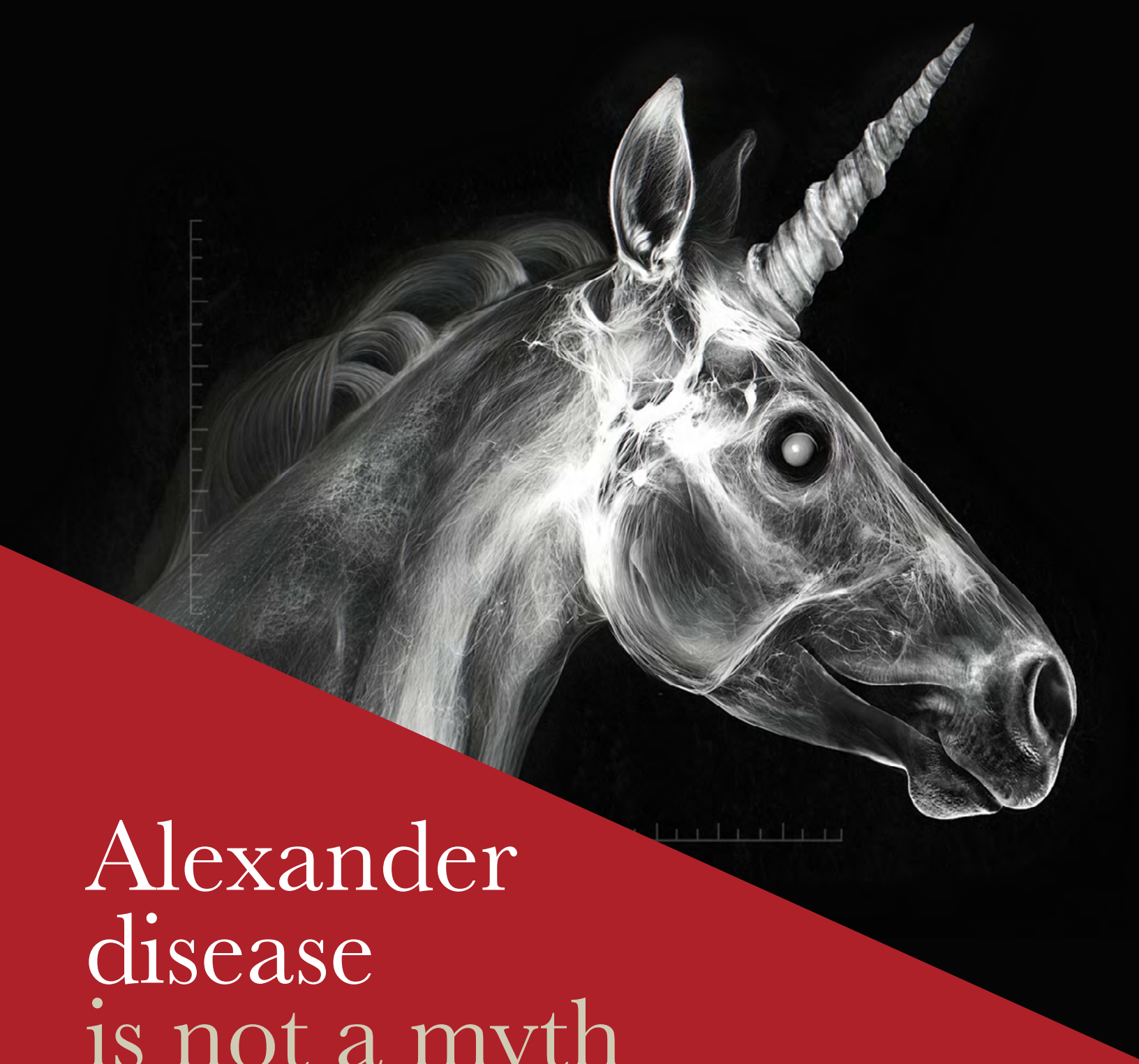


Alexander disease is not a myth

It is a rare, progressive, and ultimately fatal neurological disorder with a clinical constellation of symptoms, many of which overlap with other neurological conditions.[1-3]

Diagnosis is primarily based on symptoms and MRI findings and is confirmed by genetic testing.[1]

VERY RARE. VERY REAL.

