International Journal of Pediatric Otorhinolaryngology 74 (2010) 719–722

Contents lists available at ScienceDirect

International Journal of Pediatric Otorhinolaryngology

journal homepage: www.elsevier.com/locate/ijporl

Review article

CHARGE: An association or a syndrome?

Arzu Pampal *

Ufuk University Faculty of Medicine, Department of Pediatric Surgery, Turkey

ARTICLE INFO

Article history:
Received 9 February 2010
Received in revised form 3 March 2010
Accepted 8 March 2010
Available online 3 April 2010

Keywords:
CHARGE syndrome
Genetic basis
CHD7 gene

ABSTRACT

Introduction: CHARGE "association" is a rare clinical entity with multiple congenital anomalies that necessitates a multidisciplinary approach. Its diagnosis is important not only for the pediatric surgery practice but also for the otorhinolaryngology practice as it complicates with a number of major surgical anomalies. The aim of this paper is to present the latest evidences on the genetic basis of the disease.
Materials and methods: In order to evaluate, a computed literature review was undertaken using PubMed and OMIM databases.
Results: Heterozygous mutations within the chromodomain helicase DNA binding protein 7 (CHD7) were reported in every two of three CHARGE patients. CHD protein family is located on chromosome 8q11.2 and is known to regulate chromatin remodeling which plays an essential role in the developmental gene expression. That is why the haploinsufficiency of CHD7 gene due to heterozygous mutations results in not only the postnatal but also the prenatal developmental regulation errors. The wide expression of this gene in the prenatal period overlaps with the broad spectrum of the phenotypic symptoms of the disease.
Conclusion: CHD7 gene haploinsufficiency is expected to be the underlying basis of CHARGE. Even though the genetic basis is unsolved in one-third of the patients, the current evidence supports the term "syndrome" rather than an "association" should be more appropriate for CHARGE.

Contents

1. Introduction

CHARGE syndrome (OMIM #214800) is a rare disorder with multiple congenital anomalies. The incidence of the disease ranges from 0.1 to 1.2 in 10,000 live births. Its diagnosis is important for the pediatric practice as it complicates with not only several life threatening problems but also a number of major surgical anomalies. Even though the term "CHARGE" is an acronym summarizing the six prevalent clinical features of the disease (coloboma, heart disease, atresia of choanae, retardation, genital anomalies, and ear anomalies), the clinical definition of the disease has evolved in time.

The vast majority of the features of the disease are shown to exist in the antenatal period whereas some problems due to CHARGE like growth delay or retardation might be gained in the postnatal period as a result of the illness [1]. The 100% existence of central nervous system anomalies (arhinencephaly), bilateral and asymmetric external ear anomalies and semicircular canals anomalies in the prenatal period of CHARGE patients made us consider these anomalies as the most important features of the disease.

* Correspondence address: Ufuk Universitesi Tip Fakultesi, Dr. Ridvan Ege Egitim Arastirma Hastanesi, Konya Yolu (Mevlana Bulvarı) No: 86-88, 06520 Balgat, Ankara, Turkey. Tel.: +90 3122044201; fax: +90 3122026213.
E-mail address: ademirtola@yahoo.com.

0165-5876/$ – see front matter © 2010 Elsevier Ireland Ltd. All rights reserved.
doi:10.1016/j.ijporl.2010.03.019

Table 1
Diagnostic criteria for CHARGE.

Verloes [12]	Blake and Prasad [11]
For the diagnosis of typical CHARGE: presence of either 3/3 major signs or 2/3 major signs with 2/5 minor signs	*For the diagnosis of CHARGE: presence of either 4/4 major signs or 3/4 major signs with 3/7 minor signs*
Major signs (the 3C triad)	Major signs (classical 4C's)
Ocular coloboma	Ocular coloboma
Choanal atresia	Choanal atresia/stenosis
Hypoplastic semicircular canals	Cranial nerve dysfunction
Minor signs	Characteristic ear anomalies
Rhomboencephalic dysfunction	Minor signs
Hypothalamo-hypophyseal dysfunction	Characteristic CHARGE facies
Mental retardation	Orofacial cleft
Malformation of intrathorasic visceral organs	Cardiovascular malformations
External or middle ear malformations	Tracheoesophageal fistula
	Genital hypoplasia
	Developmental delay
	Growth deficiency
	Occasional signs
	Renal anomalies
	Spinal anomalies
	Neck/shoulder anomalies
	Hand anomalies

Both clinical definition and genetic basis of the disease became clearer with time. The multiple anomaly pattern of the disease is proven to be pathogenetically related. Even though most of the cases are sporadic, the rare familial cases support an autosomal dominant inheritance. Mutations within the chromodomain helicase DNA binding protein 7 (CHD7) were reported in 65–70% of the CHARGE patients [2–6]. Also, a mutation in semaphorin 3E gene (SEMA3E) was demonstrated in a CHARGE patient [7].

