CHARGE syndrome: A case report of two new CDH7 gene mutations

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Access this article online

Quick Response Code:

Website: www.saudijophthalmol.org

DOI: 10.4103/1319-4534.322601

Abstract:

CHARGE syndrome is a genetic disorder comprising the following clinical features: coloboma, heart defects, choanal atresia, retardation (of growth and development), as well as genitourinary and ear abnormalities. This syndrome is caused by mutations in the CDH7 gene, located on chromosome 8 (8q12). We present two new gene mutations in two patients with CHARGE syndrome, not previously reported in the scientific literature. Both of these patients clearly demonstrate the difference in the clinical expression of this syndrome, with patient 1 having a greater clinical severity compared to patient 2. We conclude that although in the scientific literature to date there is no clear correlation between a patient's genotype and phenotype expression, we can assume from the cases we present that a correlation does in fact exist. Specifically, missense mutations (as in case of patient 2) are associated with milder clinical expression, whereas mutations which result in truncation of the CDH7 protein (as in the case of patient 1 having a nonsense mutation) may be associated with a more severe clinical expression.

Keywords:

CHARGE syndrome, choanal atresia, coloboma, heart defects, hypoplasia of the semicircular canals

Introduction

CHARGE is an acronym which was first introduced in 1981 by Pagon *et al*.[1] It is also a syndrome comprising the following clinical features: coloboma, heart defects, choanal atresia, retardation (of growth and development), as well as genitourinary and ear abnormalities.[2]

This syndrome is caused by mutations in the CDH7 gene, located on chromosome 8 (8q12).[3] Until 2011, 528 mutations had already been described.[4] In humans, the CDH7 gene is part of the 9-member family of chromodomain helicase (CDH) DNA-binding proteins.[3,5]

Diagnosis is primarily based on clinical findings. In fact, the clinical criteria for this syndrome, published by Verloes,[6] have a high sensitivity, where approximately 90% of those who meet the criteria present with a CDH7 gene mutation.[2] The criteria specifically emphasize the existence of the three C's: *Coloboma, Choanal atresia,* and (*hypoplastic semicircular) Canals*.[6]

We present the ophthalmological findings of two patients with CHARGE syndrome having new CDH7 gene mutations not previously reported in the scientific literature.

Case Reports

Patient 1

A 2-year-old female child presents with multiple heart defects referred for neuro-ophthalmological assessment of her decreased visual acuity which had been noted by her parents. There is no significant family history other than first-degree consanguinity through the parents.

A previous cardiology consultation showed the following abnormalities: coarctation of the aortic arch, abnormalities of the left subclavian artery (whose origin is in the right aortic arch), and tetralogy of Fallot. She underwent successful corrective surgery shortly after birth.

On examination in our clinic, the patient exhibits intellectual impairment, hearing loss, and a mild degree of global hypotonia.

The patient can fix and follow objects with both eyes. Pupils are equal and react normally to light

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Submitted: 02-Feb-2019
Revised: 20-May-2019
Accepted: 20-Jun-2020
Published: 29-Jul-2021

How to cite this article: Galvez-Ruiz A, Galindo-Ferreiro A, Lehner AJ. CHARGE syndrome: A case report of two new CDH7 gene mutations. 2020;34:306-9.

and accommodation. There is a horizontal jerk nystagmus on lateral gaze and a 30 prismatic diopters alternating esotropia in primary gaze. Ocular motility is otherwise unremarkable.

Fundus examination shows the presence of an optic nerve coloboma and associated chorioretinal coloboma in both eyes [Figure 1a].

The patient has dysmorphic pinnae with the upper portion being larger than the lower, as well as an absence of the antihelix, giving them a cup-shaped appearance [Figure 1b]. She has severe bilateral hearing loss and there are no other evident cranial nerve abnormalities. She has overall good mobility of her extremities, although with a mild degree of hypotonia.

The patient showed no genitourinary abnormalities on previous pediatric evaluation.

