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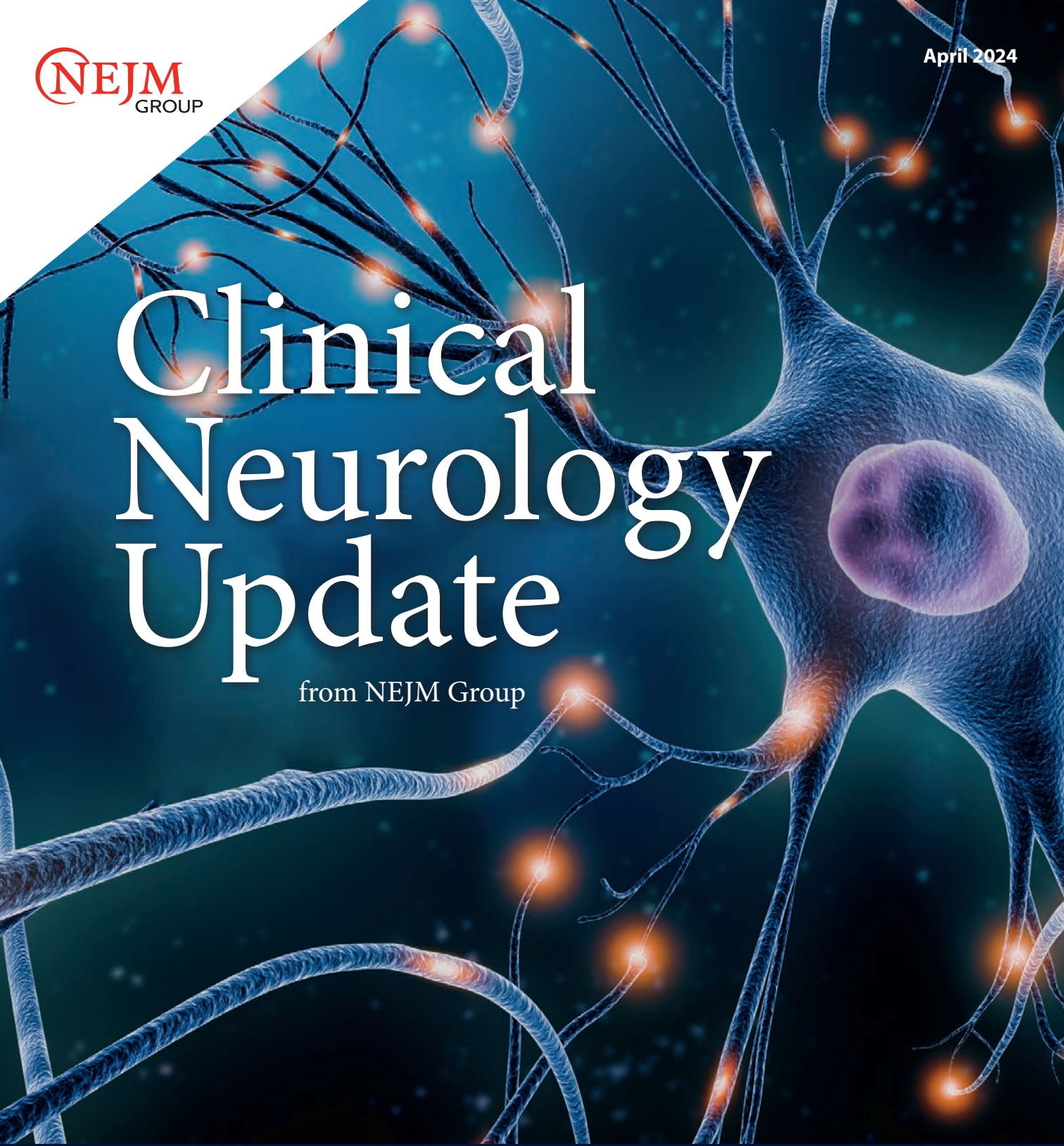

Clinical Neurology Update

from NEJM Group

- Social Media & Tics
- Autoimmune Encephalopathies
- The Future of Brain Health
- Guidelines: Brain Death Determination

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FROM the Editor

Welcome to our latest *Clinical Neurology Update*, which navigates through myriad significant discoveries in our field from the last year, each reflecting the interdisciplinary nature of neurology while collectively advancing knowledge, improving diagnostics, enhancing treatment, and ultimately contributing to the well-being of patients.

Our first Topic Update delves into the influence of social media on neurological symptoms with the phenomenon of functional tic-like behavior as observed in adolescents during the Covid-19 pandemic. Dr. Jessica Frey explores the distinct characteristics of these behaviors and how best to differentiate them from Tourette's syndrome.

Our second Topic Update from Dr. Mayra Montalvo focuses on the evolving understanding of autoimmune encephalitis. Emphasizing accurate diagnosis and management, this article underscores the importance of adherence to diagnostic criteria and ongoing therapeutic clinical trials.

The third Topic Update prepared by American Academy of Neurology (AAN) President-Elect Dr. Natalia Rost and David Evans addresses the growing AAN priority of brain health and the implications for neurology practice, emphasizing the role of neurologists in both preventive care and performance optimization throughout the lifespan.

NEJM Journal Watch summaries cover some of the more interesting articles of the year from a variety of neurology specialties. A Visual Summary illustrates the use of ubrogepant in the prodromal phase of migraine attacks, offering valuable insights into blocking acute attacks. Guideline Watches include the new AAN brain death evidence-based guidelines for adult and pediatric populations and the newest consensus recommendations for a localization-based paradigm for the diagnosis of multiple sclerosis. The Image in Clinical Medicine is a fascinating case of accumulation of manganese in the brain and includes images before and after treatment.

This issue collectively showcases the evolving landscape of neurology, emphasizing biomarkers, diagnostic tests, and treatment comparisons. There has never been a more exciting time for neurology. Within the pages of this issue, we see a variety of advances in more targeted therapeutics through pharmacology, procedural intervention, or diet and lifestyle factors. Although wide-ranging in topics, the commonality throughout lies in the advancements in knowledge within neurology and the improvement of patient care.

Michael S. Jaffee, MD, FAAN, FANA, Editor

Dr. Jaffee is Chair of the Department of Neurology and the Bob Paul Family Professor of Neurology at the University of Florida College of Medicine, Gainesville; and Director of the UF Brain Injury, Rehabilitation, and Neuroresilience (BRAIN) Center. He reports external grant support from the National Institutes of Health, the US Department of Veterans Affairs, the Florida Department of Elder Affairs, the Administration for Community Living, and Applied Cognition.

Topic Update

Social Media and Functional Tic-like Behavior

Jessica Frey, MD

During the Covid-19 pandemic, there was a surge in extreme tic-like behaviors in adolescents, with history and phenomenology that appeared to be distinct from the expected presentation of Tourette's syndrome (TS; *Psychol Res Behav Manag* 2022; 15:3575). These explosive tic presentations are now termed functional tic-like behavior (FTLB). Although the portrayal of tics on social media during the pandemic was thought to play a significant role in the development of FTLB, many complex factors were likely involved. Given the widespread development of FTLB across geographic and cultural borders, it is important to understand how to differentiate FTLB from TS. This Topic Update summarizes the current state of our knowledge about FTLB and its management.

Social Media Use During Covid-19

Even before the pandemic, social media played a role in the perception of tics. A study from 2012 found that viewers were more likely to click on videos demonstrating negative portrayals of TS (*J Child Neurol* 2012; 27:1011). As early as 2016, videos of "tic attacks" appearing on social media platforms such as YouTube more closely resembled non-epileptic seizures than tic phenomenology (*Front Pediatr* 2016; 4:46).

