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Translational medicine and varicella zoster virus: need for disease modeling

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A major goal of translational medicine is to leverage basic research and patient input into advancements in clinical practice. This goal may seem straightforward, but it is often hindered by technical roadblocks and the slow rate at which basic research findings transition into clinical practice. Both of these problems are present in the study of varicella zoster virus (VZV). VZV is a ubiquitous human pathogen typically encountered early in life when primary infection causes childhood varicella (chickenpox). During this time the neurotropic alphaherpesvirus infects ganglionic neurons at all levels of the neuraxis where the virus remains dormant (latent) in host neurons (reviewed in Eshleman et al., 2011). VZV latency is life-long and has no known effect on the individual, but if VZV reactivates, the results can be life-threatening. The fact that >95% of the world's 7 billion inhabitants have an immunologic response to VZV (Virgin et al., 2009) highlights the problem encountered when ascribing disease etiology to VZV reactivation. Simply stated; "How can one assign disease etiology to an agent that is universally present?" The problem is compounded because VZV is a strict human pathogen and there is currently no animal model that mirrors the human diseases caused when virus reactivates (Haberthur and Messaoudi, 2013). Without a disease model, Koch's postulates (the gold standard of pathology) cannot be met (Kaufmann and Schaible, 2005) and ascribing a causal relationship is tenuous. It was shown that zoster and varicella are caused by the same agent when chickenpox developed in children who were inoculated with fluid from a shingles vesicle (reviewed in Arvin and Gilden, 2013), but proof that the two viruses were the same was revealed only when both viruses showed the same DNA restriction endonuclease digestion profiles (Straus et al., 1984) and DNA sequence (Depledge et al., 2014). But current etiological assignment relies on association and logic.

VZV vasculopathy is an example that highlights the efforts required to show a causal relationship between a ubiquitous virus that reactivates predominately in the elderly and causes stroke in the elderly. An early report linking VZV to vasculopathy described 3

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patients with large-vessel cerebral vasculopathy after zoster (Eidelsberg et al., 1986). VZV was later shown to produce both large and small vessel vasculopathy (Kleinschmidt-DeMasters et al., 1996). In-depth analysis of a clinicopathologic exercise reported in the New England Journal of Medicine (Scully et al., 1997) found VZV DNA and antigen in a case of vasculopathy involving the brain and peripheral nerves and importantly demonstrated that VZV vasculopathy can involve both central and peripheral nervous system and that rash is not required (Gilden et al., 1996). Virological confirmation of VZV vasculopathy was provided when VZV antigen, typical cytopathic effects (Cowdry type A inclusion bodies), multinucleated giant cells (syncytia) and herpesvirus particles were found in affected arteries (Nagel et al., 2007). Importantly, detection of intrathecal synthesis of anti-VZV antibodies was shown to be superior to PCR to diagnose VZV vasculopathy (Nagel et al., 2007). Since then, multiple case reports have shown an association of VZV with vasculopathy. To supplement case reports and reviews, clinical data was collected to study patients diagnosed with zoster and herpes zoster ophthalmicus to determine their incidence of stroke. Age and sex matched controls were included (Lin et al., 2009, 2010; Breuer et al., 2014). The largest study (Breuer et al., 2014) analyzed 7760 zoster patients and 23,280 randomly selected matched control subjects and concluded that zoster is an independent risk factor for stroke. In light of overwhelming data showing an association between VZV and stroke, there is sufficient evidence to indicate that VZV is an often overlooked cause of stroke in the elderly, information particularly important since effective anti-VZV therapy exists (Nagel et al., 2010). Continued reports associate VZV with stroke (Sreenivasan et al., 2013) along with improved health after antiviral treatment (Silver et al., 2012).

