Case Report

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Clinical Characteristics of CHARGE Syndrome

Kuo-Fang Hsueh[1,2]
Chang-Sue Yang[1,2]
Jen-Her Lu[2,3]
Wen-Ming Hsu[1,2]

[1] *Department of Ophthalmology, Taipei Veterans General Hospital;*
[2] *National Yang-Ming University School of Medicine,*
[3] *Department of Pediatrics, Taipei Veterans General Hospital, Taipei, Taiwan, R.O.C.*

CHARGE syndrome is a specific collection of non-randomly occurring congenital anomalies. The patient of CHARGE syndrome may be presented to ophthalmologists due to ocular coloboma. The acronym CHARGE stands for the major features of this syndrome: Coloboma of the eye, Heart defects, Atresia of the choanae, Retarded growth and development, Genital hypoplasia, and Ear anomalies and/or deafness. The etiology may be genetically heterogeneous, but the majority of cases are sporadic events of unknown cause. We report 2 girls with ocular coloboma who were consistent with the diagnostic criteria of CHARGE syndrome, and review the literature. Double aortic arch has not been described in CHARGE syndrome before. Ophthalmologists should be aware of this not uncommon syndrome. Evaluation of associated defects and proper referral for timely management may be critical for patients with CHARGE syndrome.

Key Words
CHARGE syndrome;
choanae atresia;
coloboma;
congenital anomalies;
heart defects

Ocular coloboma may be seen as an isolated defect in otherwise healthy individuals, but can also be associated with a variety of congenital syndromes. One recognizable syndrome with ocular coloboma, first described by Hall[1] in 1979 and later named by Pagon *et al*.[2] in 1981, is the CHARGE syndrome. CHARGE syndrome consists of a specific group of nonrandomly occurring congenital anomalies in patients with normal karyotypes and no other recognized syndromes. This syndrome includes the following major features: C-coloboma of the eye, H-heart defects, A-atresia of the choanae, R-retarded growth or central nervous system (CNS) development, G-genital hypoplasia, and E-ear anomalies and/or hearing loss. The presence of coloboma or choanae atresia, or both, and a total of at least 4 of the 6 major features are necessary for the diagnosis criteria of CHARGE syndrome.[2] Other associated anomalies are also possible, such as facial palsy, pharyngeal incoordination and swallowing problem.[3,4]

Because the patient with CHARGE syndrome may present to ophthalmologists due to ocular coloboma, it is important for ophthalmologists to be familiar with CHARGE syndrome. Systemic evaluation and early management of the patients with CHARGE syndrome is necessary. Herein, we reported 2 girls consistent with the diagnostic criteria of CHARGE syndrome. There were anomalies of double aortic arch and persistent left superior vena cava found in our case 2. To our knowledge, there is no previous similar report in the literature.

CASE REPORTS

Case 1

This 3-month-old girl was full-term gestation with birth weight of 2700 gm. She was referred to our pediat-

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Correspondence to: Chang-Sue Yang, Department of Ophthalmology, Taipei Veterans General Hospital, 201, Sec. 2, Shih-Pai Road. Taipei 112, Taiwan.
Tel: +886-2-2875-7325; Fax: +886-2-2876-1351; E-mail: csyang@vghtpe.gov.tw

ric clinic because cough, fever, dyspnea, and the presentation of failure to thrive. Ophthalmologic examination revealed extensive inferior coloboma of the retina and choroid in her left eye. Cardiac evaluation disclosed large-flow patent ductus arteriosus (PDA), atrial septal defect (ASD), and pulmonary hypertension. Surgical ligation of PDA was performed when the patient was 4 months old. Otolaryngology consultation found right choanal atresia. Hypoplasia of the labia minor was also noted during physical examination. Brain sonography displayed severe atrophy and poor development. The diagnosis of CHARGE syndrome was made according to the above clinical characteristics. She was hospitalized 15 times due to frequent episodes of respiratory tract infection. Unfortunately, she died of cardiopulmonary failure when she was 21 months old. Chromosome analysis showed normal 46 XX. The family history was non-contributory.

