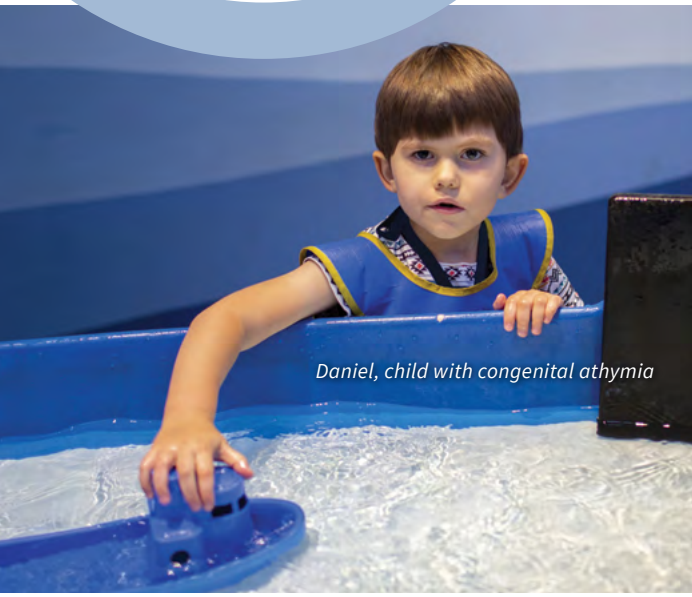
Congenital Athymia

Information for Healthcare Professionals



Daniel, child with congenital athymia

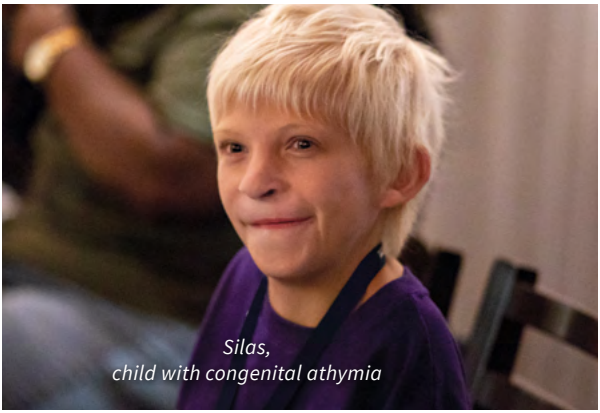
athymia insights

Definition and Incidence

With an estimated incidence of about 17 to 24 infants for every 4 million live births per year in the United States,[1] congenital athymia is an ultra-rare primary immunodeficiency disorder characterized by the lack of a functional thymus at birth.[2] The thymus is the organ responsible for the education and development of mature T cells, an essential component of the adaptive immune response.[3,4] T cells originate in the bone marrow as progenitor cells and migrate to the thymus, where they learn to recognize both self and foreign antigens.[3] Without functional thymus tissue, these progenitor cells lack an immunologic epicenter for T-cell maturation[3]; patients are thus significantly T-cell immunodeficient and unable to fight infection.[5]

Historically, children with congenital athymia typically have not survived beyond 2 years of age, generally because of fatal infections.[2]

Congenital athymia is sometimes mistaken for severe combined immunodeficiency (SCID), as patients with either disorder present with very low T-cell counts.[6,7] Although both are primary immunodeficiency disorders, SCID is rooted in the dysfunction of hematopoietic stem cells of the bone marrow, not in dysfunction or absence of the thymus.[7,8]



Silas,
child with congenital athymia

Etiology, Underlying Disorders, and Comorbid Conditions

The term *congenital athymia* was originally used interchangeably with *complete DiGeorge anomaly*. However, recent research has revealed distinct genetic and nongenetic conditions associated with congenital athymia. These associated conditions include the following:

- *DiGeorge syndrome or 22q11.2 deletion syndrome*[8,9]
- *CHARGE syndrome (coloboma, heart defects, atresia choanae, retardation of growth and development, genital hypoplasia, and ear anomalies/deafness)*[8]
- *FOXN1 deficiency*[10]

Nongenetic, environmental factors that affect embryogenesis—including maternal diabetes and exposure to alcohol, retinoids, or bis-dichloroacetylamine—also have been associated with congenital athymia.[8,11]

A range of comorbidities are commonly associated with congenital athymia, including congenital heart disease, hypoparathyroidism, laryngomalacia, esophageal atresia, palatal defects, and developmental delay with cognitive and behavioral dysfunction.[2,12,13]

Over time, some children may need hearing aids, vision support, and feeding support, as well as physical, occupational, or speech therapy.[14] Others may need major surgery for associated conditions.

