Pseudohypoparathyroidism Type Ia-Clinical Case with a Novel Mutation of GNAS1 Gene

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Abstract

Pseudohypoparathyroidism (PHP) is a rare autosomal dominant disorder resulting from loss of function mutations in the GNAS gene. Several forms of PHP are noted. PHP type 1a occurs most commonly and is characterized by physical features termed Albright's Hereditary Osteodystrophy (AHO), a constellation of physical features which may include short stature, obesity, round facies, heterotopic ossification, brachydactyly and mental retardation, and increased levels of parathyroid hormone (PTH) due to the end organ hormone resistance to its action. Here we report a new GNAS mutation in a 3.5 years old African American female patient with a history of round facies, developmental delays, obesity and seizure disorder; she was admitted for apneic episode and noted to have prolonged QTc interval on cardiac monitor. A lab evaluation showed severe hypocalcaemia, hyperphosphatemia, high PTH with normal magnesium and alkaline phosphatase levels. She also had slightly elevated Thyroid Stimulating Hormone (TSH) levels indicative of type 1a PHP where resistance to multiple Gs protein-coupled hormones (e.g. PTH, TSH, Luteinizing Hormone (LH), Follicular Stimulating Hormone (FSH), and Growth Hormone Releasing Hormone (GHRH)) is present. Full genomic DNA sequencing of the exons and adjacent intronic regions of the GNAS gene revealed a novel heterozygous mutation in intron 7, c.585+1G>A, in both the patient and her mother.

Keywords: Pseudohypoparathyroidism; Pseudopseudohypoparathyroidism; Novel mutation in GNAS gene

Abbreviations: FT: Full Term; AGA: Appropriate for Gestational Age; PCR: Polymerase Chain Reaction; PHP: Pseudohypoparathyroidism; PPHP: Pseudopseudohypoparathyroidism

Case

Here we report a case of 3.5 years old African American female, born full term (FT), appropriate for gestational age (AGA) to non-consanguineous parents. She has a history of developmental delays and seizure disorder. Her initial admission was for a hypopnea/apnea episode and during that monitoring she was noticed to have prolonged QTc interval on the cardiac monitor.

Initial laboratory work up showed a very low serum ionized calcium level of 2.6 mg/dL (4.5-5.3) and high phosphate level of 8.1 mg/dL (4.0-7.0) with normal magnesium and alkaline phosphatase levels. She was given intravenous calcium infusion to correct her serum calcium levels initially and was later switched to oral calcium with vitamin D supplements to restore her vitamin D levels. During her follow up visit in 3 months her calcium, phosphate and vitamin D levels were elevated and her vitamin D levels were significantly reduced (Table 1). She received stoss therapy in addition to her calcium supplements to restore her vitamin D levels. During her follow up visit in 3 months her calcium, phosphate and vitamin D levels were elevated and her vitamin D levels were significantly reduced (Table 1). She received stoss therapy in addition to her calcium supplements to restore her vitamin D levels. During her follow up visit in 3 months her calcium, phosphate and vitamin D

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The Proband’s Sanger Sequencing Result.

Bidirectional Sanger sequencing was analyzed using Sequence Pilot (JSI Medical Systems). Each nucleotide has a result peak area (RPA) calculated based on the areas of the 20 nucleotides before and after it. The RPA is then compared to the statistical peak area (SPA), which is the average of all of the RPAs from previously analyzed samples. Forward sequence is on the top, reverse sequence is on the bottom. To the right are the electropherograms showing the peaks from the capillary electrophoresis. To the left are charts showing the RPA and SPA results for the c.585+1 position. The blue bar represents the previously analyzed samples (72 in the forward, 74 in the reverse) having wild type sequence at that position and the green bar represents the result at this position for the proband. The ratio of RPA/SPA in forward and reverse directions for c.585+1 are 57% and 51%, respectively, for the wild type G nucleotide. In both directions there is an A nucleotide that is not usually present and that has RPAs greater than the wild type nucleotide. Overall, sequencing results are consistent with the mutation c.585+1G>A. The same results were obtained in the maternal DNA sample.

Table 1: Laboratory evaluation showing calcium levels at the time of diagnosis in seizure disorder patient.

