



Too Young to Forget

Childhood Dementia

As a bench scientist, Dr. Alexey V. Pshezhetsky does not treat patients, but his office walls bear photos of several children who were born with a very rare genetic disease that progressively robs them of their abilities and skills, eventually causing dementia-like symptoms, and finally, death.

Dr. Pshezhetsky, a professor in the departments of Pediatrics and Biochemistry at the University of Montreal, and Elisa

Linton Research Chair in Lysosomal Diseases at the CHU Sainte-Justine Research Centre, has spent 20 years studying Sanfilippo syndrome (also known as mucopolysaccharidosis type III or MPS III), a heartbreaking disorder that causes deterioration of brain cells.

"The course of the disease is just terrible," said Dr. Pshezhetsky. ➔

TYPICALLY, CHILDREN ARE DIAGNOSED AROUND THE AGE OF THREE, FIRST DEVELOPING HYPERACTIVITY AND AGITATION, AND EXTREMELY LIMITED SLEEP. OVER TIME, “THEY LOSE THEIR ABILITY TO SPEAK, THEY LOSE WEIGHT, THEY CAN NO LONGER WALK, AND BASICALLY, THEY ARE IN DEEP DEMENTIA.

“Usually these children die before the age of 20,” Dr. Pshezhetsky said. One symptom that’s particularly distressing for parents is unexplained screaming that sounds like an expression of agony, but there is no way of telling whether the child is in pain, and if so, how to ease it.

While MPS III affects only a small fraction of the population (approximately one in 70,000 newborns), according to a 2023 study published in the journal *Brain*, it is one of a long list of conditions that cause progressive cognitive decline in children.

The research was spearheaded by an Australia-based organization called the Childhood Dementia Initiative, founded by Megan Maack, the mother of two children with Sanfilippo syndrome.

“She saw there were a lot of other children with other similar conditions facing similar challenges,” explained Dr. Kristina Elvidge, Head of Research at the Childhood Dementia Initiative. “She saw there was an opportunity to bring all of these conditions under one umbrella, to achieve a greater scale of change in research and the health system.”

ESTABLISHING BURDEN OF ILLNESS

To make a case for doing so, and help bring attention to the issue, “we decided to do a burden of illness study,” Dr. Elvidge explained. “Basically, we had a panel of clinicians who look after children with these types of disorders go through a list of conditions and decide which ones fit the definition of childhood dementia.” (“Childhood dementia” is a disease classification that is not currently recognized by any diagnostic system.)

The authors of the paper describe childhood dementia as a global neurocognitive decline that emerges after a period of developmental progress. Its hallmark is the “enduring and progressive loss of previously acquired developmental skills,” such as eating and walking.

In addition to difficulties with concentration, comprehension, learning, and communication, symptoms may include confusion, personality changes, and severe sleep disturbances.

Ultimately, the researchers “came up with a list of 145 conditions,” Dr. Elvidge said. “It’s not that dissimilar to adult-

onset dementia, where there are at least 100 different types,” she noted.

However, there is one important contrast between the two groups of conditions. While most types of adult dementia are likely caused by a combination of genetic susceptibilities and environmental factors, children with one of the 145 disorders named in the study are born with genetic changes “that make it 100% certain they will get childhood dementia,” Dr. Elvidge said.

Examples include Gaucher disease types II and III, Niemann-Pick disease types A and C, four genetic subtypes of Sanfilippo syndrome, and ten childhood-onset subtypes of Batten disease.

NOT SO RARE

After compiling this list, “we worked with health economists to do some disease modelling based on the incidence and life expectancy of those disorders,” Dr. Elvidge said.

“There was a lot of data missing because some of these conditions are really very rare, but using the data we could gather, we estimate that the incidence of those conditions that are currently untreatable is one in 2,900 births.

“That’s on par with cystic fibrosis. I think this is one of the biggest health issues that nobody knows about. These families have a very high unmet need, and they need greater attention from both health systems and researchers.”

The group also found that “half of these children die before they turn ten years of age, and 70% die before adulthood,” noted Dr. Elvidge.

“It is estimated that there are more than 2,000 children and young people living with childhood dementia in Canada, and around 105 die each year.

