The medical care of people with CHARGE syndrome

Information and advice for physicians, general practitioners and dentists

General information

CHARGE syndrome is a combination of congenital abnormalities first described in 1981 (Pagon et al). The name refers to the most frequently seen symptoms: **C**oloboma, **H**eart defects, choanal **A**tresia, **R**etarded growth and development, **G**enital hypoplasia, and anomalies of the **E**ar and vestibular system and/or deafness. CHARGE syndrome is highly variable; all of the symptoms can occur in mild or severe forms.

Main features

The most characteristic symptoms are coloboma (incomplete closure of the optic cup), choanal atresia (blockage of the passage between the nasal cavity and the pharynx), and hypoplasia of the semicircular canals in the vestibular system, resulting in vestibular areflexia. Also frequently seen are congenital heart defects; postnatal growth retardation; malformations of the central nervous system; genital hypoplasia; eye defects; deafness; cranial nerve abnormalities; anosmia (no sense of smell); and cleft lip/palate. Since many people with CHARGE syndrome have hearing loss and/or vision loss, CHARGE syndrome is a common diagnosis in the deaf-blind population.

Cause and incidence

A diagnosis of CHARGE syndrome can be made based on either clinical features or DNA testing. In 2004, researchers in Nijmegen discovered the gene for CHARGE: the *CHD7* gene on chromosome 8q12.1. Roughly 90% of patients who meet the clinical criteria (typical CHARGE patients) are found to have a mutation in the *CHD7* gene. In most cases it is a *de novo* mutation with a low risk of recurrence, although familial cases have been described. After a child has been diagnosed, one of the parents is sometimes found to carry the CHD7 mutation. In these cases the recurrence risk is 50%.

Although the exact incidence of CHARGE syndrome is not known, it is estimated to occur in one in every 15,000-17,000 births. In the Netherlands about eight children with CHARGE syndrome are born each year.

Health

In some children with CHARGE syndrome, problems are already apparent shortly after birth as a result of a severe congenital heart defect or bilateral choanal atresia. Many children have severe feeding difficulties and frequent respiratory tract infections. One third of children have a cleft lip/palate. Swallowing problems can occur (because of cranial nerve dysfunction) and there is an increased risk of respiratory complications during operations/anaesthesia. In addition, some children have a severely compromised immune system, mainly due to T-cell dysfunction. Although exact numbers are not known, it is estimated that about a quarter of babies with CHARGE syndrome die in the first few years of life.

Almost all children are faced with frequent health problems and multiple hospital admissions. In early childhood, feeding problems and respiratory infections are particularly frequent. Later on, other problems become prominent (notably hypogonadotropic hypogonadism, scoliosis and behavioural problems).

Clinical features

Pregnancy and childbirth

Pregnancy is usually unremarkable, as is childbirth. The average gestation period is 38 weeks and birth weight is normal.

Development

Development is usually delayed. On average, most children with CHARGE syndrome are able to walk independently before the age of 4, and are toilet trained during the day before the age of 8. The delay in motor development is mainly explained by balance disorders (present in almost 100% of patients). Deafness and poor vision contribute to delays in the development of speech and language. The extent to which children also have mental impairment cannot easily be established. However, it is estimated to occur with a frequency of 75%, ranging from mild to severe.

Growth

There is a postnatal delay in growth, with final adult height usually below the 3rd percentile. Growth hormone deficiency is rarely seen. The majority of both boys and girls do not experience spontaneous puberty because of hypogonadotropic hypogonadism. This is often accompanied by anosmia.

External characteristics

The following features are seen in newborns: hypertelorism, broad nasal bridge and micrognathia. In older children and adults, the face is often square and flat, with facial asymmetry (unilateral facial palsy), abnormal ears (triangular concha with no lobe, or cup-shaped ears). A cleft lip may be present.

A coloboma of the iris is sometimes visible, as well as microphthalmia. The colobomas are often restricted to the retina, meaning they can only be detected with ophthalmoscopy. The palm of the hand has a characteristic transverse line ending in the space between the 2nd and 3rd finger (hockey-stick crease).

Behaviour

Some children with CHARGE syndrome have problematic behaviour in the form of aggression, tantrums, self-harm and autistic-like behaviour, partly due to their sensory deficits. Sleeping problems are frequently seen and the pain threshold is often abnormally high. Because of communication problems, patients with CHARGE syndrome are also not always able to indicate that they feel pain. Teeth grinding is sometimes seen.

