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CHARGE Syndrome

Diagnosis and Clinical Management in the NICU

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ABSTRACT

CHARGE syndrome is a condition that has historically been diagnosed on the basis of the clinical findings of **c**oloboma, **h**eart disease, **c**hoanal atresia, **r**estricted growth, and/or central nervous system anomalies, **g**enital hypoplasia, and **e**ar anomalies and/or deafness. Recently, researchers have discovered a genetic link, specifically, a strong association between the CHARGE phenotype and a mutation of the CHD7 gene on the long arm of chromosome 8. Diagnosis now can be confirmed but not excluded with a positive mutation of this gene. This article offers an explanation of the diagnostic process as well as a description of the physical assessment and corresponding clinical implications of CHARGE syndrome in the neonatal population.

Key Words: CHARGE syndrome, choanal atresia, coloboma, congenital heart disease, neonatal

The acronym CHARGE describes the association of physical anomalies including **c**oloboma, **h**eart disease, **c**hoanal atresia, **r**estricted growth and/or central nervous system (CNS) anomalies, **g**enital hypoplasia, and **e**ar anomalies and/or deafness.[1] In the past, CHARGE was understood only as an association, meaning a group of anomalies, "not pathologically related, that occur together more often than expected by chance."[2] Because of recent genetic research, however, CHARGE is now accepted as a genetic *syndrome*, differentiated from an *association* by the fact that one common pathologic anomaly causes all manifestations.[3] This distinction was brought about through the work of a group of geneticists from the Netherlands who published a study linking CHARGE syndrome to a microdeletion on the long arm of chromosome 8.[4] With this new information, the medical community is reevaluating its definition of CHARGE syndrome. For the sake of clarity, this article will use the term "clinical CHARGE" to describe patients diagnosed on the basis of phenotype only and "genetic CHARGE" to describe patients with a confirmed microdeletion of chromosome 8.

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PATHOPHYSIOLOGY

The CHD7 gene contains 38 exons,[5] 37 of which function in protein coding.[6,7] These proteins influence chromatin structure and gene expression, thereby regulating embryonic development.[8] Simply put, the CHD7 gene is "responsible for turning other genes on and off."[9] This gene's influence over a wide variety of other genes explains the extreme variability of phenotypic expression in CHARGE syndrome.

Although there is much we do not understand about the variability of expression of this gene, we do know that it plays a large part in the development of eye, olfactory epithelium, inner ear, and vascular tissues.[10] Problems occur early in the first trimester, specifically between the third and ninth weeks postconception.[5,11] Eye, ear, and cranial nerve malformations occur between days 33 and 34 of gestation when these tissues begin to form. Contruncal heart defects secondary to abnormalities in cephalic neural crest cell migration occur between the fourth and fifth weeks postconception. Finally, choanal atresia results if the primitive bucconasal membrane fails to rupture between the fifth and sixth weeks postconception.[5]

Many different types of gene mutations have been observed in patients with genetic CHARGE syndrome. These include nonsense, frameshift, missense, and splice-site mutations.[4,6,8,12,13] It is unclear

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whether the type of genetic mutation affects phenotype, but future studies may reveal significance.[6,8] We *do* know, however, that even identical genotypes can produce different phenotypes. One study analyzed monozygotic twins with identical mutations on exon 16 of chromosome 8. While both twins presented with bilateral coloboma, cardiac malformations, and growth restriction, they differed greatly in the severity of cardiac complications, and one twin additionally presented with unilateral choanal atresia, olfactory and auditory deficiencies, and unilateral cleft lip and palate.[6] This case illustrates the wide variability of phenotypic presentation associated with this genetic aberration.

