Brief report

The HDR syndrome: an example of a complex developmental disorder associated with hypoparathyroidism

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Background

Deficient or absent secretion of parathyroid hormone (PTH) is the biochemical hallmark of hypoparathyroidism, a clinical disorder which may occur in combination with other endocrine (or non-endocrine) defects or as a solitary endocrinopathy termed isolated hypoparathyroidism. Molecular genetic studies indicate that isolated hypoparathyroidism may be caused by mutations in a variety of genes, including genetic defects that impair synthesis (i.e., PTH gene defects) (1) or secretion (i.e., CASR gene defects) (2) of PTH as well as defects that impair the embryological development of the parathyroid glands (i.e. GCMB) (3). However, genetic hypoparathyroidism most commonly occurs in the context of complex development disorders that are associated with parathyroid dysembryogenesis. The HDR syndrome is an autosomal dominant disorder that in its complete form is manifested by hypoparathyroidism deafness, and renal abnormalities in association with haploinsufficiency of the *GATA3* gene located at 10p15 (4, 5). The pathogenesis of the developmental anomalies caused by *GATA3* mutations is not well understood, and the spectrum of clinical phenotypes has not been fully characterized. Given the small number of cases that have been described, molecular genetic studies offer the opportunity to develop a more comprehensive understanding of phenotypic variability among affect subjects. In this paper we report the clinical features of three affected members of an extended family with HDR.

Case report

The index patient is a 27-year-old female of Azkanazi Jewish ancestry with a past medical history of multiple childhood urinary tract infections that required urethral dilatation. At age 23, she underwent a partial right nephrectomy for an infected renal cyst. One week prior to admission to our hospital, she noted the onset of right flank pain, fever, and chills. A computed tomography scan of the abdomen showed multiple cysts in the right kidney, one of which appeared infected, and the patient was admitted for treatment with antibiotics and percutaneous drainage. Review of systems was significant for nonprogressive sensorineural deafness diagnosed at the age of five years, and mild idiopathic hirsutism that was responsive to oral contraceptives. The patient had no history of seizures or tetany. Physical examination disclosed normal blood pressure, a high-arched palate and thin, unfolded auricular helices. Chvostek's and Trousseau's signs were absent. Costovertebral angle tenderness was present on the right side. The remainder of the physical examination was normal.
Laboratory studies (Table I) revealed a serum total calcium lev-

Table I - Relevant laboratory values and medical history for the proband and her mother.

	Proband	Mother
Ionized calcium, mmol/L (normal range 1.10-1.45)	1.01	–
Serum calcium, mg/dL (9.0-10.5)	6.4	7.6
Serum phosphate, mg/dL (3.0-4.5)	6.2	3.9
Albumin, mg/dL (3.5-5.0)	3.8	4.3
Creatinine, mg/dL (0.7-1.2)	0.7	0.9
Serum-intact parathyroid hormone, pg/ml (10-65)	8	15
25-(OH) vitamin D, pg/ml (9-52)	28	–
24 hour urine calcium, mg (0-250)	186	–
Sensorineural hearing loss	Yes	Yes
Structural renal abnormalities	Yes	Unknown
Karyotype	Normal	Normal
GATA 3 sequencing	Missense mutation exon 5, Asn320Lys	Missense mutation exon 5, Asn320Lys

el of 6.4 mg/dL (normal 9.0-10.5 mg/dL), albumin 3.8 g/dL (3.5-5.0 g/dL), phosphate 6.2 mg/dL (3.0-4.5 mg/dL), and magnesium 2.1 mg/dL (1.3-2.0 mg/dL). Serum ionized calcium was 1.01 mmol/L (1.10-1.45 mmol/L), and intact-PTH was 8 pg/mL (10-65). The levels of 25(OH) vitamin D (28 ng/mL) and 1,25(OH) vitamin D (28 pg/mL) were both normal. A twenty-four hour urine collection showed a calcium excretion of 186 mg (0-250). Hepatic and renal function tests were normal. The patient was treated with IV piperacillin/tazobactam, and her infected renal cyst was drained percutaneously. She denied symptoms of hypocalcemia and was discharged after one week on antibiotics. Months later, a section of the patient's right kidney was removed surgically and histology revealed cysts, a markedly dilated calyceal system, focal tubular atrophy, interstitial fibrosis, glomerular sclerosis, lymphocytic infiltrate, and interstitial calcifications.

