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EPILEPSY: 6 AEDs with high risk for Stevens-Johnson syndrome **8**

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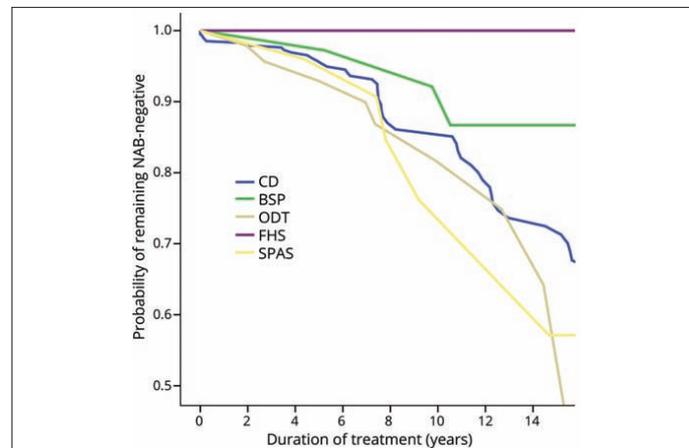


CRITICAL CARE: The pros and cons of cEEG **18**

See more highlights of the issue on page 7.

Emergent Antibodies Remain a Concern in Long-Term Botulinum Toxin Therapy

BY DAN HURLEY



KAPLAN-MEIER analysis of the probability of remaining neutralizing antibody (NAB) negative in all five patient subgroups. With duration of treatment, the decline of the Kaplan-Meier curves becomes steeper and steeper. In the other dystonia (ODT), cervical dystonia (CD), and spasticity (SPAS) subgroups, up to 40 percent of the patients had become NAB positive after a duration of treatment of 15 years. BSP=blepharospasm; FHS=facial hemispasm.

Nearly 14 percent of patients on long-term botulinum neurotoxin therapy have neutralizing antibodies to it, a large observational study from researchers in Germany has

found, a rate far higher than seen in previous, shorter-duration studies.

The rate varied based on the dose patients received, with higher doses

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WOMEN IN MS SEEK GREATER PARITY IN FIELD

BY SUSAN FITZGERALD

Women researchers and clinicians in multiple sclerosis (MS) filled a large conference room last spring at a major subspecialty meeting. They had come together to share their common professional challenges. And now they were intent on organizing, to achieve greater gender parity in their field, and ensure greater participation and representation on MS editorial boards and professional conferences.

Their intent was made clear in a letter to the editor of *Annals of Neurology* published online November 2. Under a headline titled “Gender Inequities in the Multiple Sclerosis Community: A Call for Action,” an international group of female neurologists and neuroscientists specializing in MS called for greater representation of women at all levels of professional leadership, from clinical trials to editorial boards to academic departments.

“Gender discrimination is costly, not only from a personal career perspective, but because it excludes or delays important contributions from skilled, talented individuals,”

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In a Parkinson’s Disease Model, Researchers Inhibit Spread of Toxic Alpha-Synuclein

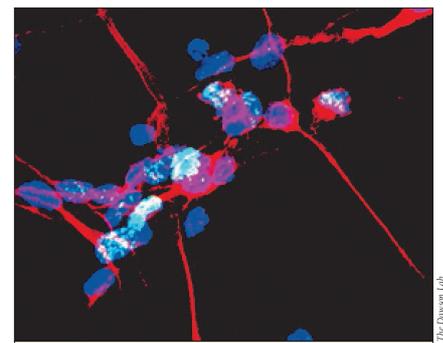
BY JAMIE TALAN

Scientists at Johns Hopkins University have identified what they believe is a novel pathway for cell death and the toxic spread of alpha-synuclein that leads to Parkinson’s disease (PD).

This pathway could be a key mediator of pathologic alpha-synuclein toxicity and transmission, and inhibiting it could potentially prevent disease progression, researchers reported in the November 2 issue of *Science*.

To better understand what was driving the cell death, the investigators used recombinant alpha-synuclein preformed fibrils, (PFF), which

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DOPAMINE NEURONS are the primary cell type targeted by parthanatos in Parkinson’s disease.

DIVERSITY

Women in MS

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ARTICLE IN BRIEF

An international group of female neurologists and neuroscientists specializing in MS has formed to advocate for greater representation of women at all levels of professional leadership, from clinical trials to editorial boards to academic departments.

the letter said. "This can affect progress toward a better understanding of the pathogenesis and treatment of neurological diseases, including MS."

