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Paper Poster Session II

Viral infections of the central nervous system

Cerebrospinal fluid cytosis in patients with tick-borne encephalitis heterozygous for the *CCR5Δ32* allele

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Objective: CCR5 is a receptor responsible for a migration of T lymphocytes in a response to CCL3, CCL4 and CCL5 chemokines. The *CCR5Δ32* deletion results in the lack of a functional CCR5 in homozygotes and in a several-fold decreased expression in heterozygotes. It was hypothesized that *CCR5Δ32* allele carriers have impaired intrathecal inflammatory/immune response to *Flavivirus* encephalitis (including tick-borne encephalitis - TBE) resulting from a decreased lymphocyte migration into central nervous system. We studied the association between presence of the *CCR5D32* variant and the CCR5 expression and cerebrospinal fluid (csf) inflammatory parameters in TBE.

Methods: Venous blood and csf samples were obtained from 35 patients infected with TBE virus (1 with a flu-like disease, 13 with meningitis, 17 with meningoencephalitis and 4 with meningoencephalomyelits) and control blood samples from 15 healthy blood donors. Genomic DNA was extracted and analyzed for the presence of *CCR5Δ32* allele by PCR with sequence specific primers. All the blood samples and 13 csf samples were studied cytometrically: activated Th lymphocytes (CD3+CD4+CD45RO) were gated and labeled with a FITC-stained CCR5-specific monoclonal antibody. Inflammatory parameters of csf (pleocytosis, lymphocyte count, protein and albumin concentration) were measured with standard laboratory techniques. Non-parametric tests were used for statistical analysis.

Results: There were no *CCR5Δ32* homozygotes and ten *CCR5Δ32/wt* heterozygotes: 5 in TBE and 5 in the control group. The median CCR5 expression in the peripheral blood activated Th lymphocytes was 12% both in the TBE patients and controls and was decreased to 7% in the *CCR5Δ32/wt* heterozygotes. In TBE, the CD3+CD4+CD45RO population in csf was over three-fold enriched in CCR5-positive cells compared with the blood. There was only one csf sample from *CCR5Δ32/wt* heterozygote available for a flow cytometry, in which CCR5 expression was lower than in wild type homozygotes, but still substantial: 26% of CD3+CD4+CD45RO cells were CCR5-positive, compared to 41% median in homozygotes. The basic inflammatory parameters of the csf from the *CCR5Δ32* allele bearing TBE patients were not decreased. To the contrary, there was a tendency for a higher pleocytosis (median 122 cells/ml versus 79/ml in wild type homozygotes) and lymphocyte count (76/ml versus 36/ml) in *CCR5Δ32*-bearers.

Conclusions: There are no evident abnormalities of csf parameters in TBE patients heterozygous for *CCR5Δ32* allele. That suggests that either 1) CCR5 is not an important factor for the lymphocyte migration into cns in TBE, 2) its impaired expression may be compensated by alternative factors or alternatively 3) its induced expression in *CCR5Δ32/wt* heterozygotes with TBE reaches a level sufficient for driving lymphocyte influx into cns. The relatively high CCR5 expression in the csf of a single *CCR5Δ32*-allele carrier TBE patient makes the last explanation probable, but requires confirmation.