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Abstract Topic:- Pharmacogenetics

Abstract Title:- Platelet ADP receptor gene (P2RY1) polymorphism determines the risk of aspirin inadequate response in patients with ischemic stroke

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Aims:-To investigate the candidate gene polymorphisms in COX1, COX2, GpIIb/IIIa, P2RY1, PEAR1, ITGB3 (platelet aggregation pathway), and UGT1A6 (aspirin metabolising pathway) that might determine the outcome of aspirin response in patients with ischemic stroke

Methods:- A total of 293 ischemic stroke patients diagnosed at the Neurological services of NIMHANS, and who were taking 150 mg of aspirin for more than 7 days for prevention of stroke recurrence, were recruited for the study. Out of 293 recruited subjects who presented with ischemic stroke, and were on aspirin therapy, serum salicylate levels in 63 patients (21.50%) were below the therapeutic range (i.e. less than 30 µg/mL). Hence, these patients were removed from the study due to probable non-compliance to aspirin. The remaining 230 patients were included in the study. According to the 'ADP+AA-combined' categorization criteria, 32 patients (13.91 %) were classified as 'Non-Responders,' 76 (33.04 %) as 'Semi-responders,' and 122 (53.04 %) as 'Responders.' We grouped the 'Non-responders' and 'Semi-responders' into one group and termed it aspirin 'Inadequate-responders' since our major goal was to find all patients with increased on-aspirin platelet reactivity

Results:- Upon comparison between Responders and Inadequate-Responders (Semi-Responders + Non-Responders), we found that the ‘TT’ genotype of P2RY1 (rs1371097) polymorphism was significantly higher in Inadequate-Responders (3.27% vs. 11.11%). Allele frequency revealed that ‘T’ allele of P2RY1 (rs1371097) polymorphism was significantly higher in Inadequate-Responders (20.08% vs. 30.09%; OR, 95%, 1.71, 1.122-2.61; p=0.0131*). We also found that the presence of a single copy of the ‘T’ allele in the P2RY1 (rs1371097) gene can increase the risk of inadequate response by 3.46 times even after adjusting for the covariates like age, gender, smoking, tobacco, alcohol, hypertension and diabetes (adjusted OR (95%), 3.46 (0.043); p=0.043*). The polymorphisms in other candidate genes including genes in platelet aggregation (COX1, COX2, PEAR1, GPIIb/IIIa and ITGB3) and aspirin metabolism (UGT1A6) pathways failed to show a significant difference between the groups in our cohort categorized based on both types of classification criteria.

Conclusions:- This is one of the largest study explored the influence of genetic predispositions on platelet response to aspirin therapy in patients with ischemic stroke in our population. The phenomena of on-aspirin platelet reactivity were found to be influenced by the polymorphisms in the P2RY1 gene polymorphism

Keywords:- aspirin non-response, platelet aggregation, ischemic stroke, P2RY1 gene, aspirin metabolism