# Case illuminates immune system-psychiatric disorder link

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The Nelsons — from left, Amanda, Paul, Mary and Paul Michael — at their home in Half Moon Bay. Paul Michael is being treated for pediatric acute-onset neuropsychiatric syndrome, which can send him into rages. Credit: Timothy Archibald

The case of Paul Michael Nelson, a boy living in Half Moon Bay, illustrates an alarming phenomenon: Your immune system can make you go crazy.

On March 2, 2009, something snapped inside Paul Michael Nelson. In the middle of the night, his parents found the 7-year-old boy stabbing the door of the family's home office with a kitchen knife, trying to get at a computer that was off-limits after his bedtime. When they stopped him, he flopped around the floor on his knees, barking like a dog. He tore at blankets with his teeth and spoke in gibberish.

It was Paul Michael's first episode of psychosis.

"It was like he was demon-possessed," says Mary Nelson, his mother.

The Nelsons rushed to their local emergency room, where staff didn't seem to believe their account of the intensity of the outburst and said it must have been just a temper tantrum. The staff wrote a referral to a psychiatrist and sent him home. The next day, the Nelsons took Paul Michael to the psychiatrist. She was about to give him an antipsychotic, but changed her mind after reading his blood work.

"She said, 'Oh, my God, he's got low platelets; I can't prescribe this,' and she shuffled us out," says Paul Nelson, the boy's father. Paul Michael's levels of platelets, the blood cells that form clots to stop bleeding, were far below normal, but the Nelsons were not sure why the psychiatrist thought this justified avoiding antipsychotics. After the family left the psychiatrist's office, Paul saw his son, who seemed to have held himself together for the doctor, becoming overwhelmed. "He's very scared; he knows something's wrong. When she shut the door, it felt like the doctor shut us off." When the family got home that day, Paul Michael exploded into another psychotic fury.

Sucked into the whirlpool of Paul Michael's compulsions, rages and delusions, neither the Nelsons nor the doctors who took on Paul Michael's case realized that the little boy's abnormal blood work held an important clue to what was wrong. It took months and several psychiatric

hospitalizations before anyone recognized that Paul Michael's case illustrated an alarming phenomenon: Your immune system can make you crazy.

When the immune system gets derailed from its usual infection-fighting role and attacks the brain, it can trigger obsessive-compulsive actions, anorexia-like refusal to eat, severe anxiety, violent outbursts and other symptoms of mental illness, as well as a host of neurological problems—in the worst cases, seizures, respiratory failure and death. Although doctors recognize a handful of immune-mediated neurologic diseases in children and adults, their awareness of the immune connection to mental illness is limited.

That's slowly changing. Instead of hot-potatoing such puzzling cases out of their offices, as the Nelsons' first psychiatrist did, some physicians are working to understand the mechanisms and develop treatments for autoimmune diseases that attack not just the brain but also the patient's personality, the intangible spark we call the self.

It's not easy. There's no diagnostic lab test for pediatric acute-onset neuropsychiatric syndrome, or PANS—the name for this list of devastating symptoms—and the list probably encompasses an array of similar but not identical brain diseases, most of which still have unknown causes. But in spite of the stumbling blocks and the scientific disputes they've engendered, answers are emerging, in large part because of a Stanford team's efforts to conduct research and treat affected children in the country's first clinic to address the disease.

## A family's agony

Paul Michael's second breakdown happened after his family returned home from that unsuccessful psychiatrist visit, March 3. It was so violent that his parents called the police. He was doing some of the same

alarming things as the night before—flopping around, speaking in gibberish—but was also tearing up his room, causing his parents to worry that he might find an object there that he could use to hurt himself. Paul tried holding the little boy to calm him, but Paul Michael fought his dad with what seemed like superhuman strength. The police took him to the hospital on a 5150, California's code for involuntary restraint of persons who are a danger to themselves or others. He was in and out of a pediatric psychiatric hospital for several months.

Meanwhile Paul and Mary began their search for answers, starting with Paul Michael's general pediatrician and the psychiatrists, social workers and counselors they found through their health insurance provider and the psychiatric hospital where Paul Michael stayed. Most of these caregivers ascribed Paul Michael's problems to a family history of psychiatric illness (both parents had depression and bipolar disorder in their extended families), poor parenting or outright child abuse.