The letter, signed by approximately 100 women from the US and other countries, followed another letter published in the same journal in July that also called out the gender gap, noting that a literature review found that women comprised fewer than a quarter of the authors of phase 3 clinical trials in MS. The July 31 letter, by researchers at the University of Cambridge, noted that pharmaceutical companies tend to repeatedly ask the same male researchers to lead the writing of clinical-trial results.

In their follow-up letter in November, the group (which identified itself as



DR. TANUJA CHITNIS:
"Having different views is important to the trial design or any problem you're looking at. Having multiple views and voices at the table is critical."

"International Women in MS") wrote: "This occurs despite the availability of a substantial number of successful female academic neurologists and neuroscientists [worldwide] who have extensive experience in clinical and basic research methodology."

The letters seemed well-timed, given that 2018 was a year in which women spoke out in many different ways, whether running for elected office in record numbers or speaking out against sexual harassment as part of the #MeToo

movement. And with women still underrepresented in leadership roles in many fields of medicine, for instance as academic department heads or principal investigators, the relevance of the female neurologists and neuroscientists' argument reaches beyond MS.

Emmanuelle Waubant, MD, PhD, FAAN, professor of clinical neurology and pediatrics at University of California, San Francisco (UCSF), helped organize International Women in MS and its journal letter. She told *Neurology Today* that in overlooking women researchers, pharmaceutical companies conducting clinical trials "may be missing out on a set of skills that are different than the set of skills they use over and over. They are losing an opportunity to think differently and to approach challenges and issues differently. The more diverse a group is, the more ideas are generated, and better discussions can occur than if the group is very homogeneous."

Dr. Waubant said International Women in MS began with a small, informal gathering of women at the AAN annual meeting last spring in Los Angeles, followed by another gathering at last summer's meeting in Berlin of the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS). She said there are now more than 200 neurologists and



DR. EMMANUELLE WAUBANT
said that the bias meeting organizers display is "not necessarily a conscious" one; "it's often an unconscious bias" that makes them turn to the same people, typically men, to give talks. The first people who come to mind when you put a program together are the people you recently saw give a great talk."

neuroscientists from more than 20 countries involved.

The group has enumerated a number of goals, including getting more female speakers at medical and scientific conferences and fostering mentorship for junior women in the field.

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Continuous EEG, Critically Ill

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documenting trends in cEEG usage over the course of a decade and informing the direction of future research.

"Even with adjustments for potential confounding elements, unknown variables may play a role in the study results, in which case cEEG's association with reduced mortality could represent "a halo effect," said Stephan A. Mayer, MD, FCCM, William T. Gossett Endowed Chair of Neurology at the Henry Ford Health System in Detroit.

As the study's authors indicated, cEEG usage mainly occurs in larger hospitals that are early adopters of technology and have implemented advanced neurocritical care programs, Dr. Mayer said. "What comes with that is a team of caregivers who believe in their ability to resuscitate patients with severe neurologic injury. They put a lot of resources into them because they believe they can make them better."

A monitoring test rather than a specific treatment may reduce mortality by guiding decision-making, Dr. Mayer explained. "A big determinant between who lives and dies is the point of view and the attitude of the team," Dr. Mayer

pointed out. "Historically people have given up early on people in a coma with brain injury. What we've learned is if you shed these preconceived notions, get rid of self-fulfilling prophecies of doom and you really give people a real chance, you will find that people can be resilient. People can recover from severe brain injuries."

Building and maintaining a robust cEEG-monitoring program presents another challenge, however. It requires a major investment in equipment and manpower, requiring technologists and physicians to be available to interpret readings 24 hours a day. "Smaller hospitals simply don't have enough of a critical mass for volume to justify the investment in cEEG monitoring," Dr. Mayer said.

Hospitals also may resist the expenses of round-the-clock staffing, which is necessary to meet the demands of such labor-intensive monitoring, said Marc R. Nuwer, MD, PhD, FAAN, professor and vice chair in the department of neurology at David Geffen School of Medicine at UCLA.

Typically a technologist or nurse will watch a patient continuously from a remote location, Dr. Nuwer said, and call the physician for review of the record upon noticing a change, such as a seizure.

