

CASE REPORTS

The eye - the window to the soul of the diagnosis: CHARGE Syndrome, a case report

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ABSTRACT

The modality of inheritance in CHARGE syndrome is autosomal dominant, classically triggered by mutations in the chromo-domain helicase DNA binding protein-7 (CHD7) gene. CHARGE syndrome is characterized by the variable occurrence of coloboma, heart defects, atresia of the choanae, retarded growth and development, genital hypoplasia, ear anomalies and deafness. In this report, we describe an infant with a typical phenotype characterized by severe psychomotor retardation, facial asymmetry, coloboma, cortical blindness, unilateral choanal atresia, congenital heart anomalies, genital hypoplasia, cranial nerve IX/X dysfunction and global developmental delay that was diagnosed clinically.

Following clinical diagnosis a complete sequencing of the CHD7 gene was carried out at the Institute for Medical Diagnostics GmbH in Ingelheim, Germany. Genomic DNA was screened for mutations in the CD7 gene (OMMIM 608892) on chromosome 8q12.1 The codon exon 2-38 and the respective exon-intron boundaries were amplified by polymerase chain reaction and analysed by direct sequencing. Resulting sequence data were compared with the reference sequence NM_017880.3 No mutation in CHD7 gene was detected as a genetic cause for the clinical phenotype of the patient. The MPLA multiplex ligation-dependent probe amplification analysis showed no copy number variation in the CHD7 gene.

This case report underscores the importance of a detailed family history and physical examination in the diagnosis of CHARGE syndrome. Additionally, it provides valuable insight into the pathogenesis and clinical presentation of the syndrome as well as highlighting the benefits of a multidisciplinary approach. With supportive nurturing care, children with CHARGE syndrome can overcome the associated disabilities and develop necessary motor skills and a life-style enhancing level of fitness.

Keywords: CHARGE syndrome; CHARGE association; Hall-Hittner syndrome; CHD7 gene; empty sella

متلازمة CHARGE مرض وراثية بالصبغي الجسدي في أغلب الوقت يكون ناتج عن طفرة في chromo-domain helicase DNA binding protein -7 جين CHD7 متلازمة CHARGE متغير يتميز بثلازمة، عيوب خلقية في القلب، رتق قمع الأنف، نمو متخلف و نماء شاذ، نقص التنسج التناسلي، شذوذات خلقية في الأذن و صمم توصيلي. الهدف من دراسة الحالة هذه وصف ملامح و مضاعفات متلازمة CHARGE ومناقشة التدبير العام لحالات متلازمة CHARGE. دراسة الحالة هذه تسلط الضوء على أهمية التاريخ المرضي العائلي و الفحص السريري في تشخيص متلازمة CHARGE. هذا إلى جانب المعرفة الجيدة للبيولوجيا السببية و الإستعلان السريري و أهمية دور إنتهاج منهج متعدد الإختصاصات للسمو بعلاج فعال في المصابين بمتلازمة CHARGE. الأطفال المصابين بمتلازمة CHARGE يملكون القدرة على التطور الطبيعي للمهارات الحركية في حال منحهم الرعاية الصحية الصحيحة لتعزيز صحتهم الإجمالية و مهاراتهم الحركية.

INTRODUCTION

The acronym CHARGE is used to designate the physical and health issues that are concomitant with the syndrome. CHARGE is a phenotypically heterogeneous syndrome which has been defined as a bundling of clinical features including Coloboma, Heart malformation, Atresia of choanae, Retardation of growth and development, Genital hypoplasia, and Ear anomalies or deafness¹. In addition, temporal bone and olfactory nerve anomalies are now considered extremely sensitive for a diagnosis of CHARGE syndrome².

CHARGE syndrome's modality of inheritance is autosomal dominant, classically triggered by mutations in the CHD7 gene in roughly two thirds of cases reported³. CHD7 descends from a large family of evolutionarily conserved

proteins that are alleged to play a part in chromatin organization. CHD7 is a regulatory element that potentially affects a large sum of developmental pathways, explaining the pleiotropic nature of its phenotypic continuum.

A clinical diagnosis of CHARGE syndrome necessitates the presence of four or more major features or three major features plus three or more minor features⁴. As a consequence, persons with CHARGE syndrome often require multiple and protracted hospitalizations which in turn can cause developmental delays because of the lack of socialization and physical activity during hospitalizations. See Tables 1 & 2 Post-neonatal death is not a rare event in patients with CHARGE syndrome and it often occurs unexpectedly. Gastro-oesophageal reflux and poor coordination of swallowing and breathing due to cranial nerve dysfunction seem to be the major risk factors⁵.

