Researchers work to help children with a rare form of autism

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Credit: Maya Szatai

Dylan started life as a typical baby, meeting his milestones for walking, talking, and other markers of normal development. In a home video from when Dylan was about 3, he climbs, bursting with energy, on the

couch and pretends to read aloud from a picture book. His conversation is animated as he talks about the book with his father, who is recording, and he speaks in full sentences. In kindergarten, his parents noticed some language delays, and Dylan received special education support, but his mother, Kim Covell, saw him as "just a quirky kid."

That changed at the end of third grade. Dylan entered a period of intense anxiety that lasted nearly six months. In a video from this phase, he frantically paces his living room, shaking his hands, scratching his shoulders, repeating over and over, "I'm upset. ... I don't like it. ... oowww, it hurts. ... I'm scared." He scratches under his shirt, giving the impression he wants to crawl out of his skin. "He cried all the time," Covell recalls. "I'm convinced when he was looking at me, he was seeing a distorted version of me." As this phase of terror ended, Dylan started new, dangerous behaviors. He jumped from high places and darted into the road. He developed tics and licked surfaces. Then he slowly ceased talking, began to lose vocabulary, and used simpler sentences. When his scores on his developmental evaluations dropped in every single area, his family convinced his school to get him evaluated at the Yale Child Study Center (YCSC).

In advance of the visit, Covell shared the videos of Dylan at the ages of 3 and 8 with clinicians at the YCSC. A final video shows him sitting limply in front of a puzzle, staring around the room. Occasionally, he picks up a piece and shows it to the camera before setting it back down. He does not speak. Minutes after the video ended, Fred R. Volkmar, M.D., the Irving B. Harris Professor in the Child Study Center and professor of psychology, and Alexander Westphal, M.D., HS '11, Ph.D. '12, FW '12, assistant professor of psychiatry in the YCSC, broke the news: her son had childhood disintegrative disorder (CDD).

The diagnosis offered little comfort. "It put a name to it, but it didn't really help," Covell says. What the family learned was terrifying: there is

no treatment for CDD, and Dylan will likely need special services and support for his entire life. But in those first few years, Covell says, things were OK. "It was challenging—he lost a lot of speech and some of the joy, but he was still involved in the family." From fifth through 10th grade, the family worked with the public school system to get Dylan the support and accommodation he needed. Covell said it was especially difficult to get the schools to understand Dylan's new reality. "He's different from your typical kid with autism."

As a result of years of advocacy, Covell, an assistant editor for the Press News Group in Southampton, N.Y., started a summer camp specifically tailored for kids on the autism spectrum, pairing them with typically developing peers. Now, she figures she has seen just about every variety of autism. This exposure, however, makes her uncomfortable putting Dylan's experience and her family's challenges on the same spectrum. "I have friends whose kids have autism and are going to college. My kid can't wash his hair. It's not only hard to think of those as the same thing; it's absurd."

The mystery of what is really going on with her son has kept her connected to Yale, and committed to participating in any research that might help scientists better understand autism and CDD.

A rare and devastating disorder

CDD, which affects between one and two children in 100,000, was first identified in 1908. It is also known as Heller's syndrome, for the Austrian educator Theodor Heller, who identified the disorder 35 years before autism was first described. Westphal, one of the doctors involved with Dylan's case, describes CDD as what happens when normal kids suddenly develop autism. They lose acquired language; motor, social, and play skills; and frequently bladder and bowel control. The loss often follows a period of such psychiatric disturbances as hallucinations and

anxiety, similar to Dylan's six-month period of terror. In 2013, CDD, then a distinct disorder, was incorporated into autism spectrum disorder (ASD) in DSM-5, the Diagnostic and Statistical Manual of Mental Disorders used by psychologists and psychiatrists. This reclassification has diminished awareness of the disorder, making it harder for families to find information and researchers to secure grant money.

This DSM-5 reclassification is a mistake, according to Abha Gupta, M.D., Ph.D., FW '07, assistant professor of pediatrics, who became interested in CDD during her fellowship at Yale. Although people with CDD meet the full criteria for autism—characterized by difficulties in social communication and restricted, repetitive patterns of behavior—the clinical history of the disorder is different. It is distinguished by its late onset—starting any time between the ages of 2 and 10—and involves dramatic regression and severe impairment.

YCSC faculty have researched CDD for more than 20 years, starting with Volkmar, the center's former director. Through word of mouth, families affected by CDD referred one another to the YCSC for evaluation, building up a community of families like Dylan's that are committed to seeking answers for a condition that has no treatment.

In addition to the desire to understand a mysterious and devastating disorder, the interest in studying CDD comes partly from what it could say about all of autism, says Westphal. The conventional wisdom on autism is that it is a developmental disorder existing from the beginning and that different individuals are affected by atypical development in various areas of communication and social learning to differing degrees, hence, its description as a spectrum disorder.

But Westphal describes CDD as more of a global catastrophe in the brain—low-functioning autism by a different pathway. "That's significant because it may illustrate that not all people with low-

functioning autism have the same kind of autism as people with high levels of function."

