The hypoparathyroidism-deafness-renal dysplasia syndrome: A case report☆

Síndrome *hypoparathyroidism-deafness-renal dysplasia*: descripción de un caso

Hypoparathyroidism-deafness-renal dysplasia [HDR] syndrome (MIM#146255) is a rare disorder with an autosomal dominant hereditary trait and variable penetrance. The syndrome is caused by mutations of the *GATA3* gene located on chromosome 10p14-15.[1] The typical clinical triad comprises the presence of primary hypoparathyroidism, neurosensory deafness and renal alterations.

We present the case of a 34-year-old woman referred to the endocrinology clinic due to obesity (body mass index [BMI]: 31 kg/m^2). Her disease history reflected gouty arthritis, impaired renal function with creatinine concentration 1.36–1.67 mg/dl, bilateral neurosensory deafness from childhood, and episodes of pyelonephritis. She had no dysmorphic features or cognitive-behavioral alterations. The patient was receiving no regular medical treatment. There were no family antecedents of hypoacusia, kidney disease or hypocalcemia, only obesity on the maternal side. The initial laboratory tests revealed hypocalcemia 7.06 mg/dl (corrected for albumin), phosphate 4.8 mg/dl, PTH 19 pg/ml, non-detectable calciuria and negative proteinuria. There were no clinical manifestations of hypocalcemia, and the Trousseau and Chvostek signs were negative. This alteration was confirmed by further laboratory tests, indicating calcium 7.6 mg/dl (corrected for albumin), phosphate 4.3 mg/dl, magnesium 1.74 mg/dl, PTH 17 pg/ml, 25-OH-vitamin-D 48 ng/ml. The 24-h urine tests revealed non-detectable calciuria, phosphaturia 552 mg/day (reference 300–400) and magnesium in urine 66 mg/day (reference 73–122). Treatment was started with oral calcium (1 g/day) and calcitriol (0.25 μg/day), and the patient was referred for genetic study. A heterozygous mutation of the *GATA3* gene, c.827G>A (p.Arg276Gln), was detected, consistent with HDR syndrome. The patient is currently subjected to controls in urology due to recurrent urinary infections (an abdominal CT scan suggestive of chronic pyelonephritis, with kidneys slightly reduced in size and presenting cortical scars), nephrology (stable renal function), the ENT department, and endocrinology. The first control laboratory tests showed calcium 8.4 mg/dl; albumin 42.1 g/l; phosphate 4.4 mg/dl; magnesium 1.65 mg/dl; creatinine 1.21 mg/dl; urea 46 mg/dl; PTH 18 pg/ml; 25-OH-vitamin-D 31 ng/ml and calciuria 77 mg/24 h. Over subsequent follow-up the hypocalcemia was seen to persist due to poor adherence to the prescribed medical treatment.

Famant and can manifest at any time in life.[2] HDR syndrome was first described in 1977 in two siblings presenting hypoparathyroidism, neurosensory deafness and renal alterations. Although the disorder is considered to be rare, its true prevalence is not known.

The origin of the syndrome is related to haploinsufficiency of the *GATA3*[1,3] gene, which encodes for a protein (GATA3) belonging to the family of zinc finger transcription factors (ZF-TFs), related to embryonic development in vertebrates.[1] The *GATA3* gene is essential for parathyroid gland, hearing organ and kidney embryogenesis.[1] The expression of this gene can be detected in human embryos from the fourth week of pregnancy.[4] It is also expressed in the central nervous system (CNS), the thymus gland,[5] the liver, the peripheral nervous system, the eyes during development, and the pharyngeal arches.[4] The gene also plays a key role in T cell development; in fact, *GATA1*, *GATA2* and *GATA3* are factors required for hematopoiesis.[4] Despite the above, no immune alterations have been observed in familial studies. This suggests that a single *GATA3* copy suffices to maintain immune function,[1,3,4,6] or that hematopoietic processes are less susceptible to *GATA3*[1] haploinsufficiency.

It is known that haploinsufficiency of genes related to development results in a broad range of penetrance, and thus of clinical expression.[7] Hypoacusia and hypoparathyroidism are present in 90% of all patients with HDR syndrome, and 80%, moreover, present renal dysplasia.[8] The most constant finding is neurosensory deafness that generally appears in childhood; the condition is bilateral and can be asymmetrical.[6] The PTH concentrations can be at the lower limit of normal or non-detectable.[4,6] The clinical manifestations related to the low calcium concentrations vary from muscle irritability or seizures to asymptomatic hypocalcemia,[6] as in our case. The renal manifestations are the most heterogeneous clinical component, and may be functional or structural. Such alterations include renal hypoplasia and dysplasia, renal cysts, nephritic syndrome, hematuria, proteinuria, pyelocaliceal anomalies, etc.[6,8] Other clinical manifestations not related to the typical triad have also been reported, such as pyloric stenosis, polycystic ovaries, congenital heart defects or recurrent cerebral infarction.[3,6] Behavioral disorders are infrequent, but can manifest in patients with extensive calcifications of the basal ganglia, which are commonly seen in hypoparathyroidism.[6,8]