Table 1. Major diagnostic characteristics of CHARGE syndrome

Characteristics	Manifestations
Ocular coloboma	Coloboma of the iris, retina, choroid, disc and microphthalmos
Choanal atresia or stenosis	Unilateral/bilateral: bony or membranous atresia/stenosis
Cranial nerve dysfunction or anomaly	I: hyposmia or anosmia
	VII: facial palsy (unilateral or bilateral)
	VIII: hypoplasia of the auditory nerve
	IX/X: swallowing problems with aspiration
CHARGE syndrome ear	Outer ear: short, wide ear with little or no lobe, "snipped off" helix, prominent antihelix often discontinuous with tragus, triangular concha, decreased cartilage (often protruding and usually asymmetric)
	Middle ear: ossicular malformations. Mixed (conductive and sensorineural) hearing loss with a wedge-shaped audiogram
	Mondini defect of the cochlea
	Temporal bone abnormalities; absent or hypoplastic semicircular canals

Table 2. Minor diagnostic characteristics of CHARGE syndrome

Characteristics	Manifestations
Genital hypoplasia	Males: micropenis, cryptorchidism Females: hypoplastic labia
	Males and females: delayed puberty secondary to hypogonadotropic hypogonadism
Developmental delay	Delayed milestones, hypotonia
Cardiovascular malformation	Including conotruncal defects (e.g. tetralogy of Fallot), AV canal defects, and aortic arch anomalies
Growth deficiency	Short stature, usually postnatal with or without growth hormone deficiency
Orofacial cleft	Cleft lip and/or palate
Tracheoesophageal fistula	All types
Distinctive facial features	Square face with broad prominent forehead, prominent nasal bridge and columella, flat midface

CASE REPORT

A Bahraini male IUGR infant aged 18 months, the 1st pregnancy to non-consanguineous phenotypically normal parents. The mother was 19 and the father was 30 years of age at the time of birth of the child.

The mother's 1st and 2nd trimester histories showed that she had anemia and calcium deficiency for which she was on supplemental iron and calcium. She was also being treated for hypothyroidism. Ultrasound identified oligohydramnios and bilateral dilated ventricles and features of an echogenic bowel. The pregnancy was completed at 36 weeks by induced vaginal delivery for IUGR. Apgar scores were 9¹ and 9⁵ with a birth weight of 1.65 kg. The neonate was admitted immediately to the NICU with transient tachypnoea of the newborn (TTN) and required mechanical ventilation for two days. His low birth weight necessitated a further twelve week NICU admission.

The pedigree study revealed that the mother had no previous

unviable pregnancies and both parents were in good health. One first degree relative was found to have trisomy 21.

The window to establishing the diagnosis was the coloboma and dysmorphism noted for the first time by the admitting paediatric resident at the age of 17 weeks. He was tracheostomised and placed on home oxygen at the age of six months due to swallowing problems and in order to avoid accumulation of copious secretion that may obstruct the upper airway. He is currently on home pump nasogastric tube feeding. The mother was instructed by the speech and language therapist on how to do oral stimulation to maintain the infants sucking reflex.

The four major diagnostic characteristics of CHARGE manifested in this specific patient were:

- **Ocular colobomas:** Bilateral coloboma affecting the iris and posterior segment of the eye. Multidirectional nystagmus. Cortical blindness.
- **Choanal atresia:** NCCT brain showed moderate dilatation of the lateral and third ventricle with the V H Q of 55% consistent with moderate hydrocephalus. The fourth ventricle is normal in size. Narrowing of the left choanal region consistent with choanal atresia.
- **Cranial nerve dysfunction:** Cranial nerve IX/X palsy and neonatal brainstem dysfunction, causing feeding difficulty and swallowing difficulty with recurrent aspiration pneumonia.
- **CHARGE syndrome ear:** small, low set ears; protruding helix in the form of a tag was noted. Lack of response to calls but not to sounds.

The five minor diagnostic characteristics of CHARGE manifested in this specific patient were:

- **Genital hypoplasia:** Genital examination showed a micropenis, hypospadias and cryptorchidism. FISH study showed one signal for both chromosome X and Y in 140 cells (XY). Scrotal and renal ultrasound: Testes could not be located in the ectopic sites.
- **Developmental milestones:** Gross motor: Axial and appendicular hypotonia with no neck support. Able to flex limb, symmetrical posture, marked head lag on pulling up but does not raise head to 45°, does not sit, crawl or walk around furniture. He has severe psychomotor delay.
Vision and fine motor: fixes but does not follow. He is unable to reach out for toys, does not transfer, does not have pincer grasp.
Hearing, speech and language: startles to loud noises. Does not respond to calls but responds to sound. He does not turn to soft sounds and does not vocalize alone or say mama and dada. A tympanogram showed mild asymmetry of hearing loss bilaterally.
Social, emotional and behavioural development: He smiles socially, but does not put food in the mouth, does not wave bye-bye or play peek-a-boo. His need for multiple and prolonged hospitalizations and lack of active management of the sensory deficit have contributed to his developmental delay.
- **Cardiovascular malformation:** He has an atrial and ventricular septal defect, and conotruncal malformation (aortic valve stenosis, aortic coarctation, interrupted

aortic arch). ECG showed right bundle branch block with right ventricular hypertrophy.

