A Case of Hypoparathyroidism, Kidney Dysplasia and Sensorineural Deafness In Adolescence

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Abstract

Background: Barakat syndrome (HDR) is a rare genetic disorder which is characterized by hypoparathyroidism (“H”), neurosensory deafness (“D”), renal disease (“R”) and is inherited in an autosomal dominant pattern. It is caused by mutations on the GATA3 gene. This syndrome can be misdiagnosed due to the phenotypic diversity and the genetic heterogeneity of the cases that have been recorded. High index suspicion as well as genetic analysis of GATA3 (molecular genetic testing) is needed to identify this very rare genetic disorder of HDR syndrome.

Case presentation: We report a teenage boy that has been observed from childhood due to hypoparathyroidism and progressively he presented with renal disease. Furthermore, hearing impairment was appreciated, thus a genetic analysis was performed applying the Invitae Renal Disease Panel that revealed a c896C>A (p. Arg299Gln) pathogenic variant of GATA3 gene.

Conclusions: Barakat syndrome (HDR syndrome) must be included in the differential diagnosis of persistent hypocalcemia with neurosensory deafness with or without renal damage. Early recognition and appropriate management is important in order to prevent adverse consequences.

Keywords: hypoparathyroidism; renal disease; hearing impairment; Barakat syndrome

Short title: Barakat syndrome in adolescence

Introduction

Hypoparathyroidism is an endocrine disorder characterized by the absence or inappropriately low concentration of circulating parathyroid hormone (PTH). Children affected by hypoparathyroidism present low serum PTH, low serum calcium, and high phosphate levels.

Hypoparathyroidism can be classified as transient neonatal, genetic permanent neonatal and acquired hypoparathyroidism. Familial isolated hypoparathyroidism is a rare disorder inherited in an autosomal dominant or autosomal recessive fashion, associated with calcium receptor (CaSR) gene mutations (GNA11) or with PTH gene mutations (GCM2, FHL1) respectively. Hypoparathyroidism can also present itself as a manifestation of a complex disorder, including Di George Syndrome (characterized by triad immune deficiency, hypoparathyroidism and congenital heart disease), Barakat Syndrome (characterized by the triad of hypoparathyroidism, sensorineural deafness and renal disease), Sanjad-Sakati Syndrome (characterized by hypoparathyroidism, severe growth failure, mental retardation, susceptibility to chest infections, and dentofacial anomalies), Kenny-Caffey Syndrome (characterized by hypoparathyroidism, severe growth failure, mental retardation, susceptibility to chest infections, and dentofacial anomalies), Kenny-Caffey Syndrome (characterized by hypoparathyroidism, severe growth failure, mental retardation, susceptibility to chest infection, and dentofacial anomalies), as well as mitochondrial disorders, such as Kearns-Sayre Syndrome (characterized by hypoparathyroidism, retinitis pigmentosa, chronic and progressive external ophthalmoplegia, heart conduction system disorders, and cerebellar ataxia).

Barakat syndrome or HDR syndrome, was first described in 1977 as an autosomal dominant disorder caused by GATA3 haploinsufficiency. It is characterized by the triad hypoparathyroidism (“H”), neurosensory deafness (“D”), renal disease (“R”) in some cases can be performed with different components, including “HD”,”HR”, “DR”, “R” or “D” making Barakat syndrome challenging to diagnose in early childhood.

Case report

The patient is an 18-year-old male monitored at the Endocrinology Outpatient Service since the age of 8.5 years old due to hypoparathyroidism. The diagnosis was established at 1.5 years of age, when the patient was hospitalized due to
seizures and thus hypocalcemia was discovered. He had been experiencing recurrent episodes of seizures, one triggered by febrile conditions when he was admitted to our hospital. He was born as a full-term vaginally delivered infant without perinatal problems, to non-consanguineous parents. His medical history includes surgical correction of congenital strabismus. His father had diabetes, hypertension and died from myocardial infarction at the age of 50. At the time of his first outpatient visit in our institution his milestones and development were normal as well as the physical examination and laboratory workup, while he received a regimen of alfacalcidol (0.06mcg/kg) and oral calcium supplements (500mg x 2). The patient was scheduled for a clinical, laboratory and imaging follow up every six months. At the age of 7yo hearing loss was detected due to learning difficulties. Tone audiometry showed bilateral mild-to-moderate hearing loss. (Figure 1A)

At the age of 9yo, the patient was referred to the nephrologist, due to his increased creatinine 1mg/dl, where he was also found with CrCl 137ml/min / 1.73m² and cystatin C 1.28mg/dl. The kidney ultrasound performed at that time revealed renal asymmetry (right kidney 8.1cm, left kidney 7.1 cm) with normal parenchymal structure and thickness, a distinct corticomedullary junction, and no indication of renal pelvis distension as well as a normal DMSA scan.

At the age of 12yo he ceased his medication and thus he developed hyperuricemia, hyperphosphatemia, hypocalcemia, hypercalcuiuria, and mild proteinuria. Kidney ultrasound was performed revealing an echogenic peripheral ring indicative of grade I nephrocalcinosis. (Figure 2A). He was therefore instructed to follow a low phosphorus diet, and oral treatment with allopurinol, alphacalcidol and calcium carbonate. Concerning his hypercalcuiuria, potassium citrate was prescribed. The previous results brought the suspicion of the Barakat syndrome, leading to further investigation. Due to the medical history of the patient the patient’s hearing was re-examined. (Figure 1B). A genetic analysis was performed that revealed a pathogenic variant in GATA3. We performed the Invitae Renal Disease Panel which is a sequence analysis and deletion/ duplication test of 401 genes. Among these, GATA3 came up as positive for one pathogenic variant. Specifically, the patient is heterozygous for the c896C>A (p.Arg299Gln) GATA3 variant. Furthermore, some additional variants of ambiguous significance were identified in ADCY10, CACNA1H, LCAT, SLX4, TTC218, WNK4 genes. The latest laboratory tests on the serum showed creatinine: 1.4mg/dl, urea: 35mg/dl, cystatin C: 1.42mg/dl, Vit D: 32ng/ml PTH: 9pg/ml while his CrCl became 102.5ml/min/1.73m². In addition, there were no abnormal findings detected by echocardiography.