2. Brief history of nomenclature of CHARGE

When Hall reported 17 patients with a group of nonrandom anomalies accompanying choanal atresia and Hittner et al. reported 10 individuals, including a mother and a child, with colobomatous microphtalmia, heart disease, external ear abnormalities and mental retardation, they both concluded that multiple other anomalies might be associated [8,9]. Pagon et al. reported 21 patients having coloboma, congenital heart defects and choanal atresia with multiple anomalies in 1981 and proposed the clever and mnemonic nomenclature CHARGE association regarding the six cardinal features of the disease (coloboma, heart disease, atresia of choanae, retarded growth and retarded development and/or CNS anomalies, genital hypoplasia, and ear anomalies and/or deafness) [10].

3. The diagnostic criteria for CHARGE

The original diagnostic criteria of CHARGE, as proposed by Pagon et al., was depending on the existence of four of six features with the absolute presence of whether coloboma or atresia of choanae. With passing time and increasing knowledge of the disease, a need for an update for the diagnostic criteria has arisen. The major and minor findings of the disease were described and tabulated. Verloes and Blake and Prasad updated new diagnostic criteria for the disease lately (Table 1) [11,12]. Amiel et al. emphasized the importance of temporal bone imaging of the disease [13]. Today the diagnosis of the disease is mainly based on the clinical findings and temporal bone imaging findings.

4. The suspicion for the genetic basis of the disease

Davenport et al. reported six familial cases in a group of 15 CHARGE patients in 1986 and concluded that the disease should be a syndrome rather than an association [14]. In the following years different authors reported familial cases and monozygotic twin [15,16]. In 1996, Tellier et al. determined an increased mean paternal age of CHARGE patients [17]. Not only the increase they demonstrated in the mean paternal age but also the existence of rare familial CHARGE cases and high concordance rate in monozygotic twin made them consider the effects of possible genetic factors on the disease such as a de novo dominant mutation or a subtle submicroscopic chromosomal rearrangement.

5. Description of the first mutation in CHD7 and cascade of case series

Despite some cytogenetic abnormalities that have been described earlier, a specific locus was not identified till 2004. With the knowledge of microdeletions and microduplications cannot be detected by conventional techniques, Vissers et al. have performed a genome wide array comparative genomic hybridization for two CHARGE patients in 2004 [2]. They have reported a de novo overlapping microdeletion on chromosome 8q12. Adding this new information to a former study by Hurst et al. dictating a balanced chromosomal translocation in a CHARGE patient, they have decided to sequence the coding regions [18]. They have performed a sequence analysis of this region and have detected heterozygous mutations in the chromodomain helicase DNA binding protein 7 (CHD7) in 10 of 17 CHARGE patients.

Chromodomain helicase DNA binding proteins are ATP dependent chromatin remodeling enzymes that belong to a superfamily of proteins and are widely expressed in all tissues and specific brain regions in variable degrees. As a member of this family CHD7 gene is located in chromosome 8q12.1 and known to contribute the dynamic changes that occur in chromatin structure during the cell cycle and regulate the early embryonic development.

Lalani et al. demonstrated CHD7 mutations in 64 of 110 CHARGE patients (58%) including three familial cases and one monozygotic twin and stated mostly unique mutations [3]. Moreover, Lalani et al. identified the semaphorin 3E (SEMA3E) gene adjacent to a breakpoint on 7q21.11 and screened a de novo mutation in the SEMA3E gene in a CHARGE patient [7]. After evaluating 107 CHARGE patients, Jongmans et al. demonstrated 69 patients (64%) with all novel CHD7 mutations but two [4]. Interestingly, this group of patients with mutations was also including 6 CHARGE cases that were previously reported by Vissers et al. not having mutations. They also demonstrated germline mosaicism in a sib pair with an unaffected mother. Wincent et al.

