

CHARGE syndrome

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Abstract

CHARGE syndrome (Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, Ear anomalies/deafness). is a non-random association of anomalies that occurs together more frequently than one would expect on the basis of chance. In 1998, an expert group defined the major and minor criteria of CHARGE syndrome. Major criteria are those findings that occur commonly in CHARGE syndrome but are relatively rare in other conditions. The minor criteria occur less frequently or are less specific to CHARGE syndrome. Individuals with all four major characteristics (the classical 4C's: Choanal atresia, Coloboma, Characteristic ears and Cranial nerve anomalies) or three major and three minor characteristics are highly likely to have CHARGE syndrome. The true incidence of CHARGE syndrome is not known, with estimates ranging from 0.1–1.2/100,000 live births. Colobomat may be unilateral or bilateral and may affect only the iris or extend to involve the retina. Congenital heart defects (the commonest is tetralogy of Fallot) occur in 75-80% of patients. Choanal atresia may be membranous or bony; bilateral or unilateral. Mental retardation is variable with IQs ranging from near normal to profound retardation. The incomplete or under-development of the external genitalia is a common finding in males and in females. Ear abnormalities include a classical finding of unusually shaped ears, hearing loss, conductive and/or nerve, ranges from mild to severe deafness. Multiple cranial nerve dysfunctions are common. Children with CHARGE syndrome require intensive medical management as well as numerous surgeries. They also need multidisciplinary follow up including cardiology consultation; complete eye examination, hearing aids and adapted educational and therapeutic services. Recently, mutations in a large gene (CHD7) responsible for the CHARGE syndrome in over 2/3 of the tested population have been identified. CHD7 encodes a novel member of the chromodomain helicase DNA protein family and is an essential gene in early embryonic development affecting multiple organ systems including heart, inner ear and retina.

Key words

Coloboma, Choanal atresia/stenosis, Cranial nerve anomalies, Choanal atresia/stenosis, Cardiovascular malformations, Genital hypoplasia, Cleft lip/palate, Tracheoesophageal-fistula, Growth deficiency, Developmental delay

Definition

The CHARGE association was first described in 1979 by Hall *et al.* in 17 children with multiple congenital anomalies who were ascertained by choanal atresia. Pagon *et al.* in 1981 first coined the acronym CHARGE association (**C**oloboma, **H**ear defect, **A**tresia choanae, **R**etarded growth and development, **G**enital hypoplasia, **E**ar anomalies/deafness). CHARGE is a non-random association of anomalies that occurs together more frequently than one would expect on the basis of chance. The original diagnostic criteria

required the presence of four out of six of the CHARGE characteristics. Over the past 15 years the specificity of this pattern of malformations has reached the level that many clinicians now consider it to be a recognizable CHARGE syndrome (#OMIM 214800).

Diagnostic criteria

With increasing experience, it has become clear that the CHARGE association criteria originally proposed by Pagon *et al.* and later revised by Mitchell *et al.* needed further refinement.

