

T-Cell Deficiency, Severe Combined Immunodeficiency (SCID), Ataxia-Telangiectasia, Wiskott-Aldrich syndrome (WAS) & DiGeorge Syndrome

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T-Cell Deficiency causes cell-mediated immunodeficiency. Examples of T cell disorders include Severe Combined Immunodeficiency (SCID), Ataxia-Telangiectasia, Wiskott-Aldrich syndrome (WAS), and DiGeorge Syndrome. SCID causes the disturbing development of functional B and T cells due to a number of genetic mutations. Ataxia telangiectasia is a combined deficiency of T cells, immunoglobulins, and neurocutaneous findings. WAS is caused by WAS gene mutation resulting in a lack of functional Wiskott-Aldrich syndrome protein. DiGeorge Syndrome results from microdeletion in a small segment of chromosome 22.



Types of T-Cell Deficiency

Complete deficiency

It results from genetic conditions like severe combined immunodeficiency (SCID)

and cartilage-hair hypoplasia. T cell function is completely insufficient in this type.

Partial deficiency

It is a partial T cell functional insufficiency. Partial T-cell disorders typically have limited T-cell defects that predispose patients to more frequent or extensive infections; these disorders often include immune dysregulation that allows autoimmune phenomena, lymphoproliferation, and malignancies. Examples include acquired immune deficiency syndrome (AIDS), ataxia-telangiectasia, chromosomal breakage syndromes, Wiskott–Aldrich syndrome, and DiGeorge syndrome. Partial T-cell defects commonly cause abnormalities of immune regulation

Primary cause

- Genetic

Secondary causes

- AIDS
- Chemotherapy
- Glucocorticoid therapy
- Lymphoma

Signs and symptoms

The initial manifestations are often hemorrhagic (usually bloody diarrhea), followed by recurrent respiratory infections, eczema, and thrombocytopenia. Cancers, especially Epstein-Barr virus lymphomas and acute lymphoblastic leukemia, develop in about 10% of patients > 10 years.

Common manifestations are:

- Viral infections
- Diarrhea
- Erythrodermatous rash
- Cachexia
- Failure to thrive

Diagnosis

Following tests can be used to ascertain the diagnosis:

- Hypersensitivity skin test
- T cell count
- Culture in the case of infection
- Immunoglobulin levels
- Platelet count and volume assessment
- WBC function tests (eg, neutrophil chemotaxis, T-cell function)

The diagnosis is based on the following:

- Decreased T-cell count and function
- Elevated IgE and IgA levels
- Low IgM levels
- Low or normal IgG levels
- Decreased natural killer cell cytotoxicity
- Impaired neutrophil chemotaxis

Severe Combined Immunodeficiency (SCID)

SCID is a genetic disorder. There is disturbed the development of functional B and T cells due to several genetic mutations. Multiple mutations result in heterogeneous symptoms. Prevalence of SCID is 1 in 100,000 births. SCID involves defective antibody response due to either direct involvement with B lymphocytes or through improper B lymphocyte activation due to non-functional T-helper cells. SCID is the most severe form of primary immunodeficiencies, and there are now at least nine different known genes in which mutations lead to a form of SCID.

Other names

- Alymphocytosis
- Glanzmann-Riniker syndrome
- Severe mixed immunodeficiency syndrome
- Thymic alymphoplasia

Types of SCID

1. **X-linked severe combined immunodeficiency:** Most cases of SCID are due to mutations in the gene encoding the common gamma chain (γ_c), a protein that is shared by the receptors for interleukins IL-2, IL-4, IL-7, IL-9, IL-15, and IL-21.
2. **Adenosine deaminase deficiency:** The second most common form of SCID after X-SCID is caused by a defective enzyme, adenosine deaminase (ADA), necessary for the breakdown of purines.
3. **Purine nucleoside phosphorylase deficiency:** An autosomal recessive disorder involving mutations of the purine nucleoside phosphorylase (PNP) gene.
4. **Reticular dysgenesis:** Inability of granulocyte precursors to form granules secondary to mitochondrial adenylate kinase 2 malfunction.
5. **Omenn syndrome:** The manufacture of immunoglobulins requires recombinase enzymes derived from the recombination activating genes RAG-1 and RAG-2.
6. **Bare lymphocyte syndrome:** there are two types of this condition: (1) MHC class 1 which is not expressed on the cell surface and (2) MHC class 2 which is expressed on the cell surface.
7. **JAK3:** Janus Kinase-3 (JAK3) is an enzyme that mediates transduction downstream of the γ_c signals

Clinical presentation

The disease typically presents in early childhood (2-6 months). Severe opportunistic infections are seen in the affected individuals.

