

Summary

CNS infections continue to be associated with a high morbidity and mortality. Thus, it is necessary to improve current diagnostic and therapeutical approaches. Better understanding to the pathophysiology of CNS infections is crucial for this process.

In this thesis, the results of 4 clinical studies and 1 experimental study were presented. The overall aim of the studies was to expand knowledge about the immunopathophysiology of infectious meningitis (IM). For this purpose, we analysed several parameters of cellular immunity, cytokine production and activation of endogenous endocrine response during IM. Also, a potential use of new biomarkers in differential diagnostics of IM was evaluated.

The results documented that the immune response during acute bacterial meningitis (BM) as well as aseptic meningitis (AM) is compartmentalized to the CNS. The most important changes take place in the subarachnoideal space; however, several alterations of the innate and adaptive immunity were found in peripheral blood as well.

Novel findings observed in our studies are as follows:

- The presence of activated macrophages (HLA-DR+) is associated with a favorable outcome of in patients with BM.
- In patients with BM, a high inflammatory response in the CNS which is associated with elevated cytokine and chemokine concentrations (especially IL-6, IL-8, TNF- α and IL-1 β) does not correlate with disease severity.
- The comparison of the clinical data from patients with invasive meningococcal infection and the results from our experimental *in vitro* model with clinical isolates of *N. meningitidis* suggests that the inflammatory response is predominantly influenced by host factors and bacterial virulence plays an additional role.
- Unlike cytokines, elevated serum and intrathecal cortisol levels correlate with BM severity assessed by clinical scores, i.e., APACHE II, SOFA and GCS.
- Cortisol levels in AM are increased compared to healthy controls, but significantly lower compared to BM. Furthermore, we documented high sensitivity and specificity of intrathecal levels of cortisol in discrimination of BM and AM.
- In patients with AM, we found the relationship between cortisol levels in the cerebrospinal fluid and the etiology of AM when the highest concentrations were observed in patients with tick-borne meningoencephalitis.

- Altogether, the findings related to cortisol levels could not only help in IM diagnosis, but also suggest the role of cortisol in the pathophysiology of IM.
- The changes in lymphocyte subsets and IFN- γ production in the intrathecal compartment depend on viral or spirochetal etiology of AM.
- Unlike in AM, lymphocytes present a minor population in the CNS during acute BM; however, we observed severe changes of lymphocyte subsets in peripheral blood. Moreover, restitution of these alterations is prolonged in gram-positive meningitis compared to meningitis of gram-negative etiology.