O619
2-hour Oral Session
Infections of the brain and meningitis

V-akt murine thymoma viral oncogene homolog 3 (AKT3) influences outcome of pneumococcal meningitis

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Background: Bacterial meningitis is a severe and deadly disease, most commonly caused by *Streptococcus pneumoniae*. Genetic association studies in pneumococcal meningitis may provide new insights in genetic risk factors for an unfavourable outcome.

Material/methods: We performed a prospective nationwide genetic association study and genotyped pneumococcal meningitis patients using a genome wide exome variants chip (Illumina Exome array v1.1). We also tested which variations were associated with unfavourable outcome. We assessed the gene expression of the top three most significant hits found in pneumococcal meningitis patients and healthy volunteers. We studied the expression of two of the hits and the function of one of the identified genes in a pneumococcal meningitis mouse model using knockout mice. Finally, we studied if patients with the deleterious variant in the identified gene had specific clinical characteristics compared to those with the non-deleterious variant.

Results: We found that single-nucleotide polymorphisms in *DCTN4* (encoding dynactin 4, rs6869603), *RAET1E* (Retinoic Acid Early Transcript 1E, rs3798763) and *AKT3* (V-Akt Murine Thymoma Viral Oncogene Homolog 3, rs10157763) were associated with poor disease outcome (p=2.414e-05, p= 9.346e-05, p= 9.95e-05). *DCTN4* transcript levels were four-fold higher (p=1.19e-06) in healthy

volunteers than in meningitis patients while those of *AKT3* were eleven-fold lower (p=2.1e-3). Transcript levels of *RAET1E* were comparable (p=0.194) between the two groups. In the murine model, consistent with the human data, *akt3* mRNA levels decreased two-fold at 30 h after infection (p=0.01). In contrast, *dctn4* transcript levels were not influenced by pneumococcal infection. *A kt3* KO mice had increased disease severity reflected by higher mortality (p=0.036), higher clinical scores (p=0.021), increased brain TNF-α (p=0.06) as compared to wild-type mice. Patients with the risk genotype (AA) for rs10157763 had an increased risk of seizures on admission (Odds ratio 2.94, 95% confidence interval 1.11-7.80), had a lower score on the Glasgow Coma Scale (median 9 vs 10, p=0.009), less frequently exhibited fever (OR 0.43, 95% CI 0.21-0.84 and they more often develop focal neurologic deficits during admission (OR 2.27, 95% CI 1.12-4.61).

Conclusions: We identified a genetic variant in *AKT3* associated with poor outcome in patients with pneumococcal meningitis. The *AKT3* polymorphism influenced the rate of seizures and focal neurologic deficits, indicating it influences the disease process in the brain.