EBSTEIN'S ANOMALY: PRESENTATION AND OUTCOME FROM FETUS TO ADULT

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Objectives. This study was conducted to investigate the presentation and outcome of patients with Ebstein's anomaly of the tricuspid valve.

Background. Ebstein's anomaly may present at any age and has a highly variable clinical course. Previous natural history studies have been based on clinical and angiographic diagnosis and have included mainly older children and adults. Echocardiography, however, has facilitated fetal and neonatal diagnosis so that the natural history needs to be redefined.

Methods. We reviewed 220 cases of Ebstein's anomaly presenting from fetal to adult life between 1958 and 1991, with 1 to 34 years of follow-up.

Results. The most common presentation in each age group was abnormal routine prenatal scan for fetuses (86%), cyanosis for neonates (74%), heart failure for infants (43%), incidental murmur for children (63%) and arrhythmia for adolescents and adults (42%). Early presentation was frequently associated with other cardiac lesions, usually pulmonary stenosis or atresia. Surgery was undertaken at some stage in 86 (39%) of the 220 patients. Actuarial survival for all liveborn patients was 67% at 1 year and 59% at 10 years. There were 58 deaths, including 26 from heart failure, 19 perioperative and 8 sudden. Predictors of death included echocardiographic grade of severity at presentation (relative risk 2.7 for each increase in grade, 95% confidence limits 1.6 to 4.6), fetal presentation (6.9, confidence limits 1.6 to 16.5) and right ventricular outflow tract obstruction (2.1, confidence limits 1.1 to 4.4). Morbidity was mainly related to arrhythmias and late hemodynamic deterioration. Of 195 survivors, 129 (63%) were in functional class I and 104 (67%) were receiving no medical therapy.

Conclusions. In Ebstein's anomaly, fetal and neonatal presentation is associated with a poor outcome and can be predicted by the echocardiographic appearance and presence of associated lesions. In older children and adults, incidental findings and arrhythmia are common and the long-term outcome is superior.

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tricuspid valve or with AV and ventriculoarterial discordance ("corrected transposition") were excluded.

Case notes, chest X-ray films, 12-lead electrocardiograms (ECGs), echocardiograms, surgical reports and autopsy data were reviewed to confirm the diagnosis. Echocardiographic grade of severity was calculated for all 74 subjects in whom an echocardiogram at presentation was available (5). This involved calculating the ratio of the combined area of the right atrium and atrialized right ventricle to that of the functional right ventricle and left heart in a four-chamber view at end-diastole. This ratio is used to define four grades of increasing severity: ratio <0.5 = grade 1, ratio 0.5 to 0.99 = grade 2, ratio 1 to 1.49 = grade 3 and ratio ≥1.5 = grade 4. Left ventricular function is difficult to quantify in Ebstein's anomaly because most patients have paradoxical motion of the ventricular septum. In this series, left ventricular dysfunction was therefore defined as severely impaired motion of the ventricular septum. In this series, left ventricular posterior wall on echocardiography or as global hypokinesia of the left ventricle on angiography.

Investigations and management decisions were determined by the patient's cardiologist in each case. Antibiotic prophylaxis against endocarditis was advised for all patients. "Functional" tachycardia refers to AV or AV node reentrant tachycardia.

Statistical methods. Kaplan-Meier survival curves for the overall group and different clinical subgroups (antenatal, ages 0 to 2, 2 to 18 and >18 years) were generated (11). Estimated postconceptional age was used for survival curves for fetal life; for all other curves, postnatal age was used. When elective termination of pregnancy occurred, the fetus was withdrawn alive from the analysis at that time. Patients contributed to each analysis only from the time of referral to our institutions; this staggered entry is relevant when an analysis was performed using only variables that could be assessed at presentation and that were available for >50% of subjects (presenting feature, associated defects, age at diagnosis, pre-excitation, era of diagnosis and chest X-ray film but not echocardiographic grade). Patients were censored at death, whether "natural" or postoperative, and survival beyond the last contact with our hospitals was not presumed. Factors predictive of outcome were explored by univariate and multivariate analysis using a Cox proportional hazards model (12). Relative risks are indicated with 95% confidence limits. Proportions were compared using the chi-square test and statistical significance was inferred at p < 0.05.

