A high COMT activity haplotype predisposes patients with medication overuse headache to a lower risk of relapse after successful withdrawal treatment

S. Terrazzino[1], S. Cargnin[1], M. Viana[2], N. Ghiotto[2], G. Sances[2], G. Nappi[2], P.L. Canonico[1], A.A. Genazzani[1]

[1]Department of Pharmaceutical Sciences and Centro di Ricerca Interdipartimentale di Farmacogenetica e Farmacogenomica (CRIFF), Università del Piemonte Orientale 'A. Avogadro', Novara, Italy; [2]Headache Science Centre, IRCCS 'National Neurological Institute C. Mondino' Foundation, Pavia, Italy.

Medication overuse headache (MOH) is a chronic secondary headache developing following overuse of acute headache medications that resolves or reverts to its previous pattern within 2 months after drug withdrawal (Headache Classification Subcommittee of the HIS, 2004). Despite the growing number of studies focusing on the role of clinical factors as predictors of long-term outcome, the genetic background of relapse of MOH patients with successful withdrawal therapy remains to be elucidated. The valine158methionine (rs4680) polymorphism of the catechol-O-methyltransferase (COMT) gene contributes to the interindividual variability in human pain phenotypes such as pain sensitivity and chronicity (Kambur et al., 2010). Given the occurrence of dysfunctions in the mesocorticolimbic dopamine circuit and in other pain-processing-related areas of MOH patients (Grazzi et al., 2010; Ferraro et al., 2012), we hypothetized that an alteration of COMT activity may have an impact on the prognosis of MOH. To test this hypothesis, we herein evaluated the role of rs4680 (G>A) and rs6269 (A>G) polymorphisms in the COMT gene, either as single variants or in haplotype combination, as predictors for relapse of MOH patients within the first year after successful drug withdrawal. In accordance with the accepted International Classification of Headache Disorders-II criteria, MOH diagnosis was confirmed only in the presence of headache improvement within 2 months after withdrawal. Relapsers were defined as those patients fulfilling, at follow-up, the new ICHD-II appendix criteria for MOH. Among MOH patients with successful drug withdrawal therapy (n=95, 69 women and 26 men, mean age at study entry of 47.6 ± 12.1 years), follow-up data were available for 73 patients (50 women and 23 men, mean age at study entry of 49.4 ± 11.6 years). Triptan overusers were found at lower risk to relapse during the first year of follow-up compared to MOH patients overusing other types of acute headache medications (OR: 0.11, 95% CI:0.01-0.88, P=0.038). All the other clinical variables considered did not significantly differ between relapsers and patients who did not experience relapse (gender, age at study entry, age of primary headache onset, familiarity for headache, primary headache diagnosis, monthly drug number before withdrawal, headache days per month before withdrawal and MOH duration before withdrawal). The rs6269A allele (OR: 2.15, 95% CI: 1.03-4.50, P=0.04) or the rs4680A allele (OR: 2.93, 95% CI: 1.41-6.09, P=0.003) of the COMT gene were more frequently found in patients who relapsed within the first year after successful drug withdrawal. Haplotype analysis in MOH patients revealed a strong pairwise linkage disequilibrium between rs6269 and rs4680 (D'=0.988). In the logistic regression analysis adjusted for triptan overuse, the G-G haplotype conferred a lower risk to relapse within the first year of follow-up, compared to the most common A-A haplotype (OR: 0.28, 95% CI:0.11-0.70, P=0.008). The current results highlight the importance of polymorphisms and haplotypes of the COMT gene as determinants for relapse of MOH patients with successful drug withdrawal. Nonetheless, further genetic and functional studies are needed to validate our findings and clarify the complex relationship between COMT activity variation, pain sensitivity and prognosis of MOH patients with successful withdrawal therapy.

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