Rare Disease in Cardiovascular Medicine (1): Myth or Reality?

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The past decade has seen the emergence of a new theme in healthcare policy dedicated to the diagnosis and management of rare disorders. The current European Union definition of a rare disease is one that is present in fewer than 1 in 2000 of the general population [1] [2]; as there are as many as 8000 distinct rare diseases, this translates into a potential healthcare issue for over 30 million people in Europe alone [1].

Eighty per cent of rare diseases are genetic in origin and many cause chronic debilitating symptoms [1]. Rare disorders often present at an early age, with 30% of affected patients dying before the age of 5 years [1]. Patients with rare diseases also suffer from delays in diagnosis due to a lack of medical knowledge and poor awareness of these conditions which contributes to a considerable social and financial burden for affected individuals as well as their families and carers [3].

The European Commission aims to reduce the number of individuals suffering from rare disorders, to preserve patients' quality of life and to reduce the socio-economic impact that these conditions impose. To achieve this, its strategy is to improve recognition of these uncommon conditions, strengthen strategic coordination between European nations, and to encourage research [4]. Disease information networks, in particular, are being developed to facilitate the exchange of knowledge and information between relevant stakeholders and thereby improve disease recognition, standardise diagnostic and management protocols, support the implementation of best clinical practice, and incentivise the development of orphan drugs [5].

This new healthcare agenda might seem of peripheral interest to the majority of cardiologists as cardiovascular disorders are anything but rare, accounting for almost 50% of all non-communicable diseases worldwide and 17.3 million deaths per annum [6] [7]. The vast majority of this disease burden is caused by common conditions such as coronary artery disease, hypertension and heart failure. The aetiology of these disorders is generally well understood and decades of research has shown how primary and secondary prevention strategies – including lifestyle and pharmacological interventions – can reduce their associated morbidity and mortality. However, in spite of the proven clinical benefit of this current paradigm to individuals and populations, there is at its core a reductionist approach to diagnosis that emphasises a small number of surrogate clinical traits – for example, systolic blood pressure and left ventricular ejection fraction. While most physicians recognise that these traits can be the consequence of many different disease processes, the clinical reality is that rare causes of common presentations are seldom considered in everyday clinical practice. Misdiagnosis is one of the biggest hurdles facing all rare conditions [5] [8].

On a daily basis, general hospitals and clinics deal with a large volume of patients with acute decompensation and chronic symptoms. In general, patients are well managed using protocols and care pathways built around broad diagnostic groupings such as acute heart failure and chest pain. *It is our contention that this approach is insufficiently refined to reliably*

detect and manage rare cardiovascular disease with adverse consequences for individuals and – in the case of heritable conditions – families. Data to support this hypothesis are still emerging, but there are already indications that some rare cardiovascular disorders are routinely overlooked. For example, in a single-centre study of patients undergoing surgical aortic valve replacement (AVR) for degenerative calcific severe aortic stenosis, 6% were subsequently diagnosed with occult wild-type transthyretin (TTR) cardiac amyloidosis which had a poor prognosis despite AVR [9]. In another single centre study of 72 patients aged 18-55 who had a permanent pacemaker implanted for second or third degree AV block, 14 (19%) had subsequent biopsy proven cardiac sarcoidosis and 4 patients (6%) giant cell myocarditis [10]. In an analysis of 145 unrelated Finnish patients with dilated cardiomyopathy (DCM), next-generation genetic sequencing identified a pathogenic or likely pathogenic mutation in 35% of cases (48% in familial DCM and 26% in sporadic DCM) [11].

The search for uncommon conditions is more than a simple academic exercise as the clinical course and treatment of many disorders is very different to that of more common mimics or phenocopies. For example, DCM caused by mutations in Lamin AC (*LMNA*) or Desmin (*DES*)– which together may account for more than 1 in 20 cases of DCM– is associated with a high risk of conduction disease and ventricular arrhythmia often well before the advent of severe left ventricular systolic dysfunction. Similarly, atrioventricular block caused by myocarditis needs more than device implantation. Failure to diagnose such conditions exposes individuals and relatives to the risk of premature and preventable death.

With constrained resources and limited access to specialist cardiac investigations, the diagnosis of rare disease can be challenging. In many cases, suspicion is triggered by an unusual or extraordinary event – for example, a sudden death in a young relative. On other occasions, the diagnosis is retrospective following delayed recognition of atypical features. While acknowledging the diagnosis of rare diseases requires some specialised knowledge and access to investigations such as genetic testing, it is our contention that a more nuanced approach to clinical assessment combined with routinely available tests can be used as a first pass filter to detect some of the most important rare cardiovascular conditions. The examples shown in **figures 1, 2 and 3** show how alertness to the clinical context, the presence of particular diagnostic red flags and a more iterative and logical use of readily available clinical tests can lead to accurate diagnosis.

