The cerebellar channelopathy of multiple sclerosis

Stephen G. Waxman, MD, PhD
Orhun Kantarci, MD

Clinical abnormalities in multiple sclerosis (MS) have traditionally been attributed to inflammation, demyelination, or degeneration of axons within the brain and spinal cord. Among those symptoms, clinical deficits due to cerebellar dysfunction, including loss of coordination, ataxia, tremor, and dysarthria, can reduce function substantially, are less likely to remit, and are more likely to be associated with progressive MS in the future. Interestingly, cerebellar signs and symptoms are sometimes seen in patients in whom structural lesions or inflammation of the cerebellum cannot be detected. These symptoms can be paroxysmal, similar to trigeminal neuralgia in patients with MS, which preferentially responds to sodium channel blockers. What is the basis for these clinical deficits?

The Na\textsubscript{V}1.8 sodium channel, encoded by gene SCN10A, was initially called SNS (sensory neuron specific) because of its preferential expression within primary sensory neurons such as dorsal root ganglion (DRG) and trigeminal ganglion neurons in the healthy nervous system. Na\textsubscript{V}1.8 displays a unique functional profile that includes reduced steady-state inactivation at depolarized potentials (a property that allows Na\textsubscript{V}1.8 channels to remain available for operation at depolarized membrane potentials where other sodium channels are inactivated) as well as slow onset of inactivation followed by a rapid recovery from inactivation. As a result of these biophysical properties, Na\textsubscript{V}1.8 produces repetitive neuronal firing in response to sustained depolarization. In 2000, Black et al. described the abnormal expression of Na\textsubscript{V}1.8, which is not normally detectable in the cerebellum, within cerebellar Purkinje neurons in the brains of mice with experimental autoimmune encephalomyelitis (EAE) and in postmortem brain tissue from humans with MS. The presence of Na\textsubscript{V}1.8 channels within these cerebellar output neurons, where they are not normally present, would be expected to perturb the pattern of activity of these cells and, indeed, subsequent studies demonstrated that expression of Na\textsubscript{V}1.8 within Purkinje neurons in vitro and in mice with EAE leads to abnormal firing by these critically important cerebellar neurons.

In this issue of Neurology, Roostaei et al. extend the evidence for a role of Na\textsubscript{V}1.8 in cerebellar dysfunction in patients with MS. With a focus on motor-behavioral and neural correlates of SCN10A polymorphisms, they assessed 161 patients with relapsing-onset MS for clinical disability and functional status. They assessed the SCN10A polymorphisms in these patients and found a relationship between SCN10A genotype and performance on tests of functional status. This association was independent of cerebellar volume, but in a subset of 62 patients with MS assessed via resting-state fMRI, there was decreased cerebellar-functional connectivity with the thalamus and midbrain in patients carrying the single nucleotide polymorphism associated with impaired performance. Consistent with the idea that Na\textsubscript{V}1.8 is expressed in the cerebellum in MS but not in the normal cerebellum, SCN10A genotype did not have an effect on performance in a control group that did not have MS.

All of this suggests that molecular mistuning of Purkinje neurons as a consequence of the abnormal presence of Na\textsubscript{V}1.8 contributes to phenotypic manifestation of MS. It may therefore be possible to reverse cerebellar symptoms in MS by treatment with drugs that block Na\textsubscript{V}1.8 channels. Because Na\textsubscript{V}1.8 plays an important role in the firing of DRG neurons, including pain-signaling cells, Na\textsubscript{V}1.8 subtype selection blockers are being developed for the treatment of pain. Two of these Na\textsubscript{V}1.8 blockers have, in fact, been studied in animal models of MS, and improve clinical function, with a time course that parallels their pharmacokinetics.

While the latest work by Roostaei et al. represents an important step forward, there is still much to learn about the cerebellar channelopathy that occurs in MS. Higher-resolution tests of cerebellar function might more definitively establish the details of the impact of the abnormally tuned Purkinje neurons on specific aspects of cerebellar function in MS. While Black et al. clearly demonstrated the anomalous presence of Na\textsubscript{V}1.8 in Purkinje neurons in the cerebellums of patients with MS, examined postmortem, and the Roostaei et al. article provides evidence for a role of
NAV1.8 in cerebellar function in vivo in patients with MS but not in a control group without MS, we do not yet understand the triggers that lead to upregulation of NAV1.8 expression in the cerebellum in MS. There are some hints that this may be related to increased levels of nerve growth factor within the inflamed nervous system, but this remains to be confirmed. Moreover, whether treatment strategies can be devised that will reverse cerebellar symptomology without blunting nociception remains to be determined. One approach might be to administer a NAV1.8 blocker intrathecally. This would be no more invasive than use of intrathecal baclofen for treatment of spasticity. There clearly is a need for more work.

Despite these unresolved issues, the Roostaei et al. article provides additional evidence pointing to a channelopathy that causes cerebellar mistuning in MS. Their findings also lead to 2 additional hypotheses: (1) it is possible that channelopathies of other types may play additional roles in shaping the clinical phenotype of patients with MS; (2) targeted approaches focusing on hypothesis-based candidate genotype–phenotype correlations may provide us with clinically and pharmaceutically relevant targets. Ultimately these may provide a basis for new therapies.

STUDY FUNDING

No targeted funding reported.

DISCLOSURE

S. Waxman has served on advisory boards for SiteOne Therapeutics; has served on the editorial boards of Journal of Neurotrauma, Clinical Neuroscience, The Neurologist, Neurobiology of Disease, The NeuronScientist, Clinical Neurology & Neurosurg, SYNAPSE: Molecular Neurobiology, Clinical Neuroscience Research, Neuroscience Letters, Brain, Nature Reviews, Neurology, Neuron-Glia Biology, Neurotherapeutics, The Journal of Physiology, Trends in Molecular Medicine, Molecular Pain, Channels, Multiple Sclerosis, and Faculty of 1000 Medicine; holds a patent for Invention of sodium channel Na1.9 (Yale University); has consulted for ChromeCell Pharmaceuticals, Amgen, Voyager Therapeutics, Janssen Pharmaceuticals, and Teva Pharmaceuticals; has received research support from Pfizer, Convergence Pharmaceuticals, Department of Veterans Affairs Center, and Paralyzed Veterans of America; and holds stock/stock options in SITE ONE Research. O Kantarci has received funding for travel and/or speaker honoraria from Novartis Pharmaceuticals; has participated in grant review for The National Multiple Sclerosis Society, and has received research support from the European Regional Development Fund, National Multiple Sclerosis Society, Mayo Foundation, and Hilton Foundation. Go to Neurology.org for full disclosures.

REFERENCES