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Abstracts

Articles appearing in the March 2019 issue

Mouse model of anti-NMDA receptor post–herpes simplex encephalitis

Objective To develop an endogenous rodent model of postinfectious anti-NMDA receptor (NMDAR) encephalitis.

Methods Six mice were inoculated intranasally with herpes simplex virus (HSV) 1 and subsequently treated with acyclovir for 2 weeks. Serum was collected at 3, 6, and 8 weeks postinoculation and tested for NMDAR antibodies through a cell-based assay. Eight weeks postinoculation, mice were killed and their brains were sectioned and immunostained with antibodies to postsynaptic density (PSD)–95 and NMDARs. Colocalization of hippocampal PSD-95 and NMDAR clusters, representing postsynaptic membrane NMDARs, was quantified via confocal imaging. Hippocampi were additionally analyzed for NMDAR and PSD-95 protein using Western blot analysis.

Results Four of 6 mice (67%) developed serum antibodies to NMDARs: 1 at 3 weeks, 1 at 6 weeks, and 2 at 8 weeks postinoculation. As compared to inoculated mice that did not develop NMDAR antibodies, immunofluorescence staining revealed decreased hippocampal postsynaptic membrane NMDARs in mice with serum antibodies at 8 weeks postinoculation. Western blot analysis showed that mice that had NMDAR antibodies at 8 weeks had decreased total NMDAR but not PSD-95 protein in hippocampal extracts ($p < 0.05$).

Conclusions Mice inoculated intranasally with HSV-1 developed serum NMDAR antibodies. These antibodies were associated with reduced hippocampal NMDARs, as has been shown in previous models where antibodies from patients with anti-NMDAR encephalitis were infused into mice, paving the way for future studies into the pathophysiology of autoimmune encephalitides.

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MRI phenotypes in MS: Longitudinal changes and miRNA signatures

Objective To classify and immunologically characterize persons with multiple sclerosis (MS) based on brain lesions and atrophy and their associated microRNA profiles.

Methods Cerebral T2-hyperintense lesion volume (T2LV) and brain parenchymal fraction (BPF) were quantified and used to define MRI phenotypes as follows: type I: low T2LV, low atrophy; type II: high T2LV, low atrophy; type III: low T2LV, high atrophy; type IV: high T2LV, high atrophy, in a large cross-sectional cohort (n = 1,088) and a subset with 5-year longitudinal follow-up (n = 153). Serum miRNAs were assessed on a third MS cohort with 2-year MRI phenotype stability (n = 98).

Results One-third of the patients had lesion–atrophy dissociation (types II or III) in both the cross-sectional and longitudinal cohorts. At 5 years, all phenotypes had progressive atrophy ($p < 0.001$), disproportionally in type II (BPF −2.28%). Only type IV worsened in physical disability. Types I and II showed a 5-year MRI phenotype conversion rate of 33% and 46%, whereas III and IV had >90% stability. Type II switched primarily to IV (91%); type I switched primarily to II (47%) or III (37%). Baseline higher age ($p = 0.006$) and lower BPF ($p < 0.001$) predicted 5-year phenotype conversion. Each MRI phenotype demonstrated an miRNA signature whose underlying biology implicates blood–brain barrier pathology: hsa.miR.22.3p, hsa.miR.361.5p, and hsa.miR.345.5p were the most valid differentiators of MRI phenotypes.

Conclusions MRI-defined MS phenotypes show high conversion rates characterized by the continuation of either predominant neurodegeneration or inflammation and support the partial independence of these 2 measures. MicroRNA signatures of these phenotypes suggest a role for blood–brain barrier integrity.

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