Neonatal Presentations of CHARGE Syndrome and VATER/VACTERL Association
Julie Kaplan and Louanne Hudgins
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Neonatal Presentations of CHARGE Syndrome and VATER/VACTERL Association

Julie Kaplan, MD,* Louanne Hudgins, MD*

Author Disclosure
Drs Kaplan and Hudgins have disclosed no financial relationships relevant to this article. This commentary does not contain a discussion of an unapproved/investigative use of a commercial product/device.

Objectives  After completing this article, readers should be able to:
1. Describe the difference between a syndrome and an association.
2. Recognize the phenotype of CHARGE syndrome as it presents in the newborn period.
3. Recognize the phenotype of VACTERL association as it presents in the newborn period.
4. Construct a differential diagnosis based on some of the common findings in these disorders.
5. Initiate a plan for diagnostic evaluation and management for these two disorders.

Abstract
Neonatologists often care for newborns who have multiple congenital anomalies. The specific diagnosis has implications for the infant’s clinical management. In this article, we examine the neonatal presentations of CHARGE syndrome and VATER/VACTERL association. Once the features of these two entities are recognized clinically, the appropriate diagnostic evaluations can be initiated.

Introduction
In evaluating a newborn who has multiple congenital anomalies, the specific diagnosis has implications for management and recurrence risk. An association originally was defined by the International Group in 1982 as a “nonrandom occurrence in two or more individuals of multiple congenital anomalies not known to be a polytypic defect, sequence or syndrome.” In general, associations do not have a known genetic cause, are not associated with developmental disabilities, and have a low recurrence risk for parents and the affected individual. A syndrome, on the other hand, generally refers to a pattern of congenital anomalies that can be explained by a common developmental or genetic cause, often is associated with developmental disabilities, and can have significant recurrence risk for the parents or the affected individual.

The field of molecular genetics has seen remarkable advances in the past decade, and the molecular causes for various genetic conditions recently have been elucidated. CHARGE syndrome is an example of a genetic disorder that was referred to previously as an association until a molecular cause was discovered. VATER/VACTERL still is referred to as an association; the acronym describes anomalies that occur together more often than by chance alone, but there is currently no known pathogenetic cause.

CHARGE Syndrome
In 1979, Hall described 17 children who had multiple congenital anomalies, all of whom had choanal atresia. Also in 1979, Hittner and associates described 10 children who had coloboma, congenital heart disease, and hearing loss. The acronym CHARGE initially was coined by Pagon and colleagues in 1981 and was defined as including Coloboma, Heart defect, Atresia choanae, Retarded growth and development, Genital hypoplasia, and Ear anomalies/deafness. Because a common pathogenetic basis was discovered in 2004, the association now is referred to as CHARGE syndrome. CHARGE syndrome has a prevalence of 1 per 10,000 to 1 per 15,000, and although it is an autosomal dominant disorder, most cases represent simplex cases (the first case discovered in a family).
Clinical Findings

Colobomas are present in 80% to 90% of patients who have CHARGE syndrome, and retinal colobomas are more common than iris colobomas (Fig. 1). Retinal involvement can affect the optic nerve or macula, leading to impaired visual acuity. Severe chorioretinal colobomas can be associated with microphthalmia. Newborns in whom CHARGE syndrome is suspected should receive an ophthalmologic evaluation for retinal colobomas and be monitored by ophthalmology with an eye examination every 6 months.

Heart defects are often complex and found in 75% to 85% of those who have CHARGE syndrome. Although cardiac defects can vary substantially, conotruncal anomalies (tetralogy of Fallot, double-outlet right ventricle, truncus arteriosus, and perimembranous ventricular septal defect) and aortic arch anomalies (interrupted aortic arch, vascular ring, and aberrant subclavian artery) comprise 38% to 40% of the defects seen in CHARGE syndrome. Other common defects include atrioventricular canal defects, atrial septal defects, ventricular septal defects, and patent ductus arteriosus.

