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مجلة جامعة دنقلا للبحث العلمي
مجلة دورية علمية محكمة
تصدر عن كلية الدراسات العليا – جامعة دنقلا

مجلة جامعة دنقلا للبحث العلمي

مجلة نصف سنوية علمية محكمة

تصدر عن كلية الدراسات العليا – جامعة دنقلا

دنقلا – السودان

مقدمـة:

مجلة جامعة دنقلا للبحث العلمي تصدر عن كلية الدراسات العليا بجامعة دنقلا، وهي مجلة نصف سنوية علمية محكمة، تسهم في توسيع دائرة العلم والمعرفة، وذلك من خلال نشر البحوث والأوراق العلمية، التي تتوافر فيها الأصالة والمنهجية والفائدة العلمية ووفق هذه الرؤية ترحب المجلة بإسهامات الأساتذة الباحثين من داخل وخارج الجامعة والتي تتوفر فيها كل أساسيات البحث العلمي، شريطة أن لا تكون الإسهامات قد نشرت من قبل أو تحت إجراء النشر في أي مجلة أخرى.

قواعد النشر:

- ترحب المجلة بالبحوث في ثلاث نسخ مطبوعة علي وجه واحد على ورق A4 بفراغات مزدوجة وهوامش 2.5 سم، على أن لا يزيد حجم البحث عن أربعين صفحة شاملة الملخصين والموضوع والمراجع والملاحق. ويكون حجم الحرف (14) وترقم الصفحات في الأسفل على الجانب الأيسر بشكل متسلسل.
- يجب أن يحتوي البحث على ملخص بحدود (10) أسطر باللغة الأصلية للبحث (عربي، الإنجليزية). بالإضافة إلى ملخصٍ وافٍ باللغة الإنجليزية إذا كان البحث مكتوباً باللغة العربية، وملخصٍ وافٍ باللغة العربية إذا كان البحث مكتوباً باللغة الإنجليزية.
- يكتب في بداية البحث: عنوان البحث، واسم الباحث، القسم، الكلية، الجامعة، المدينة، البلد، والكلمات المفتاحية Keywords باللغتين العربية والإنجليزية.
- يجب أن تتبع الطريقة العلمية المثلى لعرض البحث أو الورقة من حيث الخلاصة ومناهج ووسائل البحث، وعرض الموضوع وتحليله، والنتائج التي تم التوصل إليها، والتوصيات المقدمة، وقائمة المراجع وفق المنهج المتبع.
- يجب أن يراعى ترقيم الجداول والأشكال والرسومات والصور المرسومة بالحبر الأسود، مع الإيضاح المقابل لكلٍ، على أن تكون واضحة عند إعادة إنتاجها.
- تخضع البحوث المقدّمة للنشر، للتقويم من قبل مختصين في موضوع البحث.
- في حالة البحوث والأوراق المستلة، يجب توضيح الدرجة التي منحت للرسالة وزمانها، والجامعة التي قدمت لها، واللجنة التي قومتها.
- بعد التحكيم يطلب من الباحث تسليم البحث في قرص مدمج (CD).

- يحق لهيئة التحرير إجراء التغيرات التي تراها ضرورية لأغراض الصياغة أو تصويب الأخطاء النحوية، أو الترقيم.
- يرجي من الباحثين إرفاق سيرتهم الذاتية.
- يحق لمن ينشر له بحث في المجلة نسختين من العدد المعني.
- المجلة غير ملزمة برد الأوراق التي لم يتم اعتمادها للنشر، وترسل إفادة بعدم النشر للكاتب.
- ترسل الأوراق إلى المجلة على العنوان التالي:

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كلمة العدد

بسم الله الرحمن الرحيم

الحمد لله رب العالمين والصلاة والسلام على أشرف المرسلين سيدنا محمد وعلى آله وصحبه أجمعين أما بعد. فحمد الله تعالى أن وقفنا لإصدار هذا العدد الذي جاء على ذات النحو الذي تطل عليكم به مجلة كلية الدراسات العليا بجامعة دنقلا حين يضم عدداً من الأوراق العلمية لعدد من منسوبي الجامعة وأساتذة من جامعات السودان المختلفة بالإضافة لمشاركات بعض الباحثين من الدول العربية.