INCIDENCE AND DEMOGRAPHICS

The exact incidence of clinical CHARGE syndrome is difficult to define because of a lack of strict diagnostic parameters, but it is estimated to be between 1 in 12,000[6] and 1 in 8500.[14] The incidence of genetic CHARGE syndrome is unknown, due, in large part, to the cost prohibitive nature of genetic analysis of a wide population. Studies of individuals with genetic CHARGE suggest a slight female predominance (59%:41%), but larger studies are needed to offer a definitive female-to-male ratio.[8,12]

ETIOLOGY AND GENETIC TRANSMISSION

The majority of CHD7 mutations occur as a result of a de novo, or new mutation, meaning that the mutation occurs sporadically and is not inherited from either parent. Three studies support this, all of which have analyzed the DNA of CHD7-positive patients compared with that of their respective parents. Combining the results of these studies, approximately 97% of cases were de novo occurrences and only 3% were inherited from a parent via autosomal dominant transmission.[4,8,13,15] Advanced paternal age has been implicated as a contributing factor in de novo cases.[16]

Autosomal dominant inheritance occurs rarely because of the high incidence of sterility among individuals with genetic CHARGE secondary to delayed or absent puberty. In one study, the single case of confirmed autosomal dominant inheritance occurred in a mildly affected mother.[15] In another, inheritance also occurred in a mother with a mild presentation attributable to somatic cell mosaicism, meaning that some, but not all, of her cells contained a mutated CHD7 gene. Both of her sons were affected.[4]

It is likely that mosaicism is responsible for more cases than are currently detectable as this genetic condition is difficult to diagnose. In fact, a parent with one affected child has an empiric recurrence risk of 1% to 2% attributable to assumed germ line mosaicism.[6] Because of this, even parents of a child with an apparent de novo mutation should be offered extensive genetic counseling and prenatal diagnosis in future pregnancies.[8]

It is important to note that an individual with CHARGE syndrome who is able to have children will have a 50% chance of passing the mutated gene to his or her child. Because of the incongruence in genotype and phenotype of CHARGE syndrome, it is impossible to predict, on the basis of the affected parent's presentation, how severely affected the child will be. As clinical management of CHARGE syndrome improves and as survival and functionality of this patient population increase, genetic counseling will become increasingly important.

DIAGNOSIS OF CLINICAL CHARGE SYNDROME

Diagnosis of clinical CHARGE syndrome is a complicated task, historically achieved by the observation of some combination of the 6 previously listed attributes. Which anomaly or which combination of anomalies carries the greatest diagnostic weight is not entirely clear. Many diagnostic algorithms have been used in past years. Over 30 years ago, Dr. Bryan Hall first described an association of choanal atresia with malformations of the heart, eyes, and gastrointestinal tract.[17] Two years later, Pagon and Zonana suggested the mnemonic CHARGE and recommended that diagnosis be limited to patients who display at least 4 of the 7 anomalies represented in this mnemonic.[1] Since that time, Kim Blake[18] and Alain Verloes[11] have suggested further refinements of the original diagnostic criteria. (A comparison of the 3 algorithms is given in Tables 1–3.) As a result of this evolving diagnostic process, accurate identification of CHARGE syndrome has remained largely subjective and has been based on various algorithms.

TABLE 1. Pagon's Diagnostic Criteria

Coloboma
Heart
Atresia choanae
Postnatal growth deficiency
Retarded development and/or CNS anomalies
Genital hypoplasia
Ear
Diagnosis of CHARGE if patient has 4 out of 7 criteria. Must have coloboma and/or choanal atresia.

Abbreviation: CNS, central nervous system.

Data from Pagon.[1]

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TABLE 2. Blake's Diagnostic Criteria[a]

Major	Minor	Occasional
Coloboma of iris, retina, choroid, disc; microphthalmia	Genital hypoplasia	Thymic/parathyroid hypoplasia
Choanal atresia	Developmental delay	Renal anomalies
Characteristic ear abnormalities	CV malformations	Hand anomalies
Cranial nerve dysfunction	Growth deficiency	General appearance
	Orofacial cleft	Abdominal defects
	TEF	Spine anomalies
	Characteristic face	
Diagnosis of CHARGE if patient has:		
All 4 major criteria		
3 major and 3 minor criteria		
2 major criteria and several minor criteria		

Abbreviations: CV, cardiovascular; TEF, tracheoesophageal fistula.