During the pandemic, when social media use was reported to increase among adolescents (*Cyberpsychol Behav Soc Netw* 2021; 24:250), the "#tourette" hashtag gained enormous popularity, with tic-related content being viewed over 5 billion times on the TikTok social medial platform alone (*Front Pediatr* 2022; 10:863919). Some of these social media interactions have been positive, creating a support system for those with tics (*Psychol Res Behav Manag* 2022; 15:3575). However, tic-related content on social media raises a variety of concerns. First, since social media content is unregulated, some tic portrayals perpetuate false ideas and further stigmatize people living with TS. Second, videos that spread incorrect information about tics may lead to reinforcement of untrue beliefs or sometimes even dangerous behaviors. Third, at least some of the tic-related misinformation may be financially motivated (*Front Pediatr* 2022; 10:863919; *Mov Disord Clin Pract* 2021; 8:1200). Videos with more violent or bizarre tic-related behaviors are more likely to generate more views, which in turn generate a higher income for the content uploader. Therefore, social media influencers may be tempted to post or inadvertently post videos with content more likely to attract viewers.

FTLB Characteristics

The phenomenological characteristics of FTLB have been described in multiple case series during the pandemic (*Psychol Res Behav Manag* 2022; 15:3575; *Eur J Neurol* 2023; 30:2411) and closely resemble the characteristics of functional tics that have been described pre-pandemic (*Neurology* 2019; 93:750). Features of TS and FTLB often overlap, and it is also possible for individuals with a prior diagnosis of TS to develop FTLB, making it challenging to tease apart the characteristics. However, these case series revealed some unique features of FTLB. A high proportion of patients presenting with FTLB reported watching tic-related social media content (*Psychol Res Behav Manag* 2022; 15:3575; *Front Pediatr* 2022; 10:863919; *Mov Disord Clin Pract* 2021; 8:1200). Also, a notable difference in FTLB was that individuals frequently presented to clinic with identical or nearly identical tics to those portrayed in popular social media videos (*Mov Disord Clin Pract* 2021;

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Disclosures: Dr. Frey reports external grant support from the Tourette Association of America.

8:1200; *Brain* 2022; 145:476). The other major differences between TS and FTLB are summarized in the accompanying Table.

Diagnostic Criteria

Based on these clinical observations, the European Society for the Study of Tourette Syndrome developed diagnostic criteria for FTLB (*Eur J Neurol* 2023; 30:902). A clinically definite diagnosis of FTLB must fulfill all three major criteria, which include a tic onset after the age of 12, a rapid development of symptoms, and the presence of at least four of the nine phenomenological features of FTLB included in the published diagnostic criteria. A clinically probable diagnosis of FTLB must include at least two of the major criteria and one of the minor criteria, which include the presence of psychiatric comorbidities or other functional neurologic symptoms that are commonly seen in association with FTLB.

FTLB Etiology

This is certainly not the first time that tics have "spread" — as demonstrated by the infamous case of 19 students who developed tic-like behavior at Le Roy High School in 2012, with the symptoms eventually being termed "mass hysteria" (*Ann N Y Acad Sci* 2013; 1304:40). Given that FTLB appears to have been "spread" in large part due to increased social media consumption during the Covid-19 pandemic, the term "mass social media–induced illness" has been proposed to describe this phenomenon (*Brain* 2022; 145:476, *Ann N Y Acad Sci* 2013; 1304:40). However, the connection between social media and FTLB is likely more nuanced and complex than was originally thought. Indeed, several factors likely play a part, including predisposing genetic links, psychiatric risk factors such as underlying depression and anxiety, poor coping habits, external stressors, pandemic-specific issues such as social isolation, and increased exposure to social media leading to behavioral modeling (*Mov Disord* 2021; 36:2707; *Eur J Neurol* 2021; 28:3805; *Eur J Neurol* 2023; 30:334).

FTLB Treatment

Many patients who developed FTLB during the pandemic have reported improvement either following therapy programs or following the removal

Table. Comparison of Historical and Phenomenological Characteristics Reported in Tourette's Syndrome and Functional Tic-like Behavior

	Tourette's Syndrome	Functional Tic-like Behavior
Historical Characteristics		
Age at Tic Onset	5–7 years	12–21 years
Gender Predilection	76% male*	87% female*
Tic Progression	Gradual	Acute, explosive
Family History of Tics	Common	Uncommon
Associated Conditions	ADHD, OCD	Depression, anxiety, functional neurologic disorders
Phenomenological Characteristics		
Distribution	Rostrocaudal	Arm and trunk involvement
Variability	Consistent and stereotyped	Inconsistent, context-dependent, and highly variable
Quality	Simple tics are more common	Often complex, ballistic, self-injurious
Frequency of Tic Attacks (Episodes of Sustained Repeated Tics or Whole Body Movements)	Rare; less than 8% of patients*	More common; 36%–100% of patients*
Frequency of Coprophenomena	Less than 20% of patients*	Common

ADHD — attention deficit/hyperactivity disorder; OCD — obsessive–compulsive disorder

*Source: **Curr Devel Disord Rep** 2022; 9:146

of stressors (*New York Times* Feb 13 2023). It is important to note that most patients with FTLB do not report a benefit with tic-suppressing medications (*Eur J Neurol* 2023; 30:334; *Front Pediatr* 2022; 10:1003825). Instead, the current recommendations are to educate patients about FTLB, since early diagnosis is associated with favorable outcomes (*Front Pediatr* 2022; 10:1003825; *J Clin Med* 2022; 11:6470). To date, follow-up studies of patients with FTLB suggest that a modification of Comprehensive Behavioral Intervention for Tics (CBIT) may be beneficial for FTLB symptoms (*Mov Disord* 2021; 36:2707; *Eur J Neurol* 2021; 28:3805). In addition, treating underlying comorbid conditions such as depression and anxiety may provide some benefit (*Eur J Neurol* 2023; 30:334; *J Clin Med* 2022; 11:6470). Overall, avoiding risks for developing FTLB should be the first intervention, followed by education about the diagnosis, reduction of potential triggers, avoidance of reinforcing factors, and treatment of underlying comorbid conditions.

Conclusion

There are many distinguishing features of FTLB by history and by phenomenology. It is important to understand the natural history of this condition so as to make a correct diagnosis, offer appropriate education, and provide proper management and support for patients with FTLB.

Topic Update

Autoimmune Encephalitis: Approaches to Diagnosis and Management

Mayra Montalvo, MD

Autoimmune encephalitis is a diverse group of disorders characterized by the immune system's attack on antigens in the central nervous system. Given the potentially dramatic response to treatment, it has become one of the top differential diagnoses in patients with subacute or rapidly progressive neurological disorders. Adherence to current diagnostic criteria, as well as careful interpretation of neural antibody testing, is of paramount importance in preventing misdiagnosis. Randomized clinical trials are lacking, and multiple therapeutic clinical trials are in progress. Multicenter collaboration is key to such efforts. This Topic Update summarizes the latest research and developments in diagnosing and managing this disease.

Diagnostic Criteria

Two studies using data from clinical practice showed that sensitivity is moderate to high for the 2016 published clinical criteria for probable autoimmune encephalitis (*Neurol Clin Pract* 2023; 13:e200151; *Neurol Neuroimmunol Neuroinflamm* 2023; 10:e200148). Criteria for probable autoimmune encephalitis (N-methyl-D-aspartate [NMDA], leucine-rich, glioma-inactivated 1 [LGI1], or seronegative) and definite autoimmune limbic encephalitis have high specificity and may help guide decisions about immunotherapy early in the disease (*Neurol Neuroimmunol Neuroinflamm* 2023; 10:e200148). See Table 1 for the 2016 autoimmune encephalitis criteria (*Lancet Neurol* 2016; 15:391).

