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Why Newer Migraine Blockers Fail Some Patients

KURT SAMSON

Not all migraines result from the same neurovascular changes targeted by newer antibody drugs. And this could potentially help to explain why many migraine sufferers do not respond to such targeted migraine blockers, researchers at Beth Israel Deaconess Medical Center reported in a study published May 24 in the online edition of the *Journal of Neuroscience*.

The investigators discovered fundamental differences in how laboratory rats responded to fremanezumab (Ajovy), a

monoclonal antibody (mAb) that blocks calcitonin gene-related peptide (CGRP).

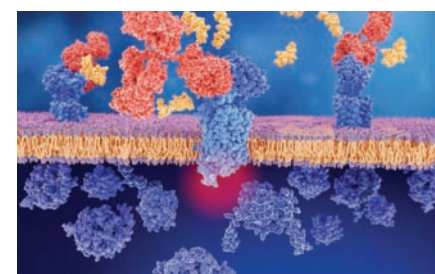
Prior research has suggested that there might be some functional connectivity between CGRP and cortical spreading depression (CSD), and that blocking CGRP might also prevent CSD and plasma protein extravasation (PPE) from affected vasculature.

CSD is a wave of neuronal depolarization thought to result in the activation of nerves that give rise to the headache phase of migraine with aura. CGRP is a potent vasodilator neuropeptide that triggers a migraine attack three to four hours after its infusion. PPE involves leakage of proteins from blood vessels into the surrounding environment in the dura.

Study Design

In the new study, the scientists used sophisticated high-resolution, real-time imaging to investigate how CSD and CGRP contribute to arterial dilatation and PPE in rats treated with fremanezumab. They were able to generate continuous views of spatial and temporal changes in dural and pial arteries and veins, as well as map how fluorescently-labeled fremanezumab diffused from blood vessels through PPE after CSD induction or systemic infusion of CGRP.

The study was designed to test the effect of the CGRP mAb on a single wave of CSD because, in migraine with aura, usually only one wave of CSD occurs, said lead author Rami Burstein, PhD, vice chairman of *Continued on page 19*



JUAN GAERTNER/SCIENCE SOURCE

The calcitonin gene-related peptide (yellow) binds to its receptor (blue) on neurons and smooth muscle cells of cerebral blood vessels, activating a signal cascade through G-proteins (dark blue) in this cells that leads to a dilatation of the blood vessels (vasodilatation). Blocking the CGRP receptor diminishes the quantity of migraine attacks.

Levetiracetam Is No More Effective Than Phenytoin in Children with Convulsive Status Epilepticus

CHRISTINE LEHMANN

Two new randomized studies have answered a longstanding clinical question: Is levetiracetam (Keppra) superior to phenytoin (Dilantin) for second-line management of convulsive status epilepticus (CSE)? The results indicate

that either drug can stop prolonged seizures in at least 50 percent of children.

These are the first robust randomized clinical trials to compare the efficacy and safety of two anti-convulsant medications in the second-line management of CSE, both published in the April 17 online edition of *The Lancet*.

“This provides new and unique scientifically-robust data to better inform pediatricians on how to improve their

management of CSE in children. Specifically, it shows that both levetiracetam and phenytoin could be used as a first-choice anticonvulsant in the second-stage of pediatric CSE,” lead investigator Richard Appleton, MD, professor of pediatric neurology at Alder Hey Children’s Health Park in Liverpool, England, told *Neurology Today* in an email.

Dr. Appleton led the Emergency treatment with Levetiracetam or Phenytoin in

convulsive Status Epilepticus in children (EcLiPSE) trial in the United Kingdom.

In addition, administering each drug sequentially rather than alone reduced the failure rate by more than 50 percent in the second randomized trial—Convulsive Status Epilepticus Paediatric Trial (ConSEPT)—adding only an additional 10 minutes to the treatment time, according to *Continued on page 17*



**Medical
Students in the
Pipeline for
Neurology**

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PERIODICALS

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PROFESSIONALISM

A Pipeline Program Inspires Future Neurologists

ARTICLE IN BRIEF: A pipeline scholarship program from the AAN brought medical students to their first AAN Annual Meeting, and it confirmed their resolve to pursue neurology.

