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Adult congenital heart disease in Greece: Preliminary data from the CHALLENGE registry

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ABSTRACT

Background: The majority of patients with congenital heart disease (CHD), nowadays, survives into adulthood and is faced with long-term complications. We aimed to study the basic demographic and clinical characteristics of adult patients with congenital heart disease (ACHD) in Greece.
Methods: A registry named CHALLENGE (Adult Congenital Heart Disease Registry. A registry from Hellenic Cardiology Society) was initiated in January 2012. Patients with structural CHD older than 16 years old were enrolled by 16 specialized centers nationwide.
Results: Out of a population of 2115 patients with ACHD, who have been registered, (mean age 38 years (SD 16), 52% women), 47% were classified as suffering from mild, 37% from moderate and 15% from severe ACHD. Atrial septal defect (ASD) was the most prevalent diagnosis (33%). The vast majority of ACHD patients (92%) was asymptomatic or mildly symptomatic (NYHA class I/II). The most symptomatic patients were suffering from an ASD, most often the elderly or those under targeted therapy for pulmonary arterial hypertension. Elderly patients (>60 years old) accounted for 12% of the ACHD population. Half of patients had undergone at least one open-heart surgery, while 39% were under cardiac medications (15% under antiarrhythmic drugs, 16% under anticoagulants, 16% under medications for heart failure and 4% under targeted therapy for pulmonary arterial hypertension).
Conclusions: ACHD patients are an emerging patient population and national prospective registries such as CHALLENGE are of unique importance in order to identify the ongoing needs of these patients and match them with the appropriate resource allocation.

1. Introduction

Few decades ago, patients with congenital heart disease (CHD) rarely reached adulthood. However, thanks to the progress of surgical techniques and the optimal medical management, the vast majority of these

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patients nowadays survives into adulthood; the estimated ratio of adults to children with CHD reaches a high of 2:1 [1–3].

Numerous studies on the epidemiology of CHD have been published, but they vary significantly mainly due to methodological differences [4]. A systematic review demonstrated that the prevalence of ACHD is 3 per 1000 adults, with more recent studies reaching 6 per 1000 adults [3,5]. Despite the reported differences between the findings of the studies/registries, more precise data through national registries are needed in order to assess the characteristics of this growing population and improve their management [6–8]. In addition, as these patients age, complications such as heart failure (HF), arrhythmias and pulmonary arterial hypertension (PAH) may appear, requiring appropriate healthcare surveillance [9–11].

Until now, no epidemiological data on ACHD were available in Greece. In this context, Hellenic Cardiological Society established a national registry of ACHD, named CHALLENGE (Adult Congenital Heart Disease Registry. A Registry from the Hellenic Cardiology Society). The goals of this project were to study the epidemiological data of ACHD patients in Greece and to create a cooperation network between the ACHD expert centers. The aim of the current study is to report the study design and the baseline characteristics of patients enrolled in the CHALLENGE registry.

2. Methods

This project was initiated in January 2012. A steadily increasing number of ACHD expert centers took part in this effort and today 16 specialized centers are participating in the registry nationwide. The study protocol conforms to the ethical guidelines of the 1975 Declaration of Helsinki and approval was acquired a priori from the scientific committees and administrative councils of the participating hospitals. Eligible candidates for inclusion in the registry were patients with structural ACHD older than 16 years. Patients suffering from bicuspid aortic valve, Marfan syndrome with aortic dilatation, mitral valve prolapse, cardiomyopathies and inherited diseases leading to cardiac arrhythmias were excluded.

After informed consent was obtained, each patient was labeled with a unique six digit personal Id. Then, the data of each patient were collected and reported anonymously, including gender, date of birth, date of visit, main and secondary anatomical diagnosis (judged by the physician who enrolled the patient), number and type of surgeries, New York Heart Association (NYHA) functional class, cardiac pharmacotherapy (YES/NO) and its subtype (antiarrhythmic, antihypertensive, antiplatelet, anticoagulant drugs and medication for HF and for PAH) (YES/NO). Regarding the severity of CHD subtypes the Bethesda classification was utilized [12].

The collection and storage of the data were done with the usage of a custom web based platform. This platform was designed and implemented according to the IT architecture standard of multiple levels (multi-tier) for collecting, storing and processing the information. This architecture was the most flexible and scalable for redundancy as well as future needs. All data was stored in a Relational Database Management System (RDBMS) more specific a MS SQL Server 2012. The platform was hosted in an Internet's provider data center, which ensure redundancy in regards to hardware malfunctions, data backup as well as network redundancy, ensuring the continuous availability of the platform and the data.