Family studies

The patient's mother had longstanding sensorineural hearing loss and hypoparathyroidism. The concentration of serum calcium was 7.6 mg/dL with an albumin level of 4.3 g/dL. Serum intact PTH was 15 pg/mL. Renal function was normal. Imaging of her kidneys was not available. The father had normal renal function and normal serum concentrations of calcium and intact PTH. There was no history of hearing or genitourinary abnormalities.
The patient's brother had a history of nonprogressive sensorineural deafness, but information regarding potential renal or parathyroid abnormalities was not available. A sister has recurrent hemolytic-uremic syndrome, but no known parathyroid or hearing abnormalities. There was no history of hearing dysfunction, renal abnormalities, or hypoparathyroidism in any of the patient's grandparents or other extended family.

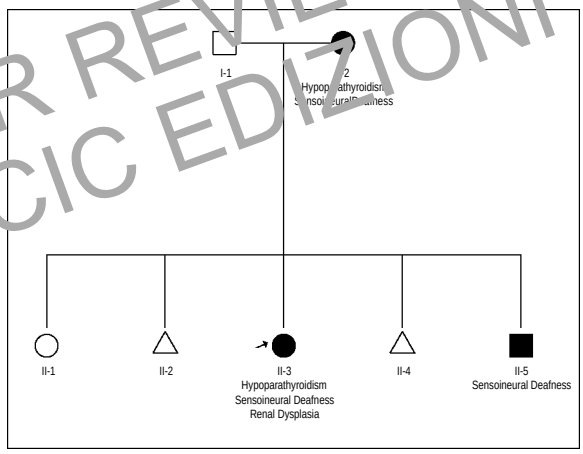

Figure 1 - Family pedigree showing affected family members. II-3 is the proband, known to be fully affected. I-2 has hypoparathyroidism and nonprogressive sensorineural deafness. II-5 also has sensorineural deafness, showing an autosomal dominant mode of transmission. II-1 has recurrent Hemolytic-Uremic Syndrome. II-2 and II-4 were first trimester miscarriages.

Genetic studies

Informed consent for genetic testing was obtained from the patient and both of her parents. This study was approved by the Joint Committee on Clinical Investigation of the Johns Hopkins University School of Medicine. High resolution karyotyping was normal in the patient (46, XX), her mother (46, XX), and her father (46,XY). Leukocyte genomic DNA was isolated by usual methods from the three subjects. Exons and flanking intronic sequences of the calcium-sensing receptor gene (CASR/PCAR1, OMIM 601199), *PTH* gene (OMIM 168450), and the *GATA3* gene (OMIM 131320) were amplified by the polymerase chain reaction and sequenced directly. Sequences of the *PTH* and *CASR* genes were normal, but a heterozygous missense mutation (AA<u>A</u>→AA<u>C</u>, Asn320Lys) in exon 5 of the GATA3 gene was identified in both the index patient and her mother and was confirmed to impair *GATA3* function (6).

Discussion

In this report we describe a patient with the complete HDR syndrome, including renal dysplasia, nonprogressive sensorineural deafness, and hypoparathyroidism, in association with a novel missense mutation in the *GATA3* gene. Genetic analysis confirmed the same mutation in the patient's mother, who manifested only hypoparathyroidism and deafness. This report emphasizes the phenotypic variability of the HDR syndrome, and suggests that future molecular genetic studies may document other GATA3 mutations in some patients who have only one or two of the three features of this syndrome.
Early clinical reports had described an association between hypoparathyroidism, renal disease, and deafness prior to the discovery of *GATA3* mutations in patients with the HDR syndrome (4). Barakat et al described two young male siblings and male twins with a steroid-resistant nephrotic syndrome that progressed to renal failure and death at an early age (7). This was accompanied by sensorineural deafness and hypoparathyroidism. One grandmother and three of her siblings had early onset deafness, but none had renal failure, and the interval generation had normal hearing, calcium levels and renal function. Dahlberg et al described two brothers with congenital diffuse lymphedema, hypoparathyroidism, small, inadequately functioning kidneys, but normal audiogram (8). The brothers also had mitral valve prolapse, bilateral cataracts, brachydactyly and other morphologic abnormalities. No renal failure, hypocalcemia, or deafness was found in any other family member. Yumita et al described three affected patients in two different families with hypoparathyroidism and progressive hearing loss (9). All but one had bilateral cataracts, and one of the three (unrelated to the other two) had hypoplasia of one kidney. No comment was made on renal abnormalities in the others. Baldellou et al described a young boy with primary hypoparathyroidism and unilateral renal agenesis, with a normal karyotype, no family history, and several dysmorphic features, such as low set ears, beaked nose, talipes equinovarus, in addition to mental retardation. No hearing deficit was noted (10). Shaw et al reported four cases from three Asian families of hypoparathyroidism, developmental delay, and renal insufficiency (11). All had a severe distal renal tubular acidosis requiring bicarbonate supplementation, with oxalate crystals seen in the collecting system of two of them. Two of these patients, who were unrelated, also had evidence of nerve deafness. Watanabe et al described a family with five family members affected by autosomal hypoparathyroidism and deafness, but all had normal kidneys. Sequencing of the *PTH1* gene and *CASR* were normal (12).
The clinical triad that constitutes the complete HDR syndrome was first described in 1992 by Bilious et al in four patients who had hypoparathyroidism, nonprogressive sensorineural deafness, and renal dysplasia (13). The original report also described additional relatives with partial or incomplete characteristics, including two patients who had renal dysplasia alone,

