Sudden cardiac death in young competitive athletes due to genetic cardiac abnormalities

Genetik kardiyak anormallikler nedeniyle genç yarışmacı atletlerde ani kalp ölümü

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ABSTRACT

Sudden cardiac death (SCD) in young athletes is generally caused by inherited cardiac disorders. While these events are relatively few compared to other cardiac deaths, they are tragic in that death occurs in a young, otherwise healthy person. The genetic abnormalities most associated with SCD are hypertrophic cardiomyopathy, arrhythmogenic right ventricular cardiomyopathy, long QT syndrome, Brugada syndrome, and catecholaminergic polymorphic ventricular tachycardia. As a result of growing awareness that these deaths can be prevented, guidelines have been issued in both Europe and the United States to help screen and determine qualification for young persons who want to participate in competitive athletics. There remains debate on the how extensive screening should be, in particular over the use of the 12-lead electrocardiogram (ECG), with European guidelines mandating ECG and United States guidelines not recommending routine use of the ECG. *(Anadolu Kardiyol Derg 2009; 9: Suppl 2; 17-23)*

Key words: Athlete, sudden cardiac death, hypertrophic cardiomyopathy, ion channelopathies, arrhythmogenic ventricular cardiomyopathy

ÖZET

Genç atletlerde ani kalp ölümüne genellikle, kalıtsal kalp hastalıkları sebep olmaktadır. Bu olaylar, diğer kardiyak ölümlerle kıyaslandığında nispeten az olsa da sağlıklı bir gençteki bu ölüm trajiktir. Ani kalp ölümü ile beraber en çok görülen genetik anormallikler, hipertrofik kardiyomiyopati, aritmojenik sağ ventriküler kardiyomiyopati, uzun QT sendromu, Brugada sendromu ve katekolaminerjik polimorfik ventriküler taşikardidir. Bu ölümlerin önlenebilirliği konusunda farkındalığın artması sonucu hem Avrupa, hem de Birleşik Devletlerde yarışmacı atlet olmak isteyen gençler için tarama ve nitelik tespitine yardımcı olan kılavuzlar yayınlandı. Kapsamlı taramanın nasıl olacağı, özellikle 12 derivasyonlu elektrokardiyografi (EKG) kullanımı üzerine, Avrupalı kılavuzlar EKG'yi zorunlu kılarken, Amerikalı kılavuzların rutin EKG kullanımını tavsiye etmemesi halen tartışılmaktadır. *(Anadolu Kardiyol Derg 2009; 9: Özel Sayı 2; 17-23)*

Anahtar kelimeler: Atlet, ani kardiyak ölüm, hipertrofik kardiyomiyopati, iyon kanalopatiler, aritmojenik ventrikül kardiyomiyopatisi

Introduction

Sudden cardiac death (SCD) of a young (under age 35) athlete is a catastrophic event not only because very often these tragedies occur in the public eye, but also because athletes are young, and considered among the healthiest members of our society. The true incidence of SCD in young athletes is not known with certainty. In the U.S. it has been reported as 1:200,000 young athletes per year in Minnesota high schools (1). In contrast, a prospective study in the Veneto region of Italy reported an incidence of SCD of 2.1 per 100,000 athletes per year from cardiovascular diseases (2). The most common causes are inherited cardiovascular disorders. In the United States, hypertrophic cardiomyopathy (HCM) accounts for 36% of the total deaths, followed by congenital coronary artery anomalies, 17%. Arrhythmogenic right ventricular cardiomyopathy (ARVC) and ion channelopathies represent 4% and 3% of the total deaths respectively (3, 4). In Europe, specifically in the Veneto region of

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Italy, the most common cause of SCD in athletes is ARVC, accounting for 22% of the total deaths, followed by anomalous origin of coronary arteries with 12%. In contrast with the U.S. experience, HCM was the cause of SCD in only 2% of the young athletes (5). Although the reasons for this difference are unclear, it may be due to the early detection of HCM by the Italian national pre-participation screening program. Italy is the only country worldwide where, since 1982, pre-participation screening is required by law. The Italian guidelines mandate use of the 12-lead electrocardiogram (ECG) in addition to history (personal and family) and physical examination. Another possible explanation is that Italy is a more homogeneous population compared to the United States and hence may have less genetic variation.