The Nelsons were willing to try anything to become better parents. "If I'm doing something wrong, I want to know," Mary says, adding that "We felt like, we've somehow got to try to survive because we love him so much." But they were grieved and confused, too: "We met with counselors at the psychiatric hospital who were saying things like, 'Mom, you're too codependent'—and I might be, but I knew I didn't cause my kid to go psychotic."

Paul ticks off the strategies they tried, following counselors' suggestions, to improve their family environment: rewards for good behavior, lists of skills to utilize, contracts, daily affirmations … until both parents chuckle ruefully at the futility of those efforts in the face of Paul Michael's uncontrollable compulsions and rages.

Although the suggestion that they were abusing their son pained them, they knew why it crossed people's minds: He was always covered in

bruises. More than once, the police showed up to a scene of one parent restraining an explosive Paul Michael, and, to an outside observer, it was hard to tell what was really going on. Paul had been a San Francisco sheriff's deputy for 27 years before retiring to return to school, so he could easily see these scenes from the officers' perspective. There were times he found himself consoling the officers because they had never seen a young child so distressed.

At first, the only dissenting medical expert's voice about the origins of Paul Michael's illness came from Mary's colleague William Benitz, MD, a professor of pediatrics at the Stanford School of Medicine, where Mary was a human resources manager in the neonatology division. Benitz urged the Nelsons to take Paul Michael to a rheumatologist who could investigate whether an autoimmune disease could be causing both their son's very low platelet count—which could explain his constant bruising—and his sudden psychiatric symptoms.

"I have a rule of thumb for pediatric patients: They're only allowed to have one disease at a time," Benitz says. "It's not 100 percent true, but for a previously healthy 7-year-old to develop what appeared to be psychiatric and hematologic symptoms from two different, independent processes didn't make sense. There had to be a unifying diagnosis."

Then, the Nelsons ended up at Stanford Hospital's emergency department during one of Paul Michael's outbursts, where they saw Richard Shaw, MD, a professor of psychiatry and behavioral sciences and a child and adolescent psychiatrist at Lucile Packard Children's Hospital Stanford. Observing Paul Michael's behavior, Shaw told the Nelsons that they weren't dealing with schizophrenia or bipolar disorder; instead, he suspected vasculitis or brain inflammation. His opinion spurred the family to keep searching for a diagnosis.

## A history of controversy

When Paul Michael became sick in 2009, the concept of autoimmune psychiatric disease was barely on doctors' radar. It wasn't until September 2012 that Lucile Packard Children's Hospital Stanford opened the country's first clinic devoted to treating children with PANS, which is still the only clinic to couple the expertise of psychiatry and immunology/rheumatology for these patients.

Children who meet diagnostic criteria for PANS have sudden, severe obsessive-compulsive behavior or anorexia, along with so many other problems that the child can barely function. These may include separation anxiety so powerful the child cannot bear to be more than a few feet from a parent, bizarre inhibitions about food, deterioration in schoolwork, intense insomnia or, as the Nelsons observed in Paul Michael, violent rages when the child's obsessions cannot be satisfied.

"In some ways, it's like having your kid suddenly become an Alzheimer's patient, or like having your child revert back to being a toddler," says Jennifer Frankovich, MD, clinical assistant professor of pediatric rheumatology at the School of Medicine and one of the clinic's founders.

"We can't say how many kids with psychiatric symptoms have an underlying immune or inflammatory component to their disorder, but given the burgeoning research indicating that inflammation drives mood disorders and other psychiatric problems, it's likely to be a large subset of children and even adults diagnosed with psychiatric illnesses," says Kiki Chang, MD, professor of psychiatry and behavioral sciences.

Chang, a pediatric bipolar expert, was drawn to collaborate with Frankovich in founding Stanford's clinic because many PANS patients are first suspected of having bipolar disorder. But although their symptoms begin as abruptly as bipolar manias, they are not manic. Talking about these mystifying children (among them Paul Michael, whom the doctors now consider their first PANS case), Chang and

Frankovich realized the only thing that was clear was that the children and their families desperately needed help. Nearly everything else about PANS was up for debate. "A lot of academic physicians have said 'This does not exist; it's just bad behavior, and there are a lot of reasons for kids to have bad behavior,'" Frankovich says.

For many years, controversy dogged PANDAS, the provisional diagnosis that preceded PANS in the medical literature. The phenomenon, which was first reported in the 1980s by Susan Swedo, MD, now a senior investigator at the National Institute of Mental Health, included sudden emergence of OCD or tics (repetitive, hard-to-control vocal or physical movements) in the wake of strep infection. Swedo's theory was that the body's response to infection went awry and triggered an autoimmune attack on the brain. She succeeded in treating some cases with either long courses of antibiotics to kill strep bacteria or, if that didn't work, various immune therapies.

