Genetic Testing for CHARGE Syndrome

Description

CHARGE syndrome is a rare genetic condition associated with multiple congenital anomalies. In many individuals, the diagnosis can be made based on clinical findings. However, the phenotype of the disease is highly variable, and some patients do not fulfill the criteria for a definite diagnosis by clinical findings. Sequence analysis of the chromodomain helicase DNA binding protein 7 (CHD7) coding region detects mutations in most individuals with CHARGE syndrome.

Background

Description of the disease

CHARGE syndrome is a rare genetic condition caused by mutations of the CHD7 gene on chromosome 8q12.1. The letters of CHARGE syndrome correspond to clinical features: C = ocular Coloboma; H = Heart defect; A = Atresia choanae; R = Retarded growth and development; G = Genital hypoplasia; and E = Ear anomalies/deafness. However, a number of other malformations are also common in this condition. In particular, hypoplasia of the semi-circular canals has emerged as a frequent and distinctive CHARGE malformation.

Newborns with CHARGE syndrome typically have a several major congenital malformations that affect vision, hearing, cardiovascular function, growth, development, neurologic function, and overall well-being. Mortality is relatively high in neonates with bilateral choanal atresia, cyanotic cardiac malformations, CNS malformations, and/or tracheoesophageal fistula. In one series, the death rate was 20% in the first month of life and about 50% by 6 months of age. (1) A formal epidemiologic study in Canada concluded that those who survived infancy were likely to have long-term survival. (2) Morbidity is chronic and multi-systemic. Cognitive outcome is difficult to assess because both motor skills and language do not necessarily reflect intellect in this group. About 75% have some degree of intellectual disability. Among the 25% with normal intelligence, many are well-educated and live independently as adults. (3) (4)

Investigators have conducted an extended debate about the relative importance of certain clinical signs. Consequently, the diagnostic criteria for CHARGE syndrome have been repeatedly revised.
Clinical diagnosis of CHARGE syndrome

The complete phenotypic spectrum of CHARGE was only revealed after identification of the causative gene in 2004, and the phenotypic spectrum of the disease is highly variable.

A 2012 review (4) proposes that the diagnosis of CHARGE syndrome be considered definite if an individual has 4 major characteristics or 3 major and 3 minor characteristics, as initially proposed by Blake (the Blake criteria), (5) and modified by Verloes. (6) Individuals with 1 or 2 major characteristics and several minor characteristics would be considered to have probable or possible CHARGE syndrome.

Major characteristics

- Ocular coloboma, which may be manifest in the iris and/or the retina, choroid, and optic disc, and sometimes as microphthalmia. (Present in 80-90% of affected individuals)
- Choanal atresia or stenosis, which may be unilateral or bilateral. Complete bilateral choanal atresia is a life-threatening emergency in a newborn, since neonates are obligate nose breathers. Some CHARGE patients have a cleft palate, in which case the cleft fulfills this criterion. (50-60%)
- Cranial nerve abnormality, including hyposmia or anosmia (CN I), facial palsy (CN VII), auditory nerve hypoplasia causing sensorineural hearing loss (CN VIII), and/or swallowing problems (70-90%) with or without aspiration (CN IX and CN X).
- Characteristic auditory manifestation of the external, middle, or inner ear. (80-100%) The external ear is often dysmorphic. A number of ossicular malformations of the middle ear are common. Sensorineural hearing loss is associated with a Mondini malformation of the cochlea, and vestibular dysfunction is caused by aplasia or hypoplasia of the semicircular canals in 95% of individuals with CHARGE. Temporal bone CT is necessary to diagnose the cochlear and semicircular canal defects.

Minor characteristics

- Genital hypoplasia in boys is manifest as micropenis and cryptorchidism, and in girls as hypoplastic labia. Puberty may be delayed because of hypogonadotrophic hypogonadism. (50%)
- Developmental delays, especially gross motor and language delays, which may be intrinsic qualities or caused by impaired balance, deafness, blindness, hypotonia, surgery, or other chronic illness. (100%)
- Congenital cardiac malformations. (80%)
- Short stature, often with postnatal onset. (75%)
- Cleft lip and/or cleft palate. (15%)
- Tracheoesophageal fistula. (15%)
- Distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal bridge. (75%)
Other, less frequent manifestations include kidney malformations (25%), immunodeficiency, various limb abnormalities, scoliosis, dental problems, omphalocele, brain malformations, attention deficit hyperactivity disorder (ADHD), and various behavioral problems.