Though the incidence of SCD in athletes is low, many support specific screening protocols to detect genetic heart disease prior to athletic participation. In Italy, mandated screening has been reported to significantly reduce SCD in competitive athletes (11). In 2005, the European Society of Cardiology (ESC) released a consensus document recommending the use of ECG in addition to history and physical examination (5). In 2007, the American Heart Association (AHA) released an update to the 1996 recommendations for pre-participation screening, leaving unchanged the recommendations of using only history and physical examination for screening. This last recommendation was based on the large number of athletes eligible for screening (10 million individuals), the apparent low prevalence of SCD in this group, and lack of trained personnel and funds that would be required. The AHA statement also concluded that implementation of expanded screening including ECG, would not be not cost effective for the U.S (4). There is concern about the specificity of ECG abnormalities and the possibility that sports participation might be proscribed in individuals with normal variant ECGs. There is often substantial emotional distress associated with the recommendation of non-participation. This must be carefully weighed against the very real and mortal danger of competing with inherited cardiac disease.

This article will review the genetic cardiovascular disorders that are most commonly associated with SCD in young competitive athletes and will discuss current recommendations for disqualification from participation in competitive athletics.

This review will focus on the inherited causes of ventricular fibrillation and will not cover Marfan's syndrome an inherited cause of sudden death, but because of aortic rupture or dissection.

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy is a familial cardiac disease with a heterogeneous genotypic and phenotypic expression, complex pathophysiology and treatment options. It is inherited as an autosomal dominant trait; and is the most common inherited cardiac disorder, occurring in 1:500 of the general population (6). About 50% of the individuals with HCM will have a relative with the disease. Those without a family history may have sporadic mutations. Approximately 50% of patients with HCM are found on genotype analysis to have a sarcomeric disease-causing mutation. Sarcomeric mutations of ≥11 genes that code for myofilaments or their supporting proteins have been identified with with myosin-binding protein C and beta-myosin heavy chain being the most common mutations. Even though the bulk of genetically determined HCM occurs in 8 genes, ≥1000 HCM-causing mutations are dispersed over many loci of these genes. These different mutations cause varying phenotypic expression, clinical course, and prognosis. Because there are so many mutations, and because many families have "private mutations" that have been infrequently or never reported elsewhere, there are no gene-specific prognostic features. However, genotype positive HCM has a worse prognosis than genotype negative HCM, with greater occurrence of the combined endpoints of cardiac death and disability.

Clinical presentation

The clinical detection of athletes with HCM can be challenging, given that many athletes may present with the nonobstructive form, which can make the disease clinically silent. Hypertrophic cardiomyopathy should be suspected in a young athlete who presents with exertional dyspnea, chest pain, unexplained syncope or prior recognition of a heart murmur. Dyspnea usually is caused by inability to increase cardiac output and left ventricular (LV) filling pressures due to the non compliant hypertrophied LV, and exacerbated by decreased filling time. It is now apparent that obstruction is frequently provocable in non-obstructive HCM after exercise. Angina may occur secondary to subendocardial ischemia caused by luminal narrowing of the intramural coronary arteries and, in patients with obstruction, by supply-demand mismatch. Syncope can occur either due to LV outflow tract obstruction resulting in decreased cardiac output leading to cerebral hypoperfusion or due to cardiac arrhythmias. Histopathologic myocardial fibrosis or myocyte fiber disarray is believed to be the substrate for malignant ventricular arrhythmias and may be triggered by ischemia or local abnormality in electrolyte concentration.

A family history of HCM, sudden cardiac death, heart disease in a close relative <50 years of age or unexplained syncope should also raise the suspicion for HCM. On the physical examination, the most important finding is a systolic murmur increased/elicited by provocative maneuvers such as Valsalva, standing or exertion.

Electrocardiographic abnormalities can be found in 75-95% of HCM patients and may precede the appearance of overt hypertrophy (8). Typical electrocardiographic abnormalities include: increased precordial voltages consistent with left ventricular hypertrophy (LVH), ST segment and T wave abnormalities, abnormally deep Q waves in inferior and lateral leads and ventricular or supraventricular arrhythmias such as atrial fibrillation, premature ventricular contractions and ventricular tachycardia can be present (9).