“This is a similar number to deaths from childhood cancer aged 0-14 years, which is 135 per year,” she added.

The study focuses on conditions caused by alterations in a single gene, approximately two-thirds of which are classified as inborn errors of metabolism (IEMs), with the largest subcategories within this group being disorders of one of two specific structures within cells - mitochondria (which

produce energy) or lysosomes (which are responsible for disposal and recycling of cellular content).

MPS III is an example of a lysosomal storage disorder. “In a way, the lysosome is a recycling plant of the cell,” explained Dr. Pshezhetsky. Inside the lysosome, different enzymes break down large biological molecules (such as proteins and complex carbohydrates) into smaller component parts (such as amino acids and simple sugars). If one of those enzymes is absent, the substance it’s responsible for digesting accumulates.

“In some cases, this (buildup) causes specific damage to the neurons that results in their dysfunction and death,” said Dr. Pshezhetsky. Children with MPS III have a problem with the breakdown of a group of long-chain sugar molecules called mucopolysaccharides or glycosaminoglycans (GAGs). Consequently, one of these GAGs – heparan sulphate – builds up within cells.

“There are four subtypes of Sanfilippo or MPS III – A, B, C, and D,” said Dr. Pshezhetsky, each of which affects a different enzyme involved in breaking down heparan sulphate. However, “there are other disorders with similar symptoms, such as Niemann-Pick disease and disorders in the Batten disease family.”

Both groups of conditions result in the accumulation of waste products within cells – fats in the case of Niemann-Pick disease, and fats, proteins, and sugars in Batten disease (a.k.a. neuronal ceroid lipofuscinosis or NCL).

RAISING PUBLIC AWARENESS

The Childhood Dementia Initiative has been piloting the concept of grouping such diseases under one umbrella for several reasons. One is to attract more public attention, since arguably, the term immediately gets across the cruel toll these conditions take on affected families.

Since these disorders are so rare individually, “it’s really challenging to create awareness and share potential research opportunities,” noted Elisabeth Linton, CEO of the Sanfilippo Children’s Research Foundation and a member of the Canadian MPS Society. (Mrs. Linton’s daughter Elisa was diagnosed with MPS IIIB at the age of four and died at the age of 22.)

CHALLENGES IN RARE DISEASE RESEARCH

The Childhood Dementia Initiative is also “seeking funding to devise a blueprint for childhood dementia research globally,” said Dr. Elvidge. Designing and running clinical trials for rare, fatal, or life-threatening childhood diseases presents numerous special challenges.

For instance, depending on the condition, “there may be only a few patients within Canada,” noted Breanne Stewart, Network Director of RareKids-CAN, a new network aimed at establishing a robust platform in Canada to support rare disease clinical trials and enable access to treatment. One challenge this presents is that it’s often not possible to conduct a study at a single institution without the need for patients and their families to travel.

Research methodology must also be very different than those used in ordinary clinical trials. “In conventional clinical trials, you have a treatment of reference, like medication A, or standard of care,” which is compared to the new therapy, explained Dr. Thierry Lacaze-Masmonteil, Nominated Principal Investigator at RareKids-CAN. In the rare disease space, there are no such existing treatments. That, and the natural trajectory of the disease make it impossible to include a control group.

“YOU CANNOT ASK PATIENTS WITH A SERIOUS CONDITION THAT IS DETERIORATING TO WAIT OR BE IN A PLACEBO ARM.”

It’s also much more challenging to obtain a regulatory approval from Health Canada to launch a clinical trial. For example, with the “explosion of novel therapies, whether it’s gene therapy, or using a piece of RNA or DNA, or stem cells,” there may be no historical data on safety for an entirely new, innovative experimental treatment, noted Dr. Lacaze-Masmonteil.

“We cannot expect these drugs to be safe at the same level,” as say, a new blood pressure medication, he added. The regulatory process “needs to be adapted to this complex situation, where patients care less about safety, because they have no other choice.”

Or, as Mrs. Linton put it, “Even if something goes awry, and (an experimental treatment) proves not to be effective or safe, it’s not going to change the outcome for our children. The bottom line is that they are going to succumb to the disease if they don’t have a treatment.”

