P0094
Poster Session I
Animal models: treatment

IN EXPERIMENTAL PNEUMOCOCCAL MENINGITIS THE EFFECTS OF ADJUVANT DAPTOMYCIN AND DEXAMETHASONE DIFFER AND ARE INFLUENCED BY DISEASE SEVERITY

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Objectives

Inflammation drives the pathogenesis of brain injury in bacterial meningitis. In experimental pneumococcal meningitis reduction of the host's inflammatory response by the bactericidal but non-bacteriolytic antibiotic daptomycin (DAP) leads to less neurological damage compared to treatment with ceftriaxone (CRO) alone. This study evaluated the neuroprotective profile of DAP when combined with CRO compared to the widely recommended adjuvant treatment with dexamethasone (DEX).

Methods

11-day-old Wistar rats (n = 108) were infected with log10 5.8 ± 5.2 cfu *Streptococcus pneumoniae*. 18 hours post infection (hpi) animals were randomized to DAP 10mg/kg/q24h (n=36), DEX 0.7mg/kg/q8h (n=36), or saline 0.85% (n=36). 15 minutes later, all animals were treated with CRO 100mg/kg/q12h. In all animals cerebrospinal fluid (CSF) was sampled at 18 hpi (prior to antibiotics), 20 hpi, 24 hpi and 42 hpi and bacterial titres were determined. Additionally the concentration of 7 cyto-/ chemokines (IFN-gamma, IL-1beta, IL-6, IL-10, MCP-1, MIP-1alpha, and TNF-alpha was measured in the CSF by a microsphere-based immunoassay (Luminex®).

At 42 hpi all animals were sacrificed. Coronal cryosections of whole brains were prepared for histological analysis. For determination of hippocampal apoptosis, the average number of morphologically apoptotic cells in the four blades of the dentate gyrus was determined in four distinct hippocampal sections per animal. The volume of cortical necrosis and – for determination of hydrocephalus – of the third and lateral ventricles were estimated by the Cavalieri method and documented as the percentage of the total cortex volume.

Results

Two hours after start of therapy bacterial titres in CSF of animals treated with DAP + CRO were significantly lower than in animals treated with CRO alone ($p = 0.004$) or DEX + CRO ($p = 0.002$). At 18 hpi and 24 hpi bacterial titres did not differ significantly between the 3 treatment groups.

At 24hpi, animals treated with DEX + CRO had significantly lower levels of IFN-gamma, IL-6, MCP-1, MIP-1alpha, and TNF-alpha than animals treated with CRO alone, also levels of IFN-gamma and TNF-alpha were significantly lower than in animals treated with DAP + CRO.

At 42 hpi, animals treated with DEX + CRO had significantly less hydrocephalus than animals treated with CRO alone ($p < 0.001$) or DAP + CRO ($p = 0.003$). In mild to moderate disease, characterized by low apoptosis (mean apoptosis score < 5), significantly less apoptosis in animals treated with DAP + CRO, compared to animals treated with CRO alone ($p = 0.009$) or DEX + CRO ($p = 0.02$) was documented. Overall, cortical necrosis and hippocampal apoptosis did not differ significantly between the 3 treatment groups.

Conclusion

In the present study, DEX reduced the development of hydrocephalus while the previously documented neuroprotective effect of DAP was exclusively observed in mild to moderate disease.