However, many healthy children carry strep bacteria, one of several factors about the biology of strep that have made it difficult to clarify the bacterium's role in the disease. So the syndrome's critics have contended that the kids simply had run-of-the-mill Tourette's or obsessive-compulsive disorder plus, perhaps, some behavioral problems caused by bad parenting.

The treatments Swedo proposed have risks. One of them, long-term antibiotic therapy, can favor development of antibiotic-resistant organisms. Another, treatment with immunosuppressants, puts kids at risk for serious infections. But the children's symptoms were extremely debilitating, and the treatments seemed to help. Swedo was frustrated that, in her view, the science was being stalled by critics' dismissal of the immune-system connection.

Frankovich and Chang acknowledge the dearth of science to explain

most cases of PANS, but say that's why Stanford's clinic is so important: It provides a critical mass of patients for answering scientific questions. Other institutions, such as Harvard-affiliated Massachusetts General Hospital and the University of South Florida in Tampa, have joined Stanford in committing resources to study and treat the disease, and more programs are under development.

"Maybe we'll go back and say, 'We were wrong; it's all parenting,'" Frankovich says, sounding simultaneously tongue-in-cheek and strained. "But we have to try."

## A discovery that changed minds

The 2007 discovery of a molecular explanation for some cases of autoimmune encephalitis—a specific form of brain inflammation caused by an immune attack—has made a big difference in convincing physicians to look for autoimmune underpinnings when patients suddenly seem to go off the deep end.

In this disease, known as anti-NMDA receptor encephalitis, an antibody made by the patient's immune system attacks a receptor for a single neurotransmitter, N-methyl-D-aspartate, producing psychiatric and neurologic disturbances. For instance, a patient may first show anxiety, paranoia and hallucinations, progressing to movement disorders and seizures. In the worst cases, patients develop irregular heartbeat and breathing, go into a coma and die. But quick diagnosis and treatment can reverse all of this. The book *Brain on Fire*, Susannah Cahalan's 2012 best-seller describing her bout with the disease, raised awareness. Though at the height of her illness, Cahalan was severely debilitated with paranoia, hallucinations, seizures and cognitive impairment, she received treatment, made a full recovery, returned to her job as a New York Post reporter and became an advocate for other autoimmune encephalitis patients.

## Quelling the symptoms

Finding a specific antibody that triggers PANS symptoms would make treatment much easier. But most patients have no known biomarker of their illness. In this, though, Paul Michael was lucky. At the beginning of the summer of 2009, a physician in the Nelsons' insurance network referred him, at Benitz's suggestion, to Frankovich. (The insurer didn't have an in-network pediatric rheumatologist within 50 miles of the family's Half Moon Bay, Calif., home, so he was able to go outside the network to see her.) From blood tests, Frankovich discovered that Paul Michael had elevated anti-B2G1 antibodies. These antibodies bind a specific component of cell membranes and target platelets for destruction; they are also associated with blood vessel disease that can cause neurological symptoms such as chorea, a movement disorder that can co-exist with behavior disorders. Paul Michael also had some blood markers of lupus, an autoimmune disease that can attack the brain, though he didn't meet full diagnostic criteria for that disease.

At first, Frankovich had no evidence to prove that the anti-B2G1 antibody or lupus markers were contributing to his psychiatric symptoms, but in a sense that didn't matter. She was a rheumatologist, and she had found an immune abnormality—autoimmune platelet disease—that clearly needed treatment.

In early June 2009, Frankovich began giving Paul Michael powerful immune-suppressing drugs. His platelet count rose and his psychiatric symptoms eased. After having spent 61 days in emergency rooms and psych hospitals between March and May, Paul Michael spent nearly all of June and July at home, visiting the emergency room only three times. Paul and Mary began to hope that things were turning around.

But then, in December 2009, Paul Michael got the flu and Frankovich stopped his immune-suppressing medications so he could recover. His

body fought off the virus, but his platelets dropped and his rages surged back.

"He had a five- to six-month flare," Mary says. "It was heartbreaking."

"We had to start over," Frankovich says. The second time she tried suppressing Paul Michael's immune system, he didn't respond to one of the medications she had used initially, so she switched to a stronger drug. In the subsequent months, Frankovich shifted the medication doses up and down to investigate whether Paul Michael's autoimmune disease was connected to his psychiatric symptoms. His regression when he had the flu, she concluded, was not a fluke: When Paul Michael's immune system was not being suppressed, his platelets fell and his rages became more frequent and intense. She became increasingly convinced an autoimmune process was causing both his low platelets and his psychiatric symptoms.

