ORIGINAL ARTICLE

AMERICAN JOURNAL OF medical genetics PART A

Developing a CHARGE Syndrome Checklist: Health Supervision Across the Lifespan (From Head to Toe)

Carrie-Lee Trider,[1] Angela Arra-Robar,[2] Conny van Ravenswaaij-Arts,[3] and Kim Blake[2]*

[1]Department of Pediatrics, Kingston General Hospital, Queen's University, Ontario, Canada

[2]Department of Pediatrics, IWK Health Center, Dalhousie University, Nova Scotia, Canada

[3]Department of Genetics, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

Manuscript Received: 1 August 2016; Manuscript Accepted: 21 November 2016

Health supervision and management considerations for individuals with CHARGE syndrome are often complex, and a comprehensive approach is essential. The Atlantic Canadian CHARGE syndrome team developed a checklist organized by body system and age to aid healthcare providers in their approach to the ongoing care of these individuals. The checklist was evaluated qualitatively using a modified Delphi method with widespread consultation from expert healthcare practitioners, parents, and individuals with CHARGE syndrome. These are the first comprehensive guidelines across the lifespan of CHARGE syndrome that suggest a consistent approach to medical surveillance, investigations, and management for the physician and the multi-disciplinary team caring for these individuals. We anticipate that these guidelines will provide improvements in care by preventing missed diagnoses, allowing for anticipatory counseling, and facilitating early referral for interventions and treatments.

Key words: CHARGE syndrome; checklist; guidelines; health supervision; management

How to Cite this Article:
Trider C-L, Arra-Robar A, van Ravenswaaij-Arts C, Blake K. 2017. Developing a CHARGE syndrome checklist: Health supervision across the lifespan (from head to toe).
Am J Med Genet Part A 173A:684–691.

INTRODUCTION

CHARGE syndrome (OMIM#214800) is an autosomal dominant disorder that leads to variable multiple congenital anomalies and is estimated to occur in 1 in 10,000 to 1 in 15,000 live births [Issekutz et al., 2005; Janssen et al., 2012; OMIM, 2016]. The acronym CHARGE stands for the association of Coloboma, heart defect, atresia choanae, retarded growth and development, genital hypoplasia, and ear anomalies/deafness. The clinical criteria for CHARGE syndrome were initially proposed by Blake et al. in 1998 and modified by Verloes in 2005, as compared in Table I [Blake et al., 1998; Verloes, 2005]. Blake et al. criteria required a patient to have four major characteristics or three major and three minor characteristics, to be diagnosed with CHARGE syndrome. Verloes criteria required typical CHARGE syndrome to be diagnosed by three major signs or two major signs and two minor signs. Recently, it has been suggested that the diagnosis should involve a molecular component in order to capture those individuals with milder features [Hale et al., 2015].

The CHARGE syndrome phenotype can occur as a result of a heterozygous loss of function mutation of *CHD7* on chromosome 8 (8q12) [Vissers et al., 2004; Janssen et al., 2012]. *CHD7* is a member of the chromodomain helicase DNA-binding (*CHD*) protein family, which regulates transcription by chromatin remodeling [Janssen et al., 2012]. *CHD7* has been demonstrated to regulate genes involved in neural crest cell migration, as well as interactions with other cells during embryogenesis [Schulz et al., 2014]. *CHD7* analysis detects mutations in more then 90% of patients with clinical CHARGE syndrome [Bergman et al., 2011]. *CHD7* mutations can also be responsible for those individuals with hypogonadotropic hypogonadism with or without anosmia [Jongmans et al., 2009]. Of those individuals who have the *CHD7* mutation and a mild clinical CHARGE syndrome phenotype, 14–17% of them would not meet Blake et al. or Verloes et al. clinical criteria for diagnosis [Bergman et al., 2011b]. There is no consensus on genetic testing in the presence of a clear clinical diagnosis. However, genetic

Conflict of interest: None.

*Correspondence to:
Kim Blake, IWK Health Centre, 5850/5980 University Avenue, PO Box 9700, Halifax, NS, Canada B3K 6R8.
E-mail: kblake@dal.ca

Article first published online in Wiley Online Library (wileyonlinelibrary.com): 4 February 2017
DOI 10.1002/ajmg.a.38085

TABLE I. Comparing Blake et al. (4 Major or 3 Major and 3 Minor) and Verloes et al. Clinical Criteria (3 Major or 2 Major and 2 Minor) for Diagnosis of Typical CHARGE Syndrome