Our patient presented the heterozygous missense mutation p.Arg276Gln (c.827G>A), already described by Yesiltepe Mutlu et al.[8]

Treatment of the syndrome depends on the severity of the symptoms. Asymptomatic patients can be treated on an ambulatory basis with oral calcium and calcitriol, with strict monitoring to dose titration.[9] Symptomatic patients require treatment with intravenous calcium.[6,9]

The difficulty during follow-up is to maintain a therapeutic balance in order to avoid possible symptomatic hypocalcemia, as well as hypercalcemia with its possible renal and CNS complications.[9] The aim is to keep calcemia at the lower limit of normal, with calciuria <300 mg/day.[9] A phosphorus-calcium product under 55 is advised.[6] Successive controls involve blood tests (renal function, calcium, phosphorus, albumin) and calciuria in 24 h urine, first monthly to dose titration and then every 6 months. Hypercalciuria can be lowered using thiazides.[9] In those cases where calcemia control is not achieved with conventional treatment, the use of recombinant PTH may be considered.[10]

☆ Please cite this article as: Gogorza MS, Mena E, Serra G, Jiménez A, Noval M, Pereg V. Síndrome *hypoparathyroidism-deafness-renal dysplasia*: descripción de un caso. Endocrinol Diabetes Nutr. 2018;65:187–188.

Follow-up by the nephrologist and ENT specialist is indicated. Annual ophthalmological controls are required for the early diagnosis of cataracts.[9]

The prognosis of HDR syndrome is determined by the degree of renal involvement. An early diagnosis of renal alterations is therefore important. Genetic counseling is essential in these families; evaluation by a geneticist is, therefore, mandatory.[6]

Although HDR syndrome is rare and is characterized by a broad clinical spectrum, it should be suspected in patients with deafness that present hypocalcemia and/or alterations in renal function or structure.

References

1. Van Esch H, Groenen P, Nesbit MA, Schuffenhauer S, Lichtner P, Vanderlinden G, et al. GATA3 haplo-insufficiency causes human HDR syndrome. Nature. 2000;406:419–22.
2. Ali A, Christie PT, Grigorieva IV, Harding B, van Esch H, Ahmed SF, et al. Functional characterization of GATA3 mutations causing the hypoparathyroidism-deafness-renal (HDR) dysplasia syndrome: insight into mechanisms of DNA binding by the GATA3 transcription factor. Hum Mol Genet. 2007;16:265–75.
3. Muroya K, Hasegawa T, Ito Y, Nagai T, Isotani H, Iwata Y, et al. GATA3 abnormalities and the phenotypic spectrum of HDR syndrome. J Med Genet. 2001;38:374–80.
4. Van Esch H, Devriendt K. Transcription factor GATA3 and the human HDR syndrome. Cell Mol Life Sci. 2001;58:1296–300.
5. Debacker C, Catala M, Labastie MC. Embryonic expression of the human GATA-3 gene. Mech Dev. 1999;85:183–7.
6. Upadhyay J, Steenkamp DW, Milunsky JM. The syndrome of hypoparathyroidism, deafness and renal anomalies. Endocr Pract. 2013;19:1035–42.
7. Fisher E, Scambler P. Human haploinsufficiency – one for sorrow, two for joy. Nat Genet. 1994;7:5–7.
8. Yesiltepe Mutlu G, Kirmizibekmez H, Nakamura A, Fukami M, Hatun S. A novel de novo. GATA binding protein 3 mutation in a Turkish boy with hypoparathyroidism, deafness, and renal dysplasia syndrome. J Clin Res Pediatr Endocrinol. 2015;7:344–8.
9. Shoback D. Clinical practice hypoparathyroidism. N Engl J Med. 2008;359:391–403.
10. Food Drug Administration (FDA). FDA news release. FDA approves Natpara to control low blood calcium levels in patients with hypoparathyroidism; 2015.

Maria Soledad Gogorza*, Elena Mena, Guillermo Serra, Ana Jiménez, Mercedes Noval, Vicente Pereg

Servicio de Endocrinología y Nutrición, Hospital Universitari Son Espases, Palma, Balearic Islands, Spain

* Corresponding author.
E-mail address: msgogorza@gmail.com (M.S. Gogorza).

2530-0180/