Case Report:
Pseudohypoparathyroidism: A Diagnosis That Traverses Specialities

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Abstract: Pseudohypoparathyroidism (PHP) is a rare, genetic disorder with variable presentation. This case report describes a young male who presented with a pathological fracture of the right humerus with spontaneous dislocation of the right shoulder joint. On evaluation, hypocalcemia, normal phosphate levels with raised parathormone levels were seen. PHP was suspected as a phenotypic manifestation of short stature, genu valgum and brachydactyly were noted. Genetic testing revealed GNAS was pending. Patient was initiated on treatment with oral calcium supplements and calcitriol. This case report stresses the importance of early recognition of the typical biochemical abnormalities in PHP as a wide spectrum of phenotypic variability is seen in these patients.

Key Words: Pseudohypoparathyroidism (PHP), Albright’s hereditary osteodystrophy (AHO), Parathyroid hormone resistance, GNAS gene

Introduction: Pseudohypoparathyroidism (PHP) is a diverse group of rare endocrine disorders characterized by resistance to the action of parathyroid hormone (PTH). PHP can be further divided into distinct subtypes: PHP type-1a, PHP type-1b, PHP type-1c, PHP type-2 and pseudopseudohypoparathyroidism (PPHP).[1] Genetic defects associated with PHP invariably involve the alpha-subunit of G stimulatory protein (Gsa), which is necessary for the actions of PTH and several other hormones. [2]

PHP-1a is characterized by defects in the maternal GNAS imprints. Patients with PHP1-b do not have AHO features and hormone resistance is limited to PTH and TSH. [6] The aim of our report is highlight the variability in clinical presentation of PHP, the role of biochemical investigations in diagnosis and monitoring of patients.

Case Report
A 26 year old Indian male, presented to the orthopedic department with a pathological fracture of the right humerus and a spontaneous dislocation of the right shoulder joint. Past history revealed development of genu valgum (knock knees) at 14 years of age with history of occasional tetanic contractions at 18 years. Family history indicated similar complaints with patient’s mother and younger sibling. No history of past medical or surgical interventions.

Chart 1: Pedigree chart showing affected individuals
The patient was referred to the department of medicine following a bone scan that suggested a metabolic bone disorder, possibly hyperparathyroidism. Physical examination of the patient revealed short stature, large head, brachydactyly, bulbous fingertips and genu valgum.
Lab investigations showed hypocalcemia with normal phosphate levels, raised PTH and Alkaline phosphatase and low vitamin D levels. A provisional diagnosis of PHP was made. While the patient was started on oral calcium (Tab. Calcimax forte TID) and calcitriol (Rocaltrol 0.25mcg BD) supplementation, genetic consultation was sought. As a definitive diagnosis could only be established using genetic testing, the patient was advised GNAS deletion/duplication analysis, in view of his family history. However, he was unable to afford the genetic test.
PHP is a rare genetic disease and its prevalence worldwide has not been accurately estimated. Genetic or epigenetic mutations of the GNAS gene (that encodes the Gsa) lead to loss of function of the Gsa. This impairs signal transmission to adenylate cyclase, preventing cyclic AMP (cAMP) production which is essential for action of PTH and other hormones like thyroid-stimulating hormone, vasopressin, gonadotropins, glucagon, adrenocorticotropin, and growth hormone—releasing hormone.

The patient first presented with a pathological fracture raising suspicion of an underlying metabolic bone disorder. Low serum calcium and normal serum phosphorus despite very high PTH levels made hyperparathyroidism an unlikely diagnosis. Due to target organ resistance to PTH, hypocalcemia along with high PTH levels is characteristic of PHP, making it the provisional diagnosis.

Of the several subtypes of PHP, patients with PHP-1a and PHP-1c present with resistance to multiple hormones, along with features of AHO. However, this patient displayed neither multiple hormonal resistance nor all the classical AHO features, therefore making PHP-1a and PHP-1c unlikely diagnoses. Patients with PHP-1b do not show typical features of AHO and usually exhibit hormone resistance in tissues where Gsa is derived from maternal allele only, like renal proximal tubules.[6]

Recently, several independent studies have shown patients with hormone resistance and mild AHO like features in whom coding Gsa mutations were excluded but GNAS imprinting defects were confirmed, indicating an overlap between molecular and clinical features of PHP-1a and PHP-1b.[3][7][8] Consequently, PHP classification fails to differentiate all patients with different clinical and molecular findings and therefore, in this case, it is crucial for the patient to undergo genetic testing to establish final diagnosis.

Presently, a new classification is being established by the EuroPHP network, based on molecular pathology.[9][10]

The treatment plan for this patient was based on the clinical diagnosis of PHP. The patient was started on oral calcium and calcitriol to correct hypocalcemia and bring down PTH levels. Regular monitoring was done using the same parameters showing improvements in serum calcium but PTH levels continued to rise.

On doubling the dose of oral calcium and calcitriol, PTH levels decreased from 1709 to 1175pg/mL. The patient was asked to come back every month for regular serum calcium, serum phosphate, Vitamin D and PTH monitoring. This allowed for therapeutic adjustments to be made till calcium-phosphate homeostasis was attained.

Table 1: Summary of the clinical, biochemical and radiological findings

<table>
<thead>
<tr>
<th>Physical examination</th>
<th>Biochemical investigations</th>
<th>X-rays</th>
<th>Bone scan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short stature</td>
<td>Serum PTH: 1550</td>
<td>Brachytelephalangy</td>
<td>Metabolic bone disorder</td>
</tr>
<tr>
<td>Large head</td>
<td>Serum calcium: 8mg/dl</td>
<td>Osteolytic lesions of the humerus</td>
<td></td>
</tr>
<tr>
<td>Brachydactyly</td>
<td>Serum phosphorus: 4.6mg/dl</td>
<td>Thick calvarium of skull</td>
<td></td>
</tr>
<tr>
<td>Bulbous fingertips</td>
<td>Alkaline phosphatase: 392</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Genu valgum</td>
<td>IU/ml</td>
<td></td>
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</tbody>
</table>


discussion

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Conclusion

As pseudohypoparathyroidism is a rare condition, a complete biochemical investigation is essential in diagnosis due to variable presentations of PHP. The final diagnosis can only be made through costly gene testing which is not feasible in the present scenario. Although treatment is fairly symptomatic and cost effective once diagnosis is made, insufficient funds halt further investigations at the molecular level. Hence, it is imperative to use high clinical suspicion in patients with the typical biochemical abnormalities of PHP to effectively diagnose this condition.

References