Hypoparathyroidism, sensorineural deafness, and renal disease

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Abstract

*The syndrome of **H**ypoparathyroidism, sensorineural **d**eafness and **r**enal disease (HDR syndrome) is an inherited condition. Patients may present with hypocalcemia, tetany, or afebrile convulsions at any age. Hearing loss is usually bilateral and may range from mild to profound impairment. Renal disease manifestations include nephrotic syndrome, cystic kidney, renal dysplasia, hypoplasia or aplasia, pelvicalyceal deformity, vesicoureteral reflux, chronic renal failure, hematuria, proteinuria and renal scarring. Mutations in the* GATA3 *gene, mapped to chromosome 10p (gene map locus 10p15, 10p15.1-p14), have been identified in several families with HDR syndrome. The mode of inheritance is believed to be autosomal dominant. The prevalence is unknown, but the disease is considered to be very rare. Management consists of treating the clinical abnormalities at the time of presentation.*

Key words

Renal disease – deafness – hypocalcemia – hypoparathyroidism - Barakat syndrome - HDR syndrome - *GATA3* gene.

Disease name and synonyms

Hypoparathyroidism, sensorineural deafness and renal disease
HDR syndrome
Barakat syndrome
Nephrosis, nerve deafness, and hypoparathyroidism

Definition/diagnostic criteria

The HDR syndrome is an inherited condition consisting of hypoparathyroidism, sensorineural deafness and renal disease (OMIM 146255) [1-2]. A gene mutation has been identified in several families and is located on gene map locus 10p15, 10p15.1-p14.

Epidemiology

The prevalence of the disorder is unknown, but it is very rare, with about a dozen patients reported in the literature. Clinical awareness of this syndrome may increase the number of cases identified.

Clinical description

In 1977, Barakat *et al.* described the association of familial nephrosis, nerve deafness and hypoparathyroidism [1]. In 1992, Bilous *et al.* [2] described two brothers and two daughters of one of the affected brothers with hypoparathyroidism, sensorineural deafness and renal dysplasia. Subsequently, other reports appeared in the literature confirming that the syndrome is associated with a wide phenotypic spectrum, consisting of hypoparathyroidism, sensorineural deafness and renal disease [3-7].

Patients may present with hypocalcemia, tetany or afebrile convulsions at any age. Hearing loss is usually bilateral (but may be asymmetric) and may range from mild to profound impairment, more severe at the higher end of the frequency spectrum. Renal diseases in these patients include nephrotic syndrome, cystic kidney, renal dysplasia, hypoplasia or aplasia, pelvicalyceal deformity, vesicoureteral reflux, chronic renal failure, hematuria, proteinuria and renal scarring [1-2,8].

The original patients described by Barakat *et al.* [1] presented with hypocalcemia and proteinuria, which progressed to a steroid resistant nephrotic syndrome, as well as with hypoparathyroidism and bilateral nerve deafness. Renal histology revealed fetal-like glomeruli and thickened glomerular basement membranes. The parathyroid glands were absent or fibrotic. All four siblings died with end-stage renal disease between the ages of 3 and 8 years.
The patients reported by Bilous *et al.* [2] had bilateral renal dysplasia. Hasegawa [5] found reports of 14 patients with deletion of 10p13; five had hypoparathyroidism or hypocalcemia, 6 had urinary tract abnormalities (renal dysplasia, unilateral renal agenesis, vesicoureteral reflux), and 2 had deafness. Other renal abnormalities included renal hypoplasia, pelvicalyceal deformity, hydronephrosis and renal scarring [6,8].

Fugimoto *et al.* [4] reported a Japanese boy with associated recurrent cerebral infarctions in the basal ganglia. Lichtner *et al*. [8] performed molecular deletion analysis of two patients with partial monosomy 10p and hypoparathyroidism, deafness and renal dysplasia or renal insufficiency, cardiac defects, cleft palate and reduced T cell levels. The classical triad of HDR syndrome was found to be variably exhibited and associated with atypical findings including retinitis pigmentosa, psoriasis and severe growth failure [6]. Despite the phenotypic variability of the syndrome and the occurrence of diverse renal abnormalities, the same authors did not exclude the causative role of a single gene mutation [6].

Etiology

The HDR syndrome is a genetic developmental disorder with clinical diversity [13,15]. The defect in the majority of cases has mapped to chromosome 10p. Hasegawa *et al.* [3] suggested that the gene responsible for this syndrome is located at a 10pter→p13 region, while Fugimoto

et al. [4] suggested involvement of 10p14-p15.1. Haploinsufficiency of zinc-finger transcription factor glutamyl amidotransferase-subunit A (*GATA3*) or mutations involving *GATA3* gene appears to be the underlying cause of this syndrome [8,13-14]. Nesbit *et al*. [7] reported the first acceptor site mutation, thus expanding the spectrum of HDR-associated *GATA3* mutations to seven mutations. Human *GATA3* expression has been detected in the developing parathyroid glands, inner ears, and kidneys, together with the thymus and central nervous system (CNS) [15-16].

Lichtner *et al*. [8] found similarly affected patients with partial monosomy 10p resembling DeGeorge syndrome, with the haploinsufficiency region mapping to a area distal to DGCR2. They concluded that hemizygosity of the proximal region (DGCR2) can cause cardiac defects and T cell deficiency and that hemizygosity for the more distal region (HDR1) can cause hypoparathyroidism, sensorineural deafness, and renal anomaly.

Although *GATA3* mutations were identified in the majority of HDR families analyzed, HDR families with no identifiable *GATA3* abnormalities have been described [6,9].

Diagnostic methods

Diagnosis is based on the clinical findings. Diagnosis of suspected patients may be assisted by the following tests: measurement of parathormone (PTH) levels, an audiogram or auditory brain stem response study, renal imaging studies, and a renal biopsy. DNA analysis may demonstrate the presence of a submicroscopic deletion on chromosome 10p. Detailed study of chromosome 10p should be undertaken in patients with well defined renal tract abnormality phenotypes, especially when there is associated hypoparathyroidism or deafness [9].

Differential diagnosis

Various combinations of the components of this syndrome have been reported including familial idiopathic hypoparathyroidism and progressive sensorineural deafness without renal disease [10-11], and autosomal recessive hypoparathyroidism with renal insufficiency and developmental delay [12]. DiGeorge syndrome (DGS) comprises similar clinical findings including parathyroid hypoplasia, thymic hypoplasia, and outflow tract defects of the heart, and is usually the result of a deletion of chromosome 22q11. Renal disease and deafness rarely occur in DGS.

Genetic counseling

Inheritance is probably autosomal dominant [2,12]. Autosomal recessive or X-linked inheritance were suspected in the original report [1], but Hasegawa *et al*. [3] suggested that inheritance in these patients might be autosomal dominant with reduced penetrance. A thorough diagnosis should be performed on every affected individual, and siblings should be studied for deafness, parathyroid and renal disease.

Antenatal diagnosis

The syndrome should be considered in infants who have been prenatally diagnosed with a chromosome 10p defect. The diagnosis should be also considered in infants who have been diagnosed with well defined renal tract abnormality phenotypes.

Management including treatment

Treatment consists of treating the clinical abnormalities associated with hypoparathyroidism, deafness and renal disease at the time of diagnosis.

Prognosis

Prognosis depends on the nature and severity of the renal disease.

Unresolved questions

The mode of inheritance should be confirmed. The modes of inheritance described so far may be due to different mutations or disruptions in the same gene and do not indicate a different syndrome. A more specific gene map may be generated in the future, or a different chromosome region or gene producing a similar clinical presentation may be identified.

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