

LTA4H promotor genotype in TB meningitis in Indonesia is associated with inflammation and *M. tuberculosis* CSF culture, but not with survival

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Objective: Since Immunopathology contributes to the high morbidity and mortality of tuberculous meningitis (TBM), corticosteroids are used as adjuvant treatment. However, recent findings from Vietnam indicate that the effect of corticosteroids depends on the patient inflammatory genotype; corticosteroids seemed beneficial for patients with the pro-inflammatory TT genotype of the rs17525495 polymorphism in Leukotriene A4 hydrolase (*LTA4H*), which determines the balance between pro- and anti-inflammatory eicosanoids, but detrimental for patients harbouring the anti-inflammatory *LTA4H* CC genotype (Tobin et al., Cell 2012). If this finding can be confirmed in other settings, corticosteroid treatment should be individualised in TBM patients.

Methods: We examined the functional *LTA4H* polymorphism (rs17525495) in a cohort of TBM patients in Bandung, Indonesia, where all patients receive corticosteroids according to guidelines. 317 HIV-negative TBM patients (53% male; median age 28), 64% with culture or PCR-confirmed TBM, and 36% with probably TBM were included. The *LTA4H* genotypes, as determined by Taqman genotyping, did not divert from Hardy-Weinberg equilibrium ($p=0.22$). Baseline characteristics were compared with a Kruskal-Wallis test for continuous variables and chi-square for non-continuous variables.

Results: The proinflammatory TT genotype was associated with significantly higher blood leukocyte count, CSF pleiocytosis and *M. tuberculosis* culture positivity (Table)

	CC	CT	TT	p-value
N	178	113	26	
Blood leukocytes ($10^6/ml$)	10.4 (7.4-13.4)	10.4 (7.4-13.4)	14.1 (9.8-17.9)	0.024
<i>Cerebro Spinal Fluid (CSF)</i>				
leukocytes total ($10^3/ml$)	126 (32-302)	99 (31-226)	210 (128-342)	0.011
neutrophils ($10^3/ml$)	26 (6-91)	21 (5-57)	38 (8-108)	0.390
mononuclear cells ($10^3/ml$)	69 (18-163)	51 (16-129)	115 (76-299)	0.002
protein (mg/ml)	1.8 (1.0-3.3)	2.4 (1.0-4.3)	1.7 (1.2-6.2)	0.111
glucose CSF/blood ratio	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.2 (0.1-0.3)	0.858
<i>M. tuberculosis</i> culture positive	111 (62%)	56 (50%)	9 (35%)	0.030

Mortality was high, especially in the first weeks after admission (Figure). In a cox regression model with age and sex as covariates, no association was found between genotype and one-year survival ($p = 0.937$), also for the subgroup of definite TBM, and with Glasgow Coma Scale as confounder or intermediate variable (not shown).

Conclusion: The TT genotype of the rs17525495 *LTA4H* polymorphism is related to more outspoken inflammation in TBM patients in Indonesia, and interestingly to culture-positivity. However, it does not predict patient survival, different from earlier published data from Vietnam. Further study is needed to help improve adjuvant treatment for TB meningitis, and to examine if such treatment should be individualised based on patient inflammatory geno- and phenotype.

Survival for LTA4H rs17525495 genotype