- Viral infections
- Candidiasis
- Mycobacterium
- Pneumocystis

Diagnosis

- CBC - Reduced T cells
- T cell morphology - abnormal
- Flow cytometry - T cell subpopulation deficiency
- Chest x-ray - absent thymus in some cases

Treatment

- Bone marrow transplantation within the first 3 months of birth
- Intravenous Immunoglobulin infusion
- Pneumocystis pneumonia (PCP) prophylaxis with Trimethoprim/Sulfamethoxazole (TMP/SMX)
- Reverse isolation
- Supportive care using immune globulin replacement therapy, antibiotics, and antifungals
- Hematopoietic stem cell transplantation
- Enzyme replacement for ADA deficiency

Ataxia telangiectasia

An autosomal recessive disease, it is a combined deficiency of T cells, immunoglobulins, and neurocutaneous findings.

It is due to a defect in the gene encoding Ataxia-telangiectasia Mutated Protein (ATM).

The hallmarks of this syndrome are poor coordination and dilatation of small blood vessels.

Other names

- Ataxia-telangiectasia syndrome
- Louis-bar syndrome

The affected individuals have various symptoms presenting at different stages of life. It is usually diagnosed during the 1st year of life. **Important features are:**

- Ataxia: It presents at an early age and worsens with time
- Truncal ataxia by 2 years of age
- Wheelchair-bound by school age
- Involuntary movements
- Telangiectasia marked on sclera and sun-exposed areas of skin. It is first seen after 5 years old. Skin Telangiectasia presents at 7
- Chronic lung disease
- Disoriented sounds
- Diabetes by adolescence
- Sinusitis
- Otitis media
- Oculomotor apraxia: It is the lack of coordination between the head and eye movement while shifting gaze from one object to another.
- Increased risk of cancers especially lymphomas and leukemias.
- Incomplete pubertal development
- Retarded growth
- Early menopause
- Drooling
- Premature changes in hairs
- Vitiligo and warts are seen in some cases
- Dysphagia during the 2nd decade of life

Treatment

- Symptomatic and supportive treatment
- Physical therapy
- occupational therapy

- speech therapy
- exercise
- anti-Parkinson drugs
- anti-epileptic drugs
- Vaccinations

Wiskott–Aldrich syndrome (WAS)

Other names

- Eczema-thrombocytopenia-immunodeficiency syndrome
- IMD2
- Immunodeficiency 2
- Wiskott syndrome

Wiskott–Aldrich syndrome is a disorder of B and T cell deficiency. It is caused by WAS gene mutation which results in lack of functional Wiskott-Aldrich syndrome protein (WASp).

Lack of WASp leads to impaired actin cytoskeleton, phagocytosis and chemotaxis, and impaired platelet development.

It also causes defective T cell signaling and interactions with antigen-presenting cells (APCs), and loss of humoral and cellular responses.

Genetics

Wiskott–Aldrich syndrome has X-linked recessive inheritance.

Prevalence of Wiskott-Aldrich syndrome is 1 to 10 cases per million males. It is rare in females.

Presentation

Individuals affected with Wiskott–Aldrich syndrome present with recurrent infections (viral, bacterial, and fungal). The frequency of these infections increases with age. Most common bacterial infections are due to *Streptococcus pneumoniae*, *Neisseria meningitidis*, and *Haemophilus influenzae*. Common viral agents are cytomegalovirus and varicella.

Candidiasis is a frequent fungal infection seen in these individuals. Hepatosplenomegaly, eczema, and thrombocytopenia are common.

Bruising, hematemesis, hematuria, petechiae, purpura and epistaxis are frequent especially in the early days of life.

30 percent of individuals have triad.

- Eczema
- Thrombocytopenia
- Chronic otitis media

Investigations

- Serology – decreased T and B cell count

- Immunoglobulins – decrease in IgG and IgM
- Increased levels of IgE and IgA
- Platelet count – 20,000/mm³– 50,000/mm³

Gene sequence analysis of WAS confirms the diagnosis.

Treatment

- Antibiotics
- Intravenous Immunoglobulin
- Hematopoietic stem cell transplantation

Prognosis

Individuals with Wiskott-Aldrich syndrome mostly die before age 10.