MRI, magnetic resonance imaging.

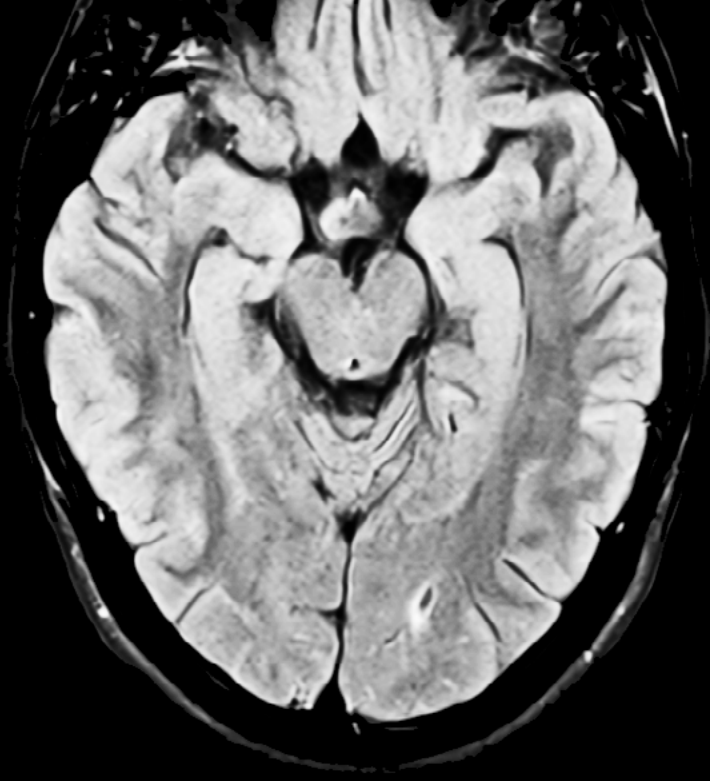
IONIS

Learn more about how to recognize and diagnose this rare leukodystrophy at **AlexanderDisease.com**

Alexander disease accounts for approximately

1.6% to 12%

of leukodystrophies—a group of rare genetic disorders that affects white matter in the central nervous system.[4-8]



UNDERSTANDING ALEXANDER DISEASE

Alexander disease is a rare, genetic neurodegenerative disorder that affects individuals across a wide age spectrum.[1,9] It is characterized by progressive neurological impairment with distinct symptoms in the infantile, juvenile, and adult forms of the disease. In infants and young children, a clinical triad of seizures, developmental delay, and macrocephaly often indicates Alexander disease, although these symptoms are not uniformly present. In juveniles and adults, the suggestive triad of symptoms includes bulbar signs, ataxia, and autonomic dysfunction.[1,2,9]

Motor symptoms in children may manifest as a delay or regression, while in adults, they may present as gait difficulties or weakness, including hemiplegia.[2,3,9,10]

Alexander disease can lead to the progressive development of severe disabilities and death.[1-3,11] Variation in the severity and progression of symptoms is high, with more severe symptoms and a poorer prognosis associated with earlier onset of the disease.[1,2,10]

