Morphological Aspects of Ebstein’s Anomaly in Adults

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The essence of the Ebstein’s malformation is that the tricuspid valve leaflets do not attach normally to the valve annulus, and the effective orifice is displaced downward into the right ventricular cavity at the junction of the inlet and trabecular components of the right ventricle. Only the septal and posterior leaflets are displaced and divide the right ventricle into two portions. The inlet portion is usually integrated functionally with the right atrium (“atrialized portion”), while the other, including the trabecular and outlet portions, constitutes the functional right ventricle. The proximal atrialized right ventricle often has a wall thinner than the distal functional right ventricle, due to partial congenital absence of myocardium. An atrial septal defect is present in more than one-third of hearts, and the majority of the remainder has a patent foramen ovale resulting in a right-to-left shunt. The downward displacement of the septal tricuspid valve leaflet is associated with discontinuity of the central fibrous body and septal atrioventricular ring, thus creating a potential substrate for accessory atrioventricular connections and ventricular pre-excitation making the patient at risk of sudden death. Angiography has demonstrated that a significant number of patients with Ebstein’s anomaly also have morphofunctional abnormalities of the left ventricle, which may be explained by increased fibrosis in the left ventricular wall and ventricular septum as demonstrated by histological studies. Regarding embryology, the leaflets and tensile apparatus of the tricuspid valve are believed to be formed mostly by a process of delamination of the inner layers of the inlet zone of the right ventricle. The downward displacement of the leaflets in Ebstein’s anomaly suggests that delamination from the inlet portion failed to occur.

Key words: Congenital heart disease – Sudden death – Tricuspid-valve dysplasia

Historical Notes

Wilhelm Ebstein was born at Jauer, in Schlesien, Prussia on November 27, 1836 [1,2]. He attended the Medical School and graduated in Medicine at the University of Berlin, where he had Virchow and Romberg as Mentors. In the time interval between 1859 and 1869, he acted as Assistant Physician at the All Saints’ Hospital, Breslau, where he was appointed as Prosector in the Laboratory of Physiology and Histology by Prof. H. Heidenhain, and became a private lecturer in 1869. In 1874, he was nominated Professor of Medicine at the University of Göttingen, where he taught until he retired in 1906. On October 22, 1912 he died at the age of 76 due to cerebral apoplexy. From graduation to retirement, he had published 237 papers on different topics of Internal Medicine: obesity, diabetes, gout, lithiasis, scurvy, purine metabolism. He has been labeled as “the forgotten founder of biochemical genetics”. Besides tricuspid valve dysplasia, his name is linked to other diseases such as the vacuolization of cytoplasm of the renal tubules in diabetic coma. He wrote only 12 articles on cardiology, two of which reported the relationship between myocardial fibrosis and arrhythmias. The first paper on cardiovascular system, published in 1866, was just the one “Concerning a very rare case of insufficiency of the tricuspid valve caused by a congenital malformation”, where he described the autopsy findings of Joseph Prescher, a 19-year-old worker who died on July 1864 with a severe malformation of the tricuspid valve [3]. The patient had been short of breath and complained of palpitations since childhood. On clinical examination, he had pronounced cyanosis of the face and “marked jugular venous pulsations synchronous with the heart beat”. “... The right auricle was considerably dilated... The fossa ovalis... in the atrial septum was not completely closed... In the valve of the foramen ovale, there were multiple openings... There was an extremely abnormal appearance of the tricuspid valve. A membrane... originated from a quite normally developed right annulus fibrosus... Fifteen mm below the right annulus fibrosus and directly under the membranous portion of the ventricular septum, a malformed leaflet about the size of 40 cent piece took its origin from the endocardium...” (Fig. 1).

The eponym “Ebsteinsche Krankheit” (Ebstein’s disease) was coined by Arnstein in 1927 [4]. A long delay exists between the first description and the general recognition of the anomaly. In 1950, Engle et al. [5] reported 3 additional cases and collected other 20 from the literature. The first diagnosis in vivo using cardiac catheterisation was made by Tourniaire et al. in 1949 [6].
The first total correction by prosthetic valve replacement was reported by Barnard and Schrire in 1963 [7]. However, this congenital malformation remained almost overlooked until Schiebler et al. translated the original paper from German into English in 1968 [8].

