DIAGNOSIS, GENETICS AND PRENATAL DIAGNOSIS IN CHARGE

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HISTORY OF CHARGE ASSOCIATION AND CHARGE SYNDROME

The collection of features which came to be known as CHARGE was first recognized by Dr. Bryan Hall, who has been collecting information about choanal atresia and related anomalies since 1968. He saw a pattern emerging in children with choanal atresia and multiple anomalies and first published his findings in 1979. In 1981, Drs. Pagon, Graham, Zonana, and Young published a series of patients with similar findings and coined the acronym "CHARGE" as an easy way to remember the condition. The name is easy to remember and catchy. Unfortunately, it does not adequately cover some of the most important features seen in CHARGE syndrome.

Many physicians are still using the 1981 criteria (below) to make or rule out the diagnosis. Revised diagnostic guidelines were published by the CHARGE Syndrome Foundation Medical Advisory Board in 1998 (Blake, et al.) The patterns of defects in CHARGE syndrome can still be difficult to diagnose, even by specialists.

Syndrome or Association?

A "syndrome" is a recognizable pattern of birth defects or malformations, typically with one recognized cause (single gene or chromosome abnormality, for example). An "association" is a nonrandom collection of birth defects which is less specific than a syndrome. Until the cause(s) of CHARGE are identified, the debate about CHARGE syndrome vs. association is likely to continue in the medical genetics community. Those of us who have been most closely involved with CHARGE over the years (and some others, see Lubinsky) feel "syndrome" is a better fit for CHARGE than "association." But don't sweat it, the difference is largely semantic.

As with any condition, the most involved, most severely affected cases are more likely to come to medical attention and be diagnosed most easily. This means the severity of the condition may be over-estimated and the frequency underestimated (because milder cases are not yet recognized and counted). As we get better at diagnosing the milder cases, we must also revise the incidence and prognosis to better fit the entire spectrum.

ORIGINAL "CHARGE" FEATURES (1981)

- C - Coloboma of the eye
- H - Heart defects
- A - Atresia of the choanae
- R - Retardation of growth and/or development
- G - Genitourinary anomalies
- E - Ear anomalies and/or deafness

The diagnostic criteria set out in 1981 required that 4 of the 6 "CHARGE" features be present to make a definite diagnosis. However, even the 1981 paper which coined the term "CHARGE" recognized these criteria were preliminary and that the acronym did not cover all the significant findings (e.g. facial palsy) in these children.

REVISED CHARGE DIAGNOSTIC CRITERIA (1998)

The revised diagnostic criteria take into account the fact that there are several features which are extremely common in CHARGE but very rare in other conditions (Major Diagnostic Criteria, Table 1) and features which are common in CHARGE but are also seen in several other conditions (Minor Diagnostic Criteria, Table 2). In addition, children with CHARGE may have a variety of other features (Common Findings, Table 3) which may not be particular helpful in making a diagnosis, but which can mean a lot to the family and medical community in terms of management. All of these features are described in more detail in following Medical sections.

A diagnosis of CHARGE should be considered in any newborn with any "Major" criterion (coloboma, choanal atresia, facial palsy, or classic CHARGE ear) in combination with any other significant birth defect. See Differential Diagnosis for overlapping syndromes.

As of this writing (2002), there is no specific test that can be done which will definitively diagnose or rule out CHARGE. CHARGE syndrome is a clinical diagnosis. That is, it is made based on physical findings along with the best judgment of the Medical Geneticist . A diagnosis of CHARGE should be made or confirmed by a Medical Geneticist who is familiar with CHARGE.

CHARGE SYNDROME: MAJOR DIAGNOSTIC CRITERIA

Features seen commonly in CHARGE, rarely in other conditions

CRITERION	INCLUDES	FREQUENCY
Coloboma	Coloboma of iris, retina, choroid, or disc Microphthalmia, anophthalmia	80 - 90%
Choanal Atresia	Unilateral (UL) or bilateral (BL); Bony or membranous; Stenosis or atresia	50 - 60%
Cranial Nerve Dysfunction	I: lack of smell VII: facial palsy (UL or BL) VIII: sensorineural hearing loss or vestibular problems IX/X: swallowing dysfunction	Frequent 40%+ 70-85% 70 - 90%
Characteristic CHARGE Ear ++	External Ear: Short, wide ear with little or no lobe, snipped off helix, prominent antihelix discontinuous with tragus, triangular concha, decreased cartilage, asymmetric, often protruding laterally Middle ear: abnormalities of stapes, absent stapedius tendon, cochlear anomalies	90% ?90%

Tables modified from Blake, et al., 1998, with permission

++The external ear abnormalities can be so specific as to suggest a diagnosis of CHARGE based on the ears alone.

