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NR3C1 gene polymorphisms in adult patients with nephrotic syndrome

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ABSTRACT

Introduction: Glucocorticoids therapy is a selective treatment strategy for cases with nephrotic syndrome (NS).

Objectives: Due to the lack of positive response of all patients to therapy and the dependency of biological effects of glucocorticoids on its receptors (GR), here, the association of the NR3C1 gene (N363S, BclI, GR-9 β , and ER22/23EK) polymorphisms with the response to glucocorticoids was investigated in patients with NS.

Patients and Methods: In this study, 55 patients with primary NS including 29 steroid-responder (SS) and 26 steroid-resistant (SR) and also 30 healthy individuals were recruited. The polymorphisms of NR3C1 gene were studied by PCR and sequencing of the amplified fragments and the results were compared between the groups.

Results: A3669 SNP was observed in 8.7% (n=2) of patients with SRNS and 6.3% (n=2) of responders (P=0.560). In 40.7% of steroid-responsive patients (n=11) and 21.4% of patients with SRNS (n=6), BclI polymorphism was detected that was not statistically significant (P=0.098). The N363S and ER22/23EK polymorphisms were not detected in the studied groups. No significant differences were observed between the frequency of the studied polymorphisms between the different subtypes of NS; focal and segmental glomerulosclerosis (FSGS), membranous glomerulonephritis (MGN), and control group.

Conclusion: The NR3C1 gene N363S, BclI, GR-9 β , and ER22/23EK polymorphisms do not affect the steroid responsiveness and the pathogenesis of NS in Azari adult patients with primary NS. Other polymorphisms within NR3C1 gene need to be explored in large cohorts.

Implication for health policy/practice/research/medical education:

NR3C1 gene polymorphisms are not significantly associated with the response to glucocorticoids in adult Azari patients with primary nephrotic syndrome.

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Introduction

Idiopathic nephrotic syndrome (NS) is a chronic glomerular disease described by proteinuria, hypercholesterolemia, peripheral edema, and hypoalbuminemia (1).

Glucocorticoids as the first line of drugs for NS are used to treat a broad spectrum of diseases due to their anti-inflammatory and immunomodulatory effects (2). Steroid-sensitive NS (SSNS) and steroid-resistant NS (SRNS) are two clinical classifications of the disease based on the

responsiveness of the patients to glucocorticoids (3). SRNS accounts for 20% of NS cases in childhood, and about 40% of adults with NS fetch up end-stage renal disease (ESRD) (4,5).

It has been documented that genetic abnormalities could interfere with the expression and function of proteins present in podocytes and alter their reaction to the prescribed medicine (6). Moreover, a genetic-based overlook in NS has revealed new avenue in the

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understanding of the disease as well as the routine approaches in the current clinical management over the past two decades. This explains the remaining challenge in the treatment of NS even with the implementation novel drug classes.

Despite the extensive use of glucocorticoids in the treatment of NS, the development of resistance is a major limitation (7). From the genetic point of view, the analysis of glucocorticoid receptor (GR) gene, its mutations, and polymorphisms has grabbed great attention in recent years. The GR as a cytoplasmic receptor is activated after the binding of steroids and stimulates the transcription of gene classes that hamper inflammatory cytokines and enhance anti-inflammatory mediators (7). *NR3C1* (nuclear receptor superfamily 3, group C, member 1) gene encodes the GR and thus the changes in this gene might affect the transcription activity of GR (8).

A surrogate splicing pathway can result in the generation of GR protein isoforms. The GR- α is the more abundant formed isoform while GR- β is the inactive type and exhibit dominant negative regulatory effects on GR- α . Changes in the expression level of GR can influence glucocorticoids-sensitivity in NS patients. Augmented expression of the mature GR- β protein which is in association with GR-9 β polymorphism has been involved in the pathogenesis of steroid resistance in different diseases (9). An enhanced expression of GR- β in NS patients has been observed in peripheral cells of patients with SRNS (10), whereas the GR- α isoform demonstrates a positive steroid response (11).

Objectives

In the current study, four SNPs (single nucleotide polymorphisms) of the *NR3C1* gene (N363S, BclI, GR-9 β , and ER22/23EK) were genotyped in a group of adult cases with NS to investigate the association between the clinico-pathological manifestations and the genotypes of the disease.