Choanal atresia is a blockage in the passages between the nasal cavity and the nasopharynx. Affected individuals may have a complete blockage (choanal atresia) or a partial blockage (choanal stenosis), and the blockage may be unilateral or bilateral. Whereas bilateral choanal atresia causes significant respiratory distress in the newborn, unilateral choanal atresia or choanal stenosis may not be detected in the newborn period; the older child who has choanal stenosis or unilateral choanal atresia may present with persistent rhinorrhea or infections. Choanal atresia or stenosis is present in 50% to 60% of patients who have CHARGE syndrome and should focus the clinician’s attention on involvement of other organ systems, such as the eye and heart. Individuals who have bilateral posterior choanal atresia often have a prenatal history of polyhydramnios, believed to be due to an insufficient swallowing mechanism. The inability to pass a nasogastric tube should alert the clinician to the possibility of choanal atresia, but computed tomography (CT) scan of the nasopharynx and nasal cavity is necessary to evaluate the quality of the blockage. Bilateral choanal atresia is a medical emergency that should be corrected surgically as soon as possible. Chronic otitis media and deafness are potential complications of choanal atresia.

Infants affected with CHARGE syndrome typically have normal growth parameters at birth, but their linear growth tends to decline by late infancy. Some children have been found to have growth hormone deficiency, but growth deceleration frequently is due to cardiac, respiratory, or feeding problems. Early intervention for feeding difficulties is important.

Most children who have CHARGE syndrome show marked delays in motor development. Such delays can be due to prolonged hospitalizations, truncal hypotonia with ligamentous laxity, decreased visual acuity, or vestibular disturbances. Language development often is delayed as well due to hearing loss. Other individuals may have central nervous system abnormalities that can include arrhinencephaly; holoprosencephaly; hypoplasia of the cerebellum, inferior cerebellar vermis, and brainstem; cerebellar heterotopias; and absence of the septum pellucidum. Due to the variable nature of the developmental delay, the extent of the delay should not be used to predict cognitive function. Cognitive function may range from learning disabilities to profound mental retardation.

Genital hypoplasia is present in about 50% to 60% of males who have CHARGE syndrome and can manifest as microphallus, hypospadias, cryptorchidism, chordee, and bifid scrotum. Female genital hypoplasia may be more difficult to recognize externally, but hypoplastic labia and clitoris and atresia of the uterus, cervix, and vagina have been reported. Renal anomalies have been reported in 25% to 40% of individuals and include unilateral renal agenesis, hydronephrosis, renal hypoplasia, duplex kidneys, and vesicoureteral reflux. Hypogonadotropic hypogonadism can occur in males and females and is associated with delays in puberty and low concentrations of luteinizing hormone and follicle-stimulating hormone.

Ear anomalies occur in approximately 90% of children and can involve the outer, middle, or inner ear. The typical “CHARGE ear” is protuberant, short, and wide, with a hypoplastic lobule, prominent antihelix, and tri-
angular concha (Fig. 2). Middle ear anomalies include ossicular malformations, an abnormal or absent oval window, and absent stapedius muscle. Among the inner ear anomalies are aplastic or hypoplastic semicircular canals, and the Mondini defect (decreased number of turns to the cochlea) is present in up to 95% of affected individuals and can be detected by CT scan of the temporal bones. Temporal bone abnormalities also may be present. The combination of ossicular malformations and inner ear defects frequently results in a mixed (conductive and sensorineural) hearing loss that can range from mild to profound.

Although not described in the original acronym, cranial nerve (CN) anomalies also are common and now are included among the major diagnostic criteria (Table). Such anomalies usually are asymmetric and can involve CN I, resulting in hyposmia or anosmia (an absent or hypoplastic olfactory bulb is highly indicative of CHARGE); CN V, resulting in the incoordination of sucking, chewing, and swallowing; CN VII, resulting in facial paralysis that is usually unilateral (Fig. 3); CN VIII, resulting in sensorineural hearing loss; and CN IX/X/ XI, resulting in dysfunctional swallowing, gastroesophageal reflux, and velopharyngeal aspiration.

