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Report on leukodystrophies highlights advances in imaging, diagnosis, care

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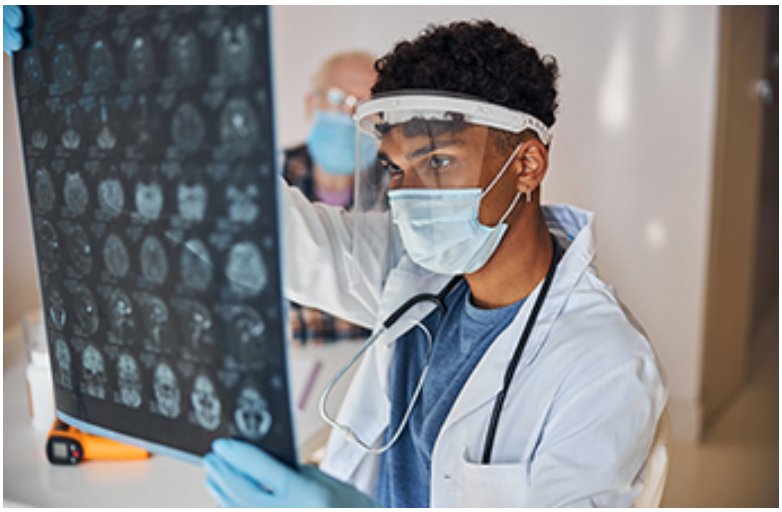

An 8-year-old boy visits his pediatrician because he has trouble seeing the chalkboard and his grades are worsening. He is referred to an optometrist. A week later, before his vision appointment, he becomes acutely confused, passes out at school and is airlifted to a hospital. He is hypotensive and is treated for sepsis.

The intensive care unit physician notes his dark skin, and the boy is found to have adrenal insufficiency. Because he remains confused, a neurology consult is obtained. A brain MRI reveals extensive white matter abnormalities, including with contrast enhancement. He is diagnosed with X-linked adrenoleukodystrophy (ALD). His symptoms are too far progressed for bone marrow transplant, and he dies less than a year later following a rapid neurological decline.

This real case highlights the challenges of care for children with leukodystrophies like ALD.

Genetic disorders of the white matter of the brain, leukodystrophies previously were believed to be rare, such that pediatricians might see only one case in their career. Leukodystrophies also were understood to be untreatable.

An AAP clinical report presents new information for pediatricians on imaging, diagnosis, new therapies and curative treatments, and care of these children in the medical home.

The report, *Leukodystrophies in Children: Diagnosis, Care and Treatment*, from the Section on Neurology and Council on Genetics, is available at https://doi.org/10.1542/peds.2021-053126 and will be published in the September issue of *Pediatrics*.

Prevalence, symptoms

Leukodystrophies affect nearly one in 4,500 births, and most pediatricians will care for a child with a leukodystrophy. Several hundred genes cause many different kinds of leukodystrophies. A single leukodystrophy, like ALD or Krabbe disease, is rare, yet as a group of disorders, they are not uncommon.

Leukodystrophies have a range of signs and symptoms that depend on the disease and the child's age. For example, infants can present with developmental delay, extreme irritability or persistent abnormal eye

movements. School-age children can have attention-deficit/hyperactivity disorder-like symptoms or new difficulties with coordination.

A brain MRI often is the first step toward diagnosis and can be started by the primary care physician. However, because diagnosis can be complex and involve specialty genetic or biochemical tests, referral or working with a specialist in leukodystrophies is recommended.

Treatments, therapies

Diagnosis is important because timely treatment can be curative for several leukodystrophies (ALD, metachromatic leukodystrophy, Krabbe disease and Aicardi-Goutières syndrome). ALD, for example, requires monitoring for Addison's disease; if brain involvement is noted on MRI, prompt treatment with hematopoietic stem cell transplantation is lifesaving. New therapies for leukodystrophies also are becoming available rapidly, and numerous clinical trials are underway.

Even without curative therapies, treatment is important for children with these disorders. Many leukodystrophies are stable for decades, and only a few leukodystrophies get worse rapidly. Treatment and prevention of disease complications and standard pediatric care also make a difference for children and families.

Newborn screening

Many states screen newborns for leukodystrophies, particularly ALD. A positive newborn screening result is important not only for the diagnosis and care of the infant but also reveals if other family members are at risk.

After a positive newborn screen result, prompt referral to a specialty center is needed. Specialist centers are particularly important because advances in leukodystrophy diagnosis and treatment are occurring rapidly.

Recommendations

Following are key take-home points from the report:

- Each type of leukodystrophy is a rare neurological disease, but as a group, leukodystrophies are not uncommon.
- Referral to or working with a specialist in leukodystrophies is recommended.
- Diagnosis for some leukodystrophies is urgent, because disease cure is possible for a few types of leukodystrophies.
- MRI of the brain is a first step in diagnosis.
- Some leukodystrophies, including ALD and Krabbe disease, can be detected through newborn screening.
- Patients with leukodystrophies need standard pediatric care, including immunizations.

Dr. Bonkowsky is a lead author of the clinical report and a former member of the AAP Section on Neurology Executive Committee.