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A murine model for the human enterovirus 71 encephalomyelitis

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We developed a two-week-old murine model for human Enterovirus 71 encephalomyelitis to study pathological changes and viral spread into and within the central nervous system (CNS). Mice infected via oral and parenteral routes with a murine-adapted virus strain originally isolated from a fatal human case, succumbed to infection after 2–5 days. Degenerate or normal appearing CNS neurons showed evidence of viral RNA, antigens and virions as demonstrated by in situ hybridization, immunohistochemistry and electron microscopy, respectively. The most severely infected neurons were in anterior horns, motor trigeminal nuclei and brainstem reticular formation. Fewer neurons in the red, lateral cerebellum and other cranial nerve nuclei, motor cortex, hypothalamus and thalamus were infected. The cerebellar hemisphere, sensory cortex, and dorsal root or autonomic ganglia were spared. Although inflammation was minimal or insignificant, this stereotyped distribution of virus in the mouse CNS, which was more or less similar for all routes, resembled the distribution of inflammation and virus in human encephalomyelitis. In a separate experiment, intramuscular-inoculated mice sacrificed over 24 to 36 h post infection timepoints showed increasing viral RNA/antigens in the ipsilateral lumbar anterior horn and adjacent efferent motor axons. From 48–72 h, motor neurons in upper cord segments, brainstem and contralateral motor cortex became infected. Viral culture from the spinal cord corroborated these findings. The data support the notion that for all inoculation routes, viral entry into the CNS was by peripheral motor nerves whereas spread within the CNS could involve motor and other neural pathways. Viral RNA/antigens were also detected early in skeletal muscle and brown adipose tissues but not in lymph node, thymus, spleen, Peyer's patches, heart, lung and gastrointestinal tissues. We hypothesize that the primary viral replication sites were skeletal muscles and adipose tissues, and that following skeletal muscle infection, virus entered motor nerves to travel up to the CNS. Genomic sequence analysis of the adapted and parental (non-neurovirulent) viral strains revealed 7 nucleotide differences including 2 each in the VP2 and VP1 regions, and 1 each in the 5'NTR, 2A and 3A regions. The corresponding deduced amino acid sequence changes could contribute to neurovirulence. With better pathological characterization, especially of the CNS, this model should be useful for further neuropathogenesis studies and anti-viral agent/vaccine testing.