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The Management of Congenital Athymia

IDFA Immune Deficiencies Foundation Australia

IPOPI INTERNATIONAL PATIENT ORGANISATION FOR PRIMARY IMMUNODEFICIENCIES

ABBREVIATIONS

CHARGE syndrome	Coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, and ear abnormalities syndrome
CHD7	Chromodomain helicase DNA binding protein 7
CMV	Cytomegalovirus
DNA	Deoxyribonucleic acid
FOXN1	Forkhead Box N1
FOXI3	Forkhead Box I3
HCT	Haematopoietic cell transplant
IPOPI	International Patient Organisation for Primary Immunodeficiencies
OFCS2	Otofaciocervical syndrome type 2
PAX1	Paired Box 1
SCID	Severe combined immunodeficiency
TBX1	T-Box Transcription Factor 1
TREC	T-cell receptor excision circles

Congenital athymia (1st edition)

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SUMMARY

Congenital athymia is an ultra-rare immune disorder in which children have profound immunodeficiency because they are born without a functioning thymus gland. The thymus plays an important role in the development of functioning T cells, a type of white blood cell central to the body's immune response.

Congenital athymia is associated with multiple genetic disorders, with the most common underlying conditions being 22q11.2 deletion syndrome and CHARGE syndrome. Congenital athymia has also been associated with environmental factors, in particular maternal diabetes.

As a result of the absence of functioning T cells, athymic babies are immunodeficient and have an increased susceptibility to infection and an increased risk of developing autoimmune manifestations. Athymic children often have additional health and development issues related to their underlying genetic condition.

Corrective treatment of congenital athymia involves a procedure with implantation of cultured thymus tissue obtained from a donor, which is also referred to as thymus transplantation. Currently, treatment is available in two centres worldwide, in the United States1 and in the United Kingdom.2 After treatment, patients typically recover enough T-cell function to clear infections and to limit autoimmunity. Before treatment can be arranged and until T-cell recovery can be achieved, social isolation, infection prevention measures—in hospital and at home—as well as antimicrobial therapies are important to protect athymic children from infections that can potentially be life-threatening.

INTRODUCTION

This booklet explains what congenital athymia is, its causes and how it is diagnosed, treated and managed.

Congenital athymia is an immune disorder where children are born without a functioning thymus, causing them to suffer from severe immunodeficiency. Its overall incidence is estimated at 1:4,000–1:9,700 live births.[3]

The thymus is a small gland located in the chest, between the lungs and above the heart (**Figure 1**), that has an important role in helping the body learn how to fight infections. The cells that develop into T cells, a type of white blood cell involved in immune responses, develop from the bone marrow and travel to the thymus to mature and develop.[1] In the thymus, these cells learn to distinguish self from non-self (i.e. that which is foreign to the body, including viruses, bacteria and other pathogens). In the absence of a thymus, T cells cannot learn how to fight off

infections and sometimes they will mistakenly attack the body's self-components, leading to autoimmunity.[3] Children born with congenital athymia lack these T cells and education system, which are critical for generating immune responses and regulating autoimmune activity, creating a deficiency in their immune system.

Without appropriate management, congenital athymia is most often fatal within the first years of life. Without a functioning thymus, common infections can often become life-threatening alongside a higher risk of developing autoimmune diseases.[3] Prompt diagnosis in newborns is essential as the sooner the condition is detected, the sooner isolation and infection prevention measures can be initiated to avoid negative outcomes.

