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CLINICAL INVESTIGATIONS

Identification of clinically relevant phenotypes in patients with Ebstein anomaly

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Background: Ebstein anomaly (EA) is a heterogeneous congenital heart defect (CHD), frequently accompanied by diverse cardiac and extracardiac comorbidities, resulting in a wide range of clinical outcomes.

Hypothesis: Phenotypic characterization of EA patients has the potential to identify variables that influence prognosis and subgroups with distinct contributing factors.

Methods: A comprehensive cross-sectional phenotypic characterization of 147 EA patients from one of the main referral institutions for CHD in Colombia was carried out. The most prevalent comorbidities and distinct subgroups within the patient cohort were identified through cluster analysis.

Results: The most prevalent cardiac comorbidities identified were atrial septal defect (61%), Wolff-Parkinson-White syndrome (WPW; 27%), and right ventricular outflow tract obstruction (25%). Cluster analysis showed that patients can be classified into 2 distinct subgroups with defined phenotypes that determine disease severity and survival. Patients in cluster 1 represented a particularly homogeneous subgroup with a milder spectrum of disease, including only patients with WPW and/or supraventricular tachycardia (SVT). Cluster 2 included patients with more diverse cardiovascular comorbidities.

Conclusions: This study represents one of the largest phenotypic characterizations of EA patients reported. The data show that EA is a heterogeneous disease, very frequently associated with cardiovascular and noncardiovascular comorbidities. Patients with WPW and SVT represent a homogeneous subgroup that presents with a less severe spectrum of disease and better survival when adequately managed. This should be considered when searching for genetic causes of EA and in the clinical setting.

KEYWORDS

Congenital Heart Defect, Ebstein Anomaly, Epidemiology, Genetics, Phenotype

1 | INTRODUCTION

Ebstein anomaly (EA) is a very infrequent congenital heart defect (CHD) involving the tricuspid valve, in which the septal or posterior leaflet, or both, are rotationally displaced downward into the right ventricle.[1] It has a prevalence of 1 in 20 000 births,[2] making the assembly of large cohorts to study the clinical features and genetic causes of the disease challenging.

Previous work indicates that EA is a highly heterogeneous disease, frequently accompanied by multiple cardiac and extracardiac manifestations. Although a few associations between EA and chromosomal abnormalities have been reported,[3] and a few studies have identified pathogenic mutations in familial cases,[4,5] little is known about the phenotypic presentation and genetic causes of the disease in nonsyndromic EA patients. It is likely that the heterogeneity in the clinical presentation of EA also reflects an underlying genetic heterogeneity, which, combined with studies of small sample sizes, makes finding relevant genetic differences very difficult. However, a strategy based on the identification of genetic variants in phenotypically defined subgroups (or endophenotypes) has the potential to empower genetic research into rare conditions like EA.[6]

This study describes the prevalence of cardiovascular (CV) and non-CV comorbidities in EA patients from a single CV center during a 20-year period. The results highlight some unexpected associations between different comorbidities and their relationship to disease severity and survival. These results can potentially aid in the phenotypic classification of EA patients for genetic studies and contribute to the understanding of the determinants of prognosis in EA.

2 | METHODS

2.1 | Study design and patient population

An observational cross-sectional study to characterize the clinical presentation of EA in Colombian patients was carried out, with ≥1 echocardiogram that confirmed the presence of the disease, which was defined as a downward displacement of the septal and/or posterior tricuspid leaflets of >0.8 cm/m^2 surface area, in relation to the anterior mitral valve leaflet.[7] Patients with left transposition of the great arteries or tricuspid dysplasia in the absence of EA were excluded, because the first has the potential to hemodynamically alter the function of the right ventricle[8] and the latter can mimic EA.[9]

The records of 147 Colombian patients with EA who attended the Fundación Cardioinfantil–Instituto de Cardiología (FCI-IC) between 1997 and 2016 were examined. Patients were identified as part of the CHD database from the PINOCCHIO (Programa para la Innovación en Cardiopatías Congénitas Humanas Infrecuentes para Colombia)[10] Cohort and through an institutional, nationwide, CHD screening program.[11] The study was approved by the institutional review board of the FCI-IC, as part of the PINOCCHIO program.

