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REVIEW ARTICLE

Diagnostic and therapeutic considerations on Brudaga syndrome

Consideraciones diagnósticas y terapéuticas sobre el Síndrome de Brudaga

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ABSTRACT

Introduction: brudaga syndrome is an inherited cardiac condition characterized by abnormal electrocardiogram (ECG) patterns. It was initially described in 1992 by the Brugada brothers and is associated with an increased risk of sudden cardiac death.
Objective: to analyze the current diagnostic and therapeutic advances in Brudaga syndrome.
Methods: analysis of original articles and bibliographic reviews previously carried out that provided information on the advances in the diagnosis of Brudaga Syndrome, in addition, the search for information in different databases such as Scielo, Elsevier, PubMed, Chrocane, Epistemonikos, and different journals including Seimic, Medigraphic Artemis, Recimundo, SCIENCE, MEDICRIT was prioritized.
Development: diagnosis is based on the identification of specific patterns in the ECG, being crucial to recognize the Brugada type 1 pattern, which shows a pronounced ST-segment elevation in certain leads. Symptoms may vary and include fainting, arrhythmias and, in severe cases, sudden cardiac death. Management of Brugada syndrome may involve the placement of implantable cardioverter defibrillators and the use of certain drugs, such as quinidine. Genetic counseling is essential, especially to identify relatives at risk. In addition, known triggers, such as certain drugs and substances, should be avoided.
Conclusions: the correct interpretation of the electrocardiogram plays a crucial role in the diagnosis of Brugada syndrome. However, it is imperative to complement this analysis with a thorough clinical evaluation, considering family history and present symptoms.

Keywords: Brugada Syndrome; Electrocardiography; Death, Sudden, Cardiac; Genetics.

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RESUMEN

Introducción: el Síndrome de Brudaga es una condición cardíaca hereditaria caracterizada por patrones anómalos en el electrocardiograma (ECG). Fue inicialmente descrito en 1992 por los hermanos Brugada y se asocia con un riesgo aumentado de muerte súbita cardíaca.
Objetivo: analizar los avances que desde el punto de vista diagnóstico y terapéutico existen hoy en día sobre el Síndrome de Brudaga.
Métodos: análisis de artículos originales y revisiones bibliográficas previamente realizadas que aportaron una información sobre los avances de en el diagnóstico sobre el Síndrome de Brudaga, además se priorizó la búsqueda de información en diferentes bases de datos como Scielo, Elsevier, PubMed, Chrocane, Epistemonikos, y diferentes revistas entre ellas Seimic, Medigraphic Artemisa, Recimundo, SCIENCE, MEDICRIT.
Desarrollo: el diagnóstico se basa en la identificación de patrones específicos en el ECG, siendo crucial reconocer el patrón Brugada tipo 1, que muestra una elevación pronunciada del segmento ST en ciertas derivaciones. Los síntomas pueden variar e incluir desmayos, arritmias y, en casos graves, muerte súbita cardíaca. El manejo del Síndrome de Brugada puede involucrar la colocación de desfibriladores automáticos implantables y el uso de ciertos fármacos, como la quinidina. Es esencial el asesoramiento genético, especialmente para identificar a familiares en riesgo. Además, se deben evitar desencadenantes conocidos, como ciertos medicamentos y sustancias.
Conclusiones: la correcta interpretación del electrocardiograma desempeña un papel crucial en el diagnóstico del Síndrome de Brugada. Sin embargo, es imperativo complementar este análisis con una evaluación clínica exhaustiva, considerando antecedentes familiares y síntomas presentes.

Palabras Clave: Síndrome de Brugada; Electrocardiograma; Muerte Súbita Cardíaca; Genética.