The immense cost of developing precision treatments such as gene therapy presents an additional hurdle. “What we want to do is streamline that process and have therapies for a lot of conditions being developed in parallel at the same time, rather than having one developed over here and another over there,” said Dr. Elvidge. “Replicating everything makes it even more expensive to develop and produce those therapies.” ➡

Another rationale for co-ordinating research efforts is that a new discovery might lead to a therapy that would offer benefit for more than one disorder, since “there are disease mechanisms overlapping in some of these conditions,” Dr. Elvidge said.

SIMILARITIES BETWEEN SANFILIPPO & ALZHEIMER’S

Research on these rare childhood conditions could potentially provide insights into adult-onset dementias, as well.

For example, some similar pathological processes occur in both Alzheimer’s disease (AD) and MPS III. “Neuroinflammation is one, where there is an increased presence of immune cells in the brain,” noted Dr. Pshezhetsky. In both conditions, microglia (brain immune cells) and astrocytes (cells that support nerve cells in the brain) are involved in promoting this inflammation, and astrocytes proliferate.

The two diseases also share an accumulation of abnormal forms of two proteins – amyloid and tau – in the brain.

Additionally, “in Sanfilippo and other neurological lysosomal disorders, you also see (a protein called) alpha-synuclein misfold and accumulate,” Dr. Pshezhetsky said, which occurs in Lewy body dementia and AD.

Dr. Pshezhetsky’s lab is working on a treatment for MPS III that is a combination of a bone marrow transplant with gene therapy, which might prevent damage if administered early in the disease. “We culture the stem blood cells, propagate them, and transduce them with a virus which incorporates a working copy of the defective gene,” he explained. (The replacement gene contains instructions for producing high levels of the missing enzyme.)

“The stem cells are transplanted back into the patient, and when white blood cells – specifically macrophages – are produced from the transplant, they travel to the brain, produce the enzyme, and supply it to other brain cells,” Dr. Pshezhetsky said. Currently, “we’re testing this method on a mouse model, and we’re obtaining results that are quite promising.

“In parallel, we’re working on other approaches that use small molecules, which is something that could probably be used for other forms of childhood dementia,” Dr. Pshezhetsky said.

“With these small molecules, we target the synapse, which is the site where neurons communicate. What we found is

that there is a severe synaptic deficiency in all the Sanfilippo disorders that starts very early, before the nerve cells start dying,” Dr. Pshezhetsky explained. Loss of these connections is a central feature of AD, and is closely linked to memory loss and cognitive decline.

MOVING TOWARD NEW TREATMENTS

“We’re using a small molecule that can boost production of synaptic proteins and formation of new synapses,” Dr. Pshezhetsky explained. “It doesn’t go to the root of the problem – you still have the genetic defect and accumulation of metabolites. But we see that if we treat mice, we can mitigate the development of behavioural symptoms. Also, when we analyzed the brain of treated Sanfilippo mice, we found that the same molecule reduced neuroinflammation.”

Even better, “we don’t need to inject this molecule into the brain,” Dr. Pshezhetsky added. “It can be given like a nasal spray.”

In Australia, some labs that have traditionally focused on “Alzheimer’s or adult dementia more broadly are now starting to work on childhood dementia alongside their adult dementia research,” Dr. Elvidge said, adding Childhood Dementia Initiative hopes to attract more researchers to the field.

In Dr. Pshezhetsky’s opinion, “getting more attention is key because these patients need to be heard and recognized,” he said. “The clock is ticking for these children. Raising money for research is important because in Canada, as is everywhere, research is underfunded. But what is also important is to get the attention of politicians and government officials to provide specific benefits and aid to these families.” 🌐

CHILDHOOD DEMENTIA RESOURCES

CANADIAN MPS SOCIETY FOR
MUCOPOLYSACCHARIDE & RELATED DISEASES
mpssociety.ca

CHILDHOOD DEMENTIA INITIATIVE
childhooddementia.org

RAREKIDS-CAN
rarekidscan.com

THE SANFILIPPO CHILDREN’S RESEARCH FOUNDATION
alifeforelisa.org