Epidemiological data were obtained from 3 main sources of information: (1) an institutional database of the nationwide CHD screening program conducted in 11 Colombian provinces (12 cities),[12] (2) a database with data harvested from the medical records of patients with EA, and (3) an institutional cardiac surgery registry. Once a central registry was consolidated, all duplicate records were excluded. Characteristics such as sex, age at first evaluation at this institution, CV and non-CV comorbidities, signs and symptoms when first assessed, mortality data, and surgeries performed were retrospectively analyzed based on the medical records of each patient.

Overall survival was assessed using publicly available data from National Social Security databases[13] and death certificates obtained from the National Civil Registry Office. These data are revised and updated periodically and used by the Colombian government to determine billing procedures for health services and national citizen identification.[14] Based on the experience of the FCI-IC, these data are accurate and reasonably updated for the majority of patients, although it is possible that deaths might not have been reported to these databases for a small number of patients. In a few cases in which information was not available, data were obtained via telephone from relatives of record. Only 6 patients were lost during follow-up.

2.2 | Statistical analysis

Data were described as the proportion of patients with a given feature. Arrhythmias (with the exception of Wolff-Parkinson-White syndrome [WPW]) that were absent before surgery and developed soon after surgery were not included in the analysis and labeled as postsurgical arrhythmias, presumably resulting from myocardial damage.[15,16]

To determine if the distribution of comorbidities showed patterns that suggested the existence of patient subtypes or endophenotypes, we carried out cluster analysis for the classification of patients based on multiple variables, where patients with more characteristics in common are grouped together into clusters.[17]

Cluster analysis has been used successfully to classify patients with congenital abnormalities into clinically relevant subgroups based on their phenotype,[18] including patient classification based on cardiac imaging.[19–22]

Adequate sample size for cluster analysis was determined considering the number of variables, which may exponentially increase data dimensionality. For this purpose, an approach has been proposed in which meaningful classifications can be obtained using a sample size of 2^x, where x is the number of variables.[23] We identified 6 relevant cardiac comorbidities, each one of them present in >10 patients, which were qualitative, dichotomic variables (hence no standardization was needed). With a sample size of 133 (excluding the 14 syndromic patients), we classified patients according to the presence or absence of atrial septal defect (ASD; including patients with ASD ostium secundum, ASD ostium primum, and patent foramen ovale); WPW; complete right bundle branch block (RBBB); obstruction of the right ventricular outflow tract (RVOTO; including pulmonary stenosis, pulmonary atresia with ventricular septal defect (VSD), pulmonary atresia without VSD, and tetralogy of Fallot) and supraventricular tachycardia (SVT).

It was considered that a patient had a syndromic presentation only if cognitive-developmental delay or a suspicion of a specific syndrome were present, not by merely the presence of any extracardiac abnormality. These patients were not included in the cluster or

survival analysis to aid in the better understanding of the heterogeneity of nonsyndromic EA. Incomplete RBBB was not included because it did not represent an important hemodynamic feature and is a frequent finding in healthy subjects. Patent ductus arteriosus was not included because in several cases it was secondary to prostaglandin treatment for ductal-dependent EA and represented a confounding factor.[7] Similarly, pulmonary hypertension can be a hemodynamic consequence of RVOT obstruction and RV insufficiency, so it was not included as a classification variable. The degree of tricuspid insufficiency varied significantly between different measurements, so it also was not included, but it was considered severe enough to require surgery in 27 (18.4%) patients.

Clustering was carried out using both hierarchical (with the Ward algorithm and Euclidean distance for the measure of similarity or dissimilarity, for binary variables) and 2-step methods,[23] and the congruence of both methods was compared. This analysis was crucial for generating hypotheses about comorbidities that might not be distributed randomly in EA patients but instead show associations with other comorbidities, so we proceeded to test for associations between patients presenting with the different comorbidities using the χ^2 test, with P values <0.05 considered significant.