A clinical diagnosis of CHARGE syndrome can be made based on the major and minor diagnostic criteria (Table) defined by Blake and associates in 1998. The presence of all four major criteria (choanal atresia, coloboma, characteristic ears, and cranial nerve anomalies) or three major and three minor characteristics indicates a diagnosis of CHARGE syndrome. The diagnosis should be considered strongly in any neonate who exhibits one of the major diagnostic criteria, and evaluation for abnormalities in other organ systems involved in CHARGE should be initiated.

**Genetic Testing**

In 2004, Vissers and colleagues identified a molecular cause for CHARGE syndrome. The responsible gene is CHD7 (chromodomain helicase DNA-binding protein 7); the encoded protein regulates gene expression by altering chromatin structure and plays a critical role in embryogenesis. Clinical testing is currently available, and the mutation detection frequency is approximately 60% to 65%.

Despite the availability of mutation analysis, CHARGE syndrome remains a clinical diagnosis. In the neonatal period, the presence of iris or retinal coloboma, choanal atresia, characteristic ears, hearing loss, facial nerve palsies, or congenital heart defects should alert the physician to the possible diagnosis. The evaluations initiated in the neonatal intensive care unit should include an ophthalmology examination, echocardiography, ear-nose-throat evaluation, renal ultrasonography, and hearing screen. The most sensitive diagnostic study, which has implications for management, is a CT scan of the temporal bones. Approximately 95% of affected patients have abnormalities of the inner and middle ear, including the Mondini defect, aplasia or hypoplasia of the semicircular canals, and ossicular malformations. A high-resolution karyotype should be performed to rule out a chromosomal abnormality as the cause of multiple malformations. CHD7 analysis may be helpful in cases where the diagnosis is not clear, especially if the family is interested in prenatal diagnosis for future pregnancies. In simplex cases, the recurrence risk for the parents is low, but prenatal testing can be offered to the family if there is a known mutation to rule out the unlikely event of germline mosaicism. The individual who has CHARGE syndrome has a 50% risk of having an affected child with each pregnancy.

**VATER/VACTERL Association**

In contrast to CHARGE syndrome, VATER (or VACTERL) association does not have a known molecular cause. VATER association initially was described by Quan and Smith in 1973, and the acronym describes the components: Vertebral defects, Anal atresia, Tracheoesophageal fistula with esophageal atresia, and Radial and Renal dysplasia. Kaufman (1973) and Nora and Nora (1975) subsequently added “C” for cardiac defects and “L” for limb defects to broaden the acronym to VACTERL.
Vertebral defects that have been described in VACTERL association include hemivertebrae, congenital scoliosis, hypersegmentation defects, and sacral dysgenesis; thoracolumbar hemivertebrae have been reported most frequently. Anal atresia or stenosis requires prompt surgical consultation and intervention. A wide range of cardiac anomalies have been described in the VACTERL association, although septal defects appear to be most common. Tracheoesophageal fistula or esophageal atresia occurs in approximately 1 in 3,500 births and is associated with other anomalies in about 50% of cases. Renal anomalies include renal agenesis, ureteropelvic junction obstruction, and severe reflux. Limb defects tend to involve the upper limbs more often than the lower limbs; with upper limb involvement, the radial bones are affected more frequently than the ulnar bones. Radial aplasia, deviation of the hand, absence of the thumb, hypoplastic and rudimentary thumb, and preaxial polydactyly have been described.

Individuals who have VACTERL association usually do not have dysmorphic facial features, abnormalities of growth, or mental deficiency. Therefore, VACTERL is a diagnosis of exclusion that should not be made until at least 1 year of age, when growth and development can be confirmed to be normal.

