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Cleft Lip and Palate in CHARGE Syndrome: Phenotypic Features That Influence Management

Kathryn V. Isaac, MD[1], Ingrid M. Ganske, MD, MPA[1], Stephen A. Rottgers, MD[1], So Young Lim, MD, PhD[1], and John B. Mulliken, MD[1]

Abstract

Objective: Infants with syndromic cleft lip and/or cleft palate (CL/P) often require more complex care than their nonsyndromic counterparts. Our purpose was to (1) determine the prevalence of CL/P in patients with CHARGE syndrome and (2) highlight factors that affect management in this subset of children.

Design: This is a retrospective review from 1998 to 2016.

Patients: Patients with CHARGE syndrome were diagnosed clinically and genetically.

Main Outcomes Measures: Prevalence of CL/P was determined and clinical details tabulated: phenotypic anomalies, cleft types, operative treatment, and results of repair.

Results: CHARGE syndrome was confirmed in 44 patients: 11 (25%) had cleft lip and palate and 1 had cleft palate only. Surgical treatment followed our usual protocols. Two patients with cardiac anomalies had prolonged recovery following surgical correction, necessitating palatal closure prior to nasolabial repair. One of these patients was too old for dentofacial orthopedics and underwent combined premaxillary setback and palatoplasty, prior to labial closure. Velopharyngeal insufficiency was frequent (n = 3/7). All patients had feeding difficulty and required a gastrostomy tube. All patients had neurosensory hearing loss; anomalies of the semicircular canals were frequent (n = 3/4). External auricular anomalies, colobomas, and cardiovascular anomalies were also common (n = 8/11). Other associated anomalies were choanal atresia (n = 4/11) and tracheoesophageal fistula (n = 2/11).

Conclusions: CHARGE syndrome is an under-recognized genetic cause of cleft lip and palate. Hearing loss and speech and feeding difficulties often occur in these infants. Diagnosis can be delayed if the child presents with covert phenotypic features, such as chorioretinal colobomas, semicircular canal hypoplasia, and unilateral choanal atresia.

Keywords

CHARGE syndrome, syndromic cleft lip and palate

Introduction

The terminological evolution of CHARGE syndrome over the past 4 decades reflects a progression from a constellation of findings (an association) to a known genetic mutation (a syndrome). The association of choanal atresia, coloboma, and other features was first described independently by Hall and Hittner in 1979 (Hall, 1979; Hittner et al., 1979). Soon after, the same disorder was labeled with the acronym "CHARGE" by Pagon et al. (1981) and the phenotype expanded to include *C*olobomas, *H*eart defects, choanal *A*tresia, *R*etarded development, *G*enital hypoplasia, and *E*ar anomalies/deafness.

As suspicion for a monogenic etiology increased, Blake et al. (1998) proposed clinical criteria to designate CHARGE as a "syndrome," rather than an association. Shortly thereafter, comparative genomic hybridization and sequencing for

[1] Department of Plastic and Oral Surgery, Boston Children's Hospital, Boston, MA, USA

Corresponding Author:
John B. Mulliken, MD, Department of Plastic and Oral Surgery, Boston Children's Hospital, 300 Longwood Avenue, Boston, MA 02115, USA.
Email: john.mulliken@childrens.harvard.edu

candidate genes revealed a mutation in *chromodomain helicase DNA 7* (*CHD7*) (Vissers et al., 2004). Because the multiple congenital anomalies of CHARGE are pathogenetically linked by a single locus, the disorder is now recognized as an autosomal dominant syndrome (Lubinsky, 1994; Graham, 2001; Verloes, 2005).

The prevalence of CHARGE syndrome (OMIM #214800) is estimated to be 1 of 8500 to 1 of 15 000 live births (Blake et al., 1998; Issekutz et al., 2005; Van Ravenswaaij-Arts et al., 2015). Our understanding of phenotypic variation in this condition is expanding as more affected children are identified. Nevertheless, labiopalatal clefting as a component of CHARGE syndrome has received little attention in the literature. The goal of this study is to determine the prevalence of cleft lip and/or cleft palate (CL/P) in our series of patients with CHARGE syndrome and to identify phenotypic features that influence the management and outcomes of surgical cleft care in this unique subset.