Blake criteria[3]	Frequency[5]	Verloes criteria[4]
Major criterion		
Coloboma of iris, retina, choroid, disc, or microphthalmia	80–90%	Coloboma (iris or choroid, with or without microphthalmia)
Choanal atresia or stenosis	50–60%	Atresia of choanae
Characteristic ear abnormalities	80–100%	Hypoplastic semi-circular canals
Cranial nerve dysfunction		
I: hyposmia	Frequent	
VII: facial palsy (unilateral or bilateral)	>40%	
VIII: hypoplasia of auditory nerve	Frequent	
IX/X: swallowing problems with aspiration	70–90%	
Minor criterion		
Genital hypoplasia		
Micropenis, cryptorchidism, hypoplastic labia	50–60%	
Delayed puberty secondary to hypogonadotropic hypogonadism	65–75% F 80–85% M	
Developmental delay	100%	
Cardiovascular malformations	75–85%	
Growth deficiency	65%	
Orofacial cleft	15–20%	
Tracheoesophageal-fistula	15–20%	
Distinctive face		
Square face with broad prominent forehead, prominent nasal bridge, flat midface	70–80%	
		Rhombencephalic dysfunction (brainstem dysfunctions, cranial nerve VII to XII palsies, and neurosensory deafness)
		Hypothalamo-hypophyseal dysfunction (including GH and gonadotrophin deficiencies)
		Abnormal middle or external ear
		Malformation of mediastinal organs (heart, esophagus)
		Intellectual disability

F, female; M, male.

testing is recommended in all suspected cases of CHARGE syndrome and especially for patients who partially meet the clinical criteria [Bergman et al., 2011b; Hale et al., 2015].

Patients with CHARGE syndrome experience a wide spectrum of medical, physical, and psychological issues. Thus, a multidisciplinary healthcare team is usually involved in their care, often beginning at birth. Guided approaches to health supervision have been developed for many other complex syndromes, but no comprehensive guidelines have been published for CHARGE syndrome. We aimed to develop and pilot a user-friendly checklist for CHARGE syndrome that reminded the physician and the multidisciplinary healthcare team what common and/or critical issues to consider at different ages across the lifespan. We planned for the checklist to be accompanied by suggestions for resources for families and healthcare providers.

METHODS

The CHARGE Syndrome Checklist was developed in three phases. First, the findings of a literature review and the expert opinions of the multi-disciplinary team from the Atlantic Canadian CHARGE syndrome clinic at a large pediatric tertiary care center were integrated. The multi-disciplinary team included a pediatrician with an extensive clinical and research background in CHARGE syndrome spanning 30 years. Second, the authors used the proposed recommendations to develop the checklist. Third, the checklist was evaluated qualitatively by a diverse international group of participants using a modified Delphi method [Dalkey, 1969; Jones and Hunter, 1995]. Participants were provided with drafts of the checklist and were asked to indicate any items they felt should be added, removed, or changed. Participants included pediatricians, experts in all fields present at the 2015 International CHARGE Syndrome Conference, parents of children with CHARGE syndrome, and individuals with CHARGE syndrome. The expert participants from the 2015 International CHARGE Syndrome Conference included deaf–blind specialists, teachers, occupational therapists, physiotherapists, speech language therapists, neurologists, psychiatrists, geneticists, endocrinologists, and general pediatricians. There was international representation from Canada, Denmark, France, Germany, the Netherlands, Mexico, the

United Kingdom, and the United States. The revised checklist was piloted in the Atlantic Canadian CHARGE syndrome clinic. A member of the National Multidisciplinary CHARGE Syndrome Clinic in the Netherlands then edited it. The finalized checklist was the result of three rounds of modifications by expert groups, with the additional participants' feedback incorporated throughout the process, as not all participants provided feedback at all rounds of modification. Supporting documentation was developed and organized in a bullet format, divided by age groups of infancy, childhood, adolescent, and adult. This document was informed by the literature of the authors and professionals that attended the 2015 International CHARGE syndrome conference.

RESULTS

There were 97 participants who provided feedback on the checklist. This resulted in a 49-item list organized into the body systems of neurology; eyes, ears, nose, and throat; cardiology and respirology, gastroenterology and genitourinary, endocrinology, allergy and immunology, genetics, musculoskeletal, psychology, and developmental. The checklist was further divided by life stages: infancy, childhood, adolescence, and adulthood. The checklist was intended to be a one-page double-sided document. The front side of the document includes the checklist, and the back side includes explanations of abbreviations used, example resources for the healthcare team and parents, as well as references. Please see Figure 1 to view the checklist.

The checklist was piloted throughout the editing process in seven multi-disciplinary CHARGE syndrome clinics led by a general pediatrician and a clinic nurse specialist at a large pediatric tertiary care center. A senior medical student without prior knowledge of CHARGE syndrome was also observed using the checklist. Any concerns were improved upon in the subsequent revisions.

DISCUSSION

Providing medical supervision and longitudinal care to an individual with CHARGE syndrome can be complex, and a structured comprehensive approach is helpful. In the CHARGE syndrome checklist, we have chosen to emphasize important issues that a physician needs to address during office visits. The CHARGE syndrome checklist is divided by stages across the lifespan: infant, childhood, adolescence, and adulthood. Each of these stages is discussed below in bullet point format as an accompaniment to the checklist. We have included information for a prenatal visit for the education of the general physician, although typically a clinical geneticist would counsel parents. Rare health issues that are commonly missed and can lead to adverse health consequences are also included. Supporting references are supplied to assist the physician in their care of individuals with CHARGE syndrome.

Diagnosis

Please see Blake et al. or Verloes criteria for clinical diagnostic guidelines [Blake et al., 1998; Verloes, 2005]. A guideline for a genetic diagnosis by *CHD7* analysis was provided by Bergman et al. [2011b]. Hale et al. [2015] recently proposed diagnostic criteria including a molecular component.

