Abstract

CHARGE association is a heterogeneous condition that affects several organ systems, including the eye, ear, nose, heart, and genitals. Hearing loss is a common finding in CHARGE association; therefore, audiologists and otolaryngologists need to be familiar with this relatively common entity.

Key Words: Choanal atresia, eye abnormalities, hearing loss, heart defects

Although the combination of choanal atresia with ocular, cardiac, and ear defects had been described by several authors prior to 1981 (Angelman, 1961; Stool and Kemper, 1968; Ho et al, 1975; Hall, 1979), Pagon et al (1981) were the first to coin the acronym "CHARGE association" to describe this pattern of anomalies (see Table 1). To date, over 150 cases have been described in the literature, and it is one of the most common multiple-anomaly conditions encountered by clinicians (Hall, 1981).

CHARGE is known as an association, in distinction from a syndrome or sequence. To review, a syndrome is a pattern of anomalies with a specific cause, such as Down syndrome, which is caused by an extra copy of chromosome 21, or Treacher-Collins syndrome, which is caused by an autosomal-dominant gene mutation. A sequence represents a pattern of anomalies that directly result from a primary anomaly. For example, in Pierre Robin sequence, the primary anomaly is a small jaw (micrognathia), which causes displacement of the tongue and, in turn, obstruction of palate closure. An association, however, is usually a heterogeneous group of anomalies that occur together more often than expected by chance. For example, in the VACTERL association, vertebral, anal, cardiac, tracheoesophageal, renal, and limb anomalies are more likely to occur in the same individual. The fact that these anomalies occur in a pattern does not give us a cause for their simultaneous occurrence; however, the recognition that these anomalies constitute an association tells us that in a child with one anomaly of an association, the other anomalies of that association should be investigated.

Clinical Findings

Coloboma

Coloboma refers to a malformation of the iris, retina, or disc. If the coloboma affects the iris, there is usually a "keyhole" appearance to the pupil. The iris may also appear small or irregular, and the defect may be unilateral or bilateral (Chestler and France, 1988). Colobomas of the retina or disc need to be diagnosed by an ophthalmologist and may occur with or without iridal colobomas. Other eye anomalies have also been described and included microphthalmia, optic nerve hypoplasia, persistent hyperplastic primary vitreous, cataract, retinal detachment, strabismus, and nystagmus (Russell-Eggitt et al, 1990). The effect of these anomalies on vision is also variable, with a range from no impairment to severe visual loss with lack of light perception (Russell-Eggitt et al, 1990). However, over 50 percent of children with CHARGE association have some visual impairment (Kaplan, 1989).

Table 1  Anomalies Most Commonly Seen in CHARGE Association

| C | coloboma |
| H | heart defects |
| A | atresia choanae |
| R | retarded growth and/or development |
| G | genital defects |
| E | ear anomalies and/or deafness |
Heart Defects

Approximately 60 to 70 percent of individuals with CHARGE association have congenital heart defects, which is usually an acyanotic lesion. In this category, the most common lesion is patent ductus arteriosus, followed by septal defects, atrioventricular canal, double outlet right ventricle, aortic arch anomaly, valvar aortic stenosis, and hypoplastic left heart. Among patients with cyanotic heart defects, tetrology of Fallot is most common, followed by transposition of the great vessels with other anomalies and Ebstein anomaly (Cyran et al, 1987).

Atresia Choanae

Approximately 56 percent of individuals with CHARGE association have choanal atresia or stenosis, which is usually bilateral but may be unilateral (Duncan et al, 1988). This results in either partial or total obstruction of the nasal airway, particularly posteriorly; thus, visual inspection of the nares is insufficient to make the diagnosis. The most common presentation of choanal atresia is respiratory distress, which may range from chronic rhinorrhea with noisy breathing to cyanosis and apnea (Kaplan, 1989). In addition, in one study, more than half of the patients had other upper airway abnormalities. Eight percent of these patients had laryngomalacia, 6 percent had subglottic stenosis, and 2 percent each had laryngeal cleft or laryngeal web (Stack and Wyse, 1991). Tracheoesophageal fistula is an infrequent finding (Lillquist et al, 1980).

