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Burden and impact of congenital syndromes and comorbidities among adults with congenital heart disease

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ABSTRACT

Background: Our aim was to assess the overall burden of congenital syndromes and non-cardiac comorbidities among adults with congenital heart disease and to assess their impact on circumstances of living and outcomes.
Methods: Within a cohort of 1725 adults with congenital heart defects (65% defects of moderate or great complexity) followed at a single tertiary care center, congenital syndromes and comorbidities were identified by chart review. Their association with arrhythmias, circumstances of living and survival was analyzed.
Results: Within the study cohort, 232 patients (13%) had a genetic syndrome, 51% at least one comorbidity and 23% ≥2 comorbidities. Most prevalent comorbidities were systemic arterial hypertension (11%), thyroid dysfunction (9%), psychiatric disorders (9%), neurologic disorders (7%), chronic lung disease (7%), and previous stroke (6%). In contrast to higher congenital heart defect complexity, the presence of comorbidities had no impact on living circumstances but patients with comorbidities were less likely to work full-time. Atrial arrhythmias were more common among patients with moderate/great disease complexity and those with comorbidities but were less common among patients with congenital syndromes ($p < 0.01$ for all comparisons). Patients with ≥2 comorbidities had lower survival estimates compared to those with ≤1 comorbidity ($p = 0.013$).
Conclusion: Congenital syndromes and comorbidities are highly prevalent in adults with congenital heart disease followed at specialist centers and add to the overall complexity of care. The presence of these additional factors has an impact on living circumstances, is associated with arrhythmias and needs to be further explored as prognostic markers.

1. Introduction

With improved surgical techniques and improved cardiology care the majority of patients born with congenital heart defects now survive to adulthood [1]. This includes patients with various forms of congenital syndromes known to be associated with congenital heart defects such as chromosomal abnormalities (e.g. trisomy 21, Turner syndrome or 22q11.2 microdeletion syndrome), single gene mutations (e.g. Holt-Oram syndrome or Marfan syndrome) or syndromes caused by exogenous factors (e.g. congenital rubella syndrome) or syndromic associations of unknown etiology (e.g. VACTERL association). Apart from their cardiac manifestations, all syndromes are associated with typical non-cardiac abnormalities. [2–4] Apart from these extracardiac comorbidities in patients with congenital syndromes, cardiac and extracardiac comorbidities in adult survivors with congenital heart disease without concomitant congenital syndromes have been increasingly recognized as important modifiers of outcome. [5] These comorbidities may be a consequence of the underlying heart defect (e.g. liver problems in Fontan patients), a sequelae of previous interventions (e.g. perioperative ischemic strokes after open heart surgery) or a consequence of medical treatment (e.g. thyroid dysfunction on treatment with amiodarone).

The overall burden of non-cardiac comorbidities in adults with congenital heart disease with or without syndromic association and its impact on social well-being and survival has not been investigated.

The aims of this study are therefore (1) to describe the frequency of congenital syndromes and the frequency of cardiac and non-cardiac comorbidities in a cohort of adults with congenital heart disease, followed at a tertiary care center, (2) to assess the association between the

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presence of congenital syndromes and comorbidities with living circumstances and employment status, and (3) to evaluate the association between congenital syndromes, comorbidities and survival estimates.

2. Methods

2.1. Study population

All patients with congenital heart disease followed by our specialized multidisciplinary team for adults with congenital heart disease at a single tertiary care center between 1996 and 2015 were identified from the administrative database.

2.2. Data abstraction and analysis

Our clinic letters follow a strict pre-defined design, including the following items: 1) exact cardiac anatomy, previous surgical and interventional procedures, 2) previous cardiac complications, (e.g. arrhythmias, defined as sustained atrial arrhythmias, sustained ventricular arrhythmias or ≥grade 2 atrioventricular block, heart failure, endocarditis and stroke), 3) important non-cardiac diagnoses, including: congenital syndromes, congenital hearing disorders/deafness, systemic arterial hypertension (defined as blood pressure measurements >140 mmHg systolic and/or >90 mmHg diastolic on 2 separate occasions, or use of antihypertensive drugs for treatment of systemic arterial hypertension), obesity, diabetes mellitus, coronary artery disease, gout, previous or current malignancies, neurologic disorders (e.g. epilepsy, migraine headaches), psychiatric disorders, lung disease (including sleep apnea), renal dysfunction, hepatic disease, thyroid dysfunction, previous thromboembolic complications, infectious diseases (e.g. HIV-infection, chronic hepatitis B or C) and other important chronic conditions as well as the current employment status and living circumstances.

For the purpose of this study, data were abstracted from clinic letters and chart review. Congenital cardiac defects were classified as simple, of moderate complexity and of great complexity (modified from previously proposed classification) [6]. For comparison between groups, congenital cardiac defects were divided into simple defects and defects of moderate and great complexity. Whether the diagnosis of a congenital syndrome was made from clinical examination by a geneticist and/or confirmed by genetic testing was not specified. Information about employment status and living circumstances were abstracted from administrative data and from clinic letters. Survival status was derived from the administrative database, which is regularly updated. Survival analysis was confined to survival free from cardiac transplantation or all-cause mortality. The study was approved by the local medical ethics board.