The phenotype for CHARGE syndrome is varied and many atypical features have been reported that are not captured in the classical diagnostic criteria. Hale et al. summarizes the literature for atypical phenotypes of the CHD7 gene [Hale et al., 2015]. Zentner et al. [2010] summarizes the literature by organ system for both CHD7 mutation positive and negative CHARGE syndrome phenotypes including atypical phenotypes.

General reviews of CHARGE syndrome have been written by Blake et al. and Hsu et al. [Blake and Prasad, 2006; Hsu et al., 2014].

The Prenatal Visit

Most cases of CHARGE syndrome are sporadic; however, there are reports of familial CHARGE syndrome with documented cases showing wide variability in phenotypes within the family [Jongmans et al., 2008]. Therefore, families should be offered genetic counseling. If the *CHD7* mutation occurred as a new mutation in the first child, the recurrence rate for siblings is estimated at 2–3%, which is explained by somatic and germline mosaicism [Jongmans et al., 2008]. Prenatal diagnosis is possible by chorionic villus sampling or amniocentesis [Blake and Prasad, 2006].

Health Supervision From Birth to 2 years: Infancy

Important issues.

- A physical exam looking for major and minor clinical criteria of CHARGE syndrome should be performed. Length, weight, and head circumference should be monitored. Birth growth parameters are usually normal; however, failure to thrive often develops due to challenges with oral intake [Blake et al., 1993]. Data collection is ongoing to establish up to date growth charts for CHARGE syndrome (www.chargesyndrome.org).
- The hips should be examined for dysplasia.
- The nasal passages should be checked for patency. Bilateral posterior choanal atresia is diagnosed at birth. However, unilateral choanal atresia and choanal stenosis can be missed.
- A dilated eye exam is necessary to check for retinal coloboma. Lubricating eye drops should be considered as protective ophthalmic care for those individuals who are unable to completely close their eyes from facial nerve palsies.
- All infants require an echocardiogram and chest x-ray. Cardiac malformations occur in 75–85%, with conotruncal defects and atrioventricular septal defects being the most common [Lalani et al., 1993]. Arch vessel abnormalities can occur on their own or in combination with other defects [Corsten-Janssen et al., 2013a]. Suspicion of a vascular ring should prompt investigation by a barium swallow study as this diagnosis can be missed or delayed. If cardiac surgery is performed, presence, absence, or removal of the thymus should be reported.
- Procedures requiring anesthesia should be combined when possible, as there is a greater risk of anesthesia complications

CHARGE Syndrome Checklist: Health Supervision Across The Lifespan (From Head To Toe)

*Shaded boxes indicate key assessment points

		INFANCY (0-2 years)	CHILDHOOD (3-11 years)	ADOLESCENCE (12-17 years)	ADULTHOOD (18+ years)
Genetics	Clinical diagnosis (Blake et al. or Verloes or Hale et al. criteria)	■	■		
	Genetic testing – Genetics consult (CHD7 analysis, array CGH)	■	■		
	Genetic counselling	■			■
Neurology	CNS malformations/hypoplasia olfactory bulb/temporal bone (semi-circular canal) malformations – requires MRI/CT	■			
	Seizures – more common at older ages – consider EEG	■	■	■	■
	Cranial nerve problems – monitor for absent sense of smell, facial nerve palsy, sensorineural hearing loss, vertigo, swallowing problems	■	■	■	■
Eyes, Ears, Nose and Throat	Coloboma, risk of retinal detachment - Ophthalmology consult (dilated eye exam in infancy, vision assessments)	■	■	■	■
	Corneal exposure – lubricating eye drops	■	■	■	■
	Photophobia – tinted glasses, sunhat		■	■	■
	Choanal atresia/cleft palate/tracheoesophageal fistula - ENT/Plastics consult	■	■		
	Audiometry and tympanometry, monitor for recurrent ear infections	■	■		
	Adaptive services for individuals with deafness/blindness	■	■	■	■
	Cochlear implant assessment if applicable		■		
	Obstructive sleep apnea – monitor for tonsil/adenoid hypertrophy	■	■		
	Excessive secretions – consider Botox, medication	■	■	■	■
	Dental issues – consider cleaning under anaesthetic		■	■	
Cardiology Respirology	Cardiac malformations common – major/minor defects, vascular ring or arrhythmias possible (echocardiogram, chest x-ray, ECG) - Cardiology consult	■	■	■	■
	Sinusitis, pneumonia, asthma - monitor	■	■	■	■
	Anesthesia risk (difficult intubations/post-op airway obstruction/aspiration) – extensive pre-operative assessment, combine surgical procedures	■	■	■	■
Gastroenterology Genitourinary	Gastroesophageal reflux – Gastroenterology consult – consider motility agents with proton pump inhibitor	■	■	■	■
	Poor suck/chew/swallow - feeding team assessment/intervention	■	■	■	■
	Aspiration risk, tracheoesophageal fistula – swallowing studies	■	■	■	■
	May need supplemental feeds – frequently requires gastrostomy tube or gastrojejunostomy tube	■	■	■	■
	Constipation – consider Senna glycoside with polyethylene glycol	■	■	■	■
	Renal anomalies – abdominal u/s +/- VCUG, blood pressure monitoring	■	■		
Endocrinology	Hypogonadotropic hypogonadism – LH, FSH by 3 months	■			
	Genital hypoplasia (if undescended testes - consider orchidoplexy)	■	■		
	Delayed puberty – Endocrinology consult - gonadotropin levels, HRT		■	■	■
	Osteoporosis – DEXA scan		■	■	■
	Poor growth – Endocrinology consult – GH stimulation test, GH therapy	■	■	■	■
	Obesity - monitor			■	■
	Fertility and contraception - discuss			■	■
Immune System	Note presence of thymus at open heart surgery	■			
	Routine immunizations/antibody titres to immunizations in adolescence	■	■	■	
	Recurrent infections – Immunology consult		■	■	
MSK	Scoliosis/kyphosis- monitor		■	■	■
	Mobility (affected by ataxia, hypotonia) - evaluate		■	■	■
Psychology Developmental	Assess gross and fine motor skills – Occupational Therapy, Physiotherapy	■	■	■	■
	Communication, language, writing abilities – Speech Language Therapy	■	■	■	■
	Consider deaf-blind consultant	■	■	■	■
	Prepare for transitions to school, situations, places, systems		■	■	■
	Psychoeducational assessment, Individualized Education Plan		■	■	
	Sleep disturbances – consider melatonin		■	■	■
	Behavior management – self-regulation, impulse control, anxiety, obsessions, compulsions, anger		■	■	■
	Toileting skills - support		■	■	■
	Life skills/adaptive behaviour/social skills/social play		■	■	■
	Address sexuality			■	■
	Family stress – offer supports and resources	■	■	■	■
	Medical self-management – work on managing medications, understanding conditions, seeing healthcare provider independently			■	■

