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Persistent left superior vena cava: an overlooked feature of CHARGE syndrome?

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Abstract

CHARGE is a well-characterized syndrome (OMIM 214840) associated with multiple congenital anomalies including cardiovascular malformations. Mutations in *CHD7* are the most common cause of CHARGE syndrome. Persistent left superior vena cava (LSVC) has been described in patients with CHARGE syndrome in one study of LSVC associations. A retrospective chart review was conducted for all patients with CHARGE syndrome, diagnosed by Blake criterion features and/or the presence of a pathogenic *CHD7* mutation. Echocardiograms were performed on a clinical basis for all patients and were systematically reviewed and classified. Persistent LSVC was present in 50% of patients with CHARGE syndrome (4/8) and was seen in 3 out of 33 patients seen by cardiovascular genetics with 22q11.2 deletion syndrome. Persistent LSVC is a common finding in patients with CHARGE syndrome and its presence may increase the index of suspicion in patients with other characteristic congenital anomalies.

Introduction

CHARGE syndrome (OMIM 214840) is an autosomal dominant, multiple congenital anomaly syndrome. Typically, the occurrence is sporadic with rare familial cases. The term *CHARGE* itself is an acronym of common features in this syndrome, including ocular Coloboma, Heart defects, choanal Atresia, Retardation of growth and development, Genitourinary and Ear anomalies including deafness. The prevalence of CHARGE syndrome is estimated to be one in 8500-10,000 live births.¹ Cardiovascular malformations (CVMs) that are typically associated with this

syndrome include conotruncal malformations [tetralogy of Fallot, double outlet right ventricle, D-transposition of the great arteries (TGA)], septal defects (atrial septal defects, ventriculoseptal defects), right ventricular outflow tract obstruction (RVOTO, *e.g.*, pulmonary valve stenosis), and patent ductus arteriosus.²

CHARGE syndrome was formerly a clinical diagnosis based on particular major and minor findings. The schema most generally used was proposed by Blake *et al.*,³ and there is an additional clinical criterion schema proposed by Verloes *et al.* (Table 1).⁴ Both systems utilize similar criteria: endocrine abnormalities (delayed pubertal development, gonadotropin or growth hormone deficiency), developmental delay or intellectual disability, and cranial nerve dysfunction, in addition to CVM.

Since 2004, the clinical diagnosis of CHARGE syndrome has been supported by sequencing of *CHD7*,⁵ Chromodomain Helicase DNA-binding protein active in the developing embryo. Among patients with a clinical diagnosis of CHARGE syndrome by Blake and/or Verloes criteria, over 90% have pathogenic mutations, deletions, or duplications of *CHD7*.⁶ Patients with truncating mutations of *CHD7* are more likely to both meet clinical criteria (Blake and/or Verloes), have CVMs, choanal atresia, and cleft lip/palate than patients with missense mutations of *CHD7*.⁷

There is difficulty in making a clinical diagnosis of CHARGE syndrome in the cardiac intensive care unit (CICU) because newborns may not have observable threshold criterion features. Unifying diagnoses impact management and therefore timely diagnoses impact care. Additional congenital anomalies or specific CVMs that increase suspicion for CHARGE syndrome would be helpful in the assessment of newborns in the CICU.

The presence of left superior vena cava (LSVC) is common in the general population (0.1-1.7%)⁸ and may be an asymptomatic congenital anomaly discovered in the course of evaluation for other conditions. LSVC is more commonly seen in individuals with concurrent CVMs (10%).^{8,9} In particular, SVC abnormalities are common in individuals with heterotaxy syndromes,¹⁰ who may have a LSVC with or without a persistent right superior vena cava (bilateral SVC with or without a communicating vein). There is a high prevalence of extracardiac findings in patients with LSVC (51%), and of these, 21% may have heterotaxy syndrome.⁸

Previously, Postema and colleagues reported a case series of 102 consecutive patients with LSVC in which five patients (5%) with CHARGE syndrome were identified.¹¹ In addition, unspecified SVC anomalies were reported in 5 patients (8%) with CHARGE in an epidemiologic survey.¹ Larger studies examining cardiac features in CHARGE syndrome have

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Key words: CHARGE syndrome; CHD7; persistent left superior vena cava; bilateral superior vena cava; congenital heart defects.

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not routinely documented SVC findings,^{2,12-14} thus the true frequency of LSVC in patients with CHARGE syndrome is unknown.

We reviewed patients with CHARGE syndrome seen by the cardiovascular genetics service at CCHMC to determine the frequency of venous anomalies. We hypothesized that there is an increased frequency of LSVC in patients with a diagnosis of CHARGE syndrome.