Methods

This is a retrospective review of all children with CHARGE syndrome referred to Boston Children's Hospital from 1998 to 2016. The study was approved by the institutional review board of the Committee on Clinical Investigation. Patients with CHARGE syndrome were identified by a search of the hospital electronic medical records for all citations of the term "CHARGE syndrome." The diagnosis was confirmed clinically and by genetic testing. The charts were examined looking for children with CHARGE syndrome who also had a cleft lip and/or cleft palate. Data were recorded for demographics, medical history, surgical procedures, and genetic findings. Details were tabulated for features of CHARGE syndrome, characteristics of the cleft lip and palate, age at labial and palatal repair, postoperative complications, and occurrence and treatment of velopharyngeal insufficiency.

CHARGE syndrome was diagnosed by phenotypic features (Blake et al., 1998; Verloes, 2005) and molecular identification of a *CHD7* mutation (Vissers et al., 2004). Sanger sequencing combined with multiplex ligation-dependent probe amplification was performed to maximize the sensitivity of the genetic analysis (Van Ravenswaaij-Arts et al., 2015). CHARGE-like syndromes were excluded because of atypical phenotypic features and negative genetic analysis (Scrambler et al., 1992; Van Ravenswaaij-Arts et al., 2015).

Results

A total of 44 patients with a diagnosis of CHARGE syndrome were identified in the Boston Children's Hospital records: 11 (25%) had cleft palate with or without cleft lip (CP ± L), of which 8 were male and 3 were female. The median age was 8 years (range 1-44 years). All patients fulfilled the clinical diagnostic criteria for CHARGE syndrome (Figure 1). Genetic testing was available in 10 of 11 patients (91%). One patient in the study had accepted the clinical diagnosis and chose not to undergo genetic testing.

The distribution of cleft types is shown in Table 1. There were nearly an equal number of unilateral and bilateral clefts. The phenotypic features of CHARGE syndrome in the CP ± L subset are listed in Table 2. Velopharyngeal insufficiency was documented in 43% (n = 3/7) of the patients with palatal repair who were old enough for perceptual speech assessment. Two of these patients required a pharyngeal flap and another remains in speech therapy. Ocular malformations included iridal and chorioretinal coloboma; 3 patients had bilateral colobomas. Choanal atresia (n = 4, 37%) was bilateral in 1 patient who only had a cleft of the soft palate. In 3 other patients with unilateral choanal atresia, laterality was opposite to the side of the cleft palate. Auricular abnormalities (n = 8, 78%) included in order of frequency: inner ear anomalies (n = 11, 100%), bilateral grade 1 microtia (n = 7, 64%), ossicular malformations (n = 6, 54%), and low-set position (n = 2, 18%). Diminished hearing was ubiquitous in our population (n = 11, 100%): all had sensorineural-type loss and 4 patients had mixed loss (37%). Semicircular canal anomalies were found in all 4 patients who had a CT scan of the temporal bones, consisting of either bilateral hypoplasia (n = 3) or absence (n = 1); the remaining 7 patients did not have a radiographic investigation of the inner ear.

Cranial nerve involvement was documented in all patients. Facial nerve weakness was evident in 4 patients (36%). Feeding and swallowing difficulties were frequent and ascribed to weakness of cranial nerves IX and X in the pharyngeal plexus; all these patients required a gastrostomy tube. Formal barium swallow studies prior to insertion of a gastrostomy tube were not available. Nissen fundoplication was needed in 3 patients (27%), and all required additional supplementation through a gastrostomy tube over the age of 6 years.

Cardiovascular anomalies were present in 73% of patients (n = 8), as listed in Table 2. Delayed growth and development was identified in 6 patients, and another patient was diagnosed with autism spectrum disorder. Genital hypoplasia was noted in 6 patients (55%); all were males with cryptorchidism.

The surgical repair of CP ± L in this group of patients with CHARGE syndrome followed protocols described previously (Mulliken and Martínez-Pérez, 1999; Mulliken, 2001, 2013; Sullivan et al., 2009). One patient with a bilateral cleft lip and palate (BCLP) and another with a unilateral cleft lip and palate (UCLP) had the repair before referral to our center. Preoperative dentofacial orthopedics was used in 8 of the 9 remaining patients. Four patients with unilateral complete or unilateral severe incomplete forms had a 2-stage repair with preliminary nasolabial adhesion and gingivoperiosteoplasty. The mean age at adhesion for unilateral CL was 3.6 months (range 2-5 months). The second stage (formal) nasolabial repair for unilateral CL and synchronous repair for bilateral CL was 8 months (range 5-12 months). Palatal closure was performed on average at 10.2 months (range 9-13 months). The majority of these patients had operative repair of the nasolabial and palatal deformities within the standard anticipated time frame. Delay or altered sequence of surgical correction was needed in 2 patients who had a prolonged recovery following repair of complex