Table 1: Diagnostic criteria for CHARGE syndrome

Features of CHARGE Syndrome		Later childhood/adolescent issues *
Major "4 C's"		
Ocular C oloboma	Coloboma – of iris, retina, choroid, disc; microphthalmia	Photophobia; retinal detachment
C hoanal atresia/stenosis	Choanal atresia (or Cleft palate) – unilateral/bilateral, membranous/bony, stenosis/atresia	Facial growth problems, recurrent closure and resurgeries, unilateral nasal discharge
C ranial nerve anomalies	Cranial nerve dysfunction – Facial palsy (unilateral or bilateral), Sensorineural deafness and/or swallowing problems	Feeding/swallowing problems; gastroesophageal reflux; hearing loss; facial palsy (appearance)
C haracteristic ear anomalies	Characteristic ear abnormalities – External ear (lop or cup shaped), Middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects	Progressive hearing loss; chronic middle ear infections; vestibular problems affecting balance and /or motor skills.
Minor		
Cardiovascular malformations	Cardiovascular malformations – All types: especially conotruncal defects (e.g. Tetralogy of Fallot), AV canal defects, and aortic arch anomalies	Arrhythmias; angina; further cardiac surgeries
Genital hypoplasia	Genital hypoplasia – Males: Micropenis, cryptorchidism, Females: Hypoplastic labia, Both: Delayed incomplete pubertal development	Pubertal delay, hormone replacement; fertility (unsure)
Cleft lip/palate	Orofacial cleft – Cleft lip and/or palate	Cosmetic concerns; self-image
Tracheoesophageal-fistula	Tracheoesophageal-fistula – Tracheoesophageal defects of all types	Reflux esophagitis; feeding/swallowing problems
Distinctive CHARGE facies	Characteristic face -- sloping forehead, flattened tip of nose	Cosmetic concerns; self-image
Growth deficiency	Growth deficiencies – Short stature	Growth hormone (GH) replacement Borderline GH stimulation tests
Developmental delay	Developmental delay – Delayed motor milestones, language delay, mental retardation (MR)	Educational, behavioural, social adjustment issues; Autistic-like problems
Occasional		
Renal anomalies	Duplex, Reflex	Renal failure
Spinal anomalies	Scoliosis; Osteoporosis	Scoliosis
Hand anomalies		Fine motor problems; cosmetic concern
Neck/shoulder anomalies		Self-image concern

Lawand C, Graham JM, Jr, Prasad C, Blake KD (2003). CHARGE association / syndrome: Looking ahead. Published by the Canadian Pediatric Surveillance Program (CPSP) 2003 Resources. <http://www.cps.ca/english/CPSP/Resources/CHARGE.htm>

Blake KD and Prasad C; CHARGE syndrome. Orphanet encyclopedia, November 2004 <http://www.orpha.net/data/patho/GB/uk-CHARGE-association.pdf>

An expert group of geneticists and developmental pediatricians defined the major and minor criteria of CHARGE syndrome (Blake *et al.*, 1998).

Major criteria are those findings that occur commonly in CHARGE syndrome but are relatively rare in other conditions. The minor criteria occur less frequently or are less specific to CHARGE syndrome (Table 1).

A diagnosis of CHARGE syndrome should be considered in any neonate with coloboma, choanal atresia, asymmetric facial palsy or classical CHARGE ears (Davenport *et al.*, 1986) in combination with other specific (See Diagnostic Criteria Table) congenital anomalies. Individuals with all four major characteristics (the classical 4C's: **C**hoanal atresia, **C**oloboma, **C**haracteristic ears and **C**ranial nerve anomalies) or three major and three minor characteristics are highly likely to have CHARGE syndrome. Some of features are difficult to detect in the neonatal period; therefore, the diagnosis needs to be considered in any infant with one or two major criteria and several minor characteristics. CHARGE syndrome can occur in an individual with no Coloboma or Choanal atresia (reported in CHARGE Accounts; Fall 2004 from Dr Conny van Ravenswaaij).

Differential diagnosis

Some characteristics of CHARGE syndrome overlap with those of other conditions including: [VACTERL association](#), [DiGeorge sequence](#), [Velocardiofacial syndrome \(VCFS\)](#), [Cat Eye Syndrome](#), retinoic acid embryopathy, and PAX2 abnormalities (The PAX2 gene is expressed in primitive cells of the kidney, ureter, eye, ear and central nervous system). Furthermore, several different structural chromosome abnormalities have been reported in children with coloboma, choanal atresia, and/or heart defect (e.g. deletion 18q22.3-qter, duplication 2q37.3-qter, deletion 3p25.1-pter, deletion 22q11.1-qter, duplication 14q22-q24.3 and duplication 8q22-qter). Consistent submicroscopic chromosomal abnormalities in patients with CHARGE syndrome have not been demonstrated, and there has been no consistency in the types of chromosome anomalies previously reported.

It is important to rule out a submicroscopic chromosomal deletion of 22q11 with FISH analysis in all patients suspected of CHARGE syndrome especially those with thymic hypoplasia and hypocalcemia. PAX2 abnormalities can lead to renal problems and ocular coloboma but few of the other features of CHARGE syndrome have been observed in such children (Martin *et al.*, 2002).

