Received: 6 July 2020 | Revised: 9 August 2020 | Accepted: 11 August 2020

DOI: 10.1002/ajmg.c.31840

RESEARCH ARTICLE

AMERICAN JOURNAL OF medical genetics PART C Seminars in Medical Genetics | WILEY

CHARGE syndrome without colobomas: Ophthalmic findings

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Abstract

To report ophthalmic findings of patients without colobomas, and with a clinical and molecular diagnosis of CHARGE Syndrome. Retrospective study of ophthalmic findings in 67 CHARGE patients—clinically confirmed diagnosis with positive CHD7 mutation—seen in the Ophthalmology department of Cincinnati Children's Hospital Medical Center between January 1, 2008 through September 25, 2018. Criteria for inclusion in this study was absence of any form of a coloboma in either eye. In our cohort, all patients had a positive CHD7 mutation, in addition to a clinical diagnosis. 19.4% (13/67) of CHARGE patients did not have a coloboma in either eye. 69.2% (9/13) had strabismus, 76.9% (10/13) had a refractive error that warranted refractive correction, 23.1% (3/13) had amblyopia, 38.5% (5/13) had nasolacrimal duct obstruction, 30.8% (4/13) had dry eye syndrome and exposure keratopathy, 15.4% (2/13) had ptosis, 15.4% (2/13) had blepharitis, 15.4% (2/13) had Cortical Visual Impairment, 7.7% (1/13) of patients had optic nerve drusen, 7.7% (1/13) had Marcus Gunn Jaw Winking, and 7.7% (1/13) with an eyelid nevus. There are numerous ophthalmic findings in individuals with CHARGE Syndrome without colobomas. No study to date has evaluated the ophthalmic findings in CHD7 positive CHARGE patients without colobomas. These findings need to be assessed and treated to ensure optimal vision in the CHARGE patient population. Absence of coloboma does not rule out a diagnosis of CHARGE syndrome, and if there is a clinical suspicion, clinical confirmation then genetic testing would be warranted.

KEYWORDS

CHARGE, CHD7, coloboma, ophthalmic findings

1 | INTRODUCTION

CHARGE syndrome (OMIM 214800) is a phenotypically heterogenous autosomal dominant syndrome (Jongmans et al., 2006). Mutations in the chromodomain (*chr*omatin *o*rganization *m*odifier) helicase DNA-binding 7 (*CHD7*) gene have been identified in up to 90% of patients with CHARGE syndrome and was used as primary inclusion criteria for this study (Mahdi & Whitehead, 2018; Mehr, Hsu, & Campbell, 2017). Major and minor criteria for CHARGE syndrome diagnoses were first established in 1998, and were further modified again in 2005 (Blake et al., 1998; Verloes, 2005). Major criteria for CHARGE diagnosis include: *coloboma*, atresia of choanae, cranial nerve involvement (often affecting multiple cranial nerves), and hypoplastic semi-circular canals (Blake et al., 1998; Verloes, 2005). Minor characteristics, that occur less frequently, include heart defects, genital hypoplasia, orofacial clefting, tracheoesophageal fistula, short stature, and developmental delay (Blake et al., 1998; Verloes, 2005). In 2016, the criteria were revised by Hale et al., to broaden the major features associated with CHARGE, and to include pathologic CHD7 variant as a major criterion (Hale, Niederriter, Green, & Martin, 2016).

The CHARGE acronym—coloboma, *h*eart defects, choanal *a*tresia, *r*etarded growth and development, *g*enital abnormalities and *e*ar anomalies (Hall, 1979; Hittner, Hirsch, Kreh, & Rudolph, 1979; Pagon, Graham Jr, Zonana, & Yong, 1981), emphasizes the *Coloboma* as the

ophthalmic finding. Coloboma is a major criterion for diagnosis of CHARGE syndrome (Blake et al., 1998; Hale et al., 2016; Verloes, 2005). Previously reported ophthalmic findings in CHARGE have reported high rates of colobomas, 70–92% (Chestler & France, 1988; Nishina et al., 2012; Russell-Eggitt, Blake, Taylor, & Wyse, 1990; Zentner, Layman, Martin, & Scacheri, 2010). These studies have also reported other ophthalmic findings in patients with CHARGE Syndrome. However, to date, there are no reports of ophthalmic findings in CHARGE individuals without colobomas. In addition, there are no dedicated studies of ophthalmic findings, in patients who have a clinical diagnosis and a molecular confirmation of CHD7 mutation, with no colobomas that have been reported. This article will discuss the ophthalmic findings in our cohort of patients with clinical diagnosis of CHARGE syndrome, who have confirmed CHD7 mutation, and no colobomas.