[a]*Data from Blake et al.*[18]

DIAGNOSIS OF GENETIC CHARGE SYNDROME

Recent genetic discoveries have provided an additional factor for consideration in the diagnostic process but have failed to provide a definitive diagnostic tool due to the fact that not all patients with clinical CHARGE syndrome test positive for genetic CHARGE. In 2004, Vissers et al[4] proposed that a mutation of the CHD7 gene on the long arm of chromosome 8 is the cause of the CHARGE phenotype. This study, however, showed that only approximately 60% of patients with clinical CHARGE syndrome also have the corresponding genetic mutation. Several subsequent studies have produced similar percentages.[8,12,13,15] These results can be interpreted in 2 ways. The first possible interpretation is that the test is only 60% accurate. The second possible interpretation is that 40% of patients diagnosed with *clinical* CHARGE syndrome do not actually have *genetic* CHARGE. Both interpretations, in fact, may be true.

First, genetic testing for a CHD7 mutation is not 100% accurate. Subsequent studies have provided examples of patients who initially tested negative for

TABLE 3. Verloes' Diagnostic Criteria[a]

Major	Minor
1. Coloboma (iris or choroid, with or without microphthalmia	1. Cranial nerve palsies or brainstem dysfunctions
2. Choanal atresia	2. Growth hormone and/or gonadotropin deficiencies
3. Hypoplastic semicircular canals	3. Abnormal middle or external ear
	4. Malformation of mediastinal organs (heart and/or esophagus)
	5. Mental retardation
Typical diagnosis of CHARGE if patient has:	
3 major criteria	
2 major criteria and 2 minor criteria	
Partial diagnosis of CHARGE if patient has:	
2 major criteria and 1 minor criteria	
Atypical diagnosis of CHARGE if patient has:	
2 major criteria	
1 major criteria and 3 minor criteria	

[a]*Data from Verloes.*[11]

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a CHD7 mutation but later tested positive with improved testing methods.[8] This means that current testing methods are not 100% precise in identifying a genetic mutation, and that as technology improves, previously undetectable mutations may be identified. In cases where mutations are not discovered by genetic sequencing, screening for intragenic deletions with multiplex ligation-dependent probe amplification is recommended.[6,13]

Second, some patients diagnosed with clinical CHARGE may indeed not have genetic CHARGE. Because of the subjective nature of a clinical CHARGE syndrome diagnosis, it is almost certain that some patients have been inappropriately diagnosed. These patients may have a different genetic aberration that produces a similar phenotypic presentation. Some clinicians argue that even a patient who lacks a CHD7 mutation but who fulfils the phenotypic criteria of CHARGE syndrome does indeed have CHARGE. They stress that a CHARGE diagnosis cannot be rejected simply because of the absence of a CHD7 mutation.[8] At some point, however, clinicians must separate genotype from phenotype, and etiology from presentation.

Toward this goal, researchers have performed genetic analysis of patients with clinical CHARGE, separated those who test positive for genetic CHARGE, and then analyzed the phenotype of only those patients. Three such studies have been published, the results of which are summarized in this article in an attempt to answer the following questions: What is the phenotype of patients with *genetic* CHARGE syndrome? Is this phenotype in alignment with the accepted algorithms for clinical diagnosis of CHARGE syndrome?

PHYSICAL ASSESSMENT

Eye

Coloboma

Coloboma is a fissure or segmental defect in the eye.[19] The presence of this rare malformation has historically been perceived as a strong indicator of clinical CHARGE syndrome, with a reported incidence of 80% to 90%.[6,18] Current studies of patients with confirmed genetic CHARGE syndrome have verified this strong association of coloboma and genetic CHARGE syndrome,[8,12,13,15] with 67 of the 85 patients (79%) included in this analysis having either unilateral or bilateral coloboma.