Survival to adulthood was calculated using Kaplan–Meier analysis, and differences between subgroups were estimated using the log-rank (Mantel-Cox) method (see Supporting Information, Appendix VII, for other test methods results). All statistical analyses were carried out using SPSS version 23 (IBM Corp., Armonk, NY) for Macintosh.

3 | RESULTS

3.1 | Patient characteristics

The study population showed an equal distribution of the sexes. Most of the patients were seen for the first time at FCI-IC before the age of 18 (Table 1). The main reasons for the first visit were dyspnea (35%) and palpitations (25%), whereas the most prominent signs during the first visit were systolic murmur (86%) and cyanosis (35%).

According to the Carpentier classification, the severity of EA in these patients was distributed evenly throughout the spectrum of the disease (Table 1). Patients with Carpentier type D had a greater mortality, as well as patients with RVOT obstruction (see Supporting Information, Appendices V and VI [Figures A and B], in the online version of this article). Also, most of the patients (n = 137; 93%) had a congenital CV comorbidity, of which 46 (31%) presented with an additional structural abnormality only, 32 (22%) presented with an arrhythmia only, and 59 (40%) presented with both a structural abnormality and an arrhythmia. A significant number of these patients had ≥1 extracardiac comorbidity (n = 39, 27%; see Supporting Information, Appendix 1 [Table A], in the online version of this article).

Consistent with their clinical status, patients were most often treated for heart failure with loop diuretics (furosemide) and aldosterone antagonists (spironolactone). A significant number (76%) also required interventional or surgical procedures (Table 2), most commonly ablation, followed by tricuspid valve repair, the preferred surgical intervention for this condition (Table 2).[7]

3.2 | Cluster analysis

Unsupervised hierarchical (Ward) cluster analysis separated the patients into 2 well-defined clusters (Figure 1A). Classification of these patients into 2 clusters using the 2-step method showed 81% concordance in cluster membership with respect to hierarchical cluster analysis. Examination of the 2 clusters revealed that ASD is almost equally distributed in both clusters with a proportion similar to that observed in the group as a whole. Complete RBBB can only be found in cluster 2; however, no statistically significant relation was found when comparing complete RBBB with other variables. Patients with WPW and SVT were almost exclusively found in cluster 1. Cluster 2 was significantly more diverse, concentrating patients with RVOT obstruction, ASD, and/or complete RBBB (Figure 2B,C).

WPW and SVT were more likely to be found in the same patient (P = 0.00025). Conversely, patients with RVOT obstruction were less likely to present with WPW (P = 0.032) or with either WPW or SVT (P = 0.034). An analysis of the patients found in each cluster revealed that patients in cluster 2 had a more severe spectrum of the disease, having an increased proportion of patients with Carpentier D scores, whereas patients in cluster 1 had a reduced proportion of patients with Carpentier D scores (Figure 1D,E). This is supported by the fact that patients with WPW were less likely to have a Carpentier D score (P = 0.039), as well as SVT patients (P = 0.02) and patients with RVOT obstruction were more likely to have a Carpentier D score (P = 0.001). Because cluster 1 contains most WPW/SVT patients and cluster 2 contains most RVOT obstruction patients, one explanation is that patients with RVOT obstruction account for a high percentage of patients having a Carpentier D score and can likely explain the observed differences between clusters concerning the severity of the disease (see Supporting Information, Appendix V [Figure A], in the online version of this article).

3.3 | Survival analysis

During a mean follow-up of 5.5 years (range, 0–19 years), 29 (21%) patients died, mostly during early childhood (n = 21; 73%). Only a minority died during adulthood (n = 5; 17%), adolescence (n = 2; 7%), and childhood (n = 1; 3%). Overall survival to adulthood (age 18 years) was high (78%; Figure 2). However, patients with WPW or SVT had significantly improved survival compared with patients without WPW and SVT (P = 0.03).

4 | DISCUSSION

The results of this study show that EA is a heterogeneous condition, frequently associated with abnormalities within and outside the CV system. However, results show that cases with WPW and/or SVT represent a homogeneous subgroup with a less severe spectrum of disease and a better clinical course.