Echocardiographic findings

Echocardiography is the most important imaging technique in the evaluation of suspected HCM. HCM is diagnosed when LV

hypertrophy occurs in the absence of a clinical condition that would cause hypertrophy. Asymmetric wall thickness ≥15 mm with a small LV cavity (<45mm) is diagnostic. Symptomatic patients most often present with wall thicknesses between 20-30 mm, but the degree of wall thickening can vary widely. Typically, the LV hypertrophy involves the septum in a greater degree, but the phenotypical presentation of the disease is diverse, with mid and apical HCM being other variants of the disorder. Other echocardiographic changes indicative of HCM include reduced early mitral annular tissue Doppler velocity (Ea) due to decreased relaxation in early diastole, systolic anterior motion (SAM) of the mitral valve and a late peaking systolic pressure gradient in the LV outflow tract. Diagnosis in some patients may require use of echocardiogram with intravenous contrast (apical HCM) or cardiac magnetic resonance (CMR) imaging.

Asymptomatic individuals who present with LV wall thickness between 13 and 15 mm represent a diagnostic dilemma and should be carefully evaluated and differentiated from athlete's hearts, benign left ventricular hypertrophy due to vigorous training. Athlete's heart, the benign condition does not occur in casual athletes; rather it occurs in elite athletes, in training for higher levels of competition. In patients with wall thickness between 13 and 15 mm, a relatively small left ventricle, asymmetric hypertrophy, SAM, impaired relaxation on tissue Doppler imaging, or decreased aerobic capacity on metabolic stress testing suggest HCM. In some patients with vexing ambiguity cessation of training and deconditioning will allow distinction to be made, since in the physiologic variant the hypertrophy decreases relatively rapidly once training is stopped, while in HCM it persists. In ambiguous cases, genotype analysis may be invaluable if there is detection of a specific disease-causing mutation.

Recommendations for qualification to participate in competitive athletics

European and U.S authorities have issued recommendations (10, 12) for competitive sport participation in athletes with HCM. Due to the scarcity of supporting clinical data, these recommendations are mainly based on the expert opinion of both groups. In athletes with a definitive diagnosis of HCM, both documents recommend the exclusion from most competitive sports, with the possible exception of low dynamic and low static sports (golf, billiards, bowling, cricket, and marksmanship) in those individuals considered to be at low risk for SCD. The groups differ in their recommendations regarding the genotype positive-phenotype negative athletes. The U.S. guidelines do not recommend exclusion of these individuals from competition due to the lack of data and unknown natural history. On the other hand, the ESC consensus document excludes these individuals from competitive sports and recommends amateur and leisure sport activities (10-12).

An agreement between the guidelines is that the implantation of a defibrillator, presence of a free-standing automated external defibrillator, pharmacologic or surgical therapy or degree of phenotypic expression of the disease do not alter the aforementioned recommendations of either panel of experts.

Arrhythmogenic Right Ventricular Cardiomyopathy

Arrhythmogenic right ventricular cardiomyopathy is an inherited cardiac disorder characterized morphologically by myocyte death with subsequent fibro-fatty tissue replacement in the right ventricle (RV); and clinically by life-threatening arrhythmias and heart failure. ARVC can be inherited as an autosomal dominant or recessive trait. This disease may be segmental or diffuse. Involvement of the LV is frequently seen (13). Mutations in the genes coding for components of the desmosomes have been recently recognized as the cause of ARVC. The genes affected by ARVC-causing mutations include those coding for plakoglobin, desmoplakin, plakophilin, desmoglein, desmocollin. The defects in the desmosomes, which are the intercellular junctions that anchor intermediate filaments to the cytoplasmic membrane in adjacent cells, cause myocyte detachment and death. Subsequently these myocytes are replaced by fibro-fatty tissue.

The prevalence of ARVC is estimated to be approximately 0.02% to 0.1% in the general population, with mortality rates range from 4% to 20% noted in major studies (14, 15). ARVC is the leading cause of sports related deaths in Veneto region of Italy, accounting for 22% of SCD in young athletes, while in the U.S. it is associated with 4% of deaths.