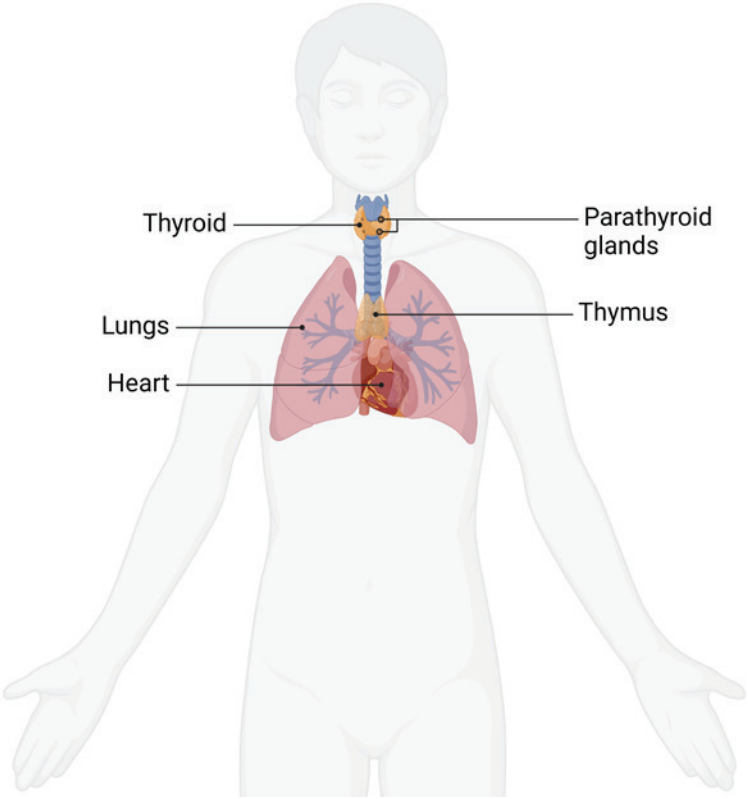

FIGURE 1. Location of the thymus

WHAT CAUSES CONGENITAL ATHYMIA?

ROLE OF GENES AND GENETIC SYNDROMES

Genetic syndromes associated with congenital athymia usually begin to manifest in the early stages of embryo development during pregnancy. The development of the thymus starts during the early stages of pregnancy and is regulated by a series of proteins, including: T-Box Transcription Factor 1 (*TBX1*, on 22q11), Chromodomain Helicase DNA Binding Protein 7 (*CHD7*), Forkhead Box N1 (*FOXN1*), Forkhead Box I3 (*FOXI3*), and Paired Box 1 (*PAX1*).[3] Several genetic syndromes result in mistakes in any of these proteins, making them inefficient and resulting in impaired development of the thymus. Sometimes, the development of other organs, such as the heart, parathyroid glands, airways and palate (the roof of the mouth), can also be affected.

The most common genetic disorders associated with absent thymus development are 22q11.2 deletion syndrome and CHARGE syndrome.[3] Other disorders are rarer and are due to errors in a number of genes, such as *FOXN1* and *PAX1*.[3]

22q11.2 deletion syndrome

In 22q11.2 deletion syndrome, a little piece of the long arm of chromosome 22 is missing. This disorder is sometimes also called DiGeorge Syndrome. This is one of the most frequent chromosomal disorders; it can affect many areas of the body but only a minority of children with 22q11.2 deletion syndrome have congenital athymia (<1%).[2] 22q11.2 deletion syndrome can be inherited from a parent but is more often due to a genetic defect that occurs unexpectedly during embryonic development.

CHARGE syndrome

CHARGE syndrome is a disorder that affects many areas of the body. CHARGE is an abbreviation for several of the features common in the disorder: coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital and urinary abnormalities, and ear abnormalities. CHARGE syndrome is caused by mutations in the *CHD7* gene. Similar to 22q11.2 deletion syndrome, only a very small group of children with CHARGE syndrome will present with congenital athymia.

FOXN1 deficiency

The *FOXN1* gene is specific to the development of the thymus, hair and nails. Athymic patients with mutations in *FOXN1* characteristically also lack hair and have nail malformations.[3] It is very rare with an estimated incidence of 1:1,000,000.

Otofaciocervical syndrome type 2

Otofaciocervical syndrome type 2 (OFCS2) is a rare disorder that is due to mutations in the *PAX1* gene. Athymic children with this condition typically also have bone malformations, mainly affecting the upper part of their back and their shoulders.

ENVIRONMENTAL EXPOSURES

Environmental factors associated with congenital athymia include unintentional (over)exposure during the first weeks of pregnancy to retinoic acid, alcohol, and poorly controlled diabetes in the mother, which can impair the development of the thymus.[3]

DIAGNOSIS OF CONGENITAL ATHYMIA

Congenital athymia cannot be detected during routine pregnancy ultrasounds, so it is not usually detected until newborn screening is performed at birth. However, prenatal diagnosis of the genetic conditions occasionally associated with congenital athymia is sometimes possible, particularly if triggered by prenatal cardiac abnormalities (for example, in babies with 22q11.2 deletion syndrome and CHARGE syndrome).

