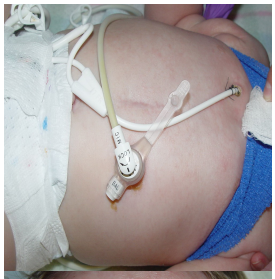

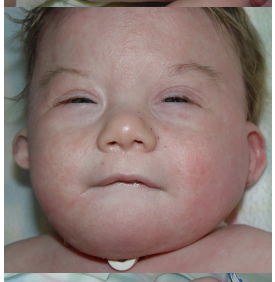

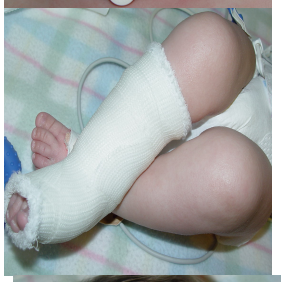

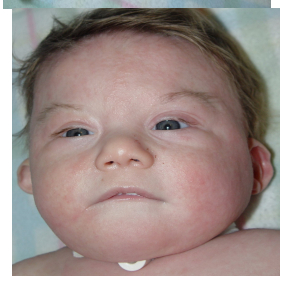

CHARGE syndrome

CHARGE syndrome is an autosomal dominant genetic disorder typically caused by mutations in the chromodomain helicase DNA-binding protein-7 (*CHD7*) gene.[1] The acronym "CHARGE" denotes the nonrandom association of coloboma, heart anomalies, choanal atresia, retardation of growth and development, and genital and ear anomalies, which are frequently present in various combinations and to varying degrees in individuals with CHARGE syndrome.
[2]

No single feature is universally present or sufficient for the clinical diagnosis of CHARGE syndrome, and numerous guidelines have been published to aid in establishing a likely clinical diagnosis.
[2,3,4]

Blake et al suggested that a typical clinical diagnosis of CHARGE syndrome requires the presence of at least 4 major features or 3 major features plus at least 3 minor features.[3] Major features include ocular coloboma or microphthalmia, choanal atresia or stenosis, cranial nerve abnormalities, and characteristic auditory and/or auricular anomalies. Minor features include distinctive facial dysmorphology, facial clefting, tracheoesophageal fistula, congenital heart defects, genitourinary anomalies, developmental delay, and short stature. Other frequently associated abnormal findings include characteristic hand dysmorphology, hypotonia, deafness, and dysphagia.
[3,5]

Although most cases of CHARGE syndrome are due to mutation or deletion of the *CHD7* gene, some individuals with CHARGE syndrome harbor disparate pathologic cytogenetic anomalies (including 22q11.2 deletions) or mutations in other genes (including
SEMA3E
) unrelated to
CHD7
.
[6,7,8,9,10]

Pathophysiology

A developmental defect involving the midline structures of the body occurs, specifically affecting the craniofacial structures.

This defect is attributed to arrest in embryologic differentiation in the second month of gestation, when the affected organs are in the formative stages (choanae at 35-38 days' gestation, eye at 5 weeks' gestation, cardiac septum at 32-38 days' gestation, cochlea at 36 days' gestation, external ear at 6 weeks' gestation). The prechordal mesoderm is necessary for the development of the mid face and exerts an inductive role on the subsequent development of the prosencephalon, the forepart of the brain.[11,12]

The mechanisms suggested are (1) deficiency in migration of cervical neural crest cells into the derivatives of the pharyngeal pouches and arches, (2) deficiency of mesoderm formation, and (3) defective interaction between neural crest cells and mesoderm, resulting in defects of blastogenesis and hence the typical phenotype.[11,4]

The complete function of *CHD7* during embryologic development remains unclear

- Deafness/hearing Loss (60-90%): Usually bilateral and of mixed type. A unique, wedge-shaped audiogram has been described with a descending bone conduction curve intersecting at low frequencies with a flat curve for air conduction. Inner ear abnormalities include Mondini malformation or partial or complete semicircular canal hypoplasia/aplasia. Vestibular or cochlear defect leads to sensorineural deafness. Middle ear problems cause conductive hearing loss and are commonly due to ossicular malformations, stapedius tendon abnormality, or serous effusion. CT scan of the temporal bone demonstrates partial or complete semicircular canal hypoplasia.
- Other anomalies
- Neurologic anomalies: Cranial nerve palsy (mainly facial nerve but also auditory), glossopharyngeal and vagus nerves, microcephaly, and neonatal brainstem dysfunction, which manifest in the form of feeding difficulty and swallowing difficulty, are observed.
- Dysmorphic features: These features include a typically asymmetric square face, malar flattening, unilateral facial nerve paralysis, and micrognathia.
- Hand dysmorphology: This includes brachydactyly and clinodactyly.