Clinical presentation

The pre-clinical detection of ARVC in young competitive athletes is difficult, and the first manifestation is often SCD. The possibility of ARVC should be entertained whenever a young patient presents with syncope of unexplained cause, cardiac arrest, ventricular arrhythmias, and heart failure. As ARVC is a familial disorder, a history of SCD, syncope or ventricular arrhythmias in close relatives can be elicited. Diagnostic criteria for ARVC have been previously established (16). To qualify as ARVC, a patient must demonstrate either two major criteria, one major criterion plus two minor criteria, or four minor criteria. Criteria include RV structural or functional abnormalities, tissue characterization, ECG depolarization/conduction abnormalities, arrhythmias, and family history.

Electrocardiographic abnormalities include abnormalities such as T wave inversions in V1 to V3 in the absence of a right bundle branch block (RBBB), complete or incomplete RBBB. These findings are seen in 54% and 15% of the cases respectively. Prolongation of the QRS in leads V1 to V3 compared with lead V6 is one of the major criterions and is satisfied if the QRS duration in leads V1 to V3 is 50 ms above the QRS duration in lead V6 in the presence of RBBB. Epsilon waves, small amplitude electrical potentials that occur at the end of the QRS complex, are another major diagnostic criterion found in up to 30% of cases of ARVC and represent delayed RV activation. Although not a sensitive finding, epsilon waves are highly specific for ARVC. When ventricular tachycardia (VT) occurs, it typically has left bundle branch block morphology, reflecting its right sided origin.

Imaging characteristics

The most common echocardiographic findings are RV dilatation and severe hypokinesis. The abnormalities can range from mild regional RV dysfunction and dilatation, including aneurysm formation- to overt and severe RV dilatation and dysfunction (17, 18). A ratio of the RV to LV end diastolic diameter >0.5 has a sensitivity of 86% and a specificity of 93%, with a positive predictive value of 86% and negative predictive value of 93% for the diagnosis of ARVC (19). Patients suspected of ARVC should also undergo CMR imaging, which offers tissue characterization as well as detailed information on cardiac structure and function.

Recommendations for qualification to participate in competitive athletics

Because of the risk of sudden death in patients with ARVC, patients with this condition should be prohibited from vigorous athletic competition. This prohibition remains in effect even after the subjects have received effective treatment such as implantable cardioverter defibrillator (ICD) placement because athletic competition may induce incessant ventricular fibrillation that cannot be terminated, given the response patterns of current devices (10-12). Moreover, ICD devices, particularly the vulnerable leads, may be damaged by athletics.

Long QT syndrome

Hereditary long QT syndrome (LQTS) is a genetic channelopathy with variable penetrance and clinical course. Clinically, it is characterized by an abnormal QT interval prolongation on the ECG and increased predisposition to syncope, polymorphous VT and SCD. It can be inherited as an autosomal dominant or recessive form. The QT prolongation is the result of delayed repolarization due to either a decrease in repolarizing potassium currents or late entry of sodium into the myocyte. Since it was first described by Jervell in 1957 (20), mutations in several genes that codify different subunits of potassium and sodium channels have been discovered. The most commonly involved genes are KCNQ1 (LQT1), KCNH2 (LQT2), SCN5A (LQT3), mink (LQT5) and MiRP1 (LQT6) (21).

The estimated prevalence of this disorder is in the range of 1:5000 in the general population. Data from the registry of the Minneapolis Heart Foundation indicates that LQTS accounts for approximately 0.8% of the total deaths in young athletes (22). Ion channelopathies in general account for 3% of total deaths in young athletes in United States (3). The Italian pre-participation screening program reported a disqualification rate for Long QT syndrome of 0.69% of all athletes, based solely on the identification of a prolonged QT segment. A study conducted in United Kingdom, involving 2000 young athletes showed a prevalence of an isolated long QT interval of 0.4% (7 athletes). Of these 7 athletes, 2 had a high probability of LQTS based Schwartz LQT diagnosis scoring system and one carried a disease causing mutation, making a prevalence of diagnosed LQTS in young athletes of 0.15% (23).

Clinical presentation

The most common presentations include syncope, SCD or malignant ventricular arrhythmia in a young adult. Obtaining a detailed family history is essential given that it may reveal episodes of syncope or SCD, not only in first degree relatives but also in remote relatives. A personal or family history of deafness can also suggest the possibility of concomitant LQTS.

