Autosomal dominant familial hypoparathyroidism and sensorineural deafness without renal dysplasia

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Abstract

Objective: A family is described which has a unique combination of autosomal dominant hypoparathyroidism and sensorineural deafness without renal dysplasia.

Case report: The proband was a male infant aged 1 month with episodes of seizures for 20 days. He was born at 35 weeks' gestation without asphyxia, weighing 2040 g. His initial calcium, phosphorus and percentage of tubular reabsorption of phosphorus were 6.8 mg/dl (normal range 8.5–10.5 mg/dl), 8.9 mg/dl (normal range 5.5–7.4 mg/dl) and 96.8% (normal range 85–95%) respectively. He had normal values for serum parathyroid hormone (PTH) and 25-hydroxyvitamin D. No abnormalities were found by renal imaging and a routine renal function study. He showed a brisk plasma cAMP increase in response to human PTH-(1–34) infusion. He had normal karyotype 46, XY, without a microdeletion in chromosome 22q11.2 by an in situ hybridization method. Five family members were affected with hypoparathyroidism with sensorineural deafness with autosomal dominant transmission. The study of calcium-sensing receptor and preproPTH gene showed a normal DNA sequence.

Conclusion: The combination of familial hypoparathyroidism with sensorineural deafness without renal dysplasia is novel and the cause may be distinct from previously reported familial hypoparathyroidism with sensorineural deafness and renal dysplasia.

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Introduction

Familial hypoparathyroidism is an unusual condition that can occur at any time from early infancy until well into adulthood (1). A patient was seen who had seizures at 10 days of age. There was a family history of hypocalcemia and sensorineural deafness in his mother, grandfather, brother and aunt. In this report, we describe a combination of autosomal dominant hypoparathyroidism and sensorineural deafness.

Case report

The proband (patient III-3)

A male infant aged 1 month was admitted because of episodes of seizures for 20 days. He was born at 35 weeks' gestation without asphyxia, weighing 2040 g. His placental weight was reported to be normal. He was breastfed. He had none of the clinical features of CATCH22, such as peculiar facies, cleft palate, absence of thymus and cardiac defect. His initial laboratory data revealed a low level of serum calcium and a high level of serum phosphorus; 6.8 mg/dl (normal range 8.5–10.5 mg/dl) and 8.5 mg/dl (normal range 4.6–7.6 mg/dl) respectively (Table 1). The urinary calcium to creatinine ratio (Ca/Cre) was inappropriately high (0.15) when considering the low serum calcium level. The percentage of tubular reabsorption of phosphorus (TRP) was high (96.8%) (normal range 85–95%). At this time, the serum levels of mid-region specific parathyroid hormone (PTH) (Yamasa RIA kit, Tokyo, Japan), 25-hydroxyvitamin D (25OHD) (competitive protein binding assay using vitamin D-deficient rat serum (2, 3)) and albumin were 310 pg/ml (normal range 180–520 pg/ml), 17 ng/ml (normal range 5–40 ng/ml) and 3.6 g/dl (normal range 3.3–4.2 g/dl) respectively. A computed tomography scan showed no evidence of calcification of the basal ganglia. No abnormalities were found by renal imaging with echosonography and a routine renal function study. He showed a sharp plasma cAMP increase in response to human PTH-(1–34)
infusion (before, 29 pmol/l; 12 min after, 390 pmol/l). He had normal karyotype 46, XY, by standard trypsin G-banding analysis and without a microdeletion in chromosome 22q11.2 as examined by a fluorescence in situ hybridization (FISH) method with D22S75 as a probe to rule out CATCH22. He was initially treated with 0.2 mg/kg alfacalcidol (1αOHD3) and calcium. Serum calcium and phosphorus levels became normal and the seizures disappeared. The patient is now being treated with 1αOHD3 alone.

**Patient II-2**

Patient II-2, the 28-year-old mother of the proband (Fig. 1), was asymptomatic at the time of diagnosis. The physical examination was normal except for sensorineural deafness. The pattern was that of a bilateral, symmetric, sensorineural deficit affecting all frequencies but slightly more marked at the higher end of the frequency range. She was 153.2 cm tall and weighed 58 kg; the serum calcium level was 5.7 mg/dl (normal range 8.5–10.0 mg/dl), serum phosphorus 6.1 mg/dl (normal range 2.5–4.5 mg/dl), alkaline phosphatase (ALP) 102 U/l (normal range 70–200 U/l), albumin 4.6 g/dl (normal range 4.0–5.0 g/dl) and intact PTH (Nichols IRMA kit, San Juan, CA, USA) 18 pg/ml (normal range 15–50 pg/ml) (Table 1). She showed a sharp increase in plasma cAMP in response to PTH infusion (before, 17 pmol/l; 6 min after, 260 pmol/l). There were no abnormalities on renal imaging with echosonography. We have treated the patient with 3 mg/day 1αOHD3.

**Patient I-1**

The maternal grandfather of this family (Fig. 1) had a history of tetany since childhood with deafness, and proven hypocalcemia, but he was not available for further study.