2 | METHODS

This study was approved by the Institutional Review Board of Cincinnati Children's Hospital Medical Center (CCHMC). A retrospective analysis was completed of all patients diagnosed with CHARGE syndrome with a confirmed CHD7 positive genetic testing that were seen by the CCHMC Division of Ophthalmology from January 1, 2008 through September 25, 2018. All individuals fulfilled clinical diagnostic criteria for CHARGE syndrome (Blake et al., 1998; Hale et al., 2016; Verloes, 2005). All these criteria were met prior to enrollment: genetically confirmed diagnosis of CHARGE syndrome, at least one ophthalmology encounter at CCHMC, and genetics records confirming diagnosis available in electronic medical record.

The following patient information was obtained by chart review: date of birth, race, ethnicity, zip code, sex and *CHD7* genetic testing results, including specific mutation information, where available. All ophthalmology encounter information was collected, including but not limited to: date of service, attending ophthalmologist, encounter type (Exam Under Anesthesia, Inpatient or Outpatient), payor type, visual acuity, pupil assessment, extraocular movement, tonometry, visual field (confrontational and automated, where applicable), automated imaging (OCT and RetCam if available), color vision, stereoacuity, strabismus exam, slit lamp exam, fundus exam, contrast sensitivity, refraction and final prescription, if indicated.

3 | RESULTS

In our cohort, 67 individuals with CHD7 mutation confirmed CHARGE were identified, 13 (19.4%) of these individuals presented without any colobomas and were analyzed in this study. The median age of individuals in our cohort was 7 years (range, one to 18 years), with 11 males and 2 females. Table 1 summarizes all the ophthalmic findings and pertinent ophthalmic clinical findings.

Visual acuity was obtained in all of the patients, binocular Tellar Acuity© was obtained in two pre-verbal patients (patients 2 and 8), one older non-verbal child (patient 13), and induced tropia testing only was performed in an older non-verbal child (patient 1) with known significant neurodevelopmental delays. A recognition acuity was obtained for the other patients, 69.2% (9/13), using age appropriate optotypes, and is documented in Table 1. Where monocular acuity testing was not tolerated/unable to be obtained, binocular acuity was obtained and induced tropia testing was performed to evaluate the monocular vision. Eight out of nine of the patients that were able to perform recognition vision acuity had vision better than 20/40, which is the threshold for mild vision impairment as defined by the World Health Organization (2019). It is also important to note that the patient without 20/40 or better was age three at the time of this visit, this was the first recognition acuity ever provided by this patient, and 20/40 is within the normal parameters for visual acuity for a child of this age. With time, there is a possibility of gaining improvement in his vision. Significant refractive errors were the most common finding in this cohort, with 76.9% (10/13) requiring spectacles to correct significant amounts of myopia, hyperopia and astigmatism, with 46.2% (6/13) demonstrating anisometropia. All visual acuity data, refractions, and refractive correction prescriptions were based on standard of care and age-adjusted for each patient. Horizontal strabismus was more common than vertical strabismus in this cohort of patients and was the second most common findings in this cohort 69.2% (9/13).

A visual field defect was found in one patient, this was secondary to Cortical Visual Impairment (CVI). With treatment of the underlying epileptic disorder and appropriate therapies for the CVI, the visual field defect, which following treatment was consistent with neglect, clinically resolved.

In Table 2, the systemic findings for CHARGE syndrome for each patient are documented, and using the diagnostic criteria set by Blake and Verloes (Blake et al., 1998; Blake & Prasad, 2006; Verloes, 2005). The frequency of these systemic findings documented in Table 2, and previously documented findings in CHD7+ positive patients as documented by Hale et al. (2016) who summarized frequency data from three other studies, are also documented. Lalani, Hefner, et al. (2006); Lalani, Safiullah, et al. (2006) also use the diagnostic criteria to determine, based on clinical findings, if the CHARGE diagnosis is definite or probable/possible. Our cohort of patients were categorized using these parameters, as well in Table 2.