In the context of quality assurance the investigators were having semiannual research meetings in order to discuss about the progress of the registry or possible problems that might encounter. Furthermore, the database administrator checked the uploaded data for duplicate entries, wrong dates, incomplete records and when a problem was detected then a query was sent to the corresponding researcher so that it could be corrected.

2.1. Statistical analysis

Continuous variables were reported as mean (standard deviation (SD)) and categorical data as counts and percentages. For intergroup comparisons, the Student's *t*-test, χ^2test and ANOVA test with Post Hoc analysis were used as appropriate. Two-tailed probability values ≤0.05 were considered statistically significant. Statistical analysis was performed with the use of SPSS Version 22.0 (SPSS, Inc., Chicago, IL).

3. Results

3.1. Total population

From January 2012 up to March 2017, 2115 ACHD patients were enrolled in the database. Mean age was 38 years (SD 16, 52% women). Most frequent main diagnosis was atrial septal defect (ASD), in one third of patients ($n = 704$) (Fig. 1). One or more cardiac operations were performed in 50% of the population; (31% one, 12% two and 7% three or more operations). Among the latter group (145 patients) who underwent three or more surgeries, the majority suffered from tetralogy of Fallot ($n = 61$, 17% of tetralogy of Fallot patients), followed by patients with single ventricle ($n = 30$, 44% of single ventricle patients) and atrioventricular/ventriculoarterial abnormal connections ($n = 20$, 14% of patients with atrioventricular/ventriculoarterial abnormal connections).

The majority of patients were asymptomatic or mildly symptomatic, as 71% were in NYHA class I, 22% in II, whereas only 7% and 1% were in NYHA class III and IV respectively. Heavily symptomatic (NYHA III/IV) were mostly patients with atrial septal defect ($n = 37$), who were elderly or under targeted therapy for PAH, tetralogy of Fallot ($n = 36$), atrioventricular/ventriculoarterial abnormal connections ($n = 25$), single ventricle ($n = 18$) and ventricular septal defect ($n = 11$).

3.2. Severity

According to Bethesda classification 15% of these patients were classified as suffering from severe, 37% from moderate and 48% from mild CHD (Table 1). Patients with severe ACHD were younger, underwent more surgical operations and were more prone to receive cardiac medical therapy.

3.3. Gender differences

Gender disparities were recorded in the basic epidemiological data. Females were older (mean age 40 years (SD 17) vs 36 years (SD 16), $p < 0.001$), suffered more often from mild ACHD (52% vs 44%, $p < 0.001$) and underwent fewer surgeries (no surgery was performed in 56% vs 44%, $p < 0.001$). Regarding ACHD subtypes, septal defects were more prevalent in female patients, whereas tetralogy of Fallot, atrioventricular/ventricoloarterial discordances and aortic arch abnormalities predominated in males (Fig. 2). At least one cardiac surgery was performed in 56% of males compared to 44% of their female counterparts ($p < 0.001$). ACHD males were more frequently under cardiac medical therapy (43% vs 35%, $p = 0.001$). Specifically, they were more frequently under HF medical treatment (19% vs 14%, $p = 0.002$) and anticoagulation (18% vs 13%, $p = 0.001$). No difference was recorded in NYHA class, as almost the same proportion (92%) of both genders was in NYHA I/II.

3.4. Elderly

Of all patients, 250 (12%) were older than 60 years of age (62% women). The vast majority (60%) of elderly ACHD patients suffered from atrial septal defect (Fig. 1). In comparison with younger patients, they had more often mild CHD and underwent fewer surgeries, while almost two thirds did not undergo any surgical procedure at all (vs 48%, $p < 0.001$). Only 38% of elderly patients were asymptomatic (vs 75%, $p < 0.001$). Elderly patients were more frequently under cardiac medical therapy (71% vs 35%, $p < 0.001$) and specifically under HF medications (40% vs 13%, $p < 0.001$), anticoagulants (36% vs 13%, $p < 0.001$) and antiarrhythmic drugs (33% vs 12%, $p < 0.001$). No difference was demonstrated in targeted medical therapy for PAH between patients over and under 60 years.

3.5. Pharmacotherapy

In terms of the medical treatment, 39% of the patients were under cardiac medication; in particular, 16% were treated with HF medical treatment, 15% with antiarrhythmic drugs, 16% with anticoagulants, 18% with antiplatelet drugs, 12% with antihypertensive drugs and 4% with targeted therapy for PAH.

