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Case Report

Seizure in a 17-Month-Old Girl who Developed Barakat Syndrome

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Abstract

Barakat syndrome is a rare autosomal dominant disease with classical triad that can occur at different ages. The classic triad of the disease includes not only hypoparathyroidism, sensorineural deafness and renal abnormalities but also nonspecific symptoms due to genetic abnormality. The cause of this syndrome is the mutation in the GATA3 gene, which is the structural displacement of the gene from its natural location. In preliminary laboratory studies, Phosphorus, Calcium and iPTH were 6.8, 7 mg/dl and 3.7 pg/ml, respectively. This study reported a 17-month-old girl presenting with tonic-clonic seizure, hypocalcemia and hyperphosphatemia.

Keywords: *Seizure; Barakat Syndrome; Hypocalcemia; Renal Aplasia*

Introduction

Barakat., *et al.* were the first who reported a syndrome named "Barakat" that was inherited autosomal dominantly, in 1977. This is a rare disorder with a triad of hypoparathyroidism, sensorineural deafness and renal dysplasia that is defined as an HDR syndrome [1,2]. There are several mutations for that, such as missense and nonsense mutations, gross deletions and small insertions that translocate GATA3 gene, structurally [3]. The mapping of this gene showed it is placed on the short arm of chromosome 10 [4,5]. Not only mutations and haplo-insufficiency of GATA3 gene cause Barakat syndrome, but also overexpression can do that [6]. GATA3 is a factor that is involved in transcription of inner ears, central nervous system, parathyroid glands, kidneys and thymus genes [5,8]. This factor is classified in zinc finger factors and has two terminal fingers with different actions: The C-terminal called ZnF2 which is involved in protein binding and the N-terminal which is stabilized C-terminal connections [8-10]. The age of the disease can be of any age and most people present with hypoparathyroidism [11]. Diagnosis is based on clinical features. Laboratory tests should be used to confirm the findings. The study of the chromosome 10p is important when patients have abnormalities in the urinary tract with one of two other symptoms of the syndrome [12]. There was a girl with a presentation of hypocalcemia, bilateral hearing loss and renal aplasia that she was experienced seizure for the first one.

Case Presentation

A patient referred to the pediatric clinic with a complaint of seizure. She hospitalized in Imam Sajjad Ramsar Hospital; then, she referred to Bou Ali Sari Hospital for further investigation. A 17-month-old Ramsay girl referred to our hospital in order to analyze the cause of the seizure. She was the second child of the family and born at term. Her older brother and her parents were normal. She was born by caesarean section and had a birth weight of approximately 2800g. She was normal at birth. She had no history of underlying disease, trauma and hospitalization. Her vital signs, at the hospital admission time, encompassed blood pressure 90/50 mmHg, Heart rate

126 bpm, respiratory rate 31/min, temperature 36.7 and O_2 saturation 94%. Neurological developmental delay (NDD) was in the form of bilateral hearing loss and hypoparathyroidism that were diagnosed 5 days after the birth; she is walking with the help of others and speaking two to three words. The patient tolerated feed well. This was the first time the patient had a seizure; tonic-clonic movements with upward eyeball deviations. The attack accompanied by palpation of the mouth, with bruising and stiffness of the limb lasting for 5 minutes. After the seizure, she experienced sleepiness phase for 20 minutes. Initial examination revealed a Ca of 6.9 [reference value (RV), 8.6 - 10.3] mg/dl and Phosphorous of 9.2 (RV, 3.5 - 6.6) mg/dl. She received Diazepam, Phenytoin and Phenobarbital. Due to the high serum levels of Phosphorus, nutritional counseling limited the consumption of meat, fish, whole grains, dairy products such as milk, cheese, yogurt and varieties of nuts. In physical examination, her head circumference was 49 cm, her height was 75 cm and her weight was 10 kg. Neurological findings included Glasgow Coma Scale (GCS) was 15/15; muscle tone, strength and deep tendon reflexes (DTR) were normal. No other abnormalities were found on examination. The highest and lowest body temperature were 39 and 36 degrees, respectively. The patient did not experience any seizure attacks during the hospitalization period. Renal ultrasonography (USG) result showed the right kidney was in small size with normal echo parenchymal; no evidence of stone or hydronephrosis was found. The left kidney was not observed in an anatomical location; even in abdominal and pelvic ultrasound. The renal function was evaluated by dimercaptosuccinic acid (DMSA) scan. It represented the normal function of the right kidney with no focal cortical defect. No function was visualized from the left kidney. She also consulted with pediatric cardiologist which results of electro cardiology and echocardiography were normal. Serum laboratory findings revealed: creatinine 0.52 (RV, 0.6 - 1.2) mg/dl, urea 19 (RV, 11 - 36) mg/dl. Blood sugar 96 (RV, < 140) mg/dl, protein total 6.55 (RV, 6 - 8)g%, albumin 3.52 (RV, 3.5 - 5.5)g%, intact PTH 3.7 (RV, 14.5 - 87.3)pg/ml, vitamin D3 (25OH) 42.4 urine (RV, 20 - 70)ng/dl, Erythrocyte sedimentation rate in the first hour 45 (RV, up to 15)mm/hr, Ca to creatinine ratio (Ca/cr) 2 (RV, up to 2.2)mmol/mmol, sodium 139 (RV, 135 - 145)mEq/L, potassium 4.5 (RV, 3.5 - 5.5)mEq/L and magnesium 1.69 (RV, 1.6 - 2.5)mEq/L. WBC: 9500/µl, (PMN = 25%, LYMPH = 68%, BASO = 2%, Monocyte = 3%, Eosinophil = 2%), RBC = 4060000/µl, HGB = 10.1g/dl, MCV = 73.2, MCH = 24.9, PLT = 530000. Other laboratory tests and echocardiography were normal. After management, patient discharged with normal level of Ca, P, PTN and with of seizure with drug therapy and good situation.