DiGeorge Syndrome

DiGeorge Syndrome results from microdeletion in a small segment of chromosome 22.

Deletion is heterozygous and involves the long arm, q, of chromosome 22 hence the name 22q11.2 deletion syndrome. Up to 50 genes may be affected as a result of such deletions. About 93% of cases are de novo mutations during early fetal development while 7% are inherited in autosomal dominant pattern from affected parents. The frequency of DiGeorge Syndrome is 1 in 4000 births.

Signs and symptoms

There are various symptoms related to DiGeorge Syndrome and marked variability in clinical expression among different individuals. **Commonly associated signs and symptoms include:**

Congenital heart disease: It is found in around 40% of the individuals. Common anomalies are:

- interrupted aortic arch
- patent truncus arteriosus
- tetralogy of Fallot
- ventricular septal defect
- Poor circulation of oxygenated blood results in
- Palatal defects, particularly cleft palate, and velopharyngeal incompetence.

Affected individuals have **characteristic facial features** like

- Hypertelorism
- Tubular nose
- Hooded eyes
- Features may be subtle
- Learning difficulties are found in 90% of the cases. Attention deficit disorders and cognitive deficits are common.
- Deficiency of growth hormone.
- **Hypoparathyroidism:** It is found in around 50% of the cases. Hypoparathyroidism leads to hypocalcemia.
- Skeletal abnormalities

- Problems related to feeding
- **Thymic aplasia due to failure to develop third and fourth pharyngeal pouches.**
- Conductive and sensorineural hearing loss.
- Seizures which may be due to hypocalcemia.
- Anomalies of respiratory and digestive tracts (Laryngotracheoesophageal problems)
- **Renal anomalies** are found in up to 37% of the patients.
- Autoimmune diseases such as Graves disease and rheumatoid arthritis
- Poor immunity due to reduced T cell
- **Psychiatric disorders** such as depression, bipolar disorder, attention deficit hyperactivity disorder (ADHD) and schizophrenia.

Diagnosis

Variations in the phenotypes of DiGeorge syndrome make the diagnosis difficult. Patients who have one or more deletion signs are more likely to have 22q11.2 deletion syndrome.

- Genetic testing is used for prenatal diagnosis using BACs-on-Beads or fluorescence in situ hybridization.
- Karyotyping may not detect microdeletions.
- Array-comparative genomic hybridization is used to detect deletions or duplications through screening the entire genome.
- Latest diagnostic methods include Quantitative Polymerase Chain Reaction and Multiplex Ligation-Dependent Probe Amplification Assay.

Other lab work and procedures include

- ECG
- Cardiac echocardiography (ECHO)
- Serum calcium and phosphorus
- Thyroid profile test
- Chest x-rays to look for thymus
- Complete blood picture (CBC)
- Immunoglobulin levels
- Renal ultrasound

Treatment

There is no cure for the 22q11.2 deletion syndrome. Management is aimed at treating the associated features of the disease. Treatment revolves around a multidisciplinary approach with the aim to improve the function of affected organ systems.

Immune problems due to the absence of thymus are necessary to be identified in the early stages. Blood transfusions and live attenuated vaccines are used with precaution in the affected individuals. In rare cases, thymus transplantation is also possible. Use of antibiotics for treating frequent bacterial infections. Lifelong calcium and vitamin D supplements are required to address hypocalcemia resulting from hypoparathyroidism. Treatment of structural abnormalities such as surgery for congenital heart abnormalities. Early intervention and developmental evaluation is key.

References

Boder, E. (1985). "Ataxia-telangiectasia: an overview." Kroc Foundation series. 19: 1-63. PMID 2415689.

Cole, TS., Cant, AJ. Clinical experience in T cell deficient patients. In: Allergy, Asthma & Clinical Immunology. 2010; **6:9**. DOI:10.1186/1710-1492-6-9

T-cell Disorders (2011). Retrieved from:

<http://emedicine.medscape.com/article/888372-overview>

Jones, J, Barbara BA.; Gillespie SH. In: Infection: Microbiology and Management. Wiley-Blackwell. 2006. ISBN 1-4051-2665-5.

Wiskott-Aldrich syndrome (2017). Retrieved from:

<https://ghr.nlm.nih.gov/condition/wiskott-aldrich-syndrome#synonyms>

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