demonstrated CHD7 mutations in 18 of 28 Swedish patients with CHARGE (64%), thirteen of which were novel [5]. Aramaki et al. reported CHD7 mutations in 17 of 24 CHARGE patients (71%) [6]. Not only missense or frame mutations truncating the CHD7 protein, but also a number chromosomal rearrangements and deletions on chromosome 8 have been demonstrated in the CHARGE patients. Johnson et al. demonstrated a de novo chromosomal rearrangement of monozygotic twins with CHARGE with the assumption that this translocation might be the causative of the syndrome [19]. This breakpoint on chromosome 8 was shown to occur between exons of CHD7 and confirmed the importance of CHD7 in CHARGE syndrome. Arrington et al. demonstrated an interstitial deletion within the bands 8q11.2–8q13 [20]. Interestingly, Udako et al. documented an exonic deletion of CHD7 with a "novel" technique in 1 patient of 13 CHARGE patients in whom detection of the mutations and small insertions/deletions in CHD7 were failed [21].

Delahaye et al. reported six de novo mutations in six CHARGE patients of two unrelated families with the existence of autosomal dominant inheritance [22]. Likewise, Jongmans et al. reported five unrelated families with de novo mutations in CHD7 [23]. Either somatic and germline mosaicism or the parent-to-child transmission of non-mosaic CHD7 were accepted to be the cause of familial CHARGE cases. Both of them have mentioned that the broad spectrum of intrafamilial variability could be explained by mutation type. They both have concluded that even no genotype–phenotype correlation was demonstrated in CHARGE patients, the missense mutations as the causatives of CHARGE could be the reason of less severe, less specific phenotype.

6. The importance CHD7 in the antenatal period

The mesenchymal formation of the head region is derived from paraxial and lateral plate mesoderm, thickened regions of ectoderm and neural crest. Neural crest cells are essential components regarding to their pioneers localized in three brain regions and their different migration rows. The abnormal differentiation in the mesoderm and ectoderm, abnormal localization, differentiation or migration of neural crest cells, abnormal interactions of these three components in the early steps of embryogenesis are considered to be the reason of CHARGE [12]. In a study by Sanlaville et al., 10 antenatal cases with a high suspicion index of CHARGE were evaluated [1]. Their diagnosis was confirmed with identification of nine different mutations on CHD7. The investigators found that CHD7 is widely expressed in the undifferentiated neuroepithelium and mesenchyme of neural crest origin in the antenatal period and has some pivotal roles in early embryonic development. Its expression in the dorsal root ganglia, cranial nerves/ganglia and auditory, pituitary, nasal tissues and neural retina is well demonstrated through the end of the first trimester. CHD7 is concluded to play a major role in neuronal migration either directly or through its interactions with various patterns. That is why a probable truncation in CHD7 protein can cause any component of CHARGE due to errors in blastogenesis and neurulation.

7. Genetic counseling

As the genetic basis of the disease is mostly solved, the genetic counseling has gained importance in terms of not only for confirming the diagnosis but also for providing accurate information to the patients and their families. The way the disease runs in the family and the risk of new members of affected families can be well described to the patients after a genetic screening of the family. Prenatal testing for risk analysis of the descendants by either amniocentesis or corion villus biopsy can also be maintained by genetic counseling. Moreover preimplantation genetic screening can be performed on embryos before implantation and can identify the embryos at risk.

8. Conclusion

CHARGE syndrome is a neurocristopathy due to the haploinsufficiency of CHD7 in nearly 65% of the patients. Molecular genetic testing indicates the heterozygous point mutations as the most common mechanism for the disease. The current evidence reveals that term "syndrome" rather than "association" should be more appropriate for the disease. Correcting our nomenclature as "CHARGE syndrome" would not only remind us about the genetic basis of the disease but also be reminiscent of the need for genetic counseling for the patients and their families.

It is obvious that we are still blind to the pathogenic mechanisms of the mutation-negative CHARGE cases. Not yet identified gene(s), not yet screened whole gene or exonic deletions or not yet defined approaches for detecting alterations might be the reason of the mutation-negative CHARGE cases. We believe that further investigations will enlighten us about the dark sides of CHARGE syndrome.