From the 342 patients who were under HF pharmacotherapy, 35 had single ventricle physiology (52% of single ventricle patients) (Fig. 3). They were older (47 years (SD 15) vs 36 years (SD 20), $p < 0.001$) and

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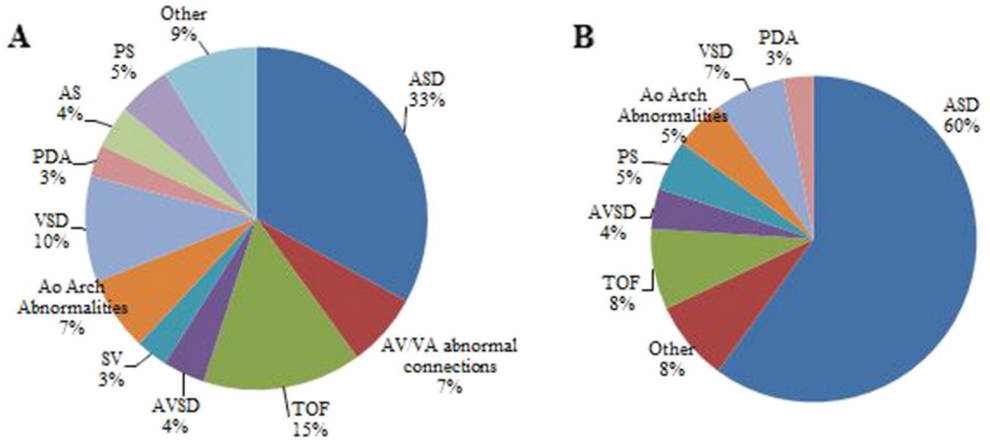

Fig. 1. a) The prevalence of subtypes of ACHD in total population b) The prevalence of ACHD in elderly ASD: atrial seprtal defect, TOF: tetralogy of Fallot, AV/VA: atrioventricular/ventriculoarterial, VSD: ventricular septal defect, PS: pulmonary valve stenosis, Ao: aortic, AS: aortic stenosis, SV: single ventricle, AVSD: atrioventricular defect, PDA: patent ductus arteriosus.

were more often males (55% vs 46%, $p = 0.002$). Furthermore, patients under HF medical treatment were more symptomatic as 25% were in NYHA III/IV (vs 4%, $p < 0.001$) and received more often antiarrhythmic drugs (40% vs 10%, $p < 0.001$).

Patients who required pharmacotherapy for arrhythmias were mainly those with a single ventricle, atrioventricular/ventriculoarterial abnormal connections, atrioventricular septal defect and tetralogy of Fallot (Fig. 3). Patients under antiarrhythmic medication were older (mean age 48 years (SD 17) vs 36 years (SD 15), $p < 0.001$), while no difference was reported according to gender ($p = 0.10$). A correlation between antiarrhythmic pharmacotherapy and the severity of CHD was found, as 25% of patients with severe CHD were receiving this type of medication, compared to 10% of patients with mild CHD ($p < 0.001$). Lastly, people who received antiarrhythmic drugs were more likely to have a history of surgical procedure ($p < 0.001$).

Patients who were under targeted treatment for PAH suffered more commonly from septal defects (18 had ventricular septal defect, 13 atrial septal defect and 9 atrioventricular septal defect), followed by patients with atrioventricular/ventriculoarterial abnormal connections ($n = 17$). About one sixth of PAH-CHD patients who were receiving PAH drugs had Down syndrome. Eisenmenger syndrome was the most common clinical category of PAH-CHD (79%), followed by left to right shunt (10%), PAH after correction (10%) and small defect (2%). Patients under PAH pharmacotherapy were older (mean age 45 years (SD 16) vs 38 years (SD 16), $p < 0.001$) and heavily symptomatic, as 48% were classified as NYHA III/IV. The majority of these patients (66%) had not undergone any surgical procedure. Although a greater proportion of females were under PAH treatment (4% vs 3%), that did not reach statistical significance. Lastly, 36% of these patients received additional heart failure pharmacotherapy, 43% anticoagulants and 33% antiarrhythmic drugs.

4. Discussion

Over the last few years, the necessity of ACHD national registries has emerged and in this context the CHALLENGE registry was launched in Greece. Within 5 years, 2115 patients have been registered, revealing a snapshot of the contemporary epidemiological data of ACHD in Greece, a country with specialist ACHD care but limited resources. Especially, in the past, there were no accessible ACHD expert surgeons in Greece and this could have influenced the national epidemiology of ACHD.

