An Appraisal about the Etiopathogenesis of the So-Called Idiopathic Cardiac Arrhythmias

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An approach to its etiopathogenesis

Certain arrhythmias are observed in healthy relatively young individuals without evidence of structural heart disease, and mostly asymptomatic that fall under the generic term of "idiopathic" to describe various forms of ventricular arrhythmias from isolated premature beats (VPBSs) to sustained tachycardia. So far, the term idiopathic arrhythmias has only be applied to ventricular arrhythmias, leaving aside many supraventricular rhythm disorders that are also of unknown etiopathogenesis.

Idiopathic ventricular arrhythmias

These arrhythmias account for approximately 10% to 15% of all patients referred for evaluation and treatment of VPBS and ventricular tachycardia (VT). Among them, those arising in the right ventricular outflow tract (RVOT) are the most common form (about 80%), already described by Gallavardin in 1992, usually with a benign course.

In the last two decades, several distinct new forms of idiopathic VPBS and VT have been identified although their etiopathogenesis is still to be determined. These ventricular arrhythmias include: 1. the fascicular VPBs and VT arising almost always in the posterior fascicle of the left bundle branch or in the area of the posterior ventricular papillary muscle. More rarely, the site of the focus is in the left anterior fascicle of the left bundle branch. Likewise, there are also left papillary muscle idiopathic ventricular arrhythmias. Interestingly, they are sensitive to verapamil and dependent on a reentrant mechanism; 2. VT arising in the left outflow tract; 3. arrhythmias originating in the aortic coronary cusps; 4. ventricular arrhythmias initiating in or above the pulmonary valve; 5. arrhythmias adjacent to the mitral and tricuspid rings; 6. epicardial idiopathic VT arising within the left main coronary artery ostium area; 7. focal epicardial ventricular tachycardia proceeding from the crux of the heart; 8. ventricular premature beats and VT occurring within the proximal segments of the intraventricular conducting system, so-called narrow ventricular premature beats [1] and 9. automatic verapamil-sensitive ventricular rhythms [2].

The modern instrumental armamentarium has allowed an accurate localization of the site of origin of each one of the above mentioned ventricular arrhythmias granting their successful radiofrequency ablation. Moreover, the systematic clinical evaluation of the cardiac structure and function has permitted to rule out the association of cardiac disease with the arrhythmia, thus giving support to the idiopathic nature of the rhythm disorder.

Are there idiopathic supraventricular arrhythmias?

All the afore mentioned ventricular arrhythmias have been classified as idiopathic in vast bibliography. In contrast, some very frequent supraventricular arrhythmias of unknown etiology have never been considered as idiopathic. In fact, lone atrial fibrillation, some forms of atrial ectopic tachycardia such as lidocaine sensitive repetitive atrial tachycardia among others; AV nodal reentrant tachycardia (AVNRT) and atrioventricular reentrant tachycardia (AVRT) in the Wolff-Parkinson-White (WPW) syndrome does not recognize a definite genetic or acquired etiology.

After atrial fibrillation, the most common form of sustained supraventricular tachycardia is AVNRT. Multiple investigations in humans and animals have shown that the AV node is a complex structure. The marked heterogeneity of its cells determines a non-uniform conduction of the impulse disclosing a pattern of nodal longitudinal dissociation, recognized by electrophysiologists as the slow and rapid pathways in normal subjects. Besides, in a limited group of patients, the disparity of conduction through these two pathways constitutes the underlying electrophysiologic mechanism of the AVNRT in patients with ostensible normal hearts. The difference between patients with and devoid of this arrhythmia must be attributed to an abnormal morphogenesis of the AV node occurring during embryonic development. So far, a genetic disorder or other causes for this arrhythmia has never been postulated.

Accessory atrioventricular pathways are strands of atrial or ventricular myocardium, persisting as a congenital malformation. The abnormal connections bypassing the AV node are the substrate for AVRT in the WPW syndrome. Right side connections across the tricuspid valve are usually composed by atrial myocardium whereas on the left side, frequently found near the origin of the mural leaflet of the mitral valve, the connections are constituted by working myocardium. Notwithstanding, very few cases with detailed electrophysiologic studies have come to histopathologic examination. Even more, it is well known that there are fascicles connecting the atrial myocardium to the distal zone of the AVN or the penetrating portion of the His bundle in cases of short PR interval with normal QRS complex (atriofascicular pathways). The same is true for nodoventricular or fasciculoventricular connections. In fact, there is unequivocal evidence of these connections in patients with paroxysmal tachycardia. Again, no definite etiopathogenic causes have been stated to explain these abnormalities that have, as the most important embryonic dismorphogenesis, an imperfect closure of the atrioventricular atrioventricular rings as well as the abnormal connections between atria and AV node or from the AV node or His bundle with the interventricular septum.