Case 2

This one-month-old infant was a premature baby with gestation age of 34 weeks and birth weight of 2900 gm. She was referred to our pediatric emergency room with shortness of breath, cough, and heart failure. The diagnosis was multiple congenital anomalies consistent with CHARGE syndrome. Ocular findings showed inferior iris coloboma of the left eye (Fig. 1), coloboma involving the retina, choroid, and optic nerve head in both eyes, and large coloboma of the macula in the left eye (Fig. 2). Congenital heart disease included large-flow PDA, ventricular septal defect (VSD) (0.8 cm), ASD, patent foramen ovale, mitral stenosis, pulmonary hypertension, double aortic arch and marked hypoplasia of the left aortic arch forming a complete vascular ring around the trachea and esophagus, persistent left superior vena cava and right-sided descending aorta. The other congenital anomalies included bilateral atresia of the choanae (Fig. 3), tracheomalacia, laryngomalacia, left bronhomalacia, left facial paralysis, left external ear deformity with triangle-shaped conchae and severe hearing impairment (Fig. 4). Brain sonography revealed brain atrophy and mild dysgenesis of the corporus callosum. Brain auditory evoked response displayed dysfunction of left hearing. Kidney sonogram showed mild pelvic dilatation (0.5 cm) of the left kidney. The patient under-

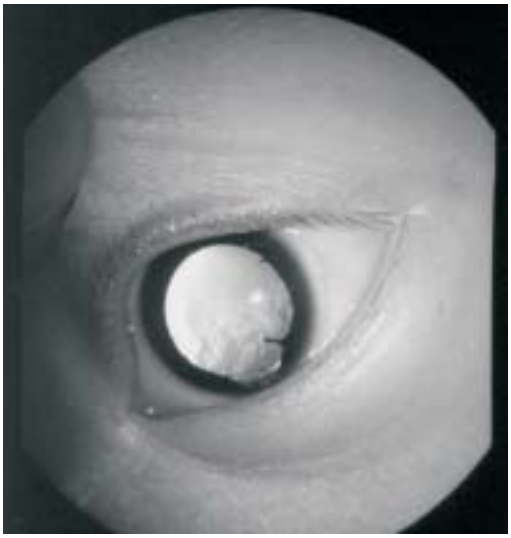

Fig. 1. Typical inferior iris coloboma at 6:00 o'clock.

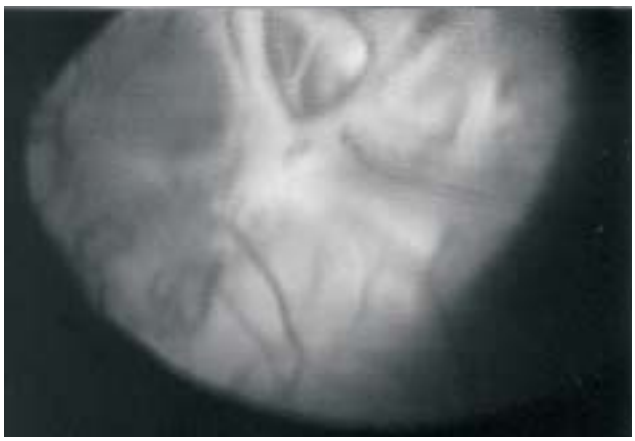

Fig. 2. Large chorioretinal coloboma involving the optic disc and macula.

Fig. 3. Bilateral atresia of choanae after choanoplasty surgery.

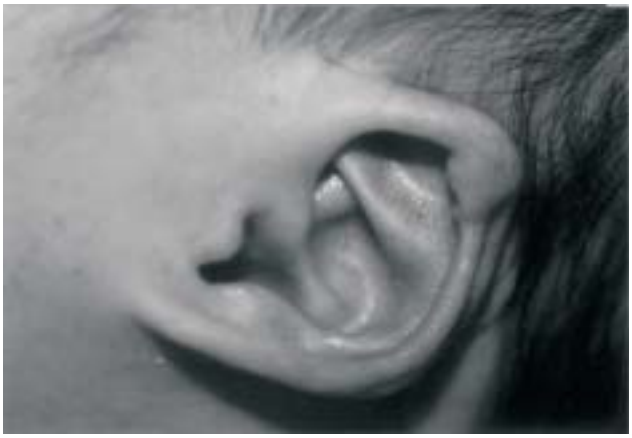

Fig. 4. External ear deformity with triangle-shaped conchae.

