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Role of P-glycoprotein and Multidrug Resistance-associated Protein-1 and effect of mdr-1 gene polymorphism on P-gp expression in Idiopathic Nephrotic Syndrome in children

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Objectives: Objective 1: To evaluate Expression and function of P-gp and MRP-1 in SSNS and SRNS patients.
Objective 2: To study the genetic polymorphism of MDR-1 gene in SSNS and SRNS patient and to correlate it with P-gp expression.
Objective 3: To evaluate expression of P-gp and MRP-1 as early biomarker for steroid resistance in Nephrotic Syndrome patients.

Methods: P-gp, MRP-1 expression were evaluated on whole blood and functional activity on peripheral blood mononuclear cells (PBMCs) in steroid sensitive nephrotic syndrome (SSNS) (n=170, male 103, mean age=8.54±4.3); steroid resistant nephrotic syndrome (SRNS) (n=81, male 43, mean age=7.43±4.6) patients. The genetic variants G2677T/A of MDR-1 gene was genotyped using PCR-RFLP technique.

Results: Percentage of P-gp (10.35±2.15 v/s 4.19±1.07, p<0.001); MRP-1(17.03±3.45 v/s 8.71±0.97, p<0.001) on PBMC were significantly higher in SRNS than SSNS. P-gp expression on CD4+ (6.08±2.06 v/s 4.34±1.97, p=0.008); and CD8+cells (8.65±2.19 v/s 3.99±1.72, p<0.001) significantly high in SRNS than SSNS respectively. MRP-1 expression on CD4+ and CD8+cells significantly higher in SRNS (12.06±2.91 v/s 3.35±1.83, p=0.043); (5.11±2.68 v/s 1.59±0.99, p<0.001) respectively. Functional activity of P-gp and MRP-1was significantly increased in SRNS compared to SSNS (66.12±12.71 v/s 28.22±7.35, p<0.001); (72.30±8.38 v/s 32.38±8.89, p<0.001) respectively. ROC curve predictive cut-off values for percentage of P-gp and MRP-1 was found to be 6.99% and 9.64 % respectively with sensitivity of 95% and 90.1% and specificity of 99.4% and 90.6% respectively. Moreover homozygous mutant allele TT+AA was significantly associated with resistant population of nephrotic syndrome (p=0.025, OR = 2.86 CI=1.14-7.14).The expression of P-gp (7.50±3.79 v/s 5.65±3.22, p=0.016) was significantly higher in the patients of homozygous mutant alleles compared to wildtype GG.

Conclusions: Overexpression of P-gp and MRP-1 contribute resistance to corticosteroids and polymorphism of variants G2677T/A may promote P-gp expression in SRNS. The expression of p-gp and MRP-1 may be used as an early biomarker for steroid resistance.

Polymorphism table of G2677T/A

Genotype/alleles G2677T/A	Groups	Steroid sensitive (n=171)	Steroid resistance (n=83)	p-value	Odds ratio
Genotypes	GG[a]	77(47.8)	35(50.0)		
	GT+GA	84(52.2)	35(50.0)	0.761	0.91(0.52-1.60)
	TT+AA	10(11.5)	13(27.1)	0.025	2.86(1.14-7.14)
	GT+GA+TT+AA	94(55.0)	48(57.8)	0.66	1.12(0.66-1.90)
	G[b]	238(69.6)	105(63.6)		
	T+A	104(30.4)	61(36.7)	0.15	1.32(0.90-1.96)

P-gp expression on mutant allele and wild type