CHARGE Syndrome and VACTERL Association — Signs and Symptoms

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CHARGE Syndrome is a rare genetic disorder in children affecting almost all body systems due to impaired gene expression as a result of inherited mutations in the specific genes. CHARGE is an abbreviation of Coloboma, Heart defects, Atresia choanae, growth retardation, genetic abnormalities, and ear abnormalities. There is no curative therapy for the syndrome. VACTERL Association stands for vertebral abnormalities, anal atresia, cardiac defects, tracheoesophageal abnormalities, renal anomalies, and limb abnormalities. It is a rare disorder. The exact genetic alterations are still not clear.

Definition of CHARGE Syndrome

CHARGE is a rare Autosomal dominant disorder in children. It is an abbreviation of defects that occur in this syndrome. Midline structures of an affected body show more abnormalities. The incidence is 1 out of 9,000 – 12,000 newborn children. CHARGE stands for:

- C for Coloboma
Coloboma is a hole in the structures of the eyes. It occurs in 70 – 80% of all cases. It can be present unilaterally or bilaterally. Choroid, retina, iris and optic disc are the sites of Coloboma. There is an impairment of vision depending on the location and size of the hole or gap. Children suffering from this syndrome can also have small eyes (microphthalmia).

Heart Defects involve 60 – 70% of the cases. Heart defects include coarctation of the aorta, aortic valve stenosis, tetralogy of Fallot, and Patent Ductus Arteriosus. Other structural defects can also occur.

Choanal Atresia affects almost 30 – 60% of cases. It is a condition in which the nasal passages become completely blocked. A less mild form is choanal stenosis, in which the nasal passages become narrowed.

Growth Retardation occurs in almost all cases of the CHARGE Syndrome. The affected children fail to thrive. This becomes noticeable in the first six months of life. The underlying endocrine causes a growth hormone deficiency and a gonadotrophin deficiency which are responsible for the growth retardation.

Genital Abnormalities. Most of the children suffer from hypogonadotropic hypogonadism. Micropenis and cryptorchidism (undescended testis) can be common abnormalities in males. Females are less commonly affected; labial dysplasia is a common defect. 70% of males and 30% of females suffer from these disorders.

Ear Problems. There is a malformation of external ears in all the cases. They are small, cup-shaped with protruding helices. Middle ears and inner ears have developmental defects that can impair the hearing capacity of the child.

Other common defects include:
- Dysmorphic features like a square face, facial nerve palsy, malar flattening, and micrognathia
- Neurological anomalies
- Renal anomalies
- Orofacial clefting
- Tracheoesophageal fistula
- Scoliosis
- Polydactyly or Oligodactyly
- Clubfoot
- Intellectual disability

Major clinical features of the CHARGE Syndrome

<table>
<thead>
<tr>
<th>Clinical finding</th>
<th>Description of finding</th>
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</thead>
<tbody>
<tr>
<td>Ocular coloboma</td>
<td>Unilateral or bilateral coloboma</td>
</tr>
<tr>
<td>Choanal atresia/stenosis</td>
<td>Unilateral/bilateral, bony or membranous choanal atresia or stenosis</td>
</tr>
<tr>
<td>Cranial nerve abnormality</td>
<td>Facial palsy, hypoplasia of auditory nerve</td>
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<tr>
<td>Ear abnormalities</td>
<td>Ossicular malformation, cochlear defects, temporal bone abnormalities</td>
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| Genital hypoplasia | • Males: micropenis, cryptorchidism  
| Development       | • Females: hypoplastic labia                                  |
| Cardiovascular    | Tetralogy of Fallot, atrioventricular canal defects, aortic  |
| Growth            | arch anomalies                                                |
| Facial features   | Square face with a broad prominent forehead, prominent      |
| Other             | nasal bridge, flat midface                                    |
|                   | Tracheoesophageal fistula, cleft palate                        |

### Genetic Changes of the CHARGE Syndrome

**Mutations occur in the CHD7 gene.** Though the role of CHD7 in embryonic development, it is believed that it produces a protein (CHD7 protein), which is involved in a process called chromatin remodeling. Chromatin is a complex of proteins and DNA, which molds the DNA into the shape of chromosomes. Chromatin remodeling controls the gene expression. Due to the gene mutation, the defective CHD7 protein breaks down prematurely. The shortage of this protein results in disrupted chromatin remodeling and poor gene expression. It leads to the various developmental defects of the syndrome.