*** see glossary and/or other medical sections for definitions of medical terms and diagrams

CHARGE SYNDROME: MINOR DIAGNOSTIC CRITERIA:

Features less specific to CHARGE and/or not consistent enough to be considered major

CRITERION	INCLUDES	FREQUENCY
Characteristic CHARGE face	Square face, broad prominent forehead, arched eyebrows, large eyes, occasional ptosis, prominent nasal bridge with square root, small nares, prominent nasal columella, flat midface, small mouth, occasional small chin; larger chin with age. Facial asymmetry even without facial palsy	> 50%
Characteristic CHARGE hand	Small thumb, broad palm with "hockey-stick" palmar crease, short fingers	50%
Genital hypoplasia	Males: micropenis, cryptorchidism Females: small labia Both: delayed or incomplete pubertal development	70 - 85% Frequent ?50%
Congenital heart defects	Most common: tetralogy of Fallot, VSD, AV canal, aortic arch anomalies	70 - 85% have CHD
Cleft palate or Cleft lip	Unilateral or bilateral cleft lip +/- cleft palate Isolated cleft palate, including submucous cleft palate Can even occur with choanal atresia or stenosis	20 - 30%
TEF	Tracheo-esophageal atresia or fistula Esophageal atresia	20% 15%
Middle ear	Frequent ear infections Many sets of PE tubes	>80%
Hypotonia	Upper body hypotonia, sloping shoulders	Frequent
Renal anomalies	Hydronephrosis or reflux; Horseshoe kidney; Small or absent kidney	40%
Growth deficiency	Short stature Growth hormone deficiency	Common Rare

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CHARGE SYNDROME: OTHER COMMON FINDINGS:

May be important for management, but not very helpful in making diagnosis

FINDING	INCLUDES	FREQUENCY
Brain abnormalities	Microcephaly, Agenesis of corpus callosum, Dilated ventricles	Rare
Apnea	? central (brain)	Rare
Seizures		Rare
Laryngomalacia	Can result in weak cry	Frequent
Nipple anomalies	Extra, poorly formed or misplaced nipples	Rare
Floppy cartilage	Includes tracheomalacia, floppy ears	Frequent
Thymic or parathyroid hypoplasia	DiGeorge sequence without chromosome 22 deletion	Rare
Webbed neck	Often looks like sloping shoulders	Rare
Abdominal wall defects	Omphalocele Umbilical hernia	Rare 15%
Scoliosis	Younger children Older children	Common Frequent
Limb/skeletal anomalies	Absent thumb, Polydactyly (extra fingers), Split hand	Rare
Autistic-like behavior	Often noted in childhood	Occasional
Behavior problems	Often not noted until school age	Common

Tables modified from Blake, et al with permission

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1. Hall BD: Choanal atresia and associated multiple anomalies. J Pediatr. 1979(95)395-398

2. Pagon RA, Graham JM, Zonana J, Young SL: Congenital heart disease and choanal atresia with multiple anomalies. J Pediatr. 1981(99): 223-227

3. Blake KD, Davenport SLH, Hall BD, Hefner MA, Pagon RA, Williams MS, Lin AE, Graham JM: CHARGE Association: An update and review for the primary pediatrician. Clin Pediatr. 1998(37)159-174

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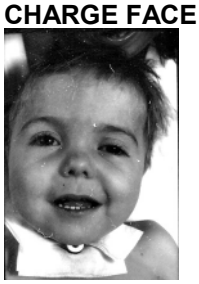
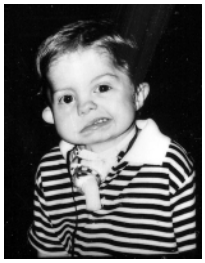
CHARGE FACE

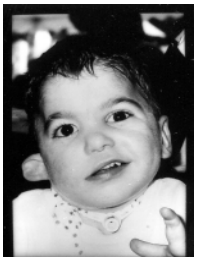


(1)

(2) iris coloboma



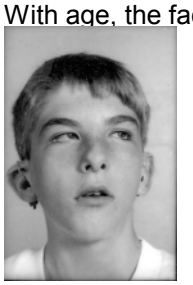
(3) R facial palsy



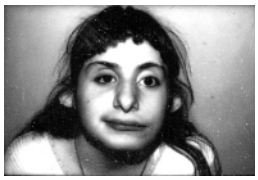
(4) R facial palsy

(5) BL facial palsy

Square, often asymmetric face, round eyes, flat cheekbones, wide nose with broad nasal bridge, and small chin. Unilateral facial palsy increases the asymmetry. Note that (3) and (4) are different children. With age, the face gets longer and the chin larger. (8) and (9) are the same child.

