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Ischemic heart disease in children and young adults with congenital heart disease in Sweden

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ABSTRACT

Background: An increasing proportion of congenital heart disease (CoHD) patients survive to an age associated with increased risk of developing ischemic heart disease (IHD). The aim was to investigate the risk of developing IHD among children and young adults with CoHD.
Methods: Using the Swedish National Patient Register, we created a cohort of all CoHD patients born between January 1970 and December 1993. Ten controls matched for age, sex, county were randomly selected from the general population for each patient (n = 219,816). Patients and controls were followed from birth until first IHD event, death, or December 31, 2011.
Results: We identified 21,982 patients with CoHD (51.6% men), mean follow-up was 26.4 (21.2–33.9) years. CoHD patients had 16.5 times higher risk of being hospitalized with or dying from IHD compared to controls (95% CI: 13.7–19.9), p < 0.0001. Patients with conotruncal defects and severe nonconotruncal defects, had the highest IHD incidence rate (71.1 and 56.3 cases per 100,000 person-years, respectively, compared to 2.9 and 2.3 in controls). Hypertension and diabetes were less common among CoHD patients with IHD than among controls with IHD (hypertension 9.7% vs 19.7%, diabetes 1.8% vs 7.7% in CoHD patients and controls). Patients with aortic coarctation did not have a specific increase in the risk of developing IHD or acute myocardial infarction.
Conclusions: In this large case-control cohort study, the relative risk of developing IHD was markedly higher in CoHD patients than in controls. However, the absolute risk was low in both groups.

1. Introduction

Congenital heart disease (CoHD) is one of the most common congenital malformations in newborns and occurs in about 1% of live births [1]. Currently, >90% of children with CoHD reach adulthood and the number of adults with CoHD is constantly growing as a result of the advances in both surgical and medical management in patients with CoHD over recent decades [2–6]. However, increasing survival and median age in patients with CoHD will result in an increased risk of developing acquired heart conditions such as ischemic heart disease (IHD), including acute myocardial infarction (AMI) [7,8].

IHD in patients with CoHD may have several causes: conventional cardiovascular risk factors have been implicated as the major cause of coronary artery disease in adult patients with CoHD [4]; anomalous coronary anatomy may be an important contributor [5]; and surgical transposition of coronary arteries, with increased risk of postoperative stenosis, may potentially promote early atherosclerosis and premature coronary artery disease [9]. In addition, shunting with paradoxical embolism to the coronary arteries may be a possible cause of AMI in patients with CoHD [10].

The overall prevalence of coronary artery disease in adults with CoHD, as determined by coincidental and/or preoperative coronary angiography, varied between 1% in a large registry study [8] to 9.2% in a single-center study [11]. In the United States, coronary artery disease is now the most common cause of death in adult patients with non-cyanotic heart defects [12]. Because of the major clinical implications of coronary artery disease such as IHD, the large discrepancies in the reported prevalence in adults with CoHD call for further studies on this matter. The aim of our study was, therefore, to investigate the risk of IHD in children and young adults with CoHD compared to matched controls.

Abbreviations: AMI, acute myocardial infarction; ASD, atrial septal defect; CI, confidence interval; CoA, coarctation of the aorta; CoHD, congenital heart disease; HR, hazard ratio; IHD, ischemic heart disease; VSD, ventricular septal defect.

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2. Methods

2.1. Study population

In the present study, we used linked data from the Swedish National Inpatient Register, the Swedish National Outpatient Register, and Cause of Death Register. The Swedish National Inpatient Register was initiated in 1964 with full national coverage from 1987 onwards. It is mandatory for all health care providers to report discharge diagnoses to the register. From 1970 onwards the register contains data from all hospitals performing cardiothoracic surgeries, and from 2001 it also contains data on all hospital outpatient visits, both in the public and the private sector. Currently, >99% of all discharge diagnoses are recorded in the Swedish National Inpatient Register [13].

From the Swedish National Inpatient Register, Swedish National Outpatient Register and the Cause of Death Register we identified 21,982 patients who were born between January 1970 and December 1993 and who had a diagnosis of CoHD as a principal or contributory diagnosis at any time until December 2011. 115 CoHD patients (0,52%) were identified from the Cause of Death Register only.

We collected follow-up data on first IHD event for all patients until death, emigration, or the end of the study (December 31, 2011). We also included in the study the following comorbidities diagnosed prior or coinciding with the index IHD event: hypertension, diabetes mellitus, atrial fibrillation, and congestive heart failure.

Each patient with a CoHD diagnosis was matched with 10 individuals from the general population without CoHD. Matching was by sex, age, and county of residence. For four of the CoHD patients, only nine controls were available for matching.

All diagnoses were coded according to the International classification of Disease (ICD) 8th, 9th, and 10th editions. For ICD-8 and ICD-9 editions, the Swedish ICD version was used. The study population has been described previously [6].

