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Multidrug Resistance-1 Gene Polymorphisms in Steroid Resistance Nephrotic Syndrome with Different Pathology

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Abstract MDR-1 expression in lymphocytes has been reported to be negatively correlated with the response to prednisone in children with nephrotic syndrome (NS). The aim of this study was to evaluate if MDR-1 gene polymorphisms are different according to pathological type of steroid resistant NS or not. We studied 15 cases with SRNS; 11 cases with focal segmental glomerulosclerosis (FSGS) and 4 cases with mesangioproliferative glomerulonepheritis. All cases were tested for 1 (MDR-1) genetic polymorphisms [C1236T, G2677T (A) and C3435T] polymorphisms; this was done by PCR-based restriction fragment length polymorphism (RFLP). By comparing these polymorphisms between FSGS cases versus mesangioproliferative glomerulonepheritis cases we didn't find any significant difference in either genotypes or alleles. Thus we concluded that there is no relation between pathological type of SRNS and MDR-1 gene polymorphism in the three tested sites [C1236T, G2677T/A, C3435T].

Keywords: *MDR-1 gene, FSGS, steroid resistant, nephrotic syndrome, children*

1. Introduction

Patients with steroid resistance nephrotic syndrome (SRNS) pose the most difficult therapeutic challenge. The reasons for the steroid resistance in treating nephrotic syndrome (NS) could be a change in the histopathologic pattern from a minimal-change disease to mesangial nephropathy or focal segmental glomerulosclerosis [1], most cases of primary FSGS are idiopathic, although 15% to 20% are familial. FSGS is classically described as the sclerotic involvement of only parts of less than 50% of the glomeruli on renal biopsy. FSGS has a worse response to treatment and poorer prognosis compared with minimal change disease and membranous glomerulopathy. Factors associated with a poor prognosis include African American ethnicity, abnormal renal function, and steroid-resistant heavy proteinuria [2].

MDR-1 expression in lymphocytes has been reported to be negatively correlated with the response to prednisone, cyclophosphamide and cyclosporine A in children with NS [3].

The aim of this study was to evaluate if MDR-1 gene polymorphisms are different according to pathological type of SRNS or not?

2 Subjects and Methods

This study was carried out at the Pediatrics and Medical Biochemistry Departments; Faculty of Medicine, Zagazig University. The research protocol was approved by the Zagazig University ethical committee.

All children's parents gave their informed consent prior to their inclusion in the study. 15 Patients with steroid resistant NS were included if fulfilling the following criteria; Nephrotic range proteinuria > 1000mg/m^2 per day, Serum albumin level <2.5g/dl, Age >1year, Absence of secondary causes of nephrotic syndrome, Duration of follow up ≥ 6 months from the time of diagnosis and resistant to steroid therapy of 60 mg/m ^{2}/ day for 4 months followed by 3 pulse methylprednisilone 30mg/kg.

Renal biopsy was done to these 15 children and revealed 11 cases of FSGS they were [6 males and 5 females and mean age was 4.4±1 years], and 4 cases were mesangioproliferative type [2 males and 2 females and mean age was 4±1.3 years].

Detection of multidrug resistance gene-1 (MDR-1) genetic polymorphisms [C1236T, G2677T (A) and C3435T] polymorphisms was done by PCR-based restriction fragment length polymorphism (RFLP) as described by Cascorbi I, et al [4].

2.1. Statistical Analysis

The obtained data were statistically analyzed using SPSS version 17.0. Comparison of categorical data were compared using chi-square test. Odds ratio and confidence interval were used. P value < 0.05 was considered statistically significant.

3. Results

Table 1. Relation of genotypes and alleles of MDR-1 gene polymorphisms to the pathological findings in steroid resistant patients

			Pathology				X^2	OR	Confidence Interval	P
			Mesangioproliferative (n=4)		FSGS (n=11)					
			No	%	No	%				
MDR1 C3435T	Genotypes	CC	-	-	3	27.3				
		CT	2	50.0	5	45.4	1.1	1.2	0.9 – 2.2	0.3
		TT	2	50.0	3	27.3	1.6	1.1	0.8 – 3.4	0.21
	Alleles	C allele	2	25.0	11	50.0				
		T allele	6	75.0	11	50.0	1.5	0.33	0.06 – 2.0	0.22
MDR1 G2677T/A	Genotypes	GG	-	-	2	18.2				
		GT	2	50.0	2	18.2	1.5	2.0	0.8 – 5.3	0.2
		GA	2	50.0	3	27.3	1.1	1.1	0.8 – 3.4	0.29
		TT	-	-	3	27.3	NA	NA	NA	NA
		AA	-	-	1	9.1	NA	NA	NA	NA
		GT+ GA	4	100.0	5	45.4				
		TT+ AA	-	-	4	36.4	2.6	0.6	0.3 - 1.0	0.11
	Alleles	G allele	4	50.0	9	40.9				
		T allele	2	25.0	8	36.4	0.34	0.9	0.5 – 1.4	0.56
		A allele	2	25.0	5	22.7				
MDR1 C1236T	Genotypes	TT	1	25.0	3	27.3				
		TC	2	50.0	7	63.6	0.01	1.1	0.05 – 1.8	0.9
		CC	1	25.0	1	9.1				
	Alleles	T allele	4	50.0	11	50.0				
		C allele	4	50.0	11	50.0	0.38	0.5	0.3 – 6.7	0.54

