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Aborted sudden cardiac death in a young patient with epilepsy and the Gorlin Goltz syndrome

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ABSTRACT

Epilepsy is one of the most common chronical neurological conditions affecting over 50 million people worldwide. In addition to the stigma and discrimination, individuals with epilepsy suffer from a nearly three-fold increased risk of premature death compared to the general population. Although these premature deaths occur due to multiple causes, sudden unexpected death in epilepsy (SUDEP) still challenges neurologists and clinicians dealing with individuals with epilepsy. Recently, an increased interest in cardiac outcomes related to acute seizures and chronic epilepsy resulted in the groundbreaking development of the "epileptic heart" concept, and sudden *cardiac* death in individuals with epilepsy, which is 4.5 times as frequent as SUDEP according to some observational data, has gained more attention. As we gather information and learn about possible comorbidities and consequences of seizures and/or chronic epilepsy, we present a clinical case of a young patient with an unusual association of epilepsy, the Gorlin Goltz syndrome, and a cardiac fibroma with Wolf-Parkinson-White (WPW), who had multiple aborted cardiac arrests. Diagnostic challenges and multiple possible causes of sudden cardiac death in this single patient report are discussed.

1. Introduction

People with epilepsy (PWE) face an increased risk of premature death compared to individuals without epilepsy. They have two to three times the risk of dying prematurely, and these odds are even higher in PWE whose seizures are not well controlled [1–4]. Although premature death in individuals with epilepsy can stem from pneumonia, suicide, accidents, drowning, or status epilepticus, sudden unexpected death in epilepsy (SUDEP) is considered the most common cause of premature mortality [1–3]. In the last few years, a growing awareness of cardiac outcomes related to acute seizures and chronic epilepsy resulted in the development of the "epileptic heart" concept by Verrier and colleagues, and an increased interest in sudden *cardiac* death in PWE [5].

We report a case of a young patient with epilepsy and the Gorlin Goltz syndrome with a cardiac fibroma and Wolf-Parkinson-White (WPW), presenting with cardiac arrest.

2. Case report

A 26-year-old male with known Gorlin-Goltz syndrome had a diagnosis of developmental and epileptic encephalopathy (DEE) associated with bilateral frontocentral epileptiform discharges, predominantly in the left hemisphere on EEG, and MRI-confirmed extensive frontobasal, insular and temporal polymicrogyria. His caregiver reported severe cognitive deficit and focal to bilateral tonic-clonic seizures beginning at 1 year of age, enduring up to 3 years, when he was successfully treated

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with phenobarbital and valproate, which were tapered off when he was 10 years old. There has been no report of seizures nor use of antiseizure medication since then. Also, a diagnosis of Shprintzen-Goldberg syndrome (SGS) was clinically suspected, and the patient, with a 46-XY karyotype, is awaiting further molecular genetic testing for confirmation.

He was admitted to the hospital last year, when he was 26-year-old, with acute respiratory failure and cardiac arrest with a shockable rhythm detected in an out-of-hospital setting. He received cardiopulmonary resuscitation (CPR) for 21 min, 7 defibrillation and orotracheal intubation. On arrival at the emergency department, a new episode of sustained wide QRS tachyarrhythmia was detected, associated with hypotension and the need for additional electrical cardioversion and vasoactive drugs. Episodes of seizures prior to the cardiac arrhythmias were not reported.

The patient was admitted to the intensive care unit and antibiotics were initiated due to findings of pulmonary consolidation due to bronchoaspiration, detected in a chest computed tomography. On the electrocardiogram (ECG), a short PR interval (90 ms) and delta wave were detected, suggestive of anomalous anteroseptal bundle (Fig. 1) [6].

Cardiac magnetic resonance imaging was performed and revealed a nodular image located in the middle portion of the free wall of the right ventricle, measuring approximately 20x25mm (Fig. 2), Late gadolinium enhancement showed important and diffuse post-contrast hypersignal, suggestive of fibroma in the right ventricle.

Due to concerns regarding anterograde electrical conduction through the accessory pathway, propafenone was initiated, but later switched to amiodarone, after the diagnosis of the cardiac fibroma.

The patient was referred to the electrophysiological study. During the study, orthodromic atrioventricular tachycardia was induced and easily interrupted by radiofrequency energy application. Pre-excited atrial fibrillation (AF) with a fast ventricular response was also induced (Fig. 3). Mapping of the tricuspid annulus revealed a shorter AV interval in the lateral/posterolateral region which received radiofrequency ablation. Ventricular arrhythmias were not inducible (Fig. 4). There was no arrhythmogenic foci near the cardiac fibroma.

