Cardiovascular deaths: What do the genes say?

Cardiovascular diseases (CVDs) are ever-increasing, and as such are considered to be one of the most concerning public health burdens worldwide. They remain the leading cause of death across the world (~17.7 million deaths were reported in 2015), accounting for 31% of all global deaths.[1]

More than 75% of these cardiovascular deaths occur in low- and middle-income countries, and although CVD is an acknowledged health concern in Africa, this priority area should receive much more attention than it currently does.[2]

Up to 50% of all cardiovascular deaths are a result of a sudden cardiac death (SCD), defined as 'a natural death due to cardiac causes, heralded by abrupt loss of consciousness within 1 hour after the onset of symptoms'. The consequences of these deaths, particularly in the young, have a greater impact and health burden in terms of life-years lost than all individual cancers and other leading causes of death. The fact that nearly 90% of SCDs are caused by an inherited disorder justifies the international focus on, and prioritisation of, the underlying genetic causes of these cardiac disorders.[3]

Disorders linked to SCDs vary greatly between different age groups, with ischaemic heart disease being the most common cause of death in the older population. In comparison, the majority of SCDs in the younger population (≤45 years) are due to inherited cardiomyopathies and arrhythmogenic disorders. Unfortunately, there is a lack of clinical symptoms or warning signs, with research showing that in 75% of SCD cases, death is the first 'symptom'.[4]

Inherited cardiomyopathy- and arrhythmogenic-related SCDs result from lethal arrhythmias. These are caused by alterations (genetic variations) in genes that all play a role in cardiomyocyte excitability and contractility. Cardiomyopathy-related genetic variations affect the structure and function of the heart muscle, whereas cardiac arrhythmogenic genetic disorders are generally associated with isolated electrical dysfunction. The four most common inherited arrhythmogenic disorders include long QT syndrome, Brugada syndrome, catecholaminergic polymorphic ventricular tachycardia and short QT syndrome. Although each of these has a characteristic electrocardiogram (ECG) profile when experiencing an arrhythmic episode, their spontaneous and sporadic nature results in a difficult clinical diagnosis.[5,6]

The same gene can be altered in different ways (different genetic variations), which can lead to vastly different clinical manifestations of a disorder. These differences are important when considering available and effective treatment for patients, as each treatment is designed to target a certain defect and/or function. Fortunately, there are various types of treatment available, which can range from anti-arrhythmic medications to implantable cardioverter defibrillators and pacemakers.[1,7]

Therefore, even for general practitioners (GPs), there is clinical importance in determining the underlying genetics of an inherited cardiac disorder, to allow for effective and individualised treatment of a patient and/or affected family members. Since diagnosis can be challenging, be it due to an absence of ECG abnormalities, overlap of clinical phenotypes or lack of symptoms, genetic testing in all individuals at risk for an inherited cardiomyopathy or arrhythmogenic disorder is crucial. This is reiterated by the marked reduction in mortality associated with the administration of proper treatment.[7]

The general medical practitioner, in particular, is in a central position in SCD prevention, and plays an essential role in the multidisciplinary team tending to affected family members. GPs have a greater personal connection to the community, and often care for different generations of the same family, which allows for earlier recognition of subtle warning signs suggestive of an inherited cardiomyopathy or arrhythmogenic disorder. Clinical practitioners should especially be cognisant of any family history of syncope, epilepsy, sudden death, deafness, heart failure or pacemaker implantation at a young age (<50 years). Primarily, the GP will be the first to recognise a possible inherited cardiac disease in an individual or family, and through appropriate genetic testing may provide the only opportunity for an early diagnosis and proper clinical management.

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