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The Diagnostic Yield of Brugada Syndrome After Sudden Death With Normal Autopsy

Michael Papadakis, MBBS, MD,[a,b] Efstathios Papatheodorou, MD,[a,b] Greg Mellor, MBChB, MD,[a,b] Hariharan Raju, MBChB, PhD,[a,b] Rachel Bastiaenen, PhD,[a] Yanushi Wijeyeratne, BMBS,[a] Sara Wasim, BSc,[a] Bode Ensam, MBChB,[a,b] Gherardo Finocchiaro, MD,[a,b] Belinda Gray, BSc(Med), MBBS, PhD,[a] Aneil Malhotra, MBBChir, MA, MSC, PhD,[a,b] Andrew D'Silva, MBBS,[a,b] Nina Edwards, BSc,[a] Della Cole, RGN BSc,[a] Virginia Attard, MSc,[a] Velislav N. Batchvarov, MD, PhD,[a] Maria Tome-Esteban, MD, PhD,[a] Tessa Homfray, MBBS,[a] Mary N. Sheppard, MB, BCh, BAO, MD,[a] Sanjay Sharma, MBChB, MD,[a,b] Elijah R. Behr, MBBS, MD[a]

ABSTRACT

BACKGROUND Familial evaluation after a sudden death with negative autopsy (sudden arrhythmic death syndrome; SADS) may identify relatives at risk of fatal arrhythmias.

OBJECTIVES This study aimed to assess the impact of systematic ajmaline provocation testing using high right precordial leads (RPLs) on the diagnostic yield of Brugada syndrome (BrS) in a large cohort of SADS families.

METHODS Three hundred three SADS families (911 relatives) underwent evaluation with resting electrocardiogram using conventional and high RPLs, echocardiography, exercise, and 24-h electrocardiogram monitor. An ajmaline test with conventional and high RPLs was undertaken in 670 (74%) relatives without a familial diagnosis after initial evaluation. Further investigations were guided by clinical suspicion.

RESULTS An inherited cardiac disease was diagnosed in 128 (42%) families and 201 (22%) relatives. BrS was the most prevalent diagnosis (n = 85, 28% of families; n = 140, 15% of relatives). Ajmaline testing was required to unmask the BrS in 97% of diagnosed individuals. The use of high RPLs showed a 16% incremental diagnostic yield of ajmaline testing by diagnosing BrS in an additional 49 families. There were no differences of the characteristics between individuals and families with a diagnostic pattern in the conventional and the high RPLs. On follow-up, a spontaneous type 1 Brugada pattern and/or clinically significant arrhythmic events developed in 17% (n = 25) of the concealed BrS cohort.

CONCLUSIONS Systematic use of ajmaline testing with high RPLs increases substantially the yield of BrS in SADS families. Assessment should be performed in expert centers where patients are counseled appropriately for the potential implications of provocation testing. (J Am Coll Cardiol 2018;71:1204–14) © 2018 by the American College of Cardiology Foundation.

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From the [a]Cardiology Clinical Academic Group, St. George's, University of London and St. George's University Hospitals NHS Foundation Trust, London, United Kingdom, European Reference Network for rare and low prevalence diseases of the heart, Guard-Heart; and the [b]University Hospital Lewisham, Lewisham, United Kingdom. Dr. Behr has received consulting fees from Medtronic; has received research funding from Biotronik; and has received a research grant from McColl's Ltd. Retail Group and the British Heart Foundation. Drs. Papadakis, Papatheodorou, Mellor, Raju, Ensam, Finocchiaro, Malhotra, and D'Silva were funded by research fellowship grants from a charitable organization called Cardiac Risk in the Young (CRY). Drs. Papadakis, Sheppard, Sharma, and Behr have received research grants from CRY. Dr. Wijeyeratne has received a research fellowship grant from McColl's Ltd. Retail Group. Dr. Raju has received a research fellowship grant from the British Heart Foundation. Drs. Edwards and Batchvarov have received support from the British Heart Foundation. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose. Drs. Papadakis and Papatheodorou contributed equally to this work and are joint first authors. Drs. Sharma and Behr contributed equally to this work and are joint senior authors.