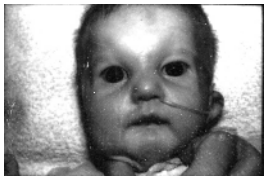


(6) teen



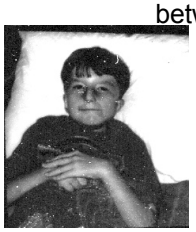
(7) teen

(11) **Hockey-stick palmar crease**: Upper crease on palm goes between index and middle fingers



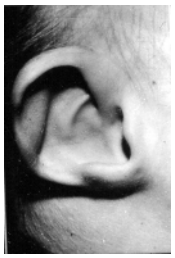
(8) baby

(9) child

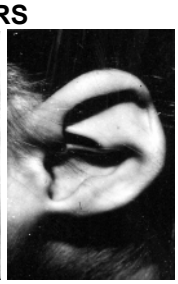


(10) teen

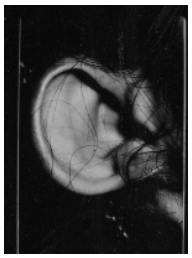
CHARGE EARS



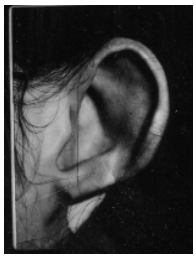
(12) R ear



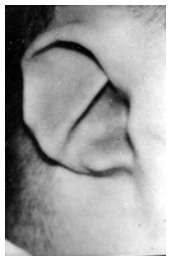
(13) L ear



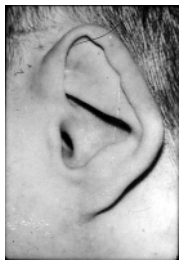
(14) R ear



(15) L ear



(16) R ear



(17) L ear

Right and left ear of three individuals. Floppy, small, wide ears with little or no lobe, often an unfolded or clipped-off appearance to the helix (outer fold), and a prominent antihelix creating a triangular concha (center of ear, esp. 17) The two ears usually are different.

DIFFERENTIAL DIAGNOSIS: What else can look like CHARGE?

Chromosome abnormalities
A variety of chromosome abnormalities can result in features which overlap with CHARGE. Most have different ear anomalies and facial features. The chromosome abnormalities which overlap with CHARGE may give us clues about where to look for an abnormal gene. See also the discussion below on VCF (22q deletion syndrome). Children with CHARGE would be expected to have normal chromosomes, including FISH for 22.

VCF (velocardiofacial) syndrome - the 22q deletion syndrome
VCF had a number of names in the past, depending on the features seen in the individual child. Now that a test is available, we know that all of these "separate" syndromes have one cause, a microdeletion of chromosome 22 detected by a special chromosome test called FISH. Some of the terms that used to be used are: Shprintzen syndrome, VCF, DiGeorge and CATCH-22. Features of VCF include

Velo - cleft palate and occasionally cleft lip
feeding difficulty – usually gets better in a few months
Cardio - heart defects – exactly the same heart defects as seen in CHARGE
Facial - typical face: long and slender, often with overfolded ears
kidney abnormalities – similar to CHARGE
small or absent thymus - leading to immune system problems
hypocalcemia (low calcium), sometimes causing seizures
learning disabilities
psychiatric problems
22 - deletion of chromosome 22q11

"DiGeorge sequence" technically refers to children with heart defects in combination with thymus abnormalities, including low blood calcium levels. Although most common in VCF, DiGeorge sequence can also be found in children with CHARGE or as an isolated finding.

Velocardiofacial syndrome (VCF) can include DiGeorge sequence and other CHARGE-like features including palate problems, renal abnormalities, ear abnormalities and even occasionally colobomas and/or hearing loss. VCF is caused by a tiny missing piece (microdeletion) of chromosome #22. It can be confirmed by a special lab test called FISH (fluorescent in-situ hybridization) for deletion 22q11.2. Children with possible CHARGE should also have FISH for 22q to rule out VCF.