Atrial fibrillation (AF) in WPW syndrome has been described in up to 39% of patients even though they do not have overt heart disease or atrial compromise. Although atrioventricular reciprocating tachycardia may be a precedent of episodes of AF in a particular patient, it has been shown that the majority do have intrinsic atrial abnormalities demonstrated during electrophysiologic tests, which became evident when WPW patients with AF were compared to controls in whom this arrhythmia failed to be induced. WPW patients with AF have longer interatrial conduction times and different atrial functional refractory periods from their control counterpart. Moreover, these patients also show short minimum wavelengths during the atrial arrhythmia onset. These findings suggest that intrinsic cellular abnormalities of the atria may account for the presence of AF in patients with WPW syndrome.

It has been demonstrated that the mitral annulus-aorta junction can also be the source of focal left atrial tachycardia in patients with structurally normal hearts. In about 30% of patients with left atrial tachycardia, the arrhythmia originates in the mitral annulus-aorta junction. In some patients, this arrhythmia was found to be associated with AVNRT and coronary sinus ostium atrial tachycardia (also idiopathic rhythm disorders). The response as well as the mode of initiation suggests triggered activity as the underlying electrophysiologic mechanism occurring in an area of low-voltage electrograms consistent with a region of slow conduction most probably related to slow response cells. In accordance with previous embryologic studies it has been proposed that the occurrence of atrial arrhythmias at this specific anatomic site may be linked to persistence of remnants of the developing conduction system in this region [3].

It is well known that about 10% to 15% of patients suffering AF do not disclose any evidence of structural heart disease and consequently, it has been coined "lone AF". Despite the absence of demonstrable cardiac sickness, there is no doubt about the presence of underlying cellular and electrophysiologic atrial abnormalities, which may be potentiated by vago-sympathetic changes provoking the arrhythmia in some patients. Most AF related to foci localized within the pulmonary veins must also be considered as pertaining to the lone AF group.

Frequent atrial ectopic premature beats and tachycardia in children and adolescents occur in structural normal hearts. In many cases, the P wave is negative in leads II, III and aVF denoting its origin in the vicinities of the tricuspid or mitral valve. When present as an atrial rhythm, the rate ranges around 60 to 100 beats/minute. These arrhythmias may be observed most part of the day. These ectopic rhythms

usually compete with the normal sinus rhythm either during rapid or slow rates depending on the vago sympathetic balance. Enhanced automatism occurring in slow response cells is the most probable underlying mechanism. The arrhythmia is usually asymptomatic, no drug therapy is needed and it generally disappears in a few years' time.

The abnormal expression of neural crest cells in heart development. An appraisal of the etiopathogenesis of idiopathic atrial and ventricular arrhythmias

The profuse number of clinical and electrophysiologic studies dealing with the wide spectrum of cardiac disorders in patients with normal hearts provided ample information about the physiopathology of the underlying mechanisms. However, the analysis of the etiopathogenesis has been systematically overlooked.

When advancing in an approach of the etiopathogenesis of the idiopathic arrhythmias, one of the most interesting point of the proposal is that either atrial or ventricular arrhythmias share the same etiology.

The contribution of neural crest cells to cardiac development was first postulated by Margaret Kirby [4] when she experimentally showed the relationship between the outflow tract and great artery malformations and the disturbed neural crest during the early stages of cardiac embryogenesis. A population of pluripotent cardiac neural crest cells migrate towards the arterial pole of the embryonic heart, playing multiple roles during development of the outflow tracts and the proximal aortic and pulmonary arteries and their valves. In addition, the cardiac neural crest cells are required for normal regulation of myocardial cell proliferation, as well as differentiation and function of the myocardium. Eventual abnormalities in the developmental process of these areas, either at the myocardial level or within the great vessels may be correlated with the ventricular arrhythmias originating in right and left outflow tracts and those from the aortic valve and the pulmonary artery. The muscle surrounding the developing arterial valves should disappear with ongoing maturation. This surely occurs when cardiac development is normal. However, when ventricular tachycardia arises above the pulmonary valve we must accept that some abnormal muscular tissue still remains up there despite maturation, probably because of incomplete apoptopic cell deletion or a still unknown genetic disorder. Moreover, the neural crest cell death program plays an active role in stimulating the outflow tract myocardialization.