The syndrome with hypoplasia of the depressor anguli oris muscle and cardiac defects also overlaps with both CHARGE syndrome and Velo-cardio-facial syndrome (VCFS), since both these syndromes are associated with malformed ears, urogenital anomalies, heart defect and growth/mental retardation. Retinoic acid embryopathy can produce ear, face, heart and cranial nerve defects, however brain malformations resulting from retinoic acid embryopathy are usually much more severe. Exposure to retinoic acid during critical periods of morphogenesis has not been reported in children with CHARGE syndrome.

Incidence

The true incidence of CHARGE syndrome is not known, with estimates ranging from 0.1–1.2/100,000 live births. A national surveillance study of CHARGE syndrome patients has been conducted through the Canadian Pediatric Surveillance Programme (CPSP) from September 2001 – 2004 (Blake *et al* Annual CPSP reports 2003 and 2004). The highest incidence of CHARGE syndrome in Canada was estimated at 1:8,500 live births in provinces with a research interest in CHARGE syndrome (Issekutz *et al.*, 2004 AJMG). The true incidence of CHARGE syndrome reported internationally may therefore be underestimated.

Clinical description

CHARGE syndrome as defined by Pagon *et al* includes the following features.

Coloboma

This feature may be unilateral or bilateral and may affect only the iris or extend to involve the retina. Vision may be normal or impaired. The eye abnormalities range from typical iris coloboma without visual impairment to microphthalmos and anophthalmos; coloboma of the choroid or optic nerve, have been reported. Eye malformations have been reported in as high as 80% of patients with CHARGE syndrome with retinal involvement being more pervasive. Testing for functional vision is important but challenging especially in CHARGE individuals with extensive bilateral chorioretinal coloboma involving the optic nerve. (www.chargesyndrome.ca for a 2004 powerpoint presentation "the Eye in CHARGE").

Heart defect

Congenital heart defects occur in 75-80% of patients with CHARGE syndrome. The commonest major heart defect is [Tetralogy of](#)

[Fallot](#) (33%). Other common anomalies are [patent ductus arteriosus](#), [double outlet right ventricle](#) with atrioventricular canal, [ventricular septal defect](#) and [atrial septal defect](#) with or without cleft mitral valve. Vascular rings and more complex heart defects need to be anticipated (Blake *et al.*, 1988, Lin *et al.*, 1990).

Atresia choanae

Choanal atresia, a narrowing or a blockage of the passages between the nasal cavity and the naso-pharynx, should serve as the primary feature which produces a high index of suspicion and focusses attention on other organ systems such as the eye and heart. Choanal atresia may be membranous or bony; bilateral or unilateral. Bilateral posterior choanal atresia (BPCA) was shown to be associated with increased neonatal mortality especially if associated with major cardiac malformations +/- tracheoesophageal atresia (Blake *et al.*, 1990). However, the Canadian epidemiological study data suggest that this population with a more severe clinical presentation of CHARGE features is surviving (Issekutz *et al.*, 2004 Am J Med Genet. in press). Polyhydramnios in pregnancy is seen in individuals with bilateral posterior choanal atresia.

Chronic middle ear infections and deafness can be associated complications of choanal atresia.

Retardation of growth and development

It usually becomes more obvious as the child matures. At birth, children with CHARGE syndrome usually have normal weights and lengths (Blake *et al.*, 1993). Growth deceleration is hypothesised due to cardiac and respiratory problems, and severe difficulties in feeding (Dobbelstein *et al.*, 2004); occasionally there is growth hormone deficiency. The majority of school-aged children with CHARGE syndrome are below the third percentile of physical growth norms (Blake *et al.*, 1993). Mental retardation is variable with IQs ranging from near normal to profound retardation. Behavioural issues and an autism-like spectrum disorder is becoming more recognized (Smith *et al.*, in press Am J Med Genet. 2004).

The adult population is at risk for obesity (personal communication and observation by Kim Blake) and growth in height can occur in the CHARGE young adults well into their 20's (Searle *et al.*, in press Am J Med Genet. 2004).

