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Impact of common functional polymorphisms in renin angiotensin system genes on the risk of renal parenchymal scarring following childhood urinary tract infection

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Summary

Background
Pathogenesis of renal parenchymal scarring (RPS) after acute pyelonephritis (APN) is unclear. The risk of RPS varies markedly among individuals, suggesting a genetic role.

Objective
To investigate a possible role of common polymorphisms in renin angiotensin system genes in APN-associated RPS in children.

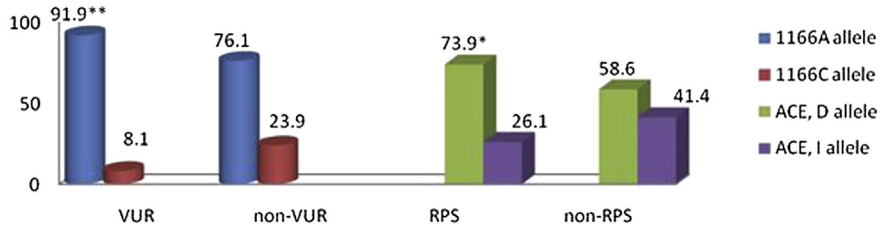
Patients and methods
This study included 104 APN children and 300 controls. APN was diagnosed by urine culture and typical findings on 99Tc-DMSA scans. Voiding cystourethrogram tested the presence of vesicoureteral reflux (VUR). Follow-up DMSA scans were performed 4–6 months later to identify new RPS. Angiotensin converting enzyme gene I/D, angiotensin II receptor type-1 A1166C and angiotensinogen M235T polymorphisms were genotyped.

Results
New RPS developed in 44.2% (46/104) of children with APN. VUR was diagnosed in 35.6% (37/104) of APN cases. RPS developed in 73% of cases of VUR. The D allele of ACE gene I/D polymorphism was significantly more common in APN cases with RPS (73.91%) than non-RPS (58.6%) and controls (54.5%) ($p = 0.021$, $p = 0.002$, respectively). The AGTR-1 A1166C A allele was significantly more common in VUR than the non-reflux children (91.9% versus 76.1%; $p = 0.005$). VUR, in contrast to the D allele (OR 6.1, 95% CI 0.878–19.7; $p = 0.05$), was an independent risk factor for RPS.

Discussion
ACE gene D allele is associated with a twofold increase in RPS risk, which could be a result of a functional effect to increase tissue levels and activity of ACE during APN. However, D allele failed to qualify as an independent risk and its RPS association could be dependent on other co-factors, such as TGFβ1 activation, or the D-allele might link with recently discovered functional polymorphisms at the 5′ end of the ACE gene. Although VUR is an independent risk for RPS, it is not clear whether this is due to exposure of the kidneys to infected urine, or VUR-associated dysplasia. In contrast with published literature, we noted higher rates of RPS and high-grade VUR, suggesting a more aggressive VUR course or local unawareness of APN. Our study has its limitations; the small number of VUR children, and the clinical and ethical difficulties of testing VCUG and DMSA in controls.

Conclusions
ACE gene D allele is associated with, but cannot independently predict, RPS in children. VUR is an independent risk for post-pyelonephritic scarring. AGTR-1 1166A/C polymorphism is associated with occurrence, but not progression, of VUR.

AGTR1 gene 1166A/C allele frequencies in VUR versus non VUR (left) and ACE gene I/D allele in RPS compared to non-RPS (right). **P=0.005 *P=0.021



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Introduction

Urinary tract infection (UTI) is common in childhood, and bacterial invasion of renal parenchyma results in acute pyelonephritis (APN) and renal parenchymal scarring (RPS) [1]. Although bacteria have a role in establishing inflammation, RPS is primarily caused by host responses [2] and individual differences in inflammatory responses (in addition to recurrence of infection, bacterial virulence, timing of antimicrobial therapy, and presence of urinary anomalies) result in diverse parenchymal outcomes [1,2]. Although vesicoureteral reflux (VUR) has been linked to APN, its association with post-infectious RPS is still controversial; RPS occurs in non-refluxing kidneys, and continues after successful correction of VUR [3]. The dilemma of diverse renal outcomes, the questionable association of VUR with RPS, and the fact that components of renal inflammation (mediators, receptors, and adhesion molecules) are proteins whose production is controlled by genes [1], has attracted attention to the possible role of genetic predisposition in RPS.