Patients and Methods

Study design

This cross-sectional study enrolled 55 patients with primary NS from Imamreza hospital of Tabriz, Iran. The age range between 18 to 60 from both gender (male/female) and having primary NS were the inclusion criteria for patients; cases with secondary NS caused by viral infections [cytomegalovirus (CMV), hepatitis B virus (HBV), and hepatitis C virus (HCV), and HIV] and autoimmune systemic lupus erythematosus (SLE) were excluded. Histopathology of patients was determined from the kidney biopsy findings. Additionally, 30 healthy volunteers were enrolled as controls; individuals with normal serum creatinine and urine analysis and matched-gender and -age with the cases. The demographic and clinical characteristics of patients were recorded.

Genotyping

Blood samples were taken from all subjects in normal and non-fasting condition and kept in CBC tubes at -20°C. Genomic DNA was extracted from whole blood samples (2 mL) and four variants in the *NR3C1* gene including A3669G, ER22/23EK (rs6189/6190), N363S (rs6195), and BclI (rs41423247) polymorphisms were identified by PCR using the designed primers (Table 1). Then, the direct sequencing of the amplified fragments were performed.

Statistical analysis

For variables with a skewed distribution, medians with interquartile ranges were used, while continuous variables with a normal distribution were expressed as means \pm SD (standard deviations). Categorical variables were presented as percentages. Analyses of the variances between qualitative variables were completed with Fisher's exact or Pearson's χ^2 tests. The IBM SPSS Statistics package v. 22 (IBM Corporation, NY, USA) was used for statistical analysis. In all tests, $P < 0.05$ was considered as a significance level.

Results

Fifty-five cases with primary NS were included in this study. Based on the patients' response to steroid therapy (1 mg/kg/d) for 8 weeks, they were divided into two groups, (i) responsive (n=29), and (ii) resistant ones (n=26). Complete or partial responsiveness was defined as excreting proteinuria (<1000 mg/dL) and SRNS was defined as having >1000 mg/dL proteinuria for at least three consecutive days after 8 weeks glucocorticoids therapy. SRNS patients failed to achieve complete remission. Moreover, based on the histopathology and clinical results, 32 patients were diagnosed as MGN and 23 patients were diagnosed as FSGS.

Individuals in NS and control groups were matched regarding gender, age, and BMI ($P > 1.57$). No statistically significant differences in age, BMI, triglyceride, and cholesterol levels were seen between the responsive and SRNS groups and also between MGN and FSGS groups ($P \geq 0.051$). However, 24 hours urine proteinuria was

Table 1. The primer sequences used in the present study

Polymorphisms	Forward/ Reverse	Primers sequences
rs41423247 (<i>BclI</i>)	F	TCTGGAGGACAGATGTACCA
	R	CTTGCAAGAACATTTGAACGTA
rs6195 (<i>N363S</i>)	F	TCTGGAGGACAGATGTACCA
	R	CTTGCAAGAACATTTGAACGTA
rs6189/rs6190 (ER22/23EK)	F	AATGTGGCATGCTGAATGGG
	R	ACCCAGAAGAAAACCTCCAAATCC
rs6198 (A3669G)	F	TTCCAGTTTCACCTAAGTCTCAT
	R	TGATGTTTCTCCATATTGGCATTG