Cranial magnetic resonance imaging (MRI) shows some degree of cortical underdevelopment predominantly in the frontal lobe region, as well as bilateral choanal atresia and hypoplasia of the semicircular canals [Figure 1c].

Electroretinography shows an overall decrease in scotopic and photopic responses.

Genetic testing for CHARGE syndrome was performed by complete coding of the region (exons 2-38). The respective exon-intron boundaries of the CHD7 gene on chromosome 8q12.1-q12.2 were amplified by polymerase chain reaction and sequenced directly. This genetic test shows that the patient carries the heterozygous nonsense mutation c.6217C>T (p.Gln2073*) in exon 31 of the CHD7 gene. This mutation implies a nucleotide exchange from C to T at position c.6217C in exon 31 of the CHD7 gene, leading to a premature stop codon (p.Gln2073*), and subsequently probably either to a degradation of the mRNA or to a truncation of the CHD7 protein. To the best of our knowledge, this variant has neither been annotated in databases nor been described in the literature so far.

Patient 2

A 2-year-old female child was referred for neuro-ophthalmological assessment of decreased vision and nystagmus present since birth. The patient had an uncomplicated birth, although the parents have noticed a certain degree of intellectual impairment. There is the first-degree consanguinity through the parents, but no family history of ophthalmological significance.

Her medical history includes the detection of a patent foramen ovale after birth, however on cardiology assessment, no intervention was required.

On examination in our clinic, the patient presents with intellectual impairment and some degree of overall hypotonia.

The patient can fix and follow lights, but not objects. Pupils are equal and react normally to light. There is a horizontal jerk nystagmus on lateral gaze with an exotropia measuring 30^. Ocular motility is otherwise unremarkable.

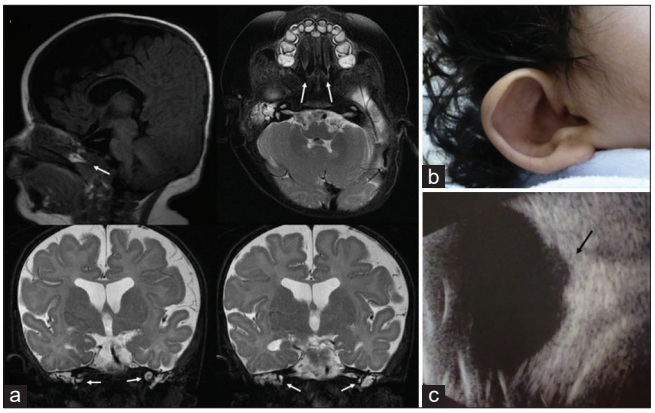

Figure 1: (a) B-scan of patient 1 showing bilateral optic nerve coloboma and associated chorioretinal coloboma. (b) Photo of patient 1, showing dysmorphic pinnae, larger toward the top of the ear with an absence of the antihelix, resulting in a cup-shaped appearance. (c) Brain magnetic resonance imaging of patient 1, showing bilateral choanal atresia (superior row in the photo composition) and semicircular canal hipoplasia (inferior row in the photo composition)

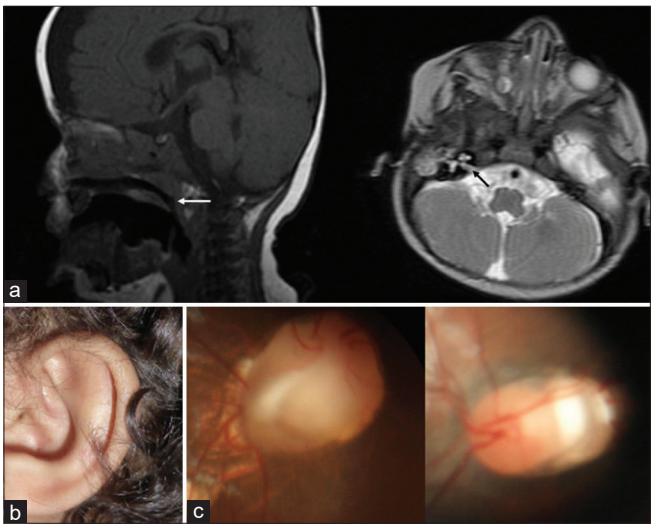

Figure 2: (a) Fundus photo of patient 2 showing optic nerve coloboma and associated bilateral chorioretinal coloboma. (b) Photo of patient 2 showing normal pinnae, although slightly larger in comparison with the patient's head. (c) Brain magnetic resonance imaging of patient 2, showing anatomical choanal permeability, with everything else including the inner ear anatomy having a normal appearance (superior row in the photo composition)