تتفرد مجلة كلية الدراسات العليا بوجود مساحة نشر للباحثين الأجانب وهذه دعوة للكل الباحثين من الدول العربية والغربية للنشر عبر مجلتكم مجلة كلية الدراسات العليا بجامعة دنقلا الواسعة الانتشار كما يمكنكم متابعة إصدارات المجلة عبر موقع الجامعة وصفحة الكلية علي الفيس بوك. كما احب أن أتقدم بالشكر الجزيل لكل الباحثين الذين تقدموا بأبحاثهم العلمية وكل الذين راسلونا خلال الفترة السابقة وأبدوا رغبتهم بالنشر ونؤكد لهم حرصنا التام حفظ حقوقهم العلمية والأدبية.

ستظل مجلة كلية الدراسات العليا نبراساً ونوراً يهتدى به والأمل والملاذ لكل عشاق البحث العلمي من ناشرين وقراء وها نحن نضع بين أيديكم العدد الخامس عشر والذ نأمل أن ينال استحسانكم كما أرجو زيارة موقعنا الإلكتروني للتعرف على أخر إصدارتنا العلمية من أوراق وأخر عناوين البحث العلمي لنيل درجة الدكتوراه والماجستير والدبلوم العالي لكافة التخصصات المجاز بكلية الدراسات العليا بجامعة دنقلا.

رئيس هيئة التحرير

الفـــهرس

Congenital arch vessel anomalies in CHARGE syndrome

Dr. Manal Elnour Osman Ahmed

Abstract:

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 CHD7mutation, with an overrepresentation of atrioventricular septal defects and conotruncal defects — including arch vessel anomalies.

المستخلص

متلازمة CHARGE هي اضطراب تشوه خلقي متعدد معقد مع تعبير متغير ينتج عن طفرات في جين CHD7. تحدث عيوب القلب المتغيرة في 74 ٪ من المرضى الذين يعانون من طفرة في CHD7 ، مع الإفراط في تمثيل عيوب الحاجز الأذيني البطيني والعيوب الخلقية – بما في ذلك الحالات الشاذة في الأوعية المقوسة

Introduction

CHARGE syndrome (MIM 214800, Coloboma, Heart disease, Choanal atresia, Retardation of growth and/or development, Genital hypoplasia and Ear 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 novoloss-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]. 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 of this complex process is not well understood, but defective remodeling results in congenital arch vessel anomalies [4], [5], [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.

Methods

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.

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, between 2004 and 2009. Patients lived in Saudi Arabia (34%) and other Arab 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.

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.

Congenital arch vessel anomalies in CHARGE syndrome:

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 vesicle 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.

The identification of abnormal aortic arch arteries can also be important for asymptomatic CHARGE syndrome patients who need interventional or surgical procedures because routine procedures may be complicated in patients with arch vessel anomalies, e.g., when associated with anomalies of the laryngeal nerve.

Given the high prevalence of arch vessel anomalies in CHARGE syndrome, it remains interesting to study how often patients with arch vessel anomalies have a CHD7 mutation. Our recent study in 46 patients with syndromic conotruncal heart defects or AVSD, including eight with an arch vessel anomaly, did not identify any pathogenic CHD7 mutations [28]. In a previous study that focused on the prevalence of bicarotid trunk in patients who underwent cardiac catheterization, genetic syndromes were also assessed; CHARGE syndrome was present in three of the 310 patients (1%) with a bicarotid trunk [29]. A study of 257 patients with a tetralogy of Fallot with pulmonary stenosis showed that the incidence of chromosomal or genetic abnormalities, including CHARGE syndrome, increased significantly in patients who had an aberrant subclavian artery with either a left or right aortic arch [30].