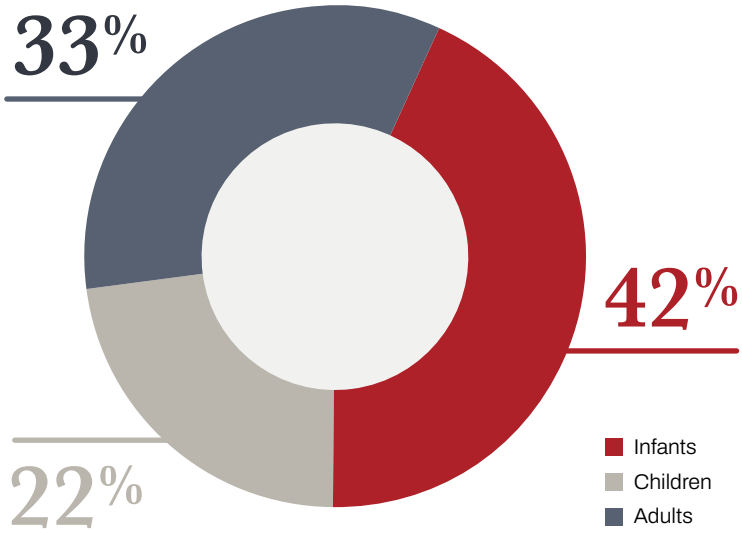
Approximately 95% of Alexander disease cases are linked to pathogenic variants in the glial fibrillary acidic protein (*GFAP*) gene.[12]

Pathogenic variants of *GFAP* exhibit an autosomal dominant pattern of inheritance, and while the majority of cases are the result of de novo mutations, familial cases are being increasingly recognized as diagnosis has improved.[13]

It is believed the toxic accumulation of GFAP aggregates (Rosenthal fibers) in astrocytes results in astrocytic dysfunction, ultimately leading to abnormal myelination and neuronal loss.[1,14]

The clinical presentation of Alexander disease varies based on the age of onset, and the diagnosis is challenging due to the nonspecific nature and heterogeneity of symptoms. Because these symptoms overlap with other more common neurological disorders—and because it is a rare disease not often seen by healthcare providers—misdiagnosis or delayed diagnosis can result.[1,2,9,15]

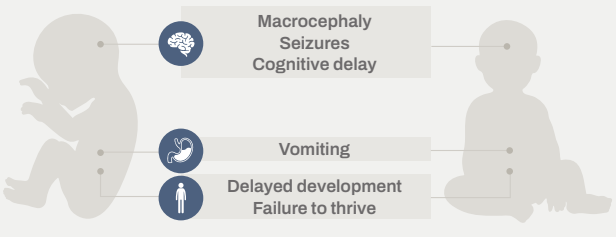
Percentage of patients with Alexander disease by age at presentation[3,a]



[a]3% of patients were asymptomatic.[3]

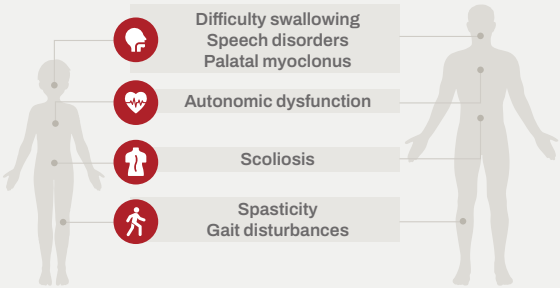
Alexander disease can present differently depending on the age of onset[1,2,16]

EARLY ONSET
(INFANTILE)



MEDIAN POST-ONSET SURVIVAL: **14.0 ± 1.8 YEARS**

LATE ONSET
(JUVENILE >4 YEARS OF AGE AND ADULT)



MEDIAN POST-ONSET SURVIVAL: **25.0 ± 2.1 YEARS**

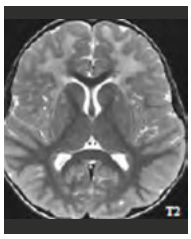
Worse prognosis → Better prognosis

The clinical manifestations of Alexander disease may overlap with more prevalent neurodegenerative disorders, which can lead to a misdiagnosis or delayed diagnosis and impact care.[2,3,13]

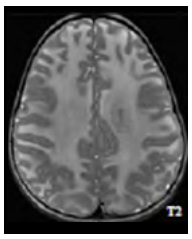
DIFFERENTIAL DIAGNOSES FOR ALEXANDER DISEASE[1-3,13,17,a]

