Uremia Secondary to Nephronophthisis in a Girl with Ellis-van Creveld Syndrome

Ting-Fang Yen, Cheng-Hsu Chen, Mei-Chin Wen, Hao-Chung Ho, and Lin-Shien Fu

Division of Nephrology, Department of Pediatrics
Division of Nephrology, Department of Internal Medicine
Department of Pathology
Division of Urology, Department of Surgery, Taichung Veterans General Hospital
Taichung, Taiwan, Republic of China

Abstract

Ellis-van Creveld (EvC) syndrome, a chondral and ectodermal dysplasia characterized by short ribs, polydactyly, growth retardation, ectodermal and heart disorder, is a rare autosomal recessive disorder. In previous English studies, the association between renal insufficiency and EvC syndrome has not been well described. We herein report a 9-year-old girl with typical EvC syndrome diagnosed since infancy and presented with renal insufficiency during her childhood. The initial presentations were hypertension, heavy proteinuria and impaired renal function. Histopathological findings from biopsy specimen were indicative of nephronophthisis. Progressive renal failure and uremia occurred in months and she received peritoneal dialysis. At 11 years old, she received cadaveric renal transplantation. The post-transplantation course was uneventful with fair renal function and no episode of rejection. The serum creatinine level after renal transplantation for two years is 0.9 mg/dL. In spite of its rarity, we suggested that nephronophthisis with subsequent renal insufficiency may be presented in patients with EvC syndrome.

KEY WORDS: nephronophthisis, Ellis-van Creveld syndrome, chronic renal failure, renal transplantation

Introduction

Ellis-van Creveld (EvC) syndrome or chondro-ectodermal dysplasia comprises a wide spectrum of developing abnormality. The typical characteristics included short stature, narrow thorax, postaxial polydactyly, upper lip and dental anomalies, hypoplastic or dysplastic nails, and congenital heart defects (1). Approximately 50-60% of affected patients have congenital heart defects, resulting in high mortality rate in infancy (2). However, associated renal anomalies in patients with EvC syndrome have been not well described in English literature so far. Only a few cases with renal agenesis, renal dysplasia, congenital megaureter and nephrocalcinosis have been reported (3, 4).

Nephronophthisis is the most common genetic cause leading to end-stage renal disease (ESRD) in childhood and young adulthood. The characteristics of nephronophthisis are tubulointerstitial fibrosis, cysts at the corticomedullary junction and normal or decreased kidney size. Nephronophthisis has been rarely described in patients with EvC syndrome. To our best knowledge, there was only one case report regarding the association between EvC syndrome and nephronophthisis (5). In the present report, we described one EvC syndrome patient complicated with histology-proved nephronophthisis and renal insufficiency. Her subsequent renal failure was rescued by subsequent successful kidney transplantation. In addition, some associations between EvC syndrome and nephronophthisis are also discussed.

Case Report

A 9-year-old girl sought help at our outpatient...
department due to proteinuria detected by health screening at school. Tracing her past medical history, proteinuria was first noted when she was six years old but she was lost to follow-up. Nausea and poor appetite for one week were noted when she returned to the outpatient department 3 years later. In addition, she also complained about polyuria and polydipsia in the past year. She and her family denied any medication or use of Chinese herbs.

She has a long history of EvC syndrome with relative short limbs accompanied by a relatively small bell-shaped thorax, right feet postaxial polydactyly, and genu valgum since birth. Cardiac anomaly with large atrial septum defect (ASD) was noted and she received surgical correction at 11-month-old. Surgical correction of polydactyly was performed when she was 1 year and 5 months old. There was no family history of consanguinity, birth defects, skeletal disorders, short stature, miscarriages, or neonatal losses.

On physical examination, her vital signs disclosed heart rate 81 beats per minute, respiratory rate 20 per minute, and high blood pressure 170/124 mmHg. She had round face, hypoplastic widely spaced conical teeth with frequent decays and brownish coloration, 146 cm height (above the 95 percentile), 54.5 kg weight (above the 95 percentile), and BMI = 25.6 kg/m². The hair was fine and straight, but not spare. The extremities were plump with marked wide hands and feet with sausage-shaped fingers without edema over extremities. There were small bell-shaped thorax, relatively short arms and legs with most striking shortening in the distal part. Moreover, genu valgum was also noted. Her nails were relatively wide and short without dysplasia. On auscultation, there were bilateral clear breathing sounds, irregular heart beats with grade two systolic heart murmurs over apex. Laboratory data revealed normal white blood cells and platelets, normocytic anemia with hemoglobin 7.9 g/dL. Serum sodium and potassium levels were within normal limits while there was hyperphosphotemia with phosphate level at 8.3 mg/dL. In addition, impaired renal function with blood urea nitrogen 95 mg/dL, and creatinine 6.9 mg/dL were noted. Blood gas analysis revealed metabolic acidosis with pH 7.329 and bicarbonate 16.5 mEq/L and base excess -7.6 mEq/L. Her plasma rennin level was 36.51 pg/mL (normal range: supine: 3-16 pg/mL, upright 3-33 pg/mL). Urinalysis revealed normal urine specific gravity, mild hematuria with occult blood 1+, 3-5 red blood cells in high power field, mild pyuria with 10-12 white blood cells in high power field. Urine dipstick also showed proteinuria (2+) without glycosuria. The spot urine protein-creatinine ratio was 1.78. Feet X-ray after surgery (for polydactyly) revealed bifurcation of right 5th metatarsal bone and independent 5th, 6th phalanges. Meanwhile, the left foot showed no abnormality. Heart sonography showed mild aortic valve regurgitation, tricuspid valve regurgitation and moderate mitral valve regurgitation.