The heart defects and swallowing problems seen in VCF can be similar to those seen in CHARGE. However, the characteristic ears, face and hands are distinctly different (e.g. long and slender hands in VCF vs. short and broad in CHARGE; long face in VCF, square face in CHARGE). Only about 5% of children with CHARGE have DiGeorge sequence. Conversely, of all the children with DiGeorge sequence, about 85% have a chromosome 22 deletion, 5% have CHARGE and 10% have something else. To date, we are not aware of a single individual with definite CHARGE who had a FISH test which was positive for the 22q11 deletion.

VATER or VACTERL association

VACTERL is a an acronym for a collection of findings which overlap with CHARGE:

V - vertebral (backbone, spine) anomalies
A - anal atresia (referring to the anus, not the nose)
C - cardiac (heart) defects
TE - tracheoesophageal fistula or esophageal atresia
R - renal (kidney) anomalies
L - limb, especially lower arm bone anomalies

Vertebral anomalies, limb anomalies and anal atresia are each very common in VACTERL and rare in CHARGE. Children with VACTERL are unlikely to have any of the Major Diagnostic Criteria of CHARGE. Neither do they have the typical physical features (face, ears, hands) associated with CHARGE. In some cases, especially in the newborn period, VACTERL and CHARGE may be difficult to distinguish from each other due to overlapping birth defects.

WHAT TESTS TO DO?

All individuals with a suspected diagnosis of CHARGE should be evaluated for chromosome anomalies, VACTERL and VCF, including chromosome analysis with FISH for the 22q11 VCF/DiGeorge locus. "FISH for 22q" is a specialized test which must be specifically requested separately from routine chromosome analysis.

PAX2

PAX2 is rare condition with features which overlap with CHARGE. Individuals with PAX2 abnormalities may have colobomas, renal (kidney) anomalies and hearing loss. They do not have the facial features or ear shape associated with CHARGE. A recent study showed that children with definite CHARGE syndrome do not have any mutations in the PAX2 gene.

Retinoic acid (Accutane)

Accutane (a drug used to treat cystic acne) taken in the first two months of pregnancy has a very high chance of causing birth defects, including unusual ears and heart defects. The ear abnormalities seen in prenatal retinoic acid exposure can be very similar to the CHARGE ear. However, the other problems caused by retinoic acid are different. Accutane taken **before** pregnancy is not known to cause any birth defects. Retin-A skin creme does not cause birth defects

WHAT DOESN'T CAUSE CHARGE

It wasn't anything you did during the pregnancy. Other than retinoic acid, no specific pregnancy exposures have been linked to the features seen in CHARGE. Exposures to pesticides, smoking, alcohol use, and/or other drug use do not appear to play a role. Because the organs involved in CHARGE are developing over a number of weeks of pregnancy, it is unlikely that any one single event (car accident, food poisoning, whatever) could cause CHARGE. There is almost never any history of CHARGE or CHARGE-like features in other family members.

HOW OFTEN DOES CHARGE HAPPEN?

The incidence of CHARGE at birth is estimated to be about 1 in 12,000 births. Many infants and young children with CHARGE do not survive due to the major medical complications. Many children with a milder expression of CHARGE may not be diagnosed until they are older or missed entirely. Therefore, the number of children with CHARGE in the general population is difficult to estimate.

HOW LONG DO CHILDREN WITH CHARGE LIVE - LIFE EXPECTANCY

Life expectancy is decreased in children with CHARGE. Infants with CHARGE have complex medical problems and many of them do not survive. The highest mortality is in the first three years. Infants with bilateral choanal atresia, a complex heart defect, and/or tracheo-esophageal fistula appear to have the lowest survival rates and poorest outcomes. There is a relatively high post-operative mortality with CHARGE, possibly due to reactions to anesthesia and/or breathing or aspiration problems. The more surgeries (and anesthesias) a child must undergo, the greater the risks. Even beyond infancy, many children with CHARGE require multiple surgeries and are medically fragile.

Children with CHARGE are also at very high risk for aspiration - sucking food or liquid into the lungs (due to TE fistula, tracheomalacia, and swallowing problems), which often leads to pneumonia. There are reports in the medical literature of as many as 30-40% of children with CHARGE not surviving to five years. However, reports in the medical literature include children with the most severe cases of CHARGE. Less severely affected children are often not diagnosed in the newborn period, and may not be included in the "survival" numbers. Nevertheless, as many as 20-25% may not survive beyond two years of age despite our best efforts. Sometimes parents are faced with very difficult decisions about how aggressively to treat their seriously ill child. Such parents are not alone. The Foundation can put you in touch with others who have been through this process.

