Cardiovascular Anomalies in Patients Diagnosed With a Chromosome 22q11 Deletion Beyond 6 Months of Age

Doff B. McElhinney, MD*; Donna McDonald-McGinn, MS‡; Elaine H. Zackai, MD‡; and Elizabeth Goldmuntz, MD*

ABSTRACT. *Objective.* **Cardiovascular anomalies are present in 75% to 80% of patients with a chromosome 22q11 deletion. In the majority of cases, the cardiovascular defect becomes evident in the neonatal period and is often the initial manifestation of the chromosome 22q11 deletion syndrome. However, a 22q11 deletion may also be associated with cardiovascular defects that are less obvious, such as a vascular ring, which may not be diagnosed until the patient is older. The objective of this study was to determine the frequency and types of cardiovascular anomalies in patients diagnosed with a chromosome 22q11 deletion beyond 6 months of age.**

Methods. **We studied 29 patients diagnosed with a chromosome 22q11 deletion at a median age of 6.2 years (9 months to 45 years) who were subsequently referred for cardiovascular evaluation. Comprehensive cardiologic evaluation was performed, with transthoracic echocardiography ($N = 28$) and/or magnetic resonance imaging ($N = 6$), including imaging of the aortic arch. The frequency of cardiovascular anomalies diagnosed in these patients and the need for intervention were assessed.**

Results. **Cardiovascular anomalies were detected in 11 (38%) patients: 3 with a vascular ring formed by a right aortic arch with an aberrant left subclavian artery and left-sided ligamentum arteriosum, 3 with a right aortic arch with mirror-image branching of the brachiocephalic arteries (no vascular ring; 1 with a patent ductus arteriosus), 4 with a left aortic arch with an aberrant right subclavian artery (no vascular ring; 1 with a patent ductus), and 1 with a left superior vena cava draining to the coronary sinus. The median age at diagnosis in these 11 patients was 3 years (9 months to 28 years). The remaining 18 patients had normal cardiovascular anatomy. All 3 patients with vascular rings subsequently underwent surgical repair, and 1 patient with a ductus arteriosus underwent transcatheter coil occlusion.**

Conclusions. **The frequency of cardiovascular anomalies necessitating intervention in patients referred for cardiovascular evaluation after diagnosis of a chromosome 22q11 deletion beyond 6 months of age is 14% in our experience. Routine screening for cardiovascular anomalies, including echocardiography and other imaging studies to identify the laterality and branching pattern of the aortic arch, is indicated in patients diagnosed with 22q11 deletion beyond 6 months of age and is particularly critical for patients with respiratory or feeding disorders.** *Pediatrics* **2001;108(6). URL: http://www.pediatrics.org/cgi/content/full/108/6/e104;** ***velocardiofacial syndrome, DiGeorge syndrome, chromosome 22q11 deletion, vascular ring, aortic arch anomalies.***

ABBREVIATIONS. CHOP, Children's Hospital of Philadelphia; MRI, magnetic resonance imaging.

A chromosome 22q11 deletion has been identified in the majority of patients with DiGeorge syndrome, velocardiofacial syndrome, and conotruncal anomaly face syndrome.[1,2] Among the wide range of phenotypic features in patients with a chromosome 22q11 deletion, congenital anomalies of the cardiovascular system are the most common, occurring in 75% to 80% of patients, and often are the first clinically apparent feature of the chromosome 22q11 deletion syndrome.[1,2] The most common cardiovascular anomalies in patients with a chromosome 22q11 deletion include tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, and ventricular septal defect, which generally come to clinical attention early in life.[1,2] However, patients with a chromosome 22q11 deletion are also diagnosed later in life. Patients diagnosed with a 22q11 deletion at a later age are less likely to have major congenital cardiovascular anomalies but may have significant defects that warrant intervention, such as anomalies of the aortic arch[3] or an atrial septal defect. Moreover, certain presenting complaints may result from any of several different anomalies often seen in the deleted patient population. For example, feeding difficulties and respiratory symptoms are common in patients with a chromosome 22q11 deletion. Multiple anomalies, including frequent infections (immunodeficiency), reactive airway disease, palatal anomalies, laryngeal anomalies, swallowing dysfunction, and vascular rings, might contribute to these symptoms and may be difficult to distinguish clinically.