4 | DISCUSSION

Based on our literature review, this is the first cohort of patients with clinically diagnosed and genetically confirmed CHARGE syndrome, who are without colobomas, to have their ophthalmic findings reported. In 2006, Lalani et al., reported on findings in CHARGE patients with and without CHD7 mutation. In their cohort, they found that 11% (7/62 patients) of their CHD7 positive patients did not have

TABLE 1 Ophthalmic findings in our CHARGE cohort without colobomas

Patient	Sex	Age	Ethnicity	Race	CHD7; pathogenic variant	CHD7 positive parent/ sibling	Developmental delay	Visual Acuity at Distance*	Visual Field Defect	Strabismus; Type	Amblyopia; Type	Ptosis	Nasolacrimal duct obstruction (NLDO)	Facial Nerve Palsy
Number, percent affected	11, 84.6% (M)	NA	NA	NA	13, 100%	3, 23.1%	13, 100%	NA	1, 7.7%	9, 69.2%	3, 23.1%	2, 15.4%	5, 38.5%	1, 7.7%
1	M	12	Non-Hispanic	White	(+); Not available	-	+	CSUM OD, CSUM OS	-	(+); Alternating esotropia	-	-	-	-
2	M	1	Non-Hispanic	White	(+); c.8067delT	-	+	TAC 20/130 OU, CSM OD, CSM OS	+	(+) Exophoria	-	+	(+), punctual atresia	-
3	M	3	Non-Hispanic	White	(+);c.5023 C>T	-	+	20/70 OU, CSM OD, CSM OS	-	(+); Accommodative esotropia	-	-	(+), epiphora	-
4	M	18	Non-Hispanic	White	(+); c.5404+1 G>T	-	+	20/20 OD, 20/20 OS	-	(+); Intermittent exotropia	-	-	-	-
5	M	4	Non-Hispanic	White	(+); c.6955C>T	-	+	20/50 OD, 20/20 OS	-	-	(+); Deprivation	+	-	-
6	M	6	Non-Hispanic	White	(+);c.3082A>G	-	+	20/25 OD, 20/20 OS	-	-	-	-	-	-
7	F	16	Non-Hispanic	White	(+); Not available	-	+	20/25 OD, 20/25 OS	-	(+); Consecutive exotropia, Dissociated vertical deviation (DVD), Inferior oblique overaction	-	-	+	-
8	M	2	Non-Hispanic	White	(+); Partial deletion, further details not available	-	+	TAC 20/94 OU, CSM OD, CSM OS	-	(+); Esophoria	(+); Refractive	-	(+), punctual atresia	+
9	M	7	Non-Hispanic	White	(+);c.3325A>T	+	+	20/25 OD, 20/25 OS	-	-	-	-	-	-
10	M	10	Non-Hispanic	White	(+);c.3325A>T	+	+	20/20 OD, 20/20 OS	-	-	-	-	-	-
11	M	12	Non-Hispanic	White	(+);c.3325A>T	+	+	20/25 OD, 20/100 OS	-	(+); Exotropia, Left Hypertropia	(+); Strabismic	-	-	-
12	F	16	Non-Hispanic	White	(+); Not available	-	+	20/30 OD, 20/30 OD	-	(+); Intermittent exotropia	-	-	+	-
13	M	7	Non-Hispanic	White	(+); Not available	-	+	TAC 20/470 OU, CSM OD, CSM OS	-	(+); Intermittent exotropia	-	-	-	-

Lagophthalmos	Dry Eye and Exposure Keratopathy	Blepharitis	Refractive error; type	Anisometropia	Warranted refractive error correction	Cortical Visual Impairment (CVI)	Drusen	Marcus Gunn jaw wink	Eyelid Nevus
3, 23.1%	4, 30.8%	2, 15.4%	13 (100%)	6, 46.2%	10, 76.9%	2, 15.4%	1, 7.7%	1, 7.7%	1, 7.7%
-	-	-	(+); Myopia, Hyperopia, Astigmatism	+	-	-	-	-	-
-	-	-	(+); Hyperopia, Astigmatism	-	+	+	-	-	-
-	-	-	(+); Hyperopia, Astigmatism	+	+	-	-	+	-
+	(+), corneal abrasion	-	(+); Myopia, Astigmatism	-	+	-	-	-	-
-	-	-	(+); Hyperopia, Astigmatism	-	-	-	+	-	-
-	+	+	(+); Myopia, Astigmatism	+	+	-	-	-	+
+	+	-	(+); Myopia, Astigmatism	-	+	-	-	-	-
+	-	-	(+); Myopia, Astigmatism	+	+	-	-	-	-
-	-	-	Hyperopia, Astigmatism	-	-	-	-	-	-

(Continues)

TABLE 1 (Continued)

Lagophthalmos	Dry Eye and Exposure Keratopathy	Blepharitis	Refractive error; type	Anisometropia	Warranted refractive error correction	Cortical Visual Impairment (CVI)	Drusen	Marcus Gunn jaw wink	Eyelid Nevus
-	-	-	(+); Astigmatism	-	+	-	-	-	-
-	-	-	(+) Myopia, Hyperopia, Astigmatism	+	+	-	-	-	-
-	+	+	(+); Hyperopia	+	+	-	-	-	-
-	-	-	(+); Hyperopia, Astigmatism	-	+	+	-	-	-

(-) absent
(+) present
Distance acuity documented, except where indicated.

colobomas, however, their study does not discuss other ophthalmic findings in this population.