### Inheritance pattern

It is transmitted in the autosomal dominant pattern. The **presence of only a single copy of a mutated gene in all cells causes the syndrome.**

### Mortality and Morbidity of the CHARGE Syndrome

- Mortality is higher in the neonatal period and early infancy.
- Swallowing problems that increase the risk of aspiration.
- Reasons for increased mortality include cyanotic heart disease, bilateral choanal atresia, and esophageal atresia and CNS anomalies.

### Diagnosis of the CHARGE Syndrome

The diagnosis can be made from the history, examination, and investigations.

### History

The following points are common to note in history.

- **Prenatally:** IUGR, congenital heart defects, poor fetal movements, and orofacial clefting
- **Neonatal period:** Dysmorphic features, SGA (small for gestational age), impaired hearing tests, and an inability to pass the nasogastric tube
- **Infantile period:** Poor growth, developmental delay, and feeding difficulties
Physical Examination of the CHARGE Syndrome

The typical features include coloboma, heart anomalies, choanal atresia, retardation of growth, genetic and ear anomalies.

Laboratory investigations

- Complete blood counts
- Renal function tests
- Analysis of CHD7 mutation
- Karyotyping
- Hormonal analysis (LHRH, HCG, and GH)
- Immunological studies
- Other tests that can be performed according to the requirement are EEG, ECG, Audiometry and Ophthalmologic tests.

Imaging studies

- Chest radiographs: To detect cardiopulmonary abnormalities
- Cranial ultrasonography: To exclude major brain malformations (is done in the neonatal period)
- Barium swallow: To diagnose esophageal dysmotility
- CT scan and MRI head: is used to detect forebrain anomalies, cerebral atrophy, and midbrain defects.
- Echocardiography: For the valvular abnormalities and structural heart defects
- Abdominal ultrasonography: For excluding the renal abnormalities
- Skeletal survey: To exclude the skeletal anomalies

Management of the CHARGE Syndrome

It is based on medical and surgical measures.

Medical treatment

At the time of birth following measures are to be taken:

- Oxygen supplementation: For cyanotic heart disease
- Nasogastric feeding: For swallowing difficulties
- Artificial tears: In facial palsy to avoid scarring of a cornea
- Androgen therapy: Given in some cases for penile growth

Surgical treatment

- Tracheostomy
- Gastrostomy
- Myringotomy
Definition of VACTERL Association

VACTERL association is a rare genetic disorder causing a group of birth defects. It can be found in 1 out of 1,000 – 40,000 newborn babies. The disease affects the median and paramedian structures. Other names like VATER or VACTERL are also used for the same disorder. The word VACTERL is more common and stands for the following defects.

- V for **Vertebral abnormalities**
- A for **Anal Artesia**
- C for **Cardiac defects**
- T and E for **Tracheoesophageal abnormalities**
- R for **Renal anomalies**
- L for **Limb abnormalities**
- S stands for single/one umbilical artery

**Other findings of the association are:**

- Facial asymmetry
- Lung defects
- Ear malformation
- Intestinal Malrotation
- Genital abnormalities
- Mental functioning is normal.

**Genetic Changes**

It is a complex condition presenting a combination of genetic and various environmental factors. The **exact genetic changes have not been identified in detail**.
Inheritance pattern

It follows a sporadic pattern. **There is no clear inheritance pattern.** It can occur in the child without having any similar case in the family. The family members may exhibit few characteristics, but not all of them have to be diagnosed as VACTERL.

Management

**Medical therapy** includes supportive therapy like oxygen and nasogastric intubation.

**Operative therapy** is based on the surgical correction of the structural abnormalities, which include tracheoesophageal fistula, valvular malformations, and anal Artesia.

**Testing includes:**
- Spinal ultrasound
- Spinal X-ray
- Echo
- Renal ultrasound
- Observation for respiratory distress/feeding problems

References


Solomon, B.David, 2011. VACTERL/VATER Association. PMC. Available at: [https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169446/](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3169446/).

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