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Case Report

Concomitant Hypoparathyroidism, Sensorineural Deafness, and Renal Agenesis: A Case of Barakat Syndrome

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Barakat syndrome, also known as hypoparathyroidism, sensorineural deafness, and renal dysplasia syndrome is an extremely rare congenital disorder. Different etiologies are described for the syndrome but the definite pathophysiology remains unclear. Hereby, we present a case of Barakat syndrome who was diagnosed on the basis of clinical and molecular data.

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Introduction

Barakat syndrome, also known as hypoparathyroidism, sensorineural deafness, and renal dysplasia (HDR) syndrome is an extremely rare congenital disorder.[1] It was first reported by Barakat et al. in 1977.[2]

Familial forms of hypoparathyroidism can be inherited in autosomal dominant, autosomal recessive, or X-linked recessive patterns.[3] Different etiologies were described for the syndrome but the definite pathophysiology remains unclear. It may occur in isolation or may be associated with other congenital abnormalities such as the absence of the thymus (Di George syndrome).[4]

Hereby, we present a case of Barakat syndrome (HDR) who was diagnosed on the basis of clinical and molecular data.

Case Report

A 20-year-old girl from Daaraab in Fars Province was brought to the Emergency Room of Nemazee Hospital in Shiraz, south of Iran because of generalized tonic-clonic movements. The patient was a known case of seizure disorder since seven years ago. Despite receiving carbamazepine and sodium valproate, seizures continued to recur. One day prior to admission she developed generalized tonic-clonic movements and was admitted to a local hospital and received phenytoin and diazepam but the convulsions did not stop and led to status epilepticus. Therefore, she was transferred to Nemazee Hospital in Shiraz.

During the initial evaluation, low levels of serum calcium were detected and the patient was admitted to the Endocrinology Ward. Her history revealed that she had complaints of paresthesia in her extremities and facial grimacing for a long time. She had a history of irregular menstrual cycle and muscle cramps especially at nights. She also complained of decreased hearing acuity since two years ago. The patient had no history of thyroid problem or surgical intervention and there was no significant illness in her medical history other than the mentioned seizure. Her uncle (on mother's side) and cousin were cases of seizure disorder since childhood. No history of hearing difficulty, mental retardation, or renal problem was reported in patient's siblings or family.

On admission to the ward the patient was conscious, her height was 161 cm, her weight was 69 kg, her temperature was 36.5°C, her blood pressure was 150/90 mmHg, and the heart rate was

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80 beats/min. On physical examination no abnormal finding was detected except for a decrease in deep tendon reflexes in both lower extremities. Her vibration and positional senses were intact. Chvostek and Trousseau signs were negative.

The initial laboratory studies showed serum calcium level: 4.8 mg/dL and serum phosphorus level: 9.9 mg/dL. The serum intact-PTH level measured by immunoradiometric assay (IRMA) was 6.8 ng/L (normal range: 10 – 71 ng/L). Other laboratory tests on the serum showed: lactate dehydrogenase level: 505 IU/L, CPK: 5090 mg/dL, urea nitrogen: 6.0 mg/dL, creatinine: 0.9 mg/dL, albumin: 4.5 g/dL, sodium: 146 mmol/L, potassium: 3.6 mmol/dL, and magnesium: 1.49 mg/dL (normal range: 1.6 – 2.3 mg/dL).

Liver function tests were normal except for a mild elevation of liver enzymes (AST: 68 mg/dL and ALT: 70 mg/dL). On her admission, urinalysis showed 3+ protein and 1+ blood with 4 – 6 RBCs/high power field, 2 – 3 WBCs/high power field, and many triple phosphate crystals. The values changed to normal in the next test repeated two days later. Erythrocyte sedimentation rate was 36 in first hour and serum C-reactive protein level was 12 mg/dL. Urine volume in 24 hours was 3,000 mL with urine calcium, phosphorus, and creatinine levels of 261 mg/dL, 570 mg/dL, and 990 mg/dL, respectively. The patient's blood sugar, complete blood count, and arterial blood gas were normal.