Although there was an increased proportion of patients with WPW compared with previous studies, most of the comorbidities previously associated with EA were similar to the proportions previously reported, suggesting that these are mostly population-independent (see Supporting Information, Appendix III, in the online version of this article). The increased frequency of WPW in this study

TABLE 1 Baseline characteristics

Characteristic	Frequency, n	%
Female sex	69	46.9
Age at first consult at institution, y		
Early childhood, 0–5	63	42.9
Childhood, 6–11	27	18.4
Adolescence, 12–17	30	20.4
Young adult, 18–26	9	6.1
Adulthood, 27–59	17	11.6
Old age, ≥60	1	0.7
Severity of disease (per Carpentier)		
Type A	33	22.4
Type B	41	27.9
Type C	45	30.6
Type D	28	19.0
Familial cases	7	4.8
Comorbidities		
ASD	89	60.5
Ostium secundum	62	42.2
PFO	22	15.0
Ostium primum	5	3.4
WPW	39	26.5
Complete RBBB	26	17.7
RVOT obstruction	23	15.6
Pulmonary stenosis	11	7.5
Pulmonary atresia with VSD	6	4.1
Pulmonary atresia without VSD	5	3.4
Tetralogy of Fallot	1	0.7
SVT	21	14.3
Incomplete RBBB	21	14.3
PDA	19	12.9
Syndromic	14	9.5
Cognitive or developmental delay	3	2.0
Down syndrome	5	3.4
Kleefstra syndrome	1	0.7
1p36 deletion syndrome	1	0.7
Turner syndrome	1	0.7
VACTERL association	1	0.7
Congenital rubella syndrome	1	0.7
Scimitar syndrome suspicion	1	0.7

Abbreviations: ASD, atrial septal defect; CHD, congenital heart defect; EA, Ebstein anomaly; PDA, patent ductus arteriosus; PVO, patent foramen ovale; RBBB, right bundle branch block; RVOT, right ventricular outflow tract; SVT, supraventricular tachycardia; VACTERL, vertebral defects, anal atresia, cardiac defects, tracheo-esophageal fistula, renal anomalies, and limb abnormalities; VSD, ventricular septal defect; WPW, Wolff-Parkinson-White syndrome.
In the 7 familial cases, only in 2 occasions was EA found in 2 members of the same family. The other familial cases (n = 5) represent recurrence of another CHD. ASD was considered if the patient had ASD type ostium secundum, PVO, or ostium primum. RVOT obstruction was considered if the patient had pulmonary stenosis, pulmonary atresia with VSD, pulmonary atresia without VSD, or tetralogy of Fallot.

may reflect genetic modifiers more prevalent in the Colombian population that increase the risk for a presentation that includes WPW or patient selection biases in FCI-IC. Because most types of EA are symptomatic, and this center is the main referral center for most symptoms of EA (both structural and electrophysiological), this study likely reflects the whole spectrum of symptomatic disease. It is, however, possible that patients suffering from EA with a concomitant symptomatic arrhythmia may be more likely to seek medical attention than patients with less severe forms of EA without arrhythmia.

The data show that management involved mainly diuretics to control heart failure and ablation (probably because of the large sample of WPW patients). However, despite appropriate treatment, mortality proved to be very high in the first years of life, as has been reported previously in EA patients.[24]

The cluster analysis of EA comorbidities identified 2 clearly defined subgroups that had not been previously reported. One of the subgroups comprised mostly patients with WPW and/or SVT, which rarely presented with either RVOT obstruction or with a Carpentier type D score, and were associated with a significantly lower mortality. The other subgroup included patients with RVOT obstruction and/or complete RBBB. The lower mortality of patients with WPW had previously been observed by Gentles et al.,[25] who attributed it to a statistical artifact, due to a small sample size. Although further subdivisions did not produce clearly defined clusters, additional clinically meaningful subgroups within cohorts of EA patients cannot be ruled out.