Coloboma may be bilateral or unilateral and may affect only the iris or extend to the choroid, retina, macula, and/or optic nerve. Patients with coloboma involving only the iris will likely have normal vision but may be predisposed to photophobia.[6] Patients with posterior involvement, or involvement of the chorioretina, macular disc, and/or optic disc, have a higher likelihood of visual impairment.[19] Patients with chorioretinal coloboma are at risk for retinal detachment.[20] It is important to note that posterior involvement may occur in the absence of iridial coloboma and therefore may be undetectable upon cursory examination. Any patient, therefore, with suspected CHARGE syndrome should be evaluated by an ophthalmologist.

Microphthalmia

Microphthalmia is defined as an eye with an axial length at least 2 standard deviations below the mean for that age group.[20] This means that the volume of the eye globe is significantly smaller than normal. It can occur in conjunction with coloboma or in isolation and is a common ocular finding in clinical CHARGE syndrome.[5-7] Specific numbers of reported incidence are neither available for clinical CHARGE syndrome nor described in current studies of patients with genetic CHARGE. This abnormality is usually grouped with coloboma.

Microphthalmia is difficult if not impossible to diagnose during the neonatal period. According to some references, the average axial length of a newborn is 18 mm, but others argue that this figure is subjective.[20] For the preterm infant, this definition is further confounded because of lack of reliable information regarding normal values. Consequently, a firm diagnosis of microphthalmia may be impossible to assign during this developmental stage.

Heart

Heart defects may include, but are not limited to, conotruncal anomalies (Tetralogy of Fallot, truncus arteriosus, and interrupted aortic arch), atrioventricular canal defects, aortic arch anomalies, and atrial septal defects, ventricular septal defects, and patent ductus arteriosus.[6] The reported incidence of heart malformations in clinical CHARGE is 75% to 85%.[8] Fifty-nine of the 85 patients (69%) included in this analysis had some form of cardiac malformation.[8,12,13] Only 1 study of patients with genetic CHARGE syndrome did separate various types of cardiac malformations in this population. This study, however, included only 17 patients; therefore, conclusions cannot be drawn regarding frequency of specific types of cardiac malformations. It seems, however, that aortic arch defects are common among patients with genetic CHARGE syndrome.[12]

Choanal Atresia

Choanal atresia is defined as a narrowing or blockage between the nasal cavity and the nasopharynx. The blockage may be bony or membranous and may occur in 1 or both nasal passages.[5] This malformation has been a strong indicator of clinical CHARGE syndrome, with a reported incidence of 50% to 60%.[5,6] According to Pagon's[1] criteria, this malformation is

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of such great importance that either it or coloboma must be present before additional diagnostic steps should even be considered (see Table 1). In addition, it is one of Blake's 4 and Verloes' 3 major criteria (see Tables 2 and 3). Interestingly, choanal atresia was observed in only 31 of the 85 patients (36%) with genetic CHARGE syndrome. It is possible that this characteristic has been assigned more significance than is prudent when predicting genetic CHARGE syndrome. It is important to note, however, that choanal atresia rarely occurs in isolation and remains, therefore, a valuable diagnostic tool.

Choanal atresia may present as respiratory failure during quiet states when the infant is attempting to breathe through his or her nose. Choanal atresia can be confirmed with a failure to pass a nasogastric tube through the nose and into the pharynx. Unilateral choanal atresia is less obvious and may present as 1-sided rhinorrhea as mucous will still be produced by the mucous membrane, but will not be able to drain into the pharynx.[6] Patients with bilateral choanal atresia will require endotracheal intubation or management with an oral airway until surgical repair can be performed.