Misdiagnosis and Pitfalls

Using data from six centers with expertise in autoimmune neurology, a recent study showed that approximately 70% of patients initially misdiagnosed with autoimmune encephalitis did not fulfill the published 2016 criteria for probable autoimmune encephalitis (*JAMA Neurol* 2023; 80:30). Red flags for misdiagnosis included an insidious course and lack of evidence of inflammation on magnetic resonance imaging (MRI) or cerebrospinal fluid (CSF) testing. Of the patients incorrectly diagnosed with autoimmune encephalitis, 25% of correct diagnosis were functional neurological disorders, 21% neurodegenerative disease, and 18% primary psychiatric disease. Other factors contributing to misdiagnoses included overinterpretation of a nonspecific positive antibody result in 50% of cases. The most common culprits include positive thyroid peroxidase antibodies of any titer, low titer anti–glutamic acid decarboxylase 65 (GAD65), anti–contactin-associated protein-like 2 (CASPR2) anti-NMDA antibody positive in serum but not on CSF, N-type calcium channel, P/Q-type calcium channel, AchR ganglionic, and voltage-gated K channel, especially when anti-LGI1 and anti-CASPR 2 antibodies are negative).

A single-center study from the Netherlands found that overinterpretation of antibodies resulted in misdiagnosis in only 12% of cases (*Neurol Neuroimmunol Neuroinflamm* 2023; 10:e200148). This may be explained by the practice in the Netherlands of performing antibody testing in a more selected patient population. The same study also emphasized the importance of bilateral limbic lesions with atypical

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Disclosures: Dr. Montalvo reports fees or compensation from Amgen Therapeutics.

Table 1. 2016 Diagnostic Criteria for Autoimmune Encephalitis

Possible Autoimmune Encephalitis

Must meet all three criteria:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptom
2. At least one of the following:
   - New focal CNS findings
   - Seizures not explained by a previously known seizure disorder
   - CSF pleocytosis (white blood cell count of more than 5 cells per mm^3)
   - MRI features suggestive of encephalitis
3. Reasonable exclusion of alternative causes

Definite Autoimmune Encephalitis

Must meet all four criteria:

1. Subacute onset (rapid progression of less than 3 months) of working memory deficits, seizures, or psychiatric symptoms suggesting involvement of the limbic system
2. Bilateral brain abnormalities on T2-weighted fluid-attenuated inversion recovery MRI highly restricted to the medial temporal lobes
3. At least one of the following:
   - CSF pleocytosis (white blood cell count of more than 5 cells per mm^3)
   - EEG with epileptic or slow-wave activity involving the temporal lobes
4. Reasonable exclusion of alternative causes

Autoantibody-Negative but Probable Autoimmune Encephalitis

Must meet all four criteria:

1. Rapid progression (less than 3 months) of working memory deficits (short-term memory loss), altered mental status, or psychiatric symptoms
2. Exclusion of well-defined syndromes of autoimmune encephalitis (e.g., typical limbic encephalitis, Bickerstaff's brainstem encephalitis, acute disseminated encephalomyelitis)
3. Absence of well-characterized autoantibodies in serum and CSF, and at least two of the following criteria:
   - MRI abnormalities suggestive of autoimmune encephalitis
   - CSF pleocytosis, CSF-specific oligoclonal bands or elevated CSF IgG index, or both
   - Brain biopsy showing inflammatory infiltrates and excluding other disorders (e.g., tumor)
4. Reasonable exclusion of alternative causes

CNS — central nervous system; CSF — cerebrospinal fluid; EEG — electroencephalogram; IgG — immunoglobulin G; MRI — magnetic resonance imaging

Source: **Lancet Neurol** 2016; 15:391

radiologic features, requiring more extensive testing as tumors can be a prominent mimicker.

Newly Discovered Neural Antibodies and Biomarkers

The number of recognized neural biomarkers that are associated with autoimmune encephalitis continues to grow. One of the most recent discoveries is the identification of Dachshund-homolog 1 (DACH1) as the antineuronal nuclear antibody-type 3 autoantigen (*Ann Neurol* 2022; 91:670). See Table 2 for a comprehensive list of antibodies associated with encephalitis syndromes.

Treatment Strategies

In general, first-line management of autoimmune encephalitis includes intravenous high-dose steroids in conjunction with intravenous immunoglobulins or plasmapheresis. Second-line therapy includes alkylating agents (e.g., cyclophosphamide) and B-cell depletion therapy (e.g., rituximab). Given its more favorable side effect profile, rituximab is most favored by clinicians. Retrospective studies on anti-NMDA receptor (NMDAR) autoimmune encephalitis suggest that rituximab might improve functional outcomes and prevent relapse (*Neurotherapeutics* 2022; 19:823).

Other treatments are being explored for treatment of refractory autoimmune encephalitis. In a small cohort series of patients with inadequate response to rituximab, tocilizumab (an interleukin [IL]-6 inhibitor) showed better outcomes at 2 years compared with patients who were continued on rituximab and patients receiving no other intervention.

Table 2. Neural Antibodies Associated with Encephalitis

Antibodies that Target Nuclear or Cytoplasmic Proteins	Antibodies that Target Plasma Membrane Proteins
PCA-1 (anti-Yo)	LGI1
PCA-2/MAP1B	CASPR2
ANNA-1 (anti-Hu)	PCA-Tr/ Anti-Tr/DNER
ANNA-2 (anti-Ri)	NMDAR
CRMP5-IgG (anti-CV2)	AMPAR
Amphiphysin-IgG	$GABA_AR$
Ma1, Ma2	$GABA_BR$
GAD65-IgG	AQP4*
AK5	GluR5
ITPR1	MOG*
GFAP	DPPX
TRIM 4	IgLON5
TRIM 9/TRIM 67	Neurexin-3α
Kelch-like protein 11	Septin-7
LUZP4	
DACH1	

Left column: PCA — Purkinje cytoplasmic antibody; MAP — microtubule-associated protein; ANNA — antineuronal nuclear antibody; CRMP5 — collapsin response mediator protein 5; IgG — immunoglobulin G; GAD65 — 65 kDa isoform of glutamic acid decarboxylase; AK5 — adenylated kinase 5; ITPR1 — inositol 1,4,5-trisphosphate receptor type 1; GFAP — glial fibrillary acidic protein; TRIM — tripartite motif; LUZP4 — leucine zipper 4; DACH1 — Dachshund-homolog 1
Right column: LGI1 — leucine-rich, glioma-inactivated 1; CASPR2 — contactin-associated protein-like 2; PCA-Tr —Purkinje cell antibody type Tr; DNER — delta/notch-like epidermal growth factor–related receptor; NMDAR — N-methyl-D-aspartate receptor; AMPAR: α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; $GABA_AR$ — γ-aminobutyric acid type A receptor; $GABA_BR$ — γ-aminobutyric acid type B receptor; AQP4 — aquaporin-4; GluR5 — glutamate receptor 5; MOG — myelin oligodendrocyte glycoprotein; DPPX — dipeptidyl-peptidase–like protein 6; IgLON5 — immunoglobulin-like adhesion molecule 5

*Antibodies tested commercially only in serum (other antibodies tested in serum and cerebrospinal fluid)

(*Neurotherapeutics* 2016; 13:824). The same researchers showed better outcomes in patients who received tumor removal, steroids, and immunoglobulins rituximab and tocilizumab (T-SIRT regimen), compared with patients who received only first-line treatment or first-line treatment plus rituximab (*Neurotherapeutics* 2021; 18:474). However, infection rates were high. Larger studies are needed to ascertain the effectiveness of tocilizumab in this setting.

Bortezomib, a proteasome inhibitor that depletes plasma cells, can be another option for refractory cases. A systematic review showed that 16 of 29 patients (55%) treated with bortezomib had favorable outcomes; however, the quality of the studies was modest. (*J Neuroimmunol* 2021; 356:577586). Multiple ongoing clinical trials are investigating other therapeutic options. Inebilizumab is a CD19 inhibitor that suppresses plasmablasts and plasma cells in addition to depleting CD20+ cells. The randomized, placebo-controlled EXTINGUISH trial will assess the efficacy of inebilizumab when added to first-line therapies in patients with autoimmune encephalitis (NCT04372615). Another trial will evaluate the efficacy, safety, and pharmacokinetics of satralizumab (an IL-6 inhibitor) in patients with NMDAR or LGI1 encephalitis (NCT05503264). Rozanolixizumab — a monoclonal antibody that targets the neonatal fragment crystallizable receptor (FcRn) and prevents immunoglobulin G recycling — is also being examined in a phase 2 study in patients with LGI1 encephalitis (NCT04875975). Finally, daratumumab (CD38 inhibitor) has been described in case reports of refractory autoimmune encephalitis (*Neurotherapeutics* 2022; 19:823).