These factors give rise to an important clinical question: Should older patients who are diagnosed with a chromosome 22q11 deletion but have no known cardiovascular disease undergo routine screening by a cardiologist to assess for cardiovascular anomalies? To address this question, we reviewed our experience with 29 patients without known cardiovascular anomalies who were diagnosed with a chromosome 22q11 deletion beyond 6 months of age

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and were subsequently referred for cardiovascular evaluation.

PATIENTS AND METHODS

Patients

Patients were included in the study if they were diagnosed with a chromosome 22q11 deletion beyond 6 months of age, had no known congenital cardiovascular anomalies before identification of the 22q11 deletion, and were subsequently referred by the genetics service or the Chromosome 22q11 Center at the Children's Hospital of Philadelphia (CHOP) to the CHOP cardiology clinic as part of their routine and complete evaluation. Patients were still considered eligible if they were first seen by a cardiologist elsewhere (after the 22q11 deletion was identified) and underwent additional cardiac evaluation at CHOP. We reviewed the clinical database of the Chromosome 22q11 Center at CHOP and identified 29 patients who met these inclusion criteria.

Cytogenetic Evaluation

Patients were diagnosed with a chromosome 22q11 deletion at a median age of 6.2 years (9 months to 45 years). Figure 1 summarizes the breakdown of patients by age at the time the chromosome 22q11 deletion was diagnosed. In the majority of patients, several factors led to genetic evaluation and ultimately the diagnosis of a chromosome 22q11 deletion (Table 1). In general, the most common reasons for screening in patients <2 years of age were nasogastric regurgitation or other feeding problems, developmental delay, and frequent upper respiratory infections. In patients diagnosed between 2 and 10 years of age, the most common indications for cytogenetic evaluation were speech problems and chronic otitis media. In older children and adolescents, learning and speech abnormalities were the most common indications for deletion screening. Both patients over 20 years of age were screened because they had a child diagnosed with a chromosome 22q11 deletion.

The chromosome 22q11 deletion was identified by fluorescence in situ hybridization of metaphase chromosomes from peripheral blood lymphocytes using the commercially available Vysis (Downers Grove, IL) cosmid probe N25 (D22S75) and control probe pH17 (D22S39), as previously described.[4]

Cardiovascular Evaluation

Study patients were examined by an attending pediatric cardiologist at CHOP at a median age of 6.6 years (9 months to 45 years). The examination included an electrocardiogram and a complete echocardiogram ($N = 28$), which evaluated the intracardiac anatomy and the laterality and branching pattern of the aortic arch. Thoracic magnetic resonance imaging (MRI) was performed in 6 patients, 1 of whom did not undergo previous echocardiography because a right aortic arch was identified on chest radiography. Clinical records and diagnostic studies were reviewed.

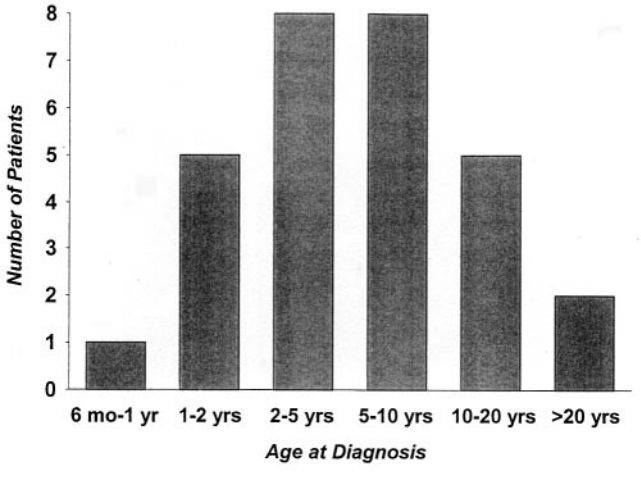

Fig 1. Breakdown of patients according to the age at the time the chromosome 22q11 deletion was diagnosed.