INTRODUCTION

Brugada Syndrome (BrS) is characterized by pathognomonic electrocardiographic changes of peak-shaped ST-segment elevation with T-wave inversion in the right precordial leads. In 1992, the Brugada brothers initially described a syndrome consisting of right bundle branch block, ST-segment elevation, and sudden cardiac death (SCD), although these ECG findings had been previously documented. Significant progress has been made in our understanding of this clinical entity over the past 30 years. Because of the potential risk of SCD, it is vital that clinicians be able to accurately identify and manage patients suspected of having BrS.[1]

Current therapeutic options include the use of medications to reduce or stop the incidence of arrhythmic events. Interventions such as the implantation of a cardioverter-defibrillator or radiofrequency ablation of abnormal tissue areas associated with the arrhythmia are also being considered.[2]

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Brugada Syndrome (BrS) was first described in 1992 by two Spanish cardiologists, Pedro and Joseph Brugada, in a report in which 8 people were resuscitated from sudden cardiac death caused by ventricular fibrillation (VF). This clinical manifestation was initially characterized as right bundle branch block, persistent ST-segment elevation, and sudden cardiac death syndrome.

This syndrome causes a cardiac arrhythmia in question and is known to increase the risk of sudden cardiac death (SCD) compared to the general population. It is diagnosed by identifying a Brugada type 1 pattern on an electrocardiogram (ECG), characterized by ST-segment elevation with a paddle-like shape in the right precordial leads. This type 1 pattern can manifest spontaneously or intermittently, often in response to various environmental factors, such as medications, illicit substances, alcohol consumption, fever, and large meals.[3]

Although the frequency of Brugada has been reported to be approximately one case per 2000 people in Western Europe and the United States, and one case per 500 people in Southeast Asia, the true prevalence of this condition is uncertain. This is due to the absence of symptoms in many people for long periods and the difficulties involved in the diagnostic process, for this it is necessary to take into account certain criteria to be able to designate the diagnosis of BrS based on the abnormalities in the ECG that we will detail throughout this bibliographic review.[4]

Brugada Syndrome (BrS), a Mendelian inheritance condition in humans according to OMIM-601144, has several subtypes depending on the gene that presents mutations. The first documented mutation was identified in the SCN5A gene (OMIM-600163), located on the short arm of chromosome 3 (3p21). Approximately 20% of individuals with BrS show mutations in this gene. The SCN5A gene is responsible for encoding the alpha subunit of the sodium channel, which determines phase 0 of the action potential in cardiac cells. Studies conducted in the last decade have identified 11 other genes related to BrS, in addition to SCN5A, which underscores the genetic variability associated with this syndrome. The inheritance of this disease follows an autosomal dominant pattern.[5]

Sudden death (SD) is the most feared complication of all heart diseases. A particularly dramatic scenario is that of cardiac SD, which occurs in young subjects or those without known previous disease. Autopsies of these subjects may reveal a structurally normal heart in up to 30% of cases, depending on the series.(1) Cardiac SD in the absence of structural heart disease is usually due to a genetic arrhythmogenic disorder. Syndromes related to cardiac SD include long QT syndrome (LQTS), Brugada Syndrome (BrS), short QT syndrome (SQTS), and catecholaminergic polymorphic ventricular tachycardia (CPVT).[6]

Out-of-hospital monitoring has shown that polymorphic ventricular tachycardia is the most prevalent arrhythmia associated with this syndrome. Patients may also experience episodes of electrical storms or recurrent ventricular arrhythmias over a short period of time. Up to 20% of patients have been observed to have dysrhythmias above the ventricles, and atrial fibrillation, a type of heart rhythm disorder, is estimated to affect between 11% and 14% of patients.[7]

Based on what has been expressed up to here, the objective of the research is:To analyze the current advances in Brudaga Syndrome from a diagnostic and therapeutic point of view.

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METHODS

For this research, a systematic, descriptive bibliographic review was conducted, limited to English and Spanish. In addition, scientific articles of medical relevance within the scientific community were considered; search criteria used were "Brugada Syndrome," "BrS," "sudden death," "drug treatment," "genetic disease," and the Boolean terms "OR," "AND," for the period from 2019 to 2024.

The inclusion criteria applied in this study are: publications since 2019, scientific articles in indexed and high-impact journals, systematic bibliographic reviews, meta-analyses, and classic references from the medical literature that address the pathology.

Using the prism methodology, updated information was identified in electronic databases such as Scielo, Elsevier, PubMed, Virtual Health Library, and Google Scholar. A total of 135 records were collected, and after eliminating duplicates, 109 reviews were found. 50 of these were eliminated after reviewing publication dates, titles, and abstracts. Among the eligible full-text articles, 59 articles remained, and after applying inclusion and exclusion criteria, 24 remained, of which 15 published articles were included for analysis and synthesis.