and two others with low serum calcium levels who died in infancy. In 1997, Hasegawa et al. described a young Japanese girl with a hypoparathyroidism, deafness, and agenesis of the right kidney (14). She also had a ventricular septal defect, psychomotor retardation, and micrognathia. A terminal deletion was found from 10pter-10p13 by karyotyping. Other family members were not affected.

In 2000, Van Esch et al discovered mutations in *GATA3* and concluded that haplo-insufficiency of *GATA3* is responsible for the HDR syndrome (4). Deletion of this region (10p15) can lead to a variant of DiGeorge's syndrome (DGS2), which includes HDR in addition to cardiac, mental, and facial defects, additional features that our patient did not have (15). The young Japanese girl described by Hasegawa had a larger deletion in this area (detectable by karyotyping), likely explaining the other physical findings noted (14).

Muroya, et al reported heterozygous mutations in seven of nine Japanese families with the HDR phenotype. These *GATA3* mutations included a missense mutation within the first zinc finger domain in exon 4, an insertional mutation also in exon 4 (900insAA plus 901insCCT or C901AACCCT) resulting in a premature stop codon with loss of the second zinc finger domain, and a nonsense mutation at exon 6. Four other families had heterozygous deletion of *GATA3* by fluorescence in situ hybridization (FISH) analysis (5).

The *GATA3* gene consists of 6 exons that span 17kb of genomic DNA, and belongs to a family of zinc-finger transcription factors that are involved in vertebrate embryonic development. Homozygous *GATA3* knockout mice display high embryonic lethality and multiple abnormalities of the central nervous system and the immune system along with features of the human HDR syndrome, but lack parathyroid defects (16). The pathogenesis of the developmental anomalies caused by *GATA3* mutations is not well understood. Therefore, given the small number of cases identified, phenotype-genotype correlations may lead to better understanding of the role of *GATA3* in the embryological development of the ear, kidney, and parathyroid gland.

There is great phenotypic variability in the families and individuals affected by the HDR syndrome (Table II). The expressivity of the three principal components is variable, and renal dysmorphism appears to be lowest at 67%, while hypoparathyroidism is highest at 89%. Age of onset of each is notable for early diagnosis of deafness, which is largely nonprogressive. Hypoparathyroisism and renal dysmorphism have been diagnosed in infancy in symptomatic patients (5, 13), but have also been diagnosed in elderly asymptomatic relatives of affected patients (4, 12). In all cases, the manifestations of HDR syndrome are believed to be early onset or congenital, though undetected well into adulthood, and no adult death has yet been attributed directly to progression of the HDR syndrome. Other manifestations, such as cardiac or facial defects, occur more commonly in patients who have large deletions that include the *GATA3* gene (5). The lack of immune deficiency in patients affected by HDR is surprising, as *GATA3* is heavily involved in T-cell development and function, especially with regard to IL-5 expression (17). Yet, none of the reported cases, nor the family that we present here had documented immune deficiency. The only infections of note in our index patient have been related to structural abnormalities in the urologic organs. Her mother and brother have had no similar course of repeated infections. The variable expression and penetrance in the HDR syndrome is consistent with other pleiotropic developmental disorders. Genes involved in human development frequently show a wide range of penetrance depending on other genetic and environmental factors.