Electrocardiographic characteristics

A prolonged QT corrected for heart rate (QTc) identified in the absence of secondary causes of QT prolongation can make the diagnosis of LQTS. Males with a QTc >440ms or females with a QTc >460ms are considered to have an abnormally prolonged QT. The Bethesda #36 consensus document defines a prolonged QTc as an interval exceeding 470ms in males and 480 ms in females. A scoring system, based on personal and family history as well as ECG, has been developed for those cases where the diagnosis is not clear (24). Holter monitoring and exercise testing can help to improve diagnostic accuracy in unclear cases.

Recommendations for qualification to participate in competitive athletics

The ESC consensus document recommends exclusion of the athlete with definitive diagnosis of LQTS from any type of competitive sports, while those asymptomatic genotype-positive, phenotype-negative athletes are discouraged from participation in competitive sports. The Bethesda conference #36 document also recommends exclusion of most competitive sports of those individuals with definitive diagnosis of LQTS, except from low dynamic and low static sports. Unlike the ESC, these guidelines allow participation in competition of genotype-positive, phenotype-negative athletes, with special consideration of individuals with LQT1 mutation. Due to the strong association between swimming deaths and LQT1 mutation, these genotype-positive, phenotype-negative athletes should refrain from competitive swimming (10, 25).

Brugada syndrome

Brugada syndrome (BS) is an autosomal dominant inherited channelopathy with variable pathophysiology and clinical expression. This syndrome as described initially by Brugada & Brugada is characterized by a right bundle branch block pattern, persistent ST segment elevation, and sudden cardiac death (26). Mutations in chromosome 3, specifically the gene encoding the alpha subunit of the cardiac sodium channel, SCN5A, are responsible for this syndrome. The ST segment elevation seen in BS is probably caused by the selective loss of the action potential dome in the right ventricular epicardium, sparing the endocardium (26). The predisposition to develop malignant ventricular arrhythmias is caused by the electrical heterogeneity within the RV epicardium, leading to closely coupled premature ventricular contractions via a phase 2 reentrant mechanism.

Clinical presentation

Brugada syndrome is 8 to 10 times more prevalent in men than in women (28). The typical presentation is syncope, SCD or ventricular arrhythmias in a young adult. Malignant ventricular arrhythmias or SCD typically occur at rest and often at night, as a consequence of increased vagal tone and/or withdrawal of sympathetic activity. This presentation in conjunction to the electrocardiographic findings of RBBB pattern and ST segment elevations in right sided precordial leads can make the diagnosis of BS. In those patients where the diagnosis of BS is not clear, diagnostic criteria have been developed by the European Society of Cardiology as noted below (29).

Electrocardiographic characteristics

Three different electrocardiographic patterns of BS have been recognized (See the ECG patterns in the article of Khan A et al of this supplement). In Brugada type 1, the QRS complex ends with a prominent J point, followed by an elevated down-sloping ST segment (coved type or dome shape) and a negative T wave with a normal QT interval. Leads V_1 to V_3 show the most prominent changes, with the degree of ST segment elevation tapering off in adjacent leads. It is a characteristic finding that the ST segment elevation in the right precordial leads is not accompanied by reciprocal ST segment depression in opposite leads. In Brugada type 2 and 3, the ST segment has a saddle-back shape. The ST segment descends to the baseline and then rises to a biphasic or monophasic T wave. If the ST segment is elevated ≥1mm is classified as BS type 2, otherwise as BS type 3. The presence of ST segment elevation in right precordial leads in the absence of secondary causes is called idiopathic ST segment elevation a definitive diagnosis of BS should be pursued with genetic testing.

Recommendations for qualification for participation in competitive athletics

Ion channelopathies as a group are responsible for 3% of total deaths in young athletes in United States (3). The contribution of BS to these deaths is not well defined. Although no association between SCD or malignant ventricular arrhythmias due to BS and exercise has been established, the general consensus in Europe and U.S. recommends exclusion of young athletes from competition. These recommendations are based on the theoretical consideration that increased vagal tone, resulting from athletic conditioning could potentially increase the risk of malignant ventricular arrhythmias and SCD at rest or even post exercise. The potential impact of hyperthermia caused by exercise, which very often unmasks the electrocardiographic manifestations of BS, further supports the recommendation of both panel of experts (10, 25).