Genitourinary problems

The incomplete or under-development of the external genitalia is a common finding in males

and in females – if looked for. Microphallus, penile agenesis, hypospadias, chordee, cryptorchidism, bifid scrotum, atresia of uterus, cervix and vagina, hypoplastic labia and clitoris are the genital anomalies described. Renal anomalies reported are solitary kidney, hydronephrosis, renal hypoplasia and duplex kidneys, vesicoureteral reflux, neurogenic bladder - secondary to spinal dysraphism, nephrolithiasis, and ureteropelvic junction obstruction.

Ear anomalies

Ear abnormalities include a classical finding of unusually shaped ears. Hearing loss, conductive and/or nerve, ranges from mild to severe deafness. Ear anomalies were reported in 80-100% in different series. Facial nerve palsies were noted to be reliable predictors of sensorineural hearing loss. The characteristic abnormality demonstrated by CT scan of the temporal bone are hypoplastic incus and absent semicircular canals. These CT findings are classical in CHARGE syndrome and can aid a diagnosis in a suspected case (Amiel J. *et al.*, 2001).

The major diagnostic criteria for CHARGE syndrome (Blake *et al.* 1998) includes the cranial nerve (CN) anomalies. Cranial nerve dysfunctions include: CN I (anosmia); CN VII (facial palsy); CN IX/X/XI (swallowing problems, reflux, and velopharyngeal aspiration); CN VIII (sensorineural hearing loss) [Lin *et al.*, 1990; Byerly *et al.*, 1993]. Cranial nerve CN V and CN II may also be involved (Lawand *et al.*, 2003).

Management

Children with CHARGE syndrome require intensive medical management as well as numerous surgeries. The most common perinatal emergencies in CHARGE syndrome involve cyanosis due to bilateral posterior choanal atresia and/or congenital heart defects, or the less common presentation of tracheoesophageal fistula. The primary foci of management should be airway stabilization and circulatory support.

All patients suspected of having CHARGE syndrome should have a cardiology consultation. If the infant has restrictive pulmonary blood flow and is dependant on a patent ductus arteriosus, the administration of prostaglandin to maintain ductal patency may be life saving. Some children require tracheostomy to manage chronic airway problems and/or gastroesophageal reflux (GER) and aspiration. Children with CHARGE syndrome require aggressive medical management of their

feeding difficulties, often needing gastrostomy and jejunostomy feeding tubes (Dobbelstein *et al.*, 2004). Gastro-oesophageal fundoplication may be required for GER that does not respond to medical management.

Any infant suspected of having CHARGE syndrome should have a complete eye examination by an ophthalmologist, with follow-up every three to six months thereafter, depending on the eye involvement. Photophobia is often a significant problem that can be ameliorated with tinted spectacles or by wearing a cap or visor with a dark brim. In the presence of facial palsy, patients should avoid corneal scarring by using artificial tears.

Hearing aids should be used as soon as hearing loss is documented. Frequent re-molding of the earpieces is necessary as the ear canals can be initially very small. Cochlear implantations have been successfully performed in CHARGE syndrome patients. Children with CHARGE syndrome who undergo cochlear implantation should be allowed to continue with their sign language in parallel with their expressive speech training (personal report to Kim Blake). Adapted educational and therapeutic services to deal with sensory impairment should be proposed early in the child's life (Blake. and Brown. 1993). However, this population is unique in their cranial nerve aberrant pathways and problems with expressive language.

In terms of endocrine issues, sex steroid therapy has been tried for penile growth and descent of testis in males with CHARGE syndrome. The main use for testosterone is for delayed male puberty in the adolescent decade. Females may also require hormone replacement at puberty (Blake *et al.*, 2004 in press).

Etiology

There is a crucial stage of embryogenesis, when failure to rupture the primitive bucconasal membrane (35th to 38th day) brings about choanal atresia. Conotruncal cardiac defects can result from aberrations in cephalic neural crest cell migration during the 4th and 5th weeks after conception. The cochlear duct begins to develop around the 36th day, and the eyes develop between days 34 and 44 days post-conception, which is also the time during which many cranial nerves are developing. All these malformations in CHARGE syndrome occur early during the first trimester.