Parathyroid agenesis/dysgenesis is also a component the DiGeorge syndrome (DGS1), which most commonly results from deletion at 22q11.2 (15). A common denominator appears to be a defect in the embryological development of neural crest cells. The 22q11.2 deletion syndrome (del22q11.2S) is considered the most common microdeletion syndrome in humans, occurring in approximately 1 out of 5000 live births. Most cases of DGS1 are sporadic, but familial occurrence with apparent autosomal dominant inheritance has been described (18, 19). In these cases a heterozygous deletion of chromosomal region 22q11.2 is inherited from a mildly affected parent (20, 21). The associated embryological defects that characterize the phenotype caused by loss of genes in the 22q11 region have been compiled to create the acronym "CATCH22", which refers to Cardiac anomalies, Abnormal facies, Thymic aplasia, Cleft palate, and Hypocalcemia with deletion at 22q. Because hypoparathyroidism in patients with DiGeorge syndrome can be transient, with resolution during infancy, all infants with congen-

Table IV - Summary of HDR phenotypes from current and prior reports.

Report	Number affected	Number with hypoparathyroidism (%)	Number with deafness (%)	Number with renal abnormalities (%)	Other abnormalities	Mean age (yrs.) at diagnosis (range)
McWilliams, et al., 2004	3	2/2 (100%)	3/3 (100%)	1/3 (33%)	Hirsutism	39 (27-51)
Bilious, et al., 1992	8	6/8* (75%)	4/8 (50%)	6/8 (75%)		12 (neonatal-38)
Hasegawa, et al., 1997	1	1/1 (100%)	1/1 (100%)	1/1 (100%)	VSD, psychomotor retardation, micrognathia, del 10pter-10p13	2 (2)
Watanabe, et al., 1998	5	5/5 (100%)	3/5 (60%)	0/5 (0%)		16 (28 days-35 years)
Muroya, et al., 2001	16	11/13 (85%)	9/11 (82%)	13/16 (81%)	VSD, pyloric stenosis, CVA	28 (1-70)
Van Esch, et al., 2000	9	9/9 (100%)	9/9 (100%)	7/9 (78%)		NR
Total	42	34/38 (89%)	29/37 (78%)	28/42 (67%)		33 (neonatal-70)

*Two died in infancy with low serum calcium, hypoparathyroidism is presumed, VSD=Ventricular Septal Defect, CVA=Cerebrovascular Accident, NR=not reported.

ital hypoparathyroidism should be thoroughly evaluated for the genetic and physical defects associated with CATCH-22 syndrome. The clinical findings in patients with del22q11 can be highly variable, and some authors have used the term “complete DGS” to describe the disorder in an infant with thymic aplasia, parathyroid aplasia, and one of the usual conotruncal cardiac defects. These infants may present with neonatal tetany, cardiac failure, recurrent infections and failure to thrive. The term “partial DGS” then refers to the disorder with less severe and often delayed manifestations. The minimal diagnostic criteria for the partial form are difficult to define. Analysis of the human DGS1 deleted region on chromosome 22q11.2 has defined a 250-kb minimal critical region that includes a variety of candidate genes, and haploinsufficiency of *Tbx1* has emerged as the likely explanation for the developmental defects of DGS1, as some patients with del22q11 phenotype but without chromosomal deletion have *Tbx1* gene mutations (22).
Hypoparathyroidism occurs as a component of other complex developmental syndromes. The Kenny-Caffey syndrome and Sanjad-Sakati syndrome are both caused by mutations in tubulin-specific chaperone E (TBCE) on 1q43 (23, 24). Renal and auditory abnormalities are not present in affected subjects. Thus, the combination of hypoparathyroidism, impaired audiological activity, and renal dysmorphism provides strong clinical evidence of HDR syndrome.

Conclusions

We report a case of HDR syndrome, a rare, inherited cause of deafness, hypoparathyroidism, and renal dysmorphism. GATA3 haplo-insufficiency has been reported in very few families with a characteristic HDR phenotype. Affected individuals have a 50% likelihood of transmitting the mutation to offspring. With the exception of those who have died from hypocalcemia in infancy, life expectancy of those affected does not appear to be altered, though long-term studies are lacking. Because the abnormalities can be largely asymptomatic as in the case we present, and because the phenotypic expression of the syndrome seems to be highly variable, clinicians should have a high index of suspicion when early onset of congenital hypoparathyroidism is identified. A thorough family history and a careful examination of hearing and renal structures are recommended. Elucidation of the role of GATA3 in embryonic development will be required to understand the basis for the HDR phenotype.

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