NEWBORN SCREENING

Newborn screening is the most important test for the early detection of congenital athymia.[2] The condition is often first identified during screening for another primary immunodeficiency disorder called severe combined immunodeficiency (SCID), which is also characterised by low or absent T cells. The screening method used to detect both SCID and congenital athymia involves measuring T-cell receptor excision circles (TRECs), which are very low or absent in dried blood spots from affected newborns. TREC screening provides the first indication of the lack of T cells. Newborns with low or absent TRECs then urgently need to undergo blood counts and white blood cell identification using a laboratory technique called flow cytometry to identify specific deficits in the different types of white blood cells, including T cells. These tests will be arranged by an immunologist and need to be done in a specialised laboratory.

WHEN NEWBORN SCREENING IS NOT AVAILABLE

If newborn screening is not available, or TREC testing is not yet included in the screening program, babies with congenital athymia may present clinically with complications that are a consequence of their T-cell deficiency, typically within the first few months of life. Symptoms may include poor weight gain, unusually persistent, severe, or opportunistic infections, persistent respiratory tract infections, persistent thrush (candidiasis), gastrointestinal infections and/or chronic diarrhoea. These symptoms, alongside specific syndromic features (see above), typically prompt clinicians to suspect a primary immunodeficiency. After referral to immunologists, flow cytometry and genetic testing are required to confirm a diagnosis of congenital athymia. Other diagnostic tools, such as imaging (for example, X-rays) are not required for conclusive diagnosis.

SIGNS AND SYMPTOMS OF CONGENITAL ATHYMIA

INFECTIONS

Because of the lack of T cells, children with congenital athymia are susceptible to chronic or recurring bacterial, viral, and fungal infections. Of particular concern are viral infections that affect the lungs or the whole body. The risk of infection can be reduced with proper prophylaxis (preventative) medications.[2,3]

AUTOIMMUNE CONDITIONS

In children with congenital athymia, circulating 'uneducated' T cells provide little to no protective immunity and can attack the child's own body; this is known as autoimmunity. Children may experience autoimmunity targeted against the skin and gut (known as the Omenn-like phenotype), or against blood cells, the liver and the thyroid gland (resulting in hypothyroidism). Some of these autoimmune issues can be treated with immunosuppressive medications.

NON-IMMUNE CLINICAL SIGNS AND SYMPTOMS

If the underlying cause of the congenital athymia is a genetic syndrome, infants may present with other non-immune clinical manifestations of the associated syndrome, which are summarised in **Table 1**[3] and can further complicate their care. There is a lot of variability among patients in their non-immune clinical signs and symptoms, with some severely affected and others hardly at all. Children with congenital athymia often have feeding issues, resulting in difficulty growing and gaining weight, which is known as failure to thrive.[3]

TREATMENT AND MANAGEMENT OF CONGENITAL ATHYMIA

Isolation and infection prevention measures, as well as prophylactic (preventative) antimicrobial therapies (in line with local centre policies for SCID), are important to protect children from potentially life-threatening infections.

Once clinical stability has been achieved, which could involve cardiac repair surgery or airway stabilisation procedures together with treatment to stabilise and normalise calcium levels, corrective treatment with thymus transplantation is available in two centres, one in the USA[1] and one in the UK.[2] If accessible, potential treatment with thymus transplantation should be discussed with the treating physician as soon as possible.

SUPPORTIVE CARE

Newborns should be urgently referred to a tertiary/quaternary care centre with high multidisciplinary expertise in managing these patients.

Isolation

As soon as congenital athymia is suspected, children should be isolated with protocols in place to minimise the risk of infection that include frequent handwashing and avoiding contact with sick relatives.[3]

Antimicrobial prophylaxis

Prophylaxis medications should be initiated, including with trimethoprim-sulfamethoxazole against *P. jirovecii* pneumonia (contraindicated before the age of 1 month), an azole antifungal, immunoglobulin replacement treatment and seasonal anti-respiratory syncytial virus prophylaxis, to manage infection risk.[2] Immunoglobulins are special proteins called antibodies that fight off infections. They can be administered intravenously every 3 to 4 weeks, or subcutaneously, typically weekly.[2]

Immunosuppressant therapy

In cases where ‘uneducated’ T cells cause autoimmune issues, children should receive immunosuppressant therapies to remove these cells and reduce the harm they can cause.[2]

