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Congenital arch vessel anomalies in CHARGE syndrome: A frequent feature with risk for co-morbidity☆,☆☆

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ABSTRACT

Background: CHARGE syndrome is a complex multiple congenital malformation disorder with variable expression that is caused by mutations in the *CHD7* gene. Variable heart defects occur in 74% of patients with a *CHD7* mutation, with an overrepresentation of atrioventricular septal defects and conotruncal defects — including arch vessel anomalies.

Methods and results: We report an index patient with an arch vessel anomaly underlying serious feeding problems that resolved after arch vessel surgery. This led us to examine the incidence of arch vessel anomalies in our previously studied cohort of 299 patients with a *CHD7* mutation. Forty-two patients (14%) had an aortic arch anomaly, mostly aberrant subclavian artery or right aortic arch, which usually occurred in combination with other congenital heart defects (81%). The majority of these patients also had feeding problems that may be linked to their arch anomaly, but insufficient information was available to exclude other causes.

Conclusions: Arch vessel anomalies occur in a significant proportion of patients with a *CHD7* mutation, and these anomalies may cause morbidity due to compression of the esophagus or trachea. Since symptoms of vascular compression can mimic those caused by other abnormalities in CHARGE syndrome, it is important to be aware of arch vessel anomalies in this complex patient category. Whether a solitary arch vessel anomaly is an indicator for CHARGE syndrome still needs to be studied, but doctors should look out for other CHARGE syndrome features in patients with arch vessel anomalies.

1. Introduction

CHARGE syndrome (MIM 214800, *C*oloboma, *H*eart disease, Choanal *a*tresia, *R*etardation of growth and/or development, *G*enital hypoplasia and *E*ar abnormalities with or without deafness) is a multiple congenital malformation disorder with variable expression and an incidence of 5.8–6.7 per 100,000 newborns [1]. CHARGE syndrome is usually a sporadic condition that is caused, in particular, by *de novo* loss-of function mutations in the *CHD7* gene (MIM 608892) [2].

Congenital heart defects occur in 74% of patients who have CHARGE syndrome due to a *CHD7* mutation, and in 80% of patients with a truncating *CHD7* mutation [3]. Our previous study showed that while the types of heart defects found in CHARGE syndrome patients are variable, atrioventricular septal defects and conotruncal defects are overrepresented compared to typically non-syndromic heart defects [3]. Congenital arch vessel anomalies such as aberrant right subclavian artery (ARSA) were highly overrepresented within our group of patients with CHARGE syndrome [3].

The aortic arch and its vessels are formed after the fourth week of embryogenesis by remodeling and re-arrangement of the aortic sac, the branchial arch arteries and the dorsal root aorta's. An embryo developing normally initially has one aortic sac which communicates with the heart via the truncus arteriosus and is connected to two dorsal root aortas via paired branchial arch arteries. The eventual left sided aortic arch derives from the aortic sac, left 4th branchial arch artery and left dorsal root aorta. The first origin, the brachiocephalic trunk, arises from the aortic sac. The right and left common carotid arteries develop from the 3rd branchial arch arteries. The root and first part of the right subclavian artery is formed by the right 4th branchial arch artery and right dorsal root aorta. The rest of the right subclavian artery and the complete left subclavian artery derive from an intersegmental artery that originates directly from the dorsal root aorta. The molecular control

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of this complex process is not well understood, but defective remodeling results in congenital arch vessel anomalies [4–6].

A common congenital arch vessel anomaly is an aberrant subclavian artery in which the right or left subclavian artery has an abnormal anatomical position. An aberrant right subclavian artery, which is also called arteria lusoria, passes posterior to the esophagus and left aortic arch. It occurs when the right fourth branchial arch artery and proximal portion of the right dorsal root aorta disappears, while the distal right dorsal root aorta persists [6]. Aberrant subclavian arteries have been found in 1–2% of pediatric patients who had echocardiograms and in cardiac autopsy specimens [7,8]. Another frequent arch vessel abnormality is a right-sided aortic arch (RAA) which is caused by the persistence of the right dorsal root aorta and disappearance of the left fourth branchial arch artery and left dorsal root aorta [6]. A RAA is usually associated with a congenital heart malformation [8,9].

Arch vessel anomalies are usually asymptomatic, but problems may occur when a complete or incomplete vascular ring causes compression of the esophagus and the trachea. A double aortic arch in which both left- and right-sided aortic arches surround the trachea and esophagus is the most common cause of vascular compression in children [10]. Presenting symptoms of vascular compression vary, but include recurrent respiratory infections, stridor, wheezing, cough, dyspnea, respiratory distress, dysphagia, feeding difficulties and vomiting [5,10].

In this study we describe CHARGE patients with congenital arch vessel anomalies and focus on the health problems that might be caused by arch vessel anomalies in these patients.

2. Patients and methods

2.1. Case report

We report a clinically diagnosed CHARGE patient with dysphagia due to an arch vessel anomaly. Clinical information was obtained from the extensive medical correspondence concerning this patient. The patient's parents have given consent for the publication of this data.