Long-Term Outcomes

Patients with autoimmune encephalitis may score low on the modified Rankin scale; therefore, disability may not be captured with that tool. Neuropsychological testing is an important objective tool for assessing response to treatment, outlining brain rehabilitation strategies, and providing normalization in research. A recent study showed that the highest-yield measurements in neuropsychological testing include visual and verbal memory, basic and sustained attention, processing speed, and executive functions (*Neurol Neuroimmunol Neuroinflamm* 2024; 11:e200179).

Future Directions

Autoimmune encephalitis constitutes a fascinating heterogenous group of diseases. As recognition of these disorders has improved, we have seen an increase in misdiagnosis, the repercussions of which include delayed treatment for the true illness and unnecessary adverse effects of immunosuppression. Further education regarding the clinical phenotype, interpretation of neural antibodies, and adherence to published diagnostic criteria can enhance diagnostic accuracy. In the research space, randomized, controlled studies targeting autoimmune encephalitis are lacking. Ongoing efforts involve multiple therapeutic clinical trials. Given the rarity of autoimmune encephalitis, multicenter collaboration will remain crucial to achieving adequate recruitment for these studies.

Topic Update

The Future of Brain Health: How Neurologists Can Lead the Way

Natalia S. Rost, MD, MPH, FAAN, FAHA, and David Evans, MBA

The concomitant growth in demand for neurological expertise, availability of diagnostics and treatments for brain and other neurological diseases, and societal emphasis on living longer and healthier lives have led to the emergence of the brain health revolution. Neurologists are uniquely positioned to champion this revolution given our specialized expertise in brain structure and function, experience in providing care through multidisciplinary collaborations, and connectedness to the patient and caregiver community. Further, neurologists can ensure that preventive neurology is a central feature of the shift to a brain health paradigm, emphasizing the importance of maintaining optimal brain health across the lifespan. This article outlines the vital importance of achieving this transition, the role of neurologists, and the vision for brain health as proposed by the American Academy of Neurology (AAN; *Neurology* 2023; 101:570).

The Right Timing for Brain Health — Evidence Meets Awareness

The concept of brain health has gained momentum due to the growing body of knowledge on this subject and increasing recognition of its fundamental impact. Over the years, brain health science has evolved from investigating various preventive measures and lifestyle choices such as physical activity, sleep, diet, vascular risk factor management (*Circulation* 2022; 146:e18), or engaging in cognitive activities (*J Neuropsychiatry Clin Neurosci* 2011; 23:149) to understanding the impact of social engagement (*J Int Neuropsychol Soc* 2011; 17:998), early life interventions (Duncan G. and Magnuson K. "The Nature and Impact of Early Achievement Skills, Attention Skills, and Behavior Problems." In: Duncan Greg J, Murnane Richard J., editors. *Whither Opportunity: Rising Inequality, Schools, and Children's Life Chances.* New York: Russell Sage Foundation; 2011. pp. 47–69), mental well-being (*JAMA Intern Med* 2014; 174:357), and importantly, the molecular underpinnings of brain health (*Stroke* 2023; 54:e251) across an individual's lifetime.

As research highlights various facets of brain health, including vascular health, mental well-being, and healthy aging, public and professional campaigns have emerged to promote brain health awareness. These initiatives, supported by organizations like the Centers for Disease Control and Prevention and the World Health Organization, reflect a growing understanding that brain health is an evolving and collaborative concept (Centers for Disease Control and Prevention. State and Local Public Health Partnerships to Address Dementia: The 2018–2023 Road Map; 2022 [cdc.gov/aging/pdf/2018-2023-Road-Map-508.pdf.]; World Health Organization. Optimizing Brain Health Across the Life Course: WHO Position Paper; 2022 [https://www.who.int/publications/i/item/9789240054561]).

Natalia S. Rost, MD, MPH, FAAN, FAHA, is the C. Miller Fisher Endowed Chair in Vascular Neurology and Chief of the Stroke Division at the Massachusetts General Hospital, where she is an MGH Research Scholar. She is also Professor of Neurology at Harvard Medical School and serves as President Elect of the American Academy of Neurology. **Disclosures:** Dr. Rost reports external grant support from the National Institute of Neurological Disorders and Stroke. She serves as an Associate Editor for *Stroke* and is a contributor to UpToDate. She was one of the authors of the AAN's position statement on brain health.

David A. Evans, MBA, is Chief Executive Officer of Texas Neurology in Dallas. He also serves as Chair of the American Academy of Neurology's Committee on Public Engagement and Chair of the AAN's Health Policy Subcommittee. **Disclosures:** Mr. Evans reports advisory board roles with TG Therapeutics, Genentech, and Lilly; speakers' bureau roles with Biogen, Genentech, Horizon Therapeutics, and Averitas; and equity ownership or stock options in NeuroNet GPO. He was one of the authors of the AAN's position statement on brain health.

Defining Brain Health

To provide a foundation for action, the AAN has developed a consensus-driven, comprehensive definition of brain health: "*Brain health is a continuous state of attaining and maintaining the optimal neurologic function that best supports one's physical, mental, and social well-being through every stage of life.*" (*Neurology* 2023; 101:570). This inclusive definition reflects the values of the AAN and emphasizes the importance of prevention, preservation, and continuous attention to brain health.

Embracing Preventive Neurology

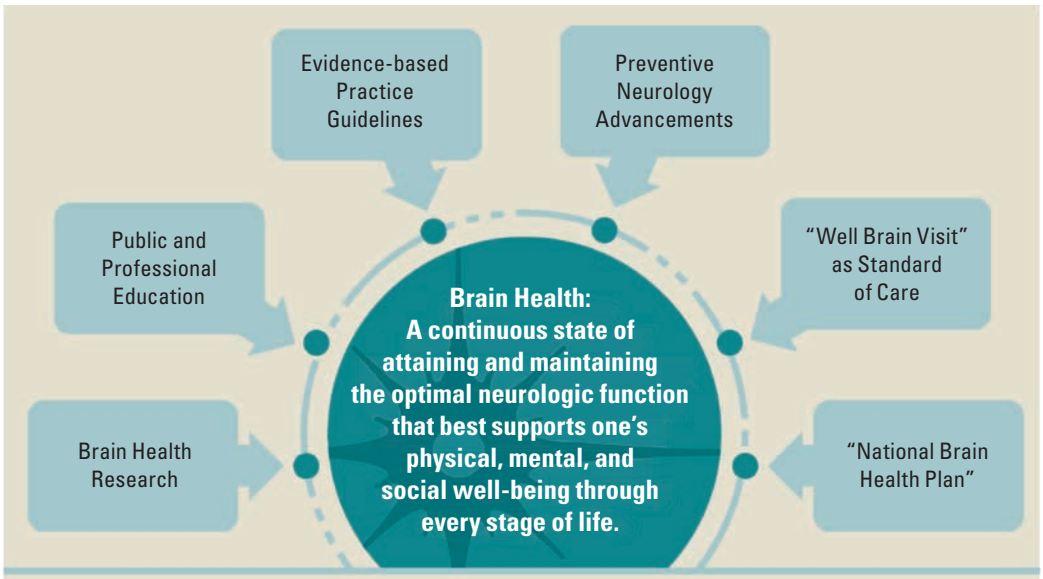
The era of preventive neurology has arrived, focusing on strategies that anticipate or mitigate the onset and progression of various neurologic diseases. This approach demands collaboration between a broad spectrum of medical subspecialists — among whom neurologists play a pivotal role — along with nonmedical professionals, stakeholders, and policymakers. The growing economic burden of neurologic disorders underscores the urgent need for preventive measures that extend beyond diagnosis and treatment (*Lancet Neurol* 2020; 19:255).