A final diagnosis of the sudden cardiac arrest due to pre-excited AF with fast ventricular rates was made. Since the patient was successfully treated with ablation of the accessory pathway, and no additional arrhythmias were detected near the cardiac fibroma or elsewhere, additional therapy with an implantable cardio-defibrillator (ICD) was not indicated.

The patient evolved with no complications from the procedure. Amiodarone was discontinued and the patient was discharged 48 h later.

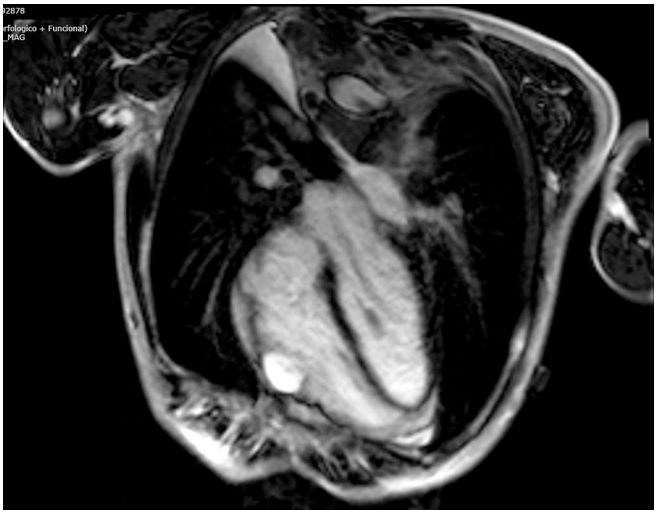

Fig. 2. Cardiac magnetic resonance imaging. Cardiac magnetic resonance imaging was performed and revealed a nodular image located in the middle portion of the free wall of the right ventricle, measuring approximately 20x25mm. Late gadolinium enhancement showed important and diffuse post-contrast hypersignal, suggestive of fibroma in the right ventricle.

3. Discussion

Although previous studies report on the association of epilepsy and WPW [7–9] and few case reports shows association of epilepsy and the Gorlin Goltz syndrome [10], this is the first report where all these comorbidities were present in a single patient, adding challenge in the diagnosis of the cause of the aborted sudden cardiac death.

Cardiac arrhythmias can be a common manifestation of seizures. In 82 % of individuals with seizures, sinus tachycardia is present. Additionally, other electrical cardiac manifestations such as ictal asystole, bradyarrhythmias, atrial fibrillation, QT interval modifications, bundle branch and atrioventricular block, have also been reported [11,12].

Recently, the long-term arrhythmic manifestations of epilepsy have been showed in observational reports. In a recent report from the UK Biobank, including nearly 2700 PWE and 330,000 controls followed from 2006 to 2010, PWE had an increased risk of all cardiac arrhythmias (hazard ratio (HR) 1.36, 95 % confidence interval (CI) 1.21–1.53), atrial fibrillation (HR 1.26, 95 % CI 1.08–1.46), and other cardiac arrhythmias (HR 1.56, 95 % CI 1.34–1.81). In that study, the associations were not modified by genetic predisposition but were stronger in those using carbamazepine or valproic acid [13].

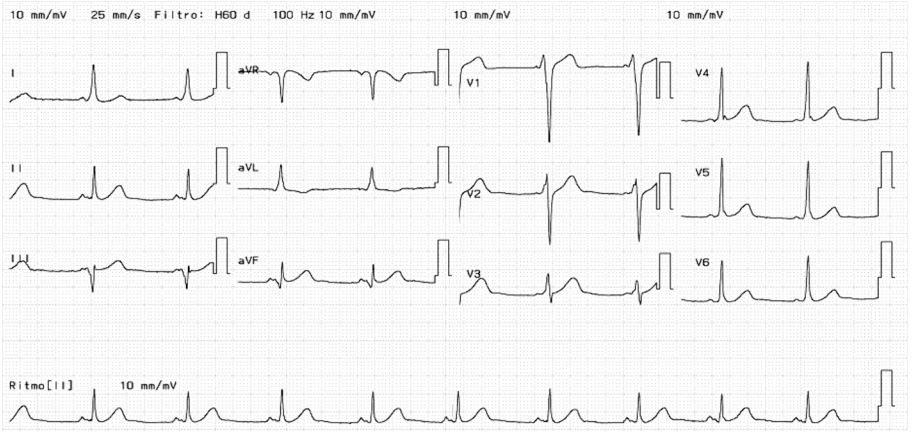

Fig. 1. (COLORED FIGURE): **Electrocardiogram (ECG) after aborted cardiac death**. On the electrocardiogram (ECG), a short PR interval (90 ms) and delta wave were detected, suggestive of anomalous anteroseptal bundle.