It is not clear why the most severe form of the disease (Carpentier type D and presence of RVOT obstruction) is so rare in patients with WPW and/or SVT, but a likely explanation is that the genetic defects or environmental insults underlying the disease in these different groups of patients could affect different genes or developmental pathways. Although unlikely, alternative explanations include the possibility that prenatal mortality is higher in patients with both WPW and/or SVT and severe forms of the disease (Carpentier type D and the presence of RVOT obstruction), and therefore fewer of these patients could be found postnatally, or the possibility that development of abnormal accessory conduction pathways might be inhibited when tricuspid valve displacement is extreme.

RVOT obstruction in EA has been hypothesized to be secondary to a low antegrade flow during outflow tract development and is likely to be more frequent in the more severe forms of the disease[26]; this may explain the association between RVOT obstruction and a Carpentier type D classification.

Identification of the genetic causes of EA has proved elusive, likely due to genetic heterogeneity that underlies the phenotypic heterogeneity of the disease. The identification of patient subtypes or endophenotypes is relevant to genetic studies because phenotypically homogeneous patients are more likely to have similar genetic defects, and statistically significant associations can therefore be found with smaller sample sizes.[6] Furthermore, patient subtypes are likely to have different prognoses or response to treatment, and this data can be useful in the clinic.

5 | CONCLUSION

In a region with limited data on the clinical presentation of CHD, this study represents a step forward in the characterization of EA patients in the Colombian population. The findings regarding the heterogeneity of EA and the likely existence of subgroups with

TABLE 2 Surgical procedures

Surgical Procedure	Frequency, n	Median Age at Operation, y
Ablation	29	14.2
Tricuspid valve repair	23	19.8
Cone technique	10	13.2
Tricuspid valve replacement	5	33.7
ASD closure	14	11.6
Cavopulmonary shunts (Glenn-Fontan)	13	14.7
Catheterization procedures	7	12.3
Pulmonary valve procedures	6	4.3
Pacemaker implantation	5	14.6
Systemic-pulmonary fistulae	4	0.3
Cardiac transplantation	2	24
Maze procedure	2	28.8
Procedures on PA and branches	2	0.1

Abbreviations: ASD, atrial septal defect; FCI-IC, Fundación Cardioinfantil–Instituto de Cardiología; PA, pulmonary artery.
Septal defect closures may have been underreported in the surgical notes, as many were done as part of another mayor intervention and/or did not involve complete closure of the defect. The surgical procedures shown were mainly, but not necessarily, done at FCI-IC. Catheterization procedures do not include diagnostic procedures or those where ablation or tricuspid valve repair was done. Most of the patients who underwent a Glenn procedure also had tricuspid valve repair or replacement, which was not always independently reported.

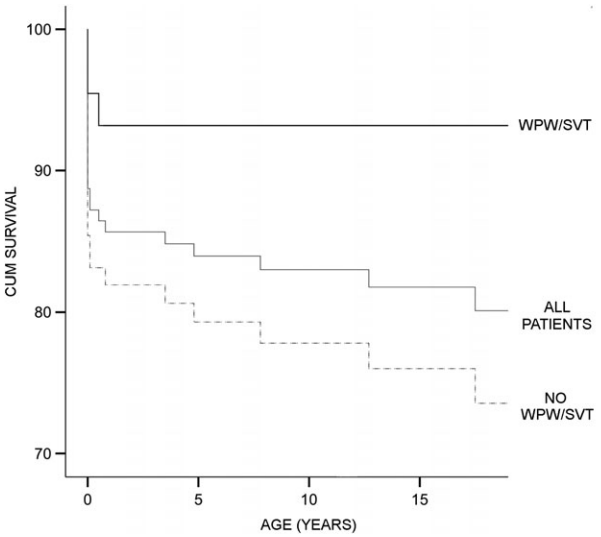

FIGURE 2 Survival to adulthood. All patients were evaluated for survival to adulthood (age 18 years) using Kaplan–Meier analysis. The thick line represents the survival to adulthood of patients with WPW and/or SVT, who had a significantly better survival than the patients without WPW and/or SVT, represented by the dotted line. Cumulative survival for all patients is shown in the intermediate line labeled "All patients." Abbreviations: CUM, cumulative; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White syndrome

distinct phenotypes and differential prognoses should be considered when searching for genetic causes of the disease and when assessing likely outcomes in the clinical setting. In the future, new research efforts should aim to identify the genetic and environmental factors underlying the heterogeneity and diverse clinical presentations of EA.

