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Proteinuria in Two Sisters with Beaulieu-Boycott-Innes Syndrome, A Case Report

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We report two sisters (13- and 4-year-old) presenting with moderate intellectual disability, dysmorphic facial features, intermittent hematuria, proteinuria, and dental caries. Their parents and other family members were not affected. Whole-exome sequencing was performed to screen the underlying genetic cause. These patients have been analyzed using Next-Generation Sequencing (NGS) method and homozygote variant (c.890delC) has been detected in the THOC6 gene. Direct Sanger sequencing confirmed that they are homozygote for the pathogenic variant mutations in the THOC6 gene, which is associated with Beaulieu-Boycott-Innes syndrome (BBIS). These patients also had proteinuria and subsequently developed hematuria. This is the first report of BBIS in association with proteinuria and hematuria without renal defects. Core clinical features include low birth weight with subsequent growth failure, short stature, and intellectual disability with language delay, characteristic faces, cardiac defects, and renal anomalies. The possible pathophysiological mechanisms associated with proteinuria and transient hematuria without renal defects are discussed.

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Case Report

INTRODUCTION

Beaulieu-Boycott-Innes syndrome (BBIS) is an autosomal recessive neurodevelopmental disorder characterized by delayed development, moderate to severe intellectual disability, and dysmorphic facial features.[1]

Core clinical features include low birth weight with subsequent growth failure, short stature, mild microcephaly, intellectual disability with language delay, characteristic facies and cardiac and renal defects. Cryptorchidism in males, submucous cleft palate, and corpus callosum dysgenesis, may also be present.[2] All patients show characteristic dysmorphic facial features including a tall forehead with high anterior hairline, short and upslanting palpebral fissures, deep-set eyes, flat philtrum, and dental malocclusion with caries.[3-7] The prognosis of this syndrome is unknown.[5] Anatomic anomalies include malformations of the genitourinary system (absent and duplicated kidneys), and cardiac defects such as ventricular septal defects and persistent ductus arteriosus.[5] These patients are the first report of BBIS in association with transient proteinuria and hematuria.

CASE REPORT

Here, we describe two sisters (13- and 4-year-old) with BBIS presented with delayed development, severe intellectual disability, and dysmorphic facial features (Figure 1 and 2).

No neonatal problems have been described except for low birth weight and small head circumference, and subsequent growth was slow. Language and learning was delayed. On presentation to the pediatric nephrology clinic, they weighed 27 kg (25th to 50th percentile) and 14 kg (< 25th percentile),

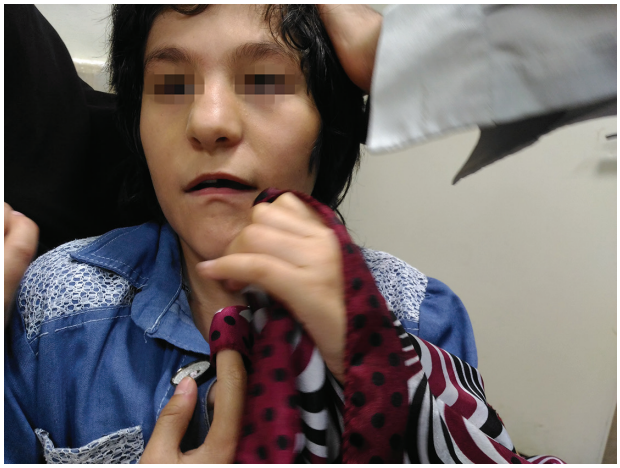

Figure 1. This photo is related to older sister

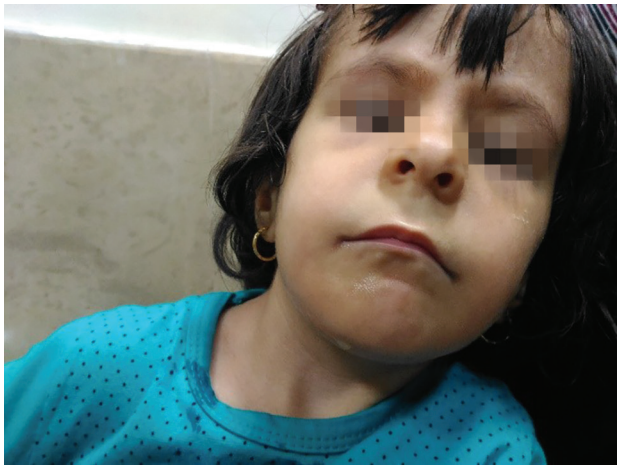

Figure 2. This photo is belonging to younger sister.

respectively. Patients were given a blood sample; urine collection cup, a urine container, and the parents grasp a written instruction for random and 24-hour urine sample collection. They also had mild proteinuria and hematuria and venous blood gases including PH and bicarbonate levels were normal. Figure 3 shows familial pedigree.

