O052

2-hour Oral Session

Severe infections in children

Genetic variation in *NFKBIE* is associated with an increased risk of pneumococcal meningitis in children

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Rationale: *Neisseria meningitidis* and *streptococcus pneumoniae* remain frequent causative pathogens of life-threatening invasive bacterial infections. Innate immune system genetic variation may predispose individuals to these infections. Nuclear factor (NF)-κB is a key immune regulator, and its activity is controlled by the inhibitors encoded by the genes *NFKBIA, NFKBIE* and *NFKBIZ*.

Objectives: To replicate previous findings of genetic variation associated with invasive pneumococcal disease (IPD). These included *NFKBIE*, *NFKBIA*, *TIRAP*, *NFKBIZ*, *TONSL* and *PTPN22*. To assess pathogen-specificity we genotyped the same single nucleotide polymorphisms in a meningococcal population.

Methods: Cases and controls were identified by linking Danish national registries. DNA was obtained from the Danish Neonatal Screening Biobank. Logistic regression analysis was used to estimate the association between genotypes and susceptibility to invasive meningococcal disease (IMD) and IPD, pneumococcal serotypes and mortality associated with IPD and IMD.

Measurements and main results: In the IPD population, we included 372 children with meningitis, 907 with bacteremia and 1273 controls. In the IMD population, 406 cases with meningitis, 272 with bacteremia and 672 controls were included.
Children with the *NFKBIE* (rs529948) GA heterozygote genotype had an overall increased risk of IPD compared to controls (Odds Ratio [OR] 1.24; 95% confidence interval [CI]: 1.03-1.49, P=0.01). In stratified analysis, the increased risk was only associated with pneumococcal meningitis (OR 1.96; 95% CI: 1.38-2.78, P=0.0001). No evidence of an association with susceptibility to IPD was found for *NFKBIA, TIRAP*, *NFKBIZ*, *TONSL* or *PTPN22*. None of the SNPs were associated with an increased risk of IMD.

Conclusions: we have identified a *NFKBIE* polymorphism associated with an increased risk of pneumococcal meningitis in Danish children