Anomalous conducting pathways were described by Lev and associated in 1955 in a patient with Wolf-Parkinson-White syndrome and Ebstein’s disease [9]. It is worth noting that in the first Mayo Clinic report on Ebstein’s malformation, Edwards emphasized the continuity of muscle between the atrium and the “atrialized” right ventricle across the atrioventricular ring [10]. Bialostozky et al. in 1972, found by reviewing 65 cases that “dysrhythmias were the most frequent cause of death and often persisted after surgical correction” [11,12].

Today, the congenital malformation of the heart known as Ebstein’s anomaly is well recognized and can be diagnosed with confidence on the basis of physical, electrocardiographic, echocardiographic and radiologic findings alone, and there can be no question that cross-sectional echocardiography is the technique of choice for diagnosis of this malformation.

**Pathological Anatomy and Classification**

The essence of the Ebstein’s malformation is the fact that the tricuspid valve leaflets do not attach normally to the tricuspid valve annulus [13 – 21] (Fig. 2 – 4). The effective tricuspid valve orifice is displaced downward into the cavity of the right ventricle, at the junction of the inlet and apico-trabecular components of the right ventricle [15,16,18].

The degree of this displacement is variable, and there are usually other abnormalities of the valve, including dysplasia and anomalous distal attachment of the leaflets [14]. Only the septal and posterior leaflets are displaced and the point of maximum displacement is usually at the commissure between these two leaflets. The two displaced leaflets vary considerably in size and are often dysplastic.

In one-third of all cases, the leaflets are adherent to the ventricular wall (“plastered down”) rather than truly displaced (Fig. 4). The anterior leaflet, although not displaced, is also anatomically abnormal. It is large with abnormal fibrous strands running through it. Also, the septal and posterior leaflets, besides being downwardly displaced, are often thickened, sometimes fenestrated, large and redundant (Fig. 2).

The displaced tricuspid valve divides the right ventricle into two parts. The inlet portion is usually integrated functionally with the right atrium (“atrialized portion”), while the other, including the apico-trabecular and outlet portions, constitutes the functional right ventricle. The proximal atrialized ventricle often has a thinner wall than the distal functional right ventricle due to partial absence of myocardium (“anatomical” atrialization) (Fig. 3 – 4).
There is some degree of atrial dilatation and circumferential enlargement of the right atrioventricular junction in all hearts with Ebstein’s anomaly.

An atrial septal defect is present in more than one-third of hearts, and most of the remainder have a patent foramen ovale accounting for the right-to-left shunt. An intact atrial septum is rare and usually seen in adults (Fig. 2).

Valve incompetence is the main hemodynamic abnormality in Ebstein’s malformation. However, hearts with abnormal distal attachment of the leaflets and absent interchordal spaces display a degree of tricuspid stenosis. When the leaflet attachment is completely linear and the anterosuperior commissure is absent, the result may be an imperforate Ebstein’s valve [16,18].

Sometimes, the large and dysplastic anterior leaflet can be responsible for right ventricular outflow obstruction, which in neonates may mimic pulmonary atresia [24].

The downward displacement of the septal tricuspid valve leaflet is associated with discontinuity of the central fibrous body and septal atrioventricular ring, thus delineating potential accessory atrioventricular connections and ventricular preexcitation (Fig. 5).

The Ebstein’s malformation can present either isolated or in association with minor and major cardiac malformations (Table 1 – 2). A frequent association is with pulmonary atresia and intact septum [22 – 24] and with corrected transposition of the great arteries [25 – 27]. In the latter condition the affected tricuspid valve is located on the left side of the heart. An
Ebstein-like anomaly can also affect a normally positioned mitral valve, although this is exceedingly rare [28].