Catecholaminergic polymorphic ventricular tachycardia

Catecholaminergic polymorphic ventricular tachycardia (CPVT) is an autosomal dominant and recessive inherited disorder characterized by bidirectional and polymorphic ventricular tachycardia in response to vigorous exercise or intense emotional stress, in the absence of identifiable precipitant factors. It is an important cause of SCD in children and young adults. The cumulative cardiac mortality is 31% by the age of 30 years (30). Pathogenic mutations have been identified in the genes encoding the ryanodine receptor 2 (chromosome 1q42-q43) and calsequestrin 2 (31). Both genes are involved with the release and handling of intracellular calcium. A proposed mechanism for the development of malignant ventricular arrhythmias is that extrasystolic activity, induced by delayed afterdepolarization, triggers catecholamine-induced VT. Dispersion of transmural depolarization by the extrasystolic activity is the nidus for the development of reentrant tachyarrhythmias (32).

Clinical presentation and electrocardiographic characteristics

The most common presentations of CPVT include recurrent syncope (79%), cardiac arrest (7%) and family history of SCD (14%) (33). These typically present during childhood or early adulthood as polymorphic VT in the absence of structural or other functional causes and are precipitated by exercise or emotional stress.

The electrocardiogram will reveal polymorphic ventricular arrhythmias; including isolated premature ventricular contractions that can progress to bigeminy, multifocal premature ventricular complexes and polymorphic ventricular tachycardia, that can degenerate in ventricular fibrillation. The most common form of CPVT is non-sustained VT (72%), followed by sustained VT (21%) and ventricular fibrillation (7%). The morphology of CPVT can be polymorphic (62%), polymorphic and bidirectional (21%), bidirectional (10%), or polymorphic with ventricular fibrillation (7%) (29). Typically these arrhythmias can be induced by exercise or catecholamine infusion.

Recommendations for qualification to participate in competitive athletics

The consensus is that individuals with a definitive diagnosis of CPVT, as well as genotype-positive athletes with evidence of exercise or pharmacologic induced VT, should be excluded from competitive sports. Similar to LQT1, athletes with a diagnosis of CPVT should be excluded from competitive swimming. The Bethesda #36 document leaves open the possibility in these individuals of practicing minimal contact, low dynamic, static activities. Furthermore, this document does not restrict the participation in competitive sports of asymptomatic, genotype-positive, phenotype-negative individuals without evidence of isoproterenol-induced VT (10, 25).

Summary

Inherited cardiac disorders are responsible for the majority of sudden cardiac deaths in young competitive athletes. These conditions have been well described allowing accurate diagnosis for most patients. Perhaps more important is formal structure that allows for these diagnoses to be made, especially for those young patients who plan to participate in vigorous exercise or

competitive athletics. Key to successful prevention of SCD in athletes are guidelines that mandate a screening protocol that has both acceptable sensitivity and specificity to detect those at risk for SCD. While European guidelines have embraced performance of an ECG, in addition to expanded family, personal history, and physical examination, guidelines in the United States have not embraced use of the ECG for reasons discussed earlier in this review. The debate will likely continue until further research provides us with information on what characteristics in the ECG should be used to determine need for disqualification and further cardiac testing.

Although, subtle differences may exist between the current U.S. and European recommendations, young athletes with a definitive diagnosis of HCM, ARVD or any of the ion channelopathies discussed here should be advised against participation in competitive athletics. A grey zone exists in the case of genotype-positive, phenotype-negative individuals, where the paucity of experimental and clinical evidence limits our capacity to provide recommendations against or in favor of participation. In this last group, recommendations should be individualized, taking in consideration the risk of sudden cardiac death based on the individual's risk factors. A close physician-patient relationship should be established to assure that the specific recommendations as to type and intensity of athletic involvement are well understood and adequately discussed. For minors parental discussion is vital as well.

Conflicts of interest

The authors have the following potential conflicts of interest to disclose: Dr. Myerson: Abbott Laboratories (Educational Grant, Research Grant), Daiichi Sankyo (consultant), GlaxoSmithKline (Speaker), Medtronic (Research Grant).

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