FIG. 1. CHARGE syndrome checklist organized by body system and age. Shaded boxes indicate key assessment points for clinic visits within that age group. [Color figure can be viewed at wileyonlinelibrary.com].

in the CHARGE syndrome population. Detailed references, a summary, and suggestions regarding anesthesia use are provided in The CHARGE Information Pack for Practitioners [Trider and Blake, 2013].

- Swallowing studies, feeding team assessments, and interventions including supplemental feeds by gastrostomy or gastrojejunostomy tubes may be necessary. Symptoms of reflux need to be treated [Dobbelsteyn et al., 2005, 2008]. There are often early feeding difficulties due to craniofacial abnormalities as well as weak chewing, sucking, and swallowing related to problems with cranial nerves [Blake et al., 2008].
- An abdominal ultrasound should be completed to look for renal anomalies including solitary kidneys, duplex kidneys, and renal hypoplasia [Blake and Prasad, 2006].
- Screening of gonadotropins should be performed by 3 months of age when there is a peak in FSH, LH, and sex steroids [Bergman et al., 2011b]. Hypogonadotropic hypogonadism can be missed, especially in girls without external hypoplastic genitalia. Diagnosis is not possible during childhood due to physiologically low levels of FSH, LH, and sex steroids. Anosmia has been shown to predict hypogonadotropic hypogonadism [Bergman et al., 2011a]. Diagnosis of hypogonadotropic hypogonadism during infancy can prevent a delay in inducing puberty with hormone replacement therapy later in life. Cryptorchidism should be checked for and treated according to general surgical guidelines.
- A complete blood count, differential and extended electrolyte panel should be completed, as lymphopenia and hypocalcemia have been reported [Hsu et al., 2015]. The overlap in phenotype of 22q11.2 deletion syndromes and CHARGE syndrome has led to ongoing research into the immune function of these individuals [Corsten-Janssen et al., 2013b; Wong et al., 2015b].

Anticipatory guidance.

- Otoacoustic emissions and automated auditory brainstem response hearing tests should be arranged so that a cochlear implant assessment can be completed early in childhood if it is required. Hearing impaired individuals should have bilingual early intervention with sign language and verbal language for best language outcomes [Birman et al., 2015].
- When imaging is performed, it is important to take appropriate views to avoid repeat scans and sedation. Consider performing imaging to look for CNS malformations, hypoplasia of the olfactory bulb and hypoplasia of the semicircular canals [Verloes, 2005; Hsu et al., 2014]. A temporal bone CT scan to look for middle ear landmarks and MRI parasagittal scanning to look for hypoplasia of the auditory nerve should be performed prior to surgery for cochlear implants [Birman et al., 2015].
- Families often experience significant stress in relation to the birth of a medically complex child. Appropriate community or hospital-based resources and supports should be offered specific to the needs of the family. For example, connection could be made with the CHARGE Syndrome Foundation, website and social media in order for parents to begin to build peer-support (http://www.chargesyndrome.org).
- Referrals to local deaf–blind resources as well as early intervention programs should be offered as a proactive step to maximize abilities.

Health Supervision From 3 Years to 11 Years of Age: Childhood

Important issues.