TABLE 1. Phenotypic and Historical Factors Cited as Indications for Deletion Screening in 29 Patients Diagnosed With a Chromosome 22q11 Deletion Beyond 6 Months of Age

Phenotypic or Historical Factor*	Number of Patients
Speech delay or abnormality	14
Developmental delay or mental retardation	9
Chronic otitis media	8
Chronic respiratory symptoms	8
Nasopharyngeal reflux or other feeding problems	7
Learning delay or disability	5
Abnormal facies	3
Submucosal cleft palate	3
Laryngeal web	3
Parent of a child with chromosome 22q11 deletion	2
Seizures	2
Hypertonia or hypotonia	2
Medially displaced carotid arteries noted during removal of tonsils and adenoids	1
Behavior problems	1
Gastroesophageal reflux	1
Craniosynostosis	1
Intestinal pseudoobstruction	1

* Multiple factors were cited for most patients.

RESULTS

By clinical history, symptoms consistent with a vascular ring were noted in 12 patients, including respiratory symptoms in 8 and feeding abnormalities in 6 (both were present in 2 patients). On physical examination, a systolic ejection murmur was auscultated in 11 patients. In 9 of these, the murmur was grade 1/6 or 2/6 and felt to be clearly innocent. In 2 patients, a grade 3/6 murmur was heard and assessed as probably innocent but sufficiently atypical to warrant echocardiographic evaluation.

In all 29 patients, the intracardiac anatomy was normal by echocardiographic or MRI imaging (Fig 2). In 18 patients, the anatomy of the thoracic vessels was also normal (left-sided aortic arch with a normal branching pattern and a single right-sided superior vena cava). In the remaining 11 patients (38%), anomalies of the thoracic vessels were detected. One of these patients was found to have a left-sided superior vena cava draining to the coronary sinus, and 10 were diagnosed with congenital anomalies of the aortic arch system (Fig 2, Table 2). A vascular ring (right aortic arch with an aberrant retroesophageal left subclavian artery and left-sided ligamentum arteriosum to the left pulmonary artery) was diagnosed in 3 of the 10 patients with aortic arch anomalies. These 3 patients had evidence of tracheal compression on MRI. The remaining 7 patients with arch anomalies did not have a vascular ring but had either a right aortic arch with mirror-image branching of the brachiocephalic arteries ($N = 3$) or a left aortic arch with an aberrant retroesophageal right subclavian artery ($N = 4$). Two of these patients also had a small patent ductus arteriosus not identified previously (1 right-sided and 1 left-sided).

Five of the 10 patients with arch anomalies, including all 3 with vascular rings, had a history of symptoms that were consistent with a ring (respiratory symptoms in 3, feeding abnormalities in 1, and both

