Commentary

Use of intravenous antiarrhythmics to identify concealed Brugada syndrome

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Abstract

Cardiology has recently witnessed the production of an overwhelming amount of data through the advances made in genetics and molecular biology research. Understanding of genetics has tremendous potential to aid in the prevention, diagnosis and treatment of the majority of diseases. Despite the high level of publicity for research discoveries, clinicians have had difficulty in discriminating between what is still basic research and what can be applied to patients. The fact is that we still lack the technology to perform genetic testing in a time frame that is acceptable to clinicians. Meanwhile, then, the only option is to rely on clinical tests that can help us better stratify the individuals at risk for a disease. For example, Brugada syndrome has benefited tremendously from genetics and molecular biology since its initial description in 1992. Genetics will provide a more definitive diagnosis for the disease in the future. For the time being, though, research has shown that the administration of an intravenous class I antiarrhythmic is very useful in identifying patients with a concealed form of the disease.

Keywords: Brugada syndrome, class I antiarrhythmics

Introduction

Over the past 50 years, the survival and quality of life of patients with cardiac disease has improved tremendously. Despite continued progress in technology and drug therapy, it seems that progress may have reached a plateau. The majority of our patients suffer from structural heart diseases, such as atherosclerosis and primary myocardial disease, that often progress despite our best efforts.

The situation is completely different, however, when cardiac arrest strikes a healthy young person with no previous medical history. In this case, there is pressure not only on the patient and physician but also on family members, as there is a higher likelihood that the patient is suffering from a genetically determined disease predisposing to sudden death. It is at this point that there is a clash between the bench and the bedside, with physicians and family demanding a genetic test that will provide a definite diagnosis. The advances in molecular cardiology and genetics have been spectacular if one thinks that it has been only 10 years since the identification of the first gene predisposing to a familial cardiac disease. It is expected that our knowledge of cardiac disease will grow exponentially in the next few years thanks to the advances in the Human Genome Project. The reality, though, is that the technology has not yet evolved enough to be able to complete a genetic screen in a few days.

Among the different diseases which are genetically determined, Brugada syndrome has benefited tremendously from the developments in molecular biology. The diagnosis is based on a clinical-electrocardiographic criteria consisting of syncopal or aborted sudden death episodes occurring in patients with a structurally normal heart, who also present with a characteristic ECG pattern of right bundle branch block and ST segment elevation in leads V1 to V3. The episodes of syncope and sudden death (aborted) are caused by fast polymorphic ventricular tachycardias [1].

Etiology and epidemiology

The first case series showing the link of the ECG pattern with sudden death was published in 1992 [2]. Since then it has been identified in all parts of the world, being the most important cause of sudden death in young males in Southeast Asia [3], and also claiming some of the deaths from sudden infant death syndrome [4]. It is a highly fatal disease, with recurrence of events of 30% at 3 years. There is no medical therapy to prevent recurrence. The implantable defibrillator is the only therapy that has been shown to possibly improve survival of these individuals [1].

This syndrome is genetically determined and in some cases is caused by mutations in the gene *SCN5A*, on chromosome 3 [5]. This gene encodes the human cardiac sodium channel. The pattern of transmission described so far in this disease is autosomal dominant. As is the case with the other familial cardiac diseases, some of the families studied do not present any mutation in the *SCN5A* gene, indicating that the disease is heterogeneous, caused by mutations in more than one gene. Functional analysis of the mutations in X*enopus* oocytes shows that the mutant channel has loss of function, creating heterogeneity of refractory periods, a perfect substrate for reentrant arrhythmias. Further electrophysiologic studies have shown that the effect of the mutation is temperature-dependent, worsening channel function at temperatures approaching the physiological range [6].

It is difficult to estimate the real prevalence of the disease due to the fact that the ECGS of affected patients are variable, normalizing during certain periods of time. Therefore, like other genetically determined diseases, such as the long QT syndrome or familial hypertrophic cardiomyopathy, the lack of clinical data pointing to the presence of disease does not exclude a family member from being affected. This complicates the identification of individuals at risk, and increases the pressure on physicians and relatives of a patient who has Brugada syndrome.

The ECG pattern can be modulated by autonomic and pharmacological interventions [7]. Administration of a sodium channel blocker may unmask the ECG pattern in those individuals who present with a normal ECG; however, this test has not been validated for identifying individuals at risk, mainly because of the lack of a gold standard. The description of one of the genes causing Brugada syndrome has enabled family members of the individuals carriers of the disease to be screened; consequently, the sensitivity and specificity of the antiarrhythmic test has been analyzed in this specific population [8]. The results of our investigation were encouraging, as the test identified all the individuals who carried the abnormal gene and all the affected individuals who had transient normalization of the ECG. None of the controls showed the characteristic ECG pattern after the administration of the class IC antiarrhythmic drug. The study also demonstrated that the risk of sudden death in individuals with the intermittent ECG pattern is the same as the risk for individuals with persistent ST segment elevation.

Genetic screening for sudden death

Genetic testing can provide firm evidence for or against the diagnosis of familial diseases. Indeed, it has the potential to be 100% sensitive and specific in identifying individuals at risk. There is at present an important limitation, however: as unbelievable as it may seem, this is actually the lack of technology to perform a fast genetic screen.

Physicians meanwhile have to rely on clinical parameters to risk stratify those individuals affected by a lethal disease. These parameters are neither sensitive nor specific enough. Despite the fact that family history of sudden death is helpful, it provides prognostic information only if the death was clearly related to the same disease [9]. For example, in hypertrophic cardiomyopathy, patients with mutations in troponin T can have subclinical hypertrophy [10], in long QT syndrome 5–15% of the patients are diagnosed incorrectly if the diagnosis is based only on the electrocardiographic criteria [11], and in Brugada syndrome, there can be transient normalization of the ECG, which complicates the identification of affected individuals.

Among the multiple clinical tests performed in individuals who present with syncope or aborted sudden death of unknown etiology and a normal ECG, the administration of intravenous ajmaline, procainamide or flecainide (doses shown in Table 1) has proven very useful for unmasking Brugada syndrome. The test is safe, but the triggering of ventricular arrhythmias during the test has been described, with an incidence of sustained ventricular arrhythmia of 0.5% (P Brugada, unpublished data). It is mandatory then that the test be performed in a safe environment, with cardiopulmonary resuscitation equipment available. The test has been shown to be reliable in identifying both the carriers of *SCN5A* mutations and the individuals who present with transient normalization of the ECG. Further research is required to validate this test in individuals with mutations in other genes.

Table 1

Intravenous agents used to unmask ECG abnormalities.

Antiarrhythmic agent	Dose	Infusion time
Ajmaline	1 mg/kg	5 min
Flecainide	2 mg/kg	10 min
Procainamide	10 mg/kg	10 min

Conclusion

Brugada syndrome is being recognized worldwide as a cause of sudden death in the young population with structurally normal hearts. Research in recent years has shown that the risk of sudden death is 30% at 3 years, both for symptomatic and asymptomatic individuals. While the ECG is variable and can normalize at follow-up, the patients remain at the same high risk of events. It is then of paramount importance to be able to diagnose these individuals.

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