- An ENT consult for cochlear implant surgery should be considered before 3 years of age to maximize verbal language learning abilities [Birman et al., 2015]. ENT may be involved for recurrent otitis media and possible need for tympanostomy tubes.
- Annual hearing and vision checks are recommended.
- Physiotherapy and occupational therapy should be involved early to help with mobility. Hypotonia and poor balance can lead to a delay in progression of motor milestones [Brown, 2005; Bergman et al., 2011b]. The wide reaching effects of poor balance and sensory integration dysfunction are examined closely in Brown's 2005 paper [Brown, 2005].
- Monitor for scoliosis, which can occur as a neuromuscular result of hypotonia [Brown, 2005].
- Communication skills should be supported with individualized therapy [Bergman et al., 2011b]. The CHARGE Information Pack for Practitioners discusses communication, delays, and interventions [Rose and Haubrich, 2013]. Speech language therapists should be involved as there are multiple obstacles to clear articulation [Brown, 2005].
- An individualized education plan and deaf–blind consultants may be needed for students to attend school successfully. Psychoeducational assessments by professionals who have an understanding of deaf-blindness should be obtained to examine cognitive abilities and identify learning strengths and difficulties. Some families find that access to technology such as tablets and computers in the classroom are useful to support the learning process.
- Feeding therapy interventions should be put in place for ongoing issues like food pocketing in the cheeks, unusual chewing, and abnormal swallowing patterns [Hudson et al., 2015, 2016]. Feeding often becomes one of the principal ongoing issues in childhood. Gastroesophageal reflux and aspiration increases the probability of ongoing feeding problems [Dobbelsteyn et al., 2008]. Depending on the issue, feeding therapy interventions may be provided by a multi-disciplinary team including a gastroenterologist, an ENT surgeon, a nutritionist, occupational therapy, or a speech-language pathologist [Dobbelsteyn et al., 2008].
- Polyethylene glycol and senna glycoside may be necessary to treat constipation. Ongoing research is indicating that these children have poor gastrointestinal motility from abnormal innervation of the gastrointestinal tract [Cloney et al., 2016]. In our experience, prokinetic agents like erythromycin or domperidone may improve refractory gut motility issues.
- Growth parameters should continue to be assessed as poor growth is prevalent for many individuals with CHARGE syndrome in the early years [Lalani et al., 1993; Bergman et al.,

2011b]. This often occurs as a result of chronic illness and difficulty feeding; however, growth hormone deficiency is associated with CHARGE syndrome. Conventional doses of growth hormone improve growth velocity [Dorr et al., 2015]. Efficacy and safety data is presented in Dörr et al.'s paper [Dorr et al., 2015].

- Immunology should be consulted if there are recurrent infections so that immunodeficiency can be screened for with complete blood count and differential, immunoglobulin levels, B and T cell numbers and subsets, and T cell function. The most common recurring infections are otitis media and pneumonia [Wong et al., 2015b]. Insufficient antibody titers after childhood vaccinations have been described in a large proportion of patients with CHARGE syndrome and studies are being conducted to investigate whether booster vaccinations should be advised [Wong et al., 2015a]. Allergies and atopic features can occur as in the typical pediatric population.
- Symptoms of obstructive sleep apnea should be reviewed as this condition is prevalent in CHARGE syndrome [Trider et al., 2012]. Improvement has been noticed after tonsillectomy and/or adenoidectomy, CPAP, or tracheostomy [Trider et al., 2012]. Difficulties with sleep can be associated with day-time behavioral symptoms, so improving sleep may improve the quality of life for the individual and family [Trider et al., 2012; Hartshorne et al., 2009]. It is hypothesized that sleep difficulties may be related to visual impairments from lack of visual cues and poor dark–light contrast [Hartshorne et al., 2009]. Trialing melatonin (sustained release) may help with initiating sleep.
- Specialized childcare should be discussed, as it may be available through integrated daycares that specialize in children with developmental needs.
- Adjunct therapies such as music or pet therapy may increase success rates in attaining milestones, easing transition difficulties, and improving mood or behaviors [Gasalberti, 2006].
- Families can be supported in trying to build a peer-support network by connecting with other families via the CHARGE Syndrome Facebook and other social media. Social networks can be further developed locally with clubs or common interest groups for children with special needs (for e.g., The Texas CHARGERs [http://texaschargers.org/]).
- The CHARGE syndrome non-verbal pain assessment is available online at the CHARGE Syndrome Foundation website. Pain assessment is challenging and often forgotten when assessing behavioral problems. Dependent on the child, regular pain assessments may be required.

Anticipatory guidance.

- It is important to discuss the potential for puberty delay and possible growth problems with parents so that they are ready to make treatment decisions once adolescence approaches. Endocrinology should be involved early, before the usual age of puberty.
- Maximizing bone health by dietary and weight bearing exercises is important.
- Transitions to school or other new settings should be put in place early with proper adaptations and good communication established between the home, the school, and the multidisciplinary healthcare team.
- Families and professionals involved in the child's care may wish to attend a focused CHARGE syndrome and family conference such as the International CHARGE Syndrome Conference. This provides a great opportunity to join education sessions, receive support from other families and for individuals with CHARGE syndrome to socialize. Planning should start early so that funding can be obtained for attendance.