While we don't yet have enough support to advise CHD7 analysis in all patients with arch vessel anomalies, current studies suggest arch vessel anomalies might be an indicator of CHARGE syndrome.We therefore do advise health care professionals to look carefully for other features of CHARGE syndrome (e.g. external ear anomalies, balance problems, deafness and coloboma) in patients with arch vessel anomalies.

Future studies are warranted to identify more precisely the frequency of symptomatic arch vessel anomalies in CHARGE syndrome. More evidence is needed to support that an arch vessel anomaly is an indicator of

CHARGE syndrome, but doctors should be aware of other features of this complex entity in patients with an arch vessel anomaly. 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.

Results

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 9^{th} and 10^{th} 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.

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. 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.

Right sided aortic arch (20 patients) and aberrant subclavian arteries (19 patients) were most frequently identified . 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. 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.

The most common extracardiovascular features were external ear anomaly (36/36), hearing loss (34/34) and semicircular canal abnormalities (23/24), which were present in almost all patients for whom the information was known. Developmental delay, genital hypoplasia (e.g. micropenis or hypogonatropic hypogonadism) and cranial nerve dysfunction were present in the majority of patients (> 80%). These extracardiovascular features did not clearly differ between our study cohort and the control cohort.

Information on feeding or swallowing history was known for 26 of 37 patients who were alive at the age of 1 month. Only one out of these 26 patients was recorded not to have feeding or swallowing problems. Thus, these problems were present in 96% of patients (range 25/37–36/37 = 68–97%). Remarkably, at least twenty patients (77%, range 20/37–36/37 = 54–97%) had feeding problems that necessitated tube feeding. Information on feeding was known for 110 patients in our control cohort, and tube feeding was necessary in 90 patients (82%, range 90/280–260/280 = 32–93%). We have no information on recurrent respiratory infections, stridor, wheezing, cough or dyspnea in both our study and control group.

In our study cohort, arch vessel anomalies were present in 14% (42/299) of patients with a *CHD7* mutation and in 19% (42/220) of patients with a *CHD7* mutation and a cardiovascular defect. We might have missed patients with an arch vessel anomaly in our retrospective study because it can be missed with echocardiography, and because we know the collected data are not complete. We also did not have enough information to classify heart defects in 18 patients (8%), and in approximately 60% we had to base

our classification on the information from the medical doctor who requested the *CHD7* analysis.

Several previous studies on smaller populations (between 47 and 83 patients) also documented arch vessel anomalies in 4 to 23% of the patients with CHARGE syndrome, or in 5 to 36% of the patients with CHARGE syndrome and a heart defect . However the data from our study and the previous studies cannot easily be compared for a number of reasons. First, not every study used the same definition for arch vessel anomalies, while the type of heart defects that are categorized as arch vessel anomaly are not clear in others. For example, we did not include hypoplastic aortic arch as an arch vessel anomaly based on the classification system we used to classify heart defects [17], [18], while a previous study did [16]. Second, we included patients with arch vessel anomalies and other cardiac anomalies in our percentages while, in at least one other study, patients with an arch vessel anomaly and another heart defect were partly categorized in a different group [16]. Finally, the populations differ because patients in all previous studies had a clinically based diagnosis of CHARGE syndrome, while we included only patients with a definite molecular diagnosis. Nonetheless, both our study and all previous studies show that arch vessel anomalies do occur more frequently in CHARGE syndrome than in the general population.

We primarily identified patients with aberrant subclavian arteries and right-sided aortic arch in our cohort, but rarer arch vessel anomalies can also occur in patients with CHARGE syndrome. For example, we identified an abnormal origin of an arch vessel in four of our patients (see Table 1). An aberrant origin has also been described previously in CHARGE patients for the left brachiocephalic trunk and left subclavian artery out of the pulmonary artery, respectively [19], [20]. In our study cohort, the arch vessel anomalies usually occurred in combination with other heart defects. However, it is important to note that arch vessel anomalies such as right aortic arch and aberrant subclavian artery were solitary in 17% of our patient cohort.