But she had trouble getting others to agree that there was a connection. "Even though our psychiatrist at Stanford believed the two problems were related, the non-Stanford psychiatrists the family was seeing through their insurance provider didn't understand what was going on medically," she says. "They were looking at this as a kid with a behavior disorder, saying it must be a parenting issue."

By June 2010, police had responded to 5150 calls from the family 17 times. Exhausted by trying to care for him, his parents felt they had no choice but to have Paul Michael live at a psychiatric institution.

For 15 months, Paul Michael became a residential patient at Edgewood Center for Children and Families, a San Francisco facility that provides the highest level of psychiatric care available below a locked psychiatric unit. Edgewood had a much more structured, predictable environment than any family could reasonably provide at home, and unlike parents

who had to be "on" 24 hours a day, the caregivers worked in shifts. Even there, though, Paul Michael's rages occasionally escalated to the point that the police were called. Paul and Mary visited several times a week, while also trying to return a sense of normalcy to the life of Paul Michael's older sister, Amanda.

Meanwhile, Frankovich struggled for months to convince even the Nelsons of the connection between their son's immune and psychiatric problems. "They were so disabled by his psychiatric disease that it was hard for them to have insight into what was going on," she says.

For a long time, Paul and Mary dissected their own behaviors to try to figure out how they might have sparked episodes of Paul Michael's rage.

"We were looking for triggers, but there was no trigger," Paul says. When the illness was at its worst, it was impossible to avoid setting the boy off. "If it wasn't going to happen at 9 when the phone rang, it would be at 9:15 when the cat wanted to go out," Paul says. The Nelsons eventually discarded the concept of triggers. "Now, when he's getting edgy, we call it 'storm season,'" Mary says.

"This illness has leveled our pride and our expectations," Paul says.

"There has been a lot of grief for both of us, his sister and for him, too," says Mary.

"But it's lucky he had the clear autoimmune blood disorder, because it allowed us to use immune-modulation therapy," says Frankovich. "Had he just come in with behavioral deterioration, he would still be in a mental hospital.

## Hunting for answers—and treatments

Because it's unclear whether PANS is actually one disease or many, Frankovich and Chang are conducting research to clarify the jumbled picture presented by all 70 children they've seen to date at Stanford's PANS clinic. In one study, they're looking for genetic markers that appear more often in PANS patients, the first step toward figuring out whether certain genes increase a child's vulnerability to the disease.

They're also using brain imaging to ask how PANS could change two brain regions. One of these, the basal ganglia, plays important roles in fine-motor control and in fine-tuning mood and anxiety. It is also a region where the blood-brain barrier tends to break down, providing a possible entry for antibodies, which researchers suspect may attack the brain.

Figuring out whether PANS patients make antibodies against their own brains is perhaps the most important key to the disease's mysteries. The research bears similarities to the discovery of anti-NMDA receptor encephalitis, and the path to that breakthrough may provide a road map of sorts for PANS researchers.

"You first need a critical mass of patients, but it doesn't need to be very big," says Josep Dalmau, MD, PhD, who led the anti-NMDA discovery. The professor of neurology at both the University of Pennsylvania and the University of Barcelona notes that his team's first report of anti-NMDA receptor encephalitis included just four patients with very similar conditions. "In my experience you need clinics, and a good group of clinicians who can see all these patients and group them in some way."

After grouping them, Dalmau's team searched the patients' cerebrospinal fluid for unusual biomarkers, finding an out-of-place antibody common to all four patients. The clincher was that this antibody attacked the brain.

"It's very clear-cut: You see the antibody beautifully reacting with neurons, and see that the antibody binds to the brain and decreases the number of NMDA receptors," Dalmau says. "There's no ambiguity. We don't see the antibodies in patients without the disease."

There are hints that PANS may also be associated with misplaced antibodies. Madeleine Cunningham, PhD, professor of microbiology and immunology at the Oklahoma University Health Sciences Center, has developed a possible PANS diagnostic panel that tests for one brain enzyme and four antibodies against different brain proteins.

"The evidence she has published is strong, but it's just the tip of the iceberg," Frankovich says. "We still have a lot more work to understand what these four antibodies mean and how reliable they are in the clinical setting." For one thing, healthy people have low levels of these antibodies; scientists still don't understand what constitutes a critical level of these antibodies and why they enter the brain. Clinical studies at several sites around the world are attempting to independently validate the panel.