Giant cell arteritis with VZV involvement is another example that highlights the need for a disease model. Giant cell arteritis (GCA) is a relatively uncommon disease of the elderly that is treated as an emergency since vision loss is a common complication. Corticosteroids are prescribed to reduce inflammation and prevent blindness (Petri et al., 2014). Since age is the most significant risk factor for VZV reactivation (Branisteanu et al., 2014) and zoster is highly associated with vasculopathies of both intracerebral and extracerebral cranial arteries (Nagel and Gilden, 2014), a concerted effort has been made to assess the contribution of VZV reactivation to GCA. Multiple case reports have detected VZV DNA or antigen in pathologically confirmed GCA temporal artery biopsies (Kosa et al., 2010; Mitchell and Font, 2001; Nagel et al., 2013). However, other reports failed to detect an association between VZV and GCA (Cooper et al., 2008; Kennedy et al., 2003; Rodriguez-Pla et al., 2004; Varez-Lafuente et al., 2005). How can these results be reconciled? As stated by Levin (2014) in his comments on Nagel et al. (2013), GCA is often present in skip lesions and a possible resolution to the problem can be found in the number of temporal artery sections analyzed. In addition, he emphasizes the significance of the problem, in that “recognition of VZV infection could prevent inappropriate and potentially harmful immunosuppressive therapy in biopsy-negative GCA, and might facilitate corticosteroid titration in biopsy-positive cases.” While prior studies that failed to show an association of VZV with GCA may have been due to the few sections analyzed, recently analysis of 50 sections from each of 86 pathologic confirmed GCA temporal artery biopsies found VZV antigen in 74% of cases (Gilden et al., *in press*). Virus antigen detection was validated by detecting VZV DNA

by PCR and herpesvirus particles by electron microscopy. Thus when sufficiently investigated VZV is highly associated with GCA, but such an in-depth analysis is difficult, costly and time consuming. These recent results showing a high association of VZV with GCA is likely to change clinical practice, however an experimental disease model is needed to formally prove a causal relationship between VZV and GCA and provide a platform to determine disease mechanism.

Ogilvie's syndrome, acute idiopathic intestinal pseudo-obstruction, is an example where an animal model may provide a platform to determine the mechanism of disease progression. Despite more than 200 peer-reviewed case reports, the etiology of Ogilvie's syndrome remains unknown. Yet VZV was found in a small bowel biopsy of a 34-yr old immunocompromised individual with small bowel pseudo-obstruction associated with disseminated cutaneous zoster (Pui et al., 2001), and an 83-yr old female developed thoracic zoster three days after hospitalization for Ogilvie's syndrome (Alph and Yandt, 1994).

VZV becomes latent in cranial nerve ganglia, dorsal root ganglia (Mahalingam et al., 1992) and autonomic ganglia (Nagel et al., 2014). VZV may also become latent in the enteric nervous system, the so called "second brain" (Gershon, 1995). VZV DNA has been detected in resected bowel from 12 of 13 children who have either had varicella or received varicella vaccine, but not in any of 7 resected bowels from control children (Chen et al., 2011). VZV may establish a latent infection in enteric neurons and reactivate to produce morbidity consistent with Ogilvie's syndrome. To test this hypothesis, wild type as well as guinea pig adapted VZV was shown to infect T cells (human or guinea pig) which successfully transferred virus to guinea pig gastrointestinal tract where latency had been established in enteric neurons (Gen et al., 2014). Latent VZV in guinea pig enteric neurons can be reactivated experimentally (Chen et al., 2003), thereby completing the VZV lifecycle. While these experiments do not show that VZV causes Ogilvie's syndrome, they do make use of a small animal model to experimentally investigate the pathogenetic events involved in virus reactivation from enteric ganglia; an event consistent with features of Ogilvie's syndrome.

Finally, VZV can reactivate in the absence of rash revealing that the full spectrum of disease produced by VZV reactivation is unknown. *Zoster sine herpette* (chronic radicular pain without rash) was described in multiple case reports (Lewis, 1958; Easton, 1970) and was later confirmed virologically (Gilden et al., 1994). Finally, VZV can reactivate asymptomatically (Mehta et al., 2004; Cohrs et al., 2008). Without a suitable model for all facets of VZV infection, latency and reactivation, understanding of VZV pathobiology will be difficult.

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Focal Points

Benchside

Suitable models for all facets of VZV infection, latency and reactivation are required to better understand the mechanism of VZV pathobiology.

Governments

Due to the increasing number of geriatric population at risk for severe disease caused by varicella zoster virus reactivation, there is immediate need to increase funding for research studies to find suitable models for VZV infection, latency and reactivation.