In our cohort, the most prevalent subtype of ACHD was the atrial septal defect, followed by tetralogy of Fallot, ventricular septal defect and atrioventricular/ventriculoarterial abnormal connections. In the registry of Québec, aortic valve dysfunction was demonstrated as the most prevalent diagnosis followed by atrial septal defect and ventricular septal defect, in the CONCOR registry tetralogy of Fallot was reported with the highest prevalence, while in the cohort of the Royal Brompton Hospital valvar disease was the most frequent ACHD subtype, followed by ASD [2,13,14]. A possible explanation for this lack of agreement might be the different proportional participation of the tertiary referral centers and the methodological heterogeneity between these studies.

Out of the total, 15% of the patients were classified as suffering from severe ACHD, a proportion that is similar with the reported in the Québec registry [3]. The mean age of patients classified in severe subgroup was 35 years, while in the Canadian registry was 25 years and in

Table 1
Differences in epidemiological data according to the severity of CHD.

	Overall $n = 2115$	Mild $n = 1008$	Moderate $n = 790$	Severe $n = 317$	p-value
Age	38.0 ± 16.2	39.3 ± 17.3	37.7 ± 15.2	34.6 ± 13.9	<0.001
Males	1008 (47.7%)	438 (43.5%)	417 (52.8%)	153 (48.3%)	<0.001
NYHA I/II	1952 (92.3%)	965 (95.7%)	744 (94.2%)	243 (76.7%)	<0.001
NrSurgeries					
0	1061 (50.2%)	745 (73.9%)	232 (29.4%)	84 (26.5%)	<0.001
1	657 (31.1%)	212 (21.0%)	344 (43.5%)	101 (31.9%)	
≥2	397 (18.8%)	51 (5.1%)	214 (27.1%)	132 (41.6%)	
Cardiac Medication Use	821 (38.8%)	311 (30.9%)	315 (39.9%)	195 (61.5%)	<0.001
Antiarrythmic drugs	314 (14.8%)	97 (9.6%)	137 (17.3%)	80 (25.2%)	<0.001
Medication for HF	342 (16.2%)	109 (10.8%)	132 (16.7%)	101 (31.9%)	<0.001
Anticoagulants	330 (15.6%)	138 (13.7%)	92 (11.6%)	100 (31.5%)	<0.001

Nr: Number; NYHA: New York Heart Association, HF: Heart Failure.

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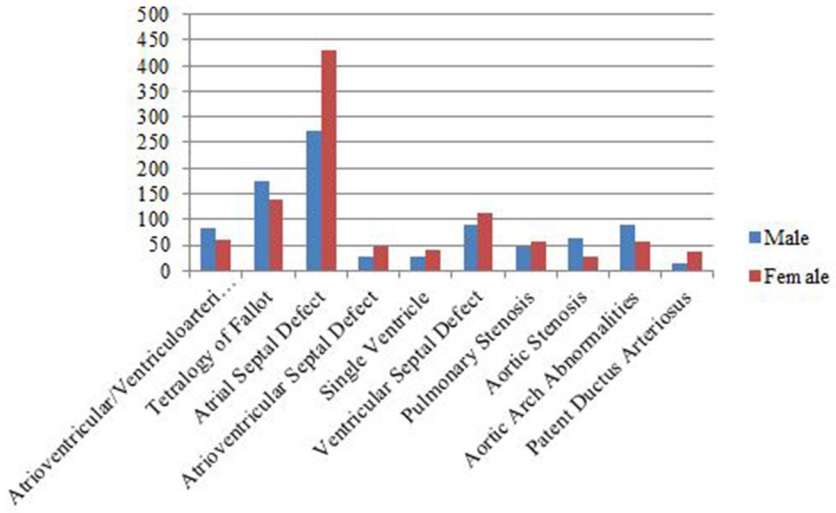

Fig. 2. The distribution of ACHD subtypes according to gender.

CONCOR 53 years [15]. Of note, in registries with higher mean age at enrollment, patients with earlier attrition had not been registered.

In accordance with the EUROSURVEY study, the vast majority of patients in CHALLENGE were reported as asymptomatic or mildly symptomatic (NYHA I/II) [16]. It is known that ACHD patients frequently underestimate their restrictions in physical activities and therefore, the use of cardiopulmonary exercise testing may be a better diagnostic modality in order to objectively assess their exercise capacity [17].

