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REVIEW ARTICLE

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Relationship Between Brugada Syndrome and Poisoning

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ABSTRACT

Brugada syndrome is an inherited arrhythmogenic disease, characterised by a coved-type ST segment elevation in right precordial leads and an increased risk of sudden cardiac death due to ventricular arrhythmia. Electrocardiographic patterns of the disease is divided into three as: a) type I, characterized by a coved-type ST-segment elevation ≥ 2 mm in more than one right precordial lead (V1-V3), followed by negative T wave; b) type II, characterized by ST-segment elevation ≥ 2 mm in right precordial leads followed by positive or biphasic T waves, resulting in a saddleback configuration; and c) type III, defined as any of the 2 previous types if ST-segment elevation is ≤ 1 mm. Although genetic basis of the disease is described (mutations in SCN5A, a cardiac sodium channel gene, transmitted in an autosomal dominant pattern), there is a lack of information about its relationship with triggering factors, particularly toxins. Even though the literature knowledge mainly depends on case reports, in this review, our aim was to investigate the relationship between BrS and toxins, and create awareness on clinicians about this fatal entity.

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Introduction

Brugada Syndrome (BrS) is a life-threatening chanellopathy developing on a genetic basis. Characteristics of BrS are right bundle branch block (RBBB) and non-ischemic ST-T wave elevation in the anterior right precordial leads on electrocardiography (ECG) [1]. Genetic basis of the disease depends on a mutation in the cardiac sodium channel SCN5A gene in 1/4 of the cases. Although the patients may have normal ECGs, coved-type ST elevation in precordial leads V1–V3 is characteristic of the disease [2]. It is a clinically important disease since most common symptoms are syncope and sudden cardiac death [1]. In this review, we aimed to clarify the role of toxins in BrS developement in the light of current literature data.

Materials and Method

The literature was reviewed for toxic agents causing Brugada Syndrome. Keywords “Brugada”, “poisoning” and “intoxication” was entered to Pubmed database. Priority was given to studies in the last 10 years. Articles without an explanatory abstract and those written in another language than English were excluded. A total of 77 articles were obtained. These articles, then, were evaluated and chosen according to inclusion criteria. Accurate articles (n=47) were reviewed.

Relationship Between Brugada Syndrome and Specific Toxic Agents

In 2001, Ortega-Carnicer et al. presented a case of a patient with massive *cocaine* ingestion who developed terminal J wave associated with coved ST-segment elevation in anterior leads resembling the BrS [3]. In another report, Brugada findings in ECG was determined in a patient with *cocaine* intoxication. It was also stated that it was difficult to determine Brugada-like cardiac effects of cocaine on cardiovascular system due to its rapid nature [4].

Cannabis abuse was also shown to cause Brugada Syndrome. In a report by Daccarett et al., a patient who demonstrated markedly elevated levels of Tetrahydrocannabinol (THC) in toxicology panel developed Brugada pattern in ECG was presented [5].

In a study, ECGs of patients with *methanol* intoxication were investigated and only one patient was reported to have BrS [6]. In another a study, a patient with both *ethanol and heroin* intoxication developed BrS [7]. There is a need for further investigations on patients with substance abuse in the perspective of pathologic ECG patterns.

Tricyclic antidepressants (TCAs) remain a common cause of fatal drug poisoning as a result of their cardiovascular toxicity manifested by ECG abnormalities, arrhythmias and hypotension. Dosulepin and amitriptyline appear to be particularly toxic in overdose. The principal mechanism of toxicity is cardiac sodium channel blockade, which increases the duration of the cardiac action potential and refractory period and delays atrioventricular conduction as in BrS pathophysiology. Electrocardiographic changes include prolongation of the PR, QRS and QT intervals, nonspecific ST segment and T wave

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changes, atrioventricular block, right axis deviation of the terminal 40 ms vector of the QRS complex in the frontal plane and the Brugada pattern (downsloping ST segment elevation in leads V1-V3 in association with right bundle branch block) [8].

In a study with 134 patients, 35 patients were intoxicated by a TCA. In 12 (34%) TCA patients no ECG abnormalities were found. An increase in QRS duration (>100 ms) was seen in 13 (37%) cases. Six (17%) of them demonstrated a Brugada like pattern [9]. In another report, a patient who presented with Brugada after intake of a high dose of *amitriptyline* was presented. The patient was treated with continuous sodium bicarbonate infusion leading to resolution of Brugada pattern in ECG [10]. In another report, reversal of Brugada pattern in ECG following TCA intake by sodium bicarbonate infusion was presented. In this case, amitriptyline overdose induced Type 1 Brugada pattern which was reversed by 150 mEq of intravenous sodium bicarbonate was reported [11].

