

MRI Estimation of Sub-Clinical Disease in Japanese Macaque Encephalomyelitis

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Introduction

A spontaneous demyelinating disease has recently been characterized in Japanese macaques (*Macaca fuscata*) resident at the Oregon National Primate Research Center (ONPRC); Japanese macaque encephalomyelitis (JME). JME bears many similarities to human multiple sclerosis (MS). Affected animals present with ataxia, paresis, or optic involvement. JME typically has an acute onset, with rapid progression, but a relapsing-remitting course is also observed (1,2). CSF analysis shows pleocytosis, slightly increased protein, and normal glucose levels. Neuropathology of acute lesions revealed focal demyelination, inflammatory infiltrate, and myelin laden macrophages. Chronic lesions showed demyelination, gliosis, and little inflammation (1,2). The MRI of **Figure 1** from an individual with JME shows multiple large areas of focal contrast enhancement on post-gadolinium T₁-weighted scans (2). Although the etiology is not yet known, it is hypothesized that a γ_2 -herpesvirus, which has been isolated from active lesions but not normal tissue, may be causal (1,2). Exposure to the virus typically occurs early in childhood, though the disease may not be clinically evident for many years. The co-existence of chronic and acute lesions in JME suggests disease dissemination in time and perhaps a sub-clinical disease phase. MRI has exceptional sensitivity for detecting white matter abnormalities that are the pathological hallmark of human MS (3). The purpose of this study was to estimate the extent of sub-clinical JME disease in the ONPRC JM colony.

Methods

The ONPRC Japanese macaque colony is housed year-round in an outdoor corral with a current total population of ~300. To date, seventy-four individuals (45 female; 29 males, 1 hermaphrodite; age range 1-25 y) have been enrolled in this IACUC approved study. All MRI data were acquired on a whole-body Siemens 3 Tesla (T) MRI instrument (Erlangen, Germany) using a quadrature radiofrequency (RF) coil with inner diameter of 15 cm. Animals were initially sedated with Telazol, intubated and maintained on 1% isoflurane in 100% O₂ and were continuously monitored by pulse oximetry, respiration, and end tidal CO₂ levels during the study. The following sequences were acquired for all animals: 1) a coronal T₁-weighted 2D gradient recalled echo sequence (TR: 23 ms, TE: 7.39 ms, FA: 30°, field-of-view (FOV) 192 mm x 192 mm, matrix: 128x128), 2) a sagittal proton-density (PD) turbo spin echo (TSE) sequence (TR: 10000 ms; TE: 17 ms; echo train length (ETL) 9; FOV 192 mm x 192 mm, matrix: 256x256, slice thickness (ST) 1.5 mm), 3) an axial 2D T₂-weighted TSE sequence (TR: 9000 ms; TE: 51 ms; ETL 9, FOV 180 mm x 160 mm, matrix: 320x240, ST 1.0 mm), 4) an axial 2D PD TSE sequence (TR: 9000 ms, TE: 13 ms, ETL 9, FOV 180 mm x 160 mm matrix: 320x240, ST 1.0 mm), and 5) a 3D T₁-weighted magnetic prepared rapid acquisition gradient echo (MPRAGE) sequence (TR: 2500 ms; TE: 3.49 ms; FA: 8°; FOV 130 mm x 97.5 mm x 96 mm, matrix: 192x144x96). All MRI were evaluated by a board-certified clinical neuroradiologist.

Results

All seventy-four animals completed the MRI screening and recovered from anesthesia without incident. Seven animals were positive for one or more WM signal hyperintensities (WMSH). A representative example is displayed in **Figure 2**. The age range of the WMSH positive animals was 5-20 y and four of the seven were female. The locations of the WMSH were distributed throughout the brain and included periventricular, posterior fossa, and spinal cord WM similar to the distribution observed at necropsy of the JME confirmed animals. There was no association between WMSH and age in this cohort. In addition to the WMSH, ten other animals had abnormal MRI findings that included a cavernous hemangioma, internal carotid artery aneurysms, myelomalacia, hypothalamic mass, and congenitally anomalous ventricles. Other observations from the MRI data include an increase in basal ganglia and dentate nucleus iron content with age. There was no clear evidence of brain atrophy with age in this cohort.

Discussion

The Japanese macaque colony was established at the ONPRC from a 55 member troop that was relocated from Japan in 1965. The first JME case was observed in 1986 with 14 individuals developing severe JME shortly thereafter (with a peak annual incidence of ~3%). Since 1990 the annual incidence has been relatively constant at ~0.5% with a total of 47 confirmed cases to date. The JME disease course is not well characterized since, for humane reasons, most affected individuals were euthanized shortly after disease onset. However, a small number of individuals have exhibited a relapsing-remitting disease course. In this study we identified MRI findings consistent with subclinical JME disease in 7 individuals. All individuals were asymptomatic at time of study and there was no indication in their medical records of any history of neurological impairment. If all of the WMSH MRI findings observed in the current study are attributed to JME disease this suggests a high disease susceptibility; a finding that has important implications for the development of an inducible model. This study also suggests that JME disease severity can vary widely, from benign to fulminant. While important insight into MS has been gained from studies of rodent experimental autoimmune encephalomyelitis (4), significant immune response differences between humans and rodents are a fundamental limitation (5). The possibility of developing of an inducible non-human primate MS model based on a naturally occurring disease such as JME is intriguing. If realized such a model could substantially accelerate drug discovery and improve understanding of pathogenesis.

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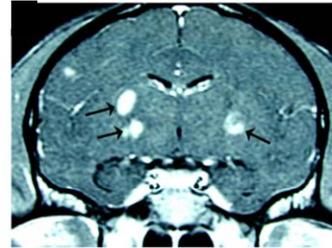


Figure 1. Coronal post-Gd T₁-w MRI of 5 y female Japanese macaque 11 days after presentation with JME. Large focal enhancing lesions (arrows) are evident throughout the brain.



Figure 2. 3T MRI of a 16 y female Japanese macaque. The left panel shows a T₂-w transverse MR image with a subtle signal hyperintensity indicated by arrow. The right panel shows a sagittal PD-w image of the same animal that provides a different view of the lesion.