Growth Retardation

The frequency of prenatal growth retardation does not seem to be above the population frequency, although postnatal growth failure is common (Pagon et al, 1981; Davenport et al, 1986). In most individuals, linear growth is slowed, so that ultimate height is at or below the third percentile. Retarded bone age is common, and some individuals may have growth-hormone deficiency (Davenport et al, 1986).

Developmental Retardation

Although most affected individuals have some degree of mental retardation, the range is extremely broad, with IQs between 80 to less than 30 reported (Goldson et al, 1986). Central nervous system abnormalities have also been described and include ventriculomegaly, holoprosencephaly and variants, small or absent olfactory tracts, and hindbrain abnormalities (Pagon et al, 1981; Lin et al, 1990). The frequency of these anomalies is 55 percent (Lin et al, 1990).

Genital Anomalies

Genital defects in males, which occur in 75 to 100 percent, include hypogonadism with cryptorchidism and/or micropenis. Kushnick et al (1992) described a karyotypic male who had embryonic testicular regression to such a degree that the individual had a female phenotype and partially female internal reproductive organs. Although most studies have not described obvious external genital defects in females, labial hypoplasia has been noted in two women over the age of 15 years (Davenport et al, 1986). Pubertal development in both sexes may be delayed or absent and may be correlated to pituitary or hypothalamic deficiency.

Ear Anomalies

Many clinicians believe that the external ear anomalies, which are present in most individuals with CHARGE association, are sufficiently distinct so that a tentative diagnosis can be made and a search for the other associated anomalies instituted. Typical features include a triangular concha, discontinuity between antihelix and antitragus, abnormal helical fold, small or absent ear lobes, and short pinnae. The ears often protrude, and asymmetry between the two ears is common (Brown and Israel, 1991). When present, hearing loss may be variable, although the most common finding is moderate to severe progressive mixed loss. The conductive component is attributable to ossicular anomalies and/or middle ear effusion. The ossicular defects may affect hearing in primarily the low frequencies, but deficits in the mid-to-high frequency range have also been reported. The conductive loss secondary to middle ear effusion may persist beyond childhood. The sensorineural component can be mild to severe and tends to be greatest in the high frequencies. The resultant audiogram yields a “wedge-shaped” pattern, with a low-frequency conductive loss and concomitant high-frequency sensorineural loss. The bone-conduction threshold curve may slope downward from low to high frequencies, whereas the air-conduction threshold curve is flat (Brown and Israel, 1991).
It is believed that both the conductive and sensorineural loss are progressive, although the rate of progression tends to be slow and may arrest (Davenport et al, 1986; Thelin et al, 1986). Histologic evaluation of the temporal bones has demonstrated the Mondini defect in some (Guyote et al, 1987) and vestibular anomalies with cochlear defects in others (Wright et al, 1986).

**Other Anomalies**

Other relatively common findings include facial asymmetry, cleft lip/palate, swallowing dysfunction, unilateral facial palsy, and renal anomalies (including hydronephrosis, posterior urethral valves, small kidneys, etc.) (Davenport et al, 1986; Gorlin et al, 1990).

Although the CHARGE association appears to be a relatively distinct condition, phenotypic overlap with some chromosome anomalies, Di George sequence, velocardiofacial syndrome, and fetal alcohol syndrome have been noted (Jones and Dunne, 1988; Gorlin et al, 1990). Recently, Menenzes and Coker (1990) suggested that Joubert syndrome and CHARGE association were the same disorder. Joubert syndrome is a condition characterized by cerebellar vermis hypoplasia and abnormal respiratory patterns; coloboma has also been reported (Joubert et al, 1968). The authors' suggestion was based on their observation of a child with CHARGE association and cerebellar vermis hypoplasia with abnormal breathing patterns. However, additional cases need to be reported before this suggestion can be verified.

