Case Report
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CASE REPORTS

TYPE-I DIABETES MELLITUS, NEPHROTIC SYNDROME, AND VUR WITH ACE GENE POLYMORPHISM

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INTRODUCTION

Angiotensin converting enzyme (ACE) is a key enzyme that converts inactive angiotensin I into a vasoactive and aldosterone-stimulating peptide angiotensin II. In some cases, the increase of ACE protein is responsible for the elevation of angiotensin II level. Elevated angiotensin II level makes deleterious effects on renal hemodynamics and induces the expression of other growth factors, leading to glomerulosclerosis[1].

The angiotensin converting enzyme (ACE) gene carries insertion (I) and deletion (D) polymorphism within its intron 16 and the DD-genotype is reportedly related to an increase in the ACE protein expression. Therefore, it has been thought that the DD genotype may link to the ACE-related pathophysiology of renal diseases[1].

D-allele is also implicated in the cause of diabetic nephropathy, myocardial infarction, and vesico-ureteric reflux, as in our patient who had left ventricular dysfunction, vesico-ureteric reflux, and nephrotic range proteinuria.

CASE REPORT

A 15 year old girl with type-1 diabetes mellitus since the age of 4 years, resident of Peshawar, was admitted through outpatient department with complaints of progressive peri-orbital puffiness, pedal edema, dyspnoea, orthopnea and paroxysmal nocturnal dyspnoea since one month, associated with polyuria, nocturnal enuresis, and frequent episodes of dysuria, fever associated with rigors and chills diagnosed and treated as recurrent urinary tract infections, with rest of the systemic inquiry being unremarkable. Her past history was significant for pulmonary Koch's for which she took anti-tuberculous therapy for 9 months three years back and nephrolithiasis also three years back. Family history was also significant as one younger brother was also a type-1 diabetic with similar complaints who died 2 months back because of hypoglycemia. In her drug history she was injecting insulin and taking antibiotics for frequent episodes of urinary tract infections. On examination she was a young girl of short stature with anasarca, dyspnoeic, unable to lie flat, with a pulse of 90/min, BP-130/90 mmHg with no postural drop, respiratory rate of 26/min, JVP was not raised, afebrile, mildly pale, pedal edema till mid calf and weighed 25 kilograms. Eye examination revealed bilateral congenital cataract. Systemic examination revealed bilateral pleural effusion and moderate ascites with rest of the examination being unremarkable.

Differential Diagnosis:

Our initial impression was of nephrotic syndrome secondary to focal segmental glomerulosclerosis (FSGS), membranoproliferative glomerulonephritis (MPGN), minimal change disease (MCD), or diabetic nephropathy.

Investigations:

The patient was investigated with the above disease processes in mind. Her investigations showed a hemoglobin of 11 g/dL, total leukocyte count and platelet count were normal, serum creatinine and serum urea were 2.6 mmol/l and 169 micro mol/l respectively, serum electrolytes and liver function tests were normal, serum albumin was 2.4 mg/dl(normal range 3.5 to 5.5 mg/dl). This hypoalbuminaemia occurred as a feature of nephrotic syndrome. She had elevated serum cholesterol and triglyceride being 9.5 mmol (normal range < 5.2 mmol/L) and 4.2 mmol

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(normal range 0.4-1.62 mmol/L) respectively, anti-nuclear antibody (ANA), hepatitis B and C serology were negative, arterial blood gases showed respiratory alkalosis, urine routine examination showed protein 4+ and active urine sediment, the 24 hour urinary protein was 15 grams, estimated glomerular filtration rate (GFR) was 12.8 ml/min (normal range 90 to 125 ml/min), urine culture and sensitivity showed no growth and pleural fluid was transudative according to the Light's Criteria. Chest x-ray showed cardiomegaly with bilateral pleural effusions (Fig.1) and ultrasound abdomen showed bilateral small kidneys with hydronephrosis, renal stones, and gross hydro-ureters with patent uretero-vesical junction (Fig.2). Echocardiography revealed hypertensive heart disease with severe left ventricular dysfunction, right ventricle, left and right atrium were dilated, ejection fraction of 23%, and minimal pericardial effusion.

In the initial hospital management she was started on diuretics with daily weight monitoring and as the ultrasound showed hydroureters, a micturation cysto urethro graphy (MCUG) was planned to look for vesico-ureteric reflux (VUR) and it showed grade 4 VUR. With the final diagnosis of VUR and nephrotic syndrome we planned to do a renal biopsy to look for the cause of nephrotic syndrome. Unfortunately the biopsy could not be performed as the patient did not give consent. As an alternative we decided to perform polymerase chain reaction (PCR) of angiotensin converting enzyme (ACE) gene polymorphism as the single determinant of her disease, which turned out to be DD ACE gene polymorphism which can be considered to represent the binding thread of all the complications in this patient (Fig.3).