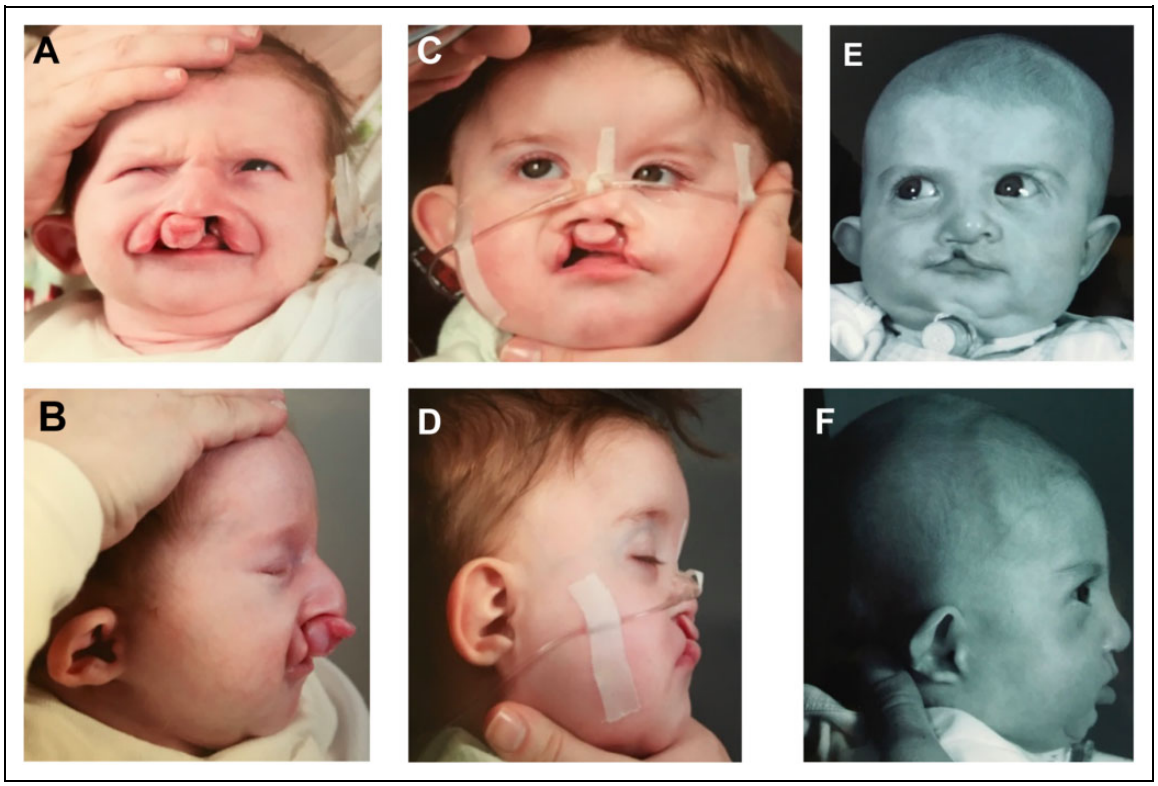

Figure 1. Examples of patients with CHARGE syndrome and associated cleft lip and palate. (A, B) External auricular anomalies: bilateral symmetric, low-set and cupped. (C, D) Characteristic facial features post dentofacial orthopedics: broad forehead, square face, small mouth. This patient also had cardiac anomalies (ventricular septal defect and repaired patent ductus arteriosus) and pulmonary disease secondary to multiple aspirations (requiring supplemental oxygen). (E, F) Incomplete unilateral cleft lip and palate (CLP) and patent ductus arteriosus; repeated aspiration necessitated tracheostomy. Note characteristic facial asymmetry and external auricular anomalies.