ORLY AVITZUR, MD, MBA, FAAN

Twenty-five-year old Christy Soares—one of this year’s youngest annual meeting attendees—could have easily gotten lost in the sea of nearly 15,000 people that crowded this year’s record-breaking annual meeting in Philadelphia. She was unsure of her future path when she first arrived at the Pennsylvania Convention Center as a recipient of a 2019 *AAN Medical Student Experience at the Annual Meeting Scholarship*, but her reception was so welcoming, and her experience so profoundly inspiring, that by the time she left, the first-year student from Florida State University College of Medicine could not imagine a career in anything else.

She described an afternoon after a plenary session in which she grabbed a plate

of hors d’oeuvres, found a standing table and met several other audience members. As they talked and ate, she was able to ask questions about their connection to neurology, and answer questions about what medical school was like today.

“Much to my delight, one of those individuals was the residency program director at Washington University in St. Louis, another an MD-PhD at Beth Israel Deaconess Medical Center, and another a sales representative for a deep brain stimulation developer,” Soares said. As people began to leave, one of the neurologists asked if they all wanted to continue their conversation at dinner, and over the next five hours, she was able to openly ask questions about residency programs, what it takes to pursue a career as an MD-PhD, what it’s like to have a medical research lab, and how the development and delivery of deep brain stimulation occurs.

Soares was one of 55 recipients of the AAN medical student scholarship which

“Being surrounded by people from all over the world who have the same passion and who were so generous with their time was extraordinary!”

—GIANA DAWOD



covered airfare, a \$300 stipend for other travel costs, and two to three nights of lodging. The 126 applicants represented medical students from 66 institutions, most of whom had heard about the scholarship through their Student Interest Group in Neurology (SIGN) sections. Each submitted an essay and a letter of recommendation, which were reviewed by a small Education Committee workgroup. Many students displayed a general interest in neuroscience but others, like Soares, who was also considering a career in oncology, were undecided. And a few were not only committed to neurology, but already certain which subspecialty they will pursue.

First-year medical student Collin Sanderson, who had been a neuroscience major at Brigham Young University, had a longstanding interest in headache medicine, as did his wife, Brianna, who had just completed her first year in graduate school training to become a *Continued on page 28*

Recommendations, Stroke Care*Continued from page 29*

nurse practitioner. Although Sanderson understood his path forward would include a neurology residency followed by a headache fellowship, Brianna was unsure how she could gain experience in neurology after school. The scholarship program was loosely enough structured to allow Sanderson to attend headache lectures along with his wife, who as a student, was able to attend the annual meeting free of charge. At one lecture, Brianna met headache specialist David W. Dodick, MD, FAAN, professor of neurology from the Mayo Clinic in Scottsdale, and by the end of their conversation, he had extended her a shadowing experience with him and his three nurse practitioners.

"It was incredible to be surrounded by people that we had only read about before who were so well-known in the field of headache," Sanderson said. "By the time I left there was no doubt in my mind I had made the right career choice," he said.

For Soares, it was serendipitous good fortune to have been paired with the clinical director of the Massachusetts General Hospital (MGH) Pappas Center for Neuro-Oncology, Justin T. Jordan, MD, MPH, an AAN Education Committee member, during an initial orientation session set up to advise her how to make the most of the meeting.

"I had not known this subspecialty existed," she said, explaining that in prior conversations with her professors about her career dilemma, they had always remarked how different neurology and oncology were. "Then I met Dr. Jordan and it like was like a lightbulb went off. The more I spoke with him about his field, the more I had this overwhelming feeling that neuro-oncology is an area of medicine making a difference in the lives of patients and their families, and where I belong" she added. By the end of the meeting, plans had been made for her to do a two-week

"When you go through each specialty rotation in med school, they tell you to ask yourself, 'Are these my people?' and the answer which resonated loud and clear to me at the Pennsylvania Convention Center, was 'Yes, these are my people.'"

—KAITLIN SANDOR

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—CHRISTY SOARES



rotation with him at the MGH this summer.

