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Congenital Athymia: From Genetic Causes to Advanced Therapeutic Approaches

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ABSTRACT:
Congenital athymia is an extremely rare disorder characterized by the absence of a functioning thymus at birth, resulting in profound immunodeficiency. This immunodeficiency is caused by the lack of T cell development, leading to increased susceptibility to infections and the risk of autologous graft-versus-host disease due to extrathymic T cell production. The condition is often associated with genetic and syndromic disorders, including FOXN1 deficiency, 22q11.2 deletion syndrome, CHARGE syndrome, and complete DiGeorge syndrome. Thymus transplantation has emerged as the most effective treatment, particularly when performed early to improve immune reconstitution and reduce the risk of infections. Supportive care, including antimicrobial prophylaxis, immunoglobulin replacement therapy, and close monitoring for viral infections, is essential while awaiting transplantation. The present review article focuses on clinical manifestations, aetiology, pathophysiological consequences, management strategies and economic burden of congenital athymia

Keywords: Congenital athymia, Immunodeficiency, T Cells

INTRODUCTION:

Congenital athymia is an ultra-rare paediatric condition (prevalence ≤1:50,000) caused by the absence of thymic development, resulting in profound immunodeficiency. It is commonly associated with genetic and syndromic conditions such as 22q11.2 deletion syndrome, complete DiGeorge syndrome, CHARGE (coloboma, heart defect, choanal atresia, growth or mental retardation, genital hypoplasia, and ear anomalies or deafness) syndrome, FOXN1 deficiency, and diabetic embryopathy. Historically, patients with congenital athymia typically die from infections or autoimmune sequelae within 2–3 years of life. [1]

CLINICAL MANIFESTATIONS:

Congenital athymia is a rare and life-threatening condition caused by the absence of a functional thymus, resulting in profound T cell immunodeficiency and autologous graft-versus-host disease (GVHD). Congenital athymia clinical symptoms are directly related to the thymus's absence and its incapacity to generate T cells with the necessary immune capabilities. An increased vulnerability to bacterial, viral, and fungal infections results from T-cell immunodeficiency. This immunodeficiency makes patients highly susceptible to severe and recurrent infections, particularly in the pulmonary and gastrointestinal systems. Pneumonia occurs in approximately 30% of patients, often caused by pathogens like *Pseudomonas aeruginosa*, *Candida albicans*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Haemophilus parainfluenzae*, which can lead to chronic lung disease. Gastrointestinal infections, including those caused

by *rotavirus*, *norovirus*, *M. bovis*, and *C. difficile*, are also common, contributing to malabsorption, chronic diarrhea, and failure to thrive. Other reported infections include urinary tract infections from *Klebsiella pneumoniae* and *Enterococcus faecium*, as well as ENT infections like meningitis, sinusitis, and oral thrush. Patients with congenital athymia are also at high risk for life-threatening opportunistic infections such as *Cytomegalovirus (CMV)*, *Candida*, *Pneumocystis jirovecii*, and *Human Herpesvirus 6 (HHV-6)*. CMV infection is particularly concerning, as it can be fatal and precludes eligibility for thymus tissue implantation.

In addition to infections, patients frequently develop autologous GVHD due to extrathymic oligoclonal T cell expansion. This condition leads to inflammatory damage in multiple organs, manifesting as eczematous rash, lymphadenopathy, transaminitis, and enteropathy. Immunosuppressive therapies, such as corticosteroids and calcineurin inhibitors, are used to manage these symptoms but can cause adverse effects like hypertension, renal complications, and thrombocytopenia. Autoimmune processes are also prevalent in congenital athymia, with patients experiencing hypothyroidism, autoimmune thyroiditis, Coombs-positive hemolytic anemia, idiopathic thrombocytopenia, and rheumatoid arthritis. [2]

AETIOLOGY:

Congenital athymia is a rare and severe condition characterized by the absence or underdevelopment of the thymus gland, which leads to profound T cell immunodeficiency. The thymus plays a critical role in the immune system by enabling the maturation of T cells from bone marrow-derived precursors. These T cells are essential for adaptive immunity, protecting the body against infections and recognizing self from non-self to prevent autoimmunity. The development of the thymus originates from the third pharyngeal pouch during early embryogenesis, and its formation involves a complex interplay of multiple genes and signalling pathways. Disruptions in these genetic mechanisms or environmental insults during foetal development can result in congenital athymia.