Table 2. Demographic characteristics of the studied cases

Characteristics	NS	MGN	FSGS	P value
No.	55	32	23	
Male/Female	35/20	21/11	14/9	0.645
Age (y)	42.68 ± 16	43.69 ± 14.742	41.14 ± 18.456	0.581
Weight (kg)	77.16 ± 14.8	76.55 ± 15.858	78.18 ± 13.368	0.708
Height (cm)	169.1 ± 24.1	165.23 ± 29	175.58 ± 10.04	0.143
BMI (kg/m ²)	26.10 ± 3.9	26.61 ± 4.33	25.27 ± 3.14	0.250
Disease length (month)	10 (4.25-36)	7 (71)	24 (239)	0.107 ^a
GFR (mL/min/1.73 m ²)	75.2 ± 32.1	80.81 ± 20.01	67.90 ± 30.2	0.180
24h urine proteinuria(mg/24 h)	2539.8 (14980)	3556.8 (14915)	409 (7710)	0.090 ^a
24h urine creatinine (mg/24 h)	1040 (1819.1)	1040 (1270)	983.5(1814)	0.664 ^a
Creatinine (mg/dL)	1.33 ± 0.6	1.16 ± 0.65	1.54 ± 0.5	0.139
Urea (mg/dL)	37.5 (127)	34.5 (120)	39 (124)	0.231 ^a
Cholesterol (mg/dL)	235.9 ± 101	264.25 ± 138	198.25 ± 46	0.094
Triglyceride (mg/dL)	183 (1771)	202.5 (1749)	121 (332)	0.051 ^a
WBC (1000/mm ³)	8.47 ± 3.4	8.05 ± 2.46	9.07 ± 4	0.440
Albumin (g/dL)	2.89 ± 0.94	2.85 ± 0.90	2.93 ± 1.07	0.881
Uric acid (mg/dL)	6.26 ± 1.41	6.14 ± 1.31	6.38 ± 1.54	0.661

Data are presented as Mean ± SD or Median (range). NS: Nephrotic syndrome, MGN: Membranous glomerulonephritis, FSGS: Focal segmental glomerulosclerosis.

^a P values indicate comparison between groups (Mann-Whitney *t* test).

significantly different between the steroid responders (166 [20-600]) and resistant groups (3500 [1003-15000], $P < 0.001$). Clinical parameters regarding kidney function including serum levels of creatinine, glomerular filtration rate (GFR), 24 h urine creatinine, uric acid, urea, and albumin were not significant between the subtypes of NS patients ($P \geq 0.090$). Table 2 summarizes the demographic and clinical characteristics of cases.

Twenty-nine responsive patients (52.7%) and 26 patients with SRNS (52.7%) had wild types of ER22/23EK and N363S polymorphisms. A3669 SNP was observed in 8.7% ($n = 2$) of patients with SRNS and 6.3% ($n = 2$) of responders ($P = 0.560$). In 40.7% of steroid responsive patients ($n = 11$) and 21.4% of patients with SRNS ($n = 6$), BcII polymorphism was detected that was not statistically significant ($P = 0.098$).

Based on the results of gene sequencing in different patients and control groups, ER22/23EK polymorphism was observed in one healthy individual (5%), whereas none of the subjects in the NS group showed this polymorphism. On the other hand, GR-9 β polymorphism (A3669) was found in a total of seven subjects (9.3%); three subjects in the control group (15%) and four patients with NS (7.3%), all of which were in MGN group (12.5%) (Table 3).

BcII polymorphism was observed in 34.7% of all participants ($n = 26$); 17 patients with NS (30.9%) and nine subjects in the control group (45%). Seven patients in MGN group (21.9%) had BcII polymorphism. None of the studied NR3C1 gene polymorphisms (ER22/23EK, GR-9 β , and N363S) were observed in the FSGS group,

except for BcII; 43.5% of FSGS patients ($n = 10$) had BcII polymorphism. N363S polymorphism did not observe in any of participants (Table 3).

Discussion

The exact pathophysiology of NS remains obscure despite extensive related investigations. Identification of the causative or genetic modulators involved in glucocorticoids response and the subsequent personalized therapy will improve the treatment strategy and hamper the amount of received drugs, which will reduce both toxicity and health costs. The results of this study and the preceding researches give us clues about the potential pharmacogenetic factors in glucocorticoids response in NS patients, while still not enough to be utilized in clinical practice.

Table 3. The results of the polymorphisms of NR3C1 gene

Groups	Polymorphisms			
	ER22/23EK	A3669	N363S	BC11
No. (%)	1 (1.3%)	7 (9.3%)	0 (0%)	26 (34.7%)
Healthy controls (%)	1 (5%)	3 (15%)	0 (0%)	9 (45%)
P value ^a	0.267	0.173	-	0.192
NS (%)	0 (0%)	4 (7.3%)	0 (0%)	17 (30.9%)
MGN (%)	0 (0%)	4 (12.5%)	0 (0%)	7 (21.9%)
FSGS (%)	0 (0%)	0 (0%)	0 (0%)	10 (43.5%)
P value ^b	-	0.105	-	0.069
Male/female	0/1	2/5	0/0	18/7

^a Control versus NS; ^b MGN versus FSGS.

