European Journal of Medical Genetics 58 (2015) 75–85

Contents lists available at ScienceDirect

European Journal of Medical Genetics

journal homepage: http://www.elsevier.com/locate/ejmg

Clinical research

Associated noncardiac congenital anomalies among cases with congenital heart defects

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ARTICLE INFO

Article history:
Received 13 August 2014
Accepted 3 December 2014
Available online 12 December 2014

Keywords:
Congenital heart defects
Congenital heart disease
Cardiac anomalies
Noncardiac anomalies
Syndromes
Surveillance
Ascertainment
Etiology

ABSTRACT

Cases with congenital heart defects (CHD) often have other associated anomalies. The purpose of this investigation was to assess the prevalence and the types of associated anomalies in CHD in a defined population. The anomalies associated with CHD were collected in all live births, stillbirths and terminations of pregnancy during 26 years in 346,831 consecutive pregnancies of known outcome in the area covered by our population based registry of congenital anomalies. Of the 4005 cases with CHD born during this period (total prevalence of 115.5 per 10,000), 1055 (26.3%) had associated major anomalies. There were 354 (8.8%) cases with chromosomal abnormalities including 218 trisomies 21, and 99 (2.5%) nonchromosomal recognized dysmorphic conditions. There were no predominant recognized dysmorphic conditions, but VACTERL association. However, other recognized dysmorphic conditions were registered including Noonan syndrome, fetal alcohol syndrome, and skeletal dysplasias. Six hundred and two (15.0%) of the cases had non syndromic, non chromosomal multiple congenital anomalies (MCA). Anomalies in the urinary tract, the musculoskeletal, the digestive, and the central nervous systems were the most common other anomalies. Prenatal diagnosis was obtained in 18.7% of the pregnancies. In conclusion the overall prevalence of associated anomalies, which was one in four infants, emphasizes the need for a thorough investigation of cases with CHD. A routine screening for other anomalies may be considered in infants and in fetuses with CHD. One should be aware that the anomalies associated with CHD can be classified into a recognizable anomaly, syndrome or pattern in one out of nine cases with CHD.

1. Introduction

Studies of other defects associated with specific congenital anomalies may be helpful to understand embryonic development, identify the causes of congenital anomalies, determine recurrence risks, and guide expectations for the efficacy of prevention strategies [Stevenson et al., 2004]. Congenital heart defects are one of the most common congenital anomaly, representing approximately 45% of all prenatally diagnosed anomalies [Stoll et al., 2001] with a reported rate per 10,000 live births or total births varying from 43 to 124 [Lowry et al., 2013]. CHD occur in as many as 1 in 100 live births and in 1 in 500 fetal ultrasonographic examination [Meberg et al., 2007; Tegnander et al., 2006]. Many cases with CHD will have a coexisting defect involving noncardiac structures. Individual cases of CHD may differ widely in their cause. Specific genetic factors, such as chromosomal abnormalities and inherited mutations in developmental genes, or environmental influences on fetal development i.e. medications [Stoll et al., 1989] may form the underlying cause.

Although it has long been known that CHD are frequently associated with other congenital anomalies, their reported frequency and the type of associated anomalies observed vary considerably among different studies. Using data from our surveillance system of congenital anomalies over a 26-year period, we evaluated the nature and frequency of anomalies associated with CHD to identify recognizable conditions and specific patterns of associated anomalies, which could give hints about the pathogenesis of CHD.

2. Material and methods

Cases with anomalies for this study were derived from 346,674 consecutive pregnancies of known outcome, including live births and stillbirths, and 157 terminations of pregnancy for fetal

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http://dx.doi.org/10.1016/j.ejmg.2014.12.002
1769-7212/

abnormality regardless of gestational age, registered by our registry of congenital anomalies described previously [Stoll and Roth, 1985]. Minor anomalies were excluded according to EUROCAT [2009] guidelines for registration of congenital anomalies (http://www.eurocat-network.eu). Cases born in 11 maternity hospitals were examined from January 1, 1979 to December 31, 2004. The region of investigation was the city of Strasbourg, France (an urban area), and the area defined by the Departement du Bas-Rhin, in which Strasbourg is situated (a rural area). Newborn pulse oximetry screening was not used in the region under study. All newborns were registered within the first 8 days postpartum, as were all fetuses aborted because of anomalies discovered at prenatal diagnosis. As everywhere in our country, no delivery took place at home in the area under study. All cases with CHD and associated anomalies, live births, stillbirths and elective terminations of pregnancy for fetal anomaly were examined by a clinical geneticist. CHD diagnoses were confirmed by echocardiography, cardiac catheterization, surgery and/or autopsy. Common to most studies, patent ductus arteriosus was included in full-term infants in whom the defect persisted for a minimum of 3 months or required surgery. Patent foramen ovale versus atrial septal defect (ASD) was excluded in full-term infants if closed within 3 months or was <3 mm with normal ventricular dimensions. Cardiomyopathy was excluded, as well as anomalies identified prenatally without postnatal confirmation [Lowry et al., 2013]. CHD cases were classified according to the literature [Bosi et al., 1999; Botto et al., 2007; Ferencz and Correa-Villasenor, 1991; Kirby, 1987; Pexieder and Bloch, 1995; Riehle-Colarusso et al., 2007] into: septal (ASD and ventricular septal defect (VSD)); conotruncal (d-transposition of the great arteries (TGA), tetralogy of Fallot (TOF)); atrioventricular septal defect (AVSD); left ventricular outflow tract obstruction (LVOTO; hypoplastic left heart syndrome (HLHS), coarctation of aorta (CoA), aortic stenosis/atresia(AS)); right ventricular outflow tract obstruction (RVOTO; pulmonary stenosis/atresia (PS), tricuspid stenosis/atresia (TS)); single ventricle (SV); heterotaxy; association (a child with more than one heart lesion was classified in the category associated CHD as for example conotruncal with AVSD, pulmonary stenosis with septal defect, and aortic stenosis with septal defect [Lowry et al., 2013]), and other CHDs (patent ductus arteriosus, aortopulmonary septal defect, anomalous pulmonary venous return, double outlet right ventricle, double outlet left ventricle, truncus arteriosus, interrupted aortic arch, bicuspid aortic valve, vascular ring, and Ebstein anomaly).