Table 1. Cleft Lip and Palate Characteristics (n = 11).

	n (%)
Cleft palate only	1 (9)
Cleft lip and palate	10 (91)
Unilateral complete	3 (27)
Unilateral incomplete	3 (27)
Bilateral complete	4 (37)
Bilateral asymmetric	0
Veau type	
I	2 (18)
II	0
III	4 (37)
IV	3 (27)
Submucous cleft palate	2 (18)

cardiac anomalies. Both patients were taken to the intensive care unit for respiratory difficulty after palatal closure. The first patient had a BCLP and was not sufficiently stable to undergo an elective procedure until 9 months of age. This infant was also too old for dentofacial orthopedics; therefore, palatal closure was performed first along with a premaxillary setback and gingivoperiosteoplasty and followed by synchronous nasolabial repair at 12 months of age. The second patient had a

Table 2. Phenotypic Features in Our Subset of Patients With CHARGE Syndrome and CP±L (n = 11).

	n (%)
Cranial nerve dysfunction	11 (100)
Sensorineural hearing loss	11 (100)
Characteristic facial features	11 (100)
Feeding difficulty	11 (100)
Auricular abnormalities	8 (73)
Coloboma	8 (73)
Iridal	4
Chorioretinal	4
Cardiovascular anomalies	8 (73)
Patent ductus arteriosus	3
Coarctation of the aorta	2
Atrial septal defects	2
Pulmonary stenosis	3
Tetralogy of Fallot	1
Ebstein anomaly	1
Growth retardation	6 (55)
Genital hypoplasia	6 (55)
Developmental delay	6 (55)
Semicircular canal abnormality	4 (37)
Choanal atresia	4 (37)
Tracheoesophageal fistula	2 (18)
Microphthalmia	1 (9)

unilateral complete CLP, and dentofacial orthopedics was not initiated until age 6 months, followed by nasolabial adhesion, gingivoperiosteoplasty, and palatoplasty at age 10 months, and formal nasolabial repair at age 12 months.

Discussion

The estimated prevalence of CHARGE syndrome is 1 of 8500 to 1 of 15 000 live births (Blake et al., 1998; Issekutz et al., 2005; Van Ravenswaaij-Arts et al., 2015). The frequency of cleft lip and palate in association with CHARGE syndrome, determined in our study, is within the wide reported range of 15% to 48% (Tellier et al., 1998; Issekutz et al., 2005; Strömland et al., 2005; Jongmans et al., 2006; Lalani et al., 2006; Sanlaville and Verloes, 2007; Wincent et al., 2008; Zentner et al., 2010; Bergman et al., 2011; Blake et al., 2011). Approximately 30% of CLP and 50% of CP-only patients are syndromic (Jugessur et al., 2008). Of 275 syndromes that include CL ± P as a primary feature, 75% have a known genetic cause (Leslie and Marazita, 2013). The most common is van der Woude syndrome, but this disorder only accounts for 2% of orofacial clefts. The overall prevalence is 1 of 34 000 births (Burdick, 1986). Our study supports CHARGE syndrome as a common cause of autosomal dominant cleft lip and palate. A conservative estimated prevalence for CHARGE syndrome with cleft lip and palate is 1 of 47 000 live births. A large European population study identified trisomy 13 as another common syndrome associated with cleft lip and palate, with an overall prevalence of 1 of 190 000 births (Calzolari et al., 2007). Thus, we highlight CHARGE syndrome as an important under-recognized cause of cleft lip and palate. It may be the second most common cause of syndromic cleft lip and palate.

Diagnosis

It is critical to promptly recognize CHARGE syndrome in a patient with CL/P. Compared to a nonsyndromic patient with cleft lip and palate, an infant with CHARGE syndrome is at greater risk for feeding and swallowing difficulty, hearing and visual loss, and growth and developmental delays (Blake et al., 2011; Van Ravenswaaij-Arts et al., 2015). CHARGE syndrome can be diagnosed clinically, but not all the associated features are obvious by physical examination (Van Ravenswaaij-Arts et al., 2015).

Coloboma

Defects of the retina or choroid disk are the most common ocular anomalies in CHARGE syndrome (Issekutz et al., 2005; Sanlaville and Verloes, 2007). Of the 8 patients in our series with coloboma, only 4 were iridal; the others were chorioretinal colobomas, which require fundoscopy for diagnosis. Thus, recognition of this ocular anomaly may be delayed.