The diagnosis of CHARGE syndrome is primarily clinical, based on the use of the diagnostic criteria above.

External ear anomalies, abnormalities of cranial nerve function, semicircular canal hypoplasia and gross motor delays seem to be consistent phenotypic manifestations in CHARGE syndrome, but fully one third of CHARGE patients will lack choanal atresia and/or ocular colobomata, with the most mildly affected showing only abnormal ears and a balance disturbance. Consequently, CHARGE syndrome can closely resemble several other genetic and teratogenic conditions, such as the 22q11.2 deletion syndrome, Kallmann syndrome, VACTERL association, Kabuki syndrome, renal coloboma syndrome, Cat eye syndrome, Joubert syndrome, Branchiootorenal syndrome, and retinoic embryopathy. In one patient with velo-cardio-facial syndrome in whom the chromosome 22q11.2 microdeletion was ruled out, a CHD7 mutation was documented. Several patients with Kallmann syndrome were found to have CHD7 mutations.

In recognition of this expanding CHARGE phenotype, Bergman et al. have proposed a revision of cardinal and supporting features and suggest that CHD7 testing be offered to individuals on the milder end of the phenotypic spectrum. (3) Their algorithmic approach to diagnosis also incorporates temporal bone CT scans as an important but not invariably necessary component of the diagnostic workup. Although CHARGE syndrome is most often related to a sporadic mutation, some investigators have proposed that family history (any first degree relative with at least one major feature of CHARGE) be incorporated into the clinical diagnosis of CHARGE syndrome as a major diagnostic criterion. (7)

**Genetics of CHARGE syndrome**

In 2004, mutations of CHD7, which encodes chromodomain helicase DNA-binding protein, were found to cause CHARGE syndrome. In mouse models, the CHD7 gene has been found to be associated with neural crest migration. (8) Almost all pathogenic mutations have proven to be point mutations, though on rare occasions there may be a chromosomal translocation with a breakpoint within the CHD7 gene. Microdeletions, as would be detected with chromosome microarray testing, are rare and probably occur in no more than 2% of individuals.

Most instances of CHARGE syndrome are sporadic events in a family and appear to be caused by de novo CHD7 mutations. On rare occasions CHARGE can be inherited as an autosomal dominant condition. Individuals with CHARGE who reproduce have a 50% chance of transmitting the mutation to their offspring. Recurrence in siblings because of germline mosaicism has also been reported. The prevalence of CHARGE syndrome is estimated at 1 in 8500 live births. (2)

Genetic testing for mutations of CHD7 is commercially available from several commercial laboratories and is generally performed through Sanger sequence analysis.
Treatment of CHARGE syndrome

Extensive management guidelines have been developed for CHARGE syndrome (2, 3, 5, 9) These include periodic examinations and treatment by ophthalmology, otolaryngology, audiology, occupational therapy, speech therapy, gastroenterology, endocrinology, cardiology, neurology, developmental pediatrics, and genetics. Routine investigations would include choanal CT, nasal endoscopy, brainstem auditory evoked responses, temporal bone CT, swallowing studies, renal ultrasound, gonadotropin testing, echocardiography, brain MRI, growth hormone testing, and genetic counseling. Immunological assessment should be considered, particularly if patients have recurrent lung or ear infections. (10) Many of these resources might be provided in due course for a child with multiple congenital anomalies in the absence of an exact etiologic diagnosis. However, a number of specific investigations and therapies might not be considered unless CHARGE syndrome was definitively diagnosed on a clinical basis, or, for mildly affected individuals, as the result of genetic testing.

Regulatory Status

No U.S. Food and Drug Administration (FDA)-cleared genotyping tests were found. Thus, genotyping is offered as a laboratory-developed test. Clinical laboratories may develop and validate tests in-house (“home-brew”) and market them as a laboratory service; such tests must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA).

Policy

*This policy statement applies to clinical review performed for pre-service (Prior Approval, Precertification, Advanced Benefit Determination, etc.) and/or post-service claims.

Genetic testing for CHARGE syndrome may be considered medically necessary to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria. (see Policy Guidelines)

Mutation testing for CHARGE syndrome is considered investigational in all other situations.