- Occasional anomalies (not consistently present)
- Renal - Hydronephrosis, vesicoureteric reflux
- Larynx - Laryngomalacia, laryngeal clefts

- Esophageal - Atresia, tracheoesophageal fistula
- Skeletal - Hemivertebrae, scoliosis, clinodactyly, syndactyly
- Orofacial clefting - Found in approximately 30-50% of patients

Causes

CHARGE syndrome is an autosomal dominant condition with genotypic heterogeneity. Most cases (58-71% in unselected CHARGE referrals and as many as 90% of patients who meet criteria for typical CHARGE syndrome) are due to mutations of the *CHD7* gene leading to haploinsufficiency. [1,6,17,19]

Microdeletions encompassing the entire *CHD7* gene or affecting individual *CHD7* gene exons occur in a minority of cases. [20,21]

One case report detailed *CHD7* duplication, which did not result in a CHARGE-like phenotype. [22]

Numerous case reports have described individuals clinically diagnosed with CHARGE syndrome who harbor various presumably pathologic cytogenetic abnormalities, including 22q11.2 deletions, 14q22-q24.3 inverted duplications, and 9p-, and single gene mutations (including *SEMA3E* gene mutation)

Laboratory Studies

- *CHD7* mutation analysis is diagnostic in 58-71% of individuals referred with presumptive CHARGE syndrome. Some studies suggest this may be as much as 90% in those meeting strict clinical criteria for definite CHARGE syndrome. Genotype-phenotype understanding is increasing. [1,6,17]
- High-resolution karyotype (chromosome analysis).
- Fluorescent in situ hybridization (FISH) or array comparative genomic hybridization (aCGH) can be used to detect submicroscopic copy number variations involving *CHD7* and at other loci in individuals in whom *CHD7* sequencing is uninformative. [1]

- BUN, creatinine, electrolytes: Evaluate and monitor renal function and exclude hypocalcemia (DiGeorge syndrome).
- Luteinizing hormone-releasing hormone (LHRH) and human chorionic gonadotropin (HCG): Perform these tests to evaluate the pituitary gonadal axis in cases of hypogenitalism.

- Growth hormone levels: Obtain growth hormone levels to exclude growth hormone deficiency contributing to growth retardation.
- CBC count and immunology studies: Immunodeficiency has been reported and is primarily T-cell based but may also be humoral, even appearing like Omenn syndrome. [23,24]

Imaging Studies

- Chest radiography: Perform chest radiography to exclude cardiopulmonary pathology and to document normal lung volume and cardiac shape and size in persons with respiratory distress, especially in the newborn period.
- Cranial ultrasonography: Perform this study in the immediate neonatal period to exclude major malformations of the brain.
- Head CT scanning and/or MRI, including the temporal bones: Perform CT scanning and/or MRI to exclude cerebral malformation and cerebral atrophy and to exclude defective formation of the ossicles of the middle ear. MRI of the brain may reveal cerebral atrophy, midline brain defects (eg, agenesis of corpus callosum), and forebrain anomalies, particularly arrhinencephaly. CT scanning of the temporal bone reveals partial or complete semicircular canal hypoplasia. Ideally, evaluate the internal ear in later infancy or early childhood, when the ear is more fully formed.
- Barium swallow: Perform this study to diagnose swallow dysfunction and/or esophageal dysmotility and tracheal aspiration.
- Abdominal ultrasonography: Perform abdominal ultrasonography to exclude renal anomalies.
- Skeletal survey: Survey the skeleton to exclude skeletal anomalies.
- Echocardiography: Perform echocardiography to identify or exclude congenital cardiac defects.

Other Tests

- Electroencephalogram: Perform EEG to diagnose seizures.
- Immune system evaluation: Evaluate the immune system to exclude cellular immunodeficiency or lymphopenia and lymphocyte function defect (DiGeorge syndrome overlap).
- ECG: Perform to identify and/or exclude congenital cardiac defects.
- Serial audiometry and auditory brainstem evoked responses
- Document the type and severity of conductive and sensorineural hearing loss.
- A characteristic wedge-shaped response is reported.

- Visual evoked response and electroretinogram

- Identify and document the severity of visual loss.
- Visual evoked response (VER) and electroretinogram (ERG) are abnormal but do not correlate with the extent or the localization of the coloboma.
- Due to cognitive defects, administering tests of visual acuity is difficult; hence, more sophisticated tests (eg, VER, ERG) that do not depend on patient behavior responses are appropriate.

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Medical Care

At birth, provide a secure airway, stabilize the patient, exclude major life-threatening congenital anomalies, and transfer the individual with CHARGE syndrome to a specialist center with pediatric otolaryngologist and other subspecialty services.

- If airway establishment does not correct cyanosis in a newborn, congenital heart disease is the most likely cause.
- Individuals with CHARGE syndrome who survive the initial neonatal and infantile period merit vigorous rehabilitation of the sensory function to enable proper psychomotor development.

- Nasogastric feeding is indicated in individuals with swallowing difficulty.
- In the presence of facial palsy, avoid corneal scarring by using artificial tears.
- In males with CHARGE syndrome, androgen therapy has been tried for penile growth.

Surgical Care

Ensure coordination of various procedures in order that operations and investigations requiring sedation or a general anesthetic can be performed at the same time and multiple anesthetic administrations can be avoided.

- Tracheostomy

- Myringotomy and tympanostomy tubes (for otitis media)
- Gastrostomy and fundoplication (may be necessary with feeding difficulty)

In patients with CHARGE syndrome who have sensorineural hearing loss, careful treatment planning can lead to auditory benefit. In a recent study of 10 patients with CHARGE syndrome and 3 patients with CHARGE-like syndrome, 9 patients demonstrated improved responsiveness with cochlear implantation.[25] Thus, cochlear implantation may be indicated after critical assessment.

Consultations

Genetic consultation is used for diagnosis, counseling, management, and coordination of services.

- Otolaryngology
- Cardiology
- Ophthalmology
- Gastroenterology
- Audiology
- Neurology
- Speech therapy
- Physiotherapy
- Occupational therapy
- Social services
- Special education