<table>
<thead>
<tr>
<th>Laboratory evaluation</th>
<th>Admission</th>
<th>On therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ionized calcium (4.5-5.3)</td>
<td>2.6 mg/dL</td>
<td>4.64 mg/dL</td>
</tr>
<tr>
<td>Total Calcium (8.5-10.6)</td>
<td>4.6 mg/dL</td>
<td>8.7 mg/dL</td>
</tr>
<tr>
<td>Phosphate (4.0-7.0)</td>
<td>8.1 mg/dL</td>
<td>8.7 mg/dL</td>
</tr>
<tr>
<td>PTH (15-65)</td>
<td>542 pg/mL</td>
<td>383 pg/mL</td>
</tr>
<tr>
<td>Alkaline phosphatase (140-400)</td>
<td>342 IU/L</td>
<td>240 IU/L</td>
</tr>
<tr>
<td>25, hydroxy vitamin D (20-100)</td>
<td>6 ng/mL</td>
<td>46 ng/mL</td>
</tr>
<tr>
<td>1,25 dihydroxy vitamin D (27-71)</td>
<td>80 pg/mL</td>
<td>32 pg/mL</td>
</tr>
<tr>
<td>TSH (0.50-4.50)</td>
<td>6.76 uIU/mL</td>
<td>5.64 uIU/mL</td>
</tr>
<tr>
<td>Free T4 (0.70-2.00)</td>
<td>1.01 ng/dL</td>
<td>0.70 ng/dL</td>
</tr>
</tbody>
</table>

levels had normalized but her PTH levels continues to stay high (Table 1). Because of her clinical and biochemical presentation we suspected pseudohypoparathyroidism and additional workup confirmed our diagnosis.

Because the proband’s mother had short stature (142 cm), brachydactyly of her fingers, but normal hormone-related labs, we suspected PPHP.

Genomic DNA was extracted from whole blood; the exons and immediately adjacent intronic regions of GNAS were amplified by Polymerase Chain Reaction (PCR), Sanger sequenced bidirectionally and then analyzed using the software Sequence Pilot (JSI Medical Systems). Sequencing identified the GNAS mutation c.585+1G>A (Figure 2) in intron 7. This is not a previously reported disease associated mutation, but occurs in a highly conserved splice donor site that is essential for normal splicing. Similar GNAS loss of function mutations (c.432+1G>A and c.839+1G>C) have been reported in the +1 splice donor site of the surrounding introns 5 and 10 [14]. Furthermore, bioinformatic analysis predicts that this single nucleotide transition oligonucleotides (wild type=6.46, mutant=1.72) the strength of the wild type splice site [15]. Thus, it is extremely likely that c.585+1G>A is a deleterious loss of function mutation. DNA testing of the proband’s mother revealed that she is also heterozygous for c.585+1G>A, thus confirming the putative clinical diagnosis of PPHP.

Discussion

Our patient had elevated PTH that did not normalize after correcting her hypocalcaemia and vitamin D deficiency. She also had persistent elevation of TSH. This observation is consistent with end organ resistance, in this case renal and thyroid, to more than one hormone sharing the same intracellular signaling pathway. She had developmental delays, obesity, round facies and short metacarpal bones (Figures 1A, 1B and 1C). This is not a previously reported disease associated mutation, but occurs in a highly conserved splice donor site that is essential for normal splicing. Similar GNAS loss of function mutations (c.432+1G>A and c.839+1G>C) have been reported in the +1 splice donor site of the surrounding introns 5 and 10 [14]. Furthermore, bioinformatic analysis predicts that this single nucleotide transition oligonucleotides (wild type=6.46, mutant=1.72) the strength of the wild type splice site [15]. Thus, it is extremely likely that c.585+1G>A is a deleterious loss of function mutation. DNA testing of the proband’s mother revealed that she is also heterozygous for c.585+1G>A, thus confirming the putative clinical diagnosis of PPHP.

Conclusion

We report a family where the proband is affected with PHP type 1a and her mother is affected with PPHP. The GNAS mutation c.585+1G>A is novel and adds to the spectrum of mutations associated with these disorders.

References


