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THE CORRELATION BETWEEN BRUGADA SYNDROME/ BRUGADA PATTERN AND FEVER

BRUGADA SENDROMU/ BRUGADA PATERNİ VE ATEŞ ARASINDAKİ İLİŞKİ

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Abstract

Brugada syndrome is a hereditary cardiac sodium channelopathy that is autosomal dominant. Despite having a structurally normal heart, people with Brugada syndrome have an increased risk of sudden cardiac death. The electrocardiogram (ECG) pattern used for diagnosis can be seen either spontaneously or during a sodium channel blocker test. Despite recent findings from sizable population cohorts, risk stratification among affected patients is still difficult. Numerous risk factors for stratifying the risk of sudden cardiac death in Brugada syndrome have recently been proposed. The Brugada pattern is defined as a significant coved or saddle-shaped ST-segment elevation followed by T wave shifts in V1–V3 and without any other obvious explanation. Brugada syndrome or Brugada pattern can be occasionally precipitated by fever and several infections. In this review, our goal was to examine the literature in relation to Brugada syndrome/ Brugada pattern and fever.

Keywords: *Brugada syndrome, Brugada pattern, fever.*

Özet

Brugada sendromu otozomal dominant olan kalıtsal bir kardiyak sodyum kanalopatisidir. Yapısal olarak normal bir kalbe sahip olmalarına rağmen, Brugada sendromlu kişilerde ani kardiyak ölüm riski yüksektir. Tanı için kullanılan elektrokardiyogram (EKG) paterni spontan olarak veya sodyum kanal bloker testi sırasında görülebilir. Büyük nüfus kohortlarından elde edilen son bulgulara rağmen, etkilenen hastalar arasında risk sınıflandırması hala zordur. Yakın zamanda Brugada sendromunda ani kardiyak ölüm riskini sınıflandırmak için çok sayıda risk faktörü önerilmiştir. Belirgin bir çukur veya eyer şeklindeki ST segment yükselmesinin ardından V1-V3'te T dalgası değişiklikleri olarak tanımlanabilir ve başka bir neden yokluğunda Brugada paterni olarak adlandırılır. Brugada sendromu, bazen ateş ve çeşitli enfeksiyonlarla tetiklenebilir. Bu derlemede amacımız Brugada sendromu, ateş ve enfeksiyonlarla ilgili literatürü incelemekti.

Anahtar Kelimeler: *Brugada sendromu, Brugada paterni, ateş.*

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OVERVIEW / GENEL BAKIŞ

A genetic electroclinical disease known as Brugada syndrome is characterized by a tendency for fatal arrhythmias and rapid heart death (1). Brugada syndrome is an autosomal dominant genetic disorder, that can manifest as a sporadic syndrome or as a familial disease (1, 2).

It happens because of an ion channel abnormality that controls the currents responsible for the generation of the activity potential (2,3). This disease has been linked to over 300 mutations in 18 genes, with the heart sodium channel accounting for 30% of all cases (1).

Typically, Brugada syndrome manifests as acute nocturnal arrhythmias (1). But most of the individuals receive incidental diagnoses and may never experience symptoms (2, 3). Due to varied and temporary electrocardiogram (ECG) abnormalities as well as nondiagnostic provocation investigations, diagnosis may be difficult. The cause can be determined by genetic testing; however, the results may be ambiguous or contain variations of unknown relevance (4). A diagnosis requires an ST-segment elevation of less than 2 mm in one precordial lead (V1-V3) located in the fourth, third, or second intercostal region (1).

The frequency is believed to be between 1 in 5,000 and 1 in 2,000 in various groups, with Southeast Asia and men having the greatest rates (5). Due to the condition's frequent concealment, it is challenging to determine the true prevalence of Brugada syndrome. In Southeast Asia, the incidence has been shown to be higher than in the primarily Caucasian populations of Europe and North America (1–7 per 10,000 people) (6-8).

Although the condition can appear at any age, it most usually does so during the third and fourth decades of life and predominantly in men, even though genetic transmission is equivalent (85%) (2, 6, 7). And in areas of the world where the hereditary disease is endemic, Brugada syndrome is the main cause of death for men under the age of 50 (9). Patients with Brugada syndrome have been recorded at all different ages, according to numerous case reports (ranging from 2 to 80 years) (1–14). The prevalences reported by various studies differ tremendously because different estimating procedures were employed. Additionally, it is challenging to quantify the exact prevalence of Brugada syndrome because the ECG is dynamic in nature and the changes are frequently hidden until revealed by fever or medications (2–16). Malignant ventricular arrhythmia, which also causes fainting and accounts for 20-50% of deaths without any known organic heart illness, causes at least 4-12% of all unexpected cardiac deaths (2).