When a suspected or confirmed case was reported, information was obtained from all available records including prenatal consultation records, maternity files, neonatal unit files, autopsy reports, outpatient clinic files, pediatric and pediatric surgery files. Surveillance for anomalies continued until 2 years of age. For each case, a complete description was obtained, including photographs, radiographs, ultrasonographic examination, and karyotype. However, this study was performed before the array CGH technology was available. Cases with CHD were divided into two groups: isolated when only CHD were present, and associated when one or more additional major anomalies were recognized. The cases with associated anomalies were subdivided into those with recognizable conditions (chromosomal or nonchromosomal) and those without recognizable conditions (cases with multiple congenital anomalies – MCA- and in whom the associated anomalies were classified according to the organ system primarily affected) [Stoll et al., 1989]. Major non cardiac anomalies within a system were counted as one defect. For example, a case with hydronephrosis and kidney agenesis was counted once as kidney agenesis and a case with omphalocele, intestinal atresia, and malrotation was counted once as omphalocele [Lowry et al., 2013]. A case with a Mendelian disorder that includes multiple anomalies e.g., Noonan syndrome (OMIM 163950) was classified as having a recognizable nonchromosomal condition.

The identification of specific patterns of anomaly varies among different programs, depending on their ability to recognize particular patterns of anomaly. Typical examples are the VACTERL association and the CHARGE syndrome. These problems were discussed by Källen et al. [1999; 2001].

3. Results

During the 26-year study period, 4005 infants with CHD were registered. Therefore, the total prevalence is 115.5 per 10,000 (Table 1). No trends in the frequency of CHD were noted during the time frame of the study. The early incidence of CHD over the period 1979 through 2004 was 115.5. Within the period the incidence varied from 97.9 in 1985 to 118.9 in 2001. The distribution and the prevalence of CHD in all malformed cases with CHD, in cases with isolated CHD and in cases with associated non-CHD anomalies as well as the sex ratio are shown on Table 2.

3.1. Associated anomalies

Of the 4005 cases with CHD, 2950 (73.6%) did not have other major congenital anomalies (isolated CHD) and 1055 (26.3%) had in addition non cardiac major anomalies (associated CHD; Table 1). In the group of associated CHD, 354 (8.8%) cases had chromosomal anomalies, 99 (2.5%) cases had nonchromosomal recognizable conditions, and 602 (15.0%) cases had multiple malformations without a recognized condition (MCA). These 602 cases had 1197 anomalies, as some children had anomalies in more than one site.

Table 3 shows the recognizable and non recognizable conditions in 1055 cases with associated CHD.

Three hundred fifty four cases had chromosomal abnormalities including 218 trisomies 21, 53 trisomies 18, 22 trisomies 13, 20 autosomal deletions including 14 22q11.2 deletions, 10 Turner syndrome, 2 triploidies, 15 unbalanced translocations, 3 autosomal duplications, and 11 other chromosomal abnormalities (Table 3). Among the 99 cases with recognizable nonchromosomal conditions (Table 3), VACTERL association (23%), Noonan syndrome (8%), fetal alcohol syndrome (7%), and skeletal dysplasias (6%), were most often present. Among the 602 cases with associated anomalies classified as nonrecognizable conditions, MCA, the most frequent anomalies were renal anomalies, musculoskeletal anomalies, digestive system anomalies, ear, face and neck anomalies, central nervous system anomalies, genital anomalies, abdominal wall anomalies, eye anomalies and cleft lip/palate (Table 3).

Prenatal diagnosis was obtained in 18.7% of the pregnancies. However, when the study period was subdivided into three parts, 1979–1988, 1989–1993, 1994–2004, prenatal diagnosis was

Table 1
Isolated and associated anomalies in 4005 cases with congenital heart defects ascertained from 1979 to 2004 in 346,831 consecutive pregnancies in Northeastern France.

	N°	%	Prevalence[a]
Associated malformations			
Recognized patterns[b]	99	2.5	2.8
Unrecognized Patterns of MCA[c]	602	15.0	17.4
Sub total	701	17.5	20.2
Chromosomal	354	8.8	10.2
Total Associated	1055	26.3	30.4
Isolated malformation	2950	73.6	85.0
Total	4005	100	115.5

[a] Total prevalence per 10,000 pregnancies.
[b] Includes syndromes, associations, sequences and spectrums.
[c] MCA: multiple congenital anomalies.