Abstract Type : Oral presentation
Abstract Submission No.: A-0150
Abstract Topic : Pediatric Nephrology + Inherited Kidney Disease

P-Glycoprotein and Multidrug Resistance-Associated Protein-1 as Biomarkers for Steroid Resistance in Idiopathic Nephrotic Syndrome: Impact of MDR-1 Gene Polymorphism on P-gp Expression in Children"

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Objectives : The objective of the study that overexpression of P-glycoprotein (P-gp) and Multidrug resistance associated protein 1 (MRP-1) modulate the pharmacokinetics of steroids and may contribute in steroid resistance.
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 : Biochemical difference were found in 24hrs urinary protein/Creatinine ratio (SSNS=0.13±.0.06, SRNS=3.67±0.91, p<0.001), total cholesterol (SSNS=144.21±34.61, SRNS=460.52±201.09, p<0.001). 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. 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 predictive cut-off values for the 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. 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). P-gp expression (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 on T-cells may contribute in resistance to corticosteroids and polymorphism of G2677T/A may promote P-gp expression in SRNS. Use of P-gp and MRP-1inhibitors may prevent SRNS status.