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CASE REPORT / OLGU SUNUMU

A 2-month-old baby with CHARGE syndrome

CHARGE sendromu tanısı alan 2 aylık bir bebek

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ABSTRACT
CHARGE is a rare syndrome characterized by association of pathogenetically related multiple congenital anomalies with six main clinical features. In this case report, we present a 2-month-old female baby admitted to our hospital for surgical correction of her congenital heart anomalies (aortic coarctation, bicuspid aortic valve and patent ductus arteriosus). In addition, she had bilateral optic disc and choroid colobomas, operated bilateral choanal atresia, right facial nerve paralysis, ear anomaly and growth retardation to make the diagnosis of CHARGE syndrome. As children with CHARGE require multiple surgical corrections and the risk of congenital anomalies increases in subsequent pregnancies, it is important to recognize and inform the family about this syndrome as soon as possible. Early interventions for correction of accompanying congenital anomalies like choanal atresia can be life saving. Therefore, we wanted to highlight CHARGE syndrome and review the relevant literature.

Key words: Congenital, Multiple anomalies, CHARGE

ÖZET
CHARGE sendromu patogenetik olarak ilintili konjenital anomalilerden oluşan ve 6 ana klinik özelliği bulunan nadir bir sendromdur. Burada hastanemize doğumsal kalp anomalilerinin (aort koarktasyonu, biküspid aortik kapak ve patent duktus arteriosus) cerrahi olarak düzeltilmesi için kabul edilen bir kız olguyu sunduk. Olgumuzun kalp anomalisine ek olarak bilateral optik disk ve koroid kolobomu, opere edilmiş çift taraflı koanal atrezisi, sağ fasiyal paralizisi, kulak anomalisi ve büyüme geriliği mevcuttu. Bu bulgularla hastamıza CHARGE sendromu tanısını koyduk. CHARGE sendromlu çocuklar çoklu cerrahi girişimlere ihtiyaç duydukları ve annenin sonraki gebeliklerinde de konjenital anomalili bebek riski arttığı için bu sendromu erken tanımak, aileyi bilgilendirmek ve genetik danışmanlık vermek oldukça önemlidir. Eşlik eden koanal atrezi ve kardiyak anomaliler gibi konjenital malformasyonlara erken müdahele etmek hayat kurtarıcı olacaktır. Bu nedenle, CHARGE sendromunu literatür eşliğinde yeniden hatırlatmak istedik.

Anahtar kelimeler: Doğumsal, Çoklu anomali, CHARGE

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Introduction

The CHARGE or Hall-Hittner Syndrome, first described by Bryan Hall and HM Hittner in 1979, is a combination of pathogenetically related multiple congenital anomalies with six cardinal features: Coloboma of the eye, Heart anomalies of any type, Atresia of the choana, Retardation (of growth and/or development), Genital anomalies and Ear anomalies. Hypopituitarism, cleft lip and palate, cranial nerve (especially facial nerve) paralysis, micrognatia, tracheoesophageal fistula and renal abnormalities may also be encountered in the CHARGE syndrome [1-4]. Its incidence is estimated between 0.1 to 1/10000 live births [5]. The etiology of CHARGE syndrome has not yet been clearly identified. Although X-linked recessive, autosomal recessive or autosomal dominant cases have been reported [6,7], the majority of the CHARGE cases are sporadic. There are also studies indicating some teratogenic agents received during pregnancy or increased paternal age as the causes of the CHARGE syndrome [8]. Recurrence rate is about 1% [9]. Management of the CHARGE syndrome requires a multidisciplinary approach and multiple surgical interventions. We report a CHARGE case presenting with major and minor symptoms. After the diagnosis we informed the family about the features of the syndrome and referred for genetic counselling.

Case report

A 2-month-old, female baby was admitted to our hospital for surgical correction of her congenital cardiac anomalies (aortic coarctation, bicuspid aortic valve, patent ductus arteriosus, mild aortic stenosis). Her preoperative evaluation was performed at the bedside. The mother of the baby was 22 and healthy. This was her first pregnancy. She did not receive regular medical follow-up during her pregnancy. She had no history of drug, alcohol or cigarette use. The father was 27 and healthy. There was no consanguinity between the mother and father. Their first degree relatives had no history of any congenital anomalies. The baby was born at term, 2900 gr., with a normal spontaneous delivery. In history before admission she had cyanosis, dyspnea and a 2/6 continuous murmur at birth. There was no passage through her nasal

cavities with a nasogastric tube. Her echocardiographic examination revealed a patent ductus arteriosus, aortic coarctation, a bicuspid aortic valve and mild aortic stenosis. She had been intubated and referred to the University hospital where bilateral choanal atresia had been revealed by flexible endoscopy and operated before she was referred to our hospital.