The AAN Brain Health Platform and Action Plan Framework

The AAN's platform articulates key positions and goals, emphasizing the importance of brain health as foundational to overall health and the need for collaboration among various disciplines (*Neurology* 2023; 101:570). The platform comprises three ambitious goals: accelerating scientific discovery, optimizing brain health through preventive care, and enhancing public and patient engagement. These goals align with the AAN's National Brain Health Vision (Figure 1), which foresees a future where brain health research leads to actionable knowledge, preventive neurology thrives, evidence-based guidelines are widely available, brain health visits become standard of practice, and education on brain health is abundant and trustworthy.

FIGURE 1: The AAN's National Brain Health Vision

By 2050, neurologists envision a future where brain health research leads to actionable knowledge, preventive neurology thrives, evidence-based guidelines are widely available, brain health visits become standard, and education on brain health is abundant and trustworthy.



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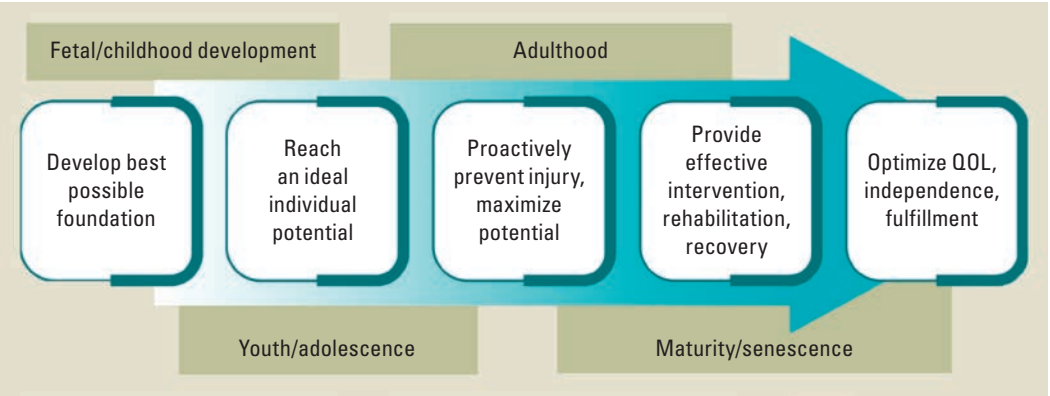
Brain Health in Neurology Clinics — Today and Tomorrow

In current practice, neurologists are pressed for time and lack an appropriate reimbursement system for dedicated preventive practice. To address these limitations, the AAN's Brain Health Action Plan (Figure 2) calls for development of evidence-based prevention strategies for each stage of life; a broad network of collaborations with primary care, family practice, pediatricians, psychiatrists, and many other health care professionals; and a clinical practice environment that promotes and supports brain health for everyone. This will require a redesign of the current "wellness visit" across the lifespan to include evidence-based brain health assessments and interventions. In concert, health policy changes will be needed that promote optimal brain health and support brain health providers of all specialties.

A Call to Action on Brain Health

Brain health is a pivotal aspect of individual and societal well-being, and neurologists have a crucial role to play in shaping its future. By leading the way in practicing preventive neurology and promoting optimal brain health, neurologists can collaborate with diverse stakeholders to reduce the burden of neurologic disorders and advance public health. The AAN Brain Health Initiative sets a course for progress, and its success depends on the collective efforts of the medical community, policymakers, and the public. Together, we can achieve and maintain optimal brain health across the lifespan, ensuring a healthier and more productive future for all.

FIGURE 2: The AAN Action Plan for Brain Health Across the Lifetime



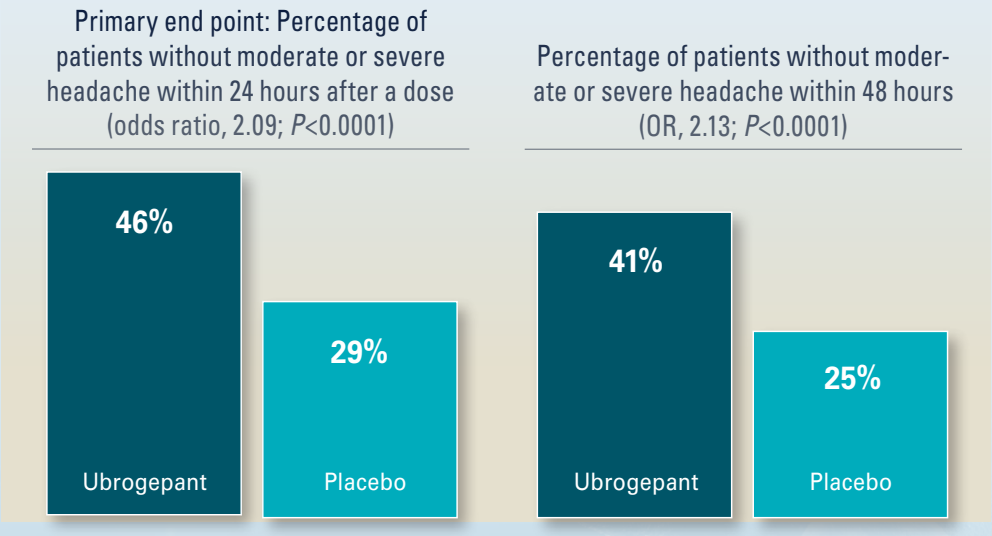
QOL — quality of life

Reproduced with permission from Wolters Kluwer Health, Inc., on behalf of the American Academy of Neurology: Avitzur O, Rost NS, and Evans DA. Neurologists have a plan for lifelong brain health. **Neurology** 2022; 99:925. (https://www.neurology.org/doi/10.1212/WNL.0000000000201339)

Visual Summary

Prodromal Use of Ubrogepant for Migraine

Researchers enrolled adults with migraine attacks, with or without aura, occurring two to eight times per month who could reliably predict migraine attacks occurring 1 to 6 hours after identifying prodromal symptoms. Nearly 500 adults were randomized to ubrogepant (100 mg) or placebo to treat the first qualifying prodromal event, followed by crossover to treat the second qualifying event.



Comment

Migraine is a multiphasic disorder that often begins with prodromal symptoms before headache. Prior studies show that treating when the pain is mild may improve triptan efficacy. However, the current trial findings represent a paradigm shift, supporting treatment during the prodromal phase in patients who can accurately identify symptoms that reliably predict onset of acute migraine attacks, to prevent migraine pain. The exact prevalence of prodromal symptoms is unclear. Discrepancies may be driven by lack of awareness of the clinical symptomatology. Further studies are needed including treatment during the prodromal phase of migraine in those with menstrual migraine, high frequencies of attacks, or a high interictal burden.

Teshamae Monteith, MD, reviewing Dodick DW et al. Ubrogepant for the treatment of migraine attacks during the prodrome: A phase 3, multicentre, randomised, double-blind, placebo-controlled, crossover trial in the USA. *Lancet* 2023 Dec 16; 402:2307.

Dr. Monteith is Associate Professor of Clinical Neurology and Chief of the Headache Division at the University of Miami Miller School of Medicine. Dr. Monteith reports coediting a textbook with Dr. Peter J. Goadsby, an author of this study. She is a site Principal Investigator for a study sponsored by the manufacturer of ubrogepant.