Mutations in a chromodomain gene family - *CHD7*

Dr Conny van Ravenswaaij and her team from the Netherlands have identified mutations in a large gene (*CHD7*) responsible for the CHARGE syndrome in over 2/3 of their tested population (Vissers *et al.*, 2004). *CHD7* encodes a novel member of the chromodomain helicase DNA protein family and is an essential gene in early embryonic development affecting multiple organ systems including heart, inner ear and retina.

Techniques, which were used, included array based comparative genomic hybridization. They screened patients with CHARGE association for submicroscopic DNA copy number alterations. Sequence analysis revealed mutations in the *CHD7* gene in 10 of the 17 patients including 7 stop codon mutations. Haploinsufficiency of the gene has been postulated to be the underlying mechanism. There are probably an array of genetic mutations that are responsible for CHARGE syndrome as in other genetic disorders. The CHARGE phenotype may be related to the actual mutations within the *CHD7* gene as may the later onset features and behavior phenotype van Ravenswaaij found that a 26 year old woman with various CHARGE features and normal intelligence tested positive for the *CHD7* mutation. This is in keeping with earlier work by Blake *et al* (1990, 1993) that demonstrated a range of intelligence, including normal intelligence in the CHARGE population.

Diagnostic methods

- Karyotype to confirm the integrity of chromosome numbers 22, 14, and 9.
- *CHD7* gene mutation testing when available on a clinical basis.
- Fluorescent in situ hybridization (FISH) to exclude 22q11 deletion.
- Blood urea nitrogen, creatinine, electrolytes and calcium to evaluate renal function and exclude hypocalcemia (frequent in DiGeorge syndrome). Abdominal ultrasound and *Voiding cystourethrogram* to exclude renal anomalies.
- In cases of hypogonadism, Luteinising Hormone Releasing Hormone (LHRH) and Human Chorionic Gonadotropin (HCG) tests to evaluate the pituitary gonadal axis (needs to be completed in the first 2 months of life).
- Growth hormone (GH) stimulation levels to exclude deficiency of GH as a cause for growth retardation.
- Head CT and/or MRI scans, including the temporal bones to exclude cerebral malformation

and defective formation of the ossicles of the middle ear, cochlear and semicircular canals.

- Frequent feeding studies (depending on the severity of the feeding issues), including combinations of barium swallow, reflux scan, pH, gastric monitoring with a pediatric gastroenterologist and feeding team to diagnose swallowing dysfunction and/or esophageal dysmotility, GER and tracheal aspiration (Dobbelstein *et al.*, 2003).
- Skeletal survey to exclude skeletal anomalies (particularly the cervical spine).
- Echocardiogram to identify and/or exclude congenital cardiac defects.
- Audiometry and auditory brainstem to document the type and severity of conductive and sensorineural hearing loss (often needs repeating, as the child matures different audiological tests can be preformed).
- Visual analysis, and electroretinogram and functional vision testing to identify and document the severity of visual loss (Russell-Eggitt *et al.*, 1990).

Genetic counselling

Most cases of CHARGE syndrome have been sporadic occurrences in an otherwise normal family. In some families there is a clear genetic component with parent to child transmission suggesting autosomal dominant inheritance and recurrences among siblings born to normal parents suggesting possible germ cell line mosaicism.

Statistically, advanced paternal age among sporadic cases of CHARGE syndrome has been reported (Blake *et al.*, 1993; Tellier *et al.*, 1996). The recent gene discovery will impact on genetic counselling and prenatal diagnosis issues.

Antenatal diagnosis

Most of the abnormalities associated with CHARGE syndrome can be difficult to diagnose antenatally through ultrasound unless there is a high index of suspicion with the presence of polyhydramnios. If the *CHD7* mutation is discovered in the index CHARGE individual then reliable prenatal diagnosis will be possible by chorionic villus sampling or amniocentesis.

Unresolved questions

"Will early recognition and treatment of infants with CHARGE syndrome improve their clinical and behavioral well being?"

"Is there a correlation between the different CHARGE features and the different mutations in the *CHD7* gene?"

"Is there a behavioural phenotype correlation with the different *CHD7* mutations?"

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