The Dream of Early Intervention in Narcolepsy

Quinn Eastman, PhD

In 2018, Kelsey Biddle was poised to participate in a unique experiment—because she had suddenly become extremely sleepy.

After graduating from college with a neuroscience degree the prior year, Biddle had begun working at Brigham and Women’s Hospital in Boston, Massachusetts, as a clinical coordinator for a team studying aging and Alzheimer disease. About a month after starting, she told her supervisor that she had been experiencing waves of unusual sleepiness, along with frequent nightmares and vivid dreams.

“It came on pretty abruptly,” Biddle said in a recent phone interview with JAMA. “What bugged me the most was the unpredictable nature of the sleepiness—not knowing when it would hit me. I might fall asleep while talking with a friend. It was happening throughout the day.”

She started having brief episodes of muscle weakness, triggered by laughter or excitement, she recalled. Several times a day, her legs might buckle, or her jaw and face would droop. When Biddle described these events to her supervisor, Nancy Donovan, MD, the psychiatrist immediately guessed what they could be: cataplexy, a distinctive symptom of narcolepsy.

The swiftness of that recognition was exceptional. Narcolepsy can be diagnosed by sleep specialists through relatively low-cost sleep studies, but most people living with narcolepsy are diagnosed months or years after they begin to experience symptoms. More common conditions such as depression or sleep apnea are often suspected instead. A 2013 survey found that more than 80% of people with narcolepsy were diagnosed more than a year after their symptoms began.

Three different physicians Biddle consulted around the time that her symptoms started brushed off the possibility that she might have narcolepsy. But Biddle’s mother, Kristin Hege, MD, who is a cancer immunologist, did not. Hege reached out to Tom Scammell, MD, a narcolepsy researcher at Beth Israel Deaconess Medical Center, whose laboratory was located across the street from Donovan’s. Scammell arranged to have Biddle admitted to Beth Israel to facilitate diagnostic procedures, such as brain imaging and a lumbar puncture.

“That is not something we normally do,” Scammell said in an interview with JAMA at the Associated Professional Sleep Societies meeting in Indianapolis, Indiana, this June. “But because her symptoms had come on quickly, inside of a month, we thought we might have an opportunity to do something.”

Preserving Hypocretin

Researchers have suspected since the 1980s that the form of narcolepsy that includes cataplexy, called narcolepsy type 1, develops because of an autoimmune attack on part of the brain.

Narcolepsy type 1 could be seen as roughly analogous to type 1 diabetes, in which the immune system eliminates insulin-secreting pancreatic cells. In narcolepsy type 1, what appear to be missing are cells in the hypothalamus that produce hypocretin, a neuropeptide also known as orexin that keeps people awake and alert. Low or absent hypocretin in cerebrospinal fluid is the most definitive diagnostic test for narcolepsy type 1, although the assay is rarely performed. (Type 2 narcolepsy, the more prevalent diagnosis, is not connected with a lack of hypocretin.)

Although effective treatments exist and symptoms can improve over time, narcolepsy is generally thought to be a lifelong condition. Starting in 2003, a few clinicians mostly in France have attempted to use immunomodulatory agents to stop, or at least slow down, the disease process in patients who have begun to experience narcolepsy symptoms. Such interventions would not be expected to help people living with the disorder for years because the critical hypocretin-producing neurons are presumably already lost. But within weeks or months of symptom onset, some experts believe it might be possible to save some endangered neurons and reduce symptom severity.

The immunomodulatory agent most frequently used has been intravenous immunoglobulin (IVIg), with mixed results. A 2017 study found that IVIg did not significantly reduce symptoms in 22 children with narcolepsy treated in an open-label, nonrandomized way. A subset of patients with high baseline symptoms did experience more rapid improvement over time than a control group that received only standard of...
care, but the authors could not determine whether they might have done so without special treatment.

Biddle began IVIg treatment at Beth Israel shortly after her diagnosis, but it gave her a strong headache, so she discontinued it after 2 days. Her sudden sleepiness, however, arrived at a time when more evidence was revealing how an autoimmune attack may occur in narcolepsy type 1. Neurologists who specialize in narcolepsy had begun pushing for a more targeted approach to immune intervention than IVIg.

The strongest genetic risk factor for narcolepsy type 1 is a common variant of a human leukocyte antigen (HLA) gene. This gene encodes a protein that guides T-cell activation. T cells that target hypocretin have been detected in the blood of patients with narcolepsy type 1, although the chain of events that may lead to loss of hypocretin production remains unclear. The apparent elimination of hypocretin cells is precise, without widespread damage; neighboring cells in the hypothalamus are left intact.

“We thought: if this is primarily a T-cell driven thing, let’s try to stop the T cells from moving into the brain,” Scammell said of Biddle’s case.