Angiography has demonstrated that a significant number of patients with Ebstein’s anomaly had morphofunctional abnormalities of the left ventricle [29–31]. A large atrialized area causes a severe reduction in the volume of the right ventricular pumping chamber, and usually produces an abnormal configuration of the muscular ventricular septum (“banana” shape of the left ventricle) [32]. Leftward displacement of the ventricular septum does not, per se, account for left ventricular dysfunction, which may be explained by increased fibrosis in the left ventricular wall and ventricular septum as demonstrated by histological morphometric studies [32].

**Embryological Considerations**

The leaflets and the tensor apparatus of the atrioventricular valves are formed by a process of delamination of the inner layers of the inlet portion of the ventricle [15,33]. In other words, the leaflets of the tricuspid valve develop equally from the endocardial cushion tissue and the myocardium. In Ebstein’s anomaly, the insertion of the septal and posterior leaflets are displaced to the junction between the inlet and apico-trabecular components of the right ventricle, which would suggest that delamination from the inlet portion failed to occur. The leaflets are said to be “plastered” out of the right ventricular myocardium, so that the fibrous transformation of the leaflets from the muscular precursors remains incomplete.

**Clinical Presentation**

The main hemodynamic abnormality producing symptoms in Ebstein’s malformation is tricuspid regurgitation. Symptoms are generally related to the degree of the regurgitation. Cyanosis is due to right to left shunting through an interatrial communication (patent foramen ovale or atrial septal defect).

Symptoms vary markedly, as would be expected from the large anatomic spectrum of alterations. Although symptoms are lacking in a few patients, cyanosis and dyspnea are present in the majority.

Patients have been noted to live into their seventies and eighties despite the presence of Ebstein’s disease, whereas others have died in infancy and early childhood. When the tricuspid valve dysplasia is particularly severe and associated with right ventricular myocardium hypoplasia, the clinical manifestation occurs very early, even in fetal or infant life, with an early death due to congestive heart failure [34,36]. Ebstein’s anomaly is one of the most frequent symptomatic congenital heart disease in utero. Early presentation is due to the association with other severe cardiac lesions, usually pulmonary stenosis or atresia [23,24].

In contrast, Ebstein’s anomaly in childhood or adolescence can present with an incidental murmur, and the outlook is good.

**Table 1** Cardiac registry of congenital heart disease of the University of Padua. Isolated Ebstein’s anomaly of the tricuspid valve: 15 cases

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age and sex</th>
<th>Minor associated anomalies</th>
<th>Cause of death</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1 d, F</td>
<td>ASD, PDA, persistent LSVC, Down’s syndrome</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>2</td>
<td>3 d, F</td>
<td>PFO, PDA, persistent LSVC</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>3</td>
<td>4 d, M</td>
<td>ASD, PDA, RV myocardium hypoplasia, dysplastic pulmonary valve</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>4</td>
<td>6 d, F</td>
<td>PFO, PDA, dysplastic pulmonary valve</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>5</td>
<td>8 d, M</td>
<td>ASD, PDA</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>6</td>
<td>8 m, M</td>
<td>ASD, RV myocardium hypoplasia</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>7</td>
<td>8 y, M</td>
<td>PFO</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>8</td>
<td>2.5 y, F</td>
<td>PFO, LV fibroelastosis</td>
<td>Heart transplantation</td>
</tr>
<tr>
<td>9</td>
<td>11 y, F</td>
<td>PFO, Kent fascicle</td>
<td>Sudden death during effort</td>
</tr>
<tr>
<td>10</td>
<td>12 y, F</td>
<td>PFO, RV myocardium hypoplasia</td>
<td>Heart transplantation</td>
</tr>
<tr>
<td>11</td>
<td>25 y, F</td>
<td>PFO, Kent fascicle</td>
<td>Sudden death at rest</td>
</tr>
<tr>
<td>12</td>
<td>34 y, M</td>
<td>ASD, RV myocardium hypoplasia, dysplastic pulmonary valve</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>13</td>
<td>35 y, F</td>
<td>ASD, dysplastic mitral valve</td>
<td>Cardiac surgery</td>
</tr>
<tr>
<td>14</td>
<td>64 y, M</td>
<td>Intact atrial septum</td>
<td>Cardiac failure</td>
</tr>
<tr>
<td>15</td>
<td>72 y, M</td>
<td>PFO</td>
<td>Cardiac failure</td>
</tr>
</tbody>
</table>