Results
The age at presentation was 18 weeks' gestation to 68 years (median 36 days). There were 21 fetuses, 88 neonates (0 to 1 month of age at presentation), 23 infants (<2 years), 50 children (<10 years), 15 adolescents (<18 years) and 23 adults (>18 years). Of the 220 subjects, 13 presented before 1960, 26 from 1961 to 1970, 45 from 1971 to 1980 and 122 from 1981 to 1990 (14 presented in 1991). There were 88 male (40%) and 120 female (55%) subjects; gender was not determined in 12 fetuses who died or were terminated before birth. Follow-up ranged from 12 months to 34 years (median 6 years, ≥5 years in 125 subjects). Of 162 survivors, 133 (82%) had been seen within the last 2 years.

Presenting features. The mode of presentation differed for each age group (Table 1). In subjects <2 years old, presentation with a hemodynamic problem was significantly more common than in older patients (72% vs. 29%, p < 0.01), whereas presentation with an electrophysiologic problem was more common in subjects >10 years of age (43% vs. 10%, p < 0.01). Associated cardiac defects (other than a patent foramen ovale or atrial septal defect) were present in 76 (35%) and were more common in the younger age groups (80% of fetuses, 50% of neonates, 48% of infants, 14% of children and 8% of adolescents and adults) (Fig. 1, Table 2).

Investigations. On the chest X-ray film at presentation (in 171 of 208 postnatal cases), the cardiothoracic ratio was 40% to 59% in 69 (40%), 60% to 89% in 99 (58%) and ≥90% in 3 (2%). The 12-lead ECG revealed pre-excitation in 41 (20%). In subjects without pre-excitation, a prolonged PR interval was present in 34%, right atrial enlargement in 71% and complete or incomplete right bundle branch block in 51%. A two-dimensional echocardiogram at presentation was available in 74 of 136 patients presenting since 1980 and showed severity of grade 1 in 13 subjects (18%), grade 2 in 32 (43%), grade 3 in 20 (27%) and grade 4 in 9 (12%).
Cardiac catheterization was performed at some stage in 103 patients and was complicated by supraventricular or ventricular tachyarrhythmia that was self-limited or responsive to intravenous medication in 12 (12%) and complicated by cardiopulmonary arrest in 7 (7%). Of these seven patients, four died at catheterization (all before 1977). Electrophysiologic study was performed in 22 patients (18 with drug-refractory arrhythmias, 2 with pre-excitation and syncope and 2 with asymptomatic pre-excitation). A total of 27 accessory connections were identified in 18 patients; 10 patients had a single connection and 8 had multiple connections. Eleven accessory connections were in the right posteroseptal region (41%), 10 in the right free wall (37%), 3 in the left posteroseptal region, 1 in the left free wall and 2 were of a Mahaim type.

Outcome. Of 220 patients, 58 (26%) died, 7 fetuses (3%) were electively terminated and 155 patients (71%) were alive at last follow-up. The actuarial survival rate was 67% at 1 year (95% confidence limits [CL] 57% to 75%) and 59% at 10 years (95% CL 49% to 68%) (Fig. 2). The annual hazard for death was 36% for the 1st year of life, 4% for the 2nd year, 1% from ages 2 to 10 years and 1.4% from ages 10 to 40 years (Fig. 3). In childhood, adolescence and adult life, there was continuing attrition related to hemodynamic deterioration, perioperative death and sudden unexpected death. Even those who had presented with an incidentally detected murmur had a small but continuing hazard for late death.