The first description of this disease was in 1992, and this report was published in the Journal of the American College of Cardiology (10). In 1996, some studies, primarily from Japan, began

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referring to the condition as Brugada syndrome (11). The recognition of the syndrome as a distinct condition did not become widespread until 1998, the year in which the first genetic basis for the syndrome was established (12). A consensus guide for the identification of Brugada syndrome was released in 2002 (13). Even though this definition was created 20 years ago, the type 1 ECG pattern's description is still the same today. However, as will be covered later, several factors considered in this consensus text are out of date. At that time, the V3 lead was supposed to be a helpful lead for diagnosis, and in some patients, it was also deemed helpful to record leads V3R and V4R. Today, we are aware that the V1 and V2 leads should be used to interpret the ECG pattern because the other leads do not provide any further benefits (14). A coved ST-segment elevation in the right precordial leads is a key characteristic of the Brugada syndrome (6).

Brugada syndrome was initially identified approximately 30 years ago; ironically, in a time of rapid technological advancement, a novel illness was identified using a method that had been around for almost a century. Since the illness was first described, a lot of scientific information has been accumulated. There have been various changes made to its definition because of our improved understanding of its pathophysiology and genetic foundation. Despite these details, the description of the ECG pattern has largely stayed the same since the first report (15).

When Brugada syndrome was first identified, there were a lot of disputes surrounding the syndrome, and we didn't know much about it. Many features of the illness are still not fully understood. There is less skepticism now that Brugada syndrome is a common cardiological condition that should be considered in patients and families with cardiac arrhythmias, syncope, and a previously normal heart, as well as in patients with isolated atrial fibrillation, which may be the first symptom of Brugada syndrome (16). Other symptoms of this disease include palpitations or chest pain, as well as nocturnal agonal breathing (perhaps brought on by self-terminating VT/VF) (17). Increased vagal tone often accompanies symptoms, which are typically brought on by the putative electrophysiological anomalies being aggravated by vagotonia. This frequently happens at rest, while sleeping, and after consuming heavy meals (18).

It was discovered that the voltage-gated sodium channel type V gene (SCN5A) and the SCN10A gene, which account for close to 50% of cases, include mutations in the cardiac sodium channel (19, 20). ECG abnormalities that indicate the SCN5A genotype include P-waves, the PR interval, and QRS lengthening (due to a prolonged HV interval) (21). There are now 18 known genes linked to the condition, with the SCN5A gene being the most prevalent one. Only 30–35% of confirmed cases, however, can be attributed to pathogenic variations in known genes, highlighting the necessity of more genetic research. Risk assessment and clinical treatment of individuals with Brugada syndrome are still difficult despite recent improvements in clinical diagnostics and genetic testing (14, 15, 17). About 75% of patients are diagnosed solely based on their clinical history and ECG findings (10).

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The following are necessary for the diagnosis of Brugada syndrome:

- Records of the type-1 ECG, which is characterized by "coved-type" ST-segment elevation of less than 2 mm in leads V1 and/or V2, located in the second, third, or fourth intercostal spaces, and occurring either naturally or with intravenous administration of Class I antiarrhythmic medications.

- In patients with a non-diagnostic type-2 or type-3 ECG, superior positioning of the leads V1-V2 up to the 2nd intercostal gap increases the sensitivity for the identification of a type-1 ECG. Brugada syndrome can only be diagnosed if a type-1 ECG is observed, either spontaneously or in response to a pharmaceutical challenge (22).

The three main morphological variations of Brugada syndrome are as follows: Type 1 is considered diagnostic. Both type 2 and type 3 can express a saddleback or coved morphology, but neither carries a definitive identity (10).

The clinical threshold to do an ECG if there is any suspicion of Brugada syndrome should remain low because people with a Brugada pattern on an ECG have a ventricular fibrillation (VF) risk of up to 12% at 10 years, even if they are asymptomatic (23).

According to the most recent European Society of Cardiology Guidelines, implanted cardioverter-defibrillator (ICD) implantation, pharmaceutical therapy, or catheter ablation are the available treatments for patients with Brugada syndrome. According to current recommendations, if a patient has genetic testing and is discovered to have a mutation known to cause Brugada, their family members should also have confirmatory testing (24).

Fever, infections and Brugada pattern

Significantly, fever-exacerbated Brugada syndrome does not appear to be mutation-specific, even though it is known that the biochemical capacity of heart sodium channels reduces at higher temperatures (25, 26). Although the precise mechanism is uncertain, it is hypothesized that since the sodium channels are temperature-sensitive, fever worsens the channel's inhibition of sodium influx (25).

This causes the right ventricle to repolarize unevenly, which increases the risk of re-entry arrhythmias (26).

Patients with Brugada syndrome may have arrhythmias in response to well-known provocative stimuli such as fever, alcohol, and drugs that cause sodium channel blockage (26). In the absence of a cardiac structural defect, the Brugada pattern is recognized on the ECG by a converging ST-segment elevation and a negative T wave in the early precordial leads. It is important to distinguish between the Brugada pattern and the Brugada syndrome since the latter is linked to a higher risk of sudden

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cardiac death (27). If the underlying issues are handled, the Brugada pattern is a generally benign illness that is largely undetected by fever. Patients with the Brugada pattern carry the same channelopathy as those with Brugada syndrome cases, but they do not have any close relatives who have had sudden cardiac death. ICD installation or antiarrhythmic drugs are not necessary for people with the Brugada pattern. The treatment of the underlying illness resolves the Brugada pattern. Patients with a Brugada pattern do not typically have symptoms, and until their disease is accidentally identified on an ECG, they are not aware of it (28).

