Factors associated with anti-TB drug-induced hepatotoxicity and genetic polymorphisms in indigenous and non-indigenous populations in Brazil

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Anti-tuberculosis drugs are responsible for the occurrence of several adverse drug reactions, including hepatotoxicity. The aim was to estimate the incidence of hepatotoxicity and its association with genetic polymorphisms and clinical-epidemiological factors by comparing indigenous and non-indigenous TB patients in the city of Dourados / MS. We investigated clinical-epidemiological variables, serum levels of liver enzymes and *NAT2*, *CYP2E1* and *GSTM1* polymorphisms. A non-conditional logistic regression was used to identify the factors associated with hepatotoxicity. Odds ratios were used as the association measures. The incidence of hepatotoxicity was 19.7% for all the patients and was 50% more frequent in the indigenous population (p=0.055). We identified a new nonsynonymous SNP of *NAT2* in indigenous patients. In total, 54.6% of the patients expressed a slow acetylation phenotype profile. The frequency of the null genotype of *GSTM1* was higher in non-indigenous patients (p=0.002), whereas no significant differences in relation to polymorphisms of *CYP2E1* were observed between the groups. Hepatotoxicity was associated with patients older than 60 years and indigenous patients (OR=26.0;95%CI:3.1-217.6; OR=3.8;95%CI:1.3-11.1, respectively). Furthermore, hepatotoxicity was associated with a slow acetylation profile in indigenous patients (OR=10.7;95%CI:1.2-97.2). Our findings suggest that there are distinct acetylation profiles in the Brazilian population, emphasizing the importance of pharmacogenetic analyses for achieving personalized therapeutic schemes and better outcomes, particularly among vulnerable populations, such as Brazil's indigenous population.

Keywords: tuberculosis, hepatotoxicity, indigenous populations**.**

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