9. Take home messages

- Even though the vast majority of CHARGE cases are sporadic, the rare familial cases are inherited mostly in an autosomal dominant manner.
- The etiology of the syndrome could be genetically heterogenous but truncating mutations seem to cause haploinsufficiency of CHD7 in two of three CHARGE patients.
- No persuasive evidence for a genotype–phenotype correlation even in monozygotic twin suggests epigenetic or nongenetic factors. But the missense mutations seem to be related to less severe, less specific phenotype. Moreover cardiovascular malformations, coloboma and facial asymmetry are determined in all patients having CHD7 mutations.
- Genetic counseling is essential not only for confirming the diagnosis but also for providing accurate information to the patients and their families.
- We are still blind to the pathogenic mechanisms of mutation-negative CHARGE cases. We believe that further investigations will enlighten us about the dark sides of CHARGE syndrome.

References

[1] D. Sanlaville, H.C. Etchevers, M. Gonzales, J. Martinovic, M. Clément-Ziza, A.L. Delezoide, M.C. Aubry, A. Pelet, S. Chemouny, C. Cruaud, S. Audollent, C. Esculpavit, G. Goudefroye, C. Ozilou, C. Fredouille, N. Joye, N. Morichon-Delvallez, Y. Dumez, J. Weissenbach, A. Munnich, J. Amiel, F. Encha-Razavi, S. Lyonnet, M. Vekemans, T. Attié-Bitach, Phenotypic spectrum of CHARGE syndrome in fetuses with CHD7 truncating mutations correlates with expression during human development, J. Med. Genet. 43 (3) (2006) 211–217.

[2] L.E. Vissers, C.M. van Ravenswaaij, R. Admiraal, J.A. Hurst, B.B. de Vries, I.M. Janssen, W.A. van der Vliet, E.H. Huys, P.J. de Jong, B.C. Hamel, E.F. Schoenmakers, H.G. Brunner, J.A. Veltman, A.G. van Kessel, Mutations in a new member of the chromodomain gene family cause CHARGE syndrome, Nat. Genet. 36 (9) (2004) 955–957.

[3] S.R. Lalani, A.M. Safiullah, S.D. Fernbach, K.G. Harutyunyan, C. Thaller, L.E. Peterson, J.D. McPherson, R.A. Gibbs, L.D. White, M. Hefner, S.L. Davenport, J.M. Graham, C.A. Bacino, N.L. Glass, J.A. Towbin, W.J. Craigen, S.R. Neish, A.E. Lin, J.W. Belmont, Spectrum of CHD7 mutations in 110 individuals with CHARGE syndrome and genotype–phenotype correlation, Am. J. Hum. Genet. 78 (2) (2006) 303–314.

[4] M.C. Jongmans, R.J. Admiraal, K.P. van der Donk, L.E. Vissers, A.F. Baas, L. Kapusta, J.M. van Hagen, D. Donnai, T.J. de Ravel, J.A. Veltman, A. Geurts van Kessel, B.B. De Vries, H.G. Brunner, L.H. Hoefsloot, C.M. van Ravenswaaij, CHARGE syndrome: the phenotypic spectrum of mutations in the CHD7 gene, J. Med. Genet. 43 (4) (2006) 306–314.

[5] J. Wincent, E. Holmberg, K. Strömland, M. Soller, L. Mirzaei, T. Djureinovic, K. Robinson, B. Anderlid, J. Schoumans, CHD7 mutation spectrum in 28 Swedish patients diagnosed with CHARGE syndrome, Clin. Genet. 74 (1) (2008) 31–38.