Materials and Methods

A retrospective case series of consecutive patients with a clinical and/or molecular diagnosis of CHARGE syndrome and 22q11.2 deletion syndrome followed by the cardiovascular genetics service at CCHMC from 7/2010-12/2012 was completed with Institutional Review Board approval. Blake criteria were ascertained and typical CHARGE was used as the standard for clinical diagnosis. We also evaluated for Verloes criteria in all patients as

these are weighted differently (Table 1). Pathogenic mutations of *CHD7* were the standard for laboratory-confirmed diagnosis. All initial echocardiograms were reviewed by a cardiologist, and CVMs were classified using an established taxonomy that identifies both specific lesions and groups of related lesions.¹⁵ As a comparison cohort, patients with 22q11.2 deletion syndrome, a condition with similar phenotype,¹⁶ were evaluated similarly.

Results

Eight patients were ascertained with CHARGE syndrome (4 female, 7 Caucasian non-Hispanic, 1 African American). There was an equal distribution of gender and median age at diagnosis of approximately 3 months (0.26 years), however two subjects were ascertained much later at 1.73 years and 12.30 years in a cardiac neurodevelopmental clinic (Table 2). The 22q11.2 deletion syndrome comparison group had 33 patients with demographics similar to the CHARGE cohort (18 female, 30 Caucasian with one Hispanic, 2 African American, 1 Asian). All patients with 22q11 Deletion syndrome had typical deletions by fluorescent *in situ* hybridization (FISH) or microarray studies, were consecutively ascertained during the same time period, and were also followed by the cardiovascular genetics service.

In the CHARGE cohort, the CVM group was predominantly conotruncal and included septal defects and RVOTs (Table 3). Four patients with CHARGE (4/8; 50%) had persistent LSVC (bilateral SVC), three patients with LSVC had TGA with additional cardiac defects. Interestingly, 5/8 patients (1-5, Table 2), including all four with LSVC, had cardiac findings consistent with a laterality disorder, a

classification that encompasses heterotaxy syndromes. In contrast, three of the 22q11.2 deletion syndrome cohort had LSVC (9%). The 22q11 deletion syndrome cohort had the following CVM groups: 22 conotruncal, 6 septal, 1 RVOTO, 4 other [aberrant subclavian artery (3), and vascular ring (1)].

Patient 1 did not meet Blake criteria, but did meet Verloes criteria as atypical CHARGE (Table 2). We did include this patient based on the pathogenic molecular findings of a splice site mutation that would truncate *CHD7*; interestingly, this patient did not have persistent LSVC.

The one patient without a pathogenic *CHD7* mutation, Patient 4, also had normal microarray and 22q11 FISH testing. LSVC was present and this patient had typical features of CHARGE including choanal stenosis, growth delay (length 0.2% at 6 months of life), striking ear anomalies (right microtia, left anotia, absent left tympanic membrane, malrotated left middle ear ossicles fused to the inferior wall, dysmorphic stapes, hypoplastic oval window, right incus fused to lateral wall, superior semicircular canal partially absent, dysmorphic, and large undeveloped horizontal semicircular canal), severe to profound hearing loss bilaterally (conductive hearing loss ipsilateral to anotia), cranial nerve anomalies (absent right facial nerve and tortuous left facial nerve) with broad forehead and square facies. Cardiac findings are listed in Table 3. No colobomas were seen on ophthalmologic evaluation. This patient also had additional rare and severe craniofacial findings including absent left internal carotid artery and absent left parotid gland, some of which have been previously described in the case report literature in association with CHARGE syndrome.¹⁷ This patient met Blake and Verloes criteria for a clinical diagnosis of typical CHARGE syndrome, and may be one of the <10% of patients

meeting this standard that do not have mutations of *CHD7*.

All patients had unique phenotypic features. Molecular findings of all patients showed a preponderance of splice site and premature stop codon mutations.

Discussion and Conclusions

Early diagnosis of genetic syndromes is important for optimal patient care in the CICU setting, as knowledge of a unifying diagnosis informs medical decision making, perioperative care, identification and management of comorbidities, improved attention to feeding difficulty in patients with increased risk of dysphagia, and postoperative rehabilitative therapy.

