4H Leukodystrophy

Summary of Medical Information for Primary Care Providers

This document for medical providers was compiled by a working group convened by the Yaya Foundation for 4H Leukodystrophy, a patient advocacy organization, at the request of families living with the disease. Work group core members include Margo Hutchison, MD, family medicine physician and board member of the Yaya Foundation; Elsa Keeler, MD, pediatrician; and Valerie Greger, PhD, research director, Yaya Foundation. With acknowledgement of original authors Anusha Klinder and Sabrina Southwick; genetic counseling interns at the Yaya Foundation.

Your patient has been diagnosed with a condition called **POLR3-Related Leukodystrophy**, **also known as 4H Leukodystrophy**, where the 4Hs stand for <u>h</u>ypomyelination, <u>h</u>ypodontia, and <u>h</u>ypogonadotropic <u>h</u>ypogonadism. This rare, hypomyelinating form of leukodystrophy is diagnosed based on clinical findings, brain MRI findings, and genetic testing.

The billable/specific ICD-10-CM code is:
G11.5 Leukodystrophy, pol III-related.

Genetics of 4H/POLR3-Related Leukodystrophy:

- It is caused by mutations in one of five genes (POLR3A, POLR3B, POLR1C, POLR3K and POLR3D). These genes encode subunits of the large enzyme complex RNA polymerase III.
- The majority of affected individuals have two mutations in either the POLR3A or the POLR3B gene, and about 5-10% have two mutations in POLR1C. Mutations in the other genes are very rare.
- It is inherited in an autosomal recessive pattern: both gene copies in the affected person's cell have a mutation in one of those genes. The parents of a patient each carry one copy of the genetic mutation and are usually asymptomatic. Each child born to a carrier couple has a 25% risk of being affected.

Common Symptoms/Findings in Patients Diagnosed with POLR3-Related Leukodystrophy;

- Neurologic:
    - gait and balance issues
    - weakness, spasticity, rapid eye movements
    - tremor, progressive ataxia

- Developmental delays including:
    - Large and small motor delay and/or loss of motor function as the disease progresses
    - Dysarthria and expressive/receptive language delay, difficulty with articulation and verbal communication
    - Intellectual learning disabilities: can be from mild to severe and/or slowly progressive over time
- Endocrine dysfunction:
    - Hypogonadotropic hypogonadism-delayed or absent puberty secondary to hypothalamus or pituitary dysfunction
    - short stature +/- growth hormone deficiency
    - Hypothyroidism (less common)
- Dental development abnormalities: delayed tooth eruption, absence of teeth (most commonly middle incisors), or atypical eruption
- Myopia-often severe and progressive

The presentation of POLR3-Related Leukodystrophy is variable. Because of this, not all patients will exhibit every symptom listed above. Although most patients present in early childhood with developmental delay, at times symptoms occur after a period of seemingly normal development.

Disease progression is variable. It is important to note that disease progression may be slow and insidious but may also occur *rapidly* at times, triggered by illness with fever. *Prompt fever management and evaluation and treatment of illness are important to support wellbeing and function*. Patients with POL III-Related Leukodystrophy have progressive and ultimately life-limiting disease.

Treatment of POLR3-Related Leukodystrophy is supportive. Current medical treatments for POLR3-Related Leukodystrophy are supportive to the patient's specific symptoms. Potential treatment avenues are being researched. Patients need a multidisciplinary team that may include primary care, neurology, clinical genetics, pulmonology, gastroenterology, endocrinology, PM&R, PT/OT/Speech therapy, orthopedics, palliative care, ENT, and ophthalmology.

<u>Resources for your Practice</u>:

- Practical Approaches and Knowledge Gaps in the Care for Children with Leukodystrophies.
  Keller et al., J Child Neurol 2020
  https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7736398/
- Revised consensus statement on the preventive and symptomatic care of patients with leukodystrophies.
  Adang et al.; Mol Genet Metab 2017
  https://pmc.ncbi.nlm.nih.gov/articles/PMC8018711/

- MedlinePlus: https://medlineplus.gov/genetics/condition/pol-iii-related-leukodystrophy/
- Other up-to-date literature on treatments and research can be found on the foundation's website: https://yayafoundation4hl.org/

Resources for your Patients

- Yaya Foundation for 4H Leukodystrophy: https://yayafoundation4hl.org/
- Facebook Groups:
  - POLR3 community: https://www.facebook.com/groups/POLR3
  - Private caretaker group: POLR3 Caretakers/4H Leukodystrophy https://www.facebook.com/groups/4hsyndrome
  - Private group for adult patients and caregivers of adult patients: POLR3 related Leuko Adult group https://www.facebook.com/groups/3404978552972302
- Healthychildren.org https://www.healthychildren.org/English/health-issues/conditions/developmental-disabilities/Pages/Leukodystrophies.aspx
- Child Neurology Foundation https://www.childneurologyfoundation.org/disorder/leukodystrophy/
- Living with Leukodystrophy eBook (free): https://www.curemld.com/product-page/living-with-leukodystrophy-ebook