The renin angiotensin system (RAS), a key regulator of renal homeostasis, has been implicated in hypertension and chronic kidney disease [4]. During kidney inflammation, angiotensin converting enzyme (ACE) and angiotensin II levels are elevated in tubular and interstitial cells. Angiotensin II exerts its pro-inflammatory actions through induction of adhesion molecules, chemokines, and transforming growth factor beta (TGFβ) [5], which increases extracellular matrix protein synthesis leading to tubule-interstitial fibrosis, parenchymal collapse, and eventually glomerulo-tubular sclerosis (typical findings in renal parenchymal scarring) [6]. Components of RAS genes are polymorphic, ACE *gene* I/D (insertion/deletion) polymorphism modulates plasma and tissue activity of ACE [7]. Angiotensinogen M235T (AGT 268 T/C) polymorphism correlates with plasma level of angiotensinogen [8]. Angiotensin II receptor type-1 gene polymorphism A/C 1166 (AGTR-1A1166C) is associated with increased responsiveness to RAS [9].

Although RAS gene polymorphisms have been studied in different adult diseases, there are few studies in children and those addressing the role of polymorphisms in post-infectious RPS in particular, have shown conflicting results [3,10—12] and a robust conclusion for the association of RAS genes with APN and VUR is lacking [13,14]. It remains difficult to ascertain which polymorphism is associated with RPS risk particularly in our populations because of different genetic peculiarities, chromosomal composition, and pattern of mating [13,14]. The purpose of this study was to evaluate the role of common functional polymorphisms of RAS genes as risk factors for RPS in Egyptian children with APN.

Methods and study design

We consecutively enrolled 104 Egyptian children at the time of their first documented APN. Patient recruitment, imaging, and bacteriologic studies were done at Assiut University Children's Hospital (Assiut, Egypt) over a period of 3 years. The study was approved by the ethics committee of Assiut University Hospitals and the Faculty of Medicine and was performed in accordance with the standards laid down in the 1964 Declaration of Helsinki and its later amendments. Written informed consent was obtained from the guardian of each child. Urine was obtained by catheter or clean-catch for urinalysis and culture.

Inclusion criteria were urinary symptoms and/or fever ≥38 °C, pyuria and/or bacteruria on urine analysis, culture-proven infection, and, at final enrollment, DMSA-confirmed APN [15]. Exclusion criteria were previous documented UTI, urinary tract operation or indwelling catheter; chronic infections or diabetes; and urinary anomalies other than VUR.

Control group

The controls comprised 300 healthy volunteers who were enrolled randomly as they attended an outpatient clinic or were admitted for elective surgery. They had negative history of UTI and normal renal ultrasound scans.

Imaging study

Abdominal ultrasound was done within 2 days of final enrollment. DMSA scans were performed to assess the presence of acute pyelonephritis (decreased uptake of the radioactive isotope tracer was differentiated by the state of renal contour; preserved contours denoted APN and loss of the contour or cortical thinning were considered renal scars [15]) within the first 72 h of presentation and were interpreted by radiologists blinded to the patients' characteristics. Follow-up scans were obtained 4—6 months later to identify the presence of RPS. Voiding cystourethrogram (VCUG) was done, only after a negative follow-up urine culture, to test the presence of VUR.

Genetic polymorphism

Venous blood was collected in EDTA-coated tubes. Genetic work was done at the Center for Children and Adolescent Health, University of Heidelberg, Germany. Genomic DNA was extracted from peripheral blood leukocytes by standard methods. Specific oligonucleotide primers were designed based on published genomic sequences [16]. I/D polymorphism of the ACE gene was determined according to previously published methods [17]; where the I allele and D allele produce 490-bp and 190-bp polymerase chain reaction (PCR) products, respectively, and the heterozygote ID genotype produces two bands of both products. The PCR products were separated and visualized using 2% agarose gel electrophoresis with nucleic acid gel stain GelRed and UV lamp. Children having the DD allele were genotyped again using insertion-specific primer PCR yielding a 335-bp product to avoid any possibility that a heterozygote ID allele was mistyped as DD. Genotyping was performed by restriction fragment length polymorphism (RFLP) analysis for AGTR-1 A1166C [18] using the Bsu RI restriction enzyme (Fermentas). For AGT M235T polymorphisms, we used tetra-primer amplification of refractory mutation screening polymerase chain reaction (ARMS-PCR) [19].

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