Genetic Causes of Congenital Athymia

Genetic causes of congenital athymia can be broadly classified into two categories: defects affecting thymus-specific organogenesis and those disrupting the broader midline region. Both types of mutations interfere with the normal development and function of the thymus, leading to T cell deficiency and increased susceptibility to infections.

1. **Thymus-Specific Genetic Defects**:

Among the genes that directly influence thymic development, *FOXN1* is the most extensively studied. *FOXN1* encodes a transcription factor essential for the differentiation and function of thymic epithelial cells, which provide the microenvironment necessary for T cell maturation. Mutations in *FOXN1* can present in three different patterns based on the inheritance and nature of the mutation: homozygous, heterozygous, and compound heterozygous. Homozygous *FOXN1* mutations result in the most severe phenotype, characterized by complete T cell immunodeficiency, congenital alopecia, and nail dystrophy. This condition is known as "nude" syndrome, reflecting the absence of hair and defective immune function. Affected individuals lack mature T cells, making them vulnerable to opportunistic infections. Heterozygous *FOXN1* mutations produce a milder phenotype, typically presenting with partial T cell lymphopenia. In these cases, T cell numbers may improve over time as other compensatory mechanisms take effect. Compound heterozygous mutations, involving two different defective *FOXN1* alleles, can also cause severe T cell deficiency without the characteristic hair and nail abnormalities. Another key gene

implicated in thymic development is *PAX1*. Mutations in *PAX1* are associated with otofaciocervical syndrome type 2 (OTFCS2), a condition marked by T cell lymphopenia, hearing loss, vertebral anomalies, and facial dysmorphism. Individuals with *PAX1* mutations often display absent thymic shadows on imaging studies, indicative of thymic aplasia. *PAX1* functions in the development of the pharyngeal region, and disruptions in its expression during embryogenesis result in a failure of the thymus to form properly.

2. Midline Developmental Defects Impacting Thymus Formation:

Several genes involved in the development of midline structures also play a crucial role in thymic organogenesis. The most well-known example is *TBX1*, a gene located within the 22q11.2 chromosomal region. Mutations or deletions in *TBX1* are responsible for DiGeorge Syndrome (DGS), a condition characterized by thymic aplasia or hypoplasia, congenital heart defects, hypoparathyroidism, and craniofacial anomalies. *TBX1* regulates the formation of the pharyngeal arches and pouches during embryogenesis, and its loss disrupts the migration of neural crest cells required for thymus formation. In mouse models, deletion of *TBX1* before embryonic day 9.5 results in a complete absence of the thymus, underscoring its essential role in early thymic development. Another critical gene involved in midline development is *CHD7*, which encodes a chromodomain helicase essential for chromatin remodeling. Mutations in *CHD7* cause CHARGE syndrome, a complex disorder involving coloboma, heart defects, atresia of the choanae, retardation of growth and development, genital anomalies, and ear abnormalities. Approximately 45% of patients with CHARGE syndrome exhibit thymic hypoplasia or aplasia and present with severe T cell lymphopenia. *CHD7* mutations disrupt the formation of the pharyngeal arches and pouches, thereby impairing thymus organogenesis. Additional genes implicated in thymic development include *TBX2* and *FOXI3*, although their precise mechanisms of action are less well understood. Mutations in these genes also disrupt the patterning of the pharyngeal region and can lead to congenital athymia and associated immunodeficiency.

Environmental Causes of Congenital Athymia

In addition to genetic mutations, environmental factors can contribute to congenital athymia by interfering with embryonic development. Maternal conditions, teratogens, and intrauterine exposures have all been implicated in disrupting thymic formation.

1. Maternal Diabetes (Diabetic Embryopathy):

Maternal diabetes is a well-recognized risk factor for congenital anomalies, including thymic aplasia. Hyperglycemia during early pregnancy interferes with normal embryogenesis and can disrupt the development of the pharyngeal region, leading to defects in the thymus and other structures. Diabetic embryopathy is associated with a spectrum of congenital malformations, including heart defects, vertebral anomalies, and immune dysfunction.