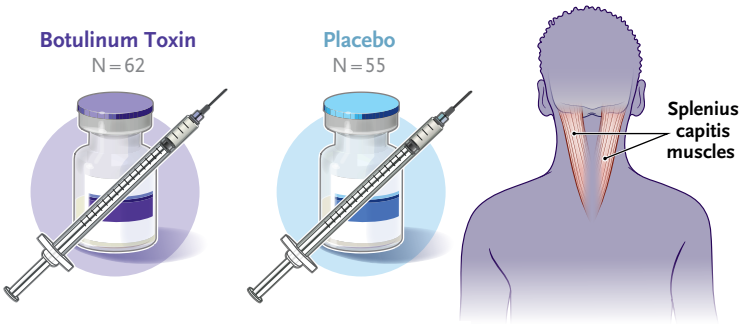
NEJM Research Summary

Trial of Botulinum Toxin for Isolated or Essential Head Tremor

Marques A et al. DOI: 10.1056/NEJMoa2304192

CLINICAL PROBLEM

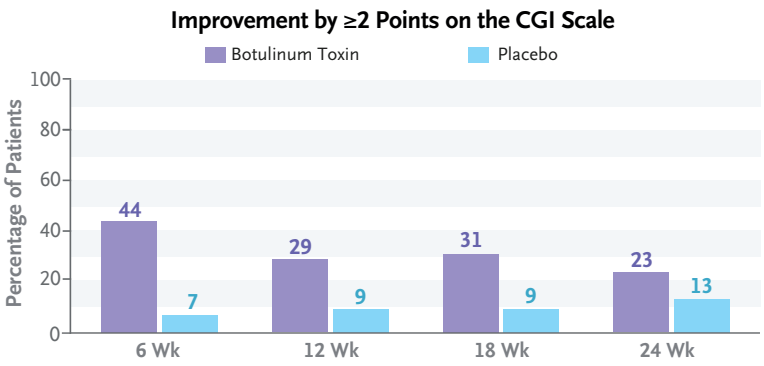
Local injection of botulinum toxin is widely used to treat head tremor, but randomized trials assessing its effects are limited. In 2019, an evidence-based review commissioned by the Movement Disorder Society concluded that there is insufficient evidence for the use of any agent in the treatment of head tremor.



CLINICAL TRIAL

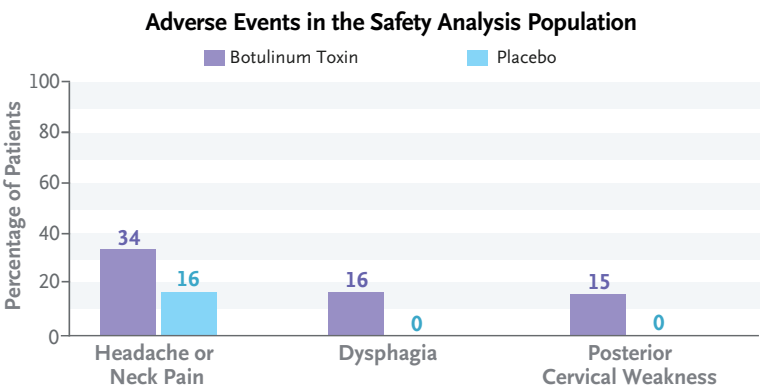
Design: A multicenter, double-blind, randomized, placebo-controlled trial conducted in France assessed the efficacy and safety of botulinum toxin injection in adults with isolated or essential head tremor.

Intervention: 117 patients were assigned to receive injections of botulinum toxin type A or placebo into each splenius capitis muscle under electromyographic guidance on day 0 and during week 12. The primary outcome was improvement by ≥2 points on the 7-point Clinical Global Impression of Change (CGI) scale at week 18.



RESULTS

Efficacy: The percentage of patients with improvement by ≥2 points on the CGI scale at week 18 was significantly greater in the botulinum toxin group than in the placebo group. However, there was no clear difference between the groups at week 24 (a secondary outcome), a time when the effect of the agent could be expected to wane.



Safety: Adverse events occurred in a higher percentage of patients in the botulinum toxin group than in the placebo group. These events were generally mild in severity and transient and included headache or neck pain, dysphagia, and posterior cervical weakness.

LIMITATIONS AND REMAINING QUESTIONS

- A higher percentage of patients in the botulinum toxin group than in the placebo group discontinued the trial after the first injection, which may have biased the analyses.
- The investigators did not assess all factors that may have influenced outcomes (e.g., patients' stress or anxiety).
- Racial diversity among the patients in the trial was limited.

CONCLUSIONS

In patients with isolated or essential head tremor, injection of botulinum toxin type A into each splenius capitis muscle on day 0 and during week 12 resulted in greater clinical improvement than placebo at 18 weeks but not at 24 weeks and was associated with posterior cervical weakness and dysphagia in some patients.

Guideline Watch

Differential Diagnosis of Multiple Sclerosis

Updated consensus recommendations on a localization-based paradigm

SPONSORING ORGANIZATION

The Multiple Sclerosis Differential Diagnosis Consortium and the Americas Committee for Treatment and Research in Multiple Sclerosis

BACKGROUND AND OBJECTIVE

These consensus recommendations for a localization-based approach to the differential diagnosis of multiple sclerosis (MS) are presented as an update to recommendations published in 2008.

KEY POINTS

- Optic neuritis, transverse myelitis, and brainstem or supratentorial presentations in MS should follow a typical pattern of patient demographics, onset, symptoms, symmetry, severity, and recovery.
- Additional paraclinical testing with MRI, optic coherence tomography, visual evoked potentials, and cerebrospinal fluid and antibody tests is recommended. MRI and CSF are particularly important in the MS diagnosis, but MS mimics may have overlapping features. The pattern of MRI involvement is often very helpful in the differential.
- Atypical features should prompt a broadened work-up and reluctance to confirm the MS diagnosis.
- Progressive and nonrelapsing presentations lasting longer than 1 year are particularly challenging and require consideration of other degenerative, inflammatory, and neoplastic conditions.

WHAT'S CHANGED

In the evaluation of atypical cases of possible MS, myelin oligodendrocyte glycoprotein and aquaporin 4 antibodies should be considered.

Comment

This article by an international group of experts will become a classic for those in training, in addition to faculty preparing as clinicopathologic conference discussants. The article includes flowsheets for diagnosing optic neuritis, transverse myelitis, and supratentorial syndromes that highlight distinctions between typical from atypical features. A comprehensive list of alternative diagnoses is presented for reference.

Robert T. Naismith, MD

Dr. Naismith serves as Neurology Clerkship Director at Washington University in St. Louis. He reports consultant or advisory board roles with Alexion Pharmaceuticals, Biogen, Bristol Myers Squibb, Genentech, Genzyme, EMD Serono, Horizon Therapeutics, Novartis, and TG Therapeutics; grant or research support from the National Institutes of Health; and leadership positions in ACTRIMS (Treasurer) and the Consortium of Multiple Sclerosis Centers (Treasurer).

Solomon AJ et al. Differential diagnosis of suspected multiple sclerosis: An updated consensus approach. **Lancet Neurol** 2023 Aug; 22:750. (https://doi.org/10.1016/S1474-4422(23)00148-5)

Guideline Watch

American Academy of Neurology Guidelines for Adult and Pediatric Brain Death Determination

These new guidelines provide important updates that all clinicians involved in the determination of brain death/death by neurologic criteria should know.

SPONSORING ORGANIZATION

American Academy of Neurology (AAN), American Academy of Pediatrics, Child Neurology Society, and Society of Critical Care Medicine

BACKGROUND AND OBJECTIVE

Passage of the Uniform Determination of Death Act in 1981 led to diagnosis of brain death/death by neurologic criteria (BD/DNC) having legal equivalence with cardiac death in all states. These recommendations, updated from 2010, have the overarching goal of ensuring that BD/DNC determination is a conservative process that minimize the risk for false-positive BD/DNC diagnosis.

