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SHORT COMMUNICATION

Presence of CAKUT: A predictor of difficult-to-control nephrotic syndrome

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KEYWORDS
congenital anomalies of the kidney and urinary tract;
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Summary Nephrotic syndrome and congenital anomalies of the kidney and urinary tract are independent causes of renal dysfunction in children. The simultaneous occurrence of these infrequent conditions is rarely reported. Whether the occurrence of one influences the outcome of the other is also not known. Defects of specific genes have been hypothesized for the occurrence of a few of these anomalies. It is possible that yet-to-be-identified genetic defects are contributing to both of these conditions in specific individuals. We report a series of 10 patients with congenital anomalies of the kidney and urinary tract and nephrotic syndrome that had a difficult course.

腎病綜合症、泌尿道先天性畸型(CAKUT)皆是兒童腎臟功能障礙的獨立成因，然而文獻鮮有對兩者的合併發生作出記載，至今醫學界亦未明瞭兩者間的相互關係；仍然有待確認的，是基因缺損在這兩種病症中的可能角色。以下我們所報告的10宗的系列案例，均同時呈現CAKUT與腎病綜合症，且在臨床上屬於難治性的個案。

Introduction

Nephrotic syndrome is an uncommon chronic disorder in childhood with an annual incidence ranging from 2 to 7 per 100,000 children and a prevalence rate of 12—16 cases per 100,000 individuals.[1,2] Most patients with idiopathic nephrotic syndrome respond to treatment with oral steroids and have a favorable outcome. About 10% of cases are resistant to steroid therapy and pose difficulty in management.[3] Nephrotic syndrome is a clinically heterogeneous disease with different histological variants and genetic determinants. Some genes coding for the structural proteins of the slit diaphragm and podocytes of the glomerular basement membrane have been identified in patients with a steroid-resistant disease course.[4] The genetics of steroid sensitive disease are less clearly defined.[5]

Congenital anomalies of the kidney and urinary tract (CAKUT) occur in about 0.5% of all pregnancies. They constitute a wide variety of defects such as ureteropelvic junction obstruction, vesicoureteric reflux, bladder outlet obstruction, primary megaureters, dysplastic, and multicystic or single kidneys. Although the etiology of CAKUT is considered to be multifactorial, many genes have been implicated in its occurrence. *PAX2* (paired box 2) gene was the first specific gene to be identified with CAKUT. Other

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identified genes are *Agtr2* (angiotensin II specific receptor), *BMP4* (bone morphometric protein), *GDNF* (glial derived neurotrophic factor), *EYa1* (eyes absent 1 protein), and *RET* (vitamin A associated protein). Abnormalities of genetic coding in either single or multiple of these factors have been implicated in the occurrence of CAKUT.[6]

However, no single gene defect has explained the occurrence of CAKUT and nephrotic syndrome to date. We only came across a single report by Vats et al[7] of a family with 13q deletion where both of these conditions coexisted.[7] We report here a series of 10 children who presented with nephrotic syndrome who also had an underlying CAKUT.

Materials and methods

This study was conducted retrospectively in the department of pediatrics at Maulana Azad Medical College, Delhi. The study was approved by the institute's ethical committee. Records of all children who presented (between January 2004 and December 2011) with nephrotic syndrome and had an underlying structural abnormality of the kidney were retrieved. Standard definitions of nephrotic syndrome, steroid-dependent, frequently relapsing, infrequently relapsing, and steroid-resistant nephrotic syndrome were used.[8] Nephrotic syndrome was defined as presence of nephrotic range proteinuria (>1 g/m^2/day or 3+ or more on dipstick examination), hypoalbuminemia <2.5 gm/dL, and/or edema. Remission was defined as urine albumin nil or trace (or proteinuria <4 mg/m^2/h) for three consecutive early morning specimens and relapse as urine albumin 3+ or 4+ (or proteinuria >40 mg/m^2/h) for three consecutive early morning specimens. Frequently relapsing nephrotic syndrome was defined as the presence of two or more relapses within 6 months of the initial response, or four or more relapses within any 12-month period. Steroid dependence was defined as two consecutive relapses occurring during steroid treatment, or within 14 days after its cessation. Initial steroid resistance was defined as failure to respond to treatment with oral prednisolone at a dose of 2 mg/kg/day for 4 weeks. Patients who responded initially but failed to respond in subsequent relapses were labeled as having late resistance.

The clinical details, anthropometry, and biochemical investigations at presentation were recorded. The details of all radiological investigations and nuclear scans were noted. The course of nephrotic syndrome and details of immunosuppressive treatment were recorded. Kidney biopsy, if done, was reviewed. The data collected was tabulated in a Excel spreadsheet and analyzed using descriptive statistics.

Results

A total of 10 patients (8 males, 2 female) presented with nephrotic syndrome and an underlying structural abnormality of the kidney and urinary tract. None of these patients had any features of facial dysmorphism or any other structural defects apart from the kidneys. The median (range) age of onset and presentation of nephrotic syndrome were 48 (16—108) months and 72 (17—108) months, respectively. The mean height and weight standard deviation scores [scores at presentation were -1.86 (-3.48 to -0.79) and -0.85 (-1.88 to -1.96)]. The median blood urea and serum creatinine at presentation were 33.5 (18—115) mg/dL and 0.75 (0.5—1.8) mg/dL, respectively. The median albumin and cholesterol values were 1.9 (1.0—2.5) mg/dL and 347 (308—667) mg/dL. The patient details are given in Table 1.

Three (30%) patients were hypertensive at presentation. Of the 10 children, two patients had unilateral pelviureteric junction obstruction (PUJO); two had B/L vesicoureteric reflux; two had single kidneys (each one with horseshoe kidney and crossed fused ectopia); two had dysplastic kidneys (1 unilateral, 1 bilateral). The PUJO was identified on diethylenetriamine pentaacetic acid (DTPA) scan, and reflux was identified on vesico cystouretherogram. The remaining defects were identified on sonography and DTPA scan. The clinical course of nephrotic syndrome was steroid dependent in two patients, frequently relapsing in three, steroid resistant in two, and infrequent relapses in two. One patient experienced only a single episode till last follow-up. The two patients with steroid-resistant disease

Table 1 Details of congenital anomalies of the kidney and urinary tract (CAKUT) and disease course of patients.

Patient no.	Age at presentation (mo)	Gender	Structural abnormality	Disease course
1.	26	M	Lt PUJO	Steroid-dependent NS
2.	60	M	Rt PUJO	Frequently relapsing NS
3.	17	F	B/L Grade IV VUR with duplex system	Infrequent relapser
4.	108	M	Crossed fused ectopia (both kidneys on Rt side)	Steroid-dependent NS
5.	48	M	B/L VUR (Rt Grade II; Lt Grade III)	Frequently relapsing NS
6.	104	M	Horse shoe kidney (renal biopsy minimal change disease)	Steroid-resistant NS
7.	108	M	Small dysplastic Rt kidney; LK normal	Infrequent relapser
8.	72	M	Single kidney (renal biopsy FSGS)	Steroid-resistant NS
9.	48	M	Single kidney	Frequently relapsing NS
10.	97	F	B/L small kidneys (dysplastic)	Single episode

B/L = bilateral, FSGS = focal segmental glomerulosclerosis; LK = left kidney, Lt = left; NS = nephrotic syndrome; PUJO = pelvic—ureteric junction obstruction; Rt = right, VUR = vesicoureteral reflux; RF = right kidney.