First Effective Treatment for Transthyretin Amyloidosis

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—MICHAEL POLYDEFKIS

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Johns Hopkins research into rare disease leads to approval of the first drug that can halt its progression.

Over the past two decades, Johns Hopkins neurologist Michael Polydefkis has cared for hundreds of patients with transthyretin (TTR) amyloidosis. This inherited disease, affecting an estimated one in 100,000 people in the U.S., causes the abnormal proteinaceous deposits known as amyloid to accumulate in the nerves, heart and other locations—leading to neuropathy, heart failure and eventually death. “It was a disease that I dreaded diagnosing in patients because I knew what they had in store,” Polydefkis says.

Now, research conducted in Polydefkis’ lab and elsewhere is providing new hope for patients, paving the way for drugs that have the potential to reverse this disease’s progression for the first time.

Polydefkis explains that this disease stems from TTR, a protein produced mainly in the liver that ferries thyroid hormone and retinol elsewhere in the body. This protein is usually bound in a normal form that disassembles into four individual pieces. In some people, these pieces misfold into a square-like shape that agglomerates, leading to amyloid deposits.

Although a subset of patients can be cured with liver transplants, and a drug that could slow the disease somewhat was approved in Europe, there were no truly effective treatments for the majority of patients with this disease in the United States.

“We’d watch patients who ride horses or go square dancing or do needlework lose the ability to do those things,” says Johns Hopkins neurology nurse practitioner Kathleen Burks. “This disease doesn’t cause any cognitive decline, so these patients were just trapped in bodies that were turning on them.”

However, several years ago, researchers devised a couple new approaches to this disease. Both centered on knocking down the levels of this protein using either an antisense oligonucleotide or RNA interference (RNAi). Polydefkis says that he, Burks, and their colleagues at Johns Hopkins leaped at the opportunity for Johns Hopkins patients to join these trials. As an aid to track patients’ progress, Polydefkis’ lab developed a protocol to test for amyloid using punch skin biopsies, a method that Polydefkis pioneered years ago to diagnose and follow various forms of neuropathy.

The results from both trials were overwhelmingly positive, says Burks. Although the first part of each trial was double-blind, it was often clear to Polydefkis what the outcome would be, because I knew what they had in store,” Polydefkis says.

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(continued on page 2)
Epilepsy Late in Life
New study highlights risk factors for seizures after age 60

**Epilepsy is often thought of as a disease that only arises in childhood. But that’s a common misconception, says Johns Hopkins neurologist Emily Johnson. Epilepsy is the highest incidence in old age, with each decade after age 60 bringing even more new cases,” she says. While some of these diagnoses can be attributed to brain damage caused by stroke and neurodegenerative disease, Johnson explains, up to half of cases have no known cause.

To help shed light on what may lead to late-onset epilepsy (LOE), Johnson recently led a study using data from the Atherosclerosis Risk in Communities (ARIC) cohort study. This prospective cohort study started in 1987 that followed nearly 16,000 men and women recruited form one of four study centers scattered across the country when the volunteers were between 45 to 64 years old. Patients in this study have been examined in person six times over the years and are contacted yearly by telephone to answer questions about their health.

Johnson and her colleagues collected the baseline health information from 10,420 of these individuals, which included both demographic factors such as age and race; lifestyle factors such as whether participants were exercisers, drinkers or smokers; and pre-existing health factors such as whether they had hypertension, diabetes, or cerebral apolipoprotein E4 gene variant, a risk factor for Alzheimer’s disease. They then used claims data to determine which of these individuals were eventually diagnosed with epilepsy after age 60 by December 2017.

Their findings show that a variety of factors appear to increase the risk of LOE, including having baseline hypertension, diabetes, stroke or dementia, or being a smoker. Having the apolipoprotein E4 gene variant also boosted LOE risk, even in patients who didn’t have dementia. Other factors included normotensive, as well as previous levels of physical activity and moderate alcohol intake.

Although these findings don’t point to a “smoking gun” for LOE’s cause, she says, they suggest that it may be possible to modify some risk factors for this condition. Future studies might focus on whether making changes later in life, such as increasing physical activity, might ward off this disease—or even whether modifying risk factors in patients who are already diagnosed might affect seizure frequency.

Regardless of age, she adds, all adults who visit a neurologist for new seizures should receive a comprehensive workup with neuroimaging and an electromyography to look for structural reasons and identify possible causes. This knowledge can help guide treatment decisions, such as choosing anticonvulsant medications. Older patients often have a higher risk for medication interactions simply because medication use rises with age. Doctors should also pay close attention to preventing falls, either from the epilepsy itself or from incontinence induced by medication, since they can be more consequential in older age.

“Our ultimate goal is to improve seizure control,” Johnson says, “so patients can live their best life no matter how old they are.”

To refer a patient, call 410-955-9441

**Understanding Neuromodulation**
New gift will help researchers study basic and applied science behind this pain-relieving approach.

For centuries, people have been applying stimuli aimed at nerves that don’t carry pain signals to affect the function of those that do, an effect known as neuromodulation. It’s the concept behind transcutaneous electrical nerve stimulation (TENS) units or implanted spinal cord stimulators. And while many patients report that these interventions provide substantial relief, exactly how they work has been a mystery.

“Although there are a lot of educated guesses about how these devices work, there’s not that one really known,” says Michael Caterina, director of the Neurosurgery Pain Research Institute at Johns Hopkins. “The science behind neuromodulation is limited.”

A recent $5 million gift from the Theodore N. Lerner Family Foundation, establishing the Lerner Family Fund for Pain Research, will provide new resources for the mechanisms behind this pain-relieving approach—potentially leading to new ways to effectively apply this strategy to more patients. This endowed fund will be split between the Neurosurgery Pain Research Institute at Johns Hopkins and the laboratory of Thomas Smith, a specialist in palliative care at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center.

The institute is using much of its part of the gift to fund basic research in the lab of Yun Guan, a researcher in Johns Hopkins’ Departments of Anesthesiology and Critical Care Medicine and Neurosurgery and the institute’s Director of Pain Neuromodulation Research. Guan is working on developing animal models to study the fundamental mechanisms of neuromodulation at the cellular and molecular level.

“Developing an essential understanding of neuromodulation at the most basic level, explains Caterina, can help researchers make these pain-fighting modalities work better and longer for a broader swath of patients. This work is already paying dividends, he adds. An article recently published study, Guan, along with Gene Fridman in Johns Hopkins’ Department of Biomedical Engineering and Electrical and Computer Engineering and their colleagues, showed that using direct current—a rather than the alternating current predominantly used to deliver this disease—or even whether modifying risk factors in patients who are already diagnosed might affect seizure frequency.

Regardless of age, she adds, all adults who visit a neurologist for new seizures should receive a comprehensive workup with neuroimaging and an electromyography to look for structural reasons and identify possible causes. This knowledge can help guide treatment decisions, such as choosing anticonvulsant medications. Older patients often have a higher risk for medication interactions simply because medication use rises with age. Doctors should also pay close attention to preventing falls, either from the epilepsy itself or from incontinence induced by medication, since they can be more consequential in older age.

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