Effect of ACE Gene Polymorphism on Response to steroid therapy In children with nephrotic syndrome

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Abstract

This study is an attempt to assess the possible effect of ACE Insertion/Deletion polymorphism on response to steroid in Egyptian children with idiopathic nephrotic syndrome.

To achieve this goal 53 patients diagnosed as idiopathic nephritic syndrome were studied. Median age at onset of the disease was 4 years (range, 1.5–13.0), visiting nephrology clinic, Pediatric Hospital of Cairo University with regular follow up period for minimum of 6 months, including 36 males (67.9%) and 17 females (32.1%). All patients received in the initial episode of nephrotic syndrome prednisolone in a dosage of 2 mg/kg/day in 3 divided doses for 4 weeks(6 weeks in the case of steroid non responsiveness), followed by a single 2 mg/kg dosage in the morning of every other day for 4 weeks. After that the alternate-day treatment continued but the dosage was reduced by 12.5% every 2 weeks for the following 3-4 months.

Key Words :

Angiotensinogen - Blood urea nitrogen. – CyclosporineA .

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The Candidate

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INTRODUCTION

It is a great challenge for physicians and pharmacologists that different patients respond in different ways to the same medication. These differences are often greater among members of a population than they are within the same person at different times **(Vesell, 1989)**. The existence of large population differences with small intra-patient variability is consistent with inheritance as a determinant of drug response; it is estimated that genetics can account for 20 to 95 percent of variability in drug disposition and effects **(Kalow et al., 1998)**. Although many nongenetic factors influence the effects of medications, including age, organ function, concomitant therapy, drug interactions, and the nature of the disease, there are now numerous examples of cases in which inter-individual differences in drug response are due to sequence variants in genes encoding drug-metabolizing enzymes, drug transporters, or drug targets **(Evans & Jonson, 2001)**. Unlike other factors influencing drug response, inherited determinants generally remain stable throughout a person's lifetime **(Evans & Mcleod, 2003)**.

Nephrotic syndrome (NS) is one of the commonest renal problem encountered in children. It is difficult to predict at onset, the clinical course in terms of steroid responsiveness or resistance **(Patil et al., 2005)**.

There is considerable percentage of patients with NS who fail to respond to steroid therapy. In *the Hemodialysis and Transplantation Center and Pediatrics, Istanbul, Turkey,* of the 114 patients who received steroid therapy, 30 children had an initial response, 25 children had

infrequent relapse, 19 had frequent relapse, 25 had steroid dependence and 15 children had steroid resistance **(Gulati et al., 1994).**

Steroid responsiveness appears to be the single most important clinical parameter in differentiating patients of primary NS and is of even greater significance than the histological features on initial biopsy. It is however, difficult to predict at onset the course of the disease in a particular child in terms of steroid responsiveness or steroid resistance **(Patil et al., 2005)**.

Various genetic markers have been studied to predict susceptibility and course of NS. Increased activity of angiotensin-II (Ang II) alters variety of growth factors and has been shown to have detrimental effect on renal disease progression **(Patil et al., 2005)**. The angiotensin converting enzyme (ACE) gene carries insertion (I) and deletion (D) polymorphism within its intron 16. The presence of D-allele in the ACE gene has been reported as a probable genetic risk factor for idiopathic nephritic syndrome (INS). The D-allele may be related to poor responsiveness to steroid therapy **(Sasongko et al., 2005).**

The D allele has a dominant effect and is associated with higher plasma (ACE) and (Ang II) levels. (Ang II) may promote proliferation of mesangial cells and matrix, leading to subsequent glomerulosclerosis. Furthermore, (Ang II) promotes alterations in renal hemodynamics that can contribute to increased intraglomerular pressure, glomerular volume and hyperfiltration. Accordingly, the effects of (Ang II) may provide a possible mechanism by which the DD genotype of the ACE gene contributes to a risk factor in renal damage or disease progression in renal disorders **(Tsai et al., 2006)**.

ACE gene I/D polymorphism has been evaluated in NS, especially in small groups of focal segmental glomerulosclerosis (FSGS) patients, with conflicting results on histology, treatment responses and disease progression **(Serdaroglu et al., 2005)**.

Some studies proved the relation between the ACE gene polymorphism and the response to steroid therapy in childhood patients with INS while other studies could not prove this relation.

This study is an attempt to determine the effect of ACE gene polymorphism on the response to steroid therapy in Egyptian children with INS. This work is aiming that in the future, the patient with INS may either receive a steroid therapy or may be subjected to an alternative line of management according to his genotype.

Aim of work

- To study the Pharmacogenetics in children with (INS) through assessing the effect of ACE gene polymorphism on the response to steroid therapy.

- To study the prevalence of the three ACE gene insertion/deletion polymorphisms in this group of patients.

Pharmacogenetics and Pharmacogenomics

Introduction:

Pharmacogenomics involves the application of genomics technologies such as gene sequencing, statistical genetics and gene expression analysis to drugs in clinical development and trials. Since many diseases develop as a result of a network of genes failing to perform correctly, pharmacogenomics can identify the genes or loci which are involved in determining the responsiveness to a given drug. In this way, genetic characterization of patient populations is becoming an integral part of the drug discovery and development process. Pharmacogenomics may aim to capitalize on these new molecular insights to discover new therapeutic targets and interventions and to elucidate the constellation of genes that determine the efficacy and toxicity of specific medications (**EMILIEN et al., 2000)**.

The field of pharmacogenomics began with a focus on drug metabolism, **(Ingelman-sundberg et al., 1999)**. But in recent years; there has been an increasing focus on genetic polymorphisms in drug targets, with an interest in defining their impact on drug efficacy and/or toxicity. A drug target is defined as the direct protein target of a drug (e.g., a receptor or enzyme), proteins involved in the pharmacologic response (e.g., signal transduction proteins or downstream proteins), or proteins associated with disease risk or pathogenesis that is altered by the drug. The broad objective of drug target pharmacogenomics research is to identify the inherited basis for interindividual variability in drug response and toxicity, particularly when this variability is not explained by

differences in drug concentration (pharmacokinetics) **(Evans & Johnson, 2001)**. (Table-1) shows some examples that are already identified in both pharmacokinetic and pharmacodynamic aspects.

Pharmacogenomics beyond monogenic traits:

Because most drug effects are determined by the interplay of several gene products that influence the pharmacokinetics and pharmacodynamics of medications, including inherited differences in drug targets (e.g., receptors) and drug disposition (e.g., metabolizing enzymes and transporters), polygenic determinants of drug effects have become increasingly important in pharmacogenomics **(Evans & McLeod, 2003)**.

Recent studies with warfarin are an excellent example **(**Figure-1). Previous work had identified variable metabolism by CYP2C9 as a major contributor to variable responses to the drug. In 2004, coding-region mutations in VKORC1, encoding a subunit of the vitamin K epoxide reductase complex (the pharmacologic target for the drug), were found to cause a rare syndrome of warfarin resistance. Subsequently, common variants in VKORC1 have been found to account for a much greater fraction of variability in warfarin response (21%) than do variants in CYP2C9 (6%) (38). The CYP2C9 variants are in the coding region and alter enzyme activity, whereas the VKORC1 variants are noncoding and are thought to alter expression of the protein **(Roden et al., 2006)**.