Peripheral Facial Paralysis in a Newborn with Charge Syndrome

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ABSTRACT

CHARGE Syndrome is a genetic disorder that affects many organs. Approximately two-thirds of the cases have CHD7 mutations. Most individuals with this syndrome have a coloboma in their eyes. Coloboma can be found in one or both eyes and may impair visual functions depending on its size and location. Moreover, patients with this syndrome often have cranial nerve abnormalities. In this infant, peripheral facial paralysis was detected in addition to the eye coloboma, choanal atresia, heart defects, growth retardation, and ear anomalies, which are the main characteristic findings of CHARGE Syndrome. The chorioretinal coloboma in our case was present in both eyes and included optic discs. He had findings such as facial weakness on the left side, lagophthalmos, and flattening of the nasolabial fold due to peripheral facial paralysis. Lubrication therapy and eye closure treatment at night were started to protect the corneas of this patient. The cases with CHARGE Syndrome should be kept under ophthalmologic control against the risk of retinal detachment, amblyopia, and refractive errors that may occur in the future. We should be careful about the VII., VIII., IX. and X. cranial nerves dysfunctions which cause severe morbidity such as lagophthalmos, deafness, the difficulty of feedings in these cases.

Keywords: CHARGE Syndrome, choanal atresia, coloboma, lagophthalmos, peripheral facial paralysis.

INTRODUCTION

The CHARGE syndrome is an autosomal-dominant multi-systemic frequently associated with CHD7 gene mutation, which affects many tissue and organ system. It is a rare disease with a prevalence of 2.8: 10,000.[1, 2]

This genetic syndrome is seen during the neonatal period, which is characterized with severe congenital anomalies. The CHARGE syndrome is an acronym standing for disorders appearing at many organs. These include coloboma in eye, heart defects, choanal atresia, growth retardation, genital abnormalities and ear abnormalities. Life-threatening medical problems may develop within first weeks of life in these patients. Mortality is associated with cyanotic cardiac disease, atrioventricular septal defect, choanal atresia as well as brainstem and cerebellum anomalies. The nutritional and visual problems are causes of major morbidity.[3, 4]

This patient was presented to emphasize presence of peripheral facial paralysis leading lagophthalmos which associated to syndrome as well as ocular coloboma, the diagnostic criterion for CHARGE syndrome.

CASE REPORT

A male infant (gestational age: 37 weeks; birth weight: 2580 g) with inability to close eyes and dysmorphic facial appearance was referred to our clinic from neonatal intensive care unit for diagnosis and treatment. In his history, the boy was born from a 25-years old mother via cesarean section. In the maternal history, there was no drug or X-ray exposure during pregnancy, smoking, diabetes mellitus or hypertension. In his family history, it was found out that his mother (25-years old) and father (28-years old) were healthy and the patient had 2 healthy siblings (a brother and sister).

The patient had a syndromic appearance and cyanosis. He was admitted to neonatal intensive care unit due to respiratory distress and received free oxygen. During follow-up, the patient was consulted with ETN department for crying in undertones and rhinorrhea and a CT scan

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was ordered for suspected bilateral choanal atresia, which revealed bilateral osseous choanal atresia and inner ear anomaly with severe hypoplasia in semicircular canals (Figure 1) On the audiogram, loss of conduction was reported in both ears. On first month of life, the patient underwent surgery due to difficulty in feeding and respiration and nasal passages were opened. In cardiovascular examination, patent ductus arteriosus and atrial septal defect were detected on echocardiography. On cranial MR imaging and cranial sonography, no malformation was detected in central nervous system. Abdominal sonography and bone scanning images were reported to be normal. In the consultation with genetic disorders, low-set ear and flattened nose were detected in the context of dysmorphic facial appearance (Figure 2). Karyotyping and DiGeorge Fish Analysis were found to be normal but CHD7 gene mutation analysis was reported to positive. No additional abnormality was detected in remaining organ systems.

In the ophthalmological examination, lagophthalmos due to peripheral facial nerve paralysis in left eyes and chorioretinal coloboma in bilateral posterior segments were detected, supporting CHARGE syndrome (Figure 3, 4, 5). There was no nystagmus and no problem in ocular movements. As treatment, eye closure during sleep, intensive lubrication therapy and tarsorrhaphy, if lagophthalmos-related complications occur, were recommended. During 4-months follow-up, no lagophthalmos-related complication was observed owing lubrication therapy and no surgical intervention was needed.

