Updates in Neurology

Editor's note: Several advances in Neurology subspecialties in the last 10 years have led to improved patient care. Developments in the fields of neuroinflammation/multiple sclerosis, neuromuscular medicine, vascular neurology, headache medicine, and epilepsy make it important for the non-neurologist to stay abreast. A few advances of which we should all be aware are summarized here by LGHP Neurology providers, who are currently implementing these evidence-based standards of care.

NEW THERAPIES FOR NEUROMYELITIS OPTICA SPECTRUM DISORDER

Wen Y. Helena Wu-Chen, MD, FAAN

Neuromyelitis optica spectrum disorder is an autoimmune disorder characterized by recurrent inflammatory attacks against the astrocyte aquaporin-4 water channel. It primarily affects the optic nerves and spinal cord, resulting in visual deficits and loss of coordination. Although this disorder is rare — affecting 1 to 10 per 100,000 patients — if left undiagnosed and untreated, it can cause blindness and paralysis. Conventional immunosuppressive treatments include rituximab, mycophenolate mofetil, azathioprine, and prednisone, and have been used based on observational clinical studies that lacked masking or control groups.[1,2]

The aquaporin-4 immunoglobin G (IgG) antibody was discovered in the early 2000s and has led to an increased understanding of how the immune system causes astrocyte damage through three crucial targets: the terminal complement system, interleukin-6 (IL-6) receptor, and B cells. Up to 80% of patients have the presence of aquaporin-4 IgG biomarkers.[3]

Because the presence of seropositivity is highly predictive of future relapses, recent treatment efforts have focused on preventive therapies.[3,4]

Recently, randomized controlled trials tested these three therapeutic approaches:

- Among the monoclonal antibodies that inhibit complement component 5 are eculizumab, given every two weeks by infusion, and ravulizumab, given every eight weeks by infusion.

  The primary associated risk is infection by encapsulated organisms such as *Neisseria meningitidis*, therefore a vaccination series must be completed at least two weeks prior to the first dose of antibody treatment.
- Satralizumab, a monoclonal antibody targeting the IL-6 receptor antagonist, is given subcutaneously every four weeks.[3]
- Inebilizumab is a humanized monoclonal antibody that binds to the CD19 surface antigen of B cells, depleting lymphocytes derived from B cell lineage. This is given by infusion every six months.[5]

All patients must be screened for active hepatitis B as well as tuberculosis and cared for appropriately prior to receiving immunotherapy.

NEW EPILEPSY CLASSIFICATION

Heather D. Harle, MD

The International League Against Epilepsy published new guidelines in 2017 regarding definitions/nomenclature of epilepsy subtypes.[6] Terms such as "simple partial" or "complex partial" are often misunderstood and therefore have been updated to be more informative to physicians and patients. The new nomenclature is more descriptive, allowing the care team to understand the different seizure types — a patient may have more than one type — and how they present.

The description outline has three parts: where in the brain seizures begin, the level of awareness during the seizure, and the semiology — that is, the appearance — of the seizure. "Simple partial" has been renamed "focal onset aware," and "complex partial" is now "focal onset impaired awareness."

Finally, whether there is left arm shaking, oral automatisms, feeling of fear, or other presentation is described. If the seizure moves from being focal to generalized tonic clonic, the new term is "focal to bilateral tonic clonic" or FBTCS.

As an example, a patient with seizures of lip smacking and staring would, according to the old system, be identified as having complex partial seizures. According to the new system of classification, we would designate this "focal onset impaired awareness seizure. Semiology: oral automatisms." This gives much more description to all providers so to improve recognition and care.

The terminology has not changed regarding generalized seizures, which are still designated as "tonic clonic," "atonic," or "absence."

AN OVERLOOKED, BUT COMMON MOVEMENT DISORDER

Gabriel Hou, MD, PhD, FAAN

Writer's cramp or hand dystonia is an abnormal unwanted hand muscle spasm that interferes with tasks, especially writing.[7] It may start with a tight grip on the pen. Hand and wrist flexions are more common, with occasional hyperextension of the fingers.[8] Writing is difficult and cannot be sustained; handwriting becomes illegible. Other hand dystonias include typing dystonia or musician's dystonia, which affects playing musical instruments by hand.

A task-specific focal dystonia, hand dystonia is common among patients ages 30 to 50 years old and affects about 15 per 100,000 people.[9] The cause is usually idiopathic. Diagnosis is through clinical history and examinations.