2. Retinoic Acid Exposure:

Foetal exposure to retinoic acid, a derivative of vitamin A, is another environmental factor that can impair thymic development. Retinoic acid regulates gene expression through nuclear receptors and plays a crucial role in embryonic patterning. Excessive retinoic acid exposure during pregnancy can disrupt the expression of key genes like *TBX1* and *PAX1*, leading to DiGeorge-like phenotypes characterized by thymic hypoplasia, heart defects, and craniofacial anomalies. Retinoic acid teratogenicity is dose-dependent, with higher levels causing more severe disruptions in pharyngeal arch development. [3]

DIAGNOSIS:

Early diagnosis of congenital athymia is crucial for timely intervention and appropriate supportive care. Identifying this condition promptly allows for better management of complications and the consideration of life-saving treatments like thymus transplantation. Congenital athymia diagnosis relies on several key diagnostic steps, particularly following abnormal findings from T-cell receptor excision circle (TREC)-based newborn screening (NBS). The diagnostic process involves immunological testing, genetic investigations, and sometimes functional assays to confirm the absence or severe dysfunction of the thymus. [4]

Role of Newborn Screening

Newborn screening is a critical tool for the early detection of congenital athymia. One of the primary screening methods is the T-cell receptor excision circle (TREC) test, which measures the number of newly formed (naïve) T cells. This test is mandatory across United States and serves as the first indicator of T-cell lymphopenia. Reduced or absent TRECs suggest a deficiency in T cells, prompting further diagnostic evaluation. TREC screening is designed to detect severe combined immunodeficiency (SCID) but can also identify other conditions with profound T-cell deficits, including congenital athymia.

Although congenital athymia and SCID both present with severe T-cell immunodeficiency and can be detected through TREC screening, they are distinct conditions with different underlying causes and treatment approaches. Congenital Athymia results from developmental defects in the thymus gland, impairing the maturation of T cells. It is often associated with genetic mutations such as *FOXN1* or *TBX1*, as seen in DiGeorge Syndrome. Whereas SCID is caused by mutations affecting the development or function of T cells, B cells, or both. The treatment for SCID typically involves hematopoietic stem cell transplantation, whereas congenital athymia may require thymus transplantation.

Accurate differentiation between these conditions through advanced immunophenotyping and genetic analysis is essential for determining the most effective treatment.

Diagnostic Workflow for Congenital Athymia

1. Initial Screening: TREC assay to identify low or absent naïve T cells.
2. Confirmatory Testing (Lymphocyte Subset Analysis): Flow cytometry to evaluate T-cell counts, subsets (CD4/CD8), and functional assays like mitogen-induced T-cell proliferation. CD3+ T-cell counts less than 300/µL suggests severe T-cell lymphopenia. Less than 5% naive T cells (CD3+CD4+CD45RA+) confirms absent thymic output, consistent with congenital athymia. Congenital athymia typically shows a T−B+NK+ or T−B+NK− profile.
3. Genetic Testing: Identify mutations in genes linked to thymic development (e.g., FOXN1, TBX1, CHD7). Cytogenetic Analysis for Detection of chromosomal abnormalities, such as 22q11.2 deletion syndrome (22q11.2DS), responsible for DiGeorge Syndrome (DGS). Gene Panel Testing for ientification of mutations in known genes related to athymia (e.g., CHD7 in CHARGE syndrome or FOXN1 mutations). Next-Generation Sequencing (NGS) for Broader genetic screening to identify rare or novel mutations in genes affecting thymic organogenesis.
4. Imaging Studies: Chest X-rays or MRIs to detect an absent or hypoplastic thymus gland.

Congenital athymia manifests in two distinct phenotypes: typical and atypical, each with unique clinical features and immunological profiles.

Typical Congenital Athymia

- Profound T-cell lymphopenia (low T-cell count).

- No evidence of autologous graft-versus-host disease (GVHD).
- Absent or severely impaired T-cell proliferation in response to mitogens like phytohemagglutinin (PHA).
- No significant lymphadenopathy or skin rash.

Atypical Congenital Athymia

- Presence of autologous GVHD-like symptoms caused by oligoclonal T-cell expansion.
- Skin rash and generalized lymphadenopathy.
- High numbers of circulating, dysfunctional T cells.
- Some degree of T-cell proliferation in response to mitogens, despite thymic absence.