Some simple-to-apply techniques have received approval from the US Food and Drug Administration (FDA), in fact, and do not require a technologist to secure them. These software alternatives only cover part of the scalp, however, and last at most a day before a technologist needs to hook up real EEG electrodes, Dr. Nuwer said.

When cEEG is done correctly, however, it reduces the amount of time patients spend in intensive care units, resulting in significant cost savings to hospitals. And as cEEG monitoring continues to expand, the training of EEG readers has been making inroads in fellowship programs, noted Dr. Nuwer, particularly in clinical neurophysiology.

Interpretation of cEEG is a fairly intensive process for the neurologist; Dr. Nuwer reads an ICU record two to three times each day and leaves a note in the patient's chart each time. Whenever he sees abrupt changes that need attention, he phones or pages the ICU physician caring for the patient. "Many EEGers may not wish to devote that much time to the service, so there is pushback about not wanting to do so much intensive work," he said.

And with a shortage of neurologists with relevant training, providing timely feedback to referring physicians is as

challenging as it is essential. It is pointless to undertake such studies if the necessary interpretation occurs three or four weeks after the fact, said Jerzy P. Szaflarski, MD, PhD, professor and director of the Epilepsy Center in the department of neurology at the University of Alabama at Birmingham.

And because the EEG is accompanied by video monitoring, generating terabytes of data on a weekly basis presents additional challenges. "Storing that data is very difficult because of the sheer volume," Dr. Szaflarski said, although with evolving technology, "today it's not as much of a challenge as it was 10 years ago."

The software packages with embedded capabilities to detect seizures in the cEEG are only 60 to 70 percent sensitive and specific. "We are far from the point where we will be able to use machines to reliably review the EEGs," Dr. Szaflarski said. •

LINK UP FOR MORE INFORMATION:

- Hill CE, Blank LJ, Thibault D. Continuous EEG is associated with favorable hospitalization outcomes for critically ill patients. *Neurology* 2018; Epub 2018 Nov 30.

Women in MS

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"If you put together a scientific program, you really need to think, 'Who are the people doing the best work on the specific topic you want to hear about?'" said Dr. Waubant, who is also director of the UCSF Regional Pediatric Multiple Sclerosis Center. Dr. Waubant noted that the bias meeting organizers display is "not necessarily a conscious one; it's often an unconscious bias" that makes them turn to the same people, typically men, to give talks. "The first people who come to mind when you put a program together are the people you recently saw give a great talk."

Dr. Waubant, who previously co-chaired the scientific program of the American Committee on Treatment and Research in Multiple Sclerosis (ACTRIMS), said efforts are ongoing to ensure that women are equitably represented among the speakers at the group's 2019 meeting in Dallas.

Jack P. Antel, MD, FAAN, president of ACTRIMS, said his group will benefit from the nudge from women neurologists. "We're excited, because we have identified women for the program who happen to be outstanding in their field," he said, noting that ACTRIMS has never had a female president.

It's important that the field of MS, and neurology overall, be known as specialties where women can excel in all areas, said Dr. Antel: clinical, research, and academics. With a better understanding of the barriers that exist, he said, more progress in gender equity can be achieved, helping to attract and retain the very best people.

"What are the issues involved we haven't looked at?" asked Dr. Antel, who is a professor of neurology and neurosurgery at McGill University. In light of the recent attention on gender inequity, he checked the makeup of the editorial board for *Multiple Sclerosis Journal*, for which he serves as editor of the Americas. Women now comprise 36 percent of the board compared with 8 percent in 2010, he said.

Last year, for the first time more women than men were attending US medical schools, the Association of American Medical Colleges reported. According to 2016 data from the AAN, slightly fewer than 25 percent of US neurologists are women, and women comprise 36.5 percent of Academy members.

WHY THE DISPARITY IN MS?

The letters in *Annals of Neurology* offered examples of gender imbalances in the MS field. The July 31 letter from the University of Cambridge researchers



DR. VIJAYSHREE YADAV:
"Every woman physician has her own journey when it comes to her profession."

presented an analysis of the authorship of phase 3 clinical trials of drug treatment for MS. Of 195 different authors for 26 trials from 1993 to 2016, 150 (77 percent) were male; 45 (23 percent) were female.

The authors, including Joseph Moneim and Alasdair Coles, PhD, hypothesized that "the gender distribution of the clinical trial authors may mirror inequities among all academic neurologists." Another possibility is that fewer women reach senior academic neurology positions. The authors also considered the possibility that pharmaceutical companies have an unconscious bias toward male researchers because they consider them "more authoritative opinion leaders."