Several weeks after stopping the IVIg, Biddle became the first person with early-onset narcolepsy—and so far, the only one—to receive natalizumab, a drug that has US Food and Drug Administration approval for use in patients with multiple sclerosis. Natalizumab was designed to interfere with the movement of immune cells across the blood-brain barrier.

The initial plan was to treat Biddle with monthly infusions of natalizumab for 1 year under a single-patient Investigational New Drug Application. At the time, there were concerns about the risk of progressive multifocal leukoencephalopathy, a serious but rare adverse effect associated with natalizumab. Biddle was willing to proceed despite the risk. Scammell’s team collaborated with a laboratory at Stanford University to analyze the T cells in her blood.

However, hypocretin levels in Biddle’s cerebrospinal fluid continued to drop. She was also being treated with wake-promoting medications, which somewhat moderated her symptoms. Scammell and his team decided to stop natalizumab treatment a few months early, but they continued to wonder if they would have observed a greater effect if they had started sooner.

Controversy and Skepticism
More recently, investigators in the Netherlands have begun a clinical trial of epigenetic agents in new-onset narcolepsy, based on research led by Mehdi Tafti, PhD, and colleagues at the University of Lausanne in Switzerland. The drugs being tested—hydralazine and valproate, a DNA methylation inhibitor and histone deacetylase inhibitor combination used for some types of cancer—work differently from immunomodulatory agents such as IVIg or natalizumab, but they are being investigated with the same goal of preserving hypocretin.

The rationale behind the trial is controversial in the narcolepsy field because it turns widely held assumptions upside down, noted Tafti, who is a professor in the university’s Department of Physiology. Tafti and his coauthors published their findings in PNAS this May. They make the case that in people with narcolepsy type 1, hypocretin-producing cells might survive an autoimmune attack. The implications are provocative: narcolepsy, once acquired, may not be permanent.

“Our findings suggest that people with narcolepsy didn’t lose their hypocretin neurons,” Tafti said in an interview. “It gives us hope that the disease state could be reversed.”

Tafti and his colleagues cite 2 lines of evidence from their study. The first is based on the marker QRFP (pyroglutamylated RF-amide peptide), a neuropeptide often found together with hypocretin in the hypothalamus. Tafti’s team demonstrated that when hypocretin-producing cells were selectively killed off by a toxin in mice, QRFP was no longer detected in the hypothalamus. But in postmortem brain tissue samples from people with narcolepsy type 1, cells in the hypothalamus continued to produce QRFP.

The second piece of evidence also comes from postmortem brain samples. A DNA methylation analysis of those samples from people with narcolepsy type 1 showed evidence that the hypocretin gene was turned off.

Tafti explains that in response to immune activity, hypocretin-producing cells may shut off the hypocretin gene, as well as genes encoding other neuropeptides, but not the QRFP gene. He goes as far as saying that narcolepsy type 1 develops through an “immune-related” mechanism but says it shouldn’t be called an “autoimmune” disease.

To support the idea that hypocretin could be reactivated, Tafti draws upon previous reports of its malleability. Hypocretin-producing cells are more abundant in postmortem brain samples from people chronically exposed to opiates than in control group samples, for example. If the cells are alive in people with narcolepsy, they could be coaxed back into their previous state, Tafti suggests.

Several narcolepsy experts contacted for this article expressed skepticism about the team’s findings but did not want to comment on the record. In an interview, Emmanuel Mignot, MD, PhD, director of the Stanford Center for Narcolepsy and a main proponent of the autoimmune mechanism of narcolepsy type 1, said that the Lausanne results need to be replicated independently.

Mignot, whose Stanford laboratory analyzed Biddle’s T cells, said that hypocretin gene silencing and cell death are not mutually exclusive mechanisms. Perhaps hypocretin cells first become senescent, and then later die, he suggested. He pointed out that in models of type 1 diabetes, a similar mechanism of epigenetic silencing has been reported to occur at the insulin gene locus in beta cells. Genes that are silenced but not killed by injury or inflammation also occur in neuropathic pain.

“What’s the difference between being dead and being a zombie?” Mignot asked. “The question is: can the cells be revived?”

The answer to that question is still unknown. There’s no direct evidence yet that hypocretin production can be reactivated.

Yves Dauvilliers, MD, PhD, director of the Sleep-Wake Disorders Center at the University of Montpellier in France, called for more evidence supporting an epigenetic mechanism in narcolepsy type 1, rather than scarring and neuron dysfunction resulting from inflammation. Dauvilliers, who collaborated with Tafti on past clinical studies of IVIg, said in an interview that it was “too soon” for epigenetics-based clinical trials.