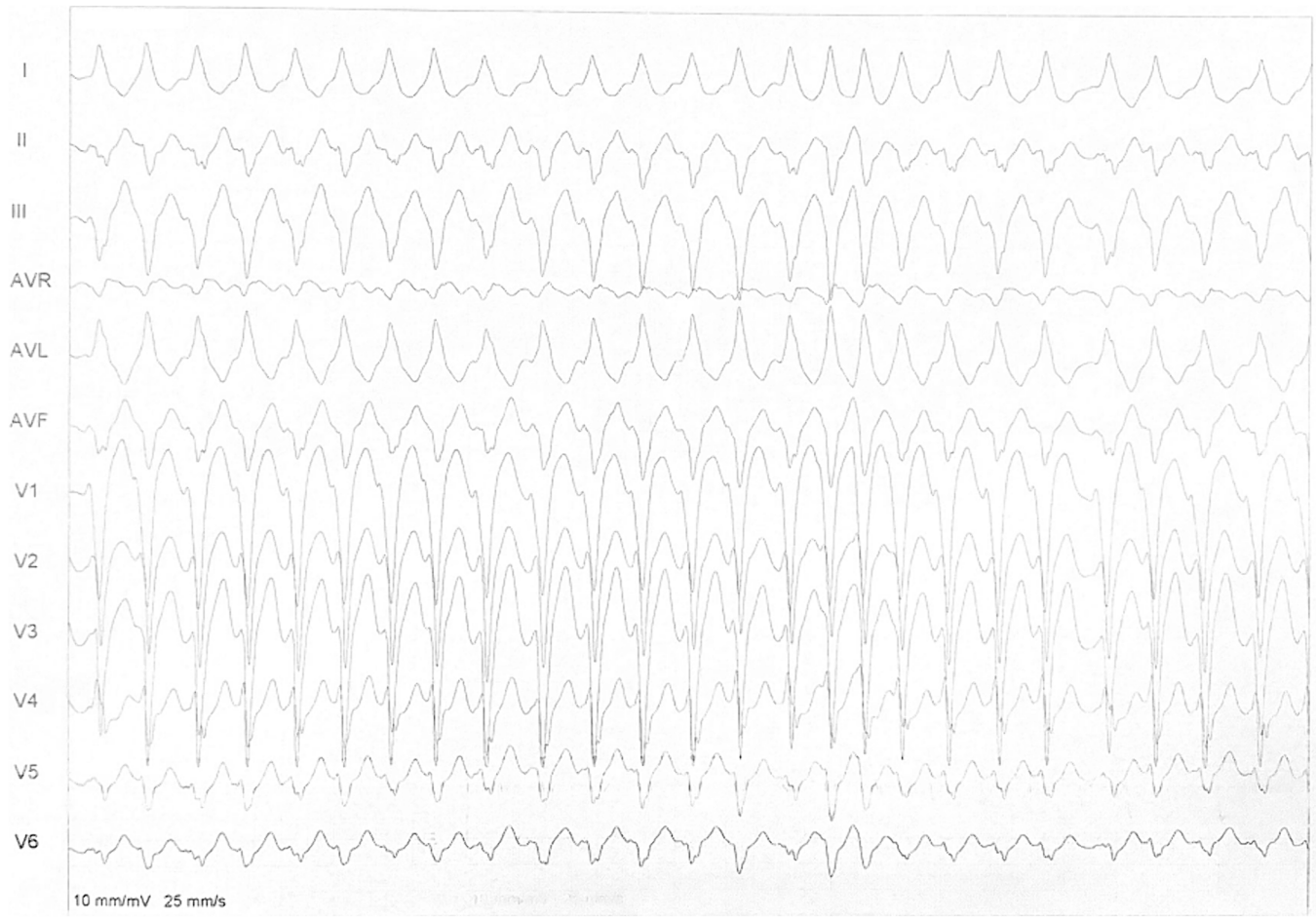

Fig. 3. Electrophysiological study. Pre-excited atrial fibrillation (AF) with a fast ventricular response induced was also induced in the electrophysiological study.