Establishing a diagnosis of CHARGE syndrome in a newborn may be delayed by failure to meet full clinical diagnostic schema in infancy, delay in molecular testing, and/or features that overlap with more common or well-known genetic syndromes such as 22q11.2 deletion syndrome. Usually in newborn care, unless suggested by genetics consult, teams will not routinely order an ophthalmology consult that may detect a retinal coloboma, facial bone imaging for unilateral choanal atresia, or audiology testing that might lead to the diagnosis of CHARGE syndrome in a newborn with conotruncal defects. Identification of additional features, which increase suspicion for CHARGE syndrome and assist in delineating it from other common syndromes, would assist in identifying patients who should have *CHD7* sequencing, and in appropriate diagnosis of patients who may be too young to meet the clinical criteria of CHARGE syndrome.

This study identifies LSVC as a possible new phenotypic association for CHARGE syndrome. Echocardiograms are routinely performed to

Table 1. Comparison of clinical criteria for CHARGE syndrome.

Author	Major criteria	Minor criteria	Clinical diagnosis
Blake ³	1. Coloboma, microphthalmia 2. Choanal atresia or stenosis 3. Characteristic external ear anomaly, middle/inner ear malformations, mixed deafness 4. Cranial nerve dysfunction	1. Cardiovascular malformations 2. Tracheo-esophageal defects 3. Genital hypoplasia or delayed pubertal development 4. Cleft lip and/or palate 5. Developmental delay 6. Growth retardation 7. Characteristic face	Typical CHARGE: 4 major or 3 major + 3 minor
Verloes ⁴	1. Ocular coloboma 2. Choanal atresia 3. Hypoplastic semicircular canals	1. Heart or esophageal malformation 2. Malformation of the middle or external ear 3. Rhombencephalic dysfunction including sensorineural deafness 4. Hypothalamo-hypophyseal dysfunction (gonadotropin or growth hormone deficiency) 5. Mental retardation	Typical CHARGE 3 major or 2 major + 2 minor Partial CHARGE 2 major + 1 minor Atypical CHARGE 2 major + 0 minor or 1 major + 1 minor

screen for cardiac defects in patients suspected of having CHARGE syndrome, so this information would be available and accessible to geneticists and cardiologists. In our small retrospective review we have found a high proportion of patients with CHARGE syndrome who had persistent LSVC, suggesting that this anomaly in the presence of another cardinal feature of CHARGE syndrome might trigger further clinical suspicion for this syndrome. Defining the frequency of LSVC in CHARGE is therefore important to this end. Other syndromes on the differential diagnosis for LSVC include heterotaxy, VACTERL association, aneuploidy, and 22q11.2 deletion syndrome.¹¹

Consideration of a potential unifying mechanism of the occurrence of LSVC in CHARGE patients suggests there is some degree of phenotypic overlap between CHARGE syndrome and laterality defects. Specific types of CVMs, including complex CVM are present in both situations, but CVMs that are common and largely present in patients without a genetic syndrome (such as conotruncal defects) do not necessarily alter the index of suspicion like specific CVMs. Our patient population had a higher than expected prevalence of TGA and right aortic arch. Most, but not all, patients with either of these CVMs also had LSVC. Interestingly, mal-arrangement in addition to structural defects is present in both conditions, suggesting consideration of arrangement may also facilitate identification of CHARGE patients. Patient 4 had additional cardiac features consistent with heterotaxy, including dextrocardia and total anomalous pulmonary venous connection. Laterality defects have been seen in *CHD7* knockdown zebrafish,¹⁸ as well as more typical cardiac anomalies similar to those generally seen in patients with CHARGE syndrome.¹⁹ It may be that *CHD7* plays a role in left-right discrimination in human cardiac development.

Limitations of this study include the fact that all patients were ascertained based on their CVMs, and we are therefore unable to assess whether patients with CHARGE syndrome may have isolated LSVC. All of the patients in this study had CVMs, whereas 75% of patients with CHARGE syndrome have CVMs,² reflecting the ascertainment of patients from a cardiovascular genetics service. Additionally, the small sample size of individuals with CHARGE syndrome in this study may overestimate this association and not be generalizable. Arguing against sampling bias, however, is the high prevalence of CHARGE syndrome in an LSVC population study¹¹ and increased SVC anomalies in an epidemiologic study of patients with CHARGE syndrome.¹ A point may be made that the frequency of this finding is related to the 10% prevalence of LSVC in patients with CVMs, however in reviewing our patient group with 22q11 dele-

Table 2. Age at diagnosis, criterion features, and *CHD7* sequencing results.

