Immunotherapy for anti-GQ1b IgG antibody-mediated disorders: role of electrophysiology in human trials

Y.-L. Lo MD

Department of Neurology, National Neuroscience Institute, Singapore General Hospital, Outram Road, Singapore 169608
E-mail: lo.yew.long@sgh.com.sg

Sir, We read with interest the use of eculizumab as a protection against complement-mediated damage in a murine model of the Miller Fisher syndrome (MFS). This monoclonal antibody not only resulted in protection against functional and morphological terminal motor neuropathy, but effectively prohibited respiratory muscle paralysis (Halstead et al., 2008). These important findings have provided the basis for human trials in MFS, its related disorders of Bickerstaff’s brainstem encephalitis (BBE) and Guillain-Barré syndrome (GBS), as well as neuropathies in which antibody-mediated complement activation may be pathophysically important (Compston, 2008; Lehmann and Hartung, 2008).

MFS, BBE and GBS are now widely regarded as part of a continuous spectrum of disorders whereby anti-GQ1b IgG antibody plays a vital part in the pathogenesis, although other antibody involvement may be contributory (Odaka et al., 2001; Lo, 2007). Evidence of anti-GQ1b IgG antibody binding to nodes of Ranvier (Chiba et al., 1993) and presynaptic terminals neuromuscular junctions, leading to complement-dependent cytotoxicity, has been a great step forward in our understanding of these conditions (O’Hanlon et al., 2001).

These findings have been shown to be relevant in humans. Using single-fiber electromyography, patients with acute ophthalmoparesis and elevated anti-GQ1b IgG antibody exhibited abnormal jitters which improved with clinical recovery (Lo et al., 2004), providing the first reported evidence of neuromuscular transmission defect in patients with MFS. Employing high-frequency repetitive nerve stimulation (Lo et al., 2006), a presynaptic neuromuscular transmission defect was demonstrated in anti-GQ1b IgG antibody-positive MFS patients up to 3 months after clinical presentation. This corroborated in vitro findings of presynaptic structural derangements occurring in the nerve terminal (Halstead et al., 2004), as opposed to a transient nerve blocking phenomena.

More proximal sites of pathology have also been elucidated. By means of serial transcranial magnetic stimulation, prolonged subclinical central motor conduction time, a reflection of corticospinal dysfunction, was shown to reduce and normalize in tandem with clinical recovery in anti-GQ1b IgG antibody-positive MFS (Lo and Ratnagopal, 2001). A reversible corticobulbar motor conduction time abnormality was also demonstrated in a MFS patient exhibiting dysarthria (Lo and Ratnagopal, 2003). These findings highlight the presence of both clinical and subclinical functional lesions in anti-GQ1b IgG antibody-positive classic MFS patients. The exact location of corticospinal conduction abnormality remains uncertain, but in view of prevailing evidence, the nerve terminal region would certainly be a possibility. The findings also strengthen the relationship between MFS and the related disorder of BBE, where upper motor neuron signs may coexist with ophthalmoplegia, ataxia or an alteration of consciousness (Odaka et al., 2003).

In addition to MFS, we have also observed similar changes recently in BBE. A 31-year-old man presenting with drowsiness, ataxia, bilateral ptosis, limb weakness and exaggerated deep tendon reflexes had significant incremental compound muscle action potential responses and marked elevation of anti-GQ1b IgG antibody titer. His clinical status and motor power improved with intravenous immunoglobulin infusion, and increments subsequently returned to normal over a 6-month period. All five other patients presenting with classic GBS features over the same period did not have elevated anti-GQ1b IgG antibody titers, or significant incremental responses. This suggests that anti-GQ1b IgG antibody is closely associated with presynaptic neuromuscular transmission defect, and these five cases without electrophysiological evidence of presynaptic dysfunction served as negative controls. It is thus possible that anti-GQ1b IgG antibody may have played a role in BBE, but the neuromuscular transmission effects observed in MFS are largely subclinical. Our experience had thus provided preliminary observations correlating electrophysiology with clinical improvement in this group of disorders.

Therefore, what are the practical implications of all these findings? In the treatment of multiple sclerosis, both imaging...
and electrophysiological methods may serve as valuable adjuncts to physical examination in clinical trials (Comi et al., 1998; Leocani and Comi, 2000). Conversely, while electrophysiological changes are well described, imaging abnormalities are often absent in anti-GQ1b IgG antibody-related disorders. As immunomodulatory therapy is emerging as possible treatment for these diseases, electrophysiological changes may serve as surrogate functional correlates, even if clinical effects are not initially evident. Therefore, electrophysiology should be incorporated in future therapeutic trials, particularly in variants such as BBE, which carry considerably greater morbidity and mortality.

References