Discussion

This syndrome can present with different symptoms, but Barakat et al reported the familial syndrome with presentation of bilateral nerve deafness, hypocalcemia, proteinuria, hypoparathyroidism and nephrotic syndrome first in 1977; it was also resistant to steroid [1]. The familial type of HDR syndrome can be inherited in autosomal dominant, recessive and X-linked recessive forms. The autosomal dominant and recessive are associated with the defects in the short arm of chromosome 10p that had similar clinical symptoms. In the X-linked pattern, the defect is at the Xq26-q27 region, the long arm of the chromosome X [5,13-15]. Ali., *et al.* divided the syndrome mutations into three categories: more than 90% of mutations are due to impairment of the binding GATA3 factor to its target. In fact, the C-terminal finger (ZnF2) plays a major role in this syndrome. Another is impaired N-terminal finger (ZnF1) and decreased affinity of binding. In few cases, neither C-terminal nor N-terminal but the conformational changes alter the efficacy of cofactors and nuclear proteins [16]. GATA3 factor is classified into two groups: one contains GATA4, -5 and -6 that are involved in the development of the gut, smooth muscle cells, heart and urogenital system. The other included GATA1, -2 and -3 that are participated in the expression of blood cells precursors [17,18]. This indicates that GATA3 is indirectly relate to other factors of the GATA family and their developmental functions. Depending on chromosomal abnormality, nonspecific presentations due to GATA3 interaction may be seen such as neurological abnormality, hypertelorism, cardiac abnormalities like ventricular septal defect (VSD) and atrial septal defect (ASD), genital tract abnormality and stenosis of pylorus [19,20]. Our patient was normal mentally and femininity. Depending on the structurally or functionally involvement of the urinary tract system, the symptoms can manifest differently. The structural disorder included vesicoureteral reflux, aplasia, cystic kidneys, dysplasia, and hypoplasia and pelvicalyceal abnormality. Functionally disturbance like hematuria, proteinuria, distal and proximal renal tubular acidosis, renal failure and nephrocalcinosis have been reported so far [21-23]. Hypoparathyroidism is the most specific and diverse symptom in HDR triad. Due to the varying serum calcium levels, it can present in mild or severe forms.

Mild form, which is often asymptomatic, included myalgia, numbness, tetany, tingling. In severe form, convulsion, positive trousseau and chvostek sign, intracranial calcification and prolonged QT interval can be seen [3,16,24-26]. Hearing loss is often the first manifestation of Barakat syndrome. In fact, the hearing loss is such that either the auditory cortex or the inner ear or vestibulocochlear nerve is involved. This hearing loss is due to gene involvement that disrupts synaptic differentiation and cochlear signaling function. The degree of hearing loss is first in low-frequency sounds and then progresses to high [5,27-35]. Although, Barakat triad is defined as a hypoparathyroidism, deafness and renal dysplasia, it often did not manifest as a triad. Urinary and renal system has the most variety of presentation [22]. Lichtner showed that patients with partial monosomy 10p may have different symptoms depending on the involvement of the proximal or distal regions of DGCR2. Patients with haploinsufficiency of the distal region show symptoms that are characteristic of HDR syndrome that overlaps with DeGeorge syndrome [36]. We can definite our diagnosis by some tests in order to confirm our clinical findings such as renal biopsy and imaging, parathormone (PTH) levels and examining auditory pathways [12]. Hypoparathyroidism is the only serum finding in the Barakat triad that can be mimicked by non-genetic conditions. We can differentiate between pseudo and real hypoparathyroidism. Shortening of metacarpal is a clue of real hypoparathyroidism. Increasing CAMP in response to PTH injection shows the normal sensitivity of PTH receptor. Our patient's iPTH level was 3.7 and very low. Hypomagnesemia, both genetically and acquired with impaired in PTH release and vitamin D activation can mimicked hypoparathyroid conditions. Our patient's magnesium and vitamin D level were 1.69 and 42.4, respectively [3,37-39]. The cause of the difference in symptoms is related to the role of genetic and environmental factors. For example, the phenomenon of anticipation causes different incidence and severity in patients with the same mutations [40-42].

Conclusion

Considering the present study and other studies in line with the above syndrome, accurate and timely diagnosis can help in treating the disease and improving the quality of treatment. In many parts of the world, the lack of accurate diagnosis and timely referral can lead to the loss of the case. So, depending on symptoms, especially seizure which is related to the hypocalcemia with deafness examining renal abnormality, magnesium, calcium, phosphate, PTH levels and even chromosomal analysis should be done.

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