The polymorphic variants have been reported from several molecules in the renal glomerular cells of NS patients and also in vivo models of proteinuria proposing the precipitation genetic components in the development of NS (12,13). In addition, the role of genetics in the metabolism of glucocorticoids as the mainstay pharmacological treatment of NS is of great interest. In the current study, we genotyped 4 SNPs from the NR3C1 gene in blood samples of INS patients from North West of Iran.

The NR3C1 gene which contains eight exons is located on chromosome 5q31.3 (14). The variations in response to glucocorticoids in NS patients are, at least, partially attributed to the polymorphisms found in NR3C1 gene, which can affect the downstream gene expression pathway (15). Some identified SNPs including ER22/23EK (rs6189/rs6190), TthIII (rs10052957), and GR-9 β (rs6198) have been linked with hampered sensitivity to exogenous/endogenous glucocorticoids, whereas an enhanced sensitivity has been observed in SNPs BclI (rs41423247) and N363S (rs6195) (15,16). An AAT>AGT nucleotide conversion at position 1220 in exon 2, which leads to a change from asparagine to serine in codon 363 is related to N363S SNP (17), while GR-9 β polymorphism results in the substitution of ATTTA sequence to GTTTA and is located the 3'-untranslated site of exon 9 β (18). The alterations of amino acid sequences in the N-terminal domain in codons 22 and 23 that converts glutamic acid-arginine (E-R) to glutamic acid-lysine (E-K) occur during the ER22/23EK polymorphism (19) and conversion of C>G nucleotides in exon 2 is connected with BclI polymorphism (20). Only a scanty number of studies have investigated the role of these SNPs on the response of NS patients to exogenous glucocorticoids. The distribution of BclI polymorphism has been evaluated in 118 NS patients with initial response to glucocorticoids and 136 healthy volunteers in which a higher sensitivity was observed in the GTA haplotype in both early and late responders to prednisolone (21). Another group also examined the BclI polymorphism in 190 Korean pediatric patients with NS. However, no connection with this SNP and initial glucocorticoids responsiveness and pathological findings in the kidneys was reported (22). Likewise, we could not find any significant association between the glucocorticoids responsiveness and the NR3C1 BclI polymorphism in the studied groups. Moreover, no variant allele regarding N363S and ER22/23EK polymorphisms was detected in these patients (22). A recent study has investigated BclI polymorphism through a cohort of 113 NS children. It was shown that a higher steroid dependency was found in carriers of GR-9 β +TthIII mutated-haplotype (13).

The results of a study in 138 Chinese children with steroid sensitive and resistant NS whose NR3C1 gene was completely sequenced showed no substantial correlation between the analyzed SNPs and steroid response (12). Similar to this result, we could not find a significant association between the N363S, GR-9 β , and ER22/23EK

polymorphisms and responsiveness to the glucocorticoids therapy and kidney pathological findings in adult patients with primary NS. However, results of Liu et al indicated that NR3C1 rs6196, rs258751, rs10052957, and their haplotypes significantly were associated with the response to GCs in adult cases with PNS. The carriers of rs6196 G allele had a reduced risk of SRNS, while the carriers of the A allele rs258751 (at exon 8) had a decreased risk of SRNS (23).

Conclusion

The NR3C1 gene N363S, BclI, GR-9 β , and ER22/23EK polymorphisms do not affect the steroid responsiveness and the pathogenesis of NS in Azari adult patients with primary NS. Other polymorphisms within NR3C1 gene need to be explored in large cohorts.

Limitations of the study

The limitation of this study was small sample size. It is suggested to study the other SNPs of the NR3C1 rather than the common studied polymorphisms involved in SRNS.

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Conflicts of interest

The authors declare that they have no competing interests.

Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki. The present study was approved by the Ethics Committee of Tabriz University of Medical Sciences, Tabriz, Iran (IR.TBZMED.REC. 1396.636).

All individuals agreed to participate in this study by signing a written informed consent. This article was extracted from the residential thesis of Amirhasan Khakpour (Thesis #58040). The authors also completely have observed the ethical issues including data fabrication, falsification, plagiarism, double publication misconduct, or submission and redundancy.

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