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## Interaction of the Lyme disease spirochete *Borrelia burgdorferi* with brain parenchyma elicits inflammatory mediators from glial cells as well as glial and neuronal apoptosis.

[Ramesh G](#), [Borda JT](#), [Dufour J](#), [Kaushal D](#), [Ramamoorthy R](#), [Lackner AA](#), [Philipp MT](#).

Division of Bacteriology and Parasitology, Tulane National Primate Research Center, Tulane University, Covington, LA 70433, USA.

Lyme neuroborreliosis, caused by the spirochete *Borrelia burgdorferi*, often manifests by causing neurocognitive deficits. As a possible mechanism for Lyme neuroborreliosis, we hypothesized that *B. burgdorferi* induces the production of inflammatory mediators in the central nervous system with concomitant neuronal and/or glial apoptosis. To test our hypothesis, we constructed an ex vivo model that consisted of freshly collected slices from brain cortex of a rhesus macaque and allowed live *B. burgdorferi* to penetrate the tissue. Numerous transcripts of genes that regulate inflammation as well as oligodendrocyte and neuronal apoptosis were significantly altered as assessed by DNA microarray analysis. Transcription level increases of 7.43-fold ( $P = 0.005$ ) for the cytokine tumor necrosis factor- $\alpha$  and 2.31-fold ( $P = 0.016$ ) for the chemokine interleukin (IL)-8 were also detected by real-time-polymerase chain reaction array analysis. The immune mediators IL-6, IL-8, IL-1 $\beta$ , COX-2, and CXCL13 were visualized in glial cells in situ by immunofluorescence staining and confocal microscopy. Concomitantly, significant proportions of both oligodendrocytes and neurons undergoing apoptosis were present in spirochete-stimulated tissues. IL-6 production by astrocytes in addition to oligodendrocyte apoptosis were also detected, albeit at lower levels, in rhesus macaques that had received in vivo intraparenchymal stereotaxic inoculations of live *B. burgdorferi*. These results provide proof of concept for our hypothesis that *B. burgdorferi* produces inflammatory mediators in the central nervous system, accompanied by glial and neuronal apoptosis.

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