The differential diagnosis in the newborn period includes CHARGE syndrome, 22q11 deletion syndrome, and Townes-Brocks syndrome. Infants who have CHARGE syndrome can have cardiac defects, tracheoesophageal fistula, vertebral anomalies, and renal anomalies. If the diagnosis of CHARGE syndrome is consid-

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### Table. Diagnostic Criteria of CHARGE Syndrome

<table>
<thead>
<tr>
<th>Feature</th>
<th>Manifestations</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major Diagnostic Criteria (4 Cs)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coloboma</td>
<td>Coloboma of the retina, iris, choroid, and disc; microphthalmia</td>
<td>80% to 90%</td>
</tr>
<tr>
<td>Choanal Atresia/stenosis</td>
<td>Unilateral or bilateral, membranous or bony, stenosis or atresia</td>
<td>50% to 60%</td>
</tr>
<tr>
<td>Cranial Nerve Dysfunction</td>
<td>Olfactory tract anomalies, unilateral or bilateral facial palsy, sensorineural hearing loss, velopharyngeal incoordination</td>
<td>75% to 95%</td>
</tr>
<tr>
<td>Characteristic Ear Anomalies</td>
<td>Outer: Short, wide, hypoplastic lobule, prominent antihelix, triangular concha</td>
<td>90%</td>
</tr>
<tr>
<td></td>
<td>Middle: Ossicular malformations</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Inner: Aplastic or hypoplastic semicircular canals, Mondini defect</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Temporal bone abnormalities</td>
<td></td>
</tr>
<tr>
<td><strong>Minor Diagnostic Criteria</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular Malformations</td>
<td>Most commonly conotruncal defects, atrioventricular canal defects, and aortic arch abnormalities</td>
<td>75% to 85%</td>
</tr>
<tr>
<td>Genital Hypoplasia</td>
<td>Males: Microphallus, cryptorchidism</td>
<td>50% to 60%</td>
</tr>
<tr>
<td></td>
<td>Females: Hypoplastic labia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Both: Hypogonadotropic hypogonadism</td>
<td></td>
</tr>
<tr>
<td>Developmental Delay</td>
<td>Delayed motor milestones, delayed language, hypotonia</td>
<td>~100%</td>
</tr>
<tr>
<td>Growth Deficiency</td>
<td>Short stature (usually postnatal), occasional growth hormone deficiency</td>
<td>70% to 80%</td>
</tr>
<tr>
<td>Orofacial Cleft</td>
<td>Cleft lip±palate</td>
<td>15% to 20%</td>
</tr>
<tr>
<td>Tracheoesophageal Fistula</td>
<td>All types</td>
<td>15% to 20%</td>
</tr>
<tr>
<td>Distinctive Facial Features</td>
<td>Square face with broad prominent forehead, prominent nasal bridge and columella, flat midface</td>
<td>70% to 80%</td>
</tr>
<tr>
<td><strong>Occasional Abnormalities</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Renal Anomalies</td>
<td>Unilateral renal agenesis, horseshoe kidney, hydronephrosis, renal hypoplasia, duplex kidney, vesicoureteral reflux</td>
<td></td>
</tr>
<tr>
<td>Spinal Anomalies</td>
<td>Scoliosis, kyphosis, osteoporosis, hemivertebrae</td>
<td></td>
</tr>
<tr>
<td>Hand Anomalies</td>
<td>Polydactyly, altered palmar flexion creases, atypical split hand/split foot deformity, clinodactyly, camptodactyly, cutaneous syndactyly</td>
<td></td>
</tr>
<tr>
<td>Neck/Shoulder Anomalies</td>
<td>Short/webbed neck, Sprengel deformity</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Omphalocele, umbilical hernia</td>
<td></td>
</tr>
</tbody>
</table>

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**Clinical Findings**

Vertebral defects that have been described in VACTERL association include hemivertebrae, congenital scoliosis, hypersegmentation defects, and sacral dysgenesis; thoracolumbar hemivertebrae have been reported most frequently. Anal atresia or stenosis requires prompt surgical consultation and intervention. A wide range of cardiac anomalies have been described in the VACTERL association, although septal defects appear to be most common. Tracheoesophageal fistula or esophageal atresia occurs in approximately 1 in 3,500 births and is associated with other anomalies in about 50% of cases. Renal anomalies include renal agenesis, ureteropelvic junction obstruction, and severe reflux. Limb defects tend to involve the upper limbs more often than the lower limbs; with upper limb involvement, the radial bones are affected more frequently than the ulnar bones. Radial aplasia, deviation of the hand, absence of the thumb, hypoplastic and rudimentary thumb, and preaxial polydactyly have been described.

