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A Fatal Neonatal Case of CHARGE Syndrome and Mini-Review of the Literature

Fatal Seyirli Bir Neonatal CHARGE Sendromu Ogusu ve Kısa Literatür Taraması

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ÖZ

Bu makalede, yenidoğan döneminde ölümcül seyreden bir CHARGE sendromu vakası sunulmuştur ve kısa bir literatür taraması yapılmıştır. Böylece CHARGE sendromlu bireylerin yaşamlarının erken dönemlerinde karşılaştıkları konjenital anomalilerin ve klinik semptomların çok çeşitli oluşunun altı çizilmek istenmiştir. Karakteristik dismorfik yüz özellikleri, konjenital kalp hastalığı ve şiddetli beslenme intoleransı ile bu hasta, sendromun çok sayıda organ-sistemi etkileyerek ne kadar karmaşık olabileceğinin ve tanı almayan çok hafif fenotipte olgular bulunmakla birlikte, ciddi erken ölümcül vakalarla da sonuçlanabileceğinin iyi bir örneğidir.

Anahtar Sözcükler: CHARGE sendromu, yenidoğan, fenotipik değişkenlik, genetik tanı

ABSTRACT

In this article, we present a neonatal fatal case of CHARGE syndrome and provide a mini-review of the literature to underline the wide range of congenital abnormalities and clinical symptoms that individuals with CHARGE syndrome face early in life. This patient, with his characteristic dysmorphic features, congenital heart defects, and severe feeding intolerance, is a good example showing the complexity of the syndrome. CHARGE syndrome might affect numerous organ systems and result in severe early lethal cases for some whereas some of the cases show a very mild phenotypic spectrum and may go unrecognized.

Keywords: CHARGE syndrome, newborn, phenotypic variability, genetic testing

INTRODUCTION

CHARGE syndrome, a multiple malformation syndrome, is a rare genetic syndrome with an estimated incidence of 1/8,500-15,000 live births (1, 2). The inheritance is autosomal dominant, and most cases result from de novo mutations. Although the name CHARGE is an acronym representing coloboma, congenital heart defects, choanal atresia, retardation of growth, developmental delay, genital abnormalities, ear abnormalities, and deafness, it is a complex syndrome with a broad phenotype that can involve almost all organ-systems including extremity, vertebra and kidney abnormalities, omphalocele and umbilical hernia, brain and cranial nerves alterations, cochlear dysplasia, cleft lip and palate, thymus/parathyroid abnormalities, tracheoesophageal fistula, and autism spec¬trum disorder. The complexity of the syndrome makes it challenging for clinicians to provide accurate and comprehensive care. There is also a striking variability in severity with both very mild cases and severe early lethal cases.

CASE REPORT

A male infant was transferred to our neonatal intensive care unit right after the delivery at 39 gestational weeks via C/S because of respiratory distress and an antenatal diagnosis of cleft lip and palate and hypoplastic left heart. He was the second child of non-consanguineous healthy parents. On physical examination, he was an appropriate-for-gestational-age infant, and he had dysmorphic features composed of cleft lip and palate, low set dysplastic ears with lack of lobes, short

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webbed neck, microphthalmia, and coloboma of the left eye. He was intubated, and mechanical ventilation was started. Transthoracic echocardiography revealed hypoplastic left heart with complete atrioventricular septal defect (complete AVSD). Cranial ultrasound (US) was normal, and the abdominal US uncovered dilated aperistaltic intestinal segments consistent with ileus so the enteral feeding had held up until the first meconium discharge was seen. Ophthalmologic examination detected wide chorioretinal coloboma in the left eye.

He remained in critical condition during hospital admission retaining any surgery for correction of the congenital defects. The multitude of issues he faced further complicated the management besides the major heart defect. He was administered broad-spectrum antibiotic treatment, inotropic agents, calcium and thyroid hormone replacement treatment, oral decongestive therapy with furosemide and captopril for late neonatal sepsis, septic shock, hypocalcemia, hypothyroidism, and congestive heart failure. Enteral feeding issues were another challenge to overcome. It took too long to reach full enteral feeding at about 38th day of life because of intermittent abdominal distention and enteral feeding intolerance periods. Extubation was tried many times but failed. Unfortunately he died on the 43rd day of life with the official cause of death identified as congenital heart defect.

Table1. Prevalance of common features in CHARGE syndrome based on three recent cohorts with moleculary confirmed CHARGE patients.