Based on these clinical observations, CHD7 probably has an effect on the embryonic development of the branchial arch arteries. This hypothesis is supported by animal studies in which knockdown of CHD7 has been shown to have an effect on pharyngeal arch development [21], [22]. We did not find an indication that truncating mutations in *CHD7* are more likely to be the cause of arch vessel anomalies, as they were present in comparable percentages in our study and control cohort (79% vs. 71%), while they are

known to be present significantly more often in CHARGE patients with a congenital heart defect [3].

CHARGE syndrome is a complex multiple congenital malformation disorder. Children with CHARGE syndrome face significant problems. Feeding problems, chronic aspiration and swallowing dysfunction are often present and can result in recurrent respiratory infections [23], [24]. Identifying the cause of feeding problems in CHARGE syndrome is complex, because they can be associated with structural problems of the oral cavity, the nasal cavity, the pharynx or larynx; cranial nerve defects; congenital heart defects; or a combination of factors. Since respiratory aspiration is a risk factor for early death in CHARGE syndrome, it is important to carefully evaluate feeding problems [25]. A vascular ring, caused by an arch vessel anomaly, may present as feeding problems and respiratory problems. Our study indicates that arch vessel anomalies are often present in patients with molecularly diagnosed CHARGE syndrome, but we could not identify predictive factors for the existence of an arch vessel anomaly, e.g. *CHD7* mutation type or other CHARGE-related congenital malformations. Furthermore feeding problems for which tube feeding was needed doesn't occur more often in patients with arch vessel anomalies (83% range 48–90%) compared to the control population of patients with a *CHD7* mutation (82%, range 32–93%,). However, the medical history described in our case report clearly illustrates that vascular compression due to an arch vessel anomaly should be taken into account in patients with CHARGE syndrome who also have respiratory and/or feeding problems, especially when choking occurs. The exact prevalence of symptomatic vascular compression of the trachea and/or esophagus in CHARGE syndrome needs to be established.

Since 74% of the patients with molecularly proven CHARGE syndrome have a heart defect, an echocardiography is usually performed in CHARGE patients [3]. However, a normal transthoracic echocardiography does not exclude an arch vessel anomaly since its sensitivity for detecting arch vessel anomalies is low [26]. To indicate the presence of a vascular ring, a regular chest X-ray for tracheal compression, and barium contrast esophagography for esophageal compression, respectively, have a higher sensitivity [9], [26]. For identifying the exact morphology of an arch vessel anomaly, non invasive imaging techniques like magnetic resonance imaging and computed tomography are warranted, and they can be used with the same efficiency as invasive angiographic techniques, which has been the gold standard for

decades [9], [27]. The identification of abnormal aortic arch arteries can also be important for asymptomatic CHARGE syndrome patients who need interventional or surgical procedures because routine procedures may be complicated in patients with arch vessel anomalies, e.g., when associated with anomalies of the laryngeal nerve.

Given the high prevalence of arch vessel anomalies in CHARGE syndrome, it remains interesting to study how often patients with arch vessel anomalies have a *CHD7* mutation. Our recent study in 46 patients with syndromic conotruncal heart defects or AVSD, including eight with an arch vessel anomaly, did not identify any pathogenic *CHD7* mutations [28]. In a previous study that focused on the prevalence of bicarotid trunk in patients who underwent cardiac catheterization, genetic syndromes were also assessed; CHARGE syndrome was present in three of the 310 patients (1%) with a bicarotid trunk [29]. A study of 257 patients with a tetralogy of Fallot with pulmonary stenosis showed that the incidence of chromosomal or genetic abnormalities, including CHARGE syndrome, increased significantly in patients who had an aberrant subclavian artery with either a left or right aortic arch [30]. While we don't yet have enough support to advise *CHD7* analysis in all patients with arch vessel anomalies, current studies suggest arch vessel anomalies might be an indicator of CHARGE syndrome. We therefore do advise health care professionals to look carefully for other features of CHARGE syndrome (e.g. external ear anomalies, balance problems, deafness and coloboma) in patients with arch vessel anomalies.

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.

Keywords: Arch vessel anomalies, CHARGE syndrome, *CHD7* gene, Feeding problems, Congenital heart defects, Aberrant subclavian artery

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