DiGeorge Syndrome (22q11.2 Deletion Syndrome) — Symptoms and Treatment

DiGeorge Syndrome results from microdeletion in a small segment of chromosome 22. When inherited from parents, it follows an autosomal dominant pattern. There are variable clinical features related to DiGeorge Syndrome. Most common ones are congenital heart diseases, thymic hypoplasia, learning difficulties, characteristic facial appearance, hypocalcemia, and psychotic disorders later in adolescence. Microarray genetic testing is used to diagnose the syndrome. Early intervention and developmental evaluation is the key to treatment which includes multidisciplinary approach.

Definition of DiGeorge Syndrome

DiGeorge Syndrome is a result of a microdeletion in a segment of chromosome 22.

Other names for this syndrome include:

- Velocardiofacial syndrome
- Shprintzen syndrome
- Conotruncal anomaly face syndrome
- 22 deletion syndrome

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.
Epidemiology of DiGeorge Syndrome

About 93% of cases have 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 to 1/7000 births. Although the disease condition is congenital, but is diagnosed at variable ages.

Clinical features of DiGeorge Syndrome

The deletion results in variable symptoms related to DiGeorge Syndrome involving head, neck, brain, skeleton, kidneys, parts of the heart, thymus and parathyroid glands. 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 can occur.

**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

![Image: “A patient with DiGeorge syndrome, showing characteristic facial appearance, with tubular nose and carp-shaped mouth.” By Prof Victor Grech. License: CC BY-SA 3.0](image)

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

**Immune function**

Patients with DGS can be divided into 2 subtypes based on the degree of thymic hypoplasia and immunologic function:

**Complete DGS**

It’s found in 1% only in patients with 22qDS where the thymus is completely absent causing **severe combined immunodeficiency (SCID)**. Peripheral blood CD3+ T cells comprise less than 1-2 % of the circulating lymphocytes. T-cells in those patients have abnormal receptors (specifically, a restricted Vbeta TCR repertoire), which have a defective function in vitro, causing extrathymic outgrowth of oligoclonal abnormally T-cells.

This form of the disease is considered fatal causing serious manifestations of recurrent infections, chronic diarrhea and failure to thrive unless it was diagnosed early in early after birth and treated properly with thymic or bone marrow transplant.

**Partial DGS**

Patients with partial DGS has a range of normal to immunodeficient T cell numbers. Infants in this subtype have initially low number of T-cells, with a subsequent slow rising of the level during the first year of life. Although the normal attrition of T cell numbers in patients with partial DGS is blunted, a **normal number of T-cells might be reached by adulthood** as a result of a proliferation of existing T-cells rather than the recovery of thymus.

Since those patients still have accepted numbers of T-cells in their circulation, they don’t usually suffer from severe life-threatening infections.

Humoral immune deficiencies are commonly associated with this subtype, such as increased risk of IgA deficiency.

**Diagnosis of DiGeorge Syndrome**

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.

**Lab work & procedures**

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Other lab work and procedures include:

- Electrocardiogram (ECG)
- Cardiac echocardiography (echo)
- Serum calcium, phosphorus
- Thyroid
- CBC – look for lymphopenia
- T and B-cell subsets
- Immunoglobulin levels
- Chest x-ray – look for thymus
- Renal ultrasound

Treatment of DiGeorge Syndrome

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 is recommended. Early intervention and developmental evaluation is the key.

Prognosis of DiGeorge Syndrome

Prognosis varies with the nature and the extent of involvement of organs. Many adults with this syndrome lead a long and normal life.

Most common cause of mortality is congenital heart disease and second most common cause of death in this syndrome is immunodeficiency. Mortality is higher in infancy.

References