TABLE 1. Non-immune clinical signs and symptoms of syndromes associated with congenital athymia[2,3]

GENETIC SYNDROME	GENE INVOLVED	NON-IMMUNE CLINICAL MANIFESTATIONS OF ASSOCIATED GENETIC SYNDROMES
22q11.2 deletion syndrome	22q11.2 chromosome, *TBX1*	• Congenital heart defects • Ear abnormalities and hearing loss • Nasal and oral cavity abnormalities • Cleft lip and/or palate • Feeding problems • Developmental delay • Low calcium levels and risk of seizures
CHARGE Syndrome	*CHD7*	• Eye coloboma (presence of a hole in one of the eye structures) • Heart defects • Airway issues; blocked or narrowed nasal passages • Retardation of growth and/or development • Genital abnormalities • Ear abnormalities and/or deafness • Low calcium levels and risk of seizures
FOXN1 deficiency	*FOXN1*	• Congenital alopecia (hair loss) • Nail development abnormalities
OFCS2	*PAX1*	• Facial abnormalities • Ear anomalies and hearing loss • Neck cysts or fistulas • Shoulder girdle anomalies • Developmental delay • Low calcium levels and risk of seizures

Blood product protocols

Hospitals managing children with congenital athymia should ensure that all blood is irradiated before transfusions and test that it does not contain cytomegalovirus (CMV).

Vaccine protocols

For children with congenital athymia, live vaccines are strictly contra-indicated. However, it is likely that all vaccines in athymic patients are ineffective due to the faulty T-cell function and inability to create the necessary immune response.[2]

Breastfeeding

If congenital athymia is suspected at birth, breastfeeding should be withheld until the mother can be tested for CMV to avoid the transfer of CMV.[2,3]

Calcium metabolism

As soon as a diagnosis of congenital athymia is suspected, parathyroid hormone levels need to be assessed. Patients with confirmed primary hypoparathyroidism are at risk of hypocalcaemic seizures and require Vitamin D supplementation, including its active form (alfacalcidol or calcitriol) to help normalise calcium levels. Referral to endocrinology specialists is recommended.

THYMUS TISSUE TRANSPLANTATION/IMPLANTATION

A corrective procedure with implantation of cultured thymus tissue from a donor, also referred to as thymus transplantation, is only currently offered at two centres, one in the USA[1] and one in the UK.[2] There are differences in how the treatment is regulated in both regions as well as differences in how the care pathways are accessed.[2]

If the patient has any uneducated T cells, for example as manifested by autoimmune symptoms, targeted immunosuppression is required prior to transplantation to prevent graft rejection. Thymus tissue is surgically implanted into the quadriceps muscle in the thighs. Once T-cell reconstitution occurs, immune suppression can be weaned off. T-cell development post-implantation is a slow process that can take 1 to 2 years. During this time, unchanged infection prophylaxis is still necessary.

HEMATOPOIETIC CELL TRANSPLANTATION

Although thymus transplantation is recognised as the only disease-specific treatment for congenital athymia, haematopoietic cell transplant (HCT) can be attempted under certain circumstances, such as geographic and/or financial constraints preventing access to thymus transplantation or in infants with severe pre-existing systemic viral infections. However, success with HCT has been limited; survival after HCT in patients with congenital athymia is low compared to survival after thymus transplantation.[2]

LIVING WITH CONGENITAL ATHYMIA

Uncorrected congenital athymia can have a significant impact on the lives of affected children and their caregivers. Studies at one centre highlight the impact of living in isolation, the emotional burden in relation to worries about infections and the future, financial worries and impact on siblings and family members as important concerns when treatment is delayed.[4] Children with the condition require vigilant care both in hospital and at home.

It is important for families to understand the reasons for supportive care and to know what they can do inside and outside the home to help protect their child. It is recommended that caregivers follow strict at-home protection measures, including:

- Educating those around them about the severity of the condition and that special precautions and isolation are needed to protect their children
- Limiting or restricting visitors in the home
- Having a “sick plan” in place for when a member of the household feels ill
- Washing hands frequently
- Cleaning items brought into the home
- It is recommended that all members of the entourage of the newborn receive immunisations.

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This booklet has been produced by the International Patient Organisation for Primary Immunodeficiencies (IPOPI).

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