Blood urea nitrogen	10.5 mg/dL
Serum creatinine	0.5 mg/dL
Serum free T3	1.5 pg/mL
Serum free T4	1.1 ng/dL
Serum thyroid stimulating hormone	12.3 uIU/mL
Urinary calcium	0.5 mg/dL
Serum C - peptide	0.3 ng/mL

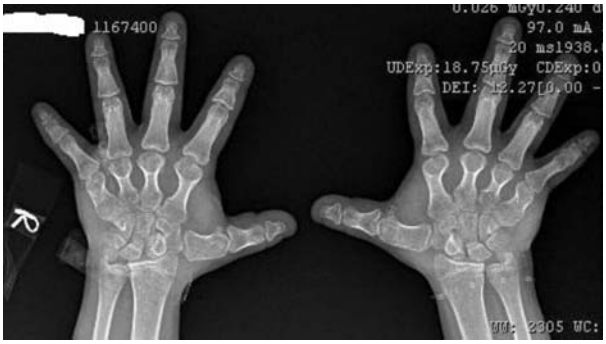

FIG. 1 *Brachydactyly of hands.*

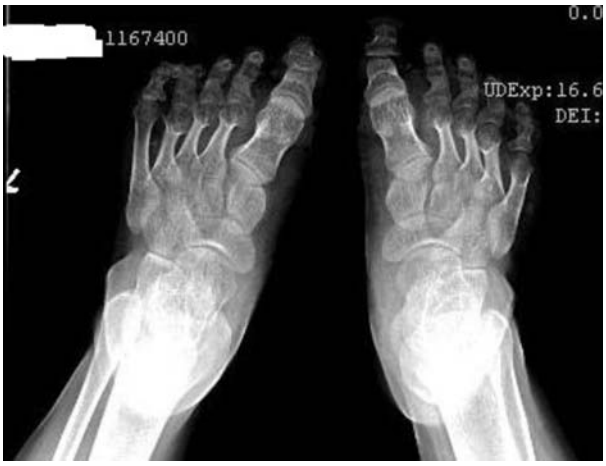

FIG. 2 *Brachydactyly of feet.*

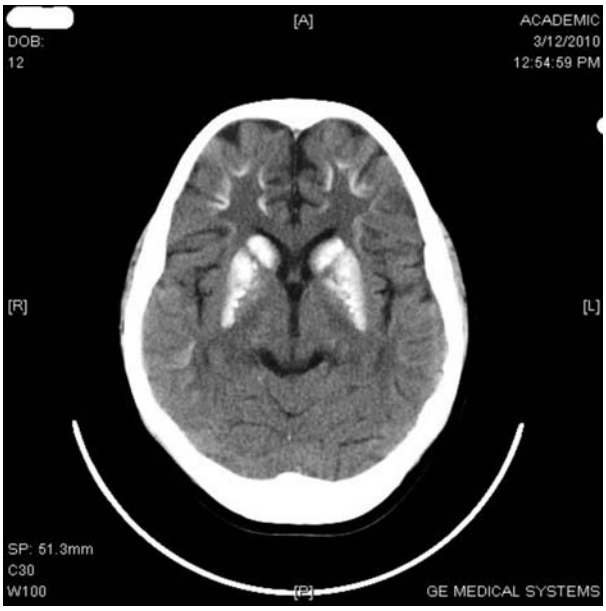

FIG. 3 *Bilateral striopeliodentate calcification.*

She was treated initially with intravenous (IV) sodium valproate to control seizures along with IV calcium and intramuscular vitamin D (Inj arachitol – 6 lac units). Later, medications were changed to oral calcium (2 gdaily) and vitamin D (alphacalcidol 2 mcg daily). Associated hypothyroidism was treated with 50 mcg levothyroxine daily.

Her mother also had abnormal morphological features, round facies, short stature (height 145cm) and brachydactyly of fingers and toes. Her serum calcium, phosphorus and alkaline phosphatase levels were normal. It was reported that the mother's father was phenotypically similar to her. There is no history of convulsions in the mother's father. He died about ten years before his granddaughter reported to us.

Two months after initial presentation, child was readmitted with diabetes mellitus. Her serum C–Peptide levels were low (0.3 ng/mL against a reference range of 1.1 – 5.0 ng/mL) suggesting type 1 diabetes mellitus (T1DM). She was put on subcutaneous insulin. Her blood sugar levels are well controlled on this. On follow up for over 2 years, she has had no further seizures after correction of her hypocalcemia.

DISCUSSION

PHP manifests on account of genetic defects in the hormone receptor adenylate cyclase system such that PTH does not raise the level of calcium or lower the level of phosphorous. In Type 1a PHP the defect is in the G protein which is a coupling factor for PTH to activate c - AMP. The G-protein defect can impact a large number of hormones besides PTH [1]. PHP Type Ia has heterozygous loss-of-function in Gs-alpha unit and is inherited from the mother. Patients are characteristically short statured with stocky habitus, obesity, round facies, brachydactyly and soft-tissue calcification. These features are typically known as the Albright Hereditary Osteodystrophy (AHO) phenotype [1]. Striopallido-dentate calcification, although uncommon, helps confirm the diagnosis of Type 1a PHP [2]. PHP Type Ib does not have the AHO phenotype and there is no resistance to other G-protein coupled hormones. PHP Type II has normal phenotype. PPHP patients have features similar to Type Ia PHP but without biochemical evidence of PTH resistance [3]. Our patient has features of Type Ia PHP, including osteoma cutis and striopellidodentate calcification. Her mother also had features suggestive of PPHP.

Primary hypothyroidism and hypogonadism are the associated hormone defects that occur most commonly. Hypothyroidism may be apparent earlier in life, prior to development of hypocalcemia of PHP. Reproductive dysfunction in the form of delayed puberty, oligomenorrhea and infertility may also occur [4]. Our patient had hypothyroidism. SMR was normal for age. She had not attained menarche at 12 years of age.

Recent studies suggest that some of the actions of insulin may be mediated by G protein [5-7]. This has been demonstrated in animal models (Zucker rats) of both insulin dependent and noninsulin dependent diabetes [8]. However, diabetes has not been associated with PHP in humans previously. The child reported here had low serum C-peptide level, suggestive of T1DM, which is an unusual association. Type 2 diabetes has been reported

earlier with both PPHP and PHP [9,10]. Coincident hypovitaminosis D in this child can result in low calcium and elevated PTH levels similar to PHP. However the other phenotypical features of PHP cannot be explained by vitamin D deficiency.

The child's maternal grandfather was also short "with features like the mother", suggesting he probably had either PPHP or PHP (grandfather was not tested to determine if he had hypocalcaemia). The sequence of inheritance in this pedigree adds credibility to the suggestion that the disorder is influenced by imprinting in a parent-of-origin dependent manner. The defective gene is a dominant gene. However, if it is inherited from the father the gene is only partially expressed (PPHP). If, on the other hand, the gene is inherited from the mother it is fully expressed (PHP). Even if the gene is only partially expressed, it has potential to be fully expressed in the next generation depending on the sex of the parent transmitting the gene. In this family study, the index case acquired the disease (PHP) from her mother who had PPHP. She in turn inherited PPHP from her father.

We did not test antibody for pancreas (autoantibodies to islet cell cytoplasm (ICA), insulin (IAA), antibodies to glutamic acid decarboxylase (GADA or GAD65) or ICA512 (IA2)). The results would have helped to understand if the child's diabetes was associated with antibodies.

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