Electrocardiography showed a prolonged QT interval. Computed tomography of the brain revealed bilateral, symmetrical calcification involving basal ganglia and some degrees of cortical calcification (Figure 1). Audiometry showed bilateral sensorineural hearing loss, which was more significant in frequencies more than 5000 Hz (Figure 2). Abdominal ultrasonography revealed agenesis of the left kidney. The right kidney was normal in size (115 mm in length) with a mildly increased echo texture.

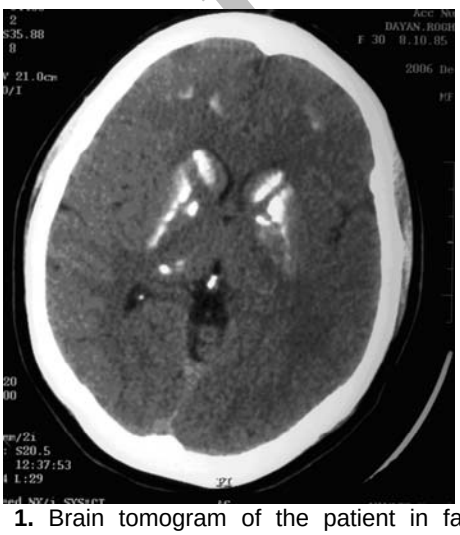

Figure 1. Brain tomogram of the patient in favor of chronic hypocalcemia.

Considering the clinical and laboratory findings, the diagnosis of HDR syndrome was made and treatment for hypocalcemia and hypertension was started.

Family study of the patient could only be done for her father and mother. They had no renal or auditory problems. Their serum calcium and phosphorus levels were normal. The patient's family was living in a village, which was far and not easily accessible for the authors, so laboratory data on her siblings or other family members could not be obtained. Chromosomal study of the patient using standard trypsin G-banding analysis showed no abnormality.

During the hospital course in the 10th day after admission, serum calcium and phosphorus levels changed into normal ranges and she was discharged with oral medications (calcium-D 500 mg per oral, three times per day).

Discussion

Barakat (HDR) syndrome, described as hypoparathyroidism, sensorineural hearing loss, and renal dysgenesis was first reported by Barakat et al. in 1977.[2] They reported steroid-resistant nephrosis with progressive renal failure and death at ages five and eight years in two brothers who also had sensorineural deafness and hypoparathyroidism. At autopsy, the parathyroid glands were absent in one child and hypoplastic in the other. They suggested a possible relation between those symptoms and also a possible genetic factor that caused that syndrome.

To the best of our knowledge the presented case is the first case of Barakat syndrome reported from Iran. Since its recognition, there have been seven reports on HDR syndrome so far.

Renal manifestations of this syndrome were first studied by Bilous et al.,[5] who described two brothers and two daughters of one of the brothers with hypoparathyroidism, sensorineural deafness, and renal dysplasia suggesting an autosomal dominant pattern of this syndrome. The results of intravenous urography were consistent with the presence of bilateral renal dysplasia. Three of the