Half of our patients had undergone at least one surgical procedure. This proportion is significantly lower than the 76% reported in CONCOR registry [13], which could be attributed to the fact that the prevalence of defects differed in the studies, as mentioned above and the difficulty in accessing ACHD expert surgical infrastructure in the past years in Greece.

Data for gender differences are in line with literature [2,18,19]. Females had more often septal defects, whereas tetralogy of Fallot, atrioventricular/ ventriculoarterial abnormal connections and aortic arch abnormalities predominated in males. Men underwent more surgical procedures and were more likely to receive medical therapy for HF and arrhythmias. In contrast, women received at a higher proportion targeted therapy for PAH without reaching statistical significance, probably due to the small size of patients receiving this kind of therapy.

Elderly (>60 years) with ACHD are an emerging population [20]. In CHALLENGE registry they accounted for 12% of the total population, suffering mainly from ASD. ASD was also shown to be the most prevalent subtype of ACHD in these patients in two previous studies [21,22].

In our cohort 16% were under HF treatment. HF was most prevalent among patients with single ventricle, followed by atrioventricular/ ventriculoarterial abnormal connections, atrioventricular septal defect and tetralogy of Fallot. Our data are similar with those in the existing literature as HF is one of the most important complications of ACHD, mainly reported in patients suffering from single ventricle, tetralogy of Fallot, transposition of great arteries and congenitally corrected transposition of great arteries. It is the leading cause of death in ACHD population and it leads to hospital admission for one fifth of patients [23–27].

In 15% of patients antiarrhythmic drugs were administered, which was in line with the proportion (18%) in the CONCOR registry [13]. Arrhythmias are the most frequent cause of hospitalization of ACHD patients [28,29].

In our study, similar to the CONCOR registry [30], 4% of the population was under PAH targeted treatment. Of note, almost half of these patients were in NYHA III/IV. The most prevalent underlying diagnoses, as expected, were septal defects. However, several patients with AV/VA abnormal connections were under PAH pharmacotherapy, probably due to the coexisting congenital heart defects and especially ventricular septal defect.

The major limitations are inherent to many registry-based studies, namely that the entire data of the patients were not accessible. We could not define HF, arrhythmias and PAH based on existing definitions, therefore, we were based on received pharmacotherapy. Furthermore, the high proportion of expert centers might induce bias by over-enrolling the more complex end of the disease spectrum. Notably, although the majority of national ACHD expert centers participate in this effort, we would expect more patients to have been registered, indicating that a number of patients still remain undiagnosed in Greece and/or are followed by non-expert centers.

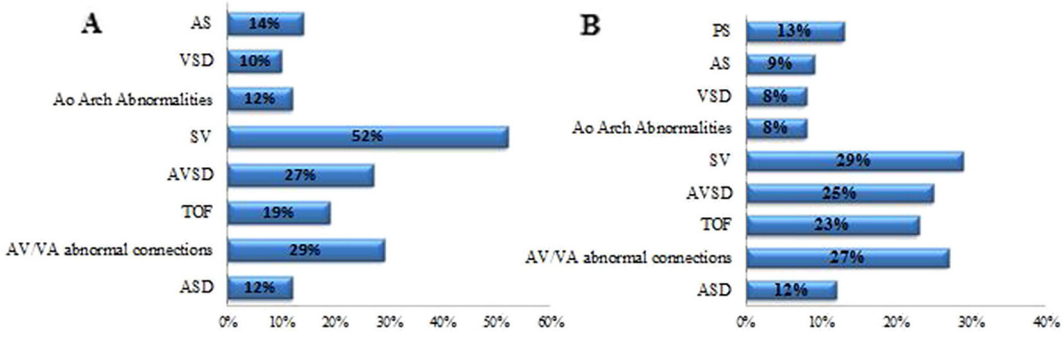

Fig. 3. Prevalence of a) HF and b) antiarrhythmic medical treatment in ACHD subgroups. ASD: atrial seprtal defect, TOF: tetralogy of Fallot, AV/VA: atrioventricular/ventriculoarterial, VSD: ventricular septal defect, Ao: aortic, AS: aortic valve stenosis, SV: single ventricle, AVSD: atrioventricular defect, PS: pulmonary valve stenosis.

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Patients with ACHD are a unique and rapidly emerging patient population. Apart from the randomized controlled trials, national registries, such as CHALLENGE, are required to address the needs of these patients and drive policy on organizing appropriate ACHD expert centers with adequately trained staff, offering high quality medical care.

Disclosures

The authors report no relationships that could be construed as a conflict of interest.

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