A renal ultrasound showed bilateral kidneys with increased echogenicity and normal size; no cyst was noted from sonography. Renal biopsy was performed which showed intraglomerular and periglomerular fibrosis (Fig. 1), cystically dilated tubules (Fig. 2) in hematoxylin and eosin (H&E) stain. Electron micrograph disclosed a tubule basement membrane of variable thickness (Fig. 3). The abovementioned pathological findings were considered suggestive of nephronophthisis. Progressive renal dysfunction was found during serial follow-up with serum creatinine up to 12.3 mg/dL after 5 months of biopsy. Tenckhoff catheter implantation was performed and she was started on continuous ambulatory peritoneal dialysis. At 11 years of age, she fortunately received a cadaveric kidney transplantation with two human leukocyte antigen-B (HLA-B) mismatched. The post-transplantation course was smooth. The serum creatinine decreased to 0.9 mg/dL (normal 0.7-1.4) after 3 years of transplantation. Neither acute nor chronic rejection was noted during follow-up.

Fig. 1. 1A: Most of the glomeruli were globally obsolete, with small size and intraglomerular fibrosis (arrows, H&E stain 100×). 1B showed one non-sclerotic glomerulus with peri-glomerular fibrosis (arrows, Masson Trichrome stain 400×).

Fig. 2. Multiple cystic dilated tubules with cellular infiltrates over tubulointerstitium in H&E stain (100×).
Renal Failure in EvC Syndrome

Discussion

Nephronophthisis is an autosomal recessive kidney disease which contributes to ESRD in the first three decades of life. Nephronophthisis-associated ciliopathies have been taken as pathologic changes leading to multiple organ involvement (6). The encoded proteins (nephrocystins, cystoproteins) of 11 different genes (NPHP1 through 11) were identified to contribute a theory that defines cystic kidney diseases as cillopathies. These proteins were expressed in the renal cilium, basal bodies, and centrosomes which effect cell mitosis. Abnormal centrosomes destroy planar cell polarity (PCP); that is, the orientation of cells in a plane perpendicular to apico-basal polarity. Abnormal PCP leads to tubular dilatation and a cystic-like structure (7). The initial symptoms may be relatively subtle, presenting with polyuria, polydipsia, failure to thrive and anemia before the onset of renal insufficiency. Lack of edema, dysuria, frequency and hypertension often lead to a delay of awareness in renal involvement. Renal ultrasound examination reveals increased echogenicity, loss of corticomedullary differentiation, normal or reduced renal size and cyst formation over corticomedullary junction in the later stage. Renal histology in nephronophthisis shows the characteristic triad of renal tubular cysts, tubular basement membrane disruption, and tubulointerstitial cell infiltrates with interstitial and peri-glomerular fibrosis (6). Our present case had history of polyuria, polydipsia, and proteinuria prior to renal insufficiency. Moreover, significant hypertension was observed, which has been reported to occur in the advanced renal disease in patients with nephronophthisis. Clinical features of nephronophthisis may mimic another renal disorder, renal dysplasia. Increased renal echogenicity, renal cyst formation and reduced renal size may be observed in both conditions. Differentiation between nephronophthisis and renal dysplasia is, however, made by renal histology (5). The characteristic histological features which distinguish nephronophthisis from other nephropathies with primarily chronic tubulointerstitial nephritis are the changes observed in the tubular basement membrane. Tubular basement membrane of variable thickness including multi-layering and extreme attenuation were suggestive of nephronophthisis, since these findings were not observed in patients with other chronic tubulointerstitial disorders (8). The presence of progressive renal failure, diffuse interstitial fibrosis, intra-glomerular and peri-glomerular fibrosis accompanied with basement membrane of variable thickness in this patient were highly suggestive of nephronophthisis. There was no effective prophylaxis or treatment to nephronophthisis. Dialysis and renal transplantation were the treatments of choice for ESRD in nephronophthisis patients. In some studies, vasopressin antagonist had been reported to have possible therapeutic effect (6).

The association between EvC syndrome and nephronophthisis has not been well described before. However, nephronophthisis has been occasionally reported in another disease, Jeune’s asphyxiating thoracic dystrophy (ATD) (9). ATD and EvC syndrome have been taken as part of a disease spectrum rather than separate disease entities because ATD shares some overlapping features including narrow thoracic cage and short-limbed dwarfism with EvC syndrome (10). However, in patients with EvC syndrome, dental and heart defects are more frequently found while pulmonary insufficiency is less common (5). Renal anomalies included agenesis, dysplasia, congenital megaureter and nephrocalcinosis were observed in around 20% of patients with EvC syndrome (5, 11). Similar presentation and nephronophthisis were reported in patients with ATD (5). This case report demonstrates that patients with EvC syndrome may develop renal failure secondary to nephronophthisis. The association further supports the hypothesis that ATD and EvC syndrome are related and represent a spectrum of disease. In addition, this is the first reported case of EvC syndrome-associated nephronophthisis treated successfully by HLA-B mismatched kidney transplantation. Continued surveillance of patients with EvC syndrome is essential for the early detection of renal failure and proper counseling.

References