In many respects this call to arms for rare cardiovascular disease is no more than a manifestation of the personalised or stratified medicine agenda that is informing policy development in European healthcare. In the U.K., NHS England defines personalised medicine as a “move away from a ‘one size fits all’ approach” towards a more comprehensive genomic and diagnostic characterisation that identifies different patient subtypes with particular symptoms or phenotypes that can be given tailored, targeted therapy” [12]. This strategy has already been successful in cancer therapy but we have only scratched the surface of this concept and its implications for cardiology.

Figures and Tables:

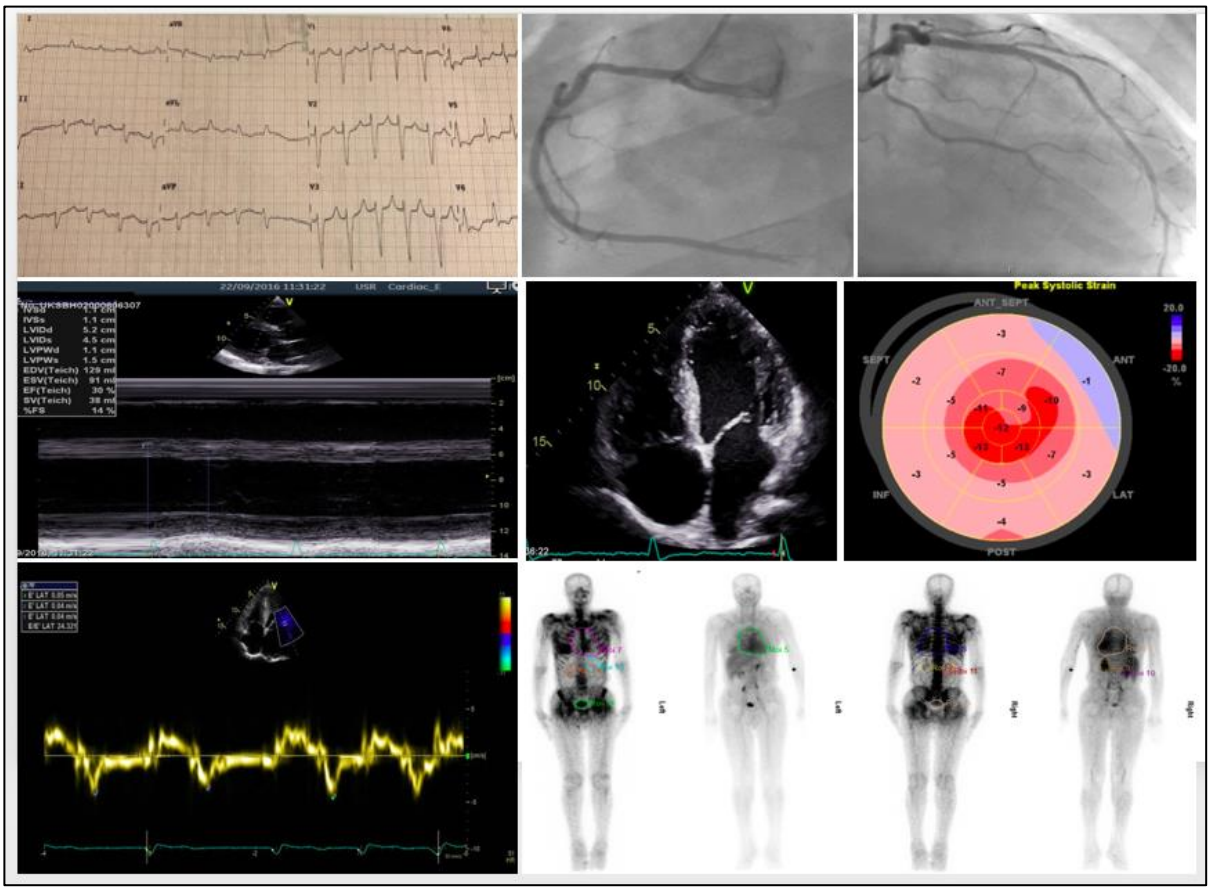

Figure 1: A 77 year old Afro-Caribbean man presented with heart failure and atrial fibrillation. The ECG demonstrated prolonged QRS duration (LBBB pattern) and atrial fibrillation. Transthoracic echocardiography confirmed severe left ventricular systolic dysfunction. Invasive coronary angiography revealed unobstructed coronary arteries. He was subsequently diagnosed with idiopathic dilated cardiomyopathy and managed symptomatically with standard heart failure medication for 4 years after which his symptoms began to deteriorate and he was referred onto specialist care in an inherited cardiovascular disease (ICVD) unit. His M-mode echocardiogram shows minimal LV wall thickening in systole and severe systolic LV dysfunction. Speckle tracking imaging and bull's eye plot shows severely reduced LV longitudinal excursion more marked in the basal and mid segments with relative preservation apically suggestive of underlying cardiac amyloid. Given his ethnicity, the presence of unexplained systolic LV dysfunction with characteristic echocardiographic appearances suggesting infiltration and conduction tissue disease, he underwent a 99mTechnetium labelled 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD) scan. This showed grade 2 perugini cardiac uptake consistent with cardiac TTR (Transthyretin) amyloidosis. This had significant implications on his prognosis and guided discussions on the use of biventricular pacing / defibrillator.