Case 1 (Older Sister)

Hemoglobin was 12.7 g/dL, total leucocyte count was 6.5 × 10^9/L (70% neutrophils, 29% lymphocytes, and 1% eosinophil) and platelet count was 198 × 10^9/L. Blood urea nitrogen was 18.5 mg/L, serum creatinine was 19.2 mg/L, serum sodium and potassium were 137 mg/dL and 4.5 mg/dL; respectively. Our patient had normal levels of lipid profile and serum albumin was normal (3.5 g/dL). Venous blood gases including PH and bicarbonate

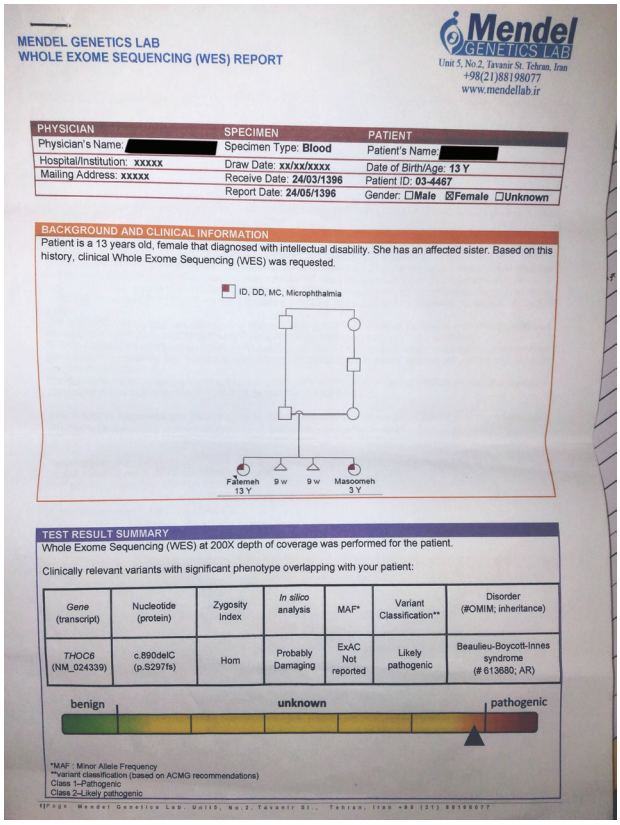

Figure 3. It shows familial pedigree.

levels were in normal range.

She also had normal vital signs but further investigation of urine sediment demonstrated mild proteinuria and hematuria. Laboratory urine tests include the following: urine analysis (PH: 5, WBC: 1-2, RBC: 8-10, SG: 1.005), urine culture: negative, 24-hour urine test (protein: 295 mg/dL, Cr: 450 mg/dL), random urine (Cr: 36 mg/dL, Na: 75 mg/dL, K: 25 mg/dL).

Case 2 (Younger Sister)

Hemoglobin was 11.5 g/dL, total leucocyte count was 5.5 × 10^9/L (60% neutrophils, 36% lymphocytes, and 1% eosinophil) and platelet count was 198 × 10^9, blood urea nitrogen was 19.8 mg/L, serum creatinine was 0.52 mg/L, serum sodium and potassium were 135 mg/dL and 3.5 mg/dL; respectively. Venous blood gases including PH and bicarbonate levels were in normal range. Our patient had normal levels of lipid profile and her serum albumin was normal (3.5 g/dL). She also had normal vital signs but further investigation of urine sediment demonstrated mild proteinuria and transient hematuria. Laboratory urine tests include

the following: urine analysis (PH: 6, WBC: 1-2, RBC: 14-16, SG: 1.025), urine culture: negative, 24-hour urine test (protein: 195 mg/dL, Cr: 350 mg/dL), random urine (Na: 75 mg/dL, K: 25 mg/dL, Cr: 56.5 mg/dL). The ultrasonographic evaluation of kidneys and urinary system was normal. There were no signs of fever, edema, lymphadenopathy or organomegaly. Results of cardiovascular, respiratory and other physical examinations were normal. There was no family history of BBIS or other syndromic disorders.

DISCUSSION

To date, some patients with BBIS and renal defect have been reported. These cases are unusual for two reasons. The development of urine sediment proteinuria and transient hematuria without renal defects is rare in BBIS and there are no similar reports in the literature.

Secondly, the patients developed intermittent dysuria during the course of this illness; the clinical feature was a discomfort in urination for more than 5 days. The dysuria rapidly resolved after administration of acetaminophen. This convincing response to therapy has been considered to represent a major diagnostic test for UTI but urine culture was negative. These patients have proteinuria and subsequently developed hematuria. Although all children with proteinuria need laboratory examination; treatment is not required in most cases.[8,9]

This is the first report of Beaulieu-Boycott-Innes syndrome (BBIS) in association with proteinuria and hematuria without renal defects. The possible pathophysiological mechanisms are not defined but more research is needed to find the reason. Regarding to BBIS in association with proteinuria and transient hematuria, our study requires kidney biopsy and no result was similar to those in other parts of the world. We recommended more studies on this syndrome especially larger and multi-center investigation.

AUTHORS' CONTRIBUTION

MAS and MHA were the principal investigators of the study. MAS, MHA, and FA participated in preparing the concept, design, and revision of the manuscript and critically evaluated the intellectual contents. The authors have read and approved the content of the manuscript and confirmed the accuracy or integrity of any part of the work.

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