At the age of 17yo, renal ultrasound revealed a mild asymmetry in the size of the kidneys with bilateral hyper echogenicity and medullary nephrocalcinosis Grade I (figure 2B). The patient was referred to adult outpatient settings for lifelong endocrinological and nephrological follow-up.
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Figure 1B: Pure tone audiogram showing bilateral mild-to-moderate sensorineural deafness and a progressive hearing loss of 10 dB at the left ear.

Figure 2A: Kidney ultrasound showing echogenic peripheral ring indicative of grade I nephrocalcinosis (indicated by the arrows)

Figure 2B: Kidney ultrasound showing a small asymmetry in the size of the kidneys with bilateral hyper echogenicity and medullary nephrocalcinosis Grade I (indicated by the arrows)
Discussion

The Barakat Syndrome, first described in 1977 [1], constitutes a rare genetic disorder that may become evident at any age and is characterized by hypoparathyroidism, sensorineural deafness and renal disease. These three symptoms are referred to as the hallmark triad of features of the Barakat Syndrome. It is inherited in an autosomal dominant pattern. Concerning causation, the syndrome is derived from defects on chromosome 10p14-15, as well as germline heterozygous mutations in GATA-binding factor 3 [3]. GATA3 is one of six members of the GATA family of transcription factors that is involved in vertebrate embryonic development of the parathyroid glands, auditory system, kidneys, thymus and central nervous system [8]. GATA3 mediates the differentiation and survival of parathyroid and thymus progenitor cells, facilitates the initial stages of parathyroid organogenesis by regulating the expression of GCM2 and is involved in PTH expression. While the syndrome is phenotypically defined by the aforementioned constellation of clinical and laboratory features, its diagnosis can be elusive due to the phenotypical heterogeneity even within a family with the same pathogenetic variant [4] as well as the temporal difference of when symptoms arise, with hypoparathyroidism being present in early childhood, while hearing loss and renal impairment arise much later. Approximately 60% of patients present with the hallmark triad of features prior to the age of 10[2], 28.6% show only hypoparathyroidism and deafness and 2.6% of patients present with only deafness and renal disease [2,7]. Hypocalcemia can be either symptomatic or clinically evident with either absent or depressed serum PTH levels. Hypoparathyroidism can be asymptomatic or present with myalgia, neuromuscular irritability, non-febrile seizure or pronounced tetany. Sensorineural deafness is most often bilateral with variable degrees of hearing impairment [2]. The higher frequency sensorineural hearing impairment is known to progressively worsen with age [3,7]. Audiological evaluation revealed a progressive hearing loss of 10 dB at the left ear in our patient. The nature and extent of renal damage dictate the prognostic severity of the disease but are also marked in their heterogeneity among patient populations. Renal involvement encompasses an array of both congenital abnormalities such as dysplasia, hypoplasia, aplasia, cystic kidneys and vesicoureteral reflux, as well as functional disorders such as proteinuria,
hematuria, renal tubular acidosis and nephrocalcinosis have been reported [2,9]. Our patient presented grade I nephrocalcinosis at the age of 12 years. We are unable to determine if nephrocalcinosis was manifested due to his syndrome or as a result of his non-adherence to therapy resulting in hypercalciuria. Mutations associated with hypercalciuria include c.324del, c.589A. The patient presented is not currying these mutations. Renal impairment is defined by the asymmetry of kidney as well as increased levels of creatinine which indicates kidney dysplasia. The treatment of kidney disease depends on the abnormality. Some minor abnormalities such as nephrocalcinosis deserve treatment and require dose observation which was also the case of the aforementioned patient. Approximately 9% of patients develop end stage renal failure and require renal replacement therapy [10]. Prognosis depends on the nature and severity of the kidney disease. Patients with minor kidney dysfunction have normal life expectancy [10].

Conclusions

The Barakat syndrome (HDR syndrome) must be included in the differential diagnosis of persistent hypocalcemia with neurosensory deafness with or without renal damage. Barakat syndrome is a medical state that demands a lifelong regular endocrinological and nephrological follow up. In cases of hypoparathyroidism, it is crucial to evaluate the kidney function since in this syndrome the renal involvement and hearing acuity appear in a later stage of life. GATA3 genetic studies should also be performed in every suspected case to exemplify the diagnosis of this uncommon medical disorder. In conclusion, adherence to therapy is essential for the prevention of adverse outcomes.

Abbreviations

PTH parathyroid hormone, CaSR calcium-sensing receptor, GCM2 Glial Cells Missing Transcription Factor 2, GNA11 G protein subunit alpha 11, FHL1 Four and A Half LIM Domains Protein 1.

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Statement of Ethics

Informed consent was obtained from the patient and all members of his family included in the study. The study was approved by the institutional Ethics Committee of the Children’s Hospital “P. & A. Kyriakou,” Athens, Greece.

Disclosure statement

The authors have no conflicts of interest to disclose concerning this publication.

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