The new Pipeline Subcommittee of the AAN Education Committee has been giving a lot of consideration to how such career decisions are made. "We have the benefit of thoughtful data based on the surveys and subsequent publication of the April 2019 article published in *Neurology*, which described characteristics of graduating US allopathic medical students pursuing a career neurology," said Rana Said, MD, residency program director for child neurology at the University of Texas Southwestern Medical Center and chair of the Pipeline Subcommittee. "What we know is that the preclinical years matter, the quality and timing of the medical student neurology clerkship matters, that mentorship is over and over again noted to be vital, and that neuroscience undergrads and PhD students are also a subset of students that have greater interest in neurology," she said.

"We have long recognized that we have a shortage of neurologists, and that there are challenges to how neurology is perceived outside our field, and that a thoughtful and targeted approach to bring a career in neurology to the forefront of our learners' experiences is key to pursuing neurology as a career," she said.

The scholarship program, one such targeted approach, also allowed medical students—who had few peers in their medical school class with an interest in neurology—to finally meet others like them. So when Kaitlin Sandor, a third-year medical student at Emory, met Giana Dawod, a third-year medical student at the University of Toledo, they had a lot to talk about. During one of the first sessions set up by AAN staff, they listened to three neurologists including Elisabeth Marsh, MD, associate director of the neurology residency program at The Johns Hopkins University School of Medicine, describe what residency programs are looking for in candidates. Dawod, who had been an undergraduate at Hopkins, is currently doing research looking at stroke protocols to decrease waiting times to thrombectomy. Sandor, who did Alzheimer's and ALS research while an undergraduate at Harvard, stayed after the session to learn more. Both women were appreciative of the advice they received on what they could do to become stronger residency candidates. Throughout the rest of the weekend they kept each other informed when they learned of sessions each thought would appeal to the other's interests.

Dawod had very carefully planned her weekend in Philadelphia. The AAN had arranged for one-on-one mentorship time for the medical students, and because of her strong interest in vascular neurology, Dawod had researched and found Randolph Marshall, MD, MS,

FAAN, chief of the stroke service at Columbia University, among the potential mentors. Unfortunately, his time slots began at a time when she would be in transit to get back to school—but that did not deter her. She emailed Dr. Marshall, and they arranged to meet at the convention center.

Both arrived with luggage-in-hand—he, just off the train and she, poised to catch a plane. They discussed what sparked her interest in neurology—an uncle with MS and a friend who died from a ruptured cerebral aneurysm—and her desire to be in New York, where she had family. By the end of that two-hour conversation, Dr. Marshall had offered to help arrange Dawod's fourth-year rotation in New York, just where she wanted to be.

"I compared this experience with other conferences I had attended in the past and this was by far the best," she raved. "Being surrounded by people from all over the world who have the same passion and who were so generous with their time was extraordinary!"

Sandor, who is very interested in neurology, but unsure of which subspecialty she will pursue, participated in a multi-specialty session that the Education Committee and staff had put together for the students. Like speed dating, for ten minutes each, she and others were able to hear about vascular, headache and other subspecialty fields, and watch short videos of various neurodiagnostic tests like EEGs and EMGs. "I appreciated the opportunity to learn more about the wide variety of options there are," she said.

"That program and others I attended reflected the breadth of time and effort put in by the AAN into trainees' experience, and how supportive the entire neurology community was," Sandor noted. She and others all spoke about the hospitality and encouragement they experienced throughout their stays. "When you go through each specialty rotation in med school, they tell you to ask yourself, 'Are these my people?' and the answer which resonated loud and clear to me at the Pennsylvania Convention Center, was 'Yes, these are my people.'" NT

Link Up for More Information

→ Medical student at the annual meeting scholarship: <http://bit.ly/AAN-medicalstudent>. Accessed June 20, 2019.

→ Gutmann L, Cahill C, Jordan JT, et al. Characteristics of graduating UUS allopathic medical students pursuing a career in neurology. *Neurology* 2019; 92(17): e2051–e203.



Christy Soares is one of the 55 recipients of the AAN medical student scholarship who attended the AAN Annual Meeting for the first time.