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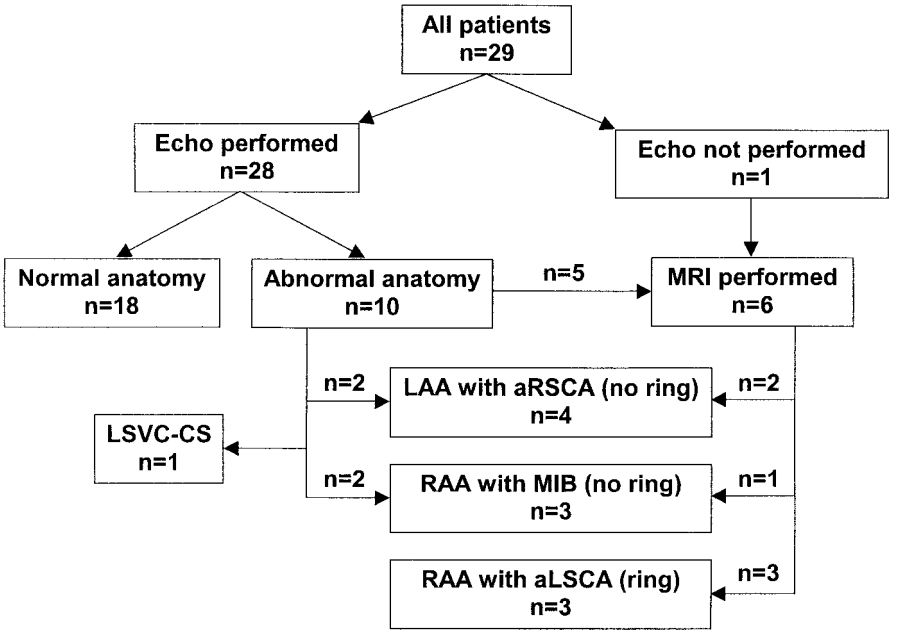

Fig 2. Imaging studies performed and cardiovascular anomalies detected in 29 patients diagnosed with a chromosome 22q11 deletion beyond 6 months of age. aLSCA, aberrant left subclavian artery; aRSCA, aberrant right subclavian artery; Echo, echocardiogram; LAA, left aortic arch; LSVC-CS, left superior vena cava draining to the coronary sinus; RAA, right aortic arch.

TABLE 2. Cardiovascular Anomalies Detected in 29 Patients Diagnosed With a Chromosome 22q11 Deletion Beyond 6 Months of Age

Cardiovascular Anomaly	Number of Patients	Age at Diagnosis (Years)
Right aortic arch with aberrant left subclavian artery and left-sided ligamentum arteriosum (vascular ring)	3	0.8, 2.6, 3.1
Right aortic arch with mirror image branching of the brachiocephalic vessels (no ring)*	3	1.4, 2.1, 17
Left aortic arch with aberrant right subclavian artery (no ring)‡	4	1, 1.8, 5.2, 27
Left superior vena cava draining to the coronary sinus	1	1.3

* One of these patients also had a patent right-sided ductus arteriosus and underwent transcatheter coil occlusion.
‡ One of these patients also had a small patent left-sided ductus arteriosus that has not yet prompted intervention.

in 1). The age at diagnosis of the 10 patients with arch anomalies ranged from 9 months to 28 years (median 3 years). Among the patients with anomalies of the aortic arch, those with a vascular ring were diagnosed at the early end of this spectrum (9, 31, and 37 months of age).

The 5 patients who underwent MRI after echocardiography all had aortic arch anomalies. The MRI was performed to define the aortic arch branching pattern, which had been identified on the echocardiogram but warranted additional definition or confirmation before intervention.

Overall, 4 (14%) of the 29 patients subsequently underwent cardiovascular intervention. All 3 patients with vascular rings underwent surgical division, and the patient with a right-sided patent ductus arteriosus underwent transcatheter coil occlusion. The other 5 patients with aortic arch anomalies and the patient with a left-sided superior vena cava did not need intervention.

DISCUSSION

Cardiovascular anomalies are present in >75% of patients with a chromosome 22q11 deletion.[1,2] In the majority of cases, the cardiovascular defect becomes evident in the neonatal period and is often the initial manifestation of the chromosome 22q11 deletion syndrome. Cardiovascular anomalies often associated with a chromosome 22q11 deletion include tetralogy of Fallot with or without pulmonary atresia, interrupted aortic arch, truncus arteriosus, and isolated aortic arch anomalies.[1–4] At many centers, identification of any of these defects prompts deletion screening, which is responsible for detecting a substantial percentage of patients with a chromosome 22q11 deletion.

