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The neutrophil infiltration of the central nervous system in patients with tick-borne encephalitis

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Background: The central nervous system (cns) pathology in tick-borne encephalitis (TBE) results from a combination of the direct cytopathic effect of TBE virus and secondary immunopathology. Neutrophils are abundant in the cerebrospinal fluid (csf) of TBE patients, but the factors responsible for their recruitment and their role in the pathogenesis remain unknown. The neutrophil-dominated inflammation is typically initiated by lymphocytes of the Th17 subset and mediated by a set of specific cytokines and chemokines, not studied in TBE so far.

Material/methods: We have analyzed the hospital records of 240 patients with TBE presenting as meningitis (n=110), meningoencephalitis (n=114) or meningoencephalomyelitis (n=16) for the correlation of the csf neutrophil count with other laboratory and clinical parameters. We have assessed expression of Th17-specific cytokines: interleukin-17A (IL-17A), IL-17F and IL-22, as well as chemokines for neutrophils: IL-8 (CXCL8), CXCL1 and CXCL2 in patients with TBE (n=15), with non-TBE aseptic meningitis (IL-22 and CXCL1 excluded; n=6) and in non-infected controls (n=7). Concentrations were measured with commercial ELISA in serum and csf on admission and on follow-up 10-16 days later. The results were analyzed with non-parametric tests, $p<0.05$ considered significant.

Results: Neutrophils constituted 25% (median) of csf pleocytosis on admission but were absent in a majority of follow-up samples. The csf neutrophil count correlated with the peripheral neutrophilia and highly significantly with csf monocyte count but did not correlate with csf albumin concentration and only marginally with csf lymphocyte count. It was twice higher in the meningoencephalomyelitis group and in patients with spinal paresis than in the remaining TBE patients. The continued presence of neutrophils in the follow-up csf correlated with long-lasting neurologic sequelae.

IL-17A was up-regulated in csf and serum and all the other studied cytokines in csf only in TBE patients on admission. Concentrations of IL-22 and IL-8 were significantly higher in csf than in serum. IL-22 and IL-17F levels in csf correlated with the neutrophil count. Cytokine csf concentrations decreased on follow-up, although IL-17A and CXCL2 remained up-regulated in comparison with controls. In non-TBE meningitis IL-17F and IL-17A concentrations were lower than in TBE while CXCL2 and IL-8 did not differ between these groups.

Conclusions: The neutrophil influx into TBE csf is regulated independently of the blood/brain barrier disruption and of the lymphocyte migration. It may be facilitated by a peripheral neutrophilia, but seems to be driven mainly by the intrathecal Th17-type response and IL-8 expression, both occurring early in the TBE neurologic phase. A vivid intrathecal expression of the Th17 cytokines distinguishes TBE from non-TBE viral meningitis. Particularly abundant neutrophils are found in patients with the spinal involvement and may play a role in its pathogenesis. The prolonged neutrophil infiltration may be a prognostic factor for long-lasting neurologic sequelae.