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Bakarat syndrome: A case study

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Abstract

Barakat syndrome (also known as HDR syndrome-hypoparathyroidism, sensorineural deafness and renal disease) an autosomal dominant disorder characterized by hypoparathyroidism, sensorineural deafness, and renal disease caused by mutation of the GATA3 gene located at chromosome 10p15, is very rare, with only about a dozen cases reported in the world literature. We report a case of 18-year-old with features consistent with Bakarat syndrome, which first presented with seizures at age two months and subsequently was diagnosed with bilateral high frequency sensorineural deafness and single kidney. Clinicians should be aware of rare inherited conditions when a patient presents with a constellation of signs and symptoms.

Case presentation

An 18-year-old male was admitted for asymptomatic hypercalcaemia (serum calcium 3.2 mmol/L), a known case of congenital hypoparathyroidism who had been taking calcium lactate, calcium carbonate and ergocalciferol (vitamin D2). At birth he was seen to have right sided ptosis and was diagnosed with congenital hypoparathyroidism at age two months when he presented with generalised tonic clonic seizures. He was found to have bilateral high frequency sensorineural deafness at age four years and fitted with a hearing aid. He was also somewhat mentally retarded. No siblings or parental relatives had nerve deafness, hypoparathyroidism or renal diseases.

His mile stones were somewhat delayed as was academic performance. The right ptosis was partially corrected by surgeries at ages 5 and 7 years. At age 8 years, renal ultrasonography revealed absence of the left kidney and DMSA revealed a satisfactory functioning right kidney (Table 1). At age 12 years ergocalciferol was stopped (and he remained on oral calcium) but developed symptomatic hypocalcaemia and this drug was restarted. At age 17 he was noted to have elevated systolic blood pressure 137 -139 mmHg and renal ultrasonography (USG) revealed renal parenchymal disease in the sole kidney. ECrCl (Bedside Schwaz) was 65 ml/min/1.73 m^2. Serum urea and creatinine were within normal ranges (Table 2) as were serum pH and bicarbonate levels and 24-hour urinary protein was 0.14 g/L.

On physical examination, he was a well-developed, well-nourished young man with partial right ptosis who apart from a hearing aid and mild systolic hypertension (138/82 mmHg) had no significant physical abnormalities. ECG was normal. Corrected serum Calcium was 3.0 mmol/L (2.16-2.50), inorganic phosphate was 1.22 mmol/L (0.76-1.65). Blood Sodium was 145 (136-145), Potassium 3.6 (3.6-5.1), Chloride 104 mmol/L (96-105). Blood urea was 8.8 mmol/L (3.20-8.20) and creatinine was 235 umol/L (82-115) (Table 2).

Calcium tablets and ergocalciferol were discontinued and 5% dextrose water two liters per day was administered as well as amlodipine 5 mg per day orally. Since serum creatinine was elevated, USG kidney was repeated and showed parenchymal right renal disease and hydronephrosis with dilation of proximal right ureter. No stones or medullary calcinosis was noted. CT urogram revealed absence of left kidney, mild hydronephrosis of right kidney with normal ureter and no identifiable cause of hydronephrosis. Routine urinalysis was normal. Blood calcium had decreased to 2.6 mmol/L and ergocalciferol was reinstituted without addition calcium. Blood pressure was 120/80 mmHg upon the discharge. He was advised to avoid high phosphate diet and continue medial follow up

Discussion

The constellation of congenital hypoparathyroidism, sensorineural deafness and left renal agenesis in this patient is consistent with Bakarat syndrome [1-5], also known as HDR syndrome (for hypoparathyroid, (sensoineural) deafness, renal disease), an autosomal dominant disease [6]. Mutation in GATA3, a gene localised to chromosome region 10p14-15 has been detected in the families affected by the syndrome. GATA3 is a transcription factor involved in the embryonic development of parathyroid gland, kidney, inner ear, thymus and central nervous system [2]. Several mutations of GATA3 leads to a spectrum of HDR phenotypes [2]. Hypoparathyroidism is a consistent

Table 1. Imaging reports from childhood and current situation.