Coloboma is typically the ophthalmic findings that is associated with CHARGE. Other findings may be overlooked/not addressed, and their implication on vision not fully evaluated in the context of eyes with and without colobomas. This cohort demonstrates that there are other significant ophthalmic findings that need to be addressed in a patient with CHARGE, without colobomas in order for the best visual potential to be obtained.

The prevalence, world-wide, of refractive errors in the children is 11% for myopia, 4.6% for hyperopia and 14.9% for astigmatism (Hashemi et al., 2017). Our cohort of patients is not able to provide prevalence data. However, the rates of refractive correction that warrant spectacle correction in our cohort is higher than documented prevalence data, at 76.9%. The prevalence of strabismus and amblyopia range between 2–5%, with Friedman et al., in the Baltimore Pediatric Eye Disease Study, finding a prevalence 2.2–3.1% for strabismus, and 0.8–1.8% prevalence for amblyopia (Friedman et al., 2009). In our cohort, 69.2% had strabismus and 23.1% had amblyopia. These findings are significant, and thus these authors recommend checking for refractive errors, amblyopia and strabismus in all individuals with CHARGE syndrome and treating these when medically and surgically indicated. In our cohort, patient 11 was treated for amblyopia, and with treatment, had a five-line improvement in visual acuity.

It is important to evaluate visual function/elucidate a history about visual function even in the setting of good measured visual acuities and no coloboma—as vision is more than visual acuity and there could be associated visual impairment/functional vision limitations secondary to neurodevelopmental delays. In our cohort, following the diagnosis of CVI, in patient 2, and recommendation for additional neurodevelopmental evaluation, the etiology of the CVI was found—epilepsy—and appropriately addressed.

The tear film to corneal interphase is very important for vision. 30.8% of our cohort had dry eye syndrome and exposure keratopathy, with one patient having a corneal abrasion, and 15.4% had blepharitis. The sensory concerns of the CHARGE patient can be aggravated by ocular surface and eyelid disease. It is important to evaluate for exposure in patients with lagophthalmos and to address any eyelid disease.

In our cohort, punctal atresia was also found in patients with nasolacrimal duct obstruction. Pre-surgical knowledge of this finding will help with surgical planning.

It is important to note the other findings of drusen, eyelid nevus and Marcus Gun Jaw Winking syndrome. These were noted in one patient each and clinically followed. These are rare findings and may be independent of CHARGE syndrome diagnosis. Marcus Gunn Jaw Winking synkinesis was first described in 1883 by Robert Marcus Gunn. It is a ptosis associated with upper eyelid contraction that is in sync with contraction of the internal or external pterygoid muscles (jaw movement) (Demirci, Frueh, & Nelson, 2010).

Table 2 provides information on the frequency of other systemic findings in our cohort of CHD7+ positive patients, without colobomas. Our data is consistent with other reported systemic findings in CHD7 + patients (Hale et al., 2016), with the exception of orofacial clefts,

TABLE 2 Systemic findings in our CHARGE cohort without colobomas

Patient	Sex	Coloboma	Choanal atresia or stenosis	Cranial Nerve Dysfunction	Ear abnormalities	Inner ear anomalies	External ear anomalies	Hearing loss	Genital anomalies
Frequency in CHD7+ CHARGE syndrome*		77-89%	38-60 %	39-100%		94-100%	91-100%	89-94%	55-81%
Number, percent affected		0, 0%	6, 46.2%	5, 38.5%	13, 100%	9, 69.2%	7, 53.8%	10, 76.9%	11, 84.6%
1	M	-	+	-	+	+	+	-	+
2	M	-	-	-	+	+	+	+	+
3	M	-	-	-	+	+	+	+	+
4	M	-	-	+	+	+	+	+	+
5	M	-	-	-	+	+	+	-	-
6	M	-	-	-	+	+	+	+	+
7	F	-	+	+	+	-	-	+	+
8	M	-	-	+	+	-	-	+	+
9	M	-	+	-	+	+	-	+	+
10	M	-	+	-	+	+	-	+	+
11	M	-	+	+	+	+	+	-	+
12	M	-	+	+	+	-	-	+	+
13	F	-	-	-	+	-	-	+	-

