Understanding 4H (POLR3-Related) Leukodystrophy: A Guide from the Yaya Foundation

This informational document was created by the Yaya Foundation to give families and friends clear, reliable information. In the following overview, you'll find resources about 4H Leukodystrophy and its clinical care.

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About the Yaya Foundation

The Yaya Foundation for 4H Leukodystrophy is a nonprofit organization dedicated to improving the lives of individuals and families affected by 4H Leukodystrophy. We work to:

- Advance scientific research and the development of treatments
- Build a supportive, informed community
- Provide resources and emotional support to families and patients facing this rare disease

We recognize that receiving a diagnosis can be overwhelming. That is why we offer personal support, regular family Zoom calls, and connections to experts and other affected families, as well as fundraising tools.

We are here to support you in any way we can. **Please do not hesitate to contact us**.

Contact information:
info@yayafoundation4hl.org
yayafoundation4hl.org
facebook.com/yayafoundation4HL

Yaya Foundation Family Conference 2023

Overview

What are Leukodystrophies?

Leukodystrophies are a group of rare inherited disorders that affect the white matter of the brain. They often occur because the body is unable to properly make or process a substance called **myelin**.

Myelin surrounds and protects nerve cells. It is important because it helps the nerves to carry messages in the brain and spinal cord.

What is 4H Leukodystrophy?

The name "4H" refers to features that are frequently found in this type of leukodystrophy:

- Hypomyelination – reduced production of myelin, the protective sheath around nerves
- Hypogonadotropic hypogonadism – delayed or absent puberty due to hormone deficiencies
- Hypodontia – teeth appear later, in a different order, or not at all

This condition is also known as POLR3-related Leukodystrophy or Pol III-Related Leukodystrophy.

Genetic Causes

What causes 4H Leukodystrophy?

4H Leukodystrophy is a genetic condition caused by changes (called pathogenic variants or mutations) in one of five genes.

Associated Genes

POL3RA
POL3RB
POLR1C
POLR3K
POLR3D

Genes are pieces of DNA that serve as instructions to tell our bodies how to function. Typically, each person has two copies of every gene—one from each parent.

4H Leukodystrophy is an autosomal recessive condition. This means:

- A person develops the condition only if both copies of the gene are affected.
- Individuals can be carriers if they have a mutation on only one copy of the gene. Carriers do not have symptoms but can pass the genetic change to their children.
- When both parents are carriers, each of their biological children has a 25% chance of being affected with 4H Leukodystrophy.

Clinical Overview

4H Leukodystrophy is a condition that varies widely with each person. These differences include:

- Age of onset. Some show first symptoms as infants, some as children, some as teenagers or even adults.
- Symptoms. Not everyone has the same combination of symptoms.
- Disease severity.
- Speed of progression.

This variability is important to remember as you talk with other families as well as research on your own.

What are possible symptoms?

Large and Small Motor Problems
stiffness of arms and/or legs; problems with walking, balance, and coordination; and trouble holding and controlling small items like pens and cups

Speech Challenges
delay in speech development and/or difficulty forming words, which impacts their ability to communicate

Learning Disabilities
intellectual difficulties ranging from mild to severe, based on progression and severity of the disease

Movement Disorders
tremor or other involuntary movements

Feeding Difficulty
difficulty chewing and swallowing

Vision Problems
trouble focusing on things far away (myopia or nearsightedness)

Stature
may be small for their age, and may not go through typical puberty

Teeth
may have delayed or different order of eruption of the teeth, missing or abnormal shape of the teeth

Explore other symptom information at:
https://medlineplus.gov/genetics/condition/pol-iii-related-leukodystrophy/

https://www.chop.edu/conditions-diseases/4h-leukodystrophy)

Medical Management

What does treatment look like?

Individuals with 4H benefit from coordinated care from a multidisciplinary team of specialists to manage symptoms. Treatment is adapted to changing needs and aims to improve quality of life. There is currently no targeted therapy or cure for 4H Leukodystrophy.

Researchers and clinicians are actively working to better understand the disease and to develop therapies to help families. The Yaya Foundation for 4H Leukodystrophy is committed to accelerating the discovery of therapies and connecting families with additional resources.

The following is a list of providers who are frequently a part of the care team for individuals with 4H. Because management is aimed at treating an individual's symptoms, the care team will be unique to each person and their symptoms. Not every person may need all the specialists listed below.

Neurologists help families understand disease progression and make recommendations about their care.

Clinical Geneticists support the family in understanding the underlying genetic differences and risk to future children.

Ophthalmologists help identify and treat vision-related symptoms of the disease.

Psychologists and/or Social Workers provide support to the patients and their loved ones. This includes psychological support as well as help in obtaining services or allocations.

Rehabilitation Specialists teams identify therapies and medications to help with mobility and stiffness. Your team may include Physical Medicine and Rehabilitation (PM&R)/Physiatry, physical therapy, occupational therapy, or speech therapy.

Pulmonologists address respiratory challenges that may result from neuromuscular problems.

Endocrinologists identify and treat effects on the body's endocrine system, such as delayed puberty and hypogonadotropic hypogonadism-related effects of 4H.

ENT/Otolaryngologists address issues involving ears, nose, throat, including excessive drooling and swallowing difficulties.

Feeding Teams help children who have problems with swallowing. The team helps create safe and nutritious feeding strategies and identify appropriate therapies to help with eating and drinking. The team may include a gastroenterologist, ENT, occupational and speech therapist, along with your primary care doctor.

Palliative care includes goals relating to quality of life, such as relief from symptoms of physical and emotional illness, as well as stress. It can be offered at the same time as treatment of an illness; this is not always related to end of life.

Leading 4H Clinicians

Dr. Geneviève Bernard
Montreal Children's Hospital, McGill University

Dr. Nicole Wolf
Amsterdam University Medical Center

Dr. Adeline Vanderver -
Children's Hospital of Philadelphia

Authors: Valerie Greger, PhD; Elsa Keeler, MD; Margo Hutchison, MD; Marin Kalista, BS.