Similarly, Bebarta et al. described a A 50-year-old male ingested 13.6 grams of amitriptyline and presented in cardiopulmonary arrest. After initial resuscitation, the patient developed a Brugada electrocardiographic pattern. Brugada electrocardiographic pattern resolved following a 5-hour sodium bicarbonate treatment [12]. Kiran et al. reported a case of Brugada like pattern with right bundle branch block following Dothiepin overdose which resolved spontaneously [13]. Meert et al. presented a case report of a 57-year-old woman with severe intoxication with dosulepine (Prothiaden) who developed a Brugada-like electrocardiographic pattern [14]. In another report, a patient was presented with type 1 Brugada ECG pattern following intentional TCA intoxication [15]. Delayed presentation of the Brugada pattern in the ICU was reported in a 48-year-old man with TCA overdose. This report underlined the importance of awareness among clinicians for long term monitorization of patients with TCA intoxication in terms of Brugada pattern [16].

Ingestion of a lethal dose of *desipramine* was also reported as a reason for simultaneous typical and variant Brugada EKG patterns with ST-segment elevation in the inferior as well as the precordial leads following [17]. Antipsychotics like thioridazine during neuroleptic overdose may also cause BrS. A previously healthy 58-year-old woman was comatose when admitted to emergency department and a Brugada like pattern on ECG was recorded the day after [18]. *Diphenhydramine* was also presented as a cause of BrS. In a 39-year-old patient with an overdose of diphenhydramine, BrS was determined. The patient was found unconscious and hypotensive. Laboratory findings revealed a potassium concentration of 8.3 mEq/L and the ECG revealed a coved-type ST-segment elevation in leads V2-V3. These repolarization abnormalities did not respond to correction of the hyperkalemia or infusion of isoproterenol.

When the patient became conscious, he was admitted the toxic ingestion of diphenhydramine and progressively the ECG normalized. A negative flecainide test confirmed that the transient ECG abnormalities were the consequence of the drug overdose and ruled out the BrS [19].

It is known that severe overdose of *flecainide* can supress cardiac Na ion channels and cause BrS [20]. Flecainide (a class 1c antiarrhythmic) decreases intracardiac conduction with a dose-dependent manner. It provokes prolongation of PR and QT intervals and the QRS complex duration on ECG. Chhabra et al. reported a case of flecainide toxicity in an elderly female who presented with a type 1 Brugada pattern who essentially had a previously normal ECG pattern on therapeutic dose of flecainide therapy. They also underlined that without clinical suspicion, the case could easily be misinterpreted as a ST-segment elevation myocardial infarction [21]. In a 70-year-old man without a known history of hereditary BrS, severe *flecainide* overdose resulted in Brugada pattern in ECG. Serial ECGs revealed intraventricular conduction defect and ST-segment elevation. Resolution of ST-segment elevation lagged behind resolution of the QRS widening by 16-20 hours. The patient was reported to recover without complications [22]. In a report, transient Brugada pattern was described in a 31-year-old man admitted due to *ketamine* overdose. Also a slowly resolvent toxic myocarditis was diagnosed in the patient.

Brugada-like ECG was suspected to be caused by the ketamine intoxication in this case [23]. Brugada pattern and long QT patterns on ECG following *methadon* intake was also reported [24].

Class IA or IC antiarrhythmic agents are used to exacerbate a Brugada ECG pattern in order to predict sudden cardiac death in risky patients. However, even rarely, the class IB agent *phenytoin*, may induce a Brugada pattern ECG at a supra-therapeutic level. Swe et al. presented a case of a patient with a phenytoin level about twice as high as the therapeutic level, whose ECG demonstrated a type 1 Brugada pattern ECG. This case indicated the relationship between supra-therapeutic phenytoin level and type 1 Brugada pattern on ECG [25].

Phosphine is a gas used for the fumigation of grain on board cargo ships [26]. In a case in 2008, a 56-year-old seafarer complained of abdominal and chest pains, associated with dizziness on board of a bulk carrier with a cargo of peas. He was rescued by helicopter 80 miles away from the coast. On admission to the hospital, he developed bradycardia and respiratory distress. He lost consciousness and convulsed. The patient died due to pulmonary oedema, major metabolic acidosis and acute multi organ failure. The following day, a 41-year-old man from the same ship also complained of abdominal pain, vomiting and dizziness.

The ECG of the patient revealed type 1 Brugada syndrome [27]. Some poisonous plants are also known to cause BrS. *Japanese yew* is a widely used ornamental plant. In a report, a patient was presented with ventricular tachycardia (VT) at a rate of 175/min following Japanese yew consumption for months. The patient promptly received electric cardioversion. The baseline ECG, 10 minutes after cardioversion, showed junctional rhythm with a rate of 62 beats/min and severe prolongation of the QRS complex with some Brugada-like pattern [28]. In another report, 52-year-old man presented to the emergency department with nausea, abdominal discomfort, and extreme fatigue after ingestion of 15 g of *yew leaves* 20 hours before admission. On his ECG, a coved-type Brugada ECG pattern with ST-segment elevation of 0.6 and 0.7 mV in leads V1 and V2, respectively, was identified [29]. A 55-year old female patient was admitted to an ED with a prediagnosis of acute coronary syndrome. The patient did not suffered chest paişn

baut severe fatigue and nausea. On ECG, the heart rhythm was sinus bradycardia at a rate of 45 bpm with first-degree atrio-ventricular block and atypical right bundle-branch block. The QRS complexes were extremely prolonged and almost fused with T waves. Occasionally, the ECG morphology resembled Brugada pattern with down-sloping ST segment elevation and T-wave inversion in leads V1 and V2, and then the ventricular tachycardia appeared. Post-mortem toxicological examination revealed the presence of taxine B and isotaxine B which are the main pseudo-alkaloids of Taxus baccata [30]. Licorice has been used as a herbal product frequently. A 50-year-old woman who was admitted to an ED due to generalized weakness, chest pain and sweating following *liquorice* ingestion. BrS related to the effects of hypokalemia was determined on ECG. After stopping liquorice ingestion, the Brugada-like electrocardiographic pattern changed progressively with potassium replacement. A diagnosis of Brugada syndrome was confirmed after the ajmaline challenge test [31]. BrS can also be induced by toxic doses of class I antiarrhythmic agents as well as toxicities with several nonantiarrhythmic drugs that possess sodium channel blocking properties. Specifically, high doses of a beta-receptor blocker *propranolol*, is known to bind to the cardiac sodium channels and inhibit sodium uptake [32].

A 26-year-old man was referred to an intensive care unit due to unconsciousness. The man was found with a butterfly-needle canalized into the vein of the left forearm and connected to an empty syringe. The patient who was a long-term *propofol* abuser. His ECG showed typical Brugada features in V1–V3. Profound hypotension and metabolic acidosis were also determined. Half an hour after admission, the patient developed prolonged QT interval, idioventricular rhythm, and ventricular fibrillation. The patient has died [33]. *Tramadol* is a synthetic analgesic agent acting centrally with opioid and non-opioid characteristics [34]. Tramadol overdose is thought to lead to some changes in the ECG through blocking of fast sodium and potassium channels [35]. In a study with 1402 patients with tramadol poisoning, Brugada pattern was observed in 2 (0.14%) patients (100% male), both symptomatized with seizure [34]. Additionally, Cole et al. reported a case of isolated tramadol overdose associated with a Brugada ECG pattern [36]. *Metallic phosphides* (of aluminum and phosphide) and yellow phosphorus are commonly used rodenticide compounds in developing countries. In a 29-year-old male patient, Brugada phenocopy and hepatic dysfunction were observed following yellow phosphorus consumption. On ECG, he had type 1 in day 1 and type 2 in day 2. According to the report, the patterns resolved spontaneously by the third day without hemodynamic compromise [37]. Zinc phosphide (ZnP) is a rodenticide and is commonly used for suicide attempts. Its characteristics are myocardial toxicity and death. Prabhu et al. reported a case of a 67-year-old male with ZnP poisoning who had a type I Brugada pattern and ventricular fibrillation on his ECG. He had no other features of toxicity and recovered later. It was also underlined that metal phosphide was the most common toxin involved in suicidal poisoning in India [38]. Also a calcium canal blocker *verapamil* which is used for antihypertensive properties is known to cause BrS [39].

Conclusion

BrS is a common cause of sudden cardiac death. It is characterized by cardiac conduction abnormalities (ST-segment abnormalities in leads V1-V3 on ECG and a high risk for ventricular arrhythmias) and it has been shown to be associated with ventricular fibrillation and sudden cardiac death, particularly in young adults. It has a genetic basis and shows its impact through mitochondrial tRNA mutations. This genetic base may be trigerred by many factors and poisoning with certain substances may be one of them. In patients with poisoning, clinicians must be aware of a potential BrS developement. Being prepared for this entity leads to early diagnosis and interventions and thus, mortality may be reduced.

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