**Patient III-2**

The 5-year-old brother of the proband (Fig. 1) was admitted to the hospital in September 1996 for convulsions associated with fever. Findings of the physical examination were within normal limits. His height was mean +0.5 S.D., serum calcium, phosphorus, albumin and intact PTH were 7.6 mg/dl (normal range 8.5–10.0 mg/dl), 5.8 mg/dl (normal range 3.8–5.8 mg/dl), 4.0 g/dl (normal range 3.8–4.8 g/dl) and 18 pg/ml (normal range 15–50 pg/ml) respectively (Table 1). No abnormalities were noted on renal imaging with echosonography. He did not cooperate in the audiometric study. We have treated the patient with 2 μg/day 1αOHD3.

**Patient II-1**

The 35-year-old aunt on the mother’s side (Fig. 1) was discovered to have hypocalcemia during the family survey. Biochemical findings confirmed the presence

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**Table 1 Laboratory data.**

<table>
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<th>Patient III-2</th>
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</table>

*Mid-region specific PTH. ND = not determined. **Normal values for neonatal and children, see text. The formula to convert SI units; Ca × 0.25 = mmol/l; P × 0.32 = mmol/l; intact PTH × 0.11 = pmol/l; 25OHD × 1 = μg/l.

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**Figure 1 Pedigree of the family affected by autosomal dominant hypoparathyroidism.** The arrow indicates the proband; closed circle and square: hypoparathyroidism; open circle and square: normal subjects. n = year of birth. Ca = serum calcium (mg/dl); P = serum phosphorus (mg/dl).
of hypoparathyroidism (serum calcium 8.4 mg/dl (normal range 8.5–10.0 mg/dl), serum phosphorus 4.0 mg/dl (normal range 2.5–4.5 mg/dl), albumin 4.1 g/dl (normal range 4.0–5.0 g/dl) and intact PTH 20 pg/ml (normal range 15–50 pg/ml)). She was known to have sensorineural deafness. As she was asymptomatic, no treatment was given.

**Patient III-1**

The 12-year-old cousin of the proband (Fig. 1) was admitted to the hospital in November 1996 for convulsions. Results of the physical examination were within normal limits except for sensorineural deafness. The pattern was that of a bilateral, symmetric; sensorineural deficit affecting all frequencies but slightly more marked at the higher end of the frequency range. His height was mean +1.2 S.D., serum calcium, phosphorus, and intact PTH were 7.6 mg/dl (normal range 8.5–10.0 mg/dl), 6.4 mg/dl (normal range 3.6–5.5 mg/dl) and 15 pg/ml (normal range 15–50 pg/ml) respectively (Table 1). We have treated the patient with 1αOHD3.

**Analysis of calcium-sensing receptor and preproPTH gene**

After informed consent was obtained, DNA was isolated from whole blood of four family members. PCR DNA fragment corresponding to the preproPTH gene and the calcium-sensing receptor were amplified as described (4). The preproPTH gene was in the segment of (a) the calcium responsive element, (b) the promoter, and (c) the preproPTH-coding region. The sequences of the calcium-sensing receptor were normal, but the proband had one previously identified nucleotide substitution of T for A in intron 2 of the preproPTH gene. In contrast, the mother of the proband had only a normal sequence, indicating that this polymorphism is not a common cause of familial PTH-deficient hypoparathyroidism.

**Discussion**

The unique combination of hypoparathyroidism and sensorineural deafness was transmitted as an autosomal dominant trait. Five members of this family had hypoparathyroidism, including one with asymptomatic hypocalcemia. Other recognized causes of hypocalcemia, such as hypomagnesemia, malabsorption and renal failure, were excluded on the basis of the clinical history and appropriate studies. Pseudohypoparathyroidism was excluded by the absence of any of its dysmorphic features, such as metacarpal shortening, and by a normal plasma and urine cAMP response to exogenous PTH.

Several types of familial hypoparathyroidism are now recognized. Failure of parathyroid glands to develop can produce hypoparathyroidism that manifests in the newborn period; it includes DiGeorge sequence, velocardio-facial syndrome and CATCH22 (5). In this family, the proband, without any stigmata of the loss of 22q11.2 syndrome except hypocalcemia, had normal karyotype 46, XY, without a microdeletion in chromosome 22q11.2 examined by the FISH method.

Familial autosomal dominant hypoparathyroidism with a single base substitution in exon 2 encoding the prepro sequence of the preproPTH gene on chromosome 11 has been reported (6). The authors' analysis of the PTH gene in this family failed to show any linkage with the PTH gene. The proband had a normal sequence in the calcium-sensing receptor.

Autosomal dominant familial hypoparathyroidism with sensorineural deafness and renal dysplasia has been found in several families (7). Some of the patients developed renal insufficiency early in life. The autosomal recessive form of hypoparathyroidism with sensorineural deafness and renal tubular dysfunction was detected in two families (8, 9). However, the family described in this report showed normal renal imaging and normal renal tubular function. This family constellation may represent a distinct clinical entity or a wide spectrum of diseases responsible for the same gene; but there is a difference in the region of the mutation in this family. Identification and characterization of familial hypoparathyroidism will allow the LOD (logarithm of the odds) score approach to linkage analysis to clarify the genetic link between parathyroid disease and deafness. Furthermore, our report demonstrates the importance of auditory function study when patient(s) with hypoparathyroidism are evaluated.

In conclusion, autosomal dominant hypoparathyroidism with sensorineural deafness, as described in this case report, may represent a new clinical entity.

**References**

7. Bilous RW, Murty G, Parkinson DB, Thakker RV, Canthard MG, Burn J et al. Autosomal dominant familial hypoparathyroidism,


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