By comparing both groups there was no significant differences between patients with mesangioproliferative and FSGS regarding MDR1 [C3435T, MDR1 G2677T/A and MDR1 C1236T] genotypes and alleles.

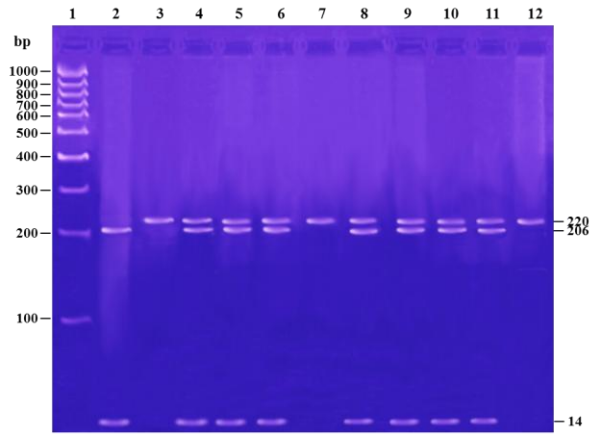

Figure 1. MDR G2677A genotyping by (PCR–RFLP). Representative agarose gel electrophoresis Marker containing (100 bp); wild G allele→ 220 bp; mutant A allele→ 206+ 14 bp in child with FSGS group

4 Discussion

There are many factors that modulate nephrotic syndrome response to pharmacological interventions, such as the expression of P-glycoprotein (P-gp), a product of multidrug resistance gene-1 (MDR-1) gene [5,6].

In our previous study in 2011 we found a significant increase in *MDR1* gene expression on lymphocytes in pediatric patients with NS in comparison with the control group both in disease activity an remission These markers were also significantly higher in activity than in remission. MDR1 gene expression was significantly elevated in SRNS patients (particularly relapse cases) than steroid sensitive NS (SSNS) patients whether in activity or in remission (7), And in a complementary study under publication we found that Homozygous mutants TT and T allele of C3435T were significantly higher in patients with NS than controls, Additionally *MDR1* TT and TA genotypes of G2677T/A were significantly more frequent in patients with NS compared to controls. On the contrary, no significant difference was observed in genotypes and allele for C1236T between patients with NS and controls. However, when considering MDR1 G2677T/A steroid resistant patients had significantly higher frequency of GA, GT + GA and TT + AA genotypes when compared with steroid responsive patients. Another finding was that patients younger than 6 years old had significantly higher frequency of MDR1 C3435T genotypes and alleles and MDR1 G2677T/A genotypes and alleles; and that finding matches Jafar et al. (8) who found that steroid resistant patients had significantly higher frequency of GA, GT + GA and TT + AA genotypes when compared with steroid responsive patients. So we hypothesized that this changes in MDR-1` gene polymorphisms may be also affected by pathological type in SRNS and to prove this we studied this polymorphism in two different pathologies FSGS versus mesangioproliferative glomerulonepheritis.

To accomplish this aim we studied 15 cases with SRNS 11 with FSGS and 4 mesangioproliferative glomerulonepheritis and tested them for MDR-1 genetic polymorphisms in 3 sites [C1236T, G2677T/A, C3435T].

By comparing these polymorphisms between FSGS cases versus mesangioproliferative glomerulonepheritis cases we didn't find any significant difference in either genotypes or alleles and thus we concluded that there is no relation between pathological type of SRNS and MDR-1 gene polymorphism in the three tested sites[C1236T, G2677T/A, C3435T].

This study was limited by small number of patients, so we recommend test MDR-1 genetic polymorphisms on larger scale to prove or disprove this finding.

By reviewing the published literature we did not find other studies comparing MDR1 polymorphism in different NS pathology, so we hypothesize that this is one of the earliest studies in this area.

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