The patient gave informed consent for use of data and photographs.

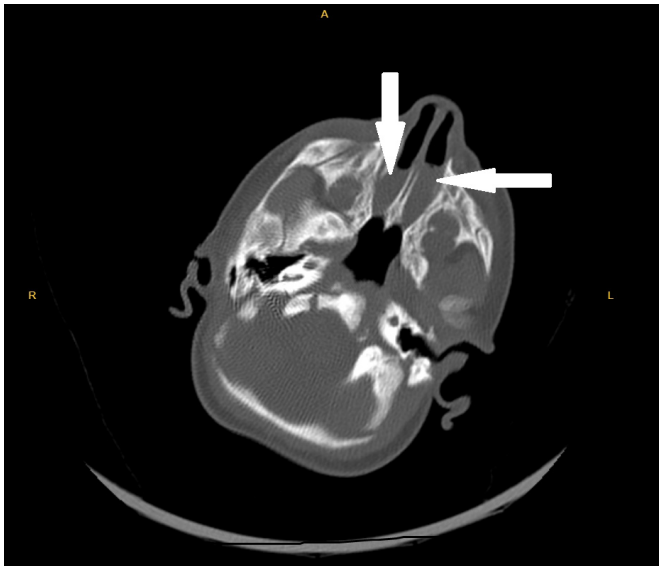

Figure 1: *Axial CT scan showing soft tissues causing obstruction of airway by fully occluding nasal passage in both sides (arrows).*