Although an X-linked pedigree described by Abruzzo and Erickson (1977) is considered by some authors to be an example of CHARGE association (Metlay et al, 1987), there are enough differences in phenotype to distinguish it as a distinct condition. Although the individuals described by Abruzzo and Erickson (1977) had short stature, hypospadias, hearing loss, and ocular coloboma, the individuals also had normal intelligence, cleft palate, and radial synostosis. The ears were soft and protruding but not misshapen, as they are in CHARGE association. Burn et al (1992) described what they believed was a new syndrome, with the phenotype of choanal atresia, cardiac defects, deafness, prominent external ears, short palpebral fissures, and normal intelligence. This condition affected two siblings each in two different families and is likely inherited as an autosomal recessive trait.

**ETIOLOGY AND PATHOGENESIS**

CHARGE association is clearly heterogeneous, in that although the majority of cases are sporadic, familial cases have been reported as well. Mitchell et al (1985) described eight affected individuals in four generations and postulated that the most likely cause in this family was an autosomal-dominant mutation, although an X-linked dominant gene as the cause could not be ruled out. Hittner et al (1979), Pagon et al (1981), and Metlay et al (1987) also reported pedigrees consistent with autosomal-dominant inheritance; it is noteworthy that choanal atresia occurred in only one family (Metlay et al, 1987). Pedigrees consistent with autosomal-recessive inheritance were reported by Awrich et al (1982) and Pagon et al (1981); Levin et al (1973) and Blake et al (1989) described concordantly affected monozygous twins, whereas Brown and Israel (1991) described concordantly affected dizygous twins. Dev et al (1985) described a child with CHARGE association and duplication of 1q (long arm of chromosome number 1). Mitter et al (1984) described a child with the CHARGE phenotype and interstitial deletion of 3p (short arm of chromosome 3), and Muneer et al (1984) described two children with CHARGE phenotype and duplications of 6p.

Since it is believed that cephalic neural crest anomalies are responsible for most, if not all, of the features of CHARGE association, it is not surprising that different gene mutations, chromosome anomalies, or teratogens could each affect these cells in slightly different ways and yet cause very similar phenotypes. Although choanal atresia was thought to be caused by persistence of the nasobuccal membrane beyond 38 days (Boyd, 1945), other mechanisms may be responsible, particularly abnormal deviation of neural crest cell flow into the area of the nasobuccal membrane, thus thickening the atretic plate (Siebert et al, 1985). Conotruncal cardiovascular defects are also explained by abnormal neural crest cell migration; these are the defects most commonly found in CHARGE association. Branchial arches, which give rise to the ear, parts of the eye, and cranial nerve ganglia also arise from neural crest cells. Finally, the genital hypoplasia and growth retardation may be associated...
with pituitary hypofunction, which in turn may be caused by neural crest cell maldevelopment (Siebert et al, 1985). Thus, all phenotypic features of CHARGE association likely have neural crest cell abnormalities as their basis.

**PROGNOSIS AND TREATMENT**

In a newborn suspected of having CHARGE association, several evaluations are indicated. If choanal atresia is suspected, the recommended protocol is computed tomography evaluation of the airway (Morgan and Bailey, 1990); as mentioned earlier, visual inspection is insufficient (Kaplan, 1989). An ophthalmologic evaluation should be performed to determine whether choroidal colobomas or other eye anomalies are present. Echocardiography to assess heart anatomy, X-rays of the chest and abdomen to seek for abnormal situs, obstructive bowel disease, tracheoesophageal fistula, or skeletal anomalies, and renal ultrasound are also indicated (Kaplan, 1989).

