



# CHARGE association/syndrome

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## Background

CHARGE association/syndrome (CAS) was first described by Hall<sup>1</sup> in 1979 in children with multiple congenital anomalies who were ascertained because of choanal atresia. Pagon<sup>2</sup> first coined the acronym CHARGE (Coloboma, Heart Defect, Choanal Atresia, Retarded Growth and Development, Genital Hypoplasia, Ear Anomalies/Deafness). The acronym was intended to emphasize that this clustering of associated malformations occurs more frequently together than one would expect on the basis of chance. 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 discrete recognizable syndrome. With increased expertise, it became clear that the criteria originally proposed by Pagon needed further refinement. The revised consensus diagnostic criteria by Blake et al,<sup>3</sup> incorporating both major and minor features for CAS, have been documented to enhance clinical diagnosis and facilitate research efforts.

The incidence of CAS is probably under-reported at 1/100,000 live births. In the Maritimes over the past three years, there have been six neonatal diagnoses of CAS, with five survivors to date. This would suggest an incidence of 1/9,000. At Cedars-Sinai Medical Center in Los Angeles, with approximately 8,000 deliveries per year, at least two new CAS cases are diagnosed each year, attesting to the frequency of this disorder. In many instances, diagnosis of this condition has been hindered by inconsistency in diagnostic criteria or has been delayed, as major features of this

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disorder may not be readily identifiable, particularly in infants. Recently, a group of geneticists and developmental paediatricians refined the diagnostic criteria of CAS in order to define a concise recognizable syndrome.<sup>3</sup> The review article, entitled “CHARGE Association: An Update and Review for the Primary Pediatrician,” also summarizes our current understanding of the management of this complex and chronic multiple congenital anomaly, thereby giving physicians a guide to the management of CAS.

To date, no predictive factors regarding the developmental prognosis of CAS infants have been identified. Because of their multiple complex medical/surgical issues, many initial care providers overestimate the severity of developmental disability in the absence of reliable data. Only by careful, prospective follow-up of a population of CAS infants that have been ascertained through the CPSP can their developmental profile be defined and compared to the reported literature. The increase in paternal age of CAS children has been recognized and needs to be further established, as does the concern with pesticides as teratogens.

### **Methods**

**Case ascertainment and reporting:** Paediatricians and specialists who report cases through the CPSP monthly survey will receive a summary protocol, including the surveillance case definition (see below), and will be asked to complete detailed reporting forms for all identified cases.

### **Objectives**

1. To determine the incidence and prevalence of CAS in Canada by ascertaining all newly diagnosed cases of CAS.
2. To obtain demographic and medical information on patients with CAS and assemble into a database in order to answer such research questions as: Do certain CAS features predict mortality and morbidity? Is paternal age increased compared to the general population? Do renal anomalies occur more frequently in CAS than has been documented in the literature?
3. To follow developmentally and behaviourally an identified group of CAS infants who were diagnosed at an early age and have obtained early intervention services (according to the revised diagnostic criteria).<sup>3</sup>

### **Case definition**

- Infant/child/adult with **all four major criteria**.
- Infant/child/adult with **three major and three minor criteria**.
- **Previously diagnosed** child with CAS that does not fit major or minor criteria, but has a combination of the above plus some occasional findings; renal, hand, spine/limb, abdominal (hernia) anomalies.

**CHARGE association/syndrome (continued)****Major inclusion criteria**

1. Coloboma – of iris, retina, choroid, disc; microphthalmia
2. Choanal atresia – unilateral/bilateral, membranous/bony, stenosis/atresia
3. Characteristic ear abnormalities – external ear (lop or cup-shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects
4. Cranial nerve dysfunction – facial palsy (unilateral or bilateral), sensorineural deafness and/or swallowing problems

**Minor inclusion criteria**

1. Genital hypoplasia – males: micropenis, cryptorchidism; females: hypoplastic labia; both males and females: delayed, incomplete pubertal development
2. Developmental delay – delayed motor milestones, language delay, mental retardation
3. Cardiovascular malformations – all types, especially conotruncal defects (e.g., tetralogy of Fallot), AV canal defects, and aortic arch anomalies
4. Growth deficiencies – short stature, growth hormone deficiency
5. Orofacial cleft – cleft lip and/or palate
6. Tracheoesophageal-fistula – tracheoesophageal defects of all types
7. Characteristic face – sloping forehead, flattened tip of nose

**Exclusion criteria**

Exclude other conditions such as velocardiofacial syndrome (VCS) and DiGeorge Sequence (DGS) using FISH test (fluorescent *in situ* hybridization) to exclude 22q 11 deletion.

**Duration**

September 2001 to August 2004

**Expected numbers of cases**

Based on the annual birth rate in Canada of 400,000, and on the current estimates of incidence of CAS 1/9,000 (Maritime data), the expected number of new cases is 30 to 35 per year.

**Ethical approval**

Research Ethics Board, IWK Health Centre



### **Funding**

IWK Health Centre  
CHARGE Foundation, USA

### **Date for analysis and publication**

- Data will be analyzed by the investigators and annual reports (along with quarterly updates) will be distributed to the CPSP participants.
- Data will be abstracted for Canadian conferences and international meetings.
- Papers will be published in peer-reviewed journals.

### **References**

1. Hall B. Choanal atresia and associated multiple anomalies. *J Pediatr* 1979; 95(3): 395-8.
2. 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(2): 223-7.
3. Blake K, Davenport SH, Hall BD, Hefner MA, Pagon R, Williams MS, Lin AE, Graham JM Jr. CHARGE association – An update and review for the primary pediatrician. *Clin Pediatr* 1998; 37: 159-74.

More references are available from the investigators or the CPSP office.

### **CHARGE parents (for families of CHARGERS in Canada)**

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