- **Growth deficiency:** He is below the 5th percentile for weight, height and head circumference secondary to growth hormone deficiency and poor caloric intake. A multi-planar multi-sequence MRI imaging of the brain showed significant loss of volume of the periventricular white matter of both cerebral hemispheres; thinning of the corpus callosum secondary to loss of volume of the white matter. The pituitary gland is small and empty sella is suspected.
- **Distinctive facial features:** Dysmorphic features with an asymmetric square face with a broad prominent forehead, prominent nasal bridge and columella, malar flattening and micrognathia.

Additional examination:

- Limb dysmorphology: bilateral syndactyly in the hands, overlapping finger, and calcaneovalgus deformity in the lower limbs.
- Skin: Hair distribution is normal with no low hairline or midline defect and the underlying skin was normal with no rashes or hyper or hypopigmentation.

Additional tests:

- EEG showed cortical irritability and supports the diagnosis of epilepsy.
- Water soluble GI series showed gastroesophageal reflux disease.

DISCUSSION

The molecular genetic test for diagnosing CHARGE syndrome is a test designed to identify a certain gene which can lead to the diagnosis of this syndrome. This test is however subject to limitations such as being expensive, the complete sequencing of the CHD7 gene costs €2000.00 and the MPLA deletion/duplication analysis of the CHD7 gene costs €500.00. Another limitation of this test is that it is sensitive but not specific as it fails to detect all cases of this syndrome, as is the case with this patient. Mutations in the CHD7 gene are detected in 65-70% of the cases. Rare mutations in the other parts of the gene than those investigated here (e.g. in regulatory regions, low grade mosaicism, larger heterozygous deletions or duplications or mutations in the other genes cannot be excluded with the molecular genetics analysis applied here. Hence, the diagnosis of CHARGE syndrome still remains rather clinical - grounded on the medical features appreciated in the child. The clinical diagnosis is reached using an amalgamation of major and minor features. Major features are features that are fairly collective in CHARGE syndrome but comparatively rare in other conditions, and mostly diagnosable in the neonatal period. Some minor characteristics and features of CHARGE syndrome are not specific to it and thus not clinically useful in distinguishing it from other syndromes.

Management of CHARGE syndrome starts from the first minute of life with providing a secure airway, stabilizing the patient, excluding major life-threatening congenital anomalies. After the initial neonatal and infantile period, individuals with CHARGE syndrome who survive require vigorous restoration of the sensory function to facilitate

adequate psychomotor development. Therefore a patient with CHARGE syndrome necessitates a multidisciplinary team approach to deal with different medical issues that arise from this complex syndrome.

It is important to highlight the implications that our greater understanding of the prognosis of CHARGE has for clinical practice and health resource allocation. To this end, it is imperative for clinicians to thoroughly follow up patients in order to tailor therapeutic approaches to their early prognostic indicators and to recognize the development of any comorbid conditions. Ultimately, this may pave the way for improved clinical care of patients with CHARGE. Future research should focus on genetic counseling and modalities to improve the quality of life of these individuals and their families.

CONCLUSION

In the right environment, patients with CHARGE syndrome have the prospect of developing essential motor skills and a health-enhancing level of fitness. Improvement in their physical activity and education is limited mainly due to the natural history of the syndrome, in addition to the lack of trained specialist to work with the patient and their families.

This report underscores the importance of a detailed family history and physical examination along with the role serendipity and sound clinical judgment played in the diagnosis of CHARGE syndrome in this infant. Good insight about the pathogenesis and the clinical presentation can improve the effectiveness of medical therapies. Further research about CHARGE syndrome is essential in the Gulf Cooperation Council region; particularly the epidemiology, diagnosis and the impact on the quality of life. Additionally, the availability and effectiveness of a multidisciplinary approach to these patients should be studied in order to provide definite evidence for implementation in clinical practice. Finally, we are most certainly in need of a non-profit, charitable organization in the Kingdom of Bahrain that caters to providing support and educational information to families of children with rare diseases. Hence, becoming instrumental in bringing together parents and professionals involved in their care.

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