Age 8	DMSA	Well-functioning kidney
Age 17	USGKUB	Single right kidney with renal parenchymal disease. No obstructive uropathy
Age 18 9.03.17	USGKUB	Single kidney with mild to moderate hydronephrosis proximal hydroureter and renal parenchymal disease. Left kidney not visualised
Age 18 10.03.17	MSCT urography	Mild right hydronephrosis, cause unknown. Left kidney and ureter not visualised

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Table 2. Laboratory Results from childhood and current situation.

AGE (years)	5	14	17	18 6.03.17	18 9.03.17	Normal range
Calcium	2.47 mmol/L	2.02	2.30	3.0	2.60	2.16-2.50
Inorganic phosphate		1.87	1.35	1.16	1.32	0.76-1.65
Magnesium		0.67	0.77	0.88		0.53-1.11
Renal Profile						
Urea	4.0 mmol /L	4.8	4	8.8	8.2	3.2-8.2
Creatinine	100 umol /L	91	100	253	242	82-115
Serum Electrolytes						
Sodium		135		145		136-145
Potassium		3.70		3.6		3.6-5.10
Chloride		103		104		96-105
Liver function test						
Total Protein		80		80 g/L		97-82
Total Bilirubin		4		9 umol/L		<21
Albumin		42		46 g/L		32-45
Globulin				34 g/L		25-36
Alanine Amino Transferase		10		34 U/L		10-49
Alkaline Phosphatase		177		133 U/L		45-129

feature in HDR syndrome occurring in 90% of patients but isolated hypoparathyroidism resulting from GATA3 haploinsufficiency has not been reported [4]. Patients may be asymptomatic despite marked hypocalcaemia. Symptomatic patients present with cramps, tetany cardiomyopathy or seizures [4]. Renal involvement is the most heterogenous feature of the triad. Hypoplasia, dysplasia, cystic kidneys, vesicouretric reflux, nephritic syndrome, pelvicalyceal abnormality, proteinuria, haematuria, proximal and distal renal tubular acidosis, nephrocalcinosis and renal failure have all been reported. Our patient had left renal agenesis, a consistent finding [2], and most probably left ureter agenesis [6-10].

The original patients described by Bakarat et al. [5] presented with proteinuria and progressed to steroid resistant nephrotic syndrome. However, our patient had no proteinuria on routine urinalysis but his renal function was deteriorating (creatinine 235 mmol/L) and was possibly progressing to chronic renal failure as do most patients with the syndrome [8]. Early accurate diagnosis of renal disease has potential prognostic significance [11]. In our patient, renal anomaly was detected at age of 11 and impairment at age of 17. Sensory neural deafness is the most consistent feature of Bakarat or HDR syndrome and is usually bilateral since birth. However, it may be asymmetric and varies for mild to profound and is worse at high frequencies. GATA3 haploinsifficiency predisposes the affected individuals to progressive morphological degeneration of the cochlea beginning with outer apex hair cells and ultimately affecting all hair and supporting cells in the entire cochlea [4]. Our patient was noted to be hearing impaired by his mother at age 4 years and was helped with hearing aids. Morphological and physiological abnormalities have been identified in the brain stem, cerebral cortex, outer and middle ear in GATA 3 haploinsufficiency [12]. Several non-triad features such as pyloric stenosis, polycystic ovaries, Mullirian duct abnormalities, congenital heart defects, recurrent cerebral infarcts, and hemimegalencephalopathy have been reported [9,10,12,13]. Our patient had none of these extra triad features but was born with complete right ptosis. Bakarat syndrome is not only rare but also difficult to diagnose or delayed due to the combination of features involving various systems. Renal involvement may not be appreciated as it is usually asymptomatic.

Our case demonstrates the diagnostic difficulty of Bakarat syndrome, which may become evident at any age. Therefore, one should test for sensory neural deafness and renal anomalies when a patient presents with seizures due to hypoparathyroidism. Likewise, when isolated bilateral sensorineural deafness, rare in children, is present, one should think of a potential systemic disease or syndrome. Renal anomalies, one of the features, have prognostic importance and early therapy might prevent and slow renal damage.

Conclusion

Bakarat syndrome is relatively rare and diagnosis difficult if the attending physicians are unaware of the syndrome.

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