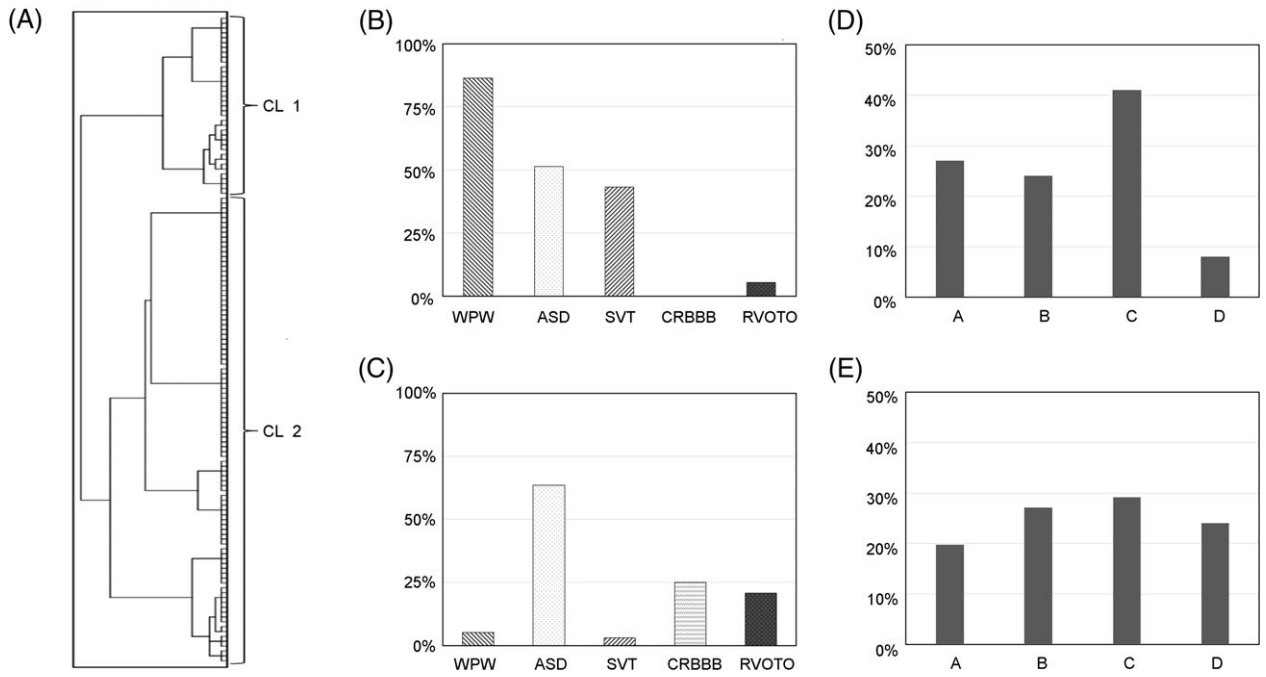

FIGURE 1 Patient classification using cluster analysis. (A) Dendrogram illustrating the 2 main clusters obtained through hierarchical cluster analysis. WPW/SVT patients were mostly assigned to CL 1, whereas RVOTO patients were mostly assigned to CL 2. (B) Distribution of comorbidities in CL 1. (C) Distribution of comorbidities in CL 2. (D) Severity of disease per Carpentier classification in CL 1. (E) Severity of disease per Carpentier classification in CL 2. Abbreviations: ASD, atrial septal defect; CL, cluster; CRBBB, complete right bundle branch block; RVOTO, right ventricular outflow tract obstruction; SVT, supraventricular tachycardia; WPW, Wolff-Parkinson-White syndrome

Conflicts of interest

The authors declare no potential conflicts of interest.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

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