The follow-up letter from International Women in MS suggested that a lack of well-credentialed women isn't the reason "eminent lead investigators have to some extent, consciously or subconsciously, nurtured a closed group for clinical trial leadership in which women are not well represented." Gender imbalance on editorial boards may be a factor, the authors said.

"In an informal examination of chief and section editors of 17 major journals that publish MS studies, we found that female representation by women was 16.6 percent," the letter noted. "This is approximately half of the proportion of female faculty in the 29 top-ranked US academic neurology programs (30.8 percent)."

Among the recommendations made by the group: Establish task forces to analyze data on gender in clinical trial leadership and representation on editorial boards, grant review panels, and professional organizations; and establish specific goals toward achieving equal representation by women.

Tanuja Chitnis, MD, FAAN, associate professor of neurology at

Harvard Medical School and director of the Translational Neuroimmunology Research Center at Brigham and Women's Hospital, signed the letter. Having women researchers involved in leading clinical trials is important, she said, not just for their professional achievement but for MS patients who stand to gain from research advances. The field of pediatric MS, one of the areas Dr. Chitnis focuses on, is heavily led by women, she noted.

"Having different views is important to the trial design or any problem you're looking at," Dr. Chitnis said. "Having multiple views and voices at the table is critical."

She has been lucky to have mentors and "to be in an environment that is quite supportive of women," Dr. Chitnis said. "There is work to be done on many different fronts, in many fields of medicine."

Bianca Weinstock-Guttman, MD, professor of neurology at the University of Buffalo Jacobs School of Medicine and Biomedical Sciences and director of the Jacobs Multiple Sclerosis Center, was another signatory for the International Women in MS' letter. Dr. Weinstock-Guttman also finds it problematic that clinical trial sponsors and organizers tend to go primarily to "the same long-time, established, mostly male" researchers, particularly since female physicians play such a big role in caring for MS patients. Female clinicians and researchers are vested in important issues that affect women and children, she said, such as the use of medication during pregnancy.

Dr. Weinstock-Guttman said the reasons for gender disparity are complex and interrelated. Getting published is key to attracting grants and lead roles in clinical trials, factors that all influence academic appointments.

"You have to put in the time and get grant funds," she said. "You have to push yourself and show you're interested in assuming leadership roles."

"We [also] have to support our younger [female] physicians, residents, and fellows," Dr. Weinstock-Guttman said, suggesting senior authors in some cases should "give the study to young investigators and not keep it to themselves."

Vijayshree Yadav, MD, FAAN, associate professor of neurology at Oregon Health & Science University, said joining the International Women in MS group has allowed her to connect, at least electronically, with other female neurologists, some of whom she only knew by names on publications.

"The email came out and people started responding from all over the world," she said.



DR. BIANCA WEINSTOCK-GUTTMAN:
"You have to put in the time and get grant funds. You have to push yourself and show you're interested in assuming leadership roles."

Dr. Yadav, who oversees the training of the MS fellows at her center, said women in neurology, like women in every field, have many balls to juggle, often having children and caring for their families just at the moment their careers are taking off. "Every woman physician has her own journey when it comes to her profession," Dr. Yadav said, though they also have much in common. "When we met at ECTRIMS in Berlin, it was like, 'My goodness!' The room was packed."

With the growing awareness around gender inequity, Dr. Yadav said, it won't be long before more women get due recognition in the field.

"I feel optimistic there will be a much better future for our young physicians," she said. •

DISCLOSURES

Dr. Bianca Weinstock-Guttman received honoraria for serving in advisory boards and educational programs from Biogen Idec, Teva Pharmaceuticals, Novartis, EMD Serono, Sanofi Genzyme, Genentech, and Mallinckrodt. She also received support for research activities from the National Multiple Sclerosis Society, EMD Serono, Biogen Idec, Teva Neuroscience, Novartis, and Genentech.

LINK UP FOR MORE INFORMATION:

- Waubant E, Amezcua L, Sicotte N, et al., for the International Women in MS. Letter to editor. Gender inequities in the multiple sclerosis community: A call for action. *Ann Neurol* 2018; Epub 2018 Nov 2.
- Moneim J, Coles A, Giovannoni, et al. Women on multiple sclerosis clinical trial steering committees. *Ann Neurol* 2018; Epub 2018 Jul 31.