Circumstantial evidence also suggests antibodies contribute to PANS, Cunningham notes, because plasmapheresis, a technique in which a patient's plasma is replaced with the plasma of a healthy individual, has successfully treated some PANS patients.

"Plasmapheresis removes antibodies and the person gets better," Cunningham says.

An immune-suppressing treatment, intravenous immunoglobulin, or IVIG, may also help. IVIG, a blood product consisting of IgG antibodies from healthy donors, is infused into the patient to tamp down inflammation. Scientists aren't entirely sure how it works, but the NIH's Swedo is now conducting a phase-3 clinical trial of IVIG versus placebo

to see if it's an effective PANS treatment, part of her larger effort to standardize PANS therapy.

And the larger scientific community is talking more about PANS and PANDAs, too. For example, the Journal of Child and Adolescent Psychopharmacology is publishing an October 2014 special issue on the diagnoses.

Without a universally accepted PANS treatment, Stanford's doctors currently approach PANS patients one symptom at a time. Depending on the patient's presentation and what the clinical workup reveals, treatments possibly employed include immune-modulating drugs if autoimmune markers or signs of inflammatory disease are present, or antibiotics for repeated sinus or throat infections. They occasionally use limited trials of high-dose steroids to help suss out whether inflammation is behind the symptoms, an approach that's also used for some forms of encephalitis. Chang often addresses psychiatric symptoms with lithium, which has a long history as a therapy for bipolar disorder, but may be generally protective for the brain. "We're trying to support these children's brains and lives as best we can," he says.

## A family looks forward

Today, Paul Michael is almost 13 and his condition is much better; Mary estimates he is "90 percent back." After 15 months living at Edgewood, he moved home and spent another two years mostly as a day patient at the facility, with some shorter hospital stays when things temporarily became worse. He transitioned in the fall of 2013 to a special-needs classroom in a public school near his family's home. He attends mainstream classes for three subjects, something the Nelsons could never have imagined during the worst days of his illness. Frankovich's attempts at weaning his immunosuppression resulted in simultaneous flares of his blood disorder and his psychiatric symptoms, so he is now

on a longer term protocol similar to that used to treat diseases like lupus. And it's been more than a year since his last serious outburst of rage.

In other diseases where the immune system can hurt the brain, such as lupus, controlling the autoimmune attack takes up to five years. So Frankovich is not disheartened by the gradual nature of Paul Michael's improvement. It also takes time for the bombarded brain to recover from immune attack, she points out. "It's the same as in brain trauma; even after we get the inflammatory response under control, it still takes time for the brain to heal," Frankovich says, adding that she thinks it is likely that Paul Michael will ultimately be able to complete school, hold a job and live independently.

Paul and Mary are grateful for how far their son has come. "Now that he's doing really well in school, and has been mainstreamed in three classes, that gives me hope," Mary says. "I'm cautiously optimistic." Paul Michael loves to make art and has excellent visual-spatial reasoning skills. In her office, Mary proudly displays several examples of this ability, among them a perfectly proportioned, 2-inch, orange-and-white guinea pig crafted out of looped-together rubber bands. Paul Michael planned and made the three-dimensional critter on a rainbow loom, a tool most kids use for much simpler projects, such as making bracelets. The family has begun talking with him about careers that might put his spatial ability to use, such as engineering or art.

Of late, they've been granting Paul Michael more independence as well. "He walked to the store alone yesterday," Paul says during a conversation in July 2014. "That's freedom a teenager needs, he can do it, and he's happy with himself. It's a real good development."

But Paul and Mary never feel like they can let their guard down, either. The disease could recur. The immune-suppressing medications Paul Michael takes have potentially serious side effects, including increased

risk for infectious diseases and some cancers. And they worry about what happens if he stops the medications.

"He can be extremely volatile," Mary says. "But when he's not, he's this perfectly wonderful, creative, artistic, loving guy."

Seeing the struggles that patients like Paul Michael endure has convinced Frankovich she'll be treating PANS patients for a long time, in spite of all the obstacles.

"Some days, I think 'Why are we doing this? It's so frustrating and hard,'" she says. "Other days, I see a kid we clearly made better. I've seen families crying, saying, 'I haven't had my kid in a year, and now I have my kid back.' We cannot give up on this. There are so many of these cases out there."

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