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ered, a CT scan of the temporal bones should be obtained to look for the suggestive middle and inner ear defects. The phenotype of 22q11 deletion syndrome is extremely variable; cardiac and renal anomalies are common, but anomalies in almost every organ system have been reported. Newborns who have a 22q11 deletion frequently exhibit a distinctive facial appearance (laterally built-up nasal bridge, small mouth, and short palpebral fissures), long fingers and toes, and possibly hypocalcemia. A fluorescence in situ hybridization study for 22q11.2 deletion can be ordered to exclude this diagnosis. Townes–Brocks syndrome is characterized by the triad of imperforate anus, dysplastic ears (with or without pits or tags and hearing loss), and thumb anomalies (triphalangeal thumbs, preaxial polydactyly, or hypoplastic thumbs). Affected infants also may have cardiac and renal anomalies. This syndrome should be considered due to the considerable overlap in phenotype. Clinically available genetic testing for Townes-Brocks syndrome has a detection rate of 70% to 75%.

Multiple case reports have linked hydrocephalus with VACTERL association (VACTERL-H). VACTERL-H may represent a distinct syndrome because both autosomal recessive and X-linked patterns of inheritance have been described. In contrast, VACTERL association is usually sporadic. VACTERL-H is associated with a poorer prognosis in terms of survival and mental handicap. Overlap in the features associated with VACTERL-H and Fanconi anemia has been reported in several cases. Fanconi anemia is an autosomal recessive disorder of DNA repair that leads to bone marrow failure in childhood and increased risk of malignancy; diagnosis can be made using chromosomal breakage studies. In 2005, Faivre and associates recommended chromosomal breakage studies in cases of VACTERL-H and cases of VACTERL in which the infant has dysmorphic features, skin pigmentation abnormalities, growth retardation, or microcephaly.

Genetic Testing
If VACTERL association is considered, evaluations in the neonatal period should include echocardiography, renal ultrasonography, radiographs of the spine, radiographs of the extremities if abnormalities are noted on examination, and an ophthalmologic evaluation. In addition, high-resolution chromosome analysis and a genetics consultation should be obtained to exclude other genetic causes. The recurrence risk for parents and for the individual is low, and the cause is unknown, although VACTERL is related to maternal diabetes in the minority of cases.

Summary
Although CHARGE syndrome and VACTERL association have several features in common, the distinction between these two entities affects management, prognosis, and recurrence risk. In addition, a broad differential diagnosis needs to be considered in any patient who has features of VACTERL association because this is a diagnosis of exclusion. A genetics evaluation should be considered for any newborn who has multiple congenital anomalies.

Suggested Reading
Blake KD, Prasad C. CHARGE syndrome. Orphanet J Rare Dis. 2006;1:34


Nora AH, Nora JJ. A syndrome of multiple congenital anomalies associated with teratogenic exposure. *Arch Environ Health.* 1975;30:17–21


Temtamy SA, Miller JD. Extending the scope of the VATER association: definition of the VATER syndrome. *J Pediatr.* 1974;85:345–349


**NeoReviews Quiz**

7. A syndrome is a pattern of congenital anomalies that can be explained by a genetic abnormality, often is associated with developmental disability, and can have a significant recurrence risk for the parents or the affected individual. The clinical manifestations of a syndrome often are classified as major and minor diagnostic criteria. Of the following, the major diagnostic criterion with the highest frequency of occurrence for CHARGE syndrome is:

A. Cardiovascular malformation.
B. Choanal atresia.
C. Cranial nerve dysfunction.
D. Genital hypoplasia.
E. Intrauterine growth restriction.

8. An association is a pattern of congenital anomalies that does not have a known genetic cause, rarely leads to developmental disability, and has a low recurrence risk for the parents or the affected individual. VACTERL association is a typical example of an association of congenital anomalies. Of the following, the congenital anomaly most characteristic of VACTERL association is:

A. Facial dysmorphism.
B. Mondini inner ear defect.
C. Tetralogy of Fallot.
D. Thoracolumbar hemivertebrae.
E. Triphalangeal thumbs.
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