Health problems

The percentages mentioned are an indication only

	0-2 years	**2-12 years**	**from 13 years**
Central nervous system	CNS malformations 55-85% Mental impairment 75% Cranial nerve abnormalities 90% (Nerves V, VII, VIII, IX, X)	ditto ditto ditto	ditto ditto ditto
Cardiovascular	Heart defects 65-85%, incl. tetralogy of Fallot, ventricular septal defects (VSD), atrial septal defects (ASD)	ditto	ditto
Endocrine	Growth < 3rd percentile 65%	Growth < 3rd percentile 65%	ditto absence of puberty ♀ 65-70%, ♂ 80-85%
Mouth	Cleft lip/palate 30%	ditto	ditto
Throat	Tracheo-oesophageal fistula Oesophageal atresia 15% Breathing problems 50%		
Urogenital	Abnormal kidney morphology 10-40% Cryptorchidism/micropenis 80%	ditto	ditto

	0-2 years	**2-12 years**	**from 13 years**
Muscles and skeleton	Hip dysplasia 10% Cleft lip/palate 15-35% Limb abnormalities (rare)	ditto ditto Scoliosis 60% ditto	ditto ditto ditto Osteoporosis ditto
Eyes	Coloboma (mainly fundus) 70-85% Microphthalmia 20% Poor vision 50%	ditto ditto ditto Refractive errors Retinal detachment (rare)	ditto ditto ditto ditto ditto
Ear, nose, throat (ENT)	Choanal atresia 35-65% Abnormality of outer ear 95-100% Middle ear infections Deafness 60-90% Hypoplasia of the semicircular canals 100% Anosmia 75-90%	ditto ditto ditto ditto ditto ditto	ditto ditto ditto ditto ditto ditto
Feeding	Feeding problems/Swallowing disorders >70% Nasogastric feeding tube needed 10% Gastro-oesophageal reflux 50%		
Thymus	Immune system disorders (rare)		
Behaviour/psychiatric problems	Self-harm, autistic-like behaviour Obsessive-compulsive behaviour, tics, partly the result of sensory deprivation	ditto	ditto

Follow-up schedule for the medical care of CHARGE patients

Age Frequency		**0-2 years** Once every 3-6 months	**2-12 years** Once every 1-2 years	**from 13 years** Once every 2-4 years
Development (1)		x	x	P
CNS (2)		x	P	P
Growth (Height, Weight)		x	x	X
Heart (3)		x	P	P
Endocrine/puberty (4)		P	P	X
Urogenital (5)		x	P	P
Skeleton:	hip dysplasia	x	P	P
	scoliosis	x	x	x
Eyes:	colobomas (6)	x	P	P
	vision (7)	x	x	x
	retinal detachment	P	P	P
ENT:	choanae	x	P	P
	otitides	x	P	P
	hearing	x	x	x
	vestibular system (8)	x	P	P
Feeding (9)		x	P	P
Gastro-oesophageal reflux		x	P	P
Immune system		P	P	P
Behaviour		x	x	X
Communication problems		x	x	X

x = close observation indicated
P = when problems or symptoms occur

(1) During psychological assessment take account of sensory deficits.
(2) Consider CT/MRI; in general few therapeutic implications.
(3) A cardiac ultrasound should be performed at least once.
(4) Growth hormone deficiency (rare); pubertal induction in case of hypogonadotropic hypogonadism (nearly always present in case of anosmia).
(5) In case of cryptorchidism: renal ultrasound to detect congenital renal anomalies.
(6) Consultation with eye specialist for ophthalmoscopy.
(7) Including refraction measurement.
(8) Consider CT scan of petrous bone.
(9) Be aware of gastro-oesophageal reflux disease

More information

- Pagon RA, Graham JM, Jr., Zonana J, Yong SL: Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association. *J Pediatr* 1981; 99: 223-227.
- Jongmans MC, Admiraal RJ, van der Donk KP *et al:* CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene. *J Med Genet* 2006; 43: 306-314.
- CHARGE Association in *Preventive Health Care for Children with Genetic Conditions* by Wilson GN and Cooley WC. Cambridge University Press, 2006
- Association of VG networks for parents of children with a rare syndrome accompanied by intellectual disability or learning difficulties (in Dutch): www.vgnetwerken.nl
- CHARGE syndrome parent network (in Dutch): www.chargesyndroom.nl
- Netherlands Society of Physicians for Persons with Intellectual Disabilities (NVAVG, in Dutch): www.nvavg.nl
- Network for people with disabilities or chronic diseases (previously Platform VG): www.iederin.nl
- National multidisciplinary CHARGE clinic of the University Medical Centre Groningen in Dutch: http://www.charge.umcg.nl

Additional information to the English version

- International CHARGE Foundation: www.chargesyndrome.org
- Information on CHARGE outpatient clinic and research projects on CHARGE syndrome in English: http://www.rug.nl/research/genetics/research/chargesyndrome/
- Bergman JE, Janssen N, Hoefsloot LH, Jongmans MC, Hofstra RM, van Ravenswaaij-Arts CM: CHD7 mutations and CHARGE syndrome: the clinical implications of an expanding phenotype. *J Med Genet* 2011; 48: 334-342.
- Bergman JE, Bocca G, Hoefsloot LH, Meiners LC, van Ravenswaaij-Arts CM: Anosmia Predicts Hypogonadotropic Hypogonadism in CHARGE Syndrome. *J Pediatr* 2011; 158: 474-479.