Policy Guidelines

A diagnosis of definite CHARGE syndrome can be made clinically in individuals with all 4 major characteristics or 3 major and 3 minor characteristics. (4) In patients without the classical clinical criteria to diagnose CHARGE, in those with a milder phenotype, and/or in those with features that overlap with and cannot be distinguished from other syndromes, genetic testing may provide a definitive diagnosis.

Major characteristics include ocular coloboma, choanal atresia or stenosis, cranial nerve abnormality, ear anomalies/deafness.

Minor characteristics include genital hypoplasia, hypogonadotrophic hypogonadism, developmental delays, cardiac malformations, short stature, cleft lip and/or cleft palate, tracheoesophageal fistula, distinctive CHARGE facial appearance, consisting of a prominent forehead and a prominent nasal
bridge. Other, less frequent manifestations include kidney malformations, immunodeficiency, various limb abnormalities, scoliosis, dental problems, omphalocele, brain malformations, attention deficit hyperactivity disorder (ADHD), and various behavioral problems.

Rationale

Literature Review

**Analytic Validity** (technical accuracy of the test in detecting a mutation that is present or in excluding a mutation that is absent)

Almost all pathogenic mutations are point mutations. More than 500 specific CDH7 mutations associated with CHARGE syndrome have been identified. (11) On rare occasions there may be a chromosomal translocation with a break point within the CDH7 gene. Microdeletions or whole-exon deletions occur in <5% of patients.

Sequencing of the CHD7 gene has high analytical sensitivity and specificity. Sequence analysis detects >99% of the (point) mutations present in the area that has been investigated. Testing that identifies deletions not readily detected by sequence analysis includes MLPA or chromosomal microarray analysis. MLPA has an estimated sensitivity of >95% for deletions and >90% for individual exons. (9)

The analytical sensitivity (proportion of positive tests if the genotype is present) depends on the method used. If only CHD7 sequencing is performed, deletions are missed less than 5% due to whole-exon or whole-gene deletions. If sequencing is combined with MLPA, it is 100%. (9)

The analytical specificity (proportion of negative tests if the genotype is not present) is almost 100% (some variants may erroneously be interpreted as pathogenic). (9)

**Clinical Validity** (diagnostic performance of the test [sensitivity, specificity, positive and negative predictive values] in detecting clinical disease)

The clinical sensitivity (proportion of patients who do not have the disease who have a positive test if the disease is present) can be dependent on variable factors such as age or family history, and may depend on the clinical criteria used. In over 95% of the patients who fulfil the Blake or Verloes criteria, a mutation is found. (9) In those with suspected CHARGE syndrome, a mutation is found in 60–70% of patients.

CHARGE syndrome sometimes can be excluded if a patient does not fulfill the clinical criteria and does not carry a mutation or deletion of CHD7. Some conditions that mimic CHARGE syndrome are 22q11 deletion syndrome, VACTERL association, chromosomal disorders (e.g., deletions 3p12p21.2) disorders caused by teratogens (e.g., maternal diabetes, Accutane), and Kallmann syndrome. (9)

The clinical specificity (proportion of patients who do not have the disease who have a negative test) can be dependent on variable factors such as age or family history. The clinical variability of CHARGE
syndrome is considerable. If the diagnosis is based on the Blake criteria, some individuals with CHARGE will be missed. The clinical specificity is greater than 95%, since less than 5% of the patients with a CHD7 mutation do not completely fulfill these criteria. However, it should be taken into account that the mild end of the phenotypic spectrum is not completely known yet. (9)

Therefore, genetic testing for CHARGE syndrome is very good for confirming a diagnosis, but a negative test does not rule out the disease.

The positive clinical predictive value (life-time risk to develop the disease if the test is positive) is 100%, but there is high clinical variability.

The negative clinical predictive value (probability of not developing the disease if the test is negative), assuming an increased risk based on family history, is 100% if the index case in the family has been tested. If the index case in the family has not been tested, it depends on the a priori chance of the index to find a mutation, which is 60-90%.

There are no known genotype-phenotype correlations for specific CHD7 mutations and CHARGE syndrome manifestations, and therefore, the phenotype cannot be predicted from the genotype.

