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Case Report

Importance of general examination in diagnosis: a rare case report of a family affected with Albright's hereditary osteodystrophy

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ABSTRACT

Albright's hereditary osteodystrophy (AHO) is rare constellation of signs associated with pseudohypoparathyroidism (PHP) associated with genomic imprinting in GNAS1 gene. We described a case report of a patient with AHO phenotype with pseudopseudohypoparathyroidism (PPHP) with associated chronic liver disease and its complications and her pedigree analysis.

Keywords: Albright's hereditary osteodystrophy, Pseudohypoparathyroidism, Pseudopseudohypoparathyroidism, Parathyroid hormone, Hypersplenism, Portal hypertension

INTRODUCTION

AHO is a rare genetic disorder with a prevalence of approximately 0.79 per 100,000.[1] It refers to a constellation of signs commonly found in patients with some of the types of PHP, which was described by Fuller Albright in 1942. AHO phenotype includes round face, short stature, brachydactyly, subcutaneous ossification, dental anomalies and varying degrees of mental retardation. It is due to mutation of GNAS1 gene located on 20q13-11.[2,3]

Although AHO and PHP are heterogeneous manifestations of the same gene mutation in the GNAS1 gene, the terms cannot be used interchangeably. AHO is a phenotype while PHP is the biochemical resistance to parathyroid hormone (PTH) which may or may not manifest as AHO.

We described a case report of a patient with PPHP whose diagnosis was obtained from proper family history, AHO phenotype and appropriate radiological and biochemical evaluation. This patient also had evidence of chronic liver disease with portal hypertension. This association of AHO and chronic liver disease needed to be further evaluated.

CASE REPORT

A 46-year-old female patient without any significant past history presented with complaints of gradual onset and progressive bilateral lower limb swelling abdominal distension yellowish discoloration of sclera, easy fatigability and palpitations over a duration of 15 days. Patient had also developed sudden onset of bleeding per rectum for which patient was brought to casualty. No history of constipation or abdominal pain or altered sensorium or other bleeding manifestations. No history of blood transfusion or previous hospital admissions.

General examination of the patient revealed pallor, icterus and anasarca. Apart from the above findings general examination revealed, short stature (height of 148 cm), dental malocclusion, brachydactyly of 5th digits of

bilateral hands and bilateral 4th toes, dental abnormalities (Figure 1). Spine examination was normal. BMI was 21.4 kg/m^2. On admission she was having tachypnea, pulse rate of 100 per min and blood pressure of 140/90 mmHg.

Figure 1: (a) dental malocclusion; (b) Archibald's sign (dimple in place of 5th metacarpal); (c) brachydactyly of upper limb and lower limb and murderer's thumb; (d) short stature of patient and her son; (e) brachydactyly of toe of patient and her son.

Figure 2: Murderer's thumb (potter's thumb).

Diagnosis of AHO was made based on clinical criteria.[4] Archibald's metacarpal sign (absence of knuckle prominence on making fist in 5th digit instead of which a dimple appears) was positive in our patient.[5] Murderer's thumb sign (potter's thumb sign) was positive.

Abdominal examination revealed gross ascites and splenomegaly. No scars or dilated veins was present over abdomen.

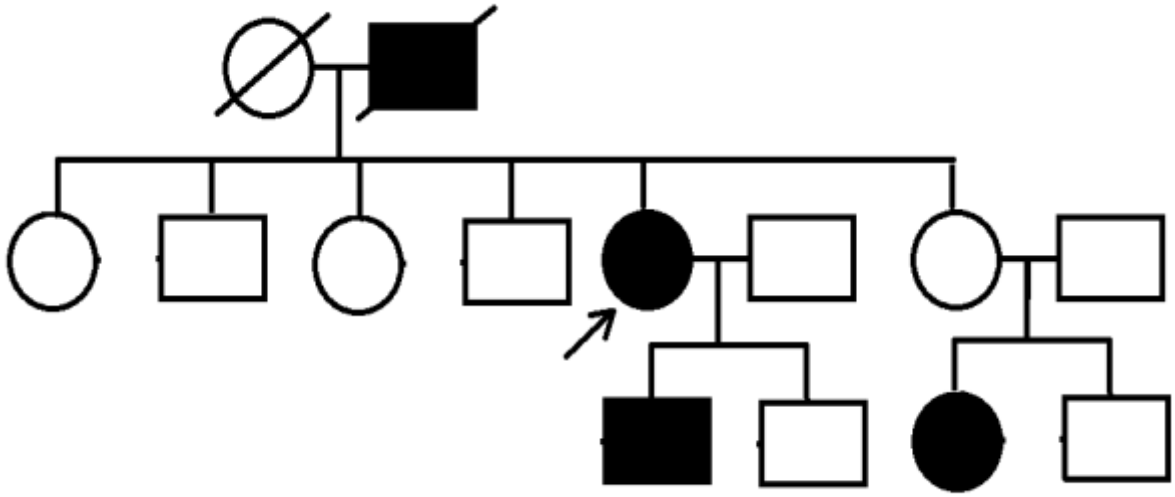

Figure 3: Index case and her family with AHO phenotype.

Table 1: Classification of PHP and clinical features.