The Missing Link
Several pharmaceutical companies are developing new drugs for narcolepsy symptom management. Some are long-anticipated hypocretin receptor agonists, which would replace the neurochemical signals lacking in people with narcolepsy type 1. Still, none of the drugs currently in clinical trials for narcolepsy are intended as modifying disease, Scammell confirmed.
Gert Jan Lammers, MD, PhD, a professor of neurology at Leiden University Medical Centre in the Netherlands and principal investigator for the trial of epigenetic agents, said in an email that the study had begun but that recruitment had been difficult for "various reasons." (Lammers also coauthored the recent article in PNAS.)

Investigators wanting to intervene in early-onset narcolepsy face 2 challenges: deciding on the proper intervention and identifying participants in the right timeframe. Some people with narcolepsy experience excessive sleepiness years before cataplexy.

Feri Ascencion, a former chair of the Netherlands Narcolepsy Association who was diagnosed with the condition in the 1990s, said that people in the Netherlands with narcolepsy might have a better chance of being recognized early than in the US because the Dutch have a national health care system and well-equipped specialty centers.

"You don’t have to fight the insurance company to get a sleep test," he said in an interview. "Still, I know many people [in the Netherlands] who have taken years to get diagnosed. The missing link is between the family doctor and the sleep specialist."

Kiran Maski, MD, MPH, a narcolepsy specialist at Boston Children’s Hospital, in Boston, Massachusetts, suggested that it may be more feasible to identify patients with new-onset narcolepsy in the pediatric population than in the adult population. Parents might notice changes in their child and bring them to a physician promptly.

"A rare presentation is abrupt narcolepsy symptom onset, occurring over days to weeks, but this is more common in pediatric [narcolepsy type 1]," she said by email.

She added that if patients presented to care within 60 days of symptom onset, she would consider an immunomodulatory treatment.

Years later, Biddle looks back on volunteering for an experimental therapy as a step she could take to reclaim her agency. She says does not regret her choice. Now a Harvard Medical School student, Biddle manages her narcolepsy with standard wake-promoting medications and co-leads a group that supports students at the school who have chronic illnesses and disabilities.

"For me, as an aspiring physician, it was empowering to be part of this study and hope for a different outcome," she said. "It made me feel like I was making a contribution—beyond my own life."

Published Online: June 28, 2023. doi:10.1001/jama.2023.10058
Conflict of Interest Disclosures: Mr Ascencion reported being a cofounder of narcolepsy patient organization PWN4PWN.org, which has received grants from Jazz Pharmaceuticals, Harmony Biosciences, Avadel Pharmaceuticals, and Takeda Pharmaceuticals; he received no funding from those companies. Ms Biddle reported being a board member for Avadel Pharmaceuticals, Jazz Pharmaceuticals, Orexia Therapeutics, Takeda Pharmaceuticals, Harmony Biosciences, Bioprojet Pharma, and Idorsia Pharmaceuticals. Dr Maski reported receiving grant funding from Jazz Pharmaceuticals and Harmony Biosciences; consulting for Jazz Pharmaceuticals, Harmony Biosciences, Zevra Therapeutics, Takeda Pharmaceuticals, and Alkermes; being on the data and safety monitoring board for Idorsia Pharmaceuticals; and serving on medical advisory boards for the Hypersomnia Foundation and Wake Up Narcolepsy. Dr Mignot reported receiving research support from Vanda Pharmaceuticals, Eisai, Jazz Pharmaceuticals, Avadel Pharmaceuticals, Assome Therapeutics, and Takeda Pharmaceuticals; consulting for Takeda Pharmaceuticals, Centessa Pharmaceuticals, Merck & Co, and Alkermes; consulting for sleep data analysis and device companies; and serving as chair emeritus of the medical advisory board for the Narcolepsy Network. Dr Scammell reported receiving grants and research support from Takeda Pharmaceuticals, Harmony Biosciences, and Jazz Pharmaceuticals; consulting for Avadel Pharmaceuticals, ConsYnance Therapeutics, Harmony Biosciences, Idorsia Pharmaceuticals, Jazz Pharmaceuticals, Merck & Co, Synchrony Healthcare Communications, Takeda Pharmaceuticals, and Woolsey Pharmaceuticals; and serving on the medical advisory board for the KLS (Kleine-Levin Syndrome) Foundation. Dr Tafti reported receiving research support from NLS Pharmaceuticals and Jazz Pharmaceuticals; consulting for NLS Pharmaceuticals; and being co-inventor of epigenetic treatments for narcolepsy for which the University of Lausanne holds a patent. Dr Eastman reported being the author of a forthcoming book on idiopathic hypersomnia and the science of sleepiness, for which he will receive royalties.
Note: Source references are available through embedded hyperlinks in the article text online.