PATHOPHYSIOLOGY AND CLINICAL CONSEQUENCES OF CONGENITAL ATHYMIA:

The thymus is a primary lymphoid organ where bone marrow-derived progenitor cells, known as prothymocytes, undergo differentiation and maturation into functional T cells. These cells enter the thymus through the vasculature at the corticomedullary junction and progress through four stages of maturation as they migrate from the sub-capsular zone to the cortex, medulla, and eventually the circulation. During this process, thymocytes undergo T cell receptor (TCR) gene rearrangement, which is essential for the expression of surface T cell receptors and the development of T cell competence. Thymocyte maturation occurs through distinct phenotypic stages: an initial double-negative (CD4−/CD8−) stage, an intermediate double-positive (CD4+/CD8+) stage, and a final single-positive stage, where cells differentiate into either helper T cells (CD4+/CD8−) or cytotoxic T cells (CD4−/CD8+), depending on their interaction with MHC class II or class I molecules, respectively. The thymus regulates T cell specificity through positive and negative selection. Positive selection allows survival of T cells capable of recognizing self-MHC molecules, while negative selection eliminates autoreactive T cells via apoptosis, preventing autoimmunity. Thymic nurse cells and dendritic cells play crucial roles in T cell differentiation and antigen presentation. Additionally, thymic hormones like thymosin and thymopoietin promote T cell maturation and enhance lymphocyte responsiveness. [5]

The absence of the thymus in congenital athymia results in profound T cell immunodeficiency. Without a functional thymus, T cell precursors from the bone marrow cannot mature into naïve T cells capable of recognizing and responding to antigens. This deficiency impairs both cellular immunity (T cell-mediated responses) and the coordination of adaptive immune mechanisms, leaving affected individuals highly susceptible to infections.

Patients with congenital athymia typically present with recurrent, severe infections early in life. Opportunistic infections caused by viruses, fungi, and intracellular bacteria are common due to the lack of functional T cells. In addition to infectious complications, the absence of central immune tolerance established in the thymus increases the risk of autoimmune manifestations. Without thymic epithelial cells to mediate negative selection, self-reactive T cells may escape deletion, leading to autoimmunity. [6]

MANAGEMENT AND FUTURE DIRECTIONS:

The primary treatment for congenital athymia is thymus transplantation, which can restore T cell immunity by providing a functional microenvironment for T cell maturation. This procedure involves implanting thymic tissue derived from infant donors, allowing the recipient to generate a functional T cell repertoire. Treating patients at a younger age is associated with improved initial immune reconstitution due to higher

thymic output following transplantation. Therefore, it is crucial to refer patients to a thymus transplantation centre without delay while providing comprehensive supportive care locally to manage their condition effectively.

Rethymic is an allogeneic processed thymus tissue therapy used to treat children with congenital athymia. It works by implanting donor-derived thymus tissue to restore immune function, a process that takes six months or longer. Common adverse reactions include high blood pressure, cytokine release syndrome, low magnesium levels, rash, low platelets, and graft-versus-host disease. Approved by the U.S. FDA in October 2021, Rethymic is the first thymus tissue product to receive approval. Dosing is customized based on the surface area of the thymus tissue slices and the patient's body surface area. [7]

Supportive care:

Supportive care and monitoring for complications in patients with congenital athymia are best managed by a local specialist paediatric immunology unit in collaboration with a thymus transplantation centre. Maintaining the patient in the best possible clinical condition while awaiting corrective treatment is crucial, as overall health status significantly impacts outcomes. Once congenital athymia is suspected, comprehensive supportive measures should be promptly initiated, often guided by established severe combined immunodeficiency (SCID) management protocols. All athymic patients should follow strict reverse isolation practices, avoid contact with sick individuals, and limit caregivers to essential staff. Antimicrobial prophylaxis is vital and should align with local SCID protocols, including trimethoprim-sulfamethoxazole for *Pneumocystis jirovecii* pneumonia prevention, an azole antifungal (such as fluconazole or itraconazole with therapeutic drug monitoring), immunoglobulin replacement therapy (IgRT), and seasonal prophylaxis for respiratory syncytial virus using monoclonal antibodies. In patients at risk of prolonged waits for thymus transplantation, antimycobacterial prophylaxis with azithromycin should also be considered. Live vaccines, such as bacillus Calmette-Guérin, rotavirus, and oral polio, are contraindicated. Blood products must be irradiated and cytomegalovirus (CMV)-negative, and breast-feeding should be withheld until maternal CMV status is confirmed. Regular monitoring for viral infections is recommended through polymerase chain reaction (PCR) testing of blood (for CMV, Epstein-Barr virus, adenovirus, and human herpesvirus 6), stool, and nasopharyngeal aspirates.