Historically, treatments included anticholinergic medications, which may be helpful for some patients. The newest and most effective treatment includes botulinum toxin injections, which LGHP neurologists now use regularly to target the dystonic carpi and digitorum flexor or extensor muscles. Occupational therapy for sensory and motor skills retuning are also beneficial and considered standard of care.[10]

MULTIPLE SCLEROSIS TREATMENT APPROACH

Neha Safi, MD, MS

Given the many treatment options now available for multiple sclerosis (MS) patients, it can be overwhelming to select which one to initiate first. Previously, clinicians recommended low-efficacy therapies to limit potential side effects and only moved to high-efficacy or escalation therapy if patients manifested breakthrough disease.[11]

Newer studies show that starting high-efficacy therapies in treatment-naïve patients can decrease annualized relapse rates and reduce long-term disability progression.[12] Therefore, choosing anti-CD20 monoclonal antibodies — ocrelizumab or ofatumumab — or an anti-integrin monoclonal antibody such as natalizumab as first-line therapy may be more beneficial in the long run. Insurance companies can be reassured that these first-line therapies are worth the cost to prevent future disability, especially in patients who present with lesions in the posterior fossa or spinal cord.

As patients with MS get older, their immune systems may be less prone to causing new disease activity due to immunosenescence, thus de-escalation or even discontinuation of high-efficacy therapy may be appropriate.[13] The DISCOMS trial was conducted to determine if MS patients age 55 years and older who were stable on disease modifying therapy (DMT) for at least five years could safely discontinue their DMT; it did not demonstrate noninferiority compared to patients who continued on treatment.[14] However, on a case-by-case basis, MS neurologists and their patients may consider stopping DMT if both neurologic exams and MRI scans remain stable and reassuring.[15]

UPDATES IN MYASTHENIA GRAVIS

Allison Crowell, MD

Myasthenia gravis is a disorder of neuromuscular junction transmission that affects approximately 14 to 20 per 100,000 people, accounting for roughly 350,000 to 600,000 cases in the United States. Although it is a relatively rare condition, advances in targeted therapeutic interventions have changed the way that neurologists treat patients with myasthenia gravis in recent years.

In patients with myasthenia gravis, complement inhibition at the neuromuscular junction can result in more acetylcholine receptors at the post-synaptic junction, improving neuromuscular junction transmission and muscle contraction.

New classes of medications include complement inhibitors, such as ravulizumab and zilucoplan. Risks of complement inhibition include infection such as meningococcal meningitis. Vaccination is required prior to the initiation of treatment.

A second class of novel treatments includes the neonatal Fc receptor (FcRn) monoclonal antibodies efgartigimod and rozanolixizumab. Autoantibodies against IgG bind to the FcRn and reduce the amount of circulating pathogenic IgG antibodies, including those that attack the neuromuscular junction in myasthenia. The overall reduction in IgG antibodies does increase the risk of upper respiratory tract and urinary tract infections.

Both of these new classes of medications result in immunomodulatory, rather than immunosuppressive, effects; therefore treatment-related adverse effects are mild to moderate and do not result in significant immune compromise.[16-18] The price of these new medications is high, but assistance programs and insurance approvals are not challenging to navigate.

UPDATES IN HEADACHE NEUROLOGY

Ellen Michelle Gibson Depoy, MD

Migraine remains a major reason for absenteeism from work and school. The past decade has witnessed robust innovation of novel drug classes. These include calcitonin gene-related peptide (CGRP) antagonist monoclonal antibodies and small molecule CGRP antagonists (gepants), the latter of which are available as oral medication and have a shorter half-life.

CGRP is a 37-amino acid neuropeptide present in the peripheral and central nervous systems that has been shown to ignite the migraine signaling pathway.[19,20] CGRP-targeting therapies were specifically developed for migraine treatment, and several randomized clinical trials demonstrate efficacy and tolerability compared to both placebo and off-label migraine preventive medications, i.e., beta blockers, antiepileptic medications, and antidepressants.

The efficacy of CGRP antagonists in preventive treatment, paired with excellent safety and tolerability profiles, has revolutionized headache treatment. Specifically, these therapies do not seem to cause liver problems and are not associated with medication-overuse headache — two issues that must be faced with more classical agents.

American Headache Society guidelines state that CGRP antagonists are first-line therapies for migraine prevention, based on efficacy, safety, and tolerability data from several randomized clinical trials.[21] A significant downside includes the high cost of CGRP antagonist medications, and this may continue to be a concern until generic formulations are available.

