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Common presentation of rare cardiac diseases: Arrhythmias

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ABSTRACT

Ventricular or supraventricular ectopic beats or atrial fibrillation may be the first presentation of uncommon cardiac disease, both acquired and genetically determined.
In some patients, these manifestations can be the first sign of the underlying cardiac disorder. In others, however, they are also important as prognostic indicators, reflecting electrical instability and risk.
Most cardiology clinics are busy environments where the implementation of complex diagnostic algorithms is not feasible. However, it is equally impossible to reach a final diagnosis, among the thousands of rare diseases that involve the heart, moving from a first line clinical and instrumental examination.
Cardiac and extra-cardiac red flags, an accurate family and clinical history and ECG interpretation may be of help in identifying a rare disease. Advanced imaging and laboratory testing at experienced referral centers is then necessary to reach a final diagnosis, but the first step in the right direction, based on these simple elements, is the most important.
We here review arrhythmic presentations of rare or relatively rare diseases, and suggest a simple "rule out–rule in" approach to help direct clinical suspicion and minimize risk of neglect.

Commonly occurring arrhythmias such as ventricular or supraventricular ectopic beats or atrial fibrillation may be the first presentation of uncommon cardiac disease, both acquired and genetically determined. In some patients, these rhythm disturbances mainly represent clinical clues to their underlying disorder. In others, however, they are also important as prognostic indicators, reflecting electrical instability and risk. Cardiologists often lend limited attention to minor arrhythmic manifestations, once the most prevalent cardiac conditions have been excluded. However, an approach exclusively based on a preliminary "rule out" of the usual suspects leads to delayed diagnosis or neglect of a vast spectrum of conditions that might be suspected or recognized with modest additional work-up [1]. Notably, young age at presentation may be a clue to rare and specifically to genetic diseases but is not a necessary pre-requisite, as onset for these conditions may occur at any age [1]. We review arrhythmic presentations of rare or uncommon diseases, and suggest a simple "rule out–rule in" approach to help direct clinical suspicion and minimize risk of missed or uncorrect diagnoses. This work focuses on arrhythmias commonly encountered in clinical practice, while major but rare arrhythmic events such as sustained ventricular tachycardia or ventricular fibrillation, extensively reviewed in the literature, will not be addressed [2].

1. Structural heart diseases

1.1. Hypertrophic cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is a common genetic disorder characterized by cardiac hypertrophy not associated with abnormal loading conditions [3]. HCM occurs in 1:500 of the general population and is a frequent cause of sudden cardiac death (SCD) in the young, although the absolute incidence of events is rare [3]. Arrhythmias are a frequent presentation of the disease. Ventricular ectopic beats are common and non-sustained ventricular tachycardia (NSVT) is detected in 20% to 30% of HCM patients [4]. These arrhythmias may be associated with a longstanding history of palpitations, but are an uncommon reason for patient self-referral. The association of ventricular ectopy with other ECG abnormalities (which occur in ≈90% of the patients with HCM) should always lead to further testing, including cardiac imaging [5]. NSVT is an established predictor of sudden cardiac death in HCM, with an inverse relation to age. In children and adolescents, NSVT is rare but is associated with a relatively high risk of SCD, whereas in older patients it is more common but less predictive [4]. The underlying mechanisms of ventricular arrhythmias in HCM are potentially very

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heterogeneous and include cardiomyocyte remodeling associated, interstitial fibrosis, microvascular ischemia, and myocyte disarray [5].

Atrial fibrillation (AF) occurs in about a quarter of patients with HCM and has an annual incidence of 2% to 3% [6]. Potential mechanisms include atrial enlargement and stretch due to diastolic dysfunction, functional mitral regurgitation due to SAM and primary atrial myopathy [6]. AF is poorly tolerated in HCM patients because the combination of loss of the atrial contribution to ventricular filling and rapid ventricular rate result in increased LV pressures and onset or exacerbation of heart failure symptoms [6]. AF is a major risk factor for heart-failure related events including death and thromboembolic stroke [6]. As left atrial size is the most potent predictor of AF and stroke, patients in sinus rhythm with LA diameter ≥ 45 mm should undergo 6–12 monthly 48-h ambulatory ECG monitoring to detect AF [7]. There are limited data on the prevalence and characteristics of other atrial arrhythmias but, as a general rule, atrial flutter should be managed conventionally and the risk of thromboembolism considered the same as for AF (Table 1).

Symptomatic bradycardia caused by sinus node dysfunction and AV block is relatively uncommon in HCM, but may be observed as a cause of pre-syncope or syncope even at very young ages. The presence of AV block should raise suspicion of rare genetic phenocopies in younger patients (e.g. Danon disease or glycogenosis) and of amyloidosis or Anderson–Fabry disease in older patients [1]. Short PR and ventricular pre-excitation associated with HCM are suggestive of storage (Danon or PRKAG2-related) or mitochondrial disease [1].