If a patient develops Omenn syndrome–like symptoms, confirmation should be sought through immunophenotyping and/or spectratyping to identify oligoclonal T-lymphocyte expansions, and skin biopsies may reveal spongiosis with T-lymphocyte infiltration. Such patients should be treated with cyclosporine A, maintaining therapeutic drug levels between 150 and 200 μg/L, with careful monitoring. Skin care with emollients and topical corticosteroids is essential for managing skin-related symptoms. In severe cases, systemic steroids may be required temporarily until cyclosporine A levels are optimized. Immunosuppression with antithymocyte globulin may be considered in refractory cases, though alemtuzumab should be avoided due to its potential to deplete dendritic cells, which are critical for successful thymus transplantation. cyclosporine A treatment must continue until after thymus transplantation.

Given that congenital athymia is frequently associated with broader syndromic conditions, managing comorbidities is vital before thymus transplantation. Patients with congenital heart defects (CHD) may require cardiac surgery, those with airway anomalies might need stabilization via positive airway pressure or tracheostomy, and hypocalcemia due to hypoparathyroidism should be corrected. In patients with severe muscle wasting from failure to thrive, nutritional support may be necessary to improve muscle mass before thymus implantation. For patients with severe life-limiting comorbidities—particularly cardiac or

neurological—palliative care may be considered in consultation with parents and multidisciplinary teams. Psychosocial support for patients and their families is essential throughout the care process. [8-9]

Advanced Therapeutic strategies:

Advancements in gene therapy hold promise for future treatment of congenital athymia. Targeted correction of pathogenic mutations in genes like *FOXN1* or *TBX1* may enable endogenous thymic regeneration and restore immune function. Research into the molecular mechanisms of thymic development continues to provide insights into novel therapeutic strategies and personalized approaches for affected individuals.

Cultured thymus tissue (CTT) is being studied as a treatment for congenital athymia, a life-threatening immune deficiency associated with conditions like complete DiGeorge syndrome and FOXN1 deficiency. In a study of 105 patients (1993–2020), 95 treatment-naive patients were analyzed for efficacy. The 1- and 2-year survival rates were 77% and 76%, respectively. Most deaths occurred within the first year before naïve T cells developed. Immune reconstitution typically occurred within 6–12 months, reducing infections and autoimmune complications. With a median follow-up of 7.6 years, CTT shows promise in improving survival and immune function in congenital athymia patients. [10]

ECONOMIC BURDEN:

The mean economic burden per patient in the first three years of life exceeds US$5.5 million, driven by the complex care required to manage infections and complications from autologous graft-versus-host disease (GVHD) caused by oligoclonal T cell expansion. Despite this intensive care, supportive treatments do not address the underlying immunodeficiency, and most patients succumb to their illness within three years. Inpatient hospitalization accounts for 79% of the total economic burden. There is significant variability in costs between patients, with a high inpatient utilization group incurring US$8.7 million in hospital expenses compared to US$0.4 million for the low utilization group. Approximately 30% of patients had hospital stays exceeding 350 days annually, with total costs surpassing US$11.7 million for those hospitalized for a full year. A key factor driving higher healthcare resource utilization (HCRU) is oligoclonal T cell expansion, which was present in 70% of patients. This condition increases the need for diagnostic tests and treatments, such as immunosuppressive therapies, which can cause complications like kidney damage (reported in 20% of patients). Patients with oligoclonal T cell expansion incurred more than double the costs of those without it (US$6.5 million vs. US$2.9 million). [11]

CONCLUSION:

Congenital athymia is a severe immunodeficiency disorder caused by the absence of a functioning thymus, leading to a lack of immunocompetent T cells. This results in increased susceptibility to infections and the risk of autologous graft-versus-host disease due to extrathymic T cell production. Patients may also present with additional complications linked to genetic or syndromic conditions such as FOXN1 deficiency, 22q11.2 deletion, CHARGE syndrome, and complete DiGeorge syndrome (cDGS). While current research has advanced the understanding of congenital athymia, significant gaps remain, particularly in understanding its full etiology. Future efforts should prioritize improving clinical management and expanding treatment options to enhance outcomes for patients with congenital athymia.

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