Health Supervision From 12 Years to 17 Years of Age: Adolescence

Important issues.

- An electrocardiogram and Holter monitoring should be completed if there is a suspicion of an arrhythmia. These have been reported in late childhood and adolescence [Searle et al., 2005].
- An annual assessment of puberty should occur because of hypogonadtropic hypogonadism. Delayed puberty is highly prevalent in CHARGE syndrome. For some individuals puberty starts but then arrests. Endocrinology should be consulted early to consider treatment with estrogen and testosterone [Hsu et al., 2014].
- Bone health is often forgotten in this complex syndrome. Hormone replacement therapy should be discussed early, especially in the cases of known hypogonadotropic hypogonadism. This will promote improved bone mineralization and reduce the risk of osteoporosis. Weight-bearing activities need to be encouraged for the same reason. Nutrition should be optimized to prevent calcium or vitamin-D deficiencies contributing to poor bone health. DEXA scans interpreted within the context of CHARGE syndrome can be helpful to document any changes in bone mineral density [Forward et al., 2007].
- Obesity has been observed to develop in the adolescent and adult years, therefore, monitoring weight gain and BMI is important [Blake et al., 2005; Forward et al., 2007]. Recreational therapists or physiotherapists can help find exercises suitable for those with hypotonia and poor balance due to their vestibular anomalies.
- Hypothyroidism is possible in CHARGE syndrome and should be investigated for if clinical features are present [Hsu et al., 2014].
- Reproductive health care concerns like risks and rights of sexuality, sexual abuse or assault, and menstrual management is an area of health often forgotten. A review of these issues in adolescents with special needs is presented in Quint's recent paper [Quint, 2015].
- In the assessment of acute behavioral issues, unrecognized pain, balance or equilibrium difficulties, communication barriers, and sensory impairments (i.e., deterioration in vision and hearing) need to be considered [Blake et al., 1998].
- Common chronic behavioral concerns or comorbid mental health diagnosis are socializing difficulties, obsessive-compulsive disorder, anxiety disorder, tics/Tourette syndrome, autism, attention deficit hyperactivity disorder, or pervasive developmental disorder. Aggressive behavior and tactile defensiveness can occur [Blake et al., 1998; Hartshorne et al., 2016].

- Sleep has been identified as the most prevalent issue affecting quality of life in individuals with CHARGE syndrome [Hartshorne et al., 2016]. Poor sleep was significantly correlated with self-abuse, anxiety, and conduct problems. It is important to consider treatments to improve sleep and to foster suitable sleep hygiene habits.

Anticipatory guidance.

- As individuals move into adulthood, they should be allowed to progress and manage their own self-care and medical care at a level appropriate to their developmental and cognitive abilities. Health care providers should encourage suitable progression of independence in activities like counting out and taking their own medications, calling in prescriptions, making appointments, and progressing to seeing the healthcare provider independently where appropriate.
- A multi-disciplinary team is required to support the development of life skills, social skills, and self-regulation to smooth the transition into adulthood. Access to appropriate mental health services is important, as a recent study indicates that individuals with CHARGE syndrome have increased difficulties with mental health due to troubles with relationships with friends and social acceptance [Hartshorne et al., 2016].
- A transition plan to adult medicine should be developed during early adolescence.

Health Supervision From 18 Years of Age and Older: Adulthood

Important issues.

- Annual checks of hearing and vision remain important. Individuals with facial palsies are more susceptible to corneal abrasions. In patients with retinal colobomas, more regular eye examinations are required to look for signs of retinal detachment. These diagnoses should also be considered in those individuals presenting with behavioral outbursts.
- Physiotherapy and occupational therapy should continue to be involved to provide help with hypotonia, as well as to improve mobility and visuospatial coordination [Bergman et al., 2011b]. Individuals may have differing needs for adaptive devices as they transition beyond the school system. Daily independent living skills will vary by individual and keeping active will help prevent obesity [Blake et al., 2005].
- Older individuals with CHARGE syndrome may wish to be referred to a genetic counselor as they anticipate having children of their own. There is a 50% chance of transmitting the *CHD7* mutation to offspring [Bergman et al., 2011b]. Because of the large intra-familial variability, the severity of CHARGE syndrome occurring in offspring cannot be predicted [Bergman et al., 2011b].

CONCLUSION AND FUTURE DIRECTION

The CHARGE Syndrome Checklist reviews the most commonly occurring issues requiring management in individuals with CHARGE syndrome, as well as the critical issues that can be missed by the physician coordinating the care of these individuals throughout their life span. We anticipate that this structured approach will prevent missed diagnoses and will allow for early interventions to support the highest level of health, development, communication, and independence for individuals with CHARGE syndrome. Family members may also find this checklist useful to determine what issues to expect at different life stages and to advocate for resources for their children. In the future, this checklist could be expanded upon to include additional clinical features and be available online with embedded links to references and resources.