PHP type 1		PHP type 2	PPHP
Type 1a	Most common (70%); AHO; defect proximal to cAMP; associated with multiple hormone resistance	Not usually familial; resistance limited to PTH; resistance distal to cAMP formation	Features of AHO without overt hormone resistance
Type 1b	Physical appearance is normal; resistance is limited to renal resistance of PTH		
Type 1 c	AHO; normal Gsα activity		

In blood investigations, CBC revealed pancytopenia with total leucocyte count of 1100 cell/ mm^3, hemoglobin of 4.3 g/dl and platelet count of 43,000/mm^3. MCV was 80.6 fl. In liver function test revealed hypoalbuminemia (serum albumin=1.58gms/dl) and with normal transaminase (ALT=33.6 IU/l and AST of 58.6 IU/l) and normal alkaline phosphatase level (164IU/l) and normal bilirubin levels. Prothrombin time was 21.6 and INR was 1.6. kidney function test was normal. Serum sodium was 140 mEq/l and serum potassium were 4 mEq/l. Vitamin B12 was 284pg/ml. Bone marrow was done for pancytopenia which revealed hypercellular bone marrow. HIV, HBsAg and anti HCV were negative. Urinary 24-hour urinary copper and ceruloplasmin were within normal limits. Slit lamp examination for K-F ring was inconclusive. ANA and autoimmune liver profile were negative. Ferritin and TIBC were with in normal limits. Patient didn't give consent for liver biopsy.

USG revealed liver parenchymal disease with changes of portal hypertension with mild splenomegaly.

Because of AHO phenotype to rule out calcium metabolism abnormalities we did calcium level, phosphate level and PTH hormone level. Total calcium was tested and was found to be normal (2.10 mmol/l) and ionic calcium was also found to be normal (1.17 mmol/l). Normal serum phosphate of 4.4 mg/dl. PTH was also with in normal limits (22 pg/ml).

CT brain didn't reveal any intracranial calcification. Thyroid function test was normal. Fasting and post prandial blood sugar was within normal limits. X-ray of pelvis with both hips was normal. Large exostosis was found at first metatarsal toe in right toe.

As her PTH were normal diagnosis of PPHP with superimposed with chronic liver parenchymal disease with portal hypertension with hypersplenism was made.

Family history was suggestive of autosomal dominant inheritance as depicted in pedigree chart shown in Figure 2. Her elder son was also having features of AHO like brachydactyly and was obese with BMI of 26 kg/m^2. Serum PTH level was 14 pg/ml. Total calcium level was 2.08 mmol/l and ionic calcium level was 4 mg/dl.

Our patient and her family denied genetic testing because of financial constraints.

Our patient was treated for her chronic liver disease, portal hypertension and hypersplenism and was discharged on medications for portal hypertension. She was on regular follow up.

DISCUSSION

AHO is a hereditary metabolic disorder usually presented with constellation of characteristic physical features which was usually associated with PHP. PHP was a heterogenous group of disorders which was classified as mentioned in Table 1.[6]

PHP type Ia was due to end organ resistance to PTH characterized by presented with biochemical features of hypoparathyroidism like hypocalcemia and hyperphosphatemia which did not respond to exogenous PTH. This was because of decreased phosphaturic action of PTH and reduced formation of 1, 25-dihydroxy vitamin-D with resultant defective mobilization of calcium from bone and reduced GIT absorption of calcium.

PPHP was an inherited disorder, was biochemically normal but phenotypically similar to PHP type 1a (AHO phenotype). It was caused by mutations resulting in loss of function of the Gsα isoform of the GNAS gene on the paternal allele and resultant expression of the protein only from the maternal allele.[6]

It was inherited in an autosomal dominant manner. PPHP was genetically related to PHP type Ia. Signs and symptoms were similar, however people with PPHP did not show resistance to parathyroid hormone while people with PHP-1A do. Both PHP-1a and PPHP were caused by mutations that affected the GNAS gene. But people who inherited the mutation from their mother developed PHP-1a; whereas those who inherited the mutation from their father developed PPHP.[7] Genetic evaluation of the family will be needed for further confirmation of this PPHAP in mother and her son.

Short stature, obesity, round face and delayed onset of puberty were mostly associated with AHO phenotype associated with PHP 1a mostly due to multiple hormone resistance and not regularly associated with PPHP. Obesity was present among 1/3rd of the patients with AHO phenotype. Obesity may be absent among people with PPHP, which was consistent with our diagnosis of PPHP in our patient as her BMI was normal. Intellectual disability was variable and inconsistent presentation and was reported only in 27% of adult cases with AHO.

Shortening of the distal phalanx of the thumb was the most common abnormality in AHO. This was evident on physical examination as a thumb in which the ratio of the width of the nail to its length was increased (so called murder's thumb or potter's thumb).[8] Our patient and her son also had similar features in their thumb (Figure 2).

Shortening of the metacarpals caused shortening of the digits, most commonly the 4th and 5th digits. Shortening of the metacarpals may also be recognized on physical exam as dimpling over the knuckles of a clenched fist (Archibald sign also known as knuckle-dimple sign), which was notable present in our patient.

Dental malocclusion was present in our case as observed by Goswami et al and Hugar in their case reports.[2,9]

CONCLUSION

In the era of advanced investigation, history and general examination is not considered significant. This case report is reminder to physicians about the importance of family history and detailed clinical examination hand and foot examination which guided us to diagnose such a rare disease which was running in a family since generations. High index of suspicion should be kept in patients with family history short stature and brachydactyly and appropriate genetic counselling should be instituted to such patients. Further evaluation is required for testing correlation between AHO phenotype and chronic liver parenchymal liver disease.

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