Patient	Age (years)	Coloboma	Choanal atresia	Ear	Cranial nerve	GU	DD	CV	Growth	Cleft	TEF	Face	Blake criteria (2M,3m)	Verloes criteria (1M, 3m)	<i>CHD7</i> sequencing
1	12.3	0	0	X	X	X	0	X	0	0	0	X	No (2M,3m)	Atypical SC anomaly (1M, 3m)	c.5404+1G>T novel Disrupts splice site donor intron 25 Pathogenic
2	0.23	X	?	X	X	?	?	X	X	0	X	X	Typical (3M,4m)	Atypical SC not assessed (1M, 3m)	c.1796_2-3del/241 p.Lys599SerfsX32 Pathogenic
3	0.13	X	X	X	X	?	X	X	X	0	X	X	Typical (4M,5m)	Typical SC anomaly (3M, 4m)	c.3289dupA p.Ile1097AsnX9 Pathogenic
4	0.61	0	X	X	X	?	X	X	X	0	0	0	Typical (3M,3m)	Typical SC anomaly (2M,2m)	c.2829G>A VUS c.8416C>G Benign Uncertain
5	0.29	X	X	X	X	X	X	X	X	0	0	X	Typical (4M,5m)	Typical SC anomaly (3M,3m)	c.3841C>T p.Gln1281Stop Pathogenic
6	1.73	X	X	X	X	?	X	X	X	0	0	X	Typical (4M,4m)	Typical SC anomaly (2M, 2m)	c.2280_2281dupTG p.Glu761ValfsX43 Pathogenic
7	0.21	X	X	X	X	X	?	X	X	0	0	X	Typical (4M,4m)	Typical SC anomaly (2M,3m)	c.6390_6391 delCTinsA p.Asn2130LysX14 Pathogenic

X, denotes presence of Blake criterion finding; 0, denotes absence; ?, unable to assess due to patient's age or death; Coloboma, iris, retina, choroid, disc, microphthalmia; Choanal atresia, unilateral/bilateral, membranous/bony, stenosis/atresia; Characteristic ear, external ear (lop or cup shaped), middle ear (ossicular malformations, chronic serous otitis), mixed deafness, cochlear defects; Cranial nerve, I: anosmia, VII: facial palsy (unilateral/bilateral), VIII: sensorineural deafness, vestibular problems; IX: swallowing problems; GU: genitourinary, males (micropenis, cryptorchidism), females (hypoplastic labia), either (delayed, incomplete pubertal development); DD (developmental delay); DD (developmental delay); Delayed motor milestones, hypotonia, intellectual disability; CV (cardiovascular) malformations, all types, especially conotruncal defects; AV canal defects, and aortic arch anomalies; Growth, short stature; Cleft, cleft lip and/or palate; TEF (tracheo-esophageal fistula), TE defects of all types; Face (facial features), broad forehead, facial asymmetry, full nasal tip; Blake and Verloes criteria, M: major criteria, m: minor criteria; SC anomaly, presence of malformation of the semicircular canals; *CHD7* sequencing, all mutations are pathogenic and result in a truncated protein except Patient 4; VUS, variant of unknown significance and benign polymorphism.

Table 3. Cardiovascular malformation and left superior vena cava status.

Patient	CVM groups	CVM lesions	LSVC
1	Conotruncal RVOTO	Double outlet right ventricle Pulmonary valve stenosis Right aortic arch	-
2	Conotruncal Septal	Interrupted aortic arch, type B Ventricular septal defect Aberrant right subclavian artery	-
3	Septal	Atrial septal defect Patent ductus arteriosus	-
4	Conotruncal APVR RVOTO	Dextrocardia D-Transposition of the great arteries Total anomalous pulmonary venous return Tricuspid stenosis	+
5	Conotruncal RVOTO	D-Transposition of the great arteries Pulmonary valve stenosis	+
6	Septal	Ventricular septal defect Patent ductus arteriosus	-
7	Conotruncal	Double outlet right ventricle Mitral atresia Right aortic arch	+
8	Conotruncal	D-Transposition of the great arteries Right aortic arch Aberrant left subclavian artery	+

CVM, cardiovascular malformation; LSVC, left superior vena cava; RVOTO, right ventricular outflow tract obstruction; APVR, right aortic arch, dextrocardia.

tion with CVMs (n=33) we found three patients with LSVC (11%), similar to the general presence of LSVC in individuals with CVMs. Larger studies of SVC anomalies in CHARGE syndrome patients are required to clarify these limitations.

In summary, we have identified LSVC as a likely common cardiovascular malformation in CHARGE, suggesting CHD7 plays a role in venous development. Other findings suggestive of abnormal development of laterality were also found in our population (right aortic arch, dextrocardia, D-TGA). Taken together with the abnormal laterality development in zebrafish with CHD7 knockdown, an additional role for CHD7 in early embryonic left-right patterning may be considered. CHARGE syndrome should be considered when LSVC and laterality abnormalities are identified.

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