[6] M. Aramaki, T. Udaka, R. Kosaki, Y. Makita, N. Okamoto, H. Yoshihashi, H. Oki, K. Nanao, N. Moriyama, S. Oku, T. Hasegawa, T. Takahashi, Y. Fukushima, H. Kawame, K. Kosaki, Phenotypic spectrum of CHARGE syndrome with CHD7 mutations, J. Pediatr. 148 (3) (2006) 410–414.
[7] S.R. Lalani, A.M. Safiullah, L.M. Molinari, S.D. Fernbach, D.M. Martin, J.W. Belmont, SEMA3E mutation in a patient with CHARGE syndrome, J. Med. Genet. 41 (7) (2004) e94.
[8] B.D. Hall, Choanal atresia and associated multiple anomalies, J. Pediatr. 95 (3) (1979) 395–398.
[9] H.M. Hittner, N.J. Hirsch, G.M. Kreh, A.J. Rudolph, Colobomatous microphthalmia, heart disease, hearing loss, and mental retardation—a syndrome, J. Pediatr. Ophthalmol. Strabismus 16 (2) (1979) 122–128.
[10] R.A. Pagon, J.M. Graham Jr., J. Zonana, S.L. Yong, Coloboma, congenital heart disease, and choanal atresia with multiple anomalies: CHARGE association, J. Pediatr. 99 (2) (1981) 223–227.
[11] K.D. Blake, C. Prasad, CHARGE syndrome, Orphanet. J. Rare Dis. 1 (2006) 34.
[12] A. Verloes, Updated diagnostic criteria for CHARGE syndrome: a proposal, Am. J. Med. Genet. A 133A (3) (2005) 306–308.
[13] J. Amiel, T. Attieé-Bitach, R. Marianowski, V. Cormier-Daire, V. Abadie, D. Bonnet, M. Gonzales, S. Chemouny, F. Brunelle, A. Munnich, Y. Manach, S. Lyonnet, Temporal bone anomaly proposed as a major criteria for diagnosis of CHARGE syndrome, Am. J. Med. Genet. 99 (2) (2001) 124–127.
[14] S.L. Davenport, M.A. Hefner, J.A. Mitchell, The spectrum of clinical features in CHARGE syndrome, Clin. Genet. 29 (4) (1986) 298–310.
[15] L.A. Metlay, P.S. Smythe, M.E. Miller, Familial CHARGE syndrome: clinical report with autopsy findings, Am. J. Med. Genet. 26 (3) (1987) 577–581.
[16] C.A. Oley, M. Baraitser, D.B. Grant, A reappraisal of the CHARGE association, J. Med. Genet. 25 (3) (1988) 147–156.
[17] A.L. Tellier, S. Lyonnet, V. Cormier-Daire, P. de Lonlay, V. Abadie, C. Baumann, D. Bonneau, P. Labrune, D. Lacombe, M. Le Merrer, A. Nivelon, N. Philip, M.L. Briard, A. Munnich, Increased paternal age in CHARGE association, Clin. Genet. 50 (6) (1996) 548–550.
[18] J.A. Hurst, P. Meinecke, M. Baraitser, Balanced t(6, 8) (6p8p, 6q8q) and the CHARGE association, J. Med. Genet. 28 (1) (1991) 54–55.
[19] D. Johnson, N. Morrison, L. Grant, T. Turner, J. Fantes, J.M. Connor, V. Murday, Confirmation of CHD7 as a cause of CHARGE association identified by mapping a balanced chromosome translocation in affected monozygotic twins, J. Med. Genet. 43 (3) (2006) 280–284.
[20] C.B. Arrington, B.C. Cowley, D.R. Nightingale, H. Zhou, A.R. Brothman, D.H. Viskochil, Interstitial deletion 8q11.2–q13 with congenital anomalies of CHARGE association, Am. J. Med. Genet. A 133A (3) (2005) 326–330.
[21] T. Udaka, N. Okamoto, M. Aramaki, C. Torii, R. Kosaki, N. Hosokai, T. Hayakawa, N. Takahata, T. Takahashi, K. Kosaki, An Alu retrotransposition-mediated deletion of CHD7 in a patient with CHARGE syndrome, Am. J. Med. Genet. A 143 (7) (2007) 721–726.
[22] A. Delahaye, Y. Sznajer, S. Lyonnet, M. Elmaleh-Bergès, I. Delpierre, S. Audollent, S. Wiener-Vacher, A.L. Mansbach, J. Amiel, C. Baumann, D. Bremond-Gignac, T. Attié-Bitach, A. Verloes, D. Sanlaville, Familial CHARGE syndrome because of CHD7 mutation: clinical intra- and interfamilial variability, Clin. Genet. 72 (2) (2007) 112–121.
[23] M.C. Jongmans, L.H. Hoefsloot, K.P. van der Donk, R.J. Admiraal, A. Magee, I. van de Laar, Y. Hendriks, J.B. Verheij, I. Walpole, H.G. Brunner, C.M. van Ravenswaaij, Familial CHARGE syndrome and the CHD7 gene: a recurrent missense mutation, intrafamilial recurrence and variability, Am. J. Med. Genet. A 146A (1) (2008) 43–50.