The question this study was designed to address is whether patients diagnosed with a chromosome 22q11 deletion beyond the early infant period should undergo routine screening by a cardiologist to assess for previously undetected cardiovascular anomalies. In our evaluation of 29 patients referred to the cardiology clinic after 6 months of age, after diagnosis of a chromosome 22q11 deletion, we found congenital cardiovascular anomalies in 11 (38%). In particular, 3 patients had vascular rings, 7 had arch anomalies that did not form rings, 2 had a patent ductus arteriosus in addition to arch anomalies, and 1 had a left superior vena cava draining to the coronary sinus. Four of these 11 patients, or 14% of the inception cohort, underwent surgical or transcatheter intervention for their anomaly. These findings suggest that cardiovascular screening with echocardiography or MRI, including evaluation of the aortic arch, is warranted in patients diagnosed with a chromosome 22q11 deletion beyond early infancy. A complete

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cardiovascular evaluation is particularly important in children with respiratory or feeding disorders.

In this study, cardiovascular anomalies in patients diagnosed with a chromosome 22q11 deletion beyond infancy generally were limited to the aortic arch. Symptoms of vascular rings or occasionally arch anomalies that do not form rings (eg, left aortic arch with aberrant right subclavian artery) may include feeding or swallowing abnormalities, chronic upper or lower respiratory infections, or respiratory symptoms such as noisy breathing, increased work of breathing (which may be interpreted as reactive airway disease), and a chronic cough. These symptoms are common in patients with a chromosome 22q11 deletion and may be caused by a variety of anomalies that occur in the chromosome 22q11 deletion syndrome. Thus, the diagnosis of a vascular anomaly in this patient cohort can be difficult to make on the basis of the clinical history alone. This supports the importance of cardiovascular screening, with clear definition of aortic arch sidedness and branching pattern in patients diagnosed with a chromosome 22q11 deletion beyond the early infant period.

The clinical value of identifying thoracic vascular anomalies that do not form a vascular ring in asymptomatic patients is arguable. Patients with such abnormalities, which have been found in autopsy and imaging studies to occur in 0.2% to 0.7% of people without known cardiovascular anomalies, may remain asymptomatic throughout their lives.[5,6] However, some arch anomalies that do not produce vascular rings may ultimately have important clinical implications.[7] For instance, a left aortic arch and aberrant right subclavian artery can cause dysphagia because of esophageal compression later in life.[8] Moreover, a retroesophageal right subclavian artery may be prone to degenerative pathologic processes at the point where it passes between the esophagus and the vertebral column or to traumatic injury at its origin from the aorta.[9,10] This anomaly may also have implications for patients undergoing thyroid or other neck surgery because the right inferior laryngeal nerve, which normally loops around the proximal right subclavian artery to assume its recurrent course, runs transversely from its cervical vagal origin to the cricothyroid membrane.[11]

CONCLUSION

Our findings indicate that routine assessment for cardiovascular defects, including aortic arch anomalies, is warranted in patients diagnosed with a chromosome 22q11 deletion beyond infancy. Cardiovascular assessment of aortic arch anatomy is particularly critical in the patient with a chromosome 22q11 deletion and respiratory or feeding disorders. Although the majority of vascular rings produce symptoms of central airway or esophageal compression in infancy, symptoms may become manifest at any age. Alternatively, symptoms may be subtle or atypical, or they may be misinterpreted, as documented in reports of vascular rings detected in adulthood after long-term treatment for assumed reactive airway disease.[12] Thus, particular attention should be given to determining the laterality and branching pattern of the aortic arch. In older children, adolescents, and adults, clear and complete imaging of the aortic arch sometimes is difficult to achieve with echocardiography alone, and MRI may be necessary. In a completely asymptomatic older patient, however, echocardiographic identification of a left aortic arch without clear delineation of the branching pattern may be adequate because vascular rings with a left aortic arch are extremely rare.

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