Clinical Utility (how the results of the diagnostic test will be used to change management of the patient and whether these changes in management lead to clinically important improvements in health outcomes)

Clinical Utility for Individuals with Suspected CHARGE Syndrome: Most cases of CHARGE syndrome can be diagnosed clinically using established major and minor criteria. Scanning of the temporal bones often elicits abnormalities in the semi-circular canals, which brings more specificity to the diagnosis. However, not all patients fulfill the clinical criteria for CHARGE syndrome, and based on clinical findings, may be considered to have possible or probable CHARGE syndrome. Mildly affected patients may only have one or a few of the features of CHARGE syndrome. Overlapping features with other syndromes may also make a clinical diagnosis challenging. Genetic testing may be useful in patients who do not have the classical CHARGE characteristics and may be at risk for the long-term complications of CHARGE syndrome. (9)

Extensive management guidelines have been developed for CHARGE syndrome. These include periodic examinations and treatment by ophthalmology, otolaryngology, audiology, occupational therapy, speech therapy, gastroenterology, endocrinology, cardiology, neurology, developmental pediatrics, and genetics. Routine investigations would include choanal CT, nasal endoscopy, brainstem auditory evoked responses, temporal bone CT, swallowing studies, renal ultrasound, gonadotropin testing, echocardiography, brain MRI, growth hormone testing, and genetic counseling.

Clinical Utility for At-Risk Relatives: Almost all patients diagnosed with CHARGE syndrome do not have an affected parent as most are de novo mutations. Only rare instances of transmission from a mildly affected parent have been reported. (12) Therefore, genetic testing in relatives of a patient with CHARGE syndrome has low clinical utility.
Preconception (carrier) testing and prenatal (in utero) testing can also be performed, but are not addressed in this literature review.

**Clinical Trials**

A search of the online site Clinical Trials.gov in June 2014 found no ongoing trial addressing the use of genetic testing for CHARGE syndrome.

**Practice Guidelines and Position Statements**

In 2011, Bergman et al proposed guidelines for CDH7 analysis, and state that while the diagnosis of CHARGE syndrome remains primarily a clinical diagnosis, molecular testing can confirm the diagnosis in mildly affected patients. (3)

**U.S. Preventive Services Task Force Recommendations**

Genetic testing for CHARGE syndrome is not a preventive service.

**Summary**

CHARGE syndrome is a rare genetic condition associated with multiple associated malformations. In many individuals, the diagnosis can be made based on clinical findings. However, the phenotype of the disease is highly variable, and some patients do not fulfill the criteria for a definite diagnosis by clinical findings. Sequence analysis of the chromodomain helicase DNA binding protein 7 (CDH7) coding region detects mutations in most individuals with CHARGE syndrome.

CDH7 is the only gene currently known to be associated with CHARGE syndrome. The analytic sensitivity and specificity for detecting mutations in the CHD7 gene is high. The clinical sensitivity and specificity are also high: among patients with a clinical diagnosis of definite CHARGE syndrome, 90-95% have a mutation of CHD7. For individuals with possible or probable CHARGE syndrome, CHD7 analysis is positive for a mutation in 65-70% of cases.

The clinical utility of making a definite diagnosis of CHARGE syndrome is high, in that confirming a diagnosis in a patient will lead to changes in clinical management, including clinical assessment and treatment recommendations that are well-defined. The clinical utility of genetic testing for CHARGE syndrome is for patients in whom a definite diagnosis cannot be made clinically. Therefore, genetic testing for CHARGE syndrome may be considered medically necessary to confirm a diagnosis in a patient with signs/symptoms of CHARGE syndrome when a definitive diagnosis cannot be made with clinical criteria.

Almost all cases of CHARGE syndrome are a result of a de novo mutation, and therefore testing of relatives of a patient with CHARGE syndrome has low clinical utility. Therefore, mutation testing for CHARGE syndrome is considered investigative in all other situations.
Medicare National Coverage

No national coverage determination is identified.

References


Policy History

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<th>Action</th>
<th>Reason</th>
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<td>New Policy</td>
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Keywords

Genetic Testing CHD7
### Table

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<thead>
<tr>
<th>Section</th>
<th>Medicine</th>
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<td>Subsection</td>
<td>Pathology/Laboratory</td>
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<tr>
<td>Subject</td>
<td>Genetic Testing for CHARGE Syndrome</td>
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<tr>
<td>Effective Date</td>
<td>January 15, 2015</td>
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<td>Original Policy Date</td>
<td>December 6, 2013</td>
</tr>
<tr>
<td>Page</td>
<td>9 of 9</td>
</tr>
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This policy was approved by the FEP® Pharmacy and Medical Policy Committee on December 5, 2014 and is effective January 15, 2015.

*Signature on File*

Deborah M. Smith, MD, MPH