Micropenis	Cryptorchidism	Hypoplastic Labia	Cardiovascular Malformation	Growth Deficiency	Orofacial Cleft	Tracheoesophageal Fistula	Developmental delay	Delayed Puberty Secondary to Hypogonadotropic Hypogonadism	CHARGE Syndrome: Definite versus probable/possible** using major and minor criteria only.
			75-92%	37-73%	30-48%	19-29%	75-100%		
6, 46.2%	8, 61.5%	0, 0%	10, 76.9%	8, 61.5%	3, 23.1%	4, 30.8%	13, 100%	9, 69.2%	
+	+	-	+	-	-	-	+	+	D
+	+	-	+	-	-	-	+	+	D
+	+	-	-	+	+	-	+	+	D
+	+	-	+	-	-	-	+	+	D
-	-	-	-	-	-	-	+	-	P
+	+	-	-	-	-	-	+	-	P
-	-	-	+	+	-	+	+	+	D
-	+	-	+	+	+	-	+	-	D
+	+	-	+	+	-	+	+	+	D
-	+	-	+	+	-	-	+	+	D
-	-	-	+	+	-	+	+	+	D
-	-	-	+	+	+	-	+	+	D

(Continues)

TABLE 2 (Continued)

Micropenis	Cryptorchidism	Hypoplastic Labia	Cardiovascular Malformation	Growth Deficiency	Orofacial Cleft	Tracheoesophageal Fistula	Developmental delay	Delayed Puberty Secondary to Hypogonadotropic Hypogonadism	CHARGE Syndrome: Definite versus probable/possible** using major and minor criteria only.
-	-	-	+	+	-	+	+	-	D

(-) absent
(+) present
(*) Frequency data obtained from Hale et al., 2016 where they provided their data and summarized data from three other studies of CHD7+ CHARGE patients.
(**) Lalani et al., 2006, updated 2012, provided information about Definite and Probable based on the Major and Minor criteria as noted by Blake et al., 1998; Verloes, 2005

which had a lower frequency in our cohort. Using previously defined clinical diagnostic criteria (Blake et al., 1998; Blake & Prasad, 2006; Lalani, Hefner, et al., 2006; Lalani, Safiullah, et al., 2006; Verloes, 2005), we further evaluated our cohort and classified our patients as definite or possible CHARGE. In our cohort, only 2/13 patients were possible/probable CHARGE diagnosis based on clinical findings only. Based on this, we would propose that an absence of colobomas, in the presence of other systemic findings does not rule out CHARGE syndrome and warrants further clinical and molecular testing.

This is not a prevalence study; however, it does provide significant information about a patient population that has not previously been reported. Another limitation is that not all the patients were seen by the same provider, and documentation varied, where it was unclear what was seen at the examination, such patients were excluded from the final analysis. This was a prospective study, and our medical center attracts patients from multiple locations, the confirmed CHD7+ information could be obtained for all the patients enrolled in the studies, however, the CHD7 variant type for each patient could not be obtained.

5 | CONCLUSIONS

There are numerous ophthalmic findings in patients with CHARGE without colobomas. Even in the absence of coloboma, a patient should have adequate ophthalmic follow-up to assess for other ophthalmic findings, and these should be interpreted in the clinical context and addressed accordingly. Thus, a newborn or baby with CHARGE that does not have a coloboma should not be ruled as having no risk for ophthalmic sequalae. The absence of a coloboma means less internal ophthalmic findings, decreased risk of a retinal detachment, and this would prognosticate increased chances of good vision. Good vision can be obtained provided all neurodevelopmental needs are met, and appropriate evaluation and treatment of other significant ophthalmic findings are performed.

In our cohort, our patients had confirmed clinical and molecular diagnosis of CHARGE Syndrome, with a CHD7 mutation, without colobomas. We propose that even in the setting of no coloboma, a careful examination of the patient that yields a positive non-ophthalmic finding(s) of CHARGE, or a high clinical suspicion, would warrant confirmation with molecular testing, and is consistent with the recommendations made by Hale et al. (2016).

ACKNOWLEDGEMENTS

The authors would like to acknowledge Patricia Cobb, Monica Sandoval, and Michael Del Busto, MD and Brittany Simpson, MD.

CONFLICT OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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How to cite this article: Dosunmu EO, Castleberry KM. CHARGE syndrome without colobomas: Ophthalmic findings. *Am J Med Genet Part C*. 2020;184C:611–617. https://doi.org/10.1002/ajmg.c.31840