



## Factsheet 3

# CHARGE syndrome: major and minor medical diagnostic criteria plus later onset features

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### Original diagnostic criteria

The initial association of coloboma and choanal atresia with other congenital abnormalities was first described by Hall and separately Hittner *et al.* in 1979 (Hall, 1979; Hittner *et al.*, 1979). In 1981 there was further description and expansion of the condition (Pagon *et al.*, 1981). It was at this stage that the acronym CHARGE (**C**–coloboma, **H**–heart disease, **A**–atresia choanae, **R**–retarded growth and retarded development and/or CNS anomalies, **G**–genital hypoplasia, and **E**–ear anomalies and/or deafness) was made.

In order to make the diagnosis of CHARGE syndrome, historically four out of six of the features of the acronym needed to be fulfilled, although one should be either choanal atresia or a coloboma (Pagon *et al.*, 1981).

### From association to syndrome

Initially CHARGE was described as an association; a nonrandom collection of birth defects, rather than a syndrome, which is a more recognisable pattern of birth defects (often with a known genetic cause). With the identification of the gene CHD7 in 2004 (Vissers *et al.*, 2004) it has now been renamed a syndrome, as CHD7 is mutated in at least 60% of patients with a clinical diagnosis of CHARGE syndrome.

### Revision of the diagnostic criteria

Whilst the original diagnostic criteria recognised that some features were more specific of CHARGE syndrome, it was also recognised that patients with CHARGE had other features not contained within the initial CHARGE acronym. There have subsequently



been several attempts to refine the diagnostic criteria, namely by Blake *et al.* (1998) and Verloes (2005). Both of these use major features which are very specific for CHARGE syndrome, along with other minor features.

The criteria suggested by Blake *et al.* consist of four major 'C's:

1. Coloboma
2. Choanal atresia
3. Characteristic ear abnormalities
4. Cranial nerve dysfunction

and those by Verloes (2005):

1. Coloboma
2. Choanal atresia
3. Hypoplasia of semicircular canals.



A summary of the various clinical scoring systems are shown below (Sanlaville and Verloes, 2007).

	Major criteria	Minor criteria	Inclusion rule
<b>Pagon</b>	<ol style="list-style-type: none"> <li>1. Choanal atresia</li> <li>2. Ocular coloboma</li> </ol>	<ol style="list-style-type: none"> <li>1. Heart defects of any type</li> <li>2. Retardation (of growth and/or of development)</li> <li>3. Genital anomalies</li> <li>4. Ear anomalies (abnormal pinnae or hearing loss)</li> </ol>	Four criteria out of six, and at least one major
<b>Blake</b>	<ol style="list-style-type: none"> <li>1. Coloboma – of iris, retina, choroid, disc; microphthalmia</li> <li>2. Choanal atresia – unilateral/ bilateral, membranous/bony, stenosis/atresia</li> <li>3. Characteristic ear abnormalities – external ear (lop or cup-shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects</li> <li>4. Cranial nerve dysfunction – facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems</li> </ol>	<ol style="list-style-type: none"> <li>1. Genital hypoplasia – males: micropenis, cryptorchidism; females: hypoplastic labia; both males and females: delayed, incomplete pubertal development</li> <li>2. Developmental delay – delayed motor milestones, language delay, mental retardation</li> <li>3. Cardiovascular malformations – all types, especially conotruncal defects (eg, Tetralogy of Fallot), AV canal defects, and aortic arch anomalies</li> <li>4. Growth deficiencies – short stature, growth hormone deficiency</li> <li>5. Orofacial cleft – cleft lip and/or palate</li> <li>6. Tracheoesophageal-fistula – tracheoesophageal defects of all types</li> <li>7. Characteristic face – sloping forehead, flattened tip of nose</li> </ol>	Four majors OR three majors + three minors
<b>Verloes</b>	<ol style="list-style-type: none"> <li>1. Ocular coloboma</li> <li>2. Choanal atresia</li> <li>3. Hypoplasia of semicircular canals</li> </ol>	<ol style="list-style-type: none"> <li>1. Rhombencephalic dysfunction (brainstem and cranial nerve III to XII anomalies, including sensorineural deafness)</li> <li>2. Hypothalamo-hypophysial dysfunction (including GH and gonadotrophin defects)</li> <li>3. Malformation of the ear (internal or external)</li> <li>4. Malformation of mediastinal organs (heart, esophagus)</li> <li>5. Mental retardation</li> </ol>	<p>Typical CHARGE: three majors OR two majors + two minors</p> <p>Partial CHARGE: two majors + one minor</p> <p>Atypical-CHARGE: two majors but no minors OR one major + two minors</p>



## Later onset features

The CHARGE features opposite are usually congenital, ie., children are born with them, although they may not always be apparent at birth. A number of features are now noted in older patients (Russell-Eggitt *et al.*, 1990; Blake *et al.*, 2005).

These include:

- Curvature of the spine (scoliosis)
- Migraine (including abdominal migraine)
- Epilepsy
- Cataracts
- Retinal detachment
- Delayed/arrested puberty
- Progressive hearing loss.

In addition, a number of behavioural disorders are more commonly described in patients with CHARGE syndrome: obsessive-compulsive disorder (OCD), attention deficit disorder (ADD), Tourette syndrome and autistic spectrum disorder (Sanlaville and Verloes, 2007).

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## GLOSSARY

**Choanal stenosis/atresia:** a narrowing or blockage of the passageway between the nose and the pharynx by tissue.

**Coloboma:** a gap in part of the structures of the eye, caused when a baby's eyes do not develop properly during pregnancy.

**Cranial nerves:** nerves that emerge directly from the brain rather than the spinal cord.

**Cryptorchidism:** undescended testicles.

**Hypoplasia:** underdevelopment or incomplete development.

**Hypothalamo-hypophyseal dysfunction:** dysfunction of the connection between the hypothalamus and the pituitary gland.

**Tetralogy of Fallot:** a congenital heart defect.

**Tracheoesophageal fistula (T-E fistula):** an abnormal connection (fistula) between the oesophagus and the trachea.

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