went bilateral choanoplasty surgery for choanae atresia when she was 2 months old, repair of membranous VSD with Gore-tex patch under cardiopulmonary bypass support at 4 months old, ligation of PDA and division of the smaller arotic arch at 5 months old. During the period of 30 months' follow-up, she was admitted to pediatirc ward for 14 times, mainly due to episodes of cyanosis, fever, and dyspnea. Therefore, tracheostomy was performed when she was 15 months old. Poor motion and rigidity of the left hip was noticed when she was 2 years and 2 months old; left hip dislocation due to neuromuscular contraction was the diagnosis by pediatric orthopedist.

The patient's body weight was only 7500 gm when she was 2 and half years old. The developmental milestone was notably delayed to below the 3rd percentile. Ophthalmologic follow-up examination disclosed no fixation movement of both eyes, horizontal jerk nystagmus, intraocular pressure 15 mmHg in the right eye and 17 mmHg in the left eye. The family history was noncontributory.

DISCUSSION

Typical ocular coloboma results from failure of the embryonic fissure to close along the inferonasal aspect of the optic cup and stalk between the 5th and 6th weeks of gestation, which leads to defects of the iris, ciliary body (Fig. 1), retina, choroids, sclera and optic nerve head (Fig. 2).[5] Coloboma can be unilateral or bilateral, which is often asymmetrical. The visual prognosis is variable depending on the number of ocular malformations and the degree of microphthalmia.

All patients with ocular coloboma should be carefully evaluated for the presence of associated anomalies of CHARGE syndrome. In CHARGE syndrome, the ocular coloboma may represent a spectrum of defects ranging from mild typical iris coloboma without visual impairment to severe anophthalmos, confirmed in a histopathological study.[6] Coloboma may occur in any combination of the iris, ciliary body, retina, choroid, sclera and optic nerve head, including microphthalmia to anophthalmos.[2-3] Colobomas are usually bilateral and somewhat asymmetric. Good visual acuity usually can be preserved in iris coloboma alone, however, there is poor visual development if the macula or optic nerve is involved.[3-5] In case 1 of our study, the coloboma of retina and choroid was found in the left eye only. In case 2, the coloboma involved the retina, choroid and optic nerve in both eyes, and coloboma of the macula in the left eye. Ocular anomalies may be missed unless the eyes are examined in detail. Complicated retinal break or retinal detachment may develop in the colobomatous area.[5] Strabismus and nystagmus (as seen in our case 2) would be noticed if the vision impairs in early childhood. Careful ophthalmologic evaluation and follow-up are highly recommended, since early onset of cataract and retinal detachment may subsequently develop in adulthood. Surgical intervention may be needed for vision salvage.

The severity and spectrum of congenital heart defects in CHARGE syndrome vary and tend to be severe. The heart defects consist of cyanotic heart disease, including tetralogy of Fallot, transposition of the great vessels, and Ebstein's anomaly; and acyanotic varieties, including PDA, VSD and ASD.[7-8] The most commom heart anomalies in CHARGE syndrome are PDA, VSD and ASD.[2,9] In case 2 of our report, there were PDA, VSD and ASD. Double aortic arch with hypoplasia of the left aortic arch, persistent left superior vena cava and right-sided descending aorta were confirmed by chest computed tomography (CT). The heart anomalies of double aortic arch and persistent left superior vena cava have not been described in CHARGE syndrome in previous literature. Prompt surgical intervention is crucial for the long-term survival of these patients.

