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EDITORIAL COMMENT

Searching for a Diagnosis After SADS

The Value of Perseverance*

Pedro Brugada, MD, PhD

In this issue of the *Journal,* Papadakis et al. (1) report a unique study in families with sudden arrhythmic death syndrome (SADS). Papadakis et al. (1) studied 911 relatives from 303 families who had 1 relative with SADS of unknown cause. They systematically used clinical history, physical examination, electrocardiogram (ECG), echocardiogram, exercise test, and ajmaline and adrenaline test to search for a possible cause of SADS. An inherited cardiac disease was diagnosed in 42% of families (22% of individuals), with Brugada syndrome (BrS) accounting for 28% of the families' diagnoses. Without an ajmaline test, only 3% of the BrS would have been recognized.

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The unique character of this study comes from the sum of several small but very specific and important details: 1) the prospective character of the study; 2) the systematic use of accurate methodology and precise evaluation of the results; 3) the clinical implications of the observations; and 4) the perseverance of the authors in doing something despite difficulty and the chance to fail.

A PROSPECTIVE STUDY

Pharmacological testing with a sodium channel blocker is performed in many centers to unmask BrS, and an adrenaline test is used in the search for the long QT syndrome. However, a prospective evaluation of a large population with SADS, as conducted by Papadakis et al. (1), has to the best of my knowledge not been reported previously. Unsurprisingly, the use of the pharmacological tests increased the number of diagnoses enormously: ajmaline brought a new diagnosis of BrS in 28% of the families and 15% relatives, with a final yield of 42% families and 22% relatives diagnosed with BrS. Thus, an ajmaline test almost doubled the number of families and relatives in whom a diagnosis was obtained. In 26% of the relatives, an ajmaline test was not possible. If all relatives had been included, the diagnostic yield for BrS would only increase. The study population was large enough to allow meaningful conclusions. The study is clearly clinical. Genetic testing was not meant to play an important role, but it may become much more relevant with future technologies. An important detail that may escape the attention of the reader is that all 303 patients who experienced sudden death had a coroner's autopsy, with about one-half undergoing an expert's autopsy, and these patients all had normal findings. At initial evaluation, only 5% of the 911 relatives had abnormal findings. Without further tests, a diagnosis would have been missed in about 50% of the families.

A SYSTEMATIC APPROACH

The methodology used was accurate for present standards and it was used in a systematic way. As shown in Figure 1 of their paper, Papadakis et al. (1) had a clear path to search for a diagnosis. The use of high right precordial leads increased the diagnosis of BrS by a remarkable 16%. This finding supports the systematic use of high right precordial leads during testing with a sodium channel blocker (2). Unfortunately, ajmaline is not available in many countries. In Belgium, our hospital pharmacy buys it from Germany via the Internet. In some countries, like Spain, the ministry of health forbids buying ajmaline from abroad and proposes the use of alternatives, such as procainamide or flecainide. In Japan, the preferred drug is pilsicainide, a strong, and believed to be a pure, sodium channel blocker (3). There are no randomized comparative studies between the different drugs in BrS and control

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From the Cardiovascular Division, UZ Brussel-VUB, Brussels, Belgium. Dr. Brugada has served as a consultant for Biotronik.

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populations. However, the limited available knowledge (4,5) suggests the following: ajmaline has a high sensitivity and specificity when compared with results of genetic testing as the gold standard. It has the shortest half-life of the 4 drugs, making it easy to use. In patients with a normal basal ECG and a positive test, return of the ECG to normal is usually seen within 10 to 15 min. Availability of procainamide is also a problem in many European countries. It is less sensitive than ajmaline, but its pharmacokinetics are also good. Flecainide is not available intravenously everywhere, and some centers use oral flecainide as pharmacologic challenge. Flecainide was less sensitive than ajmaline in a study by Wolpert et al. (6). Flecainide has a long half-life, making the care of a patient with a positive test more complex because of the longer persistence of the ST elevation compared with ajmaline and procainamide. Pilsicainide is only available in Japan and also has a relatively long half-life. It is unlikely that any of these 4 drugs will suddenly become available worldwide. Thus, there is no potential at present for a universal approach to a drug challenge for the unmasking of the BrS ECG in families with SADS. The only solution is that centers use the drugs available in their own country, choosing the one with the best balance between sensitivity and specificity and with the shortest half-life.

CLINICAL IMPLICATIONS

This study reduces to the ground everything written about families with SADS. The low diagnostic yield in previous studies and the overwhelming prevalence of the long QT syndrome (7) as a possible cause of SADS have been called into question. The use of pharmacological testing allowed Papadakis et al. (1) to recognize BrS as the most common cause of SADS. The clinical implications are clear: in the investigation of SADS, a pharmacological test of the family members is imperative to exclude or prove BrS. In their Figure 5 (1), the authors also show how guidelines based on "expert consensus" and not on scientific data, like the Shanghai score (8), can be misleading and should not be considered valid scientific evidence in clinical practice.

THE VALUE OF PERSEVERANCE

In the search for a diagnosis, it is sometimes too easy to give up. In this study on SADS, the patient was dead and the autopsy was normal, so why care about the family survivors? Well, that is the value of perseverance, the spirit of continuing to search even when you may fail. Papadakis et al. (1) did not give up and persisted in their endeavor. They certainly did not fail; on the contrary, they provided us with a fantastic model in the evaluation of families with SADS.

ADDRESS FOR CORRESPONDENCE: Dr. Pedro Brugada, Cardiovascular Division, UZ Brussel-VUB, Laarbeeklaan 101, 1090 Brussels, Belgium. E-mail: Pedro@brugada.org.

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