Predictors of outcome. Univariate analysis showed that a significant risk of death was associated with echocardiographic grade 4 (relative risk compared with grade I disease 13.3; 95% CL 1.6 to 111), cardiothoracic ratio >60% (relative risk 5.4; CL 1.9 to 15), associated right ventricular outflow tract obstruction (relative risk 2.5; CL 1.3 to 4.8) and presentation in fetal life (relative risk compared with childhood presentation 10.1; CL 2.3 to 44). Of 21 fetuses, there were 7 terminations (all with grade 3 or 4 disease), 5 intrauterine and 6 postnatal deaths and only 3 survivors, all of whom had grade 2 disease at presentation (1-year survival rate 15%). Pre-excitation and era at diagnosis were not risk factors for death. When echocardiographic grade was treated as a continuous variable, each incremental grade was associated with a relative risk of 2.7 (CL 1.6 to 4.6). On multivariate analysis, a significant risk of death was associ-
Mg-dre 3. Kaplan-Meier survival curves for the fetal cases and the ages of 0 to 2, 2 to 18 and >18 years (see Methods). The x axis for the fetal cases refers to estimated postconceptional age; for the other three survival curves, the x axis refers to postnatal age.

- The findings from 86 patients who underwent surgical treatment are shown in Figure 4. The indications for operation were persistent cyanosis or heart failure, or both, in the neonate and hemodynamic problems leading to functional class III or IV symptoms or arrhythmias refractory to drug treatment, or both, in older subjects.

In the 32 patients who had tricuspid valve surgery (at age 8 days to 46 years), the risk was more related to age at presentation than to age at operation. The perioperative mortality rate was 50% (8 of 16 patients) for those whose condition was diagnosed in the 1st year of life (13 of whom were operated on after infancy) and 0% for the 16 patients whose condition was diagnosed after age 1 year (p < 0.0001). Seventeen patients had a second operation and two required a third procedure (tricuspid valve replacement).
Morbidity. Twenty-eight neonates with initial resolution of neonatal cyanosis later developed heart failure or cyanosis, or both (2 to 18 years after initial presentation); 11 of these had evidence of left ventricular dysfunction. Of 220 patients, 74 (34%) have had arrhythmias at some stage and 13 others have pre-excitation but no symptoms to date. The most common arrhythmias were junctional tachycardia (43 patients), atrial flutter or fibrillation (28 patients) and ventricular tachycardia (15 patients); several patients had more than one type of arrhythmia documented. Supraventricular arrhythmias tended to be recurrent and drug refractory, with 42 (57%) of 74 patients requiring two or more antiarrhythmic medications to achieve symptomatic control. Bradycardia was less common: AV block occurred in five patients (in relation to surgery in two and to cardiac catheterization in three).

There were two cases of paradoxical embolism, both causing hemiparesis in young adults who had been in sinus rhythm; one child had a cerebral abscess. The only case of documented endocarditis affected the tricuspid valve of a 62-year-old man who died of progressive tricuspid regurgitation.

Mortality. Death was due to congestive heart failure in 26 (45%) of 58 patients, was perioperative in 19 (33%), sudden and unexpected in 8 (14%), related to cardiac catheterization in 4 and of noncardiac origin in one child. The deaths from heart failure occurred in neonates managed conservatively (11 patients, all before 1980), children who were initially well but developed late hemodynamic problems (13 patients, associated with left ventricular dysfunction in 8 and with progressive tricuspid valve dysfunction, right heart dilation or atrial fibrillation in 5) and 2 older adults (1 with severe disease considered inoperable and the other with tricuspid valve endocarditis). Of the eight patients who died suddenly, four had previously documented arrhythmias (atrial flutter or fibrillation late after tricuspid valve surgery in three, ventricular tachycardia in one), one had had recent symptomatic deterioration and three had no antecedent event that could be identified. No patient who died suddenly had pre-excitation.