REFERENCES

Bergman J, Bocca G, Hoefsloot LH, Meiners LC, van Ravenswaaij-Arts CMA. 2011a. Anosmia predicts hypogonatropic hypogonadism in CHARGE syndrome. J Pediatr 158:474–479.

Bergman J, Janssen N, Hoefsloot LH, Jongmans MCJ, Hofstra RMW, van Ravenswaaij-Arts CMA. 2011b. CHD7 mutations and CHARGE Syndrome: The clinical implications of an expanding phenotype. J Med Genet 48:334–342.

Birman CS, Brew JA, Gibson WPR, Elliott EJ. 2015. CHARGE syndrome and cochlear implantation: Difficulties and outcomes in the pediatric population. Int J Pediatr Otorhinolaryngol 79:487–492.

Blake K, Kirk J, Ur E. 1993. Growth in CHARGE association. Arch Dis Child 68:508–509.

Blake KD, Davenport SLH, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM. 1998. CHARGE Association: An update and review for the primary pediatrician. Clin Pediatr 37:159–173.

Blake KD, Salem-Hartshorne N, Daoud MA, Gradstein J. 2005. Adolescent and adult issues in CHARGE syndrome. Clin Pediatr 44:151–159.

Blake K, Prasad C. 2006. CHARGE syndrome. Orphanet J Rare Dis 1:34.

Blake KD, Hartshorne TS, Lawand C, Dailor AN, Thelin JW. 2008. Cranial nerve manifestations in CHARGE syndrome. Am J Med Genet Part A 146A:585–592.

Brown D. 2005. CHARGE syndrome "behaviors": Challenges or adaptations? Am J Med Genet Part A 133A:268–272.

Cloney K, Steele SL, Stoyek M, Croll RP, Smith FM, Blake K, Berman JN. 2016. Modeling CHARGE syndrome in zebrafish: A look at the innervation and function of the gastrointestinal system. 12th international CHARGE syndrome conference proceedings. Am J Med Genet Part A 170A:856–869.

Corsten-Janssen N, Kerstjens-Frederikse WS, du Marchie Sarvaas GJ, Baardman ME, Bakker MK, Bergman Jeh, Hove HD, Heimdal KR, Rustad CF, Hennekam RCM, Hofstra RMW, Hoefsloot LH, van Ravenswaaij-Arts CMA, Kapusta L. 2013a. The cardiac phenotype in patients with a CHD7 mutation. Circ Cardiovasc Genet 6:248–254.

Corsten-Janssen N, Saitta SC, Hoefsloot LH, McDonald-McGinn DM, Driscoll DA, Derks R, Dickinson KA, Kerstjens-Frederikse WS, Emanuel BS, Zackai EH, van Ravenswaaij-Arts CMA. 2013b. More clinical overlap between 22q11.2 deletion syndrome and CHARGE syndrome than often anticipated. Mol Syndromol 4:235–245.

Dalkey NC. 1969. The Delphi Method: An experimental study of group opinion. Research memorandum RM-58888-PR. Santa Monica, California: The Rand Corp.

Dobbelsteyn C, Marche DM, Blake K, Rashid M. 2005. Early oral sensory experiences and feeding development in children with CHARGE syndrome: A report of five cases. Dysphagia 20:89–100.

Dobbelsteyn C, Peacocke SD, Blake K, Crist W, Rashid M. 2008. Feeding difficulties in children with CHARGE syndrome: Prevalence, risk factors and prognosis. Dysphagia 23:127–135.

Dorr HG, Boguszewski M, Dahlgren J, Dunger D, Geffner ME, Hokken-Koelega AC, Lindberg A, Polak M, Rooman R. 2015. Short children with CHARGE syndrome: Do they benefit from growth hormone therapy? Horm Res Paediatr 84:49–53.

Forward KE, Cummings EA, Blake KD. 2007. Risk factors for poor bone health in adolescents and adults with CHARGE syndrome. Am J Med Genet Part A 143A:839–845.

Gasalberti, D. 2006. Alternative therapies for children and youth with special health care needs. J Pediatr Health Care 20:133–136.

Hale CL, Niederriter AN, Green GE, Martin DM. 2015. Atypical phenotypes associated with pathogenic CHD7 variants and a proposal for broadening CHARGE syndrome clinical diagnostic criteria. Am J Med Genet Part A 9999A:1–11.

Hartshorne TS, Heussler HS, Dailor AN, Williams GL, Papadopoulos D, Brandt KK. 2009. Sleep disturbances in CHARGE syndrome: Types and relationships with behavior and caregiver well-being. Dev Med Child Neurol 51:143–150.

Hartshorne N, Hudson A, MacCuspie J, Kennert B, Nacarato T, Hartshorne T, Blake K. 2016. Quality of life in adolescents and adults with CHARGE syndrome. Am J Med Genet Part A 170A:2012–2021.

Hsu P, Ma A, Barnes EH, Wilson M, Hoefsloot LH, Rinne T, Munns C, Williams G, Wong M, Mehr S. 2015. The immune phenotype of patients with CHARGE syndrome. J Allergy Clin Immunol Pract 4:96–103.