Fundus examination shows the presence of an optic nerve coloboma with bilateral chorioretinal involvement. The rest of the examination is unremarkable [Figure 2a].

The ears are of normal morphology, although large in comparison with the size of her head [Figure 2b].

There are no obvious abnormalities with the rest of the cranial nerves. She is mobile, although with some degree of hypotonia.

The patient showed no genitourinary abnormalities on previous pediatric evaluation. She was also assessed by an otolaryngologist for probable mild hearing loss.

Cranial MRI shows some degree of underdevelopment of the frontal lobe, with choanal permeability; everything else was within normal limits [Figure 2c].

Genetic testing for CHARGE syndrome was performed using the same method as for patient 1 and shows that the patient carries the heterozygous missense variant c.1405A>G (p.Arg469Gly) in exon 2 of the CHD7 gene. This mutation implies a nucleotide exchange from A to G at position c.1405 in exon 2 of the CHD7 gene, leading to a nonconservative exchange of the evolutionarily highly conserved amino acid arginine to glycine at position 469 of the protein (p.Arg469Gly). To the best of our knowledge, this variant has neither been annotated in databases nor been described in the literature so far. Three bioinformatics programs (Align GVGD, Mutation taster, PolyPhen2) predict a pathogenic effect of this variant.

Discussion

We present two new gene mutations in two patients with CHARGE syndrome not previously reported in the scientific literature, both with varying degrees of clinical expression.

Patient 1 presents a syndrome associated with severe heart defects, intellectual impairment, hearing loss, and bilateral optic nerve coloboma. However, patient 2 only has a mild heart defect (asymptomatic foramen ovale), mild hearing loss, and bilateral optic nerve coloboma.

CHARGE syndrome is caused by mutations in the CDH7 gene, of which single-nucleotide heterozygous mutations are the most frequent (44% nonsense, 34% frameshift, 11% spice site, and 8% missense). Less than 5% are due to whole-exon deletions or microdeletions of chromosome 8q12.1.[3,7] CDH7 gene disruptions by chromosomal abnormalities are extremely rare.[4]

Genetic analysis for patient 1 showed that they carry the heterozygous nonsense mutation c.6217C>T (p.Gln2073*) in exon 31 of the CHD7 gene. This mutation implies a nucleotide exchange from C to T at position c.6217C in exon 31 of the CHD7 gene, leading to a premature stop codon (p.Gln2073*), and subsequently either to a degradation of the mRNA (nonsense-mediated decay) or to a truncation of the CHD7 protein.

In genetics, a point-nonsense mutation is a point mutation in a sequence of DNA that results in a premature stop codon or a point-nonsense codon in the transcribed mRNA, and in a truncated, incomplete, and usually nonfunctional protein product.

This mutation found in patient 1 is in accordance with those published by Lalani *et al*., where 73% of mutations produce a truncated protein, where haploinsufficiency is thought to be the most frequent mechanism.[8,9]

On the other hand, genetic analysis showed that patient 2 presented with the heterozygous missense variant c.1405A>G (p.Arg469Gly) in exon 2 of the CHD7 gene. To me this sentence means that a missense mutation is more benign than a truncation of the CHD7 protein.

A missense mutation is the type of mutation that changes one DNA base pair and results in the substitution of one amino acid for another in the protein made by a gene. It can result in a nonfunctional protein.

To date, a clear genotype-phenotype correlation for CHARGE syndrome has not been established, although in general, missense mutations are associated with a less severe phenotype.[3,7] This can be seen in patient 2, who carries the heterozygous missense variant c.1405A>G (p,Arg469Gly) in exon 2 of the CDH7 gene, and presents with less severe clinical findings compared with patient 1.

