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CHARGE association/syndrome: Looking ahead

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Background

CHARGE association/syndrome (A/S) has emerged as one of the most common causes of deaf-blindness in children. The diagnosis of CHARGE A/S is based on the clinical assessment of distinguishing features (Table 1). It is a complex and difficult condition to manage, often presenting with physical anomalies at birth (choanal atresia, cyanotic heart disease, tracheo-esophageal fistula), which require corrective surgery. Twenty years ago, many patients did not live past infancy; however, today, with advances in technology and treatment, more children are reaching late childhood and adolescence. This increase in life expectancy has afforded researchers a better understanding of the medical, behavioural, and developmental issues associated with CHARGE A/S. As a consequence, many of these issues can be more easily managed, and some even prevented, with early intervention and careful long-term follow-up. Data from the first six months of the Canadian Paediatric Surveillance Program (CPSP) has enabled a more accurate estimation of the Canadian incidence of CHARGE A/S, which is thought to be closer to 8/100,000, based on data from the Atlantic region.

Management and long-term follow-up

The treating physician should coordinate a multidisciplinary team of paediatric subspecialists and paramedical experts to address all aspects of care for the patient with CHARGE A/S.

Developmental delay

Early signs of developmental delay are not determinants of poor outcome or mental retardation. The deaf-blind child with CHARGE A/S should receive education appropriate for dual-sensory impairment within the first few months of life, allowing the child to benefit from experts in audiology, speech therapy, otorhinolaryngology and ophthalmology. Auditory brainstem evoked potentials are recommended before discharge from the neonatal unit.

Growth deficiency/delayed puberty

Growth deficiency begins shortly after birth, and may be due to illness, hospitalization, and/or feeding difficulties, with little catch-up over time. Consequently, adolescents with CHARGE A/S are in the lower percentiles on growth charts.

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Endocrine problems resulting from delayed or incomplete puberty include irregular menses, the absence of secondary sexual characteristics and an increased risk for osteoporosis. Consequences are psychological as well as medical.

A low serum LH/FSH in the first few months of life indicates a defect in the hypothalamic-pituitary-gonadal axis (causing hypogonadotrophic hypogonadism). If not already tested at infancy, a child should be tested at 13-14 years of age or before the onset of puberty, since a random LH/FSH measurement is unreliable in children between infancy and puberty.

Feeding difficulties

Feeding difficulties are commonly severe and are likely caused by multiple cranial nerve anomalies. Dysfunction of cranial nerves IX and X causes velopharyngeal/ laryngeal incoordination resulting in serious difficulties in swallowing. Anosmia and ageusia may be the result of the dysfunction of cranial nerves I and VII, respectively.

Many children require gastrostomy/jejeunostomy feeding and may find the transition to oral feeding difficult. A team of specialists, including a dietician, a gastro-enterologist, an occupational therapist and a speech language pathologist, will help overcome these feeding difficulties.

Scoliosis

Scoliosis occurs in CHARGE A/S individuals, but is underreported. Because scoliosis tends to progress during accelerated growth, the patient should be monitored closely during periods of growth spurts and growth hormone supplementation. Expertise from a physiotherapist and an orthopedist are valuable in the management of this condition.

Ophthalmological problems

Retinal detachment can be a consequence of chorioretinal (posterior) colobomata and can be provoked by trauma such as eye-poking. A patient with photophobia can use tinted glasses and a brimmed hat to alleviate sensitivity to light.

Neurological problems

Late-onset seizures and migraines have been reported in CHARGE adolescents. Neurological problems may also present in unusual ways, such as behavioural outbursts. A thorough neurology assessment, including radiological imaging (CT/MRI), may rule out other causes.

Behavioural profile

Many older CHARGE A/S patients exhibit specific behaviours such as: difficulty in initiating activities, social detachment, aggression and behavioural outbursts, self-abuse, sleeping difficulties, poor self-esteem regarding facial appearance, and tactile defensiveness.

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Psychological/co-morbid issues

Other common diagnoses in CHARGE individuals include obsessive-compulsive disorder, pervasive developmental disorder, attention deficit disorder and hyperactivity, depression, and anxiety. Psychological/psychiatric evaluations, educational specialists' expertise and judicious pharmacotherapy are often essential for successful management of one or more co-morbid diagnoses.

