Elli Hofmeister began to show signs of Huntington's disease at an early age.

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PAEDIATRICS

Ahead of time

Huntington's disease is not just a condition of middle age — it can affect children and teenagers, too.

BY ELIE DOLGIN

Elli Hofmeister started to lag behind in school when she was 8 years old. By the age of 9, she needed an extra hour of tutoring each night to keep up. Elli's family chalked up her problems to a learning disability. But when Elli, at age 13, began to limp and slur her speech, "it all just started clicking," says her mother, Camille Tulenchik, a hair stylist from Maple Lake, Minnesota.

When Tulenchik was pregnant with Elli, she consulted a genetic counsellor because her boyfriend at the time had a family history of Huntington's disease. The boyfriend didn't know whether he had inherited a mutated copy of the gene huntingtin, which is responsible for the condition; if he had, there would be a 50% chance that Elli had done so, too. But if Elli did turn out to be a carrier of the gene, the counsellor explained, she probably would not develop symptoms until adulthood. Tulenchik recalls thinking, "We've got lots of time."

It was only when Elli began to experience physical problems in her early teenage years that Tulenchik decided to read up on her daughter's genetic risk. "I looked up Huntington's and saw 'juvenile', and said, 'Oh no.'"

When nineteenth-century physician George Huntington described the devastating neurological illness that now bears his name, he wrote that he knew of no cases in which the person affected had shown noticeable signs of disease before the age of 30. Yet the earliest documented case of juvenile Huntington's disease (JHD) pre-dates his seminal 1872 report by almost a decade — and neurologists now estimate that about 5% of cases of Huntington's disease are diagnosed before the person affected turns 20 (see 'At the extremes').

The main determinant of the age of onset is the number of repeats of a certain triplet of DNA bases in the gene huntingtin: a normal version of the gene contains 35 or fewer such repeats; 36 or more results in the formation of an unstable protein that causes Huntington's disease. The greater the number of repeats, the more unstable the protein is, and the more likely a person is to become unwell as a youngster. Elli has 65 repeats, well beyond the loosely defined threshold of 50 repeats at which JHD becomes more common. Her father has only 44 repeats, but errors in DNA replication meant that Elli inherited an even longer mutated region.

Just because someone has a large number of repeats, however, does not mean that they will show signs of Huntington's disease during their schooldays. "There must be other factors that influence the onset age," says Martha Nance, medical director of the Huntington's Disease Clinic at Hennepin County Medical Center in Minneapolis, Minnesota. "We just don't know what they are."

In fact, much of JHD remains shrouded in mystery, largely because few researchers have studied the disease in young people. Take, for example, the Genetic Modifiers of Huntington's Disease Consortium, which undertook the largest DNA-mapping study of genes associated with the progression of Huntington's disease (GeM-HD Consortium, *Cell* **162**, 516–526; 2015). Of the 4,082 participants in the study, only 29 had been diagnosed before the age of 20, according to neurogeneticist Jong-Min Lee, one of the consortium's leaders at the Massachusetts General Hospital in Boston.

In recent years, researchers' interest in JHD has picked up — and slowly the spotlight is shifting to this unique population of patients. "For too long, JHD has been under the radar," says Peg Nopoulos, a psychiatrist and neuroscientist at the University of Iowa in Iowa City. "It's time to pay attention to the kids who are suffering from this disease."

CATCH THE SIGNS

For Nopoulos, filling in the missing data meant starting with a simple catalogue of the many ways in which symptoms differ between children and adults with Huntington's disease. Among young people with the condition, muscle stiffness is perhaps the most common complaint. That's because children typically develop rigidity as one of the initial movement-related symptoms, and rarely exhibit the jerky, involuntary movements known as chorea that characterize adult-onset disease. However,

ADAPTED FROM: R. H. MYERS. *NEURORX* **1**, 255–262 (2004).

when Nopolous and her colleagues surveyed caregivers of patients with JHD, they also learned of a range of other problems found nowhere in the medical literature.

As Nopoulos and her team reported last year (A. D. Moser *et al. Neurodegener. Dis. Manag.* **7**, 307–315; 2017), more than three-quarters of the respondents said that their wards experienced tics, 69% said they were in some type of pain, and around half said they were dealing with moderate-to-severe itching. These symptoms were recorded rarely in adults, but seemed to be widespread in children with JHD. "It suggests that juvenile-onset Huntington's disease is impacting on parts of the brain in a different way than in an adult-onset disease," says Nance, who collaborated on the survey.

To further probe those neurological differences, Nopoulos has used magnetic resonance imaging to scan the brains of about 25 children with JHD (including Elli), as well as those of hundreds of healthy young people. A defining feature of Huntington's disease is that nerve cells of the striatum, a motor-control region in the centre of the brain, shrivel and die as the disease progresses — and, indeed, in the study participants with JHD, "the striatum is just toast," Nopoulos says.

However, the scans also revealed that as the striatum shrinks in these children, another movement-related brain structure — the cerebellum — gets larger. This "pathological compensation", as Nopoulos calls it, could explain why youngsters with Huntington's disease seem to skip the chorea stage of the condition and go straight to stiffness.