Hsu P, Ma A, Wilson M, Williams G, Curotta J, Munns CF, Mehr S. 2014. CHARGE syndrome: A review. J Pediatr Child Health 50:504–511.

Hudson A, Colp M, Blake K. 2015. Letter to the editor—Pocketing of food in cheeks during eating in an adolescent with CHARGE syndrome. J Pediatr Child Health 51:1143–1144.

Hudson A, MacDonald M, Blake K. 2016. Packing and problematic feeding behaviors in CHARGE syndrome: A qualitative analysis. Int J Pediatr Otorhinolaryngol 82:107–115.

Issekutz KA, Graham JM Jr, Prasad C, Smith IM, Blake KD. 2005. An epidemiological analysis of CHARGE Syndrome: Preliminary results from a Canadian study. Am J Med Genet Part A 133A:309–317.

Janssen N, Bergman J, Swertz MA, Tranebjaerg L, Lodahl M, Schoots J, Hofstra RMW, van Ravenswaaij-Arts CMA, Hoefsloot LH. 2012. Mutation update on the CHD7 gene involved in CHARGE Syndrome. Hum Mutat 33:1149–1160.

Jones J, Hunter D. 1995. Consensus methods for medical and health services research. BMJ 311:376–380.

Jongmans MCJ, Hoefsloot LH, van der Donk KP, Admiraal RJ, Magee A, van de Laar I, Hendriks Y, Verheij JBGM, Walpole I, Brunner HG, van Ravenswaaij CMA. 2008. Familial CHARGE Syndrome and the CHD7 gene: A recurrent missense mutation, intrafamilial recurrence and variability. Am J Med Genet Part A 146A:43–50.

Jongmans MCJ, van Ravenswaaij-Arts CMA, Pitteloud N, Ogata T, Sato N, Claahsen-van der Grinten HL, van der Donk K, Seminara S, Bergman J, Brunner HG, Crowley WF Jr, Hoefsloot LH. 2009. CHD7 mutations in patients initially diagnosed with Kallman syndrome—The clinical overlap with CHARGE syndrome. Clin Genet 75:65–71.

Lalani SR, Hefner MA, Belmont JW, Davenport SLH. (Updated February, 2012). CHARGE Syndrome. In: GeneReviews at GeneTests Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1993–2013. Accessed [July, 2016]. Available at http://www.genetests.org

Online Mendelian Inheritance in Man, OMIM®. John Hopkins University, Baltimore, MD. Mim Number: 214800: 2016. Available online http://omim.org/

Quint EH. 2015. Adolescents with special needs: Clinical challenges in reproductive health care. J Pediatr Adolesc Gynecol 29:2–6.

Rose S, Haubrich O. 2013. Communication and children with CHARGE syndrome. The CHARGE Information Pack for Practitioners. Available online https://www.sense.org.uk/content/charge-information-pack-practitioners

Schulz Y, Wehner P, Opitz L, Salinas-Riester G, Bongers EMHF, van Ravenswaaij-Arts CMA, Wincent J, Schoumans J, Kohlhase J, Borchers A, Pauli S. 2014. CHD7, the gene mutated in CHARGE Syndrome, regulates cells involved in neural crest cell guidance. Hum Genet 133:997–1009.

Searle LC, Graham JM, Prasad C, Blake KD. 2005. CHARGE syndrome from birth to adulthood: An individual reported on from0-33 years. Am J Med Genet Part A 133A:344–349.

Trider C, Blake K. 2013. Anesthesia issues in CHARGE syndrome: What are the risks? The CHARGE Information Pack for Practitioners. Available online https://www.sense.org.uk/content/charge-information-pack-practitioners

Trider C, Corsten G, Morrison D, Hefner M, Davenport S, Blake K. 2012. Understanding obstructive sleep apnea in children with CHARGE syndrome. Int J Pediatr Otorhinolaryngol 76:947–953.

Verloes, A. 2005. Updated diagnostic criteria for CHARGE Syndrome: A proposal. Am J Med Genet Part A 133A:306–308.

Vissers L, van Ravenswaaij CMA, Admiraal RA, Hurst JA, de Vries BBA, Janssen IM, van der Vliet WA, Huys EHLPG, de Jong PJ, Hamel BCJ, Schoenmakers EFPM, Brunner HG, Veltman JA, van Kessal AG. 2004. Mutations in a new member of the chromodomain gene family cause CHARGE syndrome. Nat Genet 36:955–957.

Wong MTY, Lambeck AJA, van der Burg M, la Bastide-van Gemert S, Hogendorf LA, van Ravenswaaij-Arts CM, Scholvinck EH. 2015a. Immune dysfunction in children with CHARGE syndrome: A cross-sectional study. PLoS ONE 10:e0142350.

Wong MTY, Schölvinck EH, Lambeck AJA, van Ravenswaaij-Arts CM. 2015b. CHARGE syndrome: A review of the immunological aspects. Eur J Hum Genet 23:1451–1459.

Zentner GE, Layman WS, Martin DM, Scacheri PC. 2010. Molecular and phenotypic aspects of CHD7 mutation in CHARGE syndrome. Am J Med Genet Part A 152A:674–686.