CASE REPORT

Identification of a Case of CHARGE Syndrome

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ABSTRACT

CHARGE syndrome is a genetic disorder characterized by a specific and recognizable pattern of anomalies. It is estimated to occur in 1:10,000 births worldwide with various clinical manifestations. The major clinical features of CHARGE syndrome include ocular coloboma, heart malformations, atresia of the choanae, growth retardation, genital hypoplasia, and ear abnormalities. The underlying defect is in the chromodomain helicase DNA-binding protein 7 (CHD7) gene, which is located on chromosome 8q12.1. Around 67% of the patients clinically diagnosed with CHARGE syndrome have CHD7 mutations[4]. So far, five hundred and twenty-eight unique alterations of CHD7 have been identified so far with no prefential domain being affected. The CHD7 gene encodes an adenosine triphosphate (ATP) dependent protein that participates in chromatin organization and plays a predominant role in neural tissue during fetal development. Majority of the CHD7 gene mutations occurs de novo. Familial transmission and germline mosaicism have rarely been identified.

KEY WORDS: *CHARGE Syndrome, CHD7, Coloboma.*

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INTRODUCTION

CHARGE syndrome is heterogenous collection of congenital anomalies. The Major clinical features are coloboma, atresia of the choanae, and hypoplasia of the semicircular canals. Minor clinical features may comprise of rhombencephalic dysfunction, hypothalamo-hypophyseal dysfunction, abnormal middle or external ears, malformation of mediastinal organs, and mental retardation. A typical case of CHARGE syndrome has three major clinical features or two major and two minor clinical features as per the criteria. Partial or incomplete CHARGE syndrome is labeled in presence of two major and one minor criteria.[11] Other clinical findings such as dysmorphic features, cleft lip/palate, and arhinencephaly may also be found to be present. Hearing loss and hypoplasia of the semicircular canals have been recently proposed as major CHARGE syndrome diagnostic criteria, because almost all patients are found to have these symptoms[2].

CASE

We report here a case of charge syndrome, which is being regularly followed on out-patient basis since its first presentation in Dr. Ziauddin hospital, 21 months ago.

A female child was born, at a hospital through cesarean section, after uneventful 38 weeks of gestation. She weighed 3 kg at birth but had poor APGAR score with compromised initiation of respiration. She was therefore admitted in nicu for 5 days after which she was sent home with the parents.

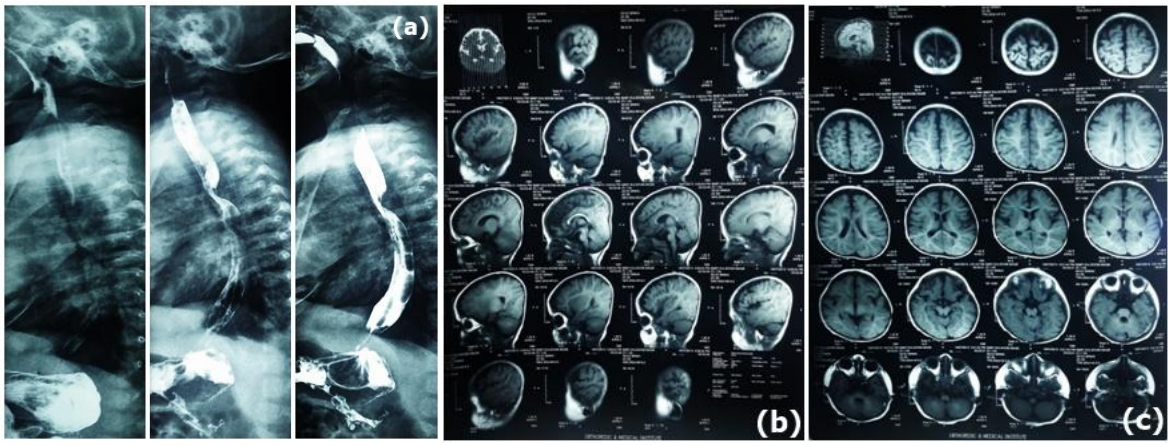
There is history of four hospital admissions due to pneumonia over past two and a half years with need for ventilator support during one of the admissions. There is no history of blood transfusion or any surgical illness. The child's parents were non-consanguinous and she is third in birth order of three children. Her elder siblings are normal with a good health status. There is no family history of chronic illness. Her vaccination is up to date as per her age.

On examination, lack of coordinated eye movements was noted along with low set ears. Murmur was noted on cardiovascular examination and the parents were advised echocardiography to rule out presence of a congenital heart defect.

Echocardiography done at 7th day of life, which showed 6 mm sized perimembranous ventricular septal defect with left to right shunt, multiple small septal defects in the atria with left to right shunt, hypertrophied right ventrile, moderate right pulmonary artery stenosis and mild pulmonary artery hypertension. Ejection fraction was 80%.