Restricted Growth

Growth restriction in CHARGE syndrome refers to postnatal growth rather than intrauterine growth. Most infants with clinical CHARGE syndrome are appropriate-for-gestational age at birth but then fail to achieve optimal growth.[5,6] The reported incidence of growth restriction in clinical CHARGE syndrome is 70% to 80%.[6] In patients with genetic CHARGE syndrome, growth restriction occurred in 38 of 51 patients or 75% of those studied.[8,13]

Growth failure may be a primary feature of CHARGE syndrome of unknown etiology,[21] or it may be caused by suboptimal nutritional intake secondary to feeding difficulties or, in few cases, a growth hormone deficiency.[6,8,21] Patients with suspected CHARGE syndrome should receive a swallow evaluation to rule out silent aspiration secondary to uncoordinated swallowing and/or gastroesophageal reflux.[6]

CNS Abnormalities

CNS abnormalities in CHARGE syndrome are highly variable and typically result from a dysfunction of 1 or more cranial nerves. Dysfunction of cranial nerve I, resulting in anosmia, or loss of smell, is highly suggestive of clinical CHARGE syndrome.[5,6] Dysfunction of cranial nerve VII results in facial palsy, and dysfunctions of cranial nerves IX, X, and XI may result in swallowing problems, aspiration, and/or gastroesophageal reflux. Dysfunction of cranial nerve VIII may cause hearing loss. These anomalies are often asymmetric.

In clinical CHARGE patients, facial palsy is reported in 50% of cases.[6] Hearing loss is reported commonly, although the exact incidence is difficult to quantify because of a wide range of hearing deficits.[6] Anosmia is likely underreported, especially in the neonatal population because of ambiguous diagnostic criteria.[22] Swallowing difficulties are reported in 70% to 90% of patients with clinical CHARGE.[6]

In patients with genetic CHARGE syndrome, analysis of all cranial nerve functions is lacking. Hearing loss is the only symptom of cranial nerve dysfunction that has been reported consistently. Of those patients studied, 78% had some form of hearing loss. It is important to note, however, that hearing loss may occur secondary to cranial nerve dysfunction but may also result from a variety of physical malformations of the inner ear, including malformation of the cochlea, absent ossicles, or absence of the oval window among others.[6] Hearing loss, therefore, cannot be used as a sole identifier of cranial nerve dysfunction. Further studies are needed to more fully understand the range of cranial nerve dysfunction in patients with genetic CHARGE syndrome.

Genitourinary

Genitourinary complications in patients with CHARGE syndrome typically present as cryptorchidism and micropenis. In patients with clinical CHARGE syndrome, the occurrence rate is 50% to 60% of male patients.[6]

Micropenis and cryptorchidism, however, occur secondary to hypogonadotropic hypogonadism,[23] is a condition in which the testes or ovaries do not function properly because of low amounts of luteinizing hormone (LH), follicle-stimulating hormone (FSH), or both.[24] Under normal circumstances, these hormones are released by the pituitary gland after signaling from the hypothalamus. They act on the ovaries or testes, stimulating the release of hormones that then bring about sexual development during puberty.[24]

In male infants, this deficiency is relatively easy to diagnose because it often manifests as micropenis and/or cryptorchidism. In female infants, however, the deficiency does not affect external genital development and therefore cannot be diagnosed by physical examination. Interestingly, ultrasound examination of females with genetic CHARGE syndrome sometimes reveals a hypoplastic uterus.[8] For both genders, this hormonal deficiency manifests later in life as delayed or absent puberty.

For female patients, despite the absence of physical presentation, diagnosis of hypogonadism is possible during infancy through the analysis of LH and FSH levels. This analysis must occur within the first 3 months of life when LH and FSH serum levels are normally high. After this time, the levels of these hormones gradually decrease until puberty. During this narrow, 3-month window, an infant with suspected CHARGE syndrome should be

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evaluated for abnormally low LH and FSH serum levels. Low levels of these hormones, in the female patient, would fulfill the "genital hypoplasia" criteria in CHARGE mnemonic. If infants are not tested during this time, they cannot be accurately evaluated until puberty.[23]

In patients with genetic CHARGE, consistent assessment parameters of genitourinary abnormalities are not available. For example, one study separated "gonadal deficiency" and "micropenis and cryptorchidism,"[25] while another study simply reported "genital anomalies."[13] With current research, it is impossible to extrapolate precise percentages of genetic CHARGE patients who indeed have hypogonadotropic hypogonadism. It is clear, however, that hypogonadotropic hypogonadism may be highly underrepresented in the female patient population. One study shows that 7 of 8 patients (88%) with genetic CHARGE past the age of puberty, and therefore able to be assessed for gonadotropin deficiency, did indeed have a gonadotropin deficiency.