Hall[1] and Pagon *et al*[2] reported high frequency of unilateral or bilateral atresia of the choanae in patients with CHARGE syndrome. Wellesley also agreed that the choanal atresia was an integral part in the diagnosis of CHARGE syndrome.[10] Atresia of the choanae may be membranous or bony, unilateral or bilateral.[11] Choanal stenosis does not present much of a functional problem, especially unilaterally, so it may be missed. Choanal stenosis may occur more frequently than previously reported because of difficult examination of this structure.[12] Wyse *et al*. mentioned that most patients have pharyngeal incoordination and swalllowing problem resulting in aspiration of secretions and more than 50% mortality.[7] In addition to cleft lip and palate, Grimm *et al.* also described the oral manifestations in CHARGE syndrome.[13]

Retarded growth and development is a common feature of CHARGE syndrome. Retarded growth and development refer to postnatal growth with significant delay of development and central nerve system anomalies or dysfunction.[2] Feeding difficulty and easy aspiration are the causes of growth dropping below the 3rd percentile in most of the babies during the first 6 months of life. Lin *et al*.[14] reported 55% patients of CHARGE syndrome had definite CNS malformation and a predominance for forebrain anomalies. The presence of CNS malformation was strongly associated with choanal atresia. Mental retardation may also be present in such patients, but diagnosis should be made with caution in anyone with impaired hearing and/or vision.

Ear anomalies in CHARGE syndrome may involve the outer, middle and inner ears with associated abnormality of hearing sensitivity.[15-16] A variety of ear malformations can be seen, including increased width, decreased height, prominent antihelix, triangular concha, and small or absent ear lobes. Davenport *et al*[15] described a specific set of pinna morphology, he believed it was distinctive enough to make a presumptive diagnosis of CHARGE syndrome. Case 2 in our study showed the characteristic feature: the external ear deformity with triangle-shaped conchae (Fig. 4). A "wedge" pattern audiogram with a low-frequency conductive loss and high-frequency sensorineural loss is also unique to this syndrome.[16] Congenital hearing loss has been reported in CHARGE syndrome, which is due to the underlying temporal bone disease.[17]

A square facial appearance with asymmetry and malar flatening is a characteristic feature in CHARGE syndrome.[4] Davenport thought that congenital facial paralysis (as seen in our case 2) is an important diagnostic feature of CHARGE because it is rarely seen in other syndromes.[4] Byerly *et al*. thought multiple cranial nerve abnormalities were the primary underlying cause for the facial paralysis, feeding difficulties and sensorineural hearing loss seen in patients with CHARGE syndrome.[18]

Limb anomalies are not common in CHARGE syndrome, including 5th digit clinodactyly and camptodactyly, clubfoot, tibial hemimelia and dimpling.[19] The hip dislocation in case 2 of our report has not been described in the literature before.

The actual etiology of CHARGE syndrome remains unknown. This association may be caused by a derangement in migration of neural crest cells and caudal presumptive mesodermal cells between the 5th and 6th weeks of gestation.[9] The majority cases are sporadic, though autosomal dominant, autosomal recessive, and X-linked recessive inheritance have been suggested in few familial cases.[20-21] Chestler reported a monozygotic twin with variable expression of the syndrome.[3] Therefore, it may reflect a common phenotypic pathway for various genetic defects, which means genetic heterogeneity. Other chromosome abnormalities, such as cat eye syndrome and abnormalities (trisomy, partial deletion, or duplication) of chromosomes 4, 11, 13, 18, and 22, have been reported to be associated with coloboma and other CHARGE-like malformations. It is important to rule out a known chromosome abnormality before making a diagnosis of CHARGE syndrome.

Ophthalmologists should be aware of both the ocular and systemic features of CHARGE syndrome. Timely surgical correction of various structure malformations, early rehabilitation and training for impaired hearing, and adequate hormone therapies for growth retardation and genital hypoplasia may be very helpful to babies with CHARGE syndrome. Nutritional supplementation may be required in cases of swallowing difficulties and/or cleft palate. The overall outcome and survival may be improved if there is good collaboration between specialists of different fields. Since some cases may be

heritable, evaluation by a medical geneticist and genetic counseling is advised. Long-term ophthalmic follow-up is mandatory, because retinal detachment can occur as a complication of chorioretinal coloboma.

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