Rossi and colleagues demonstrated that PWE or status epilepticus requiring hospitalization or emergency visits had increased risk of arrhythmias or cardiac arrest as early as the first day from the index event to as late as 180 days later [14]. Cheng et al. reported that, among 5411 PWE without baseline cardiovascular disease followed from 1997 to 2013, the risk of myocardial infarction (MI), arrhythmia, or sudden death was 1.71, 2.11 and 1.83 greater than 21,644 controls. The increased risk of MI and arrhythmia appeared 1 to 2 years after epilepsy diagnosis [15].

The mechanisms for increased risk for arrhythmias in epilepsy are not fully understood. The presence of ultrastructural damage to heart muscle has been documented in post-mortem histological studies and in echocardiography studies in PWE, showing increased myocardial stiffness, which is related to myocardial fibrosis [16]. Structural myocardial changes may predispose to cardiac electrical heterogeneity, dispersion and arrhythmias. Elevated T-wave alternans, T and P-wave heterogeneity and heightened risk for life-threatening ventricular arrhythmias, have been shown in PWE [17–19]. Additionally, cardiac arrhythmogenic genes may also be present in PWE and several antiseizure medications (ASMs) can trigger cardiac abnormalities due to ion channel effects [20,21].

In that sense, epilepsy may promote all the suggested requirements for cardiac arrhythmias as proposed by Coumel more than 30 years ago: a substrate (fibrosis), a trigger (ventricular or atrial premature beats) and modulating factors (autonomic imbalance, ischemia) [22]. This may explain why epilepsy-related cardiac arrhythmias, although expected to occur more frequently in patients with uncontrolled seizures, could also occur in patients who have seizure remission, due to subtle and cumulative cardiac disorders.

AF may be more common than once thought in PWE. Desai and colleagues reported that, among 1.4 million hospitalizations of PWE, 23.9 % had some kind of cardiac arrhythmia and AF was the most common arrhythmia found in 9.7 % of the entire cohort [23]. Recently, individuals with epilepsy were found to have increased atrial electrical dispersion (measured as P-wave heterogeneity). Importantly, P-wave heterogeneity in PWE reached levels similar to a 20-year older cohort of individuals with paroxysmal AF waiting for an ablation procedure [19].

A hindering factor in this case was the presence of a cardiac fibroma. Cardiac fibromas occur in about 3 % of cases of Gorlin-Goltz syndrome and can be the cause of arrhythmias. The Gorlin-Goltz syndrome was first described by Jarish and White in 1894, but better defined by Gorlin and Goltz in 1960. It consists of a rare condition associated with mutation of the PTCH tumor suppressor gene, located on chromosome 9q22 which acts as a component of the Hedgehog signaling pathway. It comprises the triad of basal cell carcinoma, numerous keratocytes in the mandible and skeletal abnormalities [24]. The association of Gorlin-Goltz syndrome with WPW has not been reported.

Shprintzen-Goldberg syndrome (SGS) is characterized by altered, motor, cognitive and intellectual disability. Phenotypical features include, craniosynostosis of the coronal, sagittal, or lambdoid sutures, typical craniofacial characteristics, olichostenomelia, arachnodactyly, camptodactyly, pectus excavatum or carinatum, scoliosis, joint hypermobility or contractures, pes planus, foot malposition, and C1-C2 spine malformation. Cardiovascular anomalies may include mitral valve prolapse, secundum atrial septal defect, and aortic root dilatation, none of which were found in this patient. Additional anatomical findings include a decreased subcutaneous fat, abdominal wall defects, and myopia. The combination of these craniofacial, skeletal, cardiovascular, neurologic