Table 1: Diagnostic features of CHARGE A/S with late-onset sequelae

Features of CHARGE A/S	Later childhood / adolescent issues
***Major* "4 C's"**	
Ocular coloboma	Photophobia; retinal detachment
Choanal atresia/stenosis	Facial growth problems, unilateral nasal discharge
Cranial nerve anomalies	Feeding/swallowing problems; hearing loss; facial palsy (appearance)
Characteristic ear anomalies	Progressive hearing loss; chronic middle ear infections; vestibular problems affecting balance / motor skills.
Minor	
Cardiovascular malformations	Arrhythmias; angina
Genital hypoplasia	Pubertal delay, hormone replacement; fertility (unknown)
Cleft lip/palate	Cosmetic concerns; self-image
Tracheo-esophageal fistula	Reflux esophagitis; feeding/swallowing problems
Distinctive CHARGE faces	Cosmetic concerns; self-image
Growth deficiency	Growth hormone replacement
Developmental delay	Educational, behavioural, social adjustment
Occasional	
Renal anomalies	Renal failure
Spinal anomalies	Scoliosis
Hand anomalies	Fine motor problems; cosmetic concern
Neck/shoulder anomalies	Self-image concern

* 4 major or 3 major and 3 minor features confirms diagnosis of CHARGE (Blake et al, 1998).

Velocardiofacial syndrome (VCFS) and **DiGeorge anomaly/sequence** (DGS) should be ruled out, using the FISH (fluorescent *in situ* hybridization) studies for 22q11 deletion. Clinical presentation of DGS includes thymic hypoplasia, hypocalcemia, and cono-truncal heart defects, whereas in VCFS, typical facial dysmorphic features and cleft palate are seen more commonly. These clinical features can overlap.

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Test your knowledge

1. All of the following statements are true, *except*:

a) The incidence of CHARGE across Canada ranges from 3/100,000 to 8/100,000.
b) CHARGE is now one of the most common causes of deaf-blindness.
c) There is no known genetic marker for CHARGE.
d) Endocrine dysfunction in CHARGE often results in micropenis in males, minor labial anomalies in females, and absence of secondary sex characteristics in both sexes.
e) The major criteria for CHARGE include: choanal atresia, ocular coloboma, cranial nerve defects, and characteristic ear anomalies.
f) Feeding problems in children with CHARGE are most often a result of tracheo-esophageal fistula and, thus, can usually be resolved early in life with surgery.

2. A child with ocular coloboma, choanal atresia, and characteristic ear anomalies, in addition to three of the minor criteria for CHARGE would:

a) Unquestionably have CHARGE.
b) *Not* have CHARGE.
c) Not likely have CHARGE.
d) Most likely have CHARGE, pending FISH test for 22q11 deletion.

3. (A) CHARGE adolescent issue(s) secondary to a cranial nerve anomaly would be:

a) Sensorineural hearing loss.
b) Continued feeding difficulty.
c) Psychosocial issues related to general appearance (e.g., facial palsy).
d) No sense of smell.
e) All of the above.

4. Hypogonadotrophic hypogonadotropism and, hence, high probability of delayed puberty in CHARGE children can be indicated by serum LH/FSH:

a) In the first 2-3 months of life.
b) Between the ages of about 5-12.
c) After about age 13-14 (pubertal age).
d) a) and c).
e) a) and b).

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5. Behavioural or psychological issues present in CHARGE adolescents may result from:

a) Frustration due to inability to communicate.
b) Pain or discomfort associated with an underlying medical problem.
c) Pyschosocial maladaptation related to general physical appearance and self-image.
d) A diagnosis of attention deficit disorder with hyperactivity (ADDH).
e) All of the above.

6. Adolescents with CHARGE A/S, when compared to the general adolescent population, are more likely to demonstrate all of the following, *except*:

a) Scoliosis
b) ADDH
c) Migraine
d) Seizures
e) Abdominal colic
f) Schizophrenia
g) Delayed puberty
h) Depression
i) Osteoporosis

7. All of the pictures below are individuals with CHARGE A/S; spot the similarities.

Answers:

1-f, 2-d, 3-e, 4-d, 5-e, 6-f
7- The distinctive CHARGE face consists of a broad forehead with facial asymmetry and full nasal tip. External ear is lop/cup shape (triangular concha, antihelix extends to the rim) but can vary significantly between the two sides. Iris colobома and webbed neck with sloping shoulders are also prevalent.