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ANIMAL MODELS

Borna disease virus (BDV)-induced model of autism: application to vaccine safety test design

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Viruses kill cells in the central nervous system (CNS) by direct (eg apoptosis), and indirect (eg immune mediated) mechanisms. Viruses also can persistently infect cells and disrupt specialized neural cell activities important for the organism without killing the infected neural cell. The immature nervous system is at high risk for virus-induced damage by all the above mechanisms. Not surprisingly, therefore, viruses are CNS teratogens and have been proposed as etiologic agents of neurodevelopmental disease syndromes in humans (eg intrauterine infection with rubella virus and autism).

BDV infection of neonatal rats provides an animal model system to study virus-induced injury to the immature CNS.[1] BDV is an extremely neurotropic virus that causes persistent and non-lethal infection of neural cells. Lewis rats infected with BDV at birth survive because they fail to develop classical anti-virus cellular immune response to virus replication in the brain. The outcomes of neonatal BDV infection include neuroanatomical defects in the cerebellum and limbic system, behavioral abnormalities (eg hyperreactivity, circadian rhythm disturbance, social-play deficits, cognitive deficits, chronic anxiety) and neurochemical defects (eg developmental and regional abnormalities in serotonin and norepinephrine concentrations).[1–10]

A decade of multidisciplinary research on neonatally BDV-infected rats culminated in the recognition of the value of this first virus-induced animal model of autism spectrum disorders (ASD) (as reviewed in Pletnikov *et al*[1]). Excitement about this model has grown and many laboratories in the US and abroad have now contributed to our understanding of this model system, including abnormalities in neurotrophin levels, chemokine expression, cytokine expression, microglial activation, apoptosis, synaptic pathology, and cerebellar pathology.[1]

Information from pathogenesis studies of virus-induced neurodevelopmental damage is applicable to the development of safety tests for childhood vaccines. Developmentally related host contributions to virus-induced behavioral and neurological disease include the neurodevelopmental stage of the brain at the time of BDV infection, ie the brain regions undergoing neurogenesis and migration at time of infection *vs* matured brain regions with established neural circuits.[1] As summarized in Table 1, our data indicate that all of the following possibilities can occur when characterizing virus-induced developmental CNS injury: (1) damage to developing brain regions that never recover from the insult; (2) damage to developing brain regions that recover over time; (3) possible consequences of continuing damage by a persistent viral infection including the effects on aging; and (4) preservation of some brain functions despite early and persistent virus infection of the brain.

Concerns of potential neurodevelopmental adverse events from pediatric vaccines have led to the hypothesis that live, attenuated, virus vaccines may be linked to the development of autistic-like symptoms. In order to better understand and measure any potential risk of serious neurodevelopmental consequences of vaccination, we developed a program to study and compare the neurological outcomes of wild-type and vaccine virus strains (eg mumps virus) in developmentally relevant animal models.[10–12]

Mumps virus is a highly neurotropic common child-

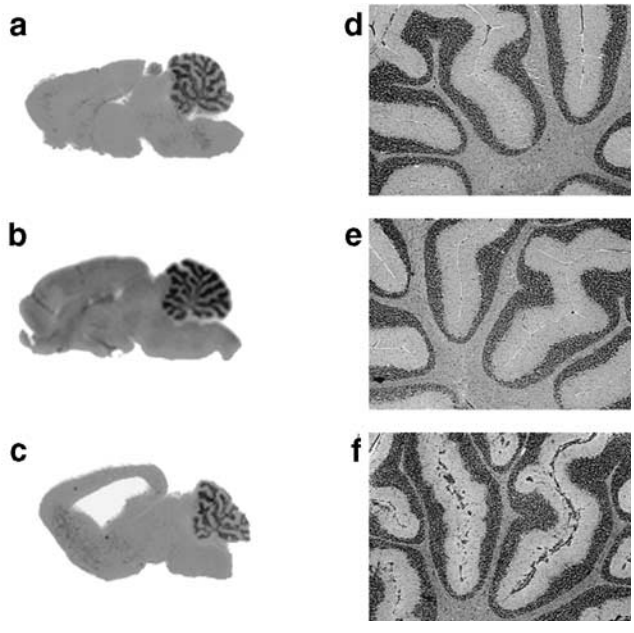

Figure 1 Rats neonatally-inoculated with uninfected control material (a, d), attenuated Jeryl Lynn strain of mumps vaccine (b, e) or a neurovirulent wild-type mumps strain 88–1961 (c, f). Note the hydrocephalus (C) and cerebellar developmental abnormalities in rat infected with 88–1961 not seen in control or vaccine-infected rats. Stained with H & E.

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Table 1 Variability in outcomes of neonatal BDV infection of Lewis rats

Outcome	*BDV infected vs uninfected rat*	*Reference*
Similar in both groups	Body righting response	Pletnikov *et al*, 2001[9]
	Bar crossing	Pletnikov *et al*, 2001[9]
	Vibrissae placing response	Pletnikov *et al*, 2001[9]
	Pre pulse inhibition-acoustic startle	Pletnikov *et al*, 2001[9]
Slower to develop	Cerebellum	Carbone *et al*, 1991[2]
	Negative geotropism	Pletnikov *et al*, 2001[9]
Increased	Activity	Bautista *et al*, 1994[3]
	Reactivity to novel environments	Bautista *et al*, 1994[3]
	Anxiety	Pletnikov *et al*, 1999[5]
	Salt taste preference	Bautista *et al*, 1994[3]
Transient increase with recovery to normal pattern	Daytime activity levels	Bautista *et al*, 1994[3]
Transient decrease with recovery to normal pattern	Limb placing tests	Pletnikov *et al*, 2001[9]
Chronic decrease	Body weight gain	Bautista *et al*, 1994[3]
	Hippocampus damage	Carbone *et al*, 1991[2]
	Social play	Pletnikov *et al*, 1999[5]
	Limb grasping tests	Pletnikov *et al*, 2001[9]
	Ability to stand on four paws	Pletnikov *et al*, 2001[9]
Failed to develop	Bar holding	Pletnikov *et al*, 2001[9]

hood pathogen. Unfortunately, pre-clinical testing using traditional primate-based mumps virus neurovirulence assays has not been reliably predictive of the relative human neurovirulence potential of some live, attenuated mumps virus strains, and neurological adverse events have been causally associated with Urabe-AM 9, Leningrad-3 and Sofia-6 strains.[10]

We created and tested the first developmentally relevant neurovirulence test using wild-type and vaccine mumps virus strains that shows a direct correlation between virus replication and development of enlarged brain ventricles (hydrocephalus) in the neonatally-infected rat brain with the virus strains' known human neurovirulence potential. As seen in Figure 1, compared to newborn rats inoculated with control material or Jeryl Lynn mumps virus strain (a vaccine strain not causally associated with human CNS damage), neonatal infection of a rat with a wild-type neurovirulent mumps virus strain (88–1961) led to significant hydrocephalus. Quantitative evidence of the severity of hydrocephalus in the rat was proportional to the neurovirulence of the virus strains in humans. In addition, significant neurodevelopmental damage was seen in the cerebellum of rats infected at birth with neurovirulent strains of mumps virus (Figure 1). Developed in response to concerns of vaccine-induced developmental brain damage, the principles of the mumps vaccine neurovirulence assay methodology are being applied to the development of neurovirulence tests for other live, attenuated virus vaccines.

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