CHILDREN AND ADOLESCENTS	ADULTS
Adrenoleukodystrophy	Adrenoleukodystrophy
Brain tumors	Ataxias
Canavan disease	Multiple sclerosis
Krabbe disease	Multisystem atrophy
Metachromatic leukodystrophy	Parkinson's disease
Pelizaeus-Merzbacher disease	Brain tumors
Zellweger spectrum disorder	

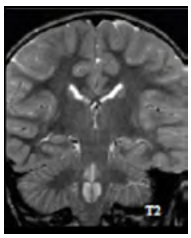
Alexander disease can present with a range of radiologic features[18,b]



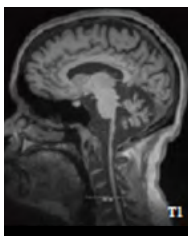
Frontally predominant white matter abnormalities



Diffuse white matter abnormalities



Brainstem lesion



Medullary atrophy

When a leukodystrophy or Alexander disease is suspected, performing a brain MRI and genetic testing is critical for a timely diagnosis.[18,19] Patients may be referred to a center that specializes in leukodystrophies and offers comprehensive care, such as a Center of Excellence, to establish a disease management plan.[19]

[a]Not a comprehensive list.

[b]Results are based on a single natural history study of 73 patients with Alexander disease at the Children's Hospital of Philadelphia. MRI images for each of the patients were reviewed by a blinded neuroradiologist and yielded case reports that included 23 variables capturing signal or tissue abnormality in distinct regions of interest.[18]

MRI, magnetic resonance imaging.

DISEASE MANAGEMENT

Management of Alexander disease focuses on alleviating symptoms and enhancing quality of life through the use of a collaborative multidisciplinary team of healthcare providers to address the range of clinical symptoms.[1,19,20]

In the absence of disease-modifying treatments, current approaches to management of Alexander disease include symptomatic therapies or devices to address physical (eg, seizures, dysphagia, mobility), speech (eg, dysphonia, dysarthria), and cognitive (eg, developmental delay, behavioral problems) difficulties.[1,3]

CURRENT APPROACHES TO SYMPTOMATIC MANAGEMENT

Medications for managing seizures, muscle spasticity, dystonia, pain, and other neurological symptoms[1,20]

GI/urinary medications and interventions for controlling reflux, vomiting, drooling, constipation, and urinary retention/incontinence[1,20]

Assistive devices to improve mobility, such as orthotics, braces, gait trainers, walkers, lifts, and standers[20]

Nutritional support and dietary modifications to address feeding difficulties due to dysphagia and/or recurrent vomiting[3]

Augmentative and alternative communication strategies for those with communication impairments[3]

Sleep hygiene optimization for those with sleep disorders, and appropriate interventions for sleep apnea[20]

Gastronomy tube to ensure adequate nutrition, minimize aspiration risk, and administer medications for those with severe dysphagia[20]

Occupational therapy to assist those with physical, cognitive, and/or developmental impairments to maintain their ability to perform everyday tasks[3]

Neuropsychological support to address learning and cognitive development, and to develop a plan to optimize learning strategies[3]

Interventions to address respiratory insufficiency, including infection prevention, airway maintenance, and mechanical support[20]

Physical therapy to improve range of motion and strength, preserve motor skills, and maximize mobility[3,20]

Orthopedic exams and interventions for scoliosis, hip dysplasia and dislocation, and low bone mass/fractures[20]

Ongoing research and a clinical trial are exploring potential disease-modifying therapies for Alexander disease.[21,22]

PATIENT ADVOCACY ORGANIZATIONS

There are several patient advocacy organizations that offer education, resources, and support for people with Alexander disease and their families.

