

## Entering the enzyme era

October 26, 2007 | Gillian Wansbrough

### **This new—and only—treatment for genetic disorder Hunter syndrome is dramatically altering patients' quality of life, but funding is a problem**

TORONTO | A new treatment for Hunter syndrome, or mucopolysaccharidosis II (MPS II), is markedly altering life for its mostly young sufferers. However, funding barriers in many provinces are precluding some families from accessing the treatment.

Hunter syndrome is a life-limiting genetic disorder, mainly affecting males, that involves a deficiency or absence of an enzyme: iduronate-2-sulfatase. This enzyme helps break down and recycle mucopolysaccharides, also known as glycosaminoglycans, or GAG. The build up of GAG interferes with tissue and organ function.

Early symptoms, which tend not to be apparent until after one year of age, include inguinal hernias, ear infections, runny noses and colds. Because it affects most organ systems, children with Hunter syndrome often go on to experience hearing loss, malformed connective tissue, declining cardiac function, respiratory problems, stunted growth, sleep apnea and enlargement of the liver and spleen. They tend to have coarse facial features, with a prominent forehead, flattened nose bridge and enlarged tongue. Those more seriously affected have central nervous system involvement.

The lysosomal storage disease is named after Manitoba physician Charles Hunter, who first described two brothers with the syndrome in 1917. It is said to afflict one in 162,000 people; in Canada about 40 cases are known. Urine screens and blood tests can aid with diagnosis but signs are often missed since they are so variable. A firm diagnosis can be made via skin biopsy.

Although often labelled mild or severe, more recently the disorder has been viewed in terms of a spectrum of severity, according to Kirsten Harkins, executive director of the Canadian Society for Mucopolysaccharide & Related Diseases.

Those more seriously afflicted may not live past their teens. Those who do not experience mental retardation can live into their 20s and 30s, and some late-onset patients live until their 70s. The latter experience the condition more as progressive arthritis or arthrosis, with little respiratory, cardiovascular or cerebral involvement.

There are important clues to diagnosing an MPS disorder, says medical geneticist and pediatrician Dr. Serge Melançon, director of the division of biochemical genetics at the Montreal Hospital for Sick Children. These are: accelerated growth in the first few years of life, a larger head, big build, thick skin, and stubby hands and feet. Limited joint motion and repeat respiratory infections with hearing loss are also red flags that should prompt a referral to a geneticist.

Harkins stressed that early diagnosis is key given the organ damage that occurs over time, as is awareness of the fact that the first and only treatment for Hunter is now available. The enzyme replacement therapy Elaprase (idursulfase), from Shire Human Genetic Therapies, was recently approved by Health Canada.

### **Quality of life**

"Besides orthopedic surgery, antibiotics and physiotherapy, we had very little to offer to patients and their families," said Dr. Melançon, who oversees treatment for four patients with Hunter, one of whom is on Elaprase. "Now with Elaprase there's a new era whereby these patients will be

improved and their overall life will be better off. They can continue to attend school, find a job and many can have their own families.”

Drug approval was based on a 2004 clinical study of 96 patients with Hunter syndrome, led by Hunter expert Dr. Joseph Muenzer, an associate professor in the department of pediatrics at the University of North Carolina. The treatment may have three modes of action, said Dr. Melançon: reversal of some disease features, arresting of disease progression and prevention of disease manifestations.

“We know mobility improved overall—this was tested by a six-minute walk—and the overall improvement was significant. In addition, there was improvement in pulmonary function. . . . Since cardiopulmonary function is the main cause of death in patients with MPS disorders, this automatically suggests there will be a gain in terms of lifespan and most likely patients will be less affected by respiratory infections,” Dr. Melançon told the Medical Post.

Participants also saw a decrease in liver and spleen size, and a lowering of GAG levels, as well as an improvement in elbow mobility. Shire continues to track health data through a worldwide long-term outcome survey, called the Hunter Outcome Survey.

While trial participants were limited to children and young adults with less severe disease—they needed the mental capacity to participate fully and follow test instructions—there is no reason to think it won’t be effective in those with more severe disease, said Harkins.

Dr. Melançon said he hopes the treatment can be refined, perhaps offered biweekly or monthly, or modified so the enzyme can reach the CNS or joints to improve more severe forms of the disorder. The therapy might also buy time to investigate the potential of chaperone therapy or gene transfer. (Chaperone therapy is a fairly new therapeutic approach that involves binding of a pharmacological chaperone/molecule to a misfolded protein of a cell—generally caused by genetic mutation—prompting it to adopt its proper shape and function. It results in stabilization/reactivation of the protein, and in turn enzyme activity and cellular function.)

In the meantime, Harkins said she would like to see the syndrome diagnosed via newborn screening. While Elaprase doesn’t cross the blood-brain barrier, she said some researchers are hopeful that by giving it at birth, some of the enzyme could pass into the brain.

### **Funding**

The bigger challenge at this point seems to be securing funding for the therapy. Some provincial governments won’t cover the cost of the drug— \$300,000 to \$350,000 per year—on the basis that there are no data to show beneficial effects in the severely affected. In the U.S. and U.K., the drug is available to all Hunter patients regardless of disease severity.

Harkins likens the situation to not treating the heart condition of someone with Down syndrome. She noted some families will choose not to pursue the treatment, but the decision should be theirs to make. She adds that an orphan drug policy must be established since the Common Drug Review, which evaluates for cost-effectiveness, by design won’t allow for funding approval of this kind of therapy. Plus, dealing with drugs for rare conditions on a case-by-case basis is too time consuming.

“If we as a society decide not to pay for these treatments, then all patients in Canada with rare disorders will suffer the consequences,” said Harkins, noting that drug companies will turn their attention elsewhere or consider not filing for approval here if Canada develops a reputation for not covering drugs.

Simon Ibell, 29, participated in the Elaprase trial, commuting to North Carolina for a year and a half. The Toronto resident was diagnosed with Hunter at the age of two. He has an attenuated

form of the disease, with no neurological involvement, and was able to participate fully in school, sports and the arts.

“Even at my age the treatment had such an impact on my quality of life . . . improved breathing, decreased organ size, improved joint flexibility,” he said. “Daily tasks were that much easier.” He is also able now to walk more easily since his gait has loosened, and he can do so without losing his breath. He no longer experiences tissue tears, his face is not as puffy, he doesn’t lose his breath talking and because his tongue is not enlarged, he can enunciate better.

Since 2005 Ibell has received treatment, paid for by Shire, at the Toronto Hospital for Sick Children. He now works full-time for Right to Play, an international organization that uses sport and play programs to help children and communities affected by war, poverty and disease. He is also a director with the MPS Society and is an advocate on behalf of Hunter patients seeking government funding of Elaprase.

“It’s black and white what I’ve seen in younger patients, not having to use wheelchairs, their breathing, overall quality of life,” he said. And Ibell argued strongly in favour of making the drug available to those with neurological involvement. The physical benefits alone are worth it, he said, and the cost of symptomatic treatment over time would be even more expensive. “It’s a human rights issue,” he concluded.