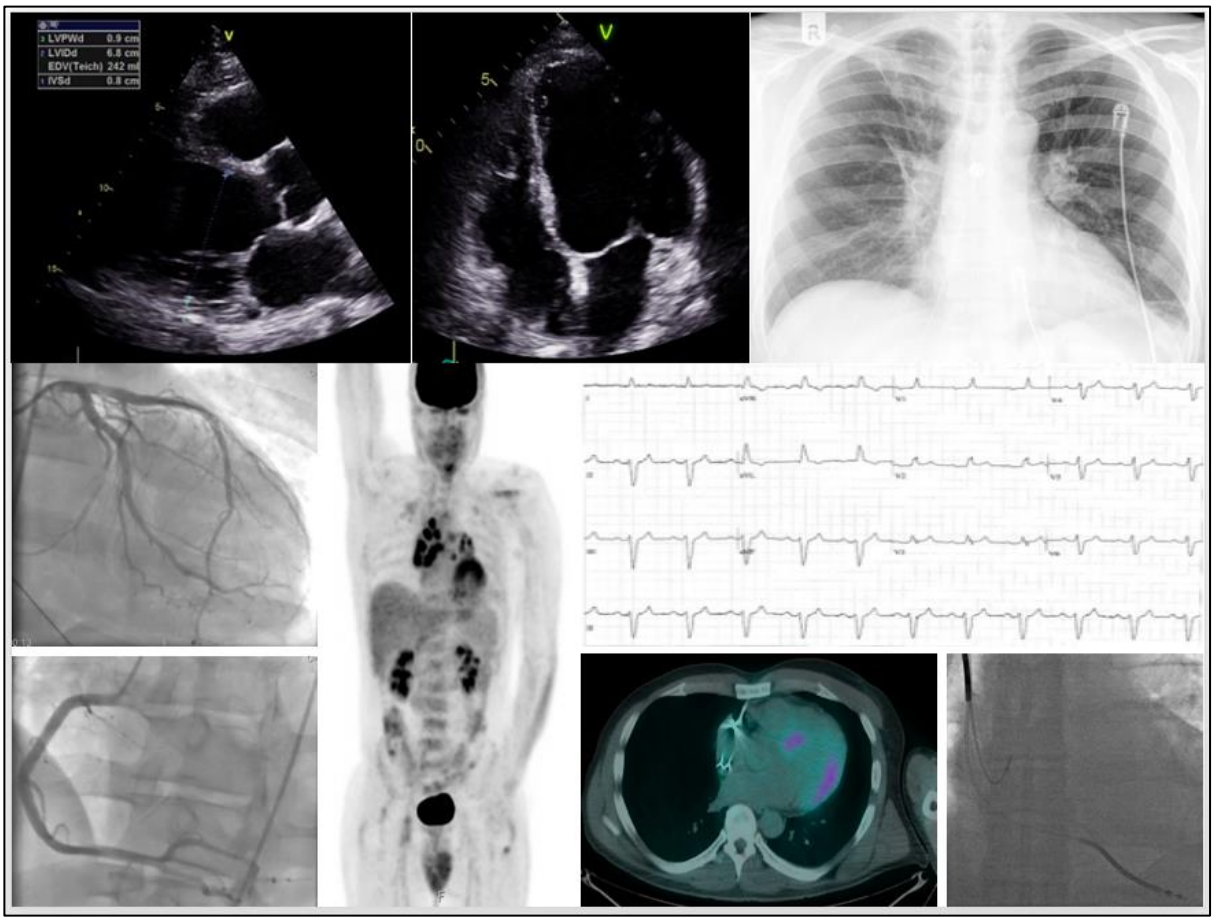

Figure 2: A 49 year old Caucasian male was admitted to his local hospital with an aborted out of hospital cardiac arrest with successful bystander cardiopulmonary resuscitation resulting in return of spontaneous circulation. His ECG on recovery showed RBBB and first degree AV block. His echocardiogram revealed a dilated left ventricle and severely impaired LV systolic function. He underwent invasive coronary angiography which revealed unobstructed coronary arteries. His chest x-ray suggested bi-hilar lymphadenopathy which was confirmed on CT Chest. He then underwent an FDG-PET (^{18}F – Fludeoxyglucose positron-emission tomography) scan which showed heterogeneous myocardial LV uptake particularly in the mid and basal anterior and anterolateral segments suggestive of active myocardial inflammation. There were also FDG avid mediastinal and bilateral hilar lymph nodes. Endobronchial Ultrasound biopsy of his mediastinal lymph nodes confirmed a diagnosis of sarcoidosis and he was commenced on immunosuppressant therapy for likely cardiac sarcoidosis with steroids and hydroxychloroquine. A secondary prevention dual chamber ICD was subsequently implanted.