ALEX, THE LEUKODYSTROPHY CHARITY

Provides access to vital support and information for all those affected by a genetic leukodystrophy and is helping to advance medical research

alextlc.org

ELISE'S CORNER

A community group focused on spreading awareness of Alexander disease and aiding research efforts to find treatments and a cure for this rare genetic disorder

elisescorner.net

END AXD

Focused on being a catalyst for research and development of a treatment—and eventual cure—of Alexander disease, and to help those with the disease get the care they need

endaxd.org

HUNTER'S HOPE

Established to address the acute need for information and research with respect to leukodystrophies, and supports and encourages those afflicted and their families as they struggle to endure, adjust, and cope with the demands of these fatal illnesses

huntershope.org

UNITED LEUKODYSTROPHY FOUNDATION

Dedicated to funding cutting-edge research and to providing leukodystrophy patients and their families with disease information and medical referrals

ulf.org

NATIONAL ORGANIZATION FOR RARE DISORDERS

Provides support for individuals with rare diseases through programs of education, advocacy, research, and patient support services

rarediseases.org

Alexander disease is not a myth

VERY RARE. VERY REAL.

To better understand how to recognize the clinical constellation of symptoms and MRI features of Alexander disease, visit **AlexanderDisease.com**

References: 1. Kuhn J, Cascella M. Alexander Disease. In: *StatPearls*. Treasure Island (FL): StatPearls Publishing; September 4, 2023. **2.** Pareyson D et al. *Brain*. 2008;131(Pt 9):2321-2331. **3.** Srivastava S et al. Alexander disease. In: Adam MP, Ardinger HH, Pagon RA, et al, eds. *GeneReviews®*. University of Washington, Seattle; 1993-2024. November 15, 2002. Updated November 12, 2020. Accessed March 24, 2025. https://www.ncbi.nlm.nih.gov/ books/NBK1172/ **4.** Stellitano LA et al. *Dev Med Child Neurol*. 2016;58(7):680-689. **5.** Cohen L et al. *Ann Hum Genet*. 2020;84(1):11-28. **6.** Schmidt JL et al. *Am J Med Genet A*. 2020;182(8):1906-1912. **7.** Bonkowsky JL et al. 2010;75(8):718-725. **8.** Vanderver A et al. *Semin Pediatr Neurol*. 2012;19(4):219-223. **9.** Joung J et al. *J Child Neurol*. 2023;38(13-14):672-678. **10.** Vaia Y et al. *Mol Genet Metab*. 2023;138(3):107540. **11.** Yoshida T et al. *J Hum Genet*. 2013;58(9):635-638. **12.** Messing A. *Handb Clin Neurol*. 2018;148:693-700. **13.** Alexander disease. National Organization for Rare Disorders. Accessed March 25, 2025. https://rarediseases.org/rare-diseases/alexander-disease/ **14.** Sosunov A et al. *Brain Pathol*. 2018;28(3):388-398. **15.** Gagliardi D et al. *J Neurol Neurosurg Psychiatry*. 2024:jnnp-2024-335089. **16.** Yoshida T et al. *J Neurol*. 2011;258(11):1998-2008. **17.** Messing A. *Alexander Disease: A Guide for Patients and Families*. Morgan & Claypool Life Sciences; 2018. Revised with Appendix 2021. **18.** Waldman A et al. Presented at: 2019 Annual Meeting of the American Academy of Neurology; May 4-10, 2019; Philadelphia, PA. **19.** Ruzhnikov MRZ et al. *Pediatr Rev*. 2021;42(3):133-146. **20.** Adang LA et al. *Mol Genet Metab*. 2017;122(1-2):18-32. **21.** Hagemann TL et al. *Sci Transl Med*. 2021;13(620):eabg4711. **22.** Clinicaltrials.gov. Bethesda, MD: National Library of Medicine (US). Identifier NCT04849741. A study to evaluate the safety and efficacy of zilganersen (ION373) in patients with Alexander disease (AxD). Updated March 25, 2025. Accessed March 26, 2025. https://clinicaltrials.gov/study/NCT04849741