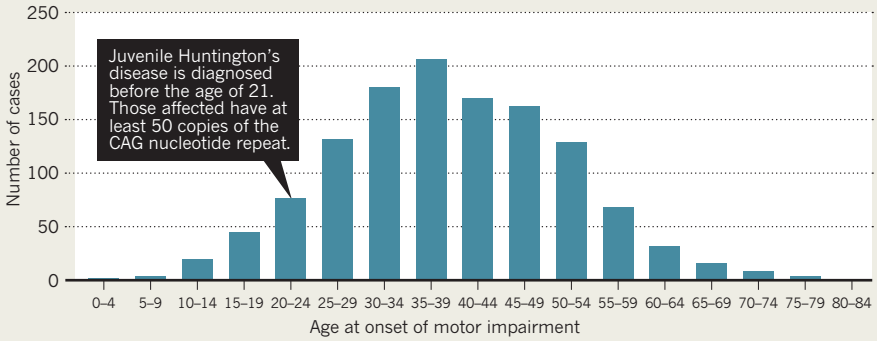
By growing too big, the cerebellum doesn't just make up for the missing motor functions of the striatum; it overshoots the mark and puts the brakes on movement entirely.

Nopoulos presented these findings in February at the 13th Annual Huntington's Disease Therapeutics Conference — at which one of the few other scientists to discuss data on JHD was Mahmoud Pouladi, a neurogeneticist at the A*STAR Translational Laboratory in Genetic Medicine and the National University of Singapore. Pouladi's team coaxed stem-cell lines generated from children with Huntington's disease to form what amount to 3D miniature brains. The disease is usually associated with neurodegeneration, but experiments with Pouladi's brain-like structures suggest that it's also linked to neurodevelopment — and the greater the number of triplet repeats, the more abnormal that development will be.

Another way to study the molecular basis of JHD — and to try to develop treatments to reverse the condition — is to use transgenic mouse models. Few scientists who genetically engineer mice to study Huntington's disease set out explicitly to model JHD rather than adult-onset disease. But according to Gillian Bates, a molecular neuroscientist at University College London, that might be what the research community has done inadvertently. "All of our mouse models are models of the juvenile form of the disease," she says.

AT THE EXTREMES

Motor impairment associated with Huntington's disease is rare in children and adolescents. People who carry the gene mutation that causes the condition develop symptoms on average at around the age of 40. Huntington's disease can strike later in life, but this is also rare.



To observe neurodegeneration during the short life of a mouse — and over a time course that's suitable for experimentation — "we often purposefully push the disease", explains Cat Lutz, director of the mouse repository at the Jackson Laboratory in Bar Harbor, Maine. For Huntington's disease, that means increasing the number of triplet repeats to a level that would cause childhood onset in people.

This protocol could explain why most mouse models show many hallmarks of JHD, including rigidity and susceptibility to seizures — and might even call into question the validity of extrapolating data from mice to adult-onset Huntington's disease. It could also mean that scientists know more about the basic neurology of JHD than they realize.

Then again, those symptoms could just be a reflection of how Huntington's disease manifests in a rodent, and might have nothing to do with the number of triplet repeats or types of the disease in people. The truth, says David Howland, director of research on new animal models for Huntington's disease at the CHDI Foundation, a US non-profit organization, is that "we don't know how good our models really are".

MATTER OF SCALE

More effort is being invested in developing tools for the clinical investigation of JHD. A working group of the European Huntington's Disease Network, led by clinical geneticist Oliver Quarrell at Sheffield Children's Hospital, UK, ran a five-year observational study that tracked 95 people who had been diagnosed with Huntington's disease at or before the age of 25 using the Unified Huntington's Disease Rating Scale, the most widely used and best-validated metric of clinical progression (see page S46).

The results are not yet published, but Quarrell says that the evaluation tool was unsuitable for measuring motor functions in these young patients because it puts great emphasis on chorea and much less on symptoms related to rigidity. He and his colleagues are now working on a modified scale to better match the distinct features of JHD.

That tool will be important in light of a ruling by the European Medicines Agency stating that, from July 2018, companies that develop drugs for Huntington's disease will have to test such treatments in paediatric populations before the products can receive marketing approval. At present, all drugs used to manage the symptoms of JHD — including dopamine modulators, anti-seizure medications, anti-anxiety agents and muscle relaxants — are taken off-label. Elli, for instance, uses a drug that is commonly prescribed for Parkinson's disease to ease her stiffness, over-the-counter pain medicines to deal with aches, and physical therapy to stay as supple as possible.

Her mother follows websites such as HDBuzz to keep on top of the latest drug trials. She then discusses options with Nance, Elli's neurologist, but is yet to find anything promising that also accepts younger participants. To enrol in a study for one of the treatments that aims to silence the mutated gene huntingtin (S39), for example, volunteers need to be at least 25 years old. "Right now I feel like we are very limited in our options," says Tulenchik.

Elli turned 20 in February. Three days a week, she attends a transition programme for young adults with special needs, where she helps to run the coffee shop. She also volunteers at a nearby nursing home, decorating the bulletin board and cleaning bingo cards, swimming-pool noodles and musical instruments. For her most recent birthday, Elli celebrated by hosting a sleepover for only her closest female relatives, including her sister Violet, which meant that her brother Zander couldn't attend. "No boys allowed!" says Elli, in a slow and indistinct manner.

They decorated masks, ate cake and ice cream, and stayed up after midnight, watching *Fly Away Home*, a feel-good, 1990s-era family drama about a teenager who teaches her pet geese to fly. "Our motto is: 'Today is our best day'," Tulenchik says. "We just focus on today." ■

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