CHARGE SYNDROME

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Abstract:

CHARGE syndrome is a disorder that affects many areas of the body. CHARGE is an abbreviation for several of the features common in the disorder: coloboma, heart defects, atresia choanae (also known as choanal atresia), growth retardation, genital abnormalities, and ear abnormalities. The pattern of malformations varies among individuals with this disorder, and the multiple health problems can be life-threatening in infancy. Affected individuals usually have several major characteristics or a combination of major and minor characteristics.

Keyword: *Coloboma, Atresia Choanae Growth Retardation*

INTRODUCTION

Charge syndrome (formerly known as CHARGE association/Hall-Hittner syndrome), is a rare syndrome caused by a genetic disorder. First described in 1979, the acronym "CHARGE" came into use for newborn children with the congenital features of coloboma of the eye, heart defects, atresia of the nasal choanae, retardation of growth and/or development, genital and/or urinary abnormalities, and ear abnormalities and deafness.[1] These features are no longer used in making a diagnosis of CHARGE syndrome, but the name remains. About two thirds of cases are due to a CHD7 mutation. CHARGE syndrome occurs only in 0.1–1.2 per 10,000 live births; as of 2009 it was the leading cause of congenital deaf and blindness.

Genetic change

Mutations in the CHD7 gene cause most cases of CHARGE syndrome. The CHD7 gene provides instructions for making a protein that regulates gene activity (expression) by a process known as chromatin remodeling. Chromatin is the complex of DNA and protein that packages DNA into chromosomes. The structure of chromatin can be changed (remodeled) to alter how tightly DNA is packaged. When DNA is tightly packed, gene expression is lower than when DNA is loosely packed. Chromatin remodeling is one way gene expression is regulated during development.

Most mutations in the CHD7 gene lead to the production of an abnormal CHD7 protein that is broken down prematurely. Shortage of this protein is thought to disrupt chromatin remodeling and the regulation of gene expression. Changes in gene expression during embryonic development likely cause the signs and symptoms of CHARGE syndrome. [1]

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Inheritance pattern:

A small percentage of individuals with CHARGE syndrome do not have an identified mutation in the CHD7 gene. Some of them may have a genetic change affecting the CHD7 gene that has not been found, and others may have a change in a different gene, although additional genes associated with CHARGE syndrome have not been identified.

When CHARGE syndrome is caused by mutations in the CHD7 gene, it follows an autosomal dominant pattern of inheritance, which means one copy of the altered gene in each cell is sufficient to cause the disorder. Most cases result from new mutations in the gene and occur in people with no history of the disorder in their family. In rare cases, an affected person inherits the mutation from an affected parent. The inheritance pattern of other cases of CHARGE syndrome is unknown.[2]

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. [2,3]

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.

Major and minor characteristics

Affected individuals usually have several major characteristics or a combination of major and minor characteristics.

The major characteristics of CHARGE syndrome are common in this disorder and occur less frequently in other disorders.

Coloboma- gap or hole in one of the structures of the eye may be present in one or both eyes and may impair a person's vision, depending on its size and location.

Microphthalmia-abnormally small or underdeveloped eyes.

Choanal stenosis- one or both nasal passages are narrowed or completely blocked choanal atresia- completely blocked which can cause difficulty breathing.

Cranial nerve abnormalities- The cranial nerves emerge directly from the brain and extend to various areas of the head and neck, controlling muscle movement and transmitting sensory information. Abnormal function of certain cranial nerves can cause swallowing problems, facial paralysis, a sense of smell that is diminished (hyposmia) or completely absent (anosmia), and mild to profound hearing loss.

Middle and Inner ear abnormalities- which can contribute to hearing problems, and unusually shaped external ears.

Minor characteristics of CHARGE syndrome are common in this disorder, they are also frequently present in people without the disorder.

The minor characteristics include heart defects; slow growth starting in late infancy; delayed development of motor skills, such as sitting unsupported and walking; and an opening in the lip (cleft lip) with or without an opening in the roof of the mouth (cleft palate). Affected individuals frequently have hypogonadotropichypogonadism, which affects the production of hormones that direct sexual development. As a result, males with CHARGE syndrome are often born with an unusually small penis (micropenis) and undescended testes (cryptorchidism). Abnormalities of external genitalia are seen less often in affected females. Puberty can be incomplete or delayed in affected males and females. Another minor feature of CHARGE syndrome is tracheoesophageal fistula, which is an abnormal connection (fistula) between the esophagus and the trachea. Most people with CHARGE syndrome also have distinctive facial features, including a square-shaped face and differences in appearance between the right and left sides of the face (facial asymmetry). Affected individuals have a wide range of cognitive function, from normal intelligence to major learning disabilities with absent speech and poor communication.

Diagnosis

The diagnosis of CHARGE syndrome is often difficult, because it is rare. The syndrome spans many disciplines, and as such, can be diagnosed by a pediatrician, oral and maxillofacial surgeon, ENT specialist, ophthalmologist, audiologist, endocrinologist, cardiologist, urologist, developmental specialist, radiologist, geneticist, physiotherapist, occupational therapist, speech therapist, or orthopedic specialist

Genetic testing

Genetic testing for CHARGE syndrome involves specific genetic testing for the CHD7 gene. The test is availableat most major genetic testing laboratories. Insurance companies sometimes do not pay for such genetic tests, though this is changing rapidly as genetic testing is becoming standard across all aspects of medicine. CHARGE syndrome is a clinical diagnosis, which means genetic testing is not required in order to make the diagnosis. Rather, the diagnosis can be made based on clinical features alone.

Screening other organ systems

Once the diagnosis is made based on clinical signs, it is important to investigate other body systems that may be involved. For example, if the diagnosis is made based on the abnormal appearance of the ears and developmental delay, it is important to check the child's hearing, vision, heart, nose, and urogenital system. Ideally, every child newly diagnosed with CHARGE syndrome should have a complete evaluation by an ENT specialist, audiologist, ophthalmologist, pediatric cardiologist, developmental therapist, and pediatric urologist.[4]

Treatment

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. Thus, cochlear implantation may be indicated after critical assessment.[5]

Education

Children with CHARGE syndrome will vary greatly in their abilities in the classroom: some may need little support, while some may require full-time support and individualized programs. Taking each of the various affected body systems into account is vital to the success of the child in the educational setting. An important step in dealing with abnormal behavior is understanding why it is occurring and helping the child learn more appropriate methods of communicating. Before a child reaches age 18 (or the age of maturity in their country) doctors and specialists need to be found that will follow the individual in adulthood.

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