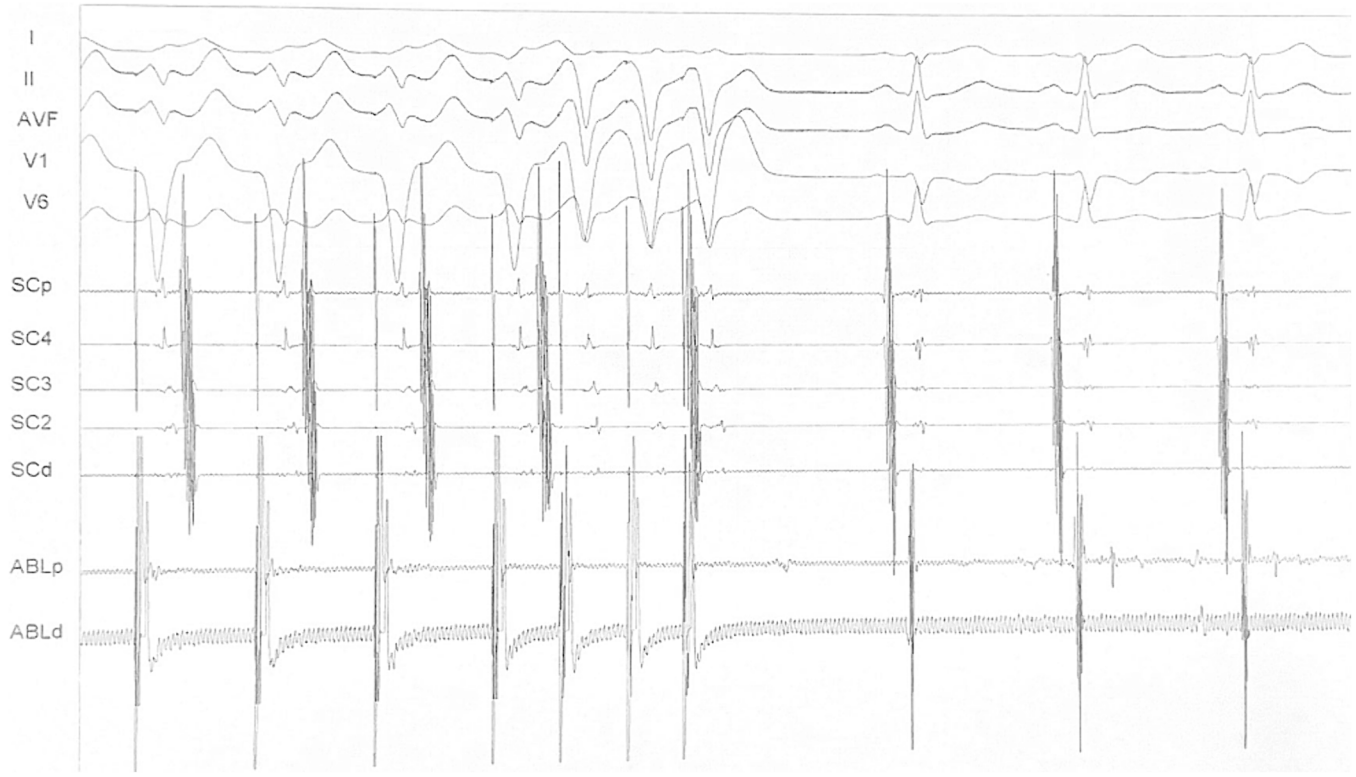

Fig. 4. Ablation of the reentry circuit. Mapping of the tricuspid annulus revealed a shorter AV interval in the lateral/posterolateral region which received radiofrequency ablation. Ventricular arrhythmias were not inducible.

features, and brain features are important for SGS diagnosis [25].

The patient did not present any cardiac features related to the SGS. However, the presence of the cardiac fibroma, which, as stated earlier, can occur in nearly 3 % of patients with the Gorlin-Goltz, was a particular challenge in this case since it could be the cause of the cardiac arrhythmia. This hypothesis was rejected by the electrophysiological study, which could not demonstrate any inducible arrhythmic tissue near the fibroma. Additionally, the electrophysiological study induced an orthodromic atrioventricular tachycardia and a pre-excited atrial fibrillation with a fast ventricular response, proving that the patient had a fast-conducting accessory pathway, which was successfully treated with ablation.

Although an increased association between epilepsy and WPW is not known, we are starting to understand that epilepsy may increase cardiac arrhythmic risk. Individuals with epilepsy with an additional cardiac condition may have a greater risk for cardiac outcomes, due to seizures, medications and/or altered brain circuitry. Possibly, the "epileptic heart" concept, which has a working definition stated by Verrier and colleagues [5], as "a heart and coronary vasculature damaged by chronic epilepsy as a result of repeated surges in catecholamines and hypoxemia leading to electrical and mechanical dysfunction", may also apply to these situations where epilepsy may predispose to worse outcomes in individuals with a primary cardiac disease.

In this unusual association of comorbidities, different possible mechanisms of cardiac arrhythmia were investigated. Although few reports describe the association of epilepsy with WPW and epilepsy with the Gorlin-Goltz syndrome, this is a unique case of diverse pathways for arrhythmogenic comorbidity in a PWE.

CRediT authorship contribution statement

Guilherme Salazar Serrano: Writing – original draft, Validation, Investigation, Formal analysis, Data curation, Conceptualization. **Alexandre Dias de Oliveira:** Writing – original draft, Validation, Investigation, Data curation, Conceptualization. **Ramsés Miotto:** Writing – review & editing, Formal analysis, Data curation. **Katia Lin:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Investigation, Formal analysis, Data curation, Conceptualization. **Guilherme Loureiro Fialho:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Methodology, Formal analysis, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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