2.3. Statistical analysis

Statistical analysis was performed using SPSS version 19.0 (SPSS, Inc., Chicago, IL). Descriptive data are presented as median (range), mean ± SD, and proportions, as appropriate. For comparisons between groups, Student's *t*-test, the Mann-Whitney test, chi-square test or Fisher's exact test were used, as appropriate. Kaplan-Meier curves were used to depict differences in survival estimates free of transplantation, stratified for defect complexity, presence or absence of a congenital syndrome and presence or absence of comorbidities. To detect significant differences for survival estimates between groups a Cox proportional hazards model was used. A p value <0.05 (2-sided) was considered significant.

3. Results

3.1. Study population

From the administrative database a total of 1725 patients (53% male) were identified who had been followed by the specialized multi-disciplinary team at our tertiary care center until December 2015. The majority of patients had defects of moderate or great complexity (35% simple defects, 43% moderate complexity, 22% great complexity). There was no difference in the gender distribution among patients with simple defects and those with moderate/severe defects but patients with simple defects were significantly older at last clinic visit (37.8 ± 15.8 years versus 35.4 ± 13.4 years, $p = 0.001$). A total of 273 patients (15.8%) had a history of sustained atrial arrhythmias (mainly intra-atrial reentrant tachycardias), 37 patients (2.1%) had a history of sustained ventricular arrhythmia and 63 patients (3.7%) had atrio-ventricular block grade II or III. During a median follow-up duration of 2.9 years (0–20 years), 92 patients (5.3%) died or underwent heart transplantation.

3.2. Congenital syndromes

A total of 232 patients (13%) had a concomitant congenital syndrome. The type and frequencies of congenital syndromes are depicted in Fig. 1. Compared to those without syndromes, patients with syndromes were younger at entry into the cohort (27.1 ± 11.1 years versus 31.7 ± 14.1 years, $p < 0.0001$). Compared to those without syndromes, they more likely had congenital heart defects of moderate (54.7% versus 41.7%, $p < 0.0001$) or great complexity (25.0% versus 21.3%, $p < 0.0001$). Compared to patients without syndromes, patients with syndromes had higher rates of concomitant comorbidities (65.5% versus 49.2%, $p < 0.0001$). Patients with syndromes more commonly had hearing problems (6.0% versus 0.8%, $p < 0.0001$), neurologic disease (19.8% versus 5.2%, $p < 0.0001$) and thyroid dysfunction (21.1% versus 7.5%, $p < 0.0001$) but less likely had a history of migraine (1.7% versus 5.9%, $p = 0.007$). The distribution of congenital cardiac defects was as expected: patients with trisomy 21 most commonly had repaired atrioventricular septal defects (32.3%), unrepaired atrioventricular septal defects

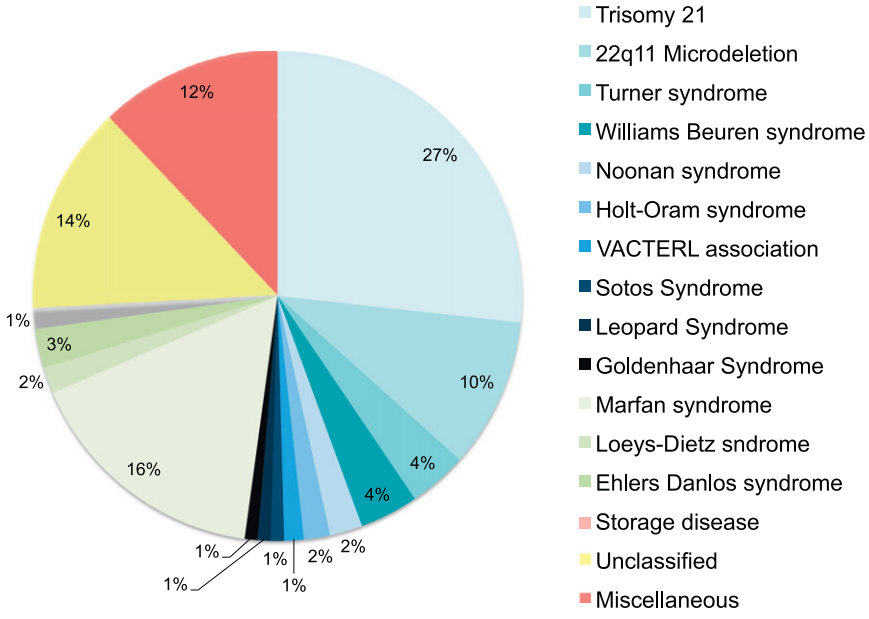

Fig. 1. Type and frequency of congenital syndromes among patients within the cohort.