2.2. Cohort of patients with an arch anomaly and a CHD7 mutation

We previously studied heart defects in 299 patients with a proven *CHD7* mutation, of whom 220 had a congenital heart defect [3]. This cohort consisted of patients tested for a *CHD7* mutation because of a clinical suspicion of CHARGE syndrome. The *CHD7* analysis was performed on a diagnostic basis at the DNA laboratory in Nijmegen, The Netherlands, between 2004 and 2009. Patients lived in The Netherlands (34%) and other European countries (54%), but also on other continents (12%). The accredited Medical Ethics Review Committee of the University Medical Center Groningen waived full ethical evaluation because, according to Dutch guidelines, no ethical approval is necessary if medical information that was already available is used anonymously and no extra tests have to be performed.

We selected patients from this previous study who had a vascular ring of any type, a RAA, an interrupted aortic arch, an aberrant left or right subclavian artery, or an aberrant origin of an aortic arch vessel. We studied cardiac phenotype and extra-cardiovascular symptoms in these patients. The patient described in the case report was not part of this cohort.

2.3. Control cohort to compare extra-cardiovascular features

The data collected about our study cohort were compared descriptively to a previously published group of 280 CHARGE patients with a known *CHD7* mutation [2]. Because there is some overlap between this group and our present study group, statistical comparisons were not possible. However, excluding these overlapping patients described here might bias the control group.

3. Results

3.1. Case report

We report new findings on a twenty-year-old male with CHARGE syndrome. He was born after an uneventful full-term pregnancy and with a birth weight of 8 lb (about 3500 g). He was evaluated directly after birth because of congenital anomalies and respiratory distress. He was diagnosed with laryngomalacia and had a tracheostoma until he was 8.5 years old. A diagnosis of CHARGE syndrome (which was then still an association) was made based on the combination of following anomalies: colobomata of the optic nerve and fundus, choanal stenosis, pulmonary valve dysplasia, genital hypoplasia with unilateral cryptorchism, small kidneys with subcortical cysts, a grade IV vesicoureteral reflux, velopharyngeal incompetence (due to 9th and 10th cranial nerve dysfunction), right sided facial nerve palsy and external ear anomalies with absent response to BAER. Further evaluation during the years showed profound sensorineural deafness with absent auditory nerves, absent semicircular canals, dysplastic cochlea, anosmia, hypogonatropic hypogonadism and significant short stature with growth hormone deficiency. He had a normal conventional karyotype, but *CHD7* analysis had never been done. He does fulfill the current diagnostic criteria for CHARGE syndrome [11,12].

The boy experienced feeding problems from birth, for which he received tube feeding until the age of 9 years. Even after decannulation and removal of the feeding tube, his feeding problems persisted; he aspirated water and could only eat soft foods. He had several swallowing studies done through the years that showed a constriction of the esophagus. From the age of 10 years his esophagus was dilated several times, but his feeding problems did not improve. He had several periods of choking, which warranted further evaluation. At the age of 18 years, he had a gastroscopy, which indicated a vessel compressing the esophagus. An angiogram confirmed an aberrant right subclavian artery as the cause. After surgical re-implantation of the aberrant subclavian artery, the boy was finally able to eat normally, and no new feeding problems or periods of choking have occurred since that time.

3.2. Arch vessel anomalies in a cohort of patients with a CHD7 mutation

Of the 299 patients with a *CHD7* mutation, 42 had a congenital arch vessel anomaly (14%). This group consists of 23 males and 19 females (see Table 1). Most patients had a truncating *CHD7* mutation (33/42, 79%). Fourteen patients were deceased (33%), ten of the twelve patients for whom the age of death was known died in the first year of life (see Table 1).

Right sided aortic arch (20 patients) and aberrant subclavian arteries (19 patients) were most frequently identified (see Table 1). A vascular ring was identified in five patients. An abnormal origin of an arch vessel was diagnosed in four patients, two concerning the subclavian artery (patient 1 and 37) and two the carotid arteries (patient 17 and 20). In patient 1, who had an interrupted aortic arch type B and a malalignment ventricular septal defect, the subclavian artery derived from the descending aorta. In patient 37, who had a right-sided aortic arch and a bicuspid aortic valve, the left subclavian artery derived from the pulmonary artery. Patient 17 had a persistent ductus arteriosus (PDA) and ARSA in combination with a right internal carotid artery that was inserted higher than usual. Patient 20 had a PDA and ARSA with a truncus bicaroticus, which means both carotid arteries originated from one common origin of the aortic arch.

Most patients had other heart defects in addition to their arch vessel anomaly (34/42, 81%), and one patient had a congenital conduction disorder. Interestingly, seven patients (17%) had an arch vessel anomaly as an isolated cardiovascular feature (see Table 1). The accompanying heart defects were variable, but often included septal defects (atrial as well as ventricular), PDA and tetralogy of Fallot or double outlet right ventricle.