Repeated ecocardiograpgy scans showed mildly enlarged left ventricle with normal function, small (5 mm) peri-membranous ventricular septal defect with left to right shunt, gradient across the defect was noted to increase from 32 mmHg at 17th day of life to 80 mmHg at 1 ½ year of age. No ASD, PDA or co-arctation seen and all cardiac valves were found to be normal.

Figure 1. Gastograffin study and MRI of Brain



a. Gastograffin study
b & c. Brain MRI with T1 image

Ultrasound brain at 19th day of life, reported normal echogenecity of the cerebral cortex, normal ventricles and no shift of the midline structures.

Gastograffin study to rule out trachea-esophageal fistula or any associated abnormality was normal. Ultrasound of kidneys, ureter and urinary bladder was found to be normal. Ophthalmology review reported bilateral retinal and iris coloboma. ENT opinion was sought and cochlear implant was advised. The MRI of the brain was done and no obvious deformity or lesion was noted.

Figure 2. At 22 months of age (produced with permission of parents)

Currently, at the age of 22 months, she has regular outpatient visits for vaccination and treatment of respiratory infections and recurrent bacterial conjunctivitis. She has marked development delay with marked mental retardation. There is no neck holding, sitting without support and occasionally rolls over on bed. Milestones for speech have not been attained and communication is usually through shrills and screams. There is unsynchronized movement of eyes. She does not seem to identify objects, unless brought very close to her face. Solid diet cannot be ingested therefore liquid to puree diet is provided. She usually indulges in silent playing with her hands and feet and often exhibits aggressive behavior

Her current medication includes treatment for congenital heart defect, hyper-reactive airway disease and recurrent bacterial conjunctivitis respectively

DISCUSSION

CHARGE syndrome is estimated to occur in 1:10,000 births worldwide with a variety in its clinical manifestations. The diagnosis is primarily by identification of the classic clinical symptoms. Coloboma, in patients with CHARGE syndrome, usually involves bilateral choroid, retina, and the optic nerve.Choanal atresia is considered a pivotal cause of respiratory difficulty during the neonatal period. Congenital heart defects are present in around 75%–85% of the patients with CHARGE syndrome, with the common heart defects as tetralogy of Fallot, patent ductus arteriosus and atrial septal defects[3]. Hearing loss can be difficult to identify in a pediatric patient, as it requires multiple brain stem audio evoked response tests over several months.

Children with CHARGE syndrome are found to have normal anthropometric measurements at birth. However, the linear growth often declines by late infancy and pituitary hormone deficiencies of growth hormone and thyroid stimulating hormone are suggested to be the cause of the growth defects[3]. Therefore, patients with CHARGE syndrome must have their growth monitored. Additionally, these children may have hypogonadotropic-hypogonadism and present during adolescence with delayed puberty [4].

Neonates with CHARGE syndrome often have multiple life-threatening medical conditions related to respiratory system, commonly manifesting as repeated respiratory distress, as in our case. Studies mention that 15%–60% of patients with CHARGE syndrome may develop respiratory compromise severe enough to favour requirement of tracheostomy. Poor prognosis was reported by Blake et al. if patients were found to have cyanotic cardiac lesions, bilateral posterior choanal atresia, and a tracheoesophageal fistula[5]. Difficulty in feeding is also a major cause of morbidity. Therefore, any neonate suspected to be a case of CHARGE syndrome should have a cardiology, ENT and pulmonology consultation to rule out presence of respective defects.

The underlying pathology of CHARGE syndrome is the alteration in CHD7 gene, which codes an ATP-dependent chromatin remodeling protein. Although the function of the CHD7 encoded protein is unclear, it has been suggested to play an important role in controlling gene expression programs in embryonic stem cells.

Therefore, CHD7 molecular testing confirms the diagnosis of CHARGE syndrome in the majority of suspected cases. A total of 528 CHD7 alterations have been identified in 802 patients with CHARGE syndrome[6]. Sequence analysis is of importance as most mutations are small deletions/insertions, missense, nonsense and splice site mutations. Although almost patients with CHARGE syndrome have a normal karyotype, chromosomal abnormalities that disrupt CHD7 have been rarely reported; balanced chromosomal translocation t(6;8)(6p8p;6q8q)13), de novo balanced chromosomal rearrangement t(8;13)(q11.2;q22)14), and interstitial deletion of 8q11.2-q1315). Therefore, the purpose of cytogenetic analysis is to exclude chromosomal abnormalities and other syndromes overlapping CHARGE syndrome.

In summary, we identified a female child with CHARGE syndrome in its typical presentation. This finding will provide more information for further genetic counseling of the family and also expands our understanding of the pathogenesis and development of this rare syndrome.

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