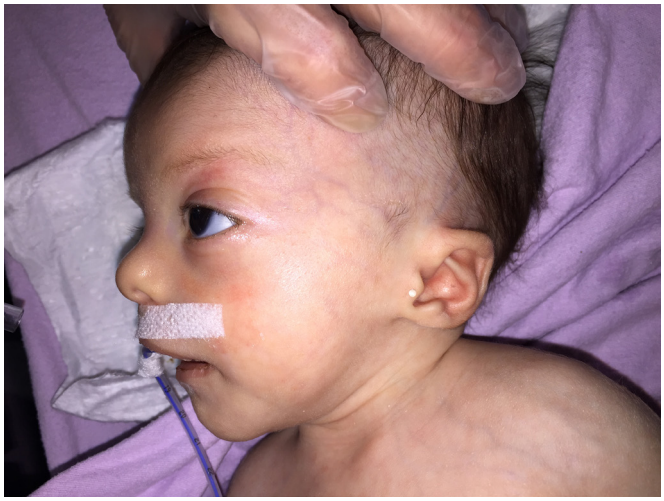

Figure 2: *Dysmorphic facial appearance and low set ear in the patient.*

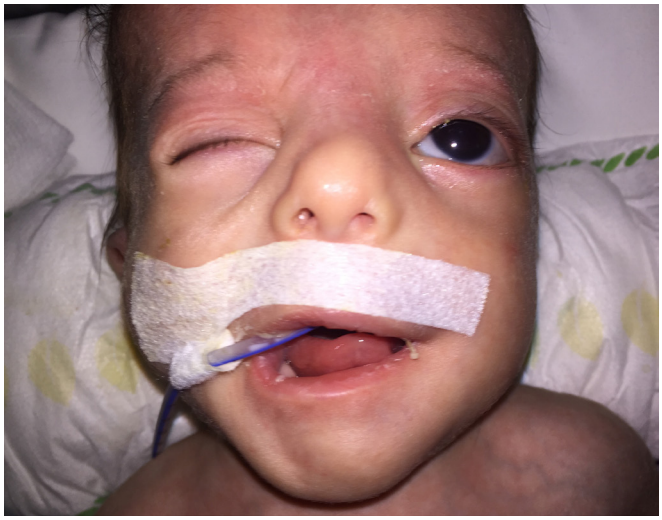

Figure 3: *Lagophthalmos due to peripheral facial paralysis on the left.*

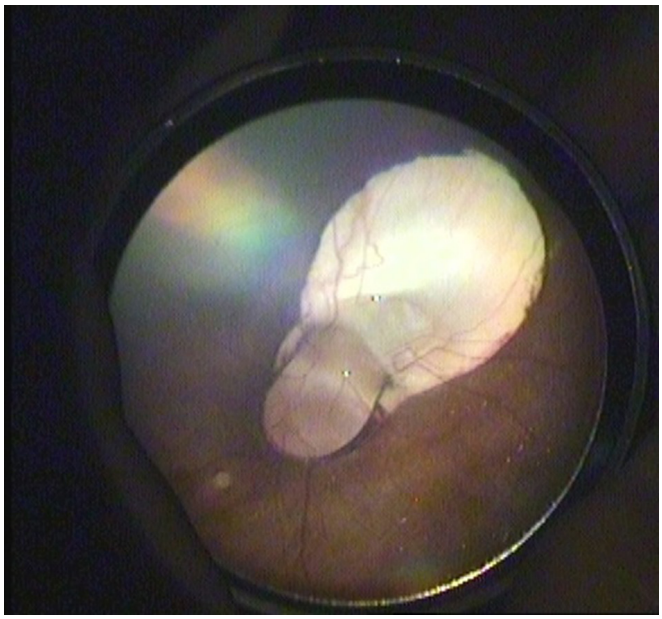

Figure 4: *Fundus image by binocular ophthalmoscope showing chorioretinal coloboma in right eye.*

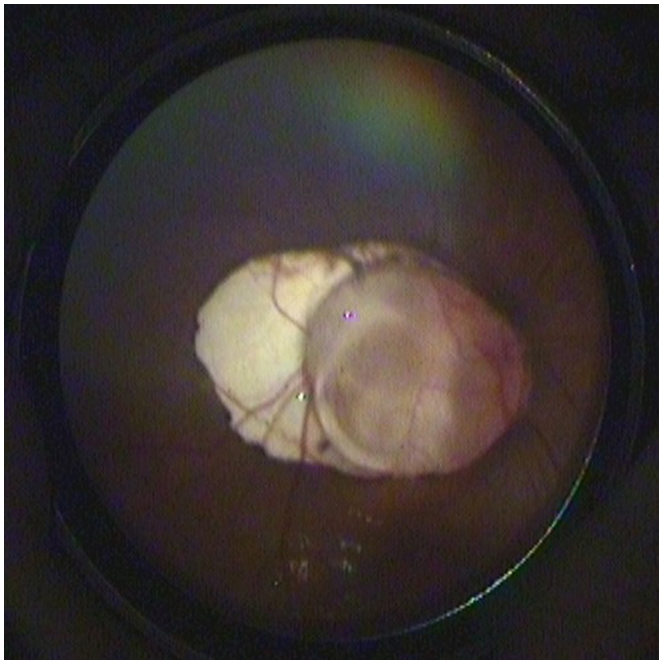

Figure 5: *Fundus image by binocular ophthalmoscope showing chorioretinal coloboma in left eye.*

DISCUSSION

The CHARGE syndrome was first described by Bryan Hall and Helen Mintz Hittnerr et al. in 1979. Multiple anomalies occurring in the disease comprise life-threatening problems upon neonatal period. Thus, its management has remained to challenging for clinicians since its first definition.[5-7] For timely treatment, collaboration among pediatricians, cardiologists, ophthalmologists, genetics specialists and ETN surgeons is important.

In CHARGE syndrome, compared to other symptoms, four more common anomaly include coloboma, choanal atresia, characteristic ear defects and cranial nerve dysfunctions (4C).[8] In our patients, presence of all these findings at birth suggested evaluation for CHARGE syndrome preferentially. In CHARGE syndrome, clinical diagnosis is made based on major and minor criteria defined by Blake et al. and modified by Verloes et al.[8, 9] The definitive diagnosis requires 3 major criteria or 2 major criteria plus 3 minor criteria.[9] In our case, coloboma, choanal atresia, ear anomaly and cranial nerve palsy were present as major criteria while dysmorphic facial appearance and growth retardation as minor criteria. Table 1 lists major and minor criteria in CHARGE syndrome.

The coloboma and other ocular anomalies have been about 80-90% of patients with CHARGE syndrome (Table 1). In their study, Russel et al. detected ocular anomalies in 44 of 50 patients with CHARGE syndrome including retinochoroidal coloboma involving optic nerve in 41 (82%) and concurrent iris coloboma in 13 patients (26%). The other ocular anomalies were facial paralysis in 22 patients (50%), microphthalmia in 21 patients (47%), nystagmus in 12 patients (27%) and optic nerve hypoplasia in 4 patients (9%).[10] In a case report from Turkey, Dilli et al. reported bilateral iris coloboma and unilateral congenital ptosis, congenital cataract and total retinal detachment in a 16-years old boy with CHARGE syndrome.[11] In our patient, choroidoretinal coloboma involving optic nerve in both eyes as well facial nerve palsy at left. In these patients, predisposition to retinal detachment due to chorioretinal coloboma and persistent cornea problems caused by lagophthalmos developed due to facial nerve palsy may cause visual disturbances later on life.

