Sudden Unexpected Death syndrome or Brugada syndrome in dentistry: suggested Guidelines in undiagnosed patients

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ABSTRACT

Aim. The Brugada syndrome is a genetic syndrome that can determine malignant ventricular arrhythmias with the risk of death for the patient. The dentist may treat these patients during his daily clinical practice with a high risk, especially if the syndrome has not been diagnosed yet; for this reason a clinical guideline for dentists, to raise the suspicion of Brugada syndrome during anamnesis, is proposed.

Results. The prevalence of Brugada syndrome is estimated as 1:2000, but this condition may remain undiagnosed until its first presentation often during anesthesia. Data suggest that anesthetics, especially those locally administered, can trigger the Brugada syndrome.

Conclusion. It is better to perform oral surgery in Brugada syndrome patients under general anesthesia, in fact general anesthetics, such as propofol, can be safe in this particular condition. The presence of several specialists may be required in the management of the patient with Brugada syndrome during oral surgery.

Introduction

The Brugada syndrome was first reported in 1992 by P. Brugada and it was described in his article as “Right Bundle Branch Block” (RBBB) (1; 2). The paper aroused much interest and in 1996 Japanese researchers named it “Brugada Syndrome” (2; 3). In 1998 a mutation in the chromosome 3 of the gene SCN5A was discovered; the gene encodes for the Na+ channels. Subsequently more than 300 mutations of the gene SCN5A were described and linked to the syndrome (2; 4). Though the heart was structurally normal (4), these mutations led to a deficit of the ionic channels in the epicardial cells, with an impaired cardiac conduction (5). It became evident that the Brugada Syndrome was linked with the electrical activity of the heart.

It is difficult to ascertain the incidence of Brugada Syndrome in the general population, but the prevalence is estimated as 1 in 2000. More specifically in South East Asia, especially in Thailand and in the Philippines, in the migrants of South Asian origin and in the Japanese population the prevalence is quoted as 0.5-1 in 1000 (6).

Thus Brugada Syndrome can be considered a rare genetic syndrome, of the world’s total population (7.4 billion people, May 2016) an estimated 3.7 million are affected.

The BrS is caused by mutations of genes that encode for the ionic cardiac channels of Na+, Ca+ and K+; this can lead to malignant ventricular arrhythmias with the risk of death for the patient (5). Nineteen genes associated with different phenotypes have been identified and they have been summarized by Antzelevitch et al. (5). These mutations can determine:

• a loss of function of the ionic cardiac channels of Na+ and/or Ca+;
• a gain of function of the ionic cardiac channels of K+.

A single mutation may be insufficient to cause the BrS and recent observations highlight a polygenic inheritance model (6).

There is a different deficit of sodium, calcium and potassium channels depending on the subunit and/or protein involved. In the epicardial cells these deficits accentuate the phase 1 repolarization. There is a spike and dome morphology due to a prominent transient outward current (Ito) in ventricular epicardium but not in the endocardium. It generates a transmural voltage gradient (due to the different PA in the epicardial and endocardial cells) with an accentuation of the J wave, causing an apparent ST segment elevation. This different PA in the epicardial cells gives rise to a phase
channel blocking drugs, such as ajmaline, flecainide, a Type 1 ECG morphology (16). This test uses sodium pattern, a provocative drug test is necessary to induce pattern. In a patient with a Type 2 or Type 3 ECG pattern. A definitive diagnosis is made with a Type 1 ECG

Clinical presentation
The BrS has 3 ECG different patterns (6).
• Type 1: there is a cove-shaped ST elevation ≥2mm (mV) in right precordial leads, followed by a negative T wave with little or no isoelectric interval.
• Type 2: ST elevation is ≥2mm (mV) with a gradually descending of this tract that remains ≥1mm (mV) above baseline; the T wave is positive or biphasic.
• Type 3: there is a saddle back type or coved type ST elevation <1mm (mV).