This paper illustrates that the severity of phenotype expression can be linked to the specific kind of mutation (nonsense vs. missense).

Clinical findings associated with CHARGE syndrome include ophthalmological findings, being the most frequent the chorioretinal coloboma seen in 75%–90% of patients, of which 70%–80% are bilateral cases. Coloboma can be accompanied by microphthalmia in 40% of cases.[9]

The ophthalmological findings in our patients are quite similar and include the presence of nystagmus, strabismus (convergent for patient 1 and divergent for patient 2), as well as the bilateral optic nerve and chorioretinal coloboma. The only difference between the two patients is that the visual acuity is worse in patient 2. Interestingly, this is the only clinical finding in patient 2 which is worse, although it should be taken with a degree of caution, given the difficulty in assessing visual acuity in children.

In terms of ear abnormalities, those affecting the pinnae are seen in 95%–100% of cases. The ears are typically cup shaped with lobe hypoplasia, and there is a tendency for the lobes to be low-set and rotated forward.

Inner ear disturbances are seen in 90% of cases and include a characteristic absence of the semicircular canals with a reduced number of cochlear turns (Mondini dysplasia).

The middle ear is also occasionally affected with an absence of the stapedius muscle and oval window as well as a hypoplastic uncus.[2,9,10]

Regarding the auditory abnormalities of our patients, the clinical findings are more severe for patient 1 who presents with dysmorphic pinnae and severe bilateral hypoacusis. Brain MRI shows bilateral hypoplasia of the semicircular canals, whereas Patient 2 presents with morphologically normal pinnae, although slightly larger in size, with probable mild hypoacusis, even though brain MRI shows an inner ear which is anatomically normal.

Early identification of hearing impairment in these patients is crucial,[7] considering 60%–90% of them may be affected by deafness.[9] Because of this, patient 1 was immediately

fitted with bilateral hearing aids after otorhinolaryngology evaluation.

Choanal atresia is present in 65% of patients with CHARGE syndrome. It presents with a bony or membranous blockage between the nasal cavity and the nasopharynx.[4]

In this regard, patient 1 presents with bilateral choanal atresia, in contrast to patient 2 who has normal choanal anatomy.

Approximately 55%–85% of patients present with central nervous system disorders.[9] Holoprosencephaly being one of the most common.[4] Other abnormalities include olfactory bulb hypoplasia with anosmia, facial paresis (50%–90% of CHARGE syndrome cases), VIII CN involvement with neurosensorial hearing loss and balance disorders, as well as IX-X-XI CN involvement including difficulty swallowing.[4]

The only central nervous disorder affecting our patients is a cortical underdevelopment of the frontal lobes seen on brain MRI (and as previously described, bilateral semicircular canal hypoplasia in patient 1).

Intellectual impairment is seen in 70% of patients with CHARGE syndrome.[9] Our patients present with mild to moderate mental delay and some degree of overall hypotonia.

Genitourinary abnormalities appear in 50%–70% of patients. The most common findings in boys include micropenis and cryptorchidism; and in girls, labial hypoplasia of the vulva.[9] Renal disorders are less common (10%–40% of patients), and may include ectopic kidney, horseshoe kidney, and ureter abnormalities.[9] Our patients did not present with any genitourinary abnormalities.

Heart defects are present in 75%–85% of patients, which consist primarily of conotruncal defects (aortic arch coarctation and tetralogy of Fallot), as well as atrioventricular septal defects.[2,9]

Patient 1 presents with severe heart defects (aortic arch coarctation, left subclavian artery abnormalities, whose origin is in the right aortic arch, and tetralogy of Fallot), in contrast to patient 2, who presents with less severe heart defects (asymptomatic patent foramen ovale).

In conclusion, we presented two cases with CHARGE syndrome, with two new mutations not previously reported in the scientific literature, which clearly demonstrate the different clinical expression between different patients having this syndrome (patient 1 with greater clinical severity compared to patient 2).

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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