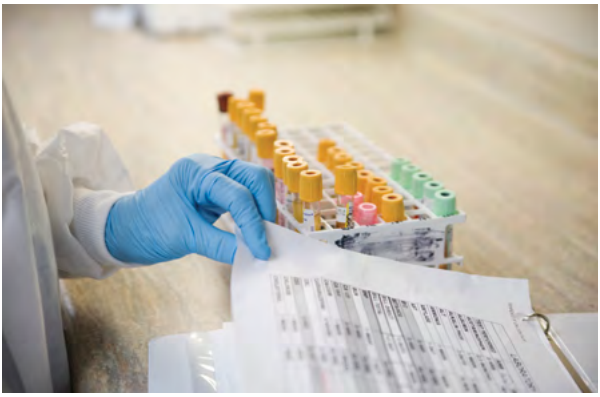
Detection and Diagnosis

Newborn screening plays a crucial role in the early detection of congenital athymia.[6] The condition is initially detected through T-cell receptor rearrangement excision circle (TREC) screening, also known as SCID testing.[6] TREC screening is critical, as it provides the first indication of an immunologic issue in an infant's T-cell development, with low TREC levels indicating the need for further testing.[6] TREC testing is now a standard part of the newborn screening panel and required in all 50 US states as of year end 2016.[15]

The definitive diagnostic technique for congenital athymia is *flow cytometry* using T-cell markers that quantify thymically derived T-cell numbers.[6] Confirmatory results for congenital athymia will show <50 thymically derived T cells per cubic millimeter or thymically derived T cells comprising <5% of the total T-cell count.[6]

Once athymia is confirmed, it is important to establish whether the initial presentation is *typical* or *atypical*.[6] In the atypical form, patients develop rash and lymphadenopathy associated with oligoclonal T cells and require immunosuppressive treatment.[2,6] Typical congenital athymia can evolve into the atypical form.[6]

Genetic testing is then used to identify associated conditions, such as 22q11.2 deletion syndrome, CHARGE syndrome, or FOXN1 deficiency.[6,10] As certain comorbidities, such as congenital heart disease and hypoparathyroidism, are commonly associated with congenital athymia,[12] it is important to test for these associated conditions after diagnosis and to appropriately manage them over the lifetime of the patient.



Standard of Care

Although treatment options continue to evolve, a standard of care for patients with congenital athymia has been established. When congenital athymia is suspected, the following recommended in-hospital protective measures are adopted and all testing for this condition should be urgently ordered and reviewed:

- *Patients should be moved to a laminar air flow (LAF) room immediately. LAF rooms follow a strict protocol that includes dedicated clean spaces for staff and visitors to properly sterilize, heavily monitored ventilation, hand washing, masks, gowns, and gloves*[6,16]
- *All blood should be irradiated prior to infusions and should be seronegative for cytomegalovirus (CMV)*[6]
- *Mothers should be instructed to stop breastfeeding until they are confirmed seronegative for CMV*[6]
- *After 1 month of age, patients should begin* Pneumocystis *prophylaxis and replacement immunoglobulin therapy*[6]
- *Antibiotic, antimycobacterial, and antifungal prophylaxis should be initiated*[14]
- *No live or inactivated vaccines should be administered prior to correction of the underlying immune disorder*[17]

Every patient with congenital athymia has different experiences, symptoms, and needs, especially if they have an underlying syndrome associated with the condition. Regardless of its cause, congenital athymia calls for the specialized care of a pediatric immunologist and an extended care team.

Guidance for At-Home Care

It is critical that parents and caregivers be advised to follow strict at-home isolation and hygiene practices, which may include but are not limited to:

- *Isolating the child so they avoid coming into contact with infectious pathogens can include:*

  - *Avoiding taking the child to public places, especially those frequented by other children who may be carrying infectious pathogens*
  - *Restricting visits by anyone outside the immediate household*

- *Wiping down any items coming into the home with disinfectant products*
- *Making it a habit for everyone in the household to frequently wash their hands with antibacterial products*
- *Having family members and visitors coming into contact with the child use masks, gowns, and gloves*
- *Asking school officials to inform family of any recent outbreaks or illnesses that siblings might bring home*
- *Establishing a sanitation station at the entrance to the home to allow visitors to disinfect, remove shoes, and put on masks, gowns, and gloves*
- *Frequently cleaning household surfaces and items that are touched routinely, such as doorknobs, cell phones, tablets, car keys, and remote controls*
- *Planning for an alternative location for household members to stay should they become ill, such as staying with a friend or family member*

Additional Information and Support

Although no organizations are dedicated specifically to congenital athymia, there are several for patients with immune system diseases that provide valuable support and education. These organizations, independent from Enzyvant, include the following:

Jeffrey Modell Foundation

This nonprofit organization is dedicated to helping patients, families, and caregivers affected by immunodeficiency disorders find support, education, awareness, advocacy, and care. To learn more, visit info4pi.org

Immune Deficiency Foundation

Physicians, their healthcare teams, and patients can find valuable information and insights related to immunodeficiency disorders. To learn more, visit primaryimmune.org

- The Immune Deficiency Foundation's *Patient and Family Handbook for Primary Immunodeficiency Diseases* offers information and tools to enhance communication between families, caregivers, and their healthcare teams. To learn more, visit primaryimmune.org/resource/idf-patient-family-handbook

22q Family Foundation

Dedicated to raising awareness of 22q11.2 deletion syndrome (DiGeorge syndrome) and offering support and accurate information to families and caregivers affected by the disorder. To learn more, visit 22qfamilyfoundation.org

Global Genes

This organization pursues positive change and aims to connect, empower, and inspire the rare disease community. To learn more, visit globalgenes.org

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