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Overexpression and function of P-glycoprotein and MRP-1 are pharmacogenomic biomarkers to determine steroid resistance phenotype in childhood idiopathic nephrotic syndrome

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Objectives: Steroid remains the mainstay of therapy for Idiopathic Nephrotic Syndrome (NS). Overexpression of P-glycoprotein (P-gp) and Multidrug resistance-associated protein 1 (MRP-1) modulate the pharmacokinetics of steroids and may contribute to steroid resistance. The objective of the study was to elucidate the predictive value of P-gp and MRP-1 for steroid resistance in Nephrotic Syndrome.

Methods: Flow cytometric evaluation of P-gp, MRP-1 expression and functional activity on peripheral blood mononuclear cells (PBMCs) was carried out in steroid-sensitive nephrotic syndrome (SSNS) (n=171, male 103, mean age=8.54±4.3); and steroid-resistant nephrotic syndrome (SRNS) (n=83, male 43, mean age=7.43±4.6) patients. The genetic variants of the MDR-1 gene were genotyped using PCR-RFLP.

Results: We found that percentage expression of P-gp (10.01±2.09and 3.79±1.13 $p<0.001$); and MRP-1(15.91±3.99and 7.40±2.33, $p<0.001$) positivity on lymphocyte gated population were significantly higher in SRNS than SSNS. The functional activity of P-gp and MRP-1was also significantly increased in SRNS as compared to SSNS (68.10±13.35 and 28.93±7.57, $p<0.001$); (72.13±8.34and 31.56±8.65, $p<0.001$) respectively. AUC-ROC curve analysis revealed that P-gp and MRP-1 expression with a cut-off value of 7.13% and 9.62% predicted SRNS with the sensitivity of 90% and 80.7%; and specificity 90% and 80%,respectively. Moreover,MDR-1 homozygous mutant allele TT+AA for G2677T/A (rs2032582) was significantly associated with SRNS ($p=0.025$, OR = 2.86 CI=1.14-7.14). Moreover,the expression of P-gp (9.68±4.99 v/s 5.88±3.38, $p=0.002$) was significantly higher in the patients of homozygous mutant alleles compared to wildtype GG.

Conclusions: Overexpression and increased functionality of P-gp and MRP-1 contribute to steroid resistance,and MDR-1 homozygous mutant G2677T/A promotessteroid resistance by inducing P-gp expression in NS.