Choanal Atresia

Choanal atresia represents a failed rupture of the bucconasal membrane in the fifth to sixth week of embryonic development (Blake et al., 1998). Bilateral choanal atresia is usually diagnosed at birth and presents as cyclical cyanosis or respiratory distress (Newman et al., 2013). Bilateral atresia does not occur in an infant with cleft of the hard palate because there is no bucconasal membrane (Jongmans et al., 2006; Zentner et al., 2010). Unilateral choanal atresia was found in our series only by radiologic investigation or endoscopy. Unilateral choanal atresia often presents later in adolescence with chronic rhinorrhea and rarely causes early feeding difficulty or airway symptoms (Wiatrak, 1998). As diagnosis of unilateral choanal atresia is often delayed, it is not often a clue to CHARGE syndrome.

Heart Defects and Ear Anomalies

Cardiac defects and external auricular anomalies are common (73%), easily recognized (Blake et al., 1998; Wyse et al., 1993), and often the first clue to the diagnosis of CHARGE syndrome. In contrast, abnormalities of the middle and inner ear, present in 100% of patients in our series, are hidden. These anomalies lead to vestibular dysfunction and sensorineural hearing loss. Audiometry and radiologic examination of the temporal bones are needed to detect these abnormalities (Morgan et al., 1993; Amiel et al., 2001).

Genetics

There is wide variability in the clinical presentation of CHARGE syndrome; there are also major differences between carriers and noncarriers of the *CHD7* mutation (Lalani et al., 2006). A mutation in *CHD7* is detected in approximately 60% of patients with CHARGE syndrome and in 66% of patients with CHARGE syndrome with CL ± P (Vissers et al., 2004; Jongmans et al., 2006; Lalani et al., 2006). *CHD7* mutations are commonly de novo and require additional specific testing (Vissers et al., 2004; Lalani et al., 2006; Blake et al., 2011; Van Ravenswaaij-Arts et al., 2015). Patients who are given a clinical diagnosis of CHARGE syndrome may not have an identifiable genetic mutation. Up to 20% of patients with CL/P and CHARGE syndrome test negative for a CHD7 mutation (Lalani et al., 2004). Given the high prevalence of orofacial clefting associated with CHARGE syndrome, *CHD7* genetic analysis should be performed in CL/P patients presenting with the aforementioned characteristic phenotypic features. Abnormalities in other candidate genes, such as *SEMA3E*, have been identified in 2 patients with CHARGE syndrome who did not carry a *CHD7* mutation (Lalani et al., 2004)—another example of genetic heterogeneity.

Management

Specialized care is needed for infants with CHARGE syndrome. Delays or alteration in the surgical repair of the cleft

lip and palate may be necessary. The majority of patients had operative correction within the standard time frame, except for patients with complex cardiac anomalies. Dentofacial orthopedics may be delayed if these patients are medically unstable and then may be too old to be candidates and necessitate a premaxillary setback at the time of palatoplasty. Palatal closure may be necessary prior to nasolabial repair. An infant with CHARGE syndrome and cleft lip with cleft palate is at increased risk for feeding difficulty and impaired speech. Prolonged feeding problems are a major cause of morbidity in these infants (Blake et al., 1998; Issekutz et al., 2005). All patients in our series required a gastrostomy because of oropharyngeal dysphasia and severe gastroesophageal reflux. In contrast, nonsyndromic CP ± L patients rarely require gastrostomy feeding. Speech issues are reported in more than 80% of patients with CHARGE syndrome. The cause is likely multifactorial: cleft palate, hearing loss, tracheostomy, learning disability, autism, developmental retardation, and rhombencephalic anomalies (Strömland et al., 2005; Sanlaville and Verloes, 2007). In our patients with CHARGE syndrome and cleft lip and palate, 43% exhibited velopharyngeal insufficiency after palatal closure, which is greater than velopharyngeal insufficiency in nonsyndromic counterparts, as previously reported by our center (Sullivan et al., 2009), as well as in the literature.

Conclusion

CHARGE syndrome is an under-appreciated cause of cleft lip and palate. The diagnosis may be delayed if the infant presents with covert phenotypic features, such as chorioretinal coloboma, semicircular canal hypoplasia, or unilateral choanal atresia. Early recognition of CHARGE syndrome in the context of cleft lip and palate is essential for appropriate management. Hearing loss, speech, and feeding difficulty are common in this subset of syndromic cleft lip and palate patients. While awaiting genetic confirmation of a clinical diagnosis of CHARGE syndrome, it is necessary to schedule ophthalmoscopy, cardiac ultrasonography, cranial CT, audiometry, and swallowing studies. Early diagnosis and proper treatment should improve the outcome.

Declaration of Conflicting Interests

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