2.2. Definitions

The list of all CoHD diagnoses is described in Supplementary Table 1. All diagnoses were made by the discharging physician, using international standards and definitions such as the WHO-definition of acute myocardial infarction. IHD was defined as codes 410–414 in ICD-8 and ICD-9 and as codes I20–I25 in ICD-10. Myocardial infarction was defined as code 410 in ICD-8 and ICD-9 and as code I21 in ICD-10. Hypertension was defined as codes 401–405 (ICD-8 and ICD-9) or I10–I15 (ICD-10). Diabetes mellitus was defined as code 250 (ICD-8 and ICD-9) or codes E10–E14 (ICD-10). Atrial fibrillation was defined as code 427.92 (ICD-8) or 427D (ICD-9) or I48 (ICD-10). Congestive heart failure was defined as code 427.00 (ICD-8) or 428 (ICD-9) or I50 (ICD-10).

2.3. CoHD classification

The CoHD diagnoses were classified according to a hierarchical classification system described by Liu et al. [14] and used in published studies [15–17]. Lesion group 1, “conotruncal defects”, was defined as common truncus, aortopulmonary septum defect, transposition of great vessels, and tetralogy of Fallot. Lesion group 2, “severe nonconotruncal defects”, was defined as endocardial cushion defects, common ventricle, and hypoplastic left heart syndrome. Lesion group 3, “CoA”, was defined as coarctation of the aorta and lesion group 4, “VSD”, included ventricular septal defect and other defects of the cardiac septum. Lesion group 5, “ASD”, was defined as atrial septal defect, and lesion group 6 included all other heart and circulatory system anomalies and all CoHD diagnoses not included in the five groups above. Supplementary Table 2 shows the ICD-8, ICD-9, and ICD-10 diagnoses for the CoHD classification.

2.4. Ethical approval

All national registration numbers were removed and replaced with a code in the final data set by the National Board of Health and Welfare in Sweden. The study complied with the Declaration of Helsinki and was approved by the Gothenburg Regional Research Ethics Board.

2.5. Statistics

Descriptive statistics were used to present the characteristics of the study population at birth. Percentages of patients and controls who were diagnosed with risk factors for IHD (hypertension and diabetes) before and up to the date of their IHD diagnosis were calculated, as well as percentages with other cardiac comorbidities (atrial fibrillation and congestive heart failure). Hazard ratios (HRs) and 95% confidence intervals (CIs) were estimated from a Cox regression model controlling for age and sex, in order to compare rates of developing IHD between cases and controls during the follow-up period. The time scale in our model was age. Those who had emigrated or were still alive at 31 December 2011 were censored, as were those who had a non-IHD-related cause of death. Cumulative incidence functions of IHD are presented for different birth periods and for cases and controls separately. Death from non-IHD-related causes is the competing event. p-Values <0.05 were considered statistically significant. We used SAS software (version 9.4; SAS Institute, Cary, NC, USA) and R software (version 3.1; R Foundation for Statistical Computing, Vienna, Austria) to perform all statistical analyses.

3. Results

We identified a total of 21,982 patients with CoHD (51.6% men) and 219,816 controls born between January 1970 and December 1993. The characteristics of the CoHD population and controls are shown in Supplementary Table 3. The median and mean age at CoHD diagnosis as indicated by the Swedish Patient Register was 4.2 (interquartile range 17.1) and 9.6 (standard deviation $\pm$11.3) years, respectively.

3.1. Risk of ischemic heart disease and acute myocardial infarction

Table 1 shows that the risk in all CoHD patients of being diagnosed with IHD was 16.5 times higher than in controls (95% CI: 13.7–19.9), $p < 0.0001$. A higher proportion of controls than CoHD patients were diagnosed with IHD in hospital outpatient clinics (controls: 23.5%, n = 43/183; CoHD patients: 18.0%, n = 50/278). 13 (4.7%) CoHD patients with IHD in our cohort were identified from the Cause of Death Register compared to 6 controls (3.3%).

Approximately one third of CoHD patients who were diagnosed with IHD had AMI as their first IHD event (33.5%, n = 93/278), which was similar to controls (30.1%, n = 55/183). For controls with a diagnosis of IHD, the prevalence of angina pectoris as the first IHD event was higher than for CoHD patients (controls: 33.9%, n = 62/183; CoHD patients: 21.2%, n = 59/278). More CoHD patients with angina were diagnosed in hospital based outpatient clinics compared to controls with angina (CoHD patients: 27.1%, n = 16/59; controls: 22.6%, n = 14/62). Female, compared to male sex was associated with a lower risk of IHD in both groups (CoHD patients: HR 0.74, CI 0.59–0.94; controls: HR 0.79, CI 0.59–1.1).

Overall, the incidence rates of IHD and AMI were much higher in the CoHD group than in the control group. Patients with the most complex congenital heart conditions, conotruncal defects and severe nonconotruncal defects (lesion groups 1 and 2), had the highest incidence rate of IHD, with 71.1 and 56.3 cases per 100,000 person-years, respectively. Patients with ventricular septal defect, who constituted almost one fifth of the CoHD population (19.9%), had the lowest incidence rate of IHD, with 31.2 IHD cases per 100,000 person-years.

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