Survivors. Of the 155 survivors, 129 (83%) were in functional class I, 23 (15%) in class II, 3 (2%) in class III and none in class IV when last assessed. Most survivors were receiving no medical therapy (104 (67%) of 155 patients; 20 were receiving digoxin only, 9 were receiving digoxin and diuretic drugs and 22 were receiving another antiarrhythmic agent).

Discussion

This study has shown that fetuses, neonates and infants with Ebstein's anomaly usually present with hemodynamic sequelae of severe tricuspid valve displacement and right ventricular abnormalities and have a poor prognosis. There is an early death hazard due to heart failure and intracardiac cardiomegaly causing pulmonary hypoplasia (13) and a continuing later hazard due to hemodynamic deterioration in childhood or adolescence, perioperative death or sudden death. In contrast, childhood Ebstein's anomaly usually presents with an incidental murmur, and the outlook is good. The main clinical problem for adolescents and adults with Ebstein's anomaly is arrhythmia. This may be due to the natural history of pre-excitation, progressive atrial dilation or the association of both.

Associated cardiac defects were common in patients presenting early (Fig. 1). In fetal life, functional and anatomic right ventricular outflow obstruction are difficult to distinguish (14), and severe tricuspid regurgitation may simulate pulmonary atresia (13). Structural pulmonary valve abnormalities are most likely secondary to the tricuspid valve anomaly (11), resulting from low antegrade flow during outflow tract development (16).

The true "natural history" of Ebstein's anomaly cannot be determined because many patients underwent surgical treatment. Survival data have therefore been presented in three ways (Fig. 2): the observed survival, the most optimistic case (patients withdrawn as alive at time of operation) and the worst case (patients withdrawn as dead at time of operation). The true natural history lies between the observed and worst case curves, but probably closer to the latter because patients in our series were usually operated on when they were severely symptomatic.

Limitations of study. This study included all 220 patients referred to five London teaching hospitals over a 30-year period, even those with minor tricuspid valve displacement and those with serious associated defects. This confirms the relative rarity of this condition. The majority of children with hemodynamic problems, unexplained murmurs and arrhythmias from Southeast England and most adults with cyanosis or arrhythmias would have been referred to one of these hospitals over the duration of the study. The proportion of patients with undiagnosed Ebstein's anomaly has probably changed over the study period. Some patients will have died without a diagnosis and others will be alive with as yet unrecognized Ebstein's anomaly; the net effect of such patients on the survival curves presented in this report is uncertain.

The median age at presentation was <1 year, underscoring the impact of echocardiography on the diagnosis of congenital heart disease in fetuses and infants and the change in pattern of referrals for Ebstein's anomaly in the last decade. These data, however, reflect only the medical practice at our institutions over a particular time frame, which has evolved during the period of the study. Important potential sources of bias also exist as a result of the inevitable individualization of the timing and type of investigations and treatment.

Morbidity and mortality. Endocarditis was rare in this series, with only one case documented in >1,000 patient-years of follow-up. Although the "natural" risk of valve infection cannot be determined, there is a low risk if antibiotic prophylaxis is recommended. Paradoxical embolism was also rare, and we do not routinely undertake anticoagulant
therapy in patients in sinus rhythm. Arrhythmias were common, particularly in the older age groups, and were usually related to accessory AV connections and atrial flutter or fibrillation. These arrhythmias tended to be recurrent and resistant to drug treatment (17). Catheter ablation for accessory connections has not been performed often in Ebstein's anomaly and is difficult because most connections are right-sided, the right atrium is large and the anatomy of the right AV ring is distorted. Arrhythmia surgery is feasible, and both short- and long-term results are good for appropriately selected cases (18). Some cases of late sudden death may be related to arrhythmias; however, it is not known whether routine noninvasive or invasive electrophysiologic testing or treatment of any detected arrhythmias will minimize the risk of this complication.

