The Syndrome of Familial Hypoparathyroidism, Sensorineural Deafness and Renal Dysplasia

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Abstract
The syndrome of familial hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR syndrome) is inherited as an autosomal dominant trait, caused by haploinsufficiency of the GATA3 gene in chromosome 10p. Although first described years ago, but the disease is considered to be very rare. Patients usually present with hypocalcemia, tetany, or afebrile convulsions at any age. Hearing loss is usually bilateral, range from mild to profound impairment. Renal disease includes dysplasia, hypoplasia or aplasia.

Introduction
HDR syndrome also known as Barakat syndrome, was first described by Amin J. Barakat.¹ HDR (hypoparathyroidism, deafness, renal dysplasia) syndrome locus maps distal to the DiGeorge syndrome region on 10p13/14.² The GATA3 gene appears essential to the embryonic development of the ears, parathyroid glands, and kidneys. Patient present with symptoms related to these organs. Once diagnosed supplemental calcium and calcitriol (vitamin D) can increase the calcium, transform the quality of life. Prognosis depends on the severity of the kidney disease. In order to raise the awareness of this syndrome of clinical and research interest for physician, we report a case of HDR Syndrome in 20 year old boy. To the best of our knowledge this is the first case report of HDR syndrome in India.

Case History
A 20 Year old male patient presented with complaints of multiple episodes of seizures (GTCS) with loss of consciousness from last two and half months. No history of head trauma or febrile illness at the onset of seizure. He was born at term after uncomplicated pregnancy, no facial dysmorphism and psychomotor retardation were noted after birth. No gross abnormality in childhood milestones and development noted by parents. He was average in physical development, playing and school performance. He was a single child of healthy parents. There no family history of recurrent abortion, consanguinity and mental retardation. At age of 12 year he had some hearing problem for which he used hearing aid.

On examination, GCS was E4V1M1 with cortical cataract and small-sized reactive pupils. During BP measurement Trousseau sign was present. BP, respiration and pulse were normal. Eczema was present on skin, and conjunctiva pale. Respiratory examination was suggestive of aspiration pneumonitis. Rest of the systemic examination was normal.

Clinical diagnosis was seizure disorder (?hypocalcemic) with B/L hearing loss and planned further investigation that revealed X-ray chest (PA) bilateral aspiration pneumonitis. ECG showed prolong QTc. Blood investigation revealed anemia with raised TLC and marked hypocalcemia (3.4 mg/dl). He was negative for HIV and HBsAg. PTH level was 8.61 pg/ml (hypoparathyroidism). CT brain revealed B/L basal ganglia and posterior fossa periventricular dense calcification (Figure 1 A1 and A2). MRI brain revealed focal areas of abnormal signal in B/L lentiform nucleus and cerebellar hemisphere (Figure 1 B1 and B2) suggestive of calcification with possibilities of idiopathic, physiological, endocrine disorder, metabolic/toxic and Fahr’s syndrome. On USG left kidney was not visualized with parapelvic cyst in right kidney (Figure 1C). IVP suggested non-opacification of left kidney. EEG recording suggested normal awake EEG record. Echocardiography was normal. Pure tone audiometry revealed B/L profound sensorineural hearing loss (Figure 1D).

While in the ward patient was administered parenteral calcium and given vitamin D with which seizures stopped and patient became conscious and oriented.

Screening of parents for hypocalcemia / hypoparathyroidism, hearing loss and renal abnormality didn’t reveal any abnormality.

Triad of (hypoparathyroidism, deafness and renal dysplasia) approached towards a very rare
syndrome HDR syndrome or Barakat syndrome.

To confirm this diagnosis we need to find out haploinsufficiency of GATA3 gene in chromosome 10p by using PCR analysis of polymorphic and FISH analysis using YAC and PAC clones that could not be done yet because of lack of genetic laboratory facility at our institute. But this clinical approach let the patient to live symptoms-free life. Presently patient is on oral calcium, vitamin D3, and last serum calcium level was 9.4 mg/dl compared to initial 3.4 mg/dl.

Discussion

The defect in the majority of cases has been mapped to chromosome 10p (gene map locus: 10pter-p13 or 10p14-p15.1). Haploinsufficiency of zinc-finger transcription factor GATA3 or mutations in the GATA3 gene appear to be the underlying cause of this syndrome. Since the spectrum of phenotypic variation in affected patients is quite large, Barakat (HDR) syndrome probably arises as a low penetrance haploinsufficient disorder in which the patient’s genetic background plays a major role in the severity of the disease. The frequency is unknown, but the disease is considered to be very rare. Differential diagnosis are DiGeorge syndrome and velocardiofacial syndrome (DGS/VCFS). Patient presented with hypocalcaemia / hypoparathyroidism, which is a feature of the DGS/VCFS spectrum. However, he did not show other typical features of DGS/VCFS, such as a cardiac defect, cleft palate. In addition to hypoparathyroidism, he presented with b/l sensorineural deafness and renal dysplasia that indicate clinical entity of HDR.

Thus HDR syndrome is a rare disease which mimics DGS/VCFS. Diagnosis is confirmed by genetic study using PCR analysis of polymorphic and FISH analysis using YAC and PAC clones but as in our case clinical diagnosis transformed the quality of life of patient with simple treatment.

References