Genital hypoplasia in a male may be so extreme as to raise the question of sex assignment; however, androgen therapy has been used successfully and may be an option for treatment (Pardo and Chua, 1985). In infancy and childhood, the numerous problems that are likely present need to be addressed in a timely fashion. Since choanal atresia and cardiac defects are potentially fatal malformations, surgery may need to be done promptly. Potentially long-term problems following surgery should also be anticipated, particularly with regards to feeding and nutrition (Kaplan, 1989). It has also been stressed that vision and hearing defects, if present, be identified early and treatment instituted as soon as possible. Hearing aids and intensive speech and language therapy intervention should be implemented as early as possible; vision correction, if possible, should be done expeditiously as well (Goldson et al, 1986; Jones and Dunne, 1988). Those children who are given every medical and educational benefit may ultimately accomplish more than originally hoped.

The parents of these children may also wonder what the chance is of having another similarly affected child. If family history is negative and chromosome studies on the child normal, then the recurrence risk is thought to be “low, but not negligible” (Pagon et al, 1981). However, genetic counselling is always encouraged in order to clarify any concerns of family members.

**CASE REPORTS**

**Patient 1**

This 6.5-year-old female was the product of a 38-week gestation, whose birth weight was 6 lbs, 8.5 oz. and length was 18.5 in. Facial paralysis was noted soon after birth, as were congenital hip dislocation and clubfoot; kidney and head ultrasounds were normal. This child was admitted to the hospital at 5 months of age for failure to thrive, but no specific cause was found. However, because a diagnosis of CHARGE was suspected, an ophthalmologic evaluation was....

**Figure 1** Mild dysmorphic features observed in a 6.5-year-old female with CHARGE association (frontal view).

**Figure 2** Mild dysmorphic features observed in a 6.5-year-old female with CHARGE association (side view).
done, and bilateral retinal colobomas were found. A hearing evaluation found profound mixed loss on the left and severe loss on the right. At 10 months, gastroesophageal reflux was diagnosed and a gastrostomy tube placed. A small ventricular septal defect was found on echocardiogram at 26 months. Although this child had delayed motor skill development (e.g., walked at 3 years), intellectual development is considered to be within normal limits, and at age 5 years the child was enrolled in a kindergarten program for the hearing impaired. Recent photographs of this child are Figures 1 and 2. Note the subtle facial characteristics found in some CHARGE association.

Patient 2

This 3-year-old male had a birth weight of 6 lbs, 10 oz., length of 52 cm, and head circumference of 35 cm, all of which are within normal limits. Small penis and testes were noted soon after birth, and a renal ultrasound demonstrated unilateral renal agenesis. Choanal stenosis was also discovered, and surgery was done almost immediately. A head ultrasound demonstrated absent corpus callosum. At 2½ months, mild optic nerve hypoplasia and mixed hearing loss on the right were diagnosed. At age 6.5 months, auditory brainstem responses (ABRs) were performed and wave V was observed at 70 dB nHL bilaterally. No repeatable responses could be elicited using click stimulus at lower presentation levels. Using a 1000-Hz tone burst, a repeatable response was demonstrated at 60 dB nHL in the left ear but absent in the right ear at 60 dB. Thus, a moderate to severe loss was diagnosed bilaterally. Figure 3 illustrates the results of an audiogram that was completed at 2.5 years confirming a moderate to moderately severe loss. At the time of testing, immittance measures were consistent with patent tubes bilaterally. This boy has had numerous surgeries for recurrent choanal restenosis, as well as surgery for dacrocystitis. Development is considered delayed, although no developmental quotient is available.

Patient 3

This little girl was born July 4, 1992 at 31-weeks gestation. Birth weight was 3 lbs, 13 oz., birth length was 41 cm, and head circumference was 30.5 cm. Pregnancy was complicated by polyhydramnios. Choanal atresia was noted soon after birth, as was a large patent ductus arteriosus and aortic coarctation on echocardiogram. An unusual shape to the ear, with small lobes and increased width, was noted (Fig. 4). A diagnosis of CHARGE was suspected, and subsequent ocular and audiologic evaluations confirmed the diagnosis, in that bilateral microcornea with retinal and optic nerve colobomas were found and hearing loss in the right ear was present. The diagnosis of hearing loss was
is sufficient to make the diagnosis, it should not be surprising that such a degree of variability exists.

**REFERENCES**