She was admitted to our hospital at 2 months of age. On pysical examination she was 3100 gr.(<3 p) and 54cm. (<3 p). Her arterial pressures were measured as 100/70 mmHg on the upper extremities and 50/40 mmHg on the lower extremities. She had a mild fever, bilateral sibilant rales and wheezing, a 2/6 continuous murmur, weak femoral pulses, incomplete closure of the right eye and warpage at the right corner of the mouth due to a right facial nerve paralysis, an anomaly in the shape of the auricle and growth retardation. Entropion of the right eyelid, bilateral colobomas of optic disc and choroid were found during the eye examination. On her echocardiography, the ascending aorta was 7.6 mm. and the transverse aorta was 10.1 mm.in diameter which decreased to 3.8 mm in the coarctation region. The coarctation gradient was 62 mmHg . The diameter of the post stenotic descending aorta was 6.7 mm. Her biochemical and microbiological tests were normal except for moderately elevated acute phase reactants. The chest X-ray showed enlarged cardiac shadow and increased bronchial markings. Her tympanogram was type B for the right ear and type C for the left, both of which indicated an ear conduction anomaly and an eustachian tube disorder. Her cranial ultrasonography was normal except for cavum pellicidum variation. The abdominal ultrasonography was normal. Her karyotype analysis was 46, XX and a flourescent in situ hybridization (FISH) analysis for chromodomain helicase DNA binding protein 7 (CHD7) gene mutation result was negative. After the treatment of infection, the case underwent cardiac surgery. The postoperative period was uneventful and she was discharged on the thirteenth postoperative day. During her follow-up visit at 5 months old, except her ophthalmic problems, she was clinically well. Written permission was obtained from the parents to publish her photographs.

Discussion

The CHARGE syndrome has been reviewed by geneticists and pediatricians several times and some major and minor criteria were defined in 1998 to make the syndrome more recognizable [8,9]. Major criteria (4 C's) of the CHARGE syndrome are: 1) Coloboma (70-80%) (with/out microphthalmia). This is usually small and may extend to the iris, the retina or the choroid disc, 2) Choanal atresia is found in 35-65% of the CHARGE cases. It may be unilateral or bilateral, membranous or bony, 3) Cranial nerve dysfunction, such as facial palsy (50-90%) mostly unilateral or olfactory anomalies or velopharyngeal incoordination related to swallowing problems, 4) Characteristic ear abnormalities such as mostly flat pinnae or a cup shaped ear (95%) or middle ear problems or deafness due to genetic mutations [8,9].

The first vital symptom of our case was cyanosis at birth and dyspnea. Cyanosis at birth is first considered to be related to cyanotic congenital heart disease and the choanal atresia is rarely observed. However, there was difficulty in passsing the nasogastric tube through the nasal cavities of our patient, thus suggesting bilateral choanal atresia. In addition to choanal atresia, she had unilateral facial nerve paralysis and mild hypotonia on neurologic examination (Figure 1). The presence of these two major symptoms allerted us to the CHARGE syndrome. Then entropion on the right eyelid, bilateral colobomas of the optic disc and choroid were diagnosed on the eye examination. Another major sypmtom suggesting the CHARGE syndrome was her abnormal pinnae shape and ear tympanogram showing a bilateral conduction anomaly and an eustachian tube disorder (Figure 2).

There are also minor criteria to support the diagnosis of the CHARGE syndrome:

1) Cardiovascular malformations of all types may be seen in 75–80% of CHARGE patients; especially conotruncal defects (e.g. Tetralogy of Fallot 33%), atrioventricular canal defects, ventricular septal defects and aortic arch anomalies. In a recent study Ahmet Irdem et al. presented a baby with CHARGE with a rare cardiovascular anomaly called the middle aortic syndrome and characterized by hypoplasia of the thoracic and abdominal aorta as well as a tubular hypoplasia of the aortic arch and an isthmic aortic coarctation [10]. 2) Genital hypoplasia (50-70%) such as a micropenis or cryptorchidism in males or hypoplastic labia in females or delayed incomplete pubertal development in either sex. 3) Orofacial cleft such as cleft lip and/or palate. 4) Tracheoesophageal fistula of all types. 5) Growth deficiencies associated with short stature or borderline growth hormone (GH) stimulation tests or developmental delays such as delayed motor milestones, language delay and mental retardation [8,9].