1.2. Arrythmogenic cardiomyopathy

Arrhythmogenic cardiomyopathy (AC) is a rare structural heart disease caused by mutations in genes encoding desmosomal proteins, which lead to progressive replacement of the right and/or left ventricular myocardium by fibrofatty tissue [8]. Due to the marked preponderance of arrhythmic over congestive manifestations, palpitations or effort-induced syncope are the most common symptoms at presentation [8]. Ventricular arrhythmias are the most common clinical expression of AC and represent a major diagnostic criterion. They are typically triggered or worsened by adrenergic stimulation, are often polymorphic, and range from isolated premature complexes to NSVT, to sustained VT or VF [9]. The distinctive QRS morphology, in the classic right dominant form of the disease, is left bundle branch block with a superior axis indicating an origin from the lower right ventricle (RV). However, arrhythmias may originate from any part of the RV, including the outflow tract, inferior wall and apex [10]. Moreover, an involvement of the LV (in isolated form or more frequently in the context of biventricular AC) is being increasingly recognized and may be associated with a spectrum of ventricular arrhythmias with RBBB morphology [10]. The diagnosis of AC can be very challenging, as ECG changes may be subtle and echocardiography may be inconclusive or even normal. ECG findings pointing to a suspicion of AC include low limb lead voltages, inverted T waves in the anteroseptal leads (or the inferolateral leads in the left dominant form), and an epsilon wave reflecting RV electrical dispersion [11]. Cardiac magnetic resonance identifies RV morphofunctional abnormalities and late gadolinium enhancement (suggestive of myocardial fibrosis) is often detected at the subepicardial level [9].

Atrial arrhythmias are common in AC and present at a younger age than in the general population [12]; AF is by far the most common (80% of atrial arrhythmias) and may occur before a recognizable structural phenotype has developed [12]. The occurrence of atrial arrhythmias strongly associates with inappropriate ICD shocks and increased long-term risk of death and heart failure [12]. Only 6% of patients present with conduction abnormalities, including complete right bundle branch block and any degree of atrioventricular block [13].

1.3. Dilated cardiomyopathy of genetic etiology

Dilated cardiomyopathy (DCM) is defined by the presence of left ventricular dilatation and contractile dysfunction [14] and is considered idiopathic if no other discernable cause such as coronary, valvular or hypertensive disease is identified. DCM is genetically determined in 20%–50% of cases and primarily autosomal dominant, although other modes of inheritance occur [14]. Up to 40 genes have been identified affecting proteins of a wide variety of cellular structures such as the sarcomere, the nuclear envelope, the cytoskeleton, the sarcolemma and the intercellular junction [15]. Specific genetic etiologies may

Table 1
Prevalence of common arrhythmias and electrocardiographic alterations among rare heart diseases.

		Short PR	WPW	BESV	AF	BEV	NSVT	AV Block
Structural heart disease								
Hypertrophic cardiomyopathy	Danon disease	+	+	+++	+++	++	++	+
	Mitochondrial diseases	+	+	+++	+++	++	++	−
	Glycogenosis	+	+	+++	+++	++	++	+
	Friedrich' ataxia	−	−	+++	+++	++	++	−
	Noonan/leopard	−	−	+++	+++	++	++	−
	Sarcomeric	−	−	+++	+++	++	++	−
Arrhythmogenic cardiomyopathy	Arrhythmogenic cardiomyopathy	−	−	+	+	+++	+++	−
Dilated cardiomyopathy	LMNA/C mutation	−	−	++	++	+++	+++	+++
	Other genes	−	−	++	++	++	+	+
Left ventricular non compaction	Left ventricular non-compaction	−	−	+	+	++	++	−
Mitral valve prolapse syndrome	Mitral valve prolapse syndrome	−	−					
Metabolic and infiltrative								
	Anderson–Fabry	+	+	+	+	+	+	++
	Amyloidosis	−	−	++	++	+	++	++
Ion channel disease								
	Long QT syndrome	−	−	−	+	−	−	−
	Short QT syndrome	−	−	+	++	−	−	−
	Brugada syndrome	−	−	+	++	−	−	−
	Catecholaminergic polymorphic ventricular tachycardia	−	−	−	−	+++	+++	−
Autoimmune and inflammatory								
	Systemic lupus erythematosus	−	−	+	+	−	−	+
	Wegner's granulomatosis	−	−	+	+	+	+	++
	Sarcoidosis	−	−	+	−	+	+	−
	Systemic sclerosis	−	−	+	+	++	++	−
	Chagas	−	−	+	+	++	++	+
Intensive training		−	−					
	Athlete's heart	−	−	+	+	+	−	+