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BRAIN RESEARCH

Research Report

Microglial response to murine leukemia virus-induced encephalopathy is a good indicator of neuronal perturbations

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ABSTRACT

The neuronal pathology caused by neonatal infection of rats with the PVC-211 murine leukemia virus (PVC-211 MuLV) and its underlying mechanisms are not well defined even though a loss of neurons and spongiform neurodegeneration has been reported to accompany the disease. Here we sought to identify sites of neurodegeneration using microglial reactivity as an indirect marker and to characterize microglial activation during disease progression. Using a panel of microglial antibodies including Iba1, OX-42, ED1, and anti-ferritin, we have studied the response of microglial cells to neonatal CNS infection with PVC-211 at post-infection survival times 7, 14, 21, and 28 days. We found that microglial activation occurred primarily in the spinal cord and brainstem where it gradually increased in intensity over the time course of this study. Other brain areas were relatively unremarkable in their microglial reaction to viral infection within this time frame. However, the presence of activated microglial cells was not correlated directly with the presence of viral glycoprotein (gp70), which was expressed in endothelial cells throughout the CNS. Although double-labeling of microglia with Iba1 and ED1 revealed numerous actively phagocytic microglia during disease progression, not all activated microglia were ED1-positive. In addition to the intense microglial activation, we found increased ferritin expression sporadically throughout the virus-infected brain. The ferritin-positive cells were mostly microglia that exhibited dystrophic changes and likely represented a degenerating subpopulation of microglial cells. Thus, activated microglia can co-exist with degenerating microglia in the same brain region. We attempted to localize degenerating neurons or neurites using Fluoro-Jade, anti-tau, and anti-alpha synuclein staining, but none of these procedures yielded results to indicate obvious neuronal pathology. We conclude that the visualization of microglial activation is a more sensitive measure of neuronal perturbations than direct detection of neuronal pathology which may be subtle and not produce overt degenerative changes.

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1. Introduction

PVC-211 MuLV is a neuropathogenic, paralysis-inducing virus that produces a neurodegenerative syndrome characterized by tremor, loss of splay reflex, ataxia, and hind limb weakness/paralysis after intracerebral inoculation into neonatal rats or mice (Hoffman et al., 1992; Kai and Furuta, 1984; Wilt et al., 2000). However, the neuropathology of this infection paradigm is not well defined or even controversial to date. Earlier studies characterized the neuropathology as being noninflammatory with perivascular astrogliosis and marked by development of spongiform vacuolar neurodegeneration where neuronal cell bodies were largely spared and neuronal drop-out was rare (Hoffman et al., 1992; Kai and Furuta, 1984). More recently, neuronal loss was reported to occur in the cerebellum and brainstem during end stage disease (Li et al., 2009). In addition, activation of microglia has been reported (Wilt et al., 2000) indicating that while not a blatantly inflammatory condition, an endogenous neuroinflammatory component does exist. In light of these disparate findings, we sought to further characterize the neuropathology of PVC-211 infection by performing a comprehensive analysis of microglial reactivity with a number of cell markers.

In previous studies (Li et al., 2009; Wilt et al., 2000), the microglial reaction to neonatal PVC-211 infection, was assessed using immunostaining with ED1 antibody, which is a macrophage marker that recognizes an intracytoplasmic, lysosomal antigen whose expression increases during phagocytic activity in monocytes and other tissue macrophages, including in microglia (Bauer et al., 1994; Dijkstra et al., 1985; Graeber et al., 1998). Thus, the endogenous neuroinflammatory response in PVC-211-infected rats has not been characterized with markers directed against microglial surface

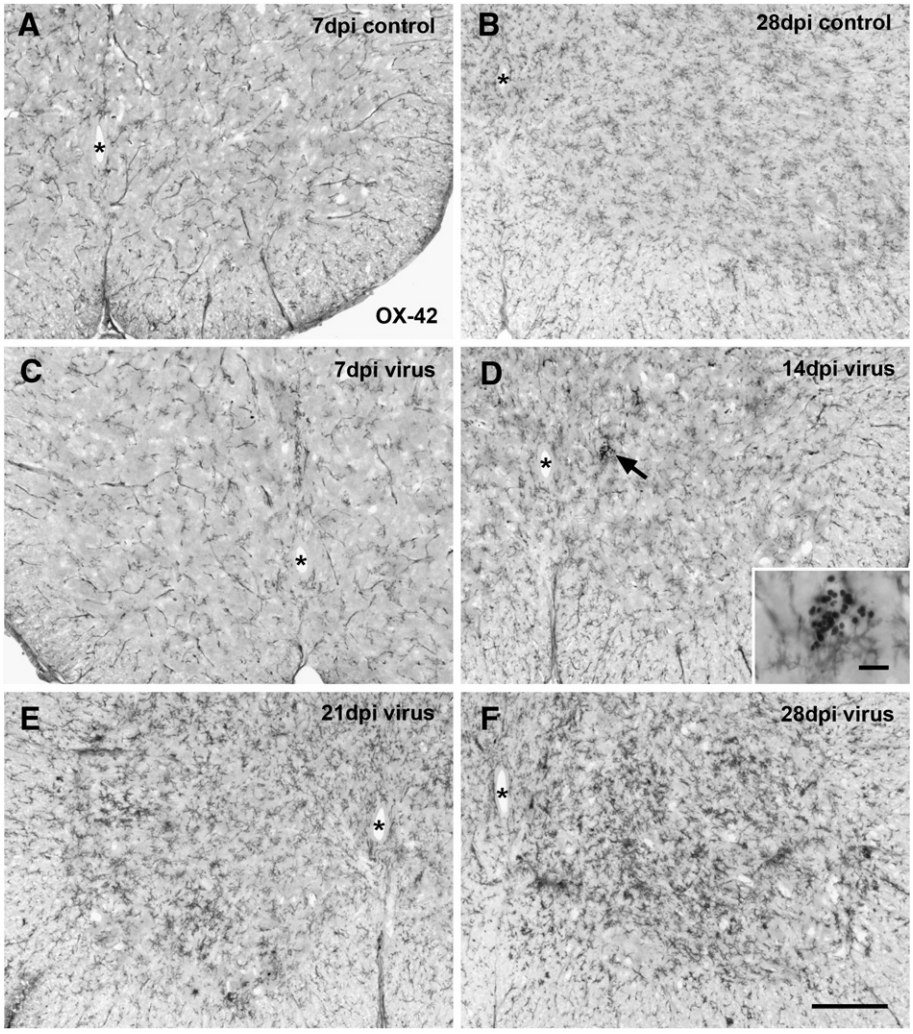

Fig. 1 – Microglia immunolabeled with OX-42 in the rat spinal cord ventral horn at different times after intracranial PVC-211 injection. (A, B) Sections from controls show normal distribution of microglia at 7 and 28 dpi. Note the increases in cell number and in differentiation during this period of postnatal development. (C–F) Virus infection does not result in apparent microglial activation at 7 and 14 dpi. A small intraparenchymal hemorrhage revealing peroxidase-positive erythrocytes is encountered in the spinal gray matter at 14 dpi without activated microglia nearby (arrow in D; enlarged in inset). Microglial activation is conspicuous in the spinal cord gray matter at 21 dpi (E) and has intensified by 28 dpi (F). Animals showed paresis (E) and paralysis (F) of hind limbs. Asterisks indicate central canal. Scale bar in panel F for all, 200 μm; inset, 20 μm.