d: day; m: month; y: year. ASD: atrial septal defect; F: female; LSVC: left superior vena cava; LV: left ventricle; M: male; PDA: patent ductus arteriosus; PFO: patent foramen ovale; RV: right ventricle
The main clinical problem for adolescents and adults is electrical instability. This may be due to ventricular pre-excitation with supraventricular reentrant tachyarrhythmias or to atrial flutter or fibrillation due to progressive atrial dilatation or the association of both. These arrhythmias tend to be recurrent and resistant to drug treatment. Paroxysmal supraventricular tachycardia, by far the most frequent rhythm disorder, is often the result of an accessory conduction pathway (Wolf-Parkinson-White syndrome). Identification of accessory connections and catheter ablation are difficult to achieve due to dilatation of right atrium, atrioventricular ring distortion and large continuity of muscle in between the atrium and the ventricle.

Sudden death is not uncommon also in patients believed to be asymptomatic [36 – 38]. The risk is particularly high, taking into account the adverse association of atrial fibrillation and pre-excitation.

Endocarditis is a rare complication, but antibiotic prophylaxis is recommended. Paradoxic embolism is uncommon.

### Ebstein’s Anomaly in the Cardiac Registry of the University of Padua

In the Anatomical Collection of Congenital Heart Disease of the University of Padua, consisting of 1320 cases, 33 specimens (2.5%) presented the typical malformation of the tricuspid valve known as Ebstein’s malformation. It was isolated in 15 cases (Table 1) and associated with other major cardiac anomalies in the remaining 18 (Table 2).

#### Table 2 Cardiac registry of congenital heart disease of the University of Padua. Ebstein’s anomaly of the tricuspid valve associated with major cardiac anomalies: 18 cases

<table>
<thead>
<tr>
<th>Major associated anomalies</th>
<th>Number of cases</th>
<th>Age and Sex</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary atresia with intact septum</td>
<td>11</td>
<td>1 d – 3 m (median 7d); 6 F, 5 M</td>
</tr>
<tr>
<td>Corrected transposition of the great arteries</td>
<td>2</td>
<td>4 d – 15 d; 2 M</td>
</tr>
<tr>
<td>Atrioventricular septal defect</td>
<td>2</td>
<td>1 d – 3 m; 2 F</td>
</tr>
<tr>
<td>Ventricular septal defect</td>
<td>2</td>
<td>1 d – 2.5 m; 2 F</td>
</tr>
<tr>
<td>Total anomalous pulmonary venous drainage</td>
<td>1</td>
<td>1 d; M</td>
</tr>
</tbody>
</table>

Among the 15 patients with isolated form of Ebstein’s anomaly, there were 8 males and 7 females, ages ranging from 1 day to 72 years (median age 8 years). The minor associated anomalies were interatrial septal defect in 6, patent foramen ovale in 8, patent ductus arteriosus in 5, partial absence of the right ventricular musculature in 3, dysplastic pulmonary valve in 3, persistent left superior vena cava in 2, dysplastic mitral valve in 1. One patient was affected by Down’s syndrome. The cause of death were congestive heart failure in 7 and sudden death in 2. Five patients died after surgical valve repair and 2 following cardiac transplantation. The histological investigation documented the presence of accessory Kent fascicles in specimens from the two patients who died suddenly.

In 18 patients, 8 male and 10 female, the Ebstein’s anomaly was associated with major cardiac anomalies: pulmonary atresia with intact septum (11 cases), corrected transposition of the great arteries (2 cases), atrioventricular septal defect (2 cases) ventricular septal defect (2 cases) and total anomalous pulmonary venous drainage (1 case). All patients of this group died in neonatal or infant life.

### Acknowledgements

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### References

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