The facial nerve paralysis develops in approximately 20-40% of patients diagnosed as CHARGE syndrome.[12,13] In

Table 1: *Major and minor criteria of CHARGE syndrome*

Major criteria	Frequency	Other findings
Ocular coloboma	80-90%	Irıs, retina, choroid and optic disc coloboma, microphthalmia, refrective errors, strabismus, ptosis
Choanal atresia	50-60%	Unilateral/bilateral osseous or membranous atresia/stenosis
Characteristics ear anomalies	80-100%	External ear anomaly, bone malformation, chronic serous otitis, Mondini defect of cochlea, temporal bone anomaly, aplasia or hypoplasia of semicircular canal
Cranial nerve dysfunction	40-90%	Hyposmia or anosmia, facial paralysis, hypoplasia, swallowing difficulties
Minor criteria	Frequency	Other findings
Genital hypoplasia	50-60%	Micro-penis in boys, hypoplastic labia in girls, delayed incomplete puberty in both sexes.
Growth retardation	<100%	Hypotonia, delayed motor skills, mental retardation
Cardiovascular malformation	75-85%	Conotruncal defects, atrioventricular defects, aorta anomalies
Cleft palate	15-20%	Cleft lip and/or cleft palate
Tracheoesophageal fistula	15-20%	All types may be present
Dysmorphic facial appearance	70-80%	Prominent forehead, flattened face

addition, sensorineural or mix type haring loss, difficulty in breastfeeding indicate involvement of cranial nerves VII, VIII, IX and X, respectively.[14] The lagophthalmos can lead to conjunctivitis and open eye keratopathy and even corneal ulcer, corneal perforation and blindness due to uncovered cornea and excessive evaporation in the eye. The facial paralysis is classified as central facial paralysis if lesions are located at brain while peripheral facial paralysis if they occur at or after level of tympanic canal. Both types of paralysis can be seen in CHARGE syndrome. In our patient, facial paralysis was made based on asymmetrical facial appearance, decreased depth of nasolabial sulcus and shifting of mouth to contralateral site. In addition, lagophthalmos, inability to wrinkle forehead and to lift eyebrows indicated peripheral type. In CHARGE syndrome, congenital occurrence of peripheral facial paralysis can be explained as follows: facial nerve development begins on gestational week 4. It is bended caudally on gestational week 6 and passes through a deep sulcus at tympanic region.[15] The CHD7 gene mutations at this period lead anomalies in nasal structures such as oval foramen atresia with anomalies in stapes, temporal bone and inner ear as well as facial nerve abnormalities by causing several migration and timing abnormalities.

To date, the CHD7 (expressed as chromodomain helicase DNA-binding protein) is the only gene known to case CHARGE syndrome. This gene is associated with many tissues and play role in migration of neural crest cells in particular. Overall, 97% of all CHD7 mutations occur de novo; thus, CHARGE syndrome presents as a novel autosomal dominant condition without family history in general. No problem was detected in family history, parents or siblings of our patient.[1, 16]

In CHARGE syndrome, 22q11 Deletion syndrome, DiGeorge syndrome (Velocardiofacial anomaly), Joubert syndrome, Kabuki Make-up syndrome, Cat Eye syndrome and VACTER/VATER association should be kept in mind in differential diagnosis. Although DiGeorge syndrome was suspected in the patient with dysmorphic facial appearance, growth retardation, respiratory distress, choanal atresia and hearing loss, negative FISH analysis for chromosome 22 deletion excluded the diagnosis. In differential diagnosis, CT scan is helpful to demonstrate choanal atresia and anomalies in temporal bone and ear. Although the diagnosis of CHARGE syndrome is made based on clinical findings, the definitive diagnosis is made by gene analysis for CHD7.

In conclusion, coloboma and findings of cranial nerve dysfunction detected in ophthalmological examination were two of four major criteria and aided the diagnosis of CHARGE syndrome. In patients with suspected CHARGE syndrome, multidisciplinary approach is beneficial. Lubrication therapy should be initiated as soon as possible in the presence of facial paralysis in patients with suspected CHARGE syndrome and periodic ophthalmological examination should be performed due risk for reflective errors, strabismus, amblyopia, corneal ulcer and retinal detachment which may develop later on course of disorder.

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