The patient was started on lipid lowering drugs and angiotensin converting enzyme-inhibitor (ACE-I) as the patient was hypertensive, had left ventricular dysfunction and they have a proven role in treatment of nephrotic syndrome, loop and potassium sparing diuretics, and insulin were continued and she was referred to a urologist for surgical management of VUR.

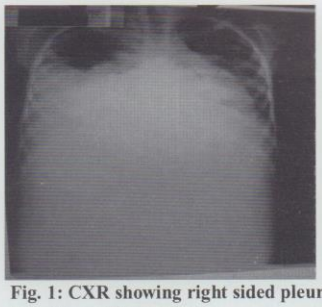

Fig. 1: CXR showing right sided pleural effusion and massive cardiomegaly

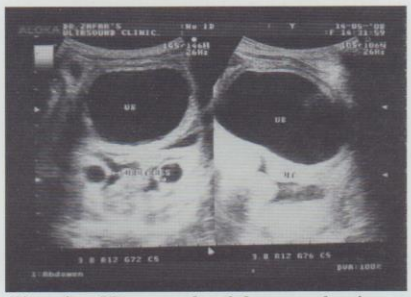

Fig. 2: Ultra-sound abdomen showing gross hydroureters.

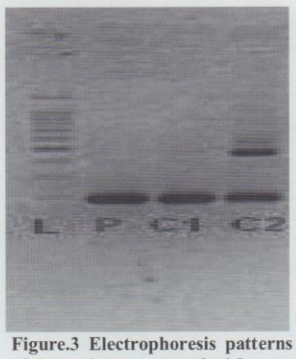

Figure.3 Electrophoresis patterns of PCR products of the patient compared with two controls.

Fig. ACE Genotyping
L= Ladder (100bp)
P=Patients (DD)
C1= Control (DD)
C2= Contril (ID)

DISCUSSION

Our patient had multiple problems i.e. diabetes mellitus, left ventricular hypertrophy, nephrotic syndrome and vesico-ureteric reflux all of which can be explained with DD ACE

gene polymorphism. The angiotensin converting enzyme (ACE) gene carries insertion (I) and deletion (D) polymorphism within its intron 16 and the DD-genotype is reportedly related to an increase in the ACE protein expression. Therefore, it has been thought that the DD genotype may link to the ACE-related pathophysiology of renal diseases. Of the ACE I/D polymorphism impacts on the renal diseases, idiopathic nephrotic syndrome (INS) holds particular attention, especially the focal segmental glomerulosclerosis (FSGS)[1]. The DD genotype has been associated with an increased risk of left ventricular hypertrophy and myocardial infarction[2]. D-allele is also implicated in the cause of diabetic nephropathy, MI and VUR, as our patient had LV dysfunction, VUR, and nephrotic range proteinuria. The pathological presence of the DD genotype leading to renal disease operates at the cellular level. Patients with DD genotype have serum ACE levels and intra-cellular ACE activity twice those of II genotype. Higher ACE activity leads to increased Angiotensin II (AII) levels, which in turn promotes proliferation of mesangial cells and matrix. AII promote expression of growth factors which in turn leads to glomerulosclerosis. In diabetic nephropathy pharmacological blockade of ACE significantly slows down the rate of decline in renal function[3]. Studies show that the D allele of ACE gene is closely related to small congenital kidneys with refluxing ureters in patients with primary VUR, and in accordance with previous reports, this allele is also related to the progression of reflux nephropathy[4] as in our patient her ultrasound abdomen showed bilateral small kidneys whereas in diabetic nephropathy the kidney size is normal or enlarged. The association of vesicoureteric reflux and chronic pyelonephritis is well recognised, and in such cases minimal proteinuria may occur[4]. In another study by Bajpai and associates conducted at All India Institute of Medical Sciences, New Delhi, the D allele was also significantly associated with renal scarring independent of known risk factors such as grade of reflux, age at diagnosis, gender and urinary tract infection[5]. Nevertheless, when heavy proteinuria (>3 g/24 hours) occurs in association with reflux a glomerular lesion should be suspected. Massive proteinuria with nephrotic syndrome has been reported in vesicoureteric reflux. Possibly the association is purely coincidental, but this would seem unlikely. Membranous glomerulonephritis has been produced experimentally by the injection of homologous renal tubular epithelial antigen and tubular epithelial antigen has been demonstrated deposited on the glomeruli in membranous glomerulonephritis. Possibly tubular epithelial antigen is released into the circulation in reflux as a consequence of renal tubular injury. Failure to recognise the antigen as "self" might result in antibody formation. With persistent antigenic stimulation, immune complexes would form, thus providing the mechanism of glomerular injury[6].

CONCLUSION

Why is this ACE GENE Important? Firstly it appears that by using molecular diagnostic techniques it is possible to predict which patient with vesicoureteral reflux will develop progressive renal parenchymal damage. Secondly it is clear that genes are not only the primary factor in determining the onset of disease but also there are genes that determine the clinical course of a disease in a patient. Thirdly treatment of both vesico-ureteric reflux and nephrotic syndrome with ACE-Inhibitors has shown to delay the time of on-set of end stage renal disease.

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