DEVELOPMENT

To gain a broader understanding of this topic, it is necessary to review in detail the anatomical structure and molecular characteristics of the RVOT (Right Ventricular Outflow Tract), as well as its role in the context of Brugada Syndrome. It is a thin, smooth-walled, tubular structure located between the pulmonary trunk and the right ventricular cavity, oriented cranially toward the tricuspid valve. This structure can be subdivided into anterior, left, right, and posterior walls; the latter is directly anterior to the LVOT and adjacent to the sinus of Valsalva.[7]

The right ventricular outflow tract (RVOT) wall consists of multiple layers with three-dimensional networks of myofibers in a fibrous tissue matrix. These myofibers differ in their spatial orientation, which influences the complexity of the heart's contractile motion. In contrast to the right ventricle (RV) and left ventricular outflow tract (LVOT), the myofiber bundles in the RVOT have a distinct orientation. While the subepicardial layer consists of circumferentially arranged myofibers, the middle and subendocardial layers consist of myofibers that extend longitudinally, i.e., along the main axis of the RVOT.[6]

In the context of Brugada Syndrome (BrS), the right ventricular outflow tract (RVOT) assumes significant importance. A peculiarity in the orientation of myofibers in this region has been noted. While in the subepicardial layer the myofibers are arranged in a circular fashion, in the middle and subendocardial layers they extend longitudinally along the main axis of the RVOT. This variation in myofiber orientation may impact the susceptibility of the RVOT to myofibrillar disorders, especially in the presence of structural abnormalities associated with BrS.[5]

Regarding the pathophysiology, several experimental studies have shed light on the mechanisms underlying the two main characteristics of Brugada Syndrome: the typical electrocardiogram configuration and the predisposition to the generation of ventricular fibrillation and sudden death. A decrease in the sodium current (INa), the most commonly observed disorder in Brugada Syndrome-related mutations in SCN5A, results in an imbalance between inward and outward currents at the end of phase 1 of the cellular action potential and resembles situations where there is a reduction in inward calcium currents (ICaL, due to mutations in CACNA1c or CACNB2b) or an increase in outward potassium currents (Ito, due to recent mutation in KCNE3).

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Whatever the mechanism, this imbalance favors the formation of a characteristic notch and the loss of a portion of the action potential, mediated by an increase (relative or absolute) in the outward Ito currents. Because the Ito density is higher in the epicardium than in the endocardium, this phenomenon occurs heterogeneously in the ventricular wall, resulting in a transmural voltage gradient and, ultimately, in the typical ST-segment elevation on the electrocardiogram. This ionic imbalance at the end of phase 1 of the action potential also explains the occurrence of ventricular arrhythmias in Brugada syndrome, which originate from a phase 2 reentry mechanism.[8]

This phenomenon also manifests itself heterogeneously between the epicardium and the endocardium, and even between different points within the epicardium, resulting in a dispersion of both transmural and epicardial repolarization. This creates an environment conducive to the development of premature ventricular complexes, resulting from the propagation of the action potential from areas where it persists to areas where it has been lost.[8]

Prolonged ECG monitoring is useful given the dynamic nature of the Brugada ECG, and high placement of the precordial electrodes (V1 and V2 at the second and third intercostal spaces) has been shown to increase diagnostic sensitivity [24]. Sodium channel blockers can be used to elicit a type 1 ECG pattern to aid diagnosis when Brugada is suspected but the resting ECG is nondiagnostic. There are currently no imaging criteria for the diagnosis of Brugada, but cardiac magnetic resonance (CMR) may be useful to rule out alternative pathologies, especially arrhythmogenic right ventricular cardiomyopathy. However, it is important to remember that subtle abnormalities in RVOT morphology may be present.[9]

Electrocardiographic patterns in Brugada Syndrome that help with the diagnosis of the pathology:

1. **Pattern Type 1**:
   - This is the most distinctive and diagnostic pattern of Brugada Syndrome.
   - It is characterized by a pronounced, concave elevation of the ST segment in at least one of the right precordial leads, typically in V1 or V2.
   - The elevation should be greater than or equal to 2mm (0.2mV) on the standard ECG setting.
   - This pattern is followed by a negative T wave, creating a "Chinese spoon" or "coved" appearance in the ST segment. [10]

2. **Pattern Type 2**:
   - This pattern presentsST elevation (or J point) greater than or equal to 2 mm, with subsequent descent but remaining above 1 mm, followed by a positive T wave. [11]

3. **Pattern Type 3**:
   - This pattern may show features of both Type 1 and Type 2, but with an ST segment trough of less than 1 mm.
   - Defined as either of the above 2 if the ST segment elevation is < 1mm. [12]

It is essential to keep in mind that these patterns may vary in presentation and may not necessarily be visible at all times in a person affected by Brugada Syndrome. Furthermore, it is vitally important to consider other clinical aspects and perform additional testing during the diagnosis and evaluation process for this hereditary heart condition.

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In addition to the electrocardiogram, we can also base our analysis on the clinical presentation of these patients:

Some of the most common clinical features include:

1. **Fainting or Syncope Episodes:**Patients with Brugada Syndrome may experience episodes of loss of consciousness, often related to cardiac arrhythmias.
2. **Sudden Cardiac Death:** It is one of the most serious and dangerous manifestations of Brugada Syndrome. It can occur in affected individuals, often without prior warning signs.
3. **Ventricular Arrhythmias:**They can manifest as palpitations or rapid, irregular heartbeats, which can cause uncomfortable sensations in the chest.
4. **Changes in the Electrocardiogram (ECG):** The characteristic ECG pattern is ST-segment elevation in the right precordial leads (V1-V3), followed by a negative T wave. However, these changes may be intermittent and are not always present.
5. **Asymptomatic:** Some people with Brugada Syndrome may not experience noticeable symptoms, and the condition may be discovered during routine medical exams or tests related to other heart problems.
6. **Family History:** Brugada syndrome often has a hereditary component. There may be a family history of sudden cardiac death or unexplained heart disease.[13]

When Brugada Syndrome is suspected in a patient, it is advisable to avoid certain factors that may aggravate ST-segment elevation. These include antiarrhythmic drugs such as procainamide and propafenone, as well as some psychotropic drugs such as amitriptyline and lithium. Caution is also advised with anesthetics and analgesics such as procaine and propofol, and avoidance of substances such as cocaine and alcohol is advised.[14]

Currently, treatment of Brugada Syndrome may include the use of certain medications such as quinidine, as well as its derivative HQ, which has multichannel blocking properties that lead to very complex and not yet fully understood electrophysiological effects, also depending on the basal conditions and the balance of the cardiac ion channel, especially to avoid resorting to the ICD because it represents a significant morbidity.[13] In cases of recurrent syncope, the best option is the use of or implantation of an implantable cardioverter defibrillator (ICD) in patients experiencing symptoms.[14]

Numerous authors, as well as the information compiled in this bibliographic review of the medical literature, agree that in patients with Brugada Syndrome and syncopal episodes, the implantation of an implantable cardioverter defibrillator (ICD) is the only proven measure to prevent death. However, it is important to note that rapid heart rhythms recorded by the ICD do not always result in sudden cardiac death, which reduces the true incidence of cases in which the ICD would be beneficial.[15]

Syncope alone is not a strong risk factor and was present in only a minority of patients with events. Due to the potential for device-associated complications, a broad indication is not justified. Furthermore, there is a risk of inappropriate shocks, especially in young patients with inherited heart rhythm disorders. Although ICD implantation may reduce device-related complications, it may increase the frequency of inappropriate shocks and does not necessarily prevent arrhythmic death. Therefore, the decision to implant an ICD in patients with Brugada syndrome and syncope should be carefully considered and weighed against the risks and benefits.[15]

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CONCLUSIONS

Correct interpretation of the electrocardiogram plays a crucial role in the diagnosis of Brugada Syndrome. However, it is imperative to complement this analysis with a thorough clinical evaluation, taking into account family history and current symptoms.

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