KEY POINTS

Given the lack of high-quality clinical evidence to guide BD/DNC determination, guideline development was performed via a formal consensus process following a detailed literature review. The resulting 85 recommendations contain several important updates from 2010:

- The authors combine previously separate adult and pediatric BD/DNC guidelines in a single document.
- For the first time, the guidelines address qualifications for individuals determining brain death, with a recommendation that only attending clinicians who are adequately trained and competent should perform these evaluations.
- While acknowledging that thresholds are arbitrary and based on limited evidence, reference ranges of normal values for key vital signs and laboratories that should be targeted prior to BD/DNC testing are provided. A temperature ≥36°C in all patients and systolic blood pressure and mean arterial pressure ≥100 and 75 mm Hg, respectively, should be achieved in adult patients, including those on extracorporeal membrane oxygenation.
- The authors reiterate that BD/DNC determination is a clinical diagnosis, with ancillary testing indicated only in specific instances.
- The guidelines include detailed descriptions of clinical exam procedures, apnea testing, and acceptable ancillary tests.
- Importantly, the guidelines again emphasize that BD/DNC evaluation should be initiated only when there is clear evidence of catastrophic, irreversible brain injury.

WHAT'S CHANGED

- An additional new special-considerations section addresses important topics such as the absence of need to obtain consent for BD/DNC testing, appropriately determining time of death, and BD/DNC determination in pregnancy.

(continued on page 18)

Comment

The determination of BD/DNC is an important responsibility that neurologists are frequently asked to perform. It is generally accepted that AAN BD/DNC guidelines are the medical standards that clinicians should follow. Consequently, it is important that all neurologists with responsibility for this key determination know and understand these guidelines. Familiarity with and consistent application of these guidelines are fundamental to ensuring that accepted medical standards are followed, so that false-positive determinations of BD/DNC never occur.

Craig A. Williamson, MD

Dr. Williamson is Clinical Associate Professor in Neurology and Neurosurgery, University of Michigan, Ann Arbor.

Greer DM et al. Pediatric and adult brain death/death by neurologic criteria consensus guideline: Report of the AAN Guidelines Subcommittee, AAP, CNS, and SCCM. **Neurology** 2023 Dec 12; 101:112. (https://doi.org/10.1212/WNL.0000000000207740)

NEJM Journal Watch Summary

Plasma Biomarkers Aid Alzheimer Disease Identification for Anti-Amyloid Treatment

Plasma p-tau217 was the best blood biomarker in identifying amyloid-positive patients with high tau burden.

Identifying patients with Alzheimer disease (AD) who would be most appropriate for anti-amyloid immunotherapies is needed. To determine whether plasma biomarkers can help identify amyloid positivity and tau burden in patients seen at memory clinics for subjective cognitive decline, mild cognitive impairment, or dementia, investigators tested patients' plasma biomarkers, including phosphorylated tau 181 (p-tau181), p-tau217, p-tau231, N-terminal tau, glial fibrillary acidic protein, and neurofilament light chain. They also tested cerebrospinal fluid (CSF) levels of p-tau217, amyloid-beta 42 (Aβ42), and amyloid beta 40 (Aβ40) and obtained positron emission tomography (PET) imaging of Aβ and tau. Aβ positivity was based on a CSF Aβ42/40 ratio <0.08 or an Aβ-PET cutoff of 0.693.

Among 912 participants (55% male; mean age, 71 years), 358 were Aβ negative and 554 were Aβ positive. Ninety-eight percent of Aβ-negative participants had low tau PET. Among Aβ-positive participants, 53% had low tau, 26% had intermediate tau, and 21% had high tau PET status. A plasma p-tau217 cutoff point of 0.22 ng/L had a sensitivity of 84% and specificity of 88% in identifying Aβ positivity in an independent cohort. Using a 2-cutpoint approach, sensitivity for Aβ positivity was 94% and specificity was 90%; only 13% of participants had intermediate plasma p-tau217 levels (0.159 ng/L to 0.219 ng/L) and needed CSF testing or PET imaging to clarify Aβ status. Plasma p-tau217 also best identified Aβ-positive participants with high tau PET or CSF burden. Allowing a false-negative rate of <10% for high tau, plasma p-tau217 measurement could lead to avoiding tau-PET scans in 57% of patients. Results were replicated after excluding those with subjective cognitive decline and were validated in the independent cohort.

Comment

Measuring plasma p-tau217 levels may be a cost-effective, less-invasive way to identify amyloid and tau burden. The authors note that patient-specific factors and the performance of different assays may influence p-tau levels, supporting the need for standardization, rigorous protocols, and the appropriate infrastructure to determine which patients with AD may benefit most from anti-amyloid therapies.

Jennifer Rose V. Molano, MD

Dr. Molano is Associate Professor at the University of Cincinnati. She reports receiving grant or research support from the National Center for Advancing Translational Science — Cincinnati Center for Clinical and Translational Science and Training and serves on the editorial board of *Brain & Life*.

Mattsson-Carlgren N et al. Plasma biomarker strategy for selecting patients with Alzheimer disease for antiamyloid immunotherapies. **JAMA Neurol** 2024 Jan; 81:69. (https://doi.org/10.1001/jamaneurol.2023.4596)

NEJM Journal Watch Summary

Thinning Retina as an Early Feature of Parkinson Disease

Both patients with PD and those who later developed it had thinner retinal layers than people who never developed PD.

Although retinal changes have been associated with Parkinson disease (PD), in vivo retinal imaging rarely has been applied. In this study, investigators used optical coherence tomography (OCT) in the AlzEye cohort to compare the integrity of the inner retinal layers in 700 patients with prevalent PD versus 105,770 controls. They analyzed the thickness of the macular retinal nerve fiber layer (mRNFL), the ganglion cell–inner plexiform layer (GCIPL), and inner nuclear layer (INL). In a second, large, publicly available dataset, the UK Biobank, the researchers examined whether retinal changes were associated with incident cases of PD.

Patients with prevalent PD manifested thinner GCIPL and INL retinal layers. Additionally, in the UK Biobank cases there were thinner GCIPL and thinner INL retinal layers in 53 individuals who developed new-onset PD a mean of more than 7 years after retinal imaging.

Comment

Accumulating evidence strongly suggests a reduced retinal thickness in most patients with PD. Replication of the findings in early disease and in pre-manifest disease will be important. The finding could, for example, in the future be applied as an objective measure for use in clinical trials, in PD risk stratification, and for use in measuring disease progression, although much work will be required for all of these potential applications. The incident PD cases within this study revealed retinal thinning several years before PD diagnosis. Thus it will be important for future works to document thinning as a consistent prodromal manifestation. The assertion that a thin retina is a risk factor for PD is tantalizing. However, this study did not provide enough data and a sufficient effect size to support this conclusion.

Michael S. Okun, MD

Dr. Okun is Adelaide Lackner Professor and Chair of Neurology and Executive Director of the Fixel Institute for Neurological Diseases at the University of Florida McKnight Brain Institute, Gainesville. He reports consultant or advisory board roles with the Parkinson's Foundation and the Tourette Association of America; speaker's bureau fees from Medscape/WebMD CME, Movement Disorders Society CME, and American Academy of Neurology CME; royalties from Books4Patients, Demos, Cambridge, Taylor and Francis, Henry Stewart Talks, Robert Rose, and Public Affairs; grant or research support from the National Institutes of Health, the Parkinson's Foundation, the Tourette Association of America, and the University of Florida Foundation; editorial board roles with *Tremor and Other Hyperkinetic Movements* and *JAMA Neurology*; and leadership positions with the Parkinson's Foundation (Medical Advisor) and the Tourette Association of America (Medical Advisory Board Member).

Wagner SK et al. Retinal optical coherence tomography features associated with incident and prevalent Parkinson disease. **Neurology** 2023 Oct 17; 101:e1581. (https://doi.org/10.1212/WNL.0000000000207727)

NEJM Journal Watch Summary

Levetiracetam vs. Lamotrigine in Women with Idiopathic Generalized Epilepsy

The risk for treatment failure is lower in women using levetiracetam instead of lamotrigine for first-line treatment of juvenile myoclonic epilepsy.