Late hemodynamic deterioration may be due to increased right to left shunting and right or left heart failure, or both. The incidence of late left ventricular dysfunction cannot be estimated from this study because serial measurements were not routinely performed. Furthermore, left ventricular dysfunction is especially difficult to assess in Ebstein's anomaly because of paradoxical septal motion, which influences the estimation of ejection fraction and fractional shortening. The true incidence of left ventricular dysfunction is probably underestimated because only patients with very poor posterior wall contraction were included.

The association between Ebstein's anomaly and left ventricular abnormalities has been previously noted (19,20), and Saxena et al. (21) have recently documented unsuspected abnormalities in left ventricular function and limitation in exercise capacity in mildly symptomatic adults. Exercise testing may therefore be useful in assessing cardiac performance, given the limitations of echocardiographic indexes. The cause of left ventricular dysfunction is unclear, but may be due to chronic cyanosis, right heart dilation and septal abnormalities (22) and increased left ventricular fibrosis (16).

Management. Echocardiography is the most important diagnostic test in Ebstein's anomaly, permitting accurate assessment of the anatomy and distal attachments of the tricuspid valve, the size and contractility of the functional right ventricle and the overall grade of disease severity. Cardiac catheterization is rarely required, other than for electrophysiologic study or for investigation of associated cardiac defects.

Neonates. Newborns with isolated Ebstein's anomaly and cyanosis usually show spontaneous improvement as pulmonary vascular resistance decreases (23). Those in whom persistent cyanosis is due to associated right ventricular outflow obstruction do well after surgical palliation if their Ebstein's anomaly is not severe (echocardiographic grade 1 or 2). The results of tricuspid valve surgery were poor, however, for neonates and infants with symptomatic heart failure and severe Ebstein's anomaly, and this probably reflects more severe disease requiring intervention in early life. Possible strategies for these children include the creation of functional tricuspid atresia (by closing the tricuspid valve and excising the atrial septum) with insertion of a systemic to pulmonary artery shunt (24), with a view to later Fontan-type surgery, or heart transplantation (25).

Older children and adults. In this group the most common indication for tricuspid valve surgery was worsening congestive heart failure. Operations early in this series were usually valve replacement, but valve repair has been undertaken where possible since the reports of excellent perioperative results in highly selected patients by Mair et al. (26), who described creation of a monocusp valve and transverse plication of the atrialized right ventricle, and by Carpentier et al. (27), who described longitudinal plication.

In patients whose heart failure is due to increasing tricuspid regurgitation and right atrial enlargement, tricuspid valve surgery should improve symptomatic status. In many of our patients with late hemodynamic deterioration, however, there was evidence of poor left ventricular function; in these patients, tricuspid valve surgery may not necessarily improve functional status or long-term outcome. Prospective study is required to determine whether serial measurement of echocardiographic grade of disease severity, left ventricular function or exercise tolerance might predict symptomatic deterioration and the need for surgery.

Some investigators (28) have suggested on the basis of retrospective data that tricuspid valve surgery is indicated for asymptomatic patients with a cardiothoracic ratio ≥65% because this may be a better predictor than functional status of late sudden death. In our series, sudden death was rare in patients who did not undergo operation, even in those with cardiomegaly. Furthermore, sudden death may occur in patients with mild disease and a normal heart size on the chest X-ray film (29). Because surgery carries a significant risk, even in older children and adults, and there is no evidence to date that it reduces the hazard for sudden death, we do not currently perform tricuspid valve surgery in asymptomatic patients.

Clinical implications. The management of Ebstein's anomaly therefore depends on the age at presentation, anatomic severity of the lesion, presence of associated defects and clinical features. Fetal Ebstein's anomaly has an appalling outlook, and prenatal counseling should take this into account. Grade 1 or 2 disease in neonates and infants has a good outcome and palliation should be undertaken for associated lesions, but grade 3 or 4 disease in young children has a poor prognosis. Older children and adults can be managed medically until symptoms appear, when good results may be obtained by valve surgery, particularly valve repair. In all age groups, however, there is an increasing risk of arrhythmias (17) and a persistent risk of late hemodynamic deterioration and sudden death.

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References