	Zentner et al. (2010)	Bergman et al. (2011)	Legendre et al. (2017)
Coloboma	190/253 (75%)	189/234 (81%)	67/92 (73%)
Heart malformations	193/250 (77%)	191/252 (76%)	58/92 (63%)
Choanal atresia	95/247 (38%)	99/179 (55%)	38/89 (43%)
Retarded growth	101/141 (72%)	35/94 (37%)	
Developmental delay	107/141 (76%)	147/149 (99%)	
Inner ear abnormalities	98%	110/117 (94%)	87/88 (99%)
External ear malformations	214/235 (91%)	224/233 (97%)	78/91 (86%)
Facial nerve palsy	72/187 (39%)	80/121 (66%)	
Cleft lip and/or cleft palate	79/242 (33%)	79/163 (48%)	18/91 (20%)
Tracheoesophageal anomaly	35/185 (19%)	42/146 (29%)	20/84 (%24)
Genital anomalies	61%	118/145 (81%)	43/77 (56%)
Renal anomalies			25/80 (31%)
Craniaı nerve dysfunction		173/174 (99%)	64/87 (74%)
Feeding difficulties		90/110 (82%)	

Genetic analysis revealed a heterogeneous variant mutation in the CHD7 gene (c.2959C>T p.(R987*) p.Arg987*). Genetic screening for 22q11.2 deletion was negative.

DISCUSSION

The diagnosis of CHARGE syndrome is based on clinical findings criteria that continue to be refined. The most commonly used clinical criteria were described by Blake, Verloes, and Hale in 1998, 2005, and 2016, respectively (3-5). All three sets of criteria make a distinction between major and minor characteristics and slightly differ from each other in the number of characteristics that must be present. The major diagnostic criteria include ocular coloboma, choanal atresia, specific ear anomalies, cranial nerves involvement, and pathogenic CHD7 gene variant. Minor diagnostic criteria include genital anomalies, developmental delay, congenital heart defects, growth deficiency, orofacial cleft, tracheoesophageal fistula, and minor facial anomalies such as a square face with broad prominent forehead, a prominent nasal bridge and a flat columella and midface. Establishment of a clinical diagnosis requires a pathogenic CHD7 variant plus one other major characteristic. If CHD7 testing is absent or the result is negative, then at least three major or two major and three minor characteristics are sufficient for diagnosis.

Our patient fits the diagnostic criteria for CHARGE syndrome with his cleft lip and palate, characteristic external ear anomaly (a highly valuable diagnostic clue), microphthalmia, coloboma, heart malformation, feeding difficulties and pathogenic CHD7 variant mutation. CHD7, encoding the chromodomain helicase DNA binding protein, is the only gene currently known to be associated with CHARGE syndrome. The gene is located on region q12 of chromosome 8 and is crucial for the mitigation of neural crest cells affecting a wide variety of tis¬sues. Studies have shown that CHARGE syndrome patients exhibit defects in neural crest migration (6, 7).

To date, several reviews document the frequency of the major features. Table 1 shows the prevalence of specific anomalies found in the CHARGE syndrome population, on the basis of three recent cohorts of molecularly confirmed CHARGE patients from Zentner et al., 2010, Bergman et al., 2011, Legendre et al., 2017 (8-10).

Gastrointestinal tract problems such as gastroesophageal reflux disease, aspiration, and swallowing dysfunction are common in children with CHARGE syndrome and are primarily the result of anatomical malformations that interfere with feeding and cranial nerve IX/X abnormalities affecting gut motility. Our patient's anatomic malformation and ongoing mechanical ventilation necessitated O/G tube feeding. He also showed vagal nerve disfunction from the first day of life documented with abdominal US findings consistent with dysmotility and severe enteral feeding intolerance. Long-term and complex feeding issues can contribute to morbidity and mortality. Feeding difficulties are highly prevalent, often begin at birth and can persist throughout the entire lifespan (11).

The spectrum of congenital heart disease is highly variable in CHARGE syndrome as every type of cardiac defect (except heterotaxy and cardiomyopathy) has been documented. These defects encompass mild cardiac malformations to more severe malformations that require cardiothoracic surgery. As seen in our patient, conotruncal defects and atrioventricular septal defects are relatively over represented (12).

CHARGE syndrome patients can have features that overlap with DiGeorge like hypocalcemia and varying degrees of immune deficiency (13). Our patient suffered from hypocalcemia and severe sepsis that may be a result of underlying immunodeficiency and thymus dysfunction although not documented. FISH analysis for 22q11 deletion was negative.

Neonates with CHARGE syndrome often have multiple life-threatening medical conditions. Poor life expectancy correlated with combinations of major cardiovascular malformations, bilateral choanal atresia, esophageal atresia, severe T-cell deficiencies, and central nervous system anomalies. Feeding difficulties were also found to be a major cause of morbidity at all ages (1, 9, 14-16). Our patient had two major risk factors for poor prognosis, which were the congenital heart anomaly and feeding difficulties, and unfortunately he died on the 43rd day of life.

Optimal management of individuals with CHARGE syndrome should ideally take place in a tertiary center that can undertake all areas of specialist treatment and management, but details of the management are beyond the scope of this article. In 2017 Trider et al., published a comprehensive checklist for the follow up of CHARGE syndrome patients.(17). Our patient is a good example showing the complexity of this syndrome that can affect numerous organ-systems and result in severe early lethal cases, whereas some of the cases show a very mild phenotypic spectrum and may go unrecognized.

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