Levetiracetam and lamotrigine are considered the least teratogenic among antiseizure medications (ASMs) that are effective for idiopathic generalized epilepsy (IGE), but little evidence is available to guide initial ASM selection in women of childbearing age. In a multicenter, retrospective cohort study including 543 women with IGE who received either levetiracetam or lamotrigine as initial monotherapy, investigators assessed time from ASM prescription to treatment failure due to ineffectiveness or adverse effects. Two authors report receiving fees from the manufacturer of levetiracetam for work unrelated to the study.

Compared with lamotrigine use, levetiracetam use was associated with lower risk for treatment failure and a higher likelihood of seizure freedom at 12 months, after adjustment for all baseline variables. In secondary analyses, levetiracetam use had a lower risk for ineffectiveness than lamotrigine use, but no difference in ASM withdrawal due to adverse effects alone or ASM retention (ineffectiveness plus adverse-effect withdrawals) despite more frequently reported adverse effects with levetiracetam. Behavioral symptoms and drowsiness were more frequent with levetiracetam, whereas dermatologic symptoms were more frequent with lamotrigine. Among IGE subsyndromes, levetiracetam performed better than lamotrigine only for juvenile myoclonic epilepsy. Clinicians more commonly noted worsening myoclonic seizures in women using lamotrigine. Time to treatment failure did not differ between the two ASMs for absence epilepsy or generalized tonic-clonic seizures.

Comment

Study strengths include the inclusion of patients from primary, secondary, and tertiary care settings, and epilepsy syndrome classification according to International League Against Epilepsy criteria. Limitations include insufficient sample size for subanalysis by IGE syndrome and selection bias due to the retrospective design. As the study population was mainly white and no other information was collected about race and ethnicity, generalizability of the findings for nonwhite women is unclear. Still, evidence supporting the superiority of levetiracetam over lamotrigine in juvenile myoclonic epilepsy will help clinicians treating women of childbearing age.

Tanya J.W. McDonald, MD, PhD

Dr. McDonald is Assistant Professor of Neurology, Department of Neurology, Division of Epilepsy, Johns Hopkins University School of Medicine, Baltimore.

Cerulli Irelli E et al. Levetiracetam vs lamotrigine as first-line antiseizure medication in female patients with idiopathic generalized epilepsy. **JAMA Neurol** 2023 Nov 1; 80:1174. (https://doi.org/10.1001/jamaneurol.2023.3400)

NEJM Journal Watch Summary

Macronutrients Associated with Slower Disease Progression in Patients with ALS

An observational study linked higher glycemic index and glycemic load to slower ALS progression.

Weight loss in patients often precedes the onset of amyotrophic lateral sclerosis (ALS) and is associated with faster disease progression and shorter survival. The underlying mechanisms are not clearly defined. To examine the relationship between dietary components (including calories, carbohydrates, fat, fiber, protein, glycemic index [GI], and glycemic load [GL]) and ALS progression and survival, researchers analyzed data from 304 patients enrolled in the ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS). Participants (mean age, 62; mean disease duration, 12 months) completed an 85-item self-administered questionnaire on eating habits in the previous 6 months.

Higher GI and GL were associated with slower disease progression in analyses adjusting for baseline clinical characteristics including age, sex, disease duration and severity, body-mass index, and forced vital capacity. A 1-unit increase in GI was associated with 0.13-point slower decline on the ALS Functional Rating Scale–Revised at 3 months. When patients' GL and GI were examined in quartiles, the three quartiles with higher GI values showed slower progression than the lowest quartile, but not in a dose-dependent manner (quartile 2, –1.9; quartile 3, –2.0; quartile 4, –1.6). Higher caloric intake and fat consumption were initially linked to slower functional decline, but not after adjustment for all covariates. Survival curves nonsignificantly favored the higher GI quartiles compared with the lowest quartile.

Comment

The researchers acknowledge that this questionnaire has limitations in estimating usual dietary intake and macronutrient content. Recall bias might have led to underestimation or overestimation of intake of certain dietary components, and daily variation is not well accounted for. The lack of dose dependence is challenging to explain but might reflect the complexities of glucose regulation. Interventional trials are warranted to confirm the benefit of diets with a higher GI for patients with ALS.

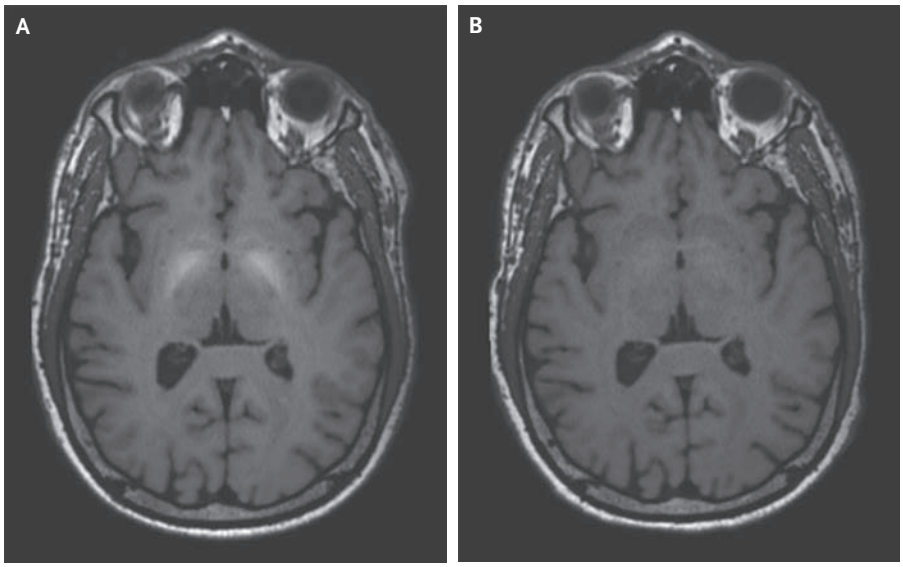
Leana Doherty, MD

Dr. Doherty is Assistant Professor at the University of Pittsburgh Medical Center. Dr. Doherty completed her internship in internal medicine in her home state at the University of Rochester School of Medicine and Dentistry. She serves on the editorial boards of the Neurohospitalist Society and InterACTN (*Annals of Clinical and Translational Neurology*).

Lee I et al. Higher glycemic index and glycemic load diet is associated with slower disease progression in amyotrophic lateral sclerosis. **Ann Neurol** 2024 Feb; 95:217. (https://doi.org/10.1002/ana.26825)

Images in Clinical Medicine

Manganese Accumulation in the Brain



A 55-year-old man presented to the neurology clinic with a 10-year history of progressive handwriting impairment and rapid, slurred speech. In his thirties, he had worked as a welder without access to personal protective equipment. Neurologic examination was notable for reduced facial expression, blepharospasm, and cluttered, dysarthric speech. The patient's handwriting was disorganized and micrographic. Postural reflexes were mildly impaired. The patient's occupational exposure, parkinsonism, and blepharospasm aroused concern for toxic effects from exposure to heavy metals. Subsequent magnetic resonance imaging (MRI) of the head showed a nonenhancing, T1-weighted, hyperintense signal in the basal ganglia on both sides (Panel A). Results of laboratory tests, including a serum iron panel and measurements of ceruloplasmin and urinary copper excretion, were normal. On the basis of the patient's welding history and neurologic syndrome, a diagnosis of manganese poisoning was made. Serum and urine manganese levels were not obtained, since these values are often normal in cases of chronic or previous exposure. Whole-exome sequencing did not identify an inherited error in manganese metabolism. Treatment with intravenous EDTA was administered for 6 months, and the patient's symptoms subsequently abated and the abnormal findings on MRI resolved (Panel B).

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October 5, 2023; **N Engl J Med** 2023; 389:14; DOI: 10.1056/NEJMicm2301805