There is a second route of migratory pluripotent cardiac neural crest cells using the venous pole as entrance to the heart [5]. The participation of these cells is crucial to the morphogenesis of the future location and structure of the AV node, His bundle and bundle branches. It also contributes to the development of the atrial tissues, particularly the low anterolateral septum as well as closing the primary atrial septal foramen and septating the AV canal. Likewise, they are involved in the morphogenesis of the pulmonary veins and hence, with the presence of abnormal remnants of myocardial cells within the veins, which constitute the pathophysiologic substrate of many cases of lone AF, nowadays treated by radiofrequency isolation of the pulmonary veins.

There are a couple of examples of cardiac rhythm disorders that show the association of at least two defects related to its phenotypes. One is the WPW syndrome in which there is an anatomic abnormality (the accessory pathways) connecting atria and ventricles or other abnormal pathways connecting parts of the conduction system with each other or with the proximal myocardium. The anomalous connections between atria and ventricles require another abnormality which is the incomplete closure of the atrioventricular rings. As mentioned before, the WPW presents a higher incidence of AF which is obviously related to intrinsic structural and functional abnormalities of the atrial myocardium.

Another example of combined abnormalities in cardiac morphogenesis is the Brugada syndrome [6,7]. At least three anomalies are present in this syndrome: the anatomic and functional alterations of the RVOT: the higher incidence of atrial arrhythmias and AF and prolonged AV conduction times.

All the above anatomic and functional disturbances may be linked to the complex neural crest cell program related to heart morphogenesis with persistence of abnormal myocardium or subtle functional changes in any of the involved structures.

Relationship between neural crest cell migration and connexins

Among different molecules, the connexins (Cxs), particularly Cx43, are known to be strongly involved in neural crest cell migration and are expressed in adult working myocardium. They have been proposed to mediate signaling during several developmental processes which include patterning, differentiation tissue induction, cell migration and proliferation, tissue growth, tissue condensation, attachment and fusion of tissues and epithelial mesenchymal interactions [5].

Concluding Remarks

Regarding the clinical presentation of the wide spectrum of atrial and ventricular arrhythmias and its severity or magnitude, we may speculate that they correlate with the existence of a wide spectrum of the underlying cellular abnormalities of the tissues involved in every rhythm disorder.

We have emphasized the role of neural crest cell migration during development of the heart, which play a fundamental role in normal cardiac morphogenesis using two main routes: the arterial and the venous poles using the pharyngeal arches and the dorsal myocardium, respectively [5]. Neural crest cells using the arterial pole are involved in the development of the right and left outflow tracts, the aorto pulmonary septum, part of the interatrial septum, the semilunar aortic and pulmonary valves and the initial segments of the great vessels. It is understandable that any error in the normal anatomic or functional embryogenic development of the above-mentioned areas of the heart may become the site of origin of these idiopathic atrial and ventricular arrhythmias.

Neural crest cells that reach the heart via the venous pole are involved in the morphogenesis of the proximal segments of the AV conducting system, part of the interatrial septum, AV valves, coronary sinus and pulmonary vein area and mitral annulus-aortic junction. As already stated, each of these cardiac structures are the site of origin of atrial arrhythmias, whose etiopathogenesis has been so far disregarded or ignored and not even labelled as idiopathic.

Altogether, this long list of supraventricular and ventricular arrhythmias may have similar underlying electrophysiologic mechanisms that may include reentrant circuits, enhanced automatism, phase 2 reentry and triggered activity due to early or delayed afterpotentials depending on the cellular substrate that can be composed of fast or slow response cells according to the anatomic site.

The heart and its main great vessels and veins are anatomically, phylogenetically and developmentally one of the most complex organs. Such complexity accounts for the occurrence of congenital abnormalities that include rhythm disorders. This article has pointed out the possible role of the abnormal neural crest cell migration in the etiopathogenesis and pathophysiology of atrial and ventricular arrhythmias. Although speculative, a different hypothesis may stimulate and encourage researchers to explore these challenging but still unresolved electric cardiac disorder. The most interesting approach will be to decipher the cellular and molecular interactions that mediate the erroneous programming of the cardiac neural crest cells involved in normal embryologic development of the different areas related to the origin of the atrial and ventricular rhythm disorders.

In conclusion, the successful definite solution to the etiopathogenesis puzzle of arrhythmias in individuals without structural heart disease will probably require the conjunction and collaborative effort of clinical investigators, electrophysiologists, physiologists, molecular biologists, geneticists and biophysicists. The hardest task, of course, will be for geneticists to tell whether the neural crest hypothesis is valid or there exist specific genetic mutations that account for the etiopathogenesis of the so-called idiopathic arrhythmias.

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