REFERENCES

1. Paul F, Murphy O, Pardo S, Levy M. Investigational drugs in development to prevent neuromyelitis optica relapses. *Expert Opin Investig Drugs.* 2018;27(3):265-271.
2. Wingerchuk DM, Weinshenker BG. Neuromyelitis optica (Devic's syndrome). *Handb Clin Neurol.* 2014;122:581-599.
3. Levy M, Fujihara K, Palace J. New therapies for neuromyelitis optica spectrum disorder. *Lancet Neurol.* 2021;20(1):60-67.
4. Matiello M, Lennon VA, Jacob A, et al. NMO-IgG predicts the outcome of recurrent optic neuritis. *Neurology.* 2008;70(23):2197-2200.
5. Frampton JE. Inebilizumab: first approval. *Drugs.* 2020;80(12):1259-1264.
6. Scheffer IE. ILAE classification of the epilepsies: position paper of the ILAE Commission for Classification and Terminology. *Epilepsia.* 2017;58(4):512-521.
7. Hallett M. Pathophysiology of writer's cramp. *Hum Mov Sci.* 2006;25(4-5):454-463.
8. Albanese A. Phenomenology and classification of dystonia: a consensus update. *Mov Disord.* 2013;28(7):863-873.
9. Steeves TD, Day L, Dykeman J, Jette N, Pringsheim T. The prevalence of primary dystonia: a systematic review and meta-analysis. *Mov Disord.* 2012;27(14):1789-1796.
10. Park JE, Shamim EA, Panyakaew P, et al. Botulinum toxin and occupational therapy for writer's cramp. *Toxicon.* 2019;169:12-17.
11. Casanova B, Quintanilla-Bordás C, Gascón F. Escalation vs. early intense therapy in multiple sclerosis. *J Pers Med.* 2022;12(1):119.
12. Freeman L, Longbrake EE, Coyle PK, Hendin B, Vollmer T. High-efficacy therapies for treatment-naïve individuals with relapsing-remitting multiple sclerosis. *CNS Drugs.* 2022;36(12):1285-1299.
13. Goldschmidt CH, Glassman J, Ly B, Harvey T, Hua LE. A retrospective study on the effects of de-escalation of disease-modifying therapy in patients with multiple sclerosis. Presented at: *CMSC Annual Meeting,* May 31-June 3, 2023; Aurora, CO.
14. Corboy JR, Fox RJ, Kister I, et al. Risk of new disease activity in patients with multiple sclerosis who continue or discontinue disease-modifying therapies (DISCOMS): a multicentre, randomised, single-blind, phase 4, non-inferiority trial. *Lancet Neurol.* 2023;22(7):568-577.
15. Rae-Grant A, Day GS, Marrie RA, et al. Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology [published correction appears in Neurology. 2019 Jan 8;92(2):112]. *Neurology.* 2018;90(17):777-788.
16. Narayanaswami P, Sanders DB, Wolfe G, et al. International consensus guidance for management of myasthenia gravis: 2020 update. *Neurology.* 2021;96(3):114-122.
17. Uzawa A, Utsugisawa K. Biological therapies for myasthenia gravis. *Expert Opin Biol Ther.* 2023;23(3):253-260.
18. Menon D, Bril V. Pharmacotherapy of generalized myasthenia gravis with special emphasis on newer biologicals. *Drugs.* 2022;82(8):865-887.
19. Ibekwe A, Perras C, Mierzwinski-Urban M. Monoclonal antibodies to prevent migraine headaches. In: *CADTH Issues in Emerging Health Technologies.* Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; February 1, 2018, 1-17.
20. Goadsby PJ, Holland PR, Martins-Oliveira M, Hoffmann J, Schankin C, Akerman S. Pathophysiology of migraine: a disorder of sensory processing. *Physiol Rev.* 2017;97(2):553-622.
21. Charles AC, Digre KB, Goadsby PJ, Robbins MS, Hershey A; American Headache Society. Calcitonin gene-related peptide-targeting therapies are a first-line option for the prevention of migraine: an American Headache Society position statement update. *Headache.* 2024;64(4):333-341.

Corresponding Author
Heather D. Harle, MD
Managing Physician, LGHP Neurology
2150 Harrisburg Pike, Ste. 200, Lancaster, PA 17601
717-396-9167
Heather.Harle@pennmedicine.upenn.edu