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Sudden arrhythmic death syndrome (SADS) refers to a sudden cardiac death with negative toxicology, where no structural pathology is identified despite detailed postmortem histopathologic examination (1-3). During the past decade, SADS has emerged as an important subset of sudden death in young individuals, including athletes, and is reported in up to 40% of cases (4-6). Studies in relatives of SADS victims detect an inherited cardiac disease in 22% to 53% of the families, identifying asymptomatic individuals at potential risk of fatal arrhythmias. Ion channelopathies are consistently the predominant diagnosis, although the exact diagnostic yield and the individual conditions identified are dependent on the clinicogenetic protocols used (2,3,5,7-12).

Brugada syndrome (BrS) accounts for a small proportion of diagnoses in most SADS series (2,3,5,7-11). Its prevalence, however, may have been underestimated by selective use of sodium channel blocker provocation testing, the main diagnostic tool for concealed BrS. In addition, studies in patients with established diagnoses of BrS suggest that assessment with higher right precordial leads (RPLs) on electrocardiogram (ECG) increases the detection rate of the Brugada phenotype by up to 40% (13-15). Consequently, placement of leads V_1 and V_2 in the third and second intercostal space (IS), is advocated in the 2013 diagnostic criteria for BrS and a recent expert consensus report endorsed by the international scientific communities (1,16).

Contemporary studies in relatives of SADS victims but also in individuals with low a priori risk of BrS suggest that systematic use of sodium channel blocker provocation testing with higher RPLs significantly increases the yield of the Brugada phenotype in both populations, raising concerns about its specificity (17,18). We report on the diagnostic yield of a large consecutive cohort of SADS families who underwent standardized comprehensive clinical evaluation including systematic ajmaline provocation testing with higher RPLs as part of the investigative protocol.

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METHODS

SETTING. We prospectively studied 303 consecutive, unselected SADS families referred to our dedicated inherited cardiac diseases clinics between 2006 and 2015. The authors established a "one-stop-shop" model at St. George's, University Hospitals, and University Hospital Lewisham in London, where relatives of the deceased from throughout the United Kingdom undergo comprehensive evaluation during a single visit.

SADS was defined as a sudden unexpected death in an individual age 1 to 64 years who was last seen alive and well within 12 h of being found dead, had no prior recorded cardiac disease, and who underwent a normal full coroner's postmortem examination with a negative toxicology screen.

FAMILIAL EVALUATION. Our investigation protocol included routine use of clinical history and noninvasive evaluation with baseline ECG with conventional (fourth IS) and high (third and second IS) RPLs, echocardiography, and ECG monitoring. Exercise testing was performed in relatives aged above 16 years. An ajmaline provocation test was offered to all first-degree relatives who were older than 16 years, and in younger relatives with cardiac symptoms in whom the aforementioned investigations were normal, or in the presence of the type 2 Brugada ECG pattern. Ajmaline provocation tests were performed using conventional and high RPLs, as per established protocol (13,19). A MAC 5000 or a Cardiosoft recorder (GE Medical, Milwaukee, Wisconsin; 500 samples/s, 4.88 mcV) was used for digital ECG acquisition. All ECGs were subsequently exported to a customized software program where tracings could be magnified to measure basic intervals accurately with on-screen calipers. Further investigations, including signal-averaged ECG, cardiac magnetic resonance imaging (MRI) and epinephrine provocation testing were performed in accordance with clinical findings. Standard diagnostic criteria for inherited cardiac disease were used (1,20-22). The diagnosis of BrS required the presence of a type 1 Brugada pattern in ≥1 of the RPLs (1,16).

GENETIC TESTING. This study places emphasis on the comprehensive clinical evaluation of SADS families. Because of a historic limitation of funds and the poor yield in conditions such as BrS (23), genetic testing was not offered in a systematic manner and performed in a limited number of family members with a positive clinical phenotype. Similarly, because of historic limitations on blood and tissue retention, "molecular autopsy" was only available in a small number of cases. Pathogenicity was assessed using the American College of Medical Genetics guidelines (24).

FOLLOW-UP. Individuals diagnosed with a cardiac condition were followed-up at our institute or their local cardiology department on an annual basis or more regularly if clinically indicated. Repeat evaluation during follow-up included as a minimum a 12-lead

ABBREVIATIONS AND ACRONYMS

BrS = Brugada syndrome

CPVT = catecholaminergic polymorphic ventricular tachycardia

DCM = dilated cardiomyopathy

ARVC = arrhythmogenic right ventricular cardiomyopathy

ICD = implantable cardioverter-defibrillator

LQTS = long QT syndrome

LVNC = left ventricular noncompaction

RPLs = right precordial leads

SADS = sudden arrhythmic death syndrome