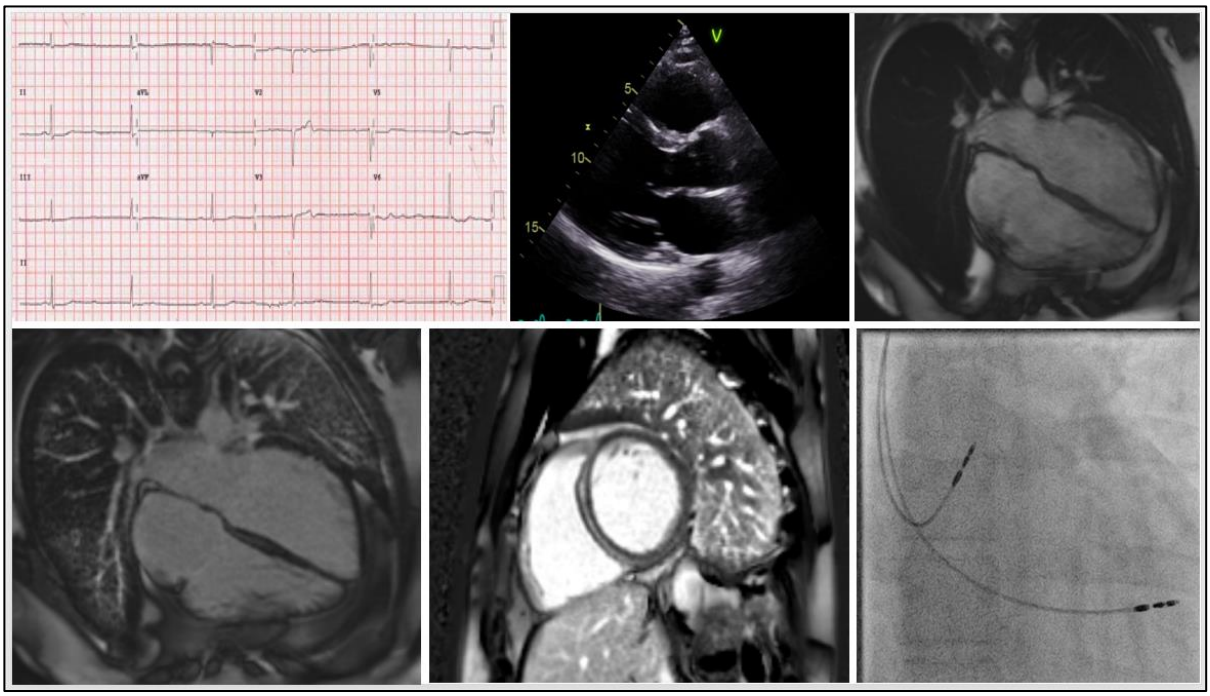

Figure 3: A 36 year old male presented to his GP with headaches. He was found to be bradycardic on routine examination and ECG showed a junctional rhythm with intermittent complete heart block. Echocardiogram revealed a borderline dilated LV cavity. Cardiac MRI was undertaken and showed a dilated LV with preserved LV systolic function and mid-wall fibrosis in the septal and inferior segments. A dual chamber pacemaker was subsequently implanted in his local hospital. He was re-admitted via the device clinic with SOB and found to be in new onset atrial flutter with 2:1 block and was anticoagulated with a view to consideration for a cavo-tricuspid isthmus ablation. He was subsequently referred onto the inherited disease team where a diagnosis of laminopathy was considered based on the presence of AV block, atrial dysrhythmias and mildly dilated LV. Subsequent genetic testing confirmed a pathogenic mutation in the Lamin AC gene. This has a significantly different natural course to other forms of AV block and prompted upgrade of his device to an implantable cardioverter defibrillator.

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