Gupta and Westphal were two of the lead researchers on a team composed of geneticists, clinicians, neuroimaging experts, and eye-tracking scientists to perform a neurogenetic analysis of CDD. They identified genetic mutations associated with it, mapped its pattern of abnormal brain activity through functional magnetic resonance imaging (fMRI), and charted its social activity through eye tracking. In every area, patients with CDD were compared to those with autism, both with intellectual disability and without, and to typically developing controls. The team hoped these data could help them understand what happens in the brains of kids like Dylan, and how similar it is to more common subtypes of autism.

The genetic analyses showed important differences between CDD and most forms of autism. Not only were different genes involved, but so were the brain regions where these genes were active. The genes most likely to be involved in CDD were expressed strongly in non-neocortical regions of the brain, which help control eye movements and attention to social information. ASD genes are more strongly expressed in neocortical regions. Another analysis showed that the pattern of expression of potential CDD genes had the most similarity to autism cases with a history of regression, suggesting that regression might have a distinctive genetic pattern. The symptoms seen in CDD, this finding suggests, are likely caused by a genetic mechanism in the brain different from most other subtypes of autism.

The team used non-sedated fMRI to see patterns of brain activity when the research participants looked at images of emotional faces (a social stimulus) and houses (a neutral stimulus). The study also, for the first time, included patients with intellectual disabilities in addition to their autism—a group that is underrepresented in imaging studies because it is

difficult to get these patients to cooperate with the study protocols.

The CDD cohort had an abnormal pattern of activity in nonneocortical brain regions when viewing faces versus houses, a departure from the abnormal pattern that people with high-functioning autism exhibit. The low-functioning group had a pattern between those of the CDD and high-functioning autism groups.

The researchers also found a surprising convergence between the genetic and neuroimaging tests—the regions that were abnormally overactive in people with CDD were the same regions where CDD candidate genes are most active.

Eye-tracking studies record what research participants look at when shown pictures or videos. When viewing faces, most of us look at the eyes, while high-functioning individuals with autism split their time between the mouth and eyes. This difference is thought to explain some social skills deficits found in people with ASD. Because people with CDD are more severely affected than average, Gupta expected to find an abnormal eye-tracking pattern. Instead, she found that people with CDD focused on the same things as typically developing people did. "They also favored the eyes when viewing faces," Gupta says.

The clinical observations, genetic analyses, and imaging and eye-tracking data converged in several areas. First, the genes that are most likely to be involved in CDD are very active in the same areas that are overactive when people with CDD looked at faces. Along with this abnormal overactivity came increased attention to the eyes. The researchers speculate that because CDD surfaces after prolonged normal development, the neural circuits that control attention to faces may be preserved. If so, then whatever is happening in the brain during the regression in CDD does not change how the brain processes faces. Why the preservation of some neural circuits is still accompanied by the

severe behavioral symptoms of CDD remains a mystery.

A distinct disorder

Studies like this, says Westphal, are notable and should push a rethinking of the definition of autism. He favors modeling it as "a converging constellation," in which multiple pathways meet to present similar symptoms. "For me, CDD is so much at the center," says Westphal. "It's the canary in the coal mine, marking the possibility that gradual developmental accounts do not explain all forms of autism."

The distinction has clinical implications. With a CDD diagnosis, the initial push is to hunt for a reversible cause. If the patient is diagnosed with autism and intellectual disability instead, that hunt never happens. "This means we may be missing a whole world of possible treatments for kids on the low-functioning end," says Westphal.

Pamela Ventola, Ph.D., FW '08, assistant professor in the YCSC, helped lead the team that evaluated the research participants. She believes that this study supports her hunch that CDD is its own entity. In other research, she has predicted the effectiveness of a particular treatment based on brain images of patients. CDD "feels very different, clinically," she says. Even though many of the behavioral features are the same as those of autism after the regression has passed, Ventola thinks the results suggest that CDD may be an entity distinct from ASD. "This interdisciplinary research is really the key—none of these methods alone would have given these results," she says.

James C. McPartland, Ph.D., an associate professor in the YCSC who wasn't involved in this study, is skeptical about abandoning the spectrum model for kids who also have intellectual disability or severe regression. Previous attempts to define subtypes based on clinical evaluations were unreliable and inconsistent, he says, something that does families and

patients no favors. And he points out that the sample of 17 participants with CDD is still relatively small. It is impossible to figure out the degree of heterogeneity that exists in CDD. "The reason we stay with the spectrum is because we haven't found anything better."

Dylan's story continues

Dylan continued to lose speech skills. Two years ago, at 16, he was diagnosed with catatonia, a disorder characterized by stupor, mutism, loss of motor skills, and periods of hyperactivity that can be combative and destructive. Dylan has since started at the behavioral clinic of a private autism school that has experience working with students who have catatonia. After over a year of working with him, they have found a communication system for him. Covell describes it as an "old-school" picture system—laminated icons. Many kids use iPads to communicate using pictures, but Dylan's unpredictable behavior—he can become destructive when frustrated—makes that impractical. He can stay in the school until he is 21, and there is no clear answer for what will be best for him after that.

For Kim Covell, the most elusive mystery is the sense, shared by many people who have loved ones with CDD, that the old Dylan is still in there somewhere. He becomes verbal when he gets agitated, but he refers to people and events in his pre-CDD past—teachers from preschool, classmates, things he did with his family. "There's something—it's there," Covell says. "But it's not."

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