It was discovered that sodium channels rapidly inactivate at temperatures over the physiologic range, pointing to a potential basis for the Brugada pattern in a febrile illness. Indicating that some people might be more sensitive to fever episodes, the Brugada patients' ECG features reveal for the first time a cardiac sodium channel mutation whose arrhythmogenicity shows only at temperatures approaching the physiological range (29, 30).

According to the results of a comprehensive review, fever from any source, most commonly in connection with a chest infection, typically reveals the Brugada pattern (28, 31). Fever was connected to the Brugada pattern in 83% of patients who were presenting. In addition, pneumonia and upper respiratory tract infections were reported as the most frequently associated infections with the Brugada pattern. In addition, 21% of the people had a cough, 10% had a sore throat, 18% had syncope, 8% had abdominal discomfort, and 7% had chest pain (27). Regardless of the presence of a hereditary predisposition, Junttila et al. (32) discovered that a large proportion of their patients with fever and Brugada-type ECGs developed malignant arrhythmias immediately after the beginning of fever. Antipyretics should be used to treat fever aggressively in these patients. It is advised that these patients use loop recorder monitoring when making therapy decisions (33).

Brugada syndrome is predominantly described in adults, and there is little information on how it manifests in children. Even in people with previously normal ECGs, a febrile illness may reveal an underlying Brugada pattern ECG in both adults and children (34).

Younger ages, male gender, and the effect of temperature on either the mutant type or wild type sodium channels leading to a reduction in sodium current, hence delaying conduction, have all been linked to fever as the cause of Brugada patterns (35). Only a few investigations have described electrocardiographic patterns of the Brugada type caused by fever (35–37). In the Turkish study, which included 103 febrile male individuals, only 10 cases of type 2 Brugada-type electrocardiographic patterns were seen; as a result, no Brugada syndrome cases were identified (36). There were 402 and 158 patients in the studies from Israel and Thailand, respectively. The Brugada syndrome involved 8 of the 402 (2%) and 6 of the 158 (4%) individuals, respectively. There were 11 Brugada syndrome cases in another Indian study (38). The Indian report's mean age was 35 years, which was younger than the prior cohorts' means of 46 and 48.2 years. All three investigations had similar average

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temperatures (38). According to the fever-free control group used in the Israeli (35) and Thai (37) studies, the Brugada syndrome is more common when there is a fever than when there is not. The predominance in Asia has been attributed to ethnicity, either due to the higher prevalence of disease-causing mutations in these populations, the modifying effect of the mutation, or the increased susceptibility to arrhythmias (38). Also, it has been reported that fever can cause ventricular arrhythmias in addition to emphasizing the Brugada ECG pattern (39–41).

A large series of studies of patients with symptomatic Brugada syndrome revealed that temperature was the cause of arrhythmias in 18% of cases of cardiac arrest (42). In patients with type I Brugada arrhythmias, mutations were evaluated by Keller et al. (43). When the temperature was physiological, these mutated channels showed a severe to complete loss of sodium current. As this was the case, further loss of function during the fire could not be expected. But this was discovered when expression studies of the same channels were performed at higher temperatures. The prevalence of type I Brugada ECG in patients with fever is 20 times higher than in patients without fever, according to Adler et al. (36), highlighting the influence of fever in revealing this ECG phenomenon. These findings may also suggest that the number of Brugada patients with no symptoms who have been identified so far is merely the tip of the iceberg, as many more would have been identified if their ECGs had been taken while they were experiencing febrile illnesses. This may have effects on the proportion of patients who may be at risk of proarrhythmic complications if they take any of the many drugs that happen to block the cardiac sodium channel (36).

Case reports have described febrile illnesses misdiagnosed as acute myocardial infarction to the point where sepsis-induced Brugada syndrome was mistakenly interpreted as ST-elevation myocardial infarction (STEMI), a 29-year-old man with fever who met 7 out of 8 diagnostic criteria for hemophagocytic syndrome caused by Chlamydophila pneumoniae (44), and a 76-year-old who underwent syncope (45).

Monitoring variables like fever can enable Brugada syndrome to be shown on ECG in those who are sensitive, as has recently been seen in multiple patients infected with the 2019 new coronavirus (COVID-19). To help lower the arrhythmic risk in these COVID-19 patients, current recommendations call for aggressive antipyretic medication and frequent ECG monitoring until the fever resolves (9).

In recent years, COVID-19-related cases have been reported in the literature (46-49).

SUMMARY / SONUÇ

When a patient has a history of cardiac arrest and fever, Brugada syndrome should be kept in mind. Furthermore, to avoid ventricular arrhythmias in Brugada patients, a correct diagnosis and quick treatment of fever are necessary. Furthermore, little is known about this phenomenon's actual

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prevalence. Therefore, in order to determine how frequently fever exposes a type of Brugada ECG, further studies are needed.

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