Ear

Ear abnormalities may involve the inner ear, outer ear, or both. External malformations usually involve an abnormal shape and position of the pinnae, specifically, reduced vertical height of the pinna and a cup-shaped, wide helix.[7] The ears may protrude from the head and may be asymmetric.[6] Preauricular tags may also be observed.[7]

Inner ear, or auditory canal, abnormalities may include a hypoplastic incus, decreased numbers of turns in the cochlea, or absent semicircular canals.[26] These malformations must be evaluated through computed tomographic scan or magnetic resonance imaging of the temporal bone. Abnormalities of the semicircular canals are highly suggestive of genetic CHARGE syndrome.[8,13,15] Of the 85 patients with a confirmed genetic CHARGE syndrome, 83 (98%) had external ear malformations, and 56 of 72 patients (78%) had some form of hearing loss.

Occasional Findings

During the prenatal period, polyhydramnios may be observed secondary to bilateral posterior choanal atresia or cranial nerve dysfunction, resulting in an insufficient swallowing mechanism.[18] Esophageal atresia and tracheoesophageal fistulas as well as cleft lip and/or palate have also been reported.[6] One study also reported a high incidence of hypocalcemia in CHARGE patients. Hypocalcemia paired with cardiac malformations often leads clinicians to suspect DiGeorge syndrome, but CHARGE syndrome should not be ruled out.

OUTCOMES

Mortality of patients with CHARGE syndrome is highly dependent on phenotype. Patients with cyanotic heart lesions, tracheoesophageal fistula (TEF), or bilateral choanal atresia have the poorest likelihood of survival.[18] Delivery at a tertiary center is critical for initial stabilization of these patients.

Morbidity is highly influenced by feeding difficulties[14] and immune function.[27] Feeding difficulties are caused by cranial nerve IX and X dysfunction and can be complicated by choanal atresia, TEF, and/or cleft lip and palate.[22] One study found that feeding difficulties occurred in 70% of patients with genetic CHARGE syndrome.[8] Recent studies have revealed that immune compromise is an often-missed complication of CHARGE syndrome. In 2009, Jyonouchi et al[27] found that 60% of patients with genetic CHARGE syndrome had immune compromise presenting as lymphopenia. Of the 8 patients in this study who died during infancy, 7 had profoundly low lymphocyte numbers (<2000 cells/mL). Other studies have produced similar results, demonstrating that T-cell lymphopenia, impaired T-cell function, low immunoglobulins, and severe T-cell deficiency all occur in patients with CHARGE syndrome.[28] Although immune compromise is not part of the broadly accepted spectrum of anomalies in clinical CHARGE syndrome, research suggests that clinicians should be aware of the high risk of cell mediated and humoral immunity defects in this patient population.[27] Patients with severe compromise should receive irradiated blood to avoid graft versus host disease and should not receive live vaccines.[27]

CONCLUSION

In response to the question, "What is the phenotype of genetic CHARGE syndrome?" this analysis of the literature shows that external ear malformations are the strongest indicator of a CHD7 mutation followed by coloboma. Hearing loss, restricted growth, and gonadotropin deficiency are also strong indicators, but these characteristics cannot be assessed directly after birth and therefore lack utility in early diagnosis. Heart malformations are common in genetic CHARGE, occurring in 69% of cases. Choanal atresia, surprisingly, is the least suggestive characteristic, with an incidence of 36%. It is important to remember that immune compromise is a common and often overlooked characteristic of this population.

Although the diagnostic process of CHARGE syndrome is not yet perfect, 30 years of research *have* revealed a great deal about how to promote health in this patient population despite the complex nature of this syndrome. Precise and rapid genetic diagnosis, while ideal, is less important than multisystem management and multidisciplinary care coordination.

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