There was growth retardation in our case. Her weight and height were below the 3rd percentile. Although she had no cleft lip or palate or other gastrointestinal symptoms, she had gained only 200 grams in a 2 month period. This might have resulted from her facial nerve paralysis leading to difficulty in opening her mouth and sucking. The increased energy demand as a consequence of the chronic metabolic stress response to congestive heart failure or the inefficient nutrient absorption due to the edema of the small bowel wall depending on the right sided heart failure might cause poor weight gain [11]. Moreover, repeated operations in two months might have prevented the mother from adapting to her child and feeding effectively. Echocardiography of our case performed before she was referred to our hospital and repeated by our pediatric cardiologists before the cardiac operation had revealed patent ductus arteriosus, aorict coarctation, a bicuspid aortic valve and mild aortic stenosis with a gradient of 33 mmHg.

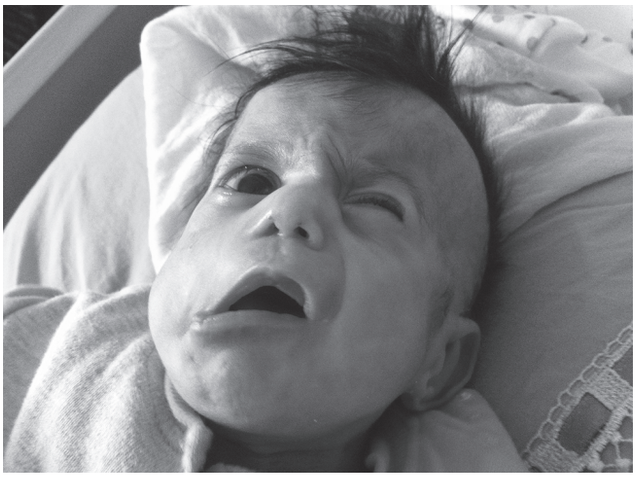

Figure 1. Facial nerve paralysis as a major symptom of the CHARGE syndrome.

Figure 2. Ear shape anomaly as a major symptom of the CHARGE syndrome.

Because she was 2 months old, we could not perform psycomotor and mental development tests. Another minor symptom of CHARGE is genital hypoplasia, however, our case did not have hypoplastic labia. Reported renal anomalies include a solitary kidney, hydronephrosis, renal hypoplasia, duplex kidneys and vesicoureteral reflux [8,9]. The urinary ultrasonography of our case was normal, voiding cystourethrography was planned.

The presence of 4 major or 3 major and 3 minor criteria is sufficient for the diagnosis of the CHARGE syndrome in infants [12,13]. We had 4 major criteria; the choanal atresia, facial nerve palsy, colobomas of the optic disc and choroid and the ear anomaly and 2 minor criteria, the cardiac anomaly and the growth retardation.

Most cases of CHARGE are sporadic. In two large independent series of patients with the CHARGE syndrome [14,15] mutations of the chromodomain helicase DNA binding protein gene were found in 69 out of 107(64%) and 64 of 110(58%) CHARGE patients, respectively. There was no consanguinity between parents of our case. They had no congenital anomaly. Their first degree relatives had no history of any congenital anomalies, either. FISH analysis for the CHD7 gene mutation and karyotype analysis results of our case were normal.

There are also studies implicating either some teratogenic agents received during pregnancy or increased paternal age as the causes of the CHARGE syndrome [16,17]. The mother of our case was young and had no history of drug,alcohol or cigarette use. The father was young and healthy.

Most of the abnormalities associated with the CHARGE syndrome are difficult to diagnose antenatally through ultrasound unless there is polyhydramnios or risk factors raising the suspicion of CHARGE [17]. However, focused ultrasound for detection of external ear anomalies, choanal atresia or semicircular canal agenesis may increase prenatal detection rate [18]. Fetal echocardiography may be helpful in the detection of cardiac anomalies [17,18]. If there is a high suspicion of CHARGE, reliable prenatal detection of CHD7 mutation is possible by chorionic villus sampling or amniocentesis [19,20]. The mother of our case was 22 years old and healthy. This was her first pregnancy. She had not gone for doctor visits regularly during the pregnancy, so detailed ultrasonography or amniocentesis had not been performed for antenatal diagnosis. After explaining the features of the CHARGE syndrome, we warned the family about the importance of genetic counselling and amniocentesis for her subsequent pregnancies.

In conclusion, it is crucial to recognize CHARGE and to complete the necessary investigations as soon as possible to decrease the morbidity and mortality by treating associated anomalies such as choanal atresia,cardiac anomalies or tracheoesaphageal fistula. As the children with CHARGE require multiple surgical corrections and the risk of having children with congenital anomalies increases in subsequent pregnancies, psychologic support and family counselling are as crucial as medical and surgical treatment for CHARGE patients and their families.

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