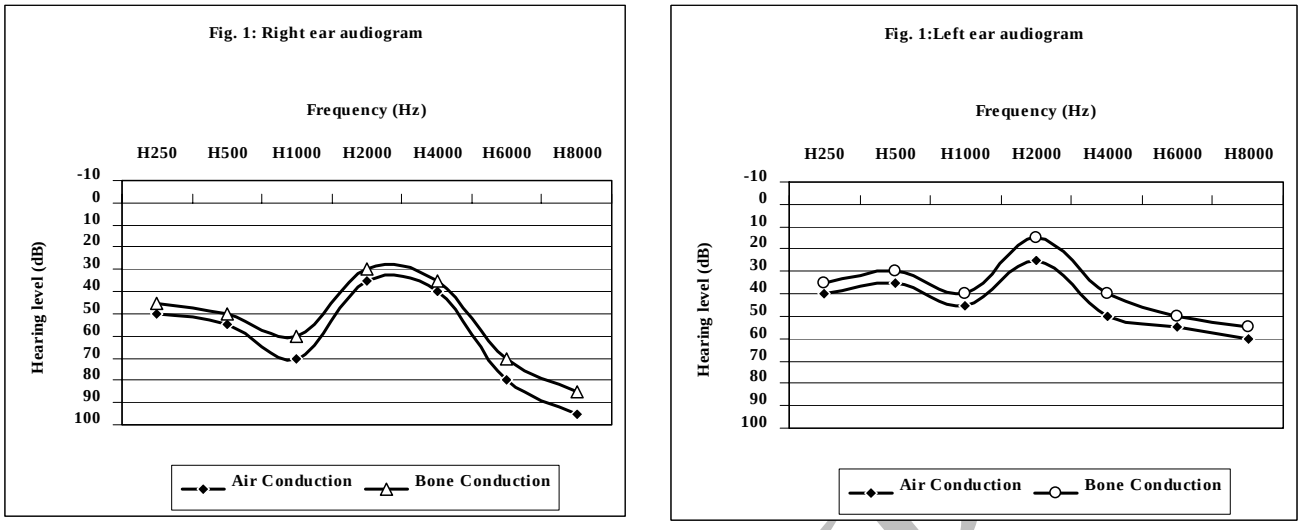

Figure 2. Audiography of the patient (normal hearing level is between 0 to +10 dB).

patients had abnormal creatinine concentrations and reduced estimated glomerular filtration rate (GFR).

In this syndrome many different renal anomalies have been observed with variable penetrance including renal dysplasia, hypoplasia, aplasia, and vesicoureteral reflux.[6–8] Up to this report there had been three reported cases of HDR syndrome, whose renal manifestations were shown to be a unilateral renal agenesis.[9–11] Our patient also had left renal agenesis and a normal size right kidney, which is compatible with renal manifestations in individuals reported by the mentioned groups. However, our patient had normal GFR and normal concentrations of serum creatinine in oppose to the report by Bilous et al.[5]

In 1998 Watanabe et al. reported a family with HDR syndrome who interestingly lacked any renal anomalies but had other features of HDR syndrome.[12] These data together suggest that a combination of genetic, environmental, and stochastic factors are likely involved in determining the clinical expression of HDR syndrome. And a probable gene polymorphism and different genetic mutations in conjunction with environmental factors lead to diverse renal manifestations of the disease.

Unlike the renal anomalies, there has been no significant difference in characteristics of hearing loss in patients with HDR syndrome.[13] The present case suffered from bilateral sensorineural hearing loss, which was more significant at frequencies more than 5000 Hz. The results of audiometry in our patient, compared with the previous reports, shows that hearing loss in HDR syndrome is moderate to severe, slightly worse at higher end of the frequency spectrum, and is usually progressive with age.[14] The results were in favor of a role for outer hair cells in development of the hearing loss in this syndrome, considering loss of frequency selectivity.[14] Our findings on audiography are the same as those reported by Bilous et al.,[5] Ishida et al.,[11] and Yumita et al.[10]

Since the initial recognition of this syndrome, major advancements have been made in elucidating the pathophysiology of HDR syndrome. It was first shown by Hasegawa et al. in 1997 that *de novo* deletion of chromosome 10 might result in this syndrome. They concluded that the gene responsible for HDR syndrome was located in the 10pter-p13 region.[9] Different study by Fujimoto et al. in 1999 showed that the mentioned gene was located on chromosome 10p15.1-p14.[15] In the present case, no abnormality was found in chromosomal study of our patient using standard trypsin G-banding analysis. This can lead to the results of similar studies indicating that some common genetic mutations can be the cause of the triad of hypoparathyroidism, hearing loss, and renal dysplasia in Barakat syndrome. More studies including vast genetic analysis of these patients are needed to determine the type of mutation leading to this syndrome. However, it is recommended that in those patients who suffer from convulsions due to hypocalcemia, performing audiometry and renal studies can probably reveal the triad of HDR syndrome in some of the cases. This can provide the potential for further genetic studies to discover exact genetic mutations or environmental factors leading to this syndrome.

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