Mucopolysaccharidosis Type 1H Information Sheet for Health Care Providers

Starting in late July 2020, all babies born in Ontario who have a newborn screening sample (heel prick) collected will be screened for Mucopolysaccharidosis Type 1H (MPS1H).

What is Mucopolysaccharidosis Type 1H?

- MPS1H, also known as Hurler Disease, is a rare genetic lysosomal storage disorder
- Lysosomes are subcellular organelles which contain a multitude of enzymes including those needed to degrade complex sugar molecules called glycosaminoglycans (GAGs), which form part of mucopolysaccharides (MPS)
- MPS1H occurs when an enzyme called alpha-L-iduronidase (IDUA) is deficient. A deficiency in IDUA leads to the accumulation of specific GAGs in the lysosomes and cells, and in turn this causes problems in multiple organ systems
- MPS1H (the severe form of the disorder) is characterized by symptoms that typically appear within the first year of life, and rapid progression including neurodegeneration
- Attenuated forms, known as Hurler-Scheie Disease (MPS1HS) and Scheie Disease (MPS1S) are characterized by symptoms that can range from mild to serious, but do not involve the CNS. Individuals with attenuated forms can begin to show symptoms in childhood

What are the signs and symptoms of MPS1H?

- Developmental delay and progressive neurodegeneration
- Cardiomyopathy and heart valve abnormalities
- Dysostosis multiplex
- Joint contractures and stiffness
- Macrocephaly
- Distinct facial features that appear “coarse”
- Corneal clouding
- Recurrent upper and lower respiratory tract infections
- Frequent otitis media and hearing loss
- Hepatosplenomegaly
- Inguinal or umbilical hernia

Who is at risk?

- MPS1 (all forms) has a birth prevalence of approximately 1 in 35,000, and is inherited in an autosomal recessive manner
- The IDUA gene provides the instruction to make the IDUA enzyme. An individual with MPS1 has two non-working IDUA gene copies (i.e. two genetic variants) and as a result the enzyme is absent or deficient
- Each parent of a child with MPS1H usually has one non-working copy of the gene and is considered a “carrier”
- Carriers do not have MPS1H because they have a working copy of the gene that produces sufficient enzyme to prevent GAGs from accumulating in the cells
- Individuals who are diagnosed with a form of MPS1 typically have a negative family history of the disease
- Parents who have had a child with MPS1 have a 25% recurrence risk in each future pregnancy

How does NSO screen for MPS1H?

- Measurement of the IDUA enzyme level occurs in all samples (first tier biochemical testing)
- In samples where the IDUA enzyme level is determined to be below a certain cut off, additional tests are done. Second tier testing involves another enzymatic test and if the IDUA level is still below a cutoff, a third tier test is performed. Third tier testing involves sequencing of the IDUA gene to look for genetic variants that can cause MPS1H.

- The screening approach is focused on MPS1 detection; other mucopolysaccaridoses are not detected through newborn screening in Ontario.

What does a screen positive result for MPS1H mean?

- A *screen positive* result means that a baby has an increased chance of having MPS1H and further testing is indicated. Babies with screen positive results for MPS1H are referred by NSO to a Newborn Screening Regional Treatment Centre for follow-up
- A baby can screen positive for MPS1H if either ≥ 2 IDUA genetic variants* are identified OR <2 genetic variants and a very low IDUA enzyme level are detected. *Exception: in the IDUA gene there are several well-known pseudodeficiency variants, or genetic variants that can result in a false positive result on enzyme testing but are not known to cause clinical symptoms or lead to disease. Cases with known pseudodeficiency variants identified through screening are considered screen negative by NSO and will not be referred for follow-up.

How is MPS1 diagnosed?

- Confirmatory testing for a baby with a screen positive result for MPS1H typically includes:
  - Blood and urine tests; occasionally skin biopsy is required
  - Investigations to assess for symptoms of the disorder (e.g. x-rays, hearing tests, physical exam)
  - An appointment with a metabolic genetics specialist
- The likelihood is high that a baby with a screen positive result will be diagnosed to have a form of MPS1.
- NSO estimates that 4-8 cases of MPS1 will be identified through newborn screening each year in Ontario.
- Conversely, one possible explanation for a false positive newborn screen (i.e. baby is *not* diagnosed with a form of MPS1 after confirmatory testing) is that a baby could have a pseudodeficiency variant that has not previously been recognized.

What does management and treatment of MPS1H involve?

- Children with MPS1H are typically followed by a multidisciplinary team (i.e. specialists from metabolic genetics, cardiology, neurology, orthopedics, otolaryngology, ophthalmology etc.).
- There are two main options for the treatment of MPS1H and they include:
  1. Hematopoietic stem cell transplant (HSCT)
     - When indicated, a referral to The Hospital for Sick Children will be made such that timely HSCT (as early as safely possible, and not later than two years of age) can be performed
     - Evidence to date suggests that when HSCT is done, cognitive decline can be slowed and/or stabilize. HSCT can also improve overall growth, liver size, and the cardiac, respiratory, and joint symptoms of MPS1H
     - Significant medical issues related to MPS1H can still occur in those who have HSCT
     - HSCT is not performed for patients with attenuated forms of MPS1
  2. Enzyme replacement therapy (ERT)
     - The name of the ERT product is laronidase (Aldurazyme)
     - In Ontario, there is drug coverage for laronidase for individuals with MPS1H who meet certain criteria
     - If ERT is started prior to the onset of symptoms, improvements with breathing, liver size, overall growth, the joints and heart have been shown
     - ERT cannot treat the CNS aspects of MPS1H

Do you have more questions?

Please contact NSO at newbornscreening@cheo.on.ca or 1-613-738-3222 if you have other questions about newborn screening for MPS1H.