Beyond early childhood, the mortality remains higher than in children who do not have CHARGE. This may be due to a combination of factors, including residual heart defects, continued swallowing problems, anesthesia risks and general medical fragility. Because CHARGE is a relatively recently recognized syndrome, long-term life expectancy is unknown. There are many adults with CHARGE who appear to be in good health and have relatively few remaining medical concerns.

RECURRENCE RISK

WILL CHARGE HAPPEN AGAIN IF I HAVE ANOTHER CHILD?

For parents with one child with CHARGE, the recurrence risk is low, probably around 1-2%. There are only a handful of families with more than one child with CHARGE. The 1-2% recurrence risk is based on surveys of over 300 families with a child with CHARGE and extensive review of the medical literature. Most of the "familial" cases reported in the older medical literature probably would not be diagnosed as CHARGE today based on the revised criteria. Even using a very loose definition of CHARGE (i.e. anyone diagnosed as CHARGE, regardless of the expertise of the person making the diagnosis, the certainty of the diagnosis or the criteria used), the recurrence risk is still only about 1-2%. Using strict diagnostic criteria, the risk would probably be even lower.

WILL CHARGE HAPPEN AGAIN TO ANYONE ELSE IN THE FAMILY?

Aunts, uncles and siblings of individuals with CHARGE probably are not at increased risk for having a child with CHARGE, although this information may change as we learn more about the cause of CHARGE.

Some individuals with CHARGE may be capable of having their own children when they become adults (many may not, due to hormone abnormalities). If CHARGE syndrome is caused by a single gene or chromosomal microdeletion, the risk to children of affected individuals could be as high as 50%. Information in this area may change very quickly, so be sure you have current information before making family planning decisions.

FUTURE PREGNANCIES/PRENATAL DIAGNOSIS

The recurrence risk is low, but it is not zero. Parents are understandably worried about attempting another pregnancy and want to know what can be done to look for signs of CHARGE during a pregnancy. **There is nothing that can be done to prevent CHARGE**. However, as much reassurance as possible during the pregnancy that things appear to be going well is helpful.

The way to get the most information about CHARGE during a pregnancy is to have a directed ultrasound to look for features associated with CHARGE. This should be a **Level II ultrasound exam** and should be performed at a **tertiary care center** by an experienced ultrasound technologist using state-of-the-art equipment. This is not a procedure that can be done in the typical obstetrician's office. The ideal would be two ultrasound exams, the first at 18-20 weeks (post LMP) and the second about a month later, at 22-24 weeks. Take along the following checklist to give the sonographer the best information possible about what to look for.

ULTRASOUND EXAM FOR FEATURES OF CHARGE SYNDROME:
THIS WILL NOT DIAGNOSE OR RULE OUT CHARGE

The ultrasound evaluation should include a **complete standard anatomic survey** with particular attention to the following:

- Amniotic fluid measurement:
  Look for polyhydramnios (excess amniotic fluid) associated (especially in late pregnancy) with choanal atresia, esophageal atresia or poor swallowing.
- Cardiac evaluation:
  Many centers can do a formal fetal echocardiogram. Heart defects most common in CHARGE include tetralogy of Fallot with or without AV canal, and right-sided anomalies, including VSD and aortic arch anomalies.
- Kidney:
  Any kidney anomaly can be associated with CHARGE, including hydronephrosis (excess fluid in the kidneys), small or absent kidney, horseshoe kidney, posterior urethral valves.
- Brain:
  Dilated ventricles, absence of the corpus callosum or any other structural abnormality of the brain.
- Face: cleft lip or cleft palate
- Ear: abnormal shape or placement (take along a photo of CHARGE ears)
- Genitalia: small penis in a known male fetus

Many abnormal findings would not be present early on and/or would be undetectable until later in pregnancy. Don't be shy about asking how confident they are about the accuracy and completeness of the ultrasound exam. Every exam is different and none will detect every birth defect during pregnancy. The accuracy will depend on a number of things, including how far along you are, the position of the baby, your weight (the image is not as clear when it has to travel through a lot of maternal tissue before it reaches the fetus), the quality of the equipment, and the expertise of the sonographer. What can be seen one day may not be visible another day.

Remember, **none** of the major diagnostic criteria for CHARGE (coloboma, choanal atresia, cranial nerve abnormalities, characteristic CHARGE ear) can be definitively diagnosed by prenatal ultrasound exam. Although finding evidence of some problem or potential problem through the ultrasound exam would certainly raise the suspicion of CHARGE, and can help parents be prepared for that possibility, it is not diagnostic. And remember, **even a completely normal ultrasound exam cannot rule out CHARGE.**