A patient with a spontaneous Type 1 ECG has a moderate risk of life threatening arrhythmias (6). Several factors can induce a Brugada ECG pattern (4).
• Febrile state: it is necessary to use pharmacological agents in case of slight temperature increases (7; 8).
• Heavy meals at night just before sleeping (9).
• VF and sudden BrS usually occur at rest and at night because the bradycardia, caused by an altered sympatho-vagal balance, can contribute to arrhythmia initiation (5).
• Excessive stress (10).
• A combination of glucose and insulin (11).
• Excessive vomiting (12).
• Hot humid climatic conditions.
• Hyperkalaemia, hypokalaemia, hypercalcaemia (13).
• Alcohol toxicity.
• Cocaine toxicity.
• Many drugs can induce a BrS, as some classes of antiarrhythmic drugs, psychotropic drugs and some kind of anesthetic/analgesic drugs. Dentists must have extreme caution when administering these drugs, especially with local anesthetics. An updated list of these drugs to avoid in the BrS can be found in www.brugadadrugs.com (14; 15).

Diagnosis
A definitive diagnosis is made with a Type 1 ECG pattern. In a patient with a Type 2 or Type 3 ECG pattern, a provocative drug test is necessary to induce a Type 1 ECG morphology (16). This test uses sodium channel blocking drugs, such as ajmaline, flecainide, pilisicainide and procainamide. Drug administration differs for each drug. A 12-lead Holter placed on precordial leads V1, V2 e V3 in the 2nd and 3rd intercostal space can also assist in diagnosis as a typical Brugada pattern can arise during nocturnal bradycardia (6). Moreover genetic tests can locate one or more of the 19 known mutations (5). Other clinical criteria can help to confirm the diagnosis, such as a documented VF, polymorphic VT, family history of sudden cardiac death under the age of 45 years, coved-type ECGs in the family members, inducibility of VT with programmed electrical stimulation (PES), syncope and nocturnal agonal respiration (16).

Medical management and treatment
Therapy differs depending on the clinical presentation and ECG pattern of the patient; it can consist in the following (5).
• Implantable Cardioverter Defibrillator (ICD): it is the first line therapy in patients with aborted SCD or documented VT/VF, with or without syncope.
• Pacemaker therapy: Typical BrS ventricular arrhythmias generally occur during sleep or at rest and they appear associated with slow activity of the heart. Pacemaker therapy could be useful, but its role remains largely unexplored, limited to a few case reports.
• Ablation Therapy: the radiofrequency ablation can be used to reduce BrS manifestations; it is performed in the epicardial sites generating extrasystoles; the ablation at these sites is able to render VT/VF noninducible and to normalize the BrS ECG pattern in most patients for a period of weeks or months. This therapy may be lifesaving in BrS cases in which ICD therapy is impractical or in uncontrolled cases.

A pharmacological treatment has been studied for those patients in whom ICD implantation is not an appropriate solution, as in infants and young children, or in patients residing in economically disadvantaged areas. Amiodarone and β blockers have been shown to be ineffective; whereas Class 1C antiarrhythmic drugs (antiarrhythmic agents do not significantly affect the action potential, such as flecainide and propafenone) and Class 1A (antiarrhythmic agents lengthen the action potential; such as procainamide) are contraindicated as they can unmask the BrS and induce life-threatening arrhythmias (5).

The only therapeutic drug used is quinidine; it may be useful as adjunctive therapy to that with ICD or as an alternative to ICD in cases in which it can not be used. Quinidine has been proposed as a preventive measure in asymptomatic patients (5).

Agents that increase the L-type calcium channel current have also been shown to be useful (such as isoproterenol, denopamine, orciprenaline) (6).
Dental management of the patient in oral surgery

When a patient requires oral surgery, he/she must have a local or general anesthesia, depending on the procedure. Several factors influence selection of the anesthetic drug. The dentist generally uses local anesthesia, mostly using the aminoamides class such as ropivacaine, bupivacaine and lidocaine.

Local anesthetics block the sodium channels through two mechanisms:
- Chemical interaction with sodium channels on which the local anesthetic has a binding site;
- Physical interaction: the anesthetic molecule imposes a crystalline-liquid form to the cellular phospholipid membrane; the phospholipid tails fill the spaces in the membrane closing the sodium channels.

General anesthesia can be scheduled in some selected patients, such as those with neurological deficits (e.g. Down syndrome, autism), children, odontophobic patients and in all those cases in which the patient’s systemic diseases will require greater monitoring during surgery.

A patient with BrS, mostly with a Type 1 ECG pattern, can suffer from ventricular tachycardia/ventricular fibrillation, with a risk of death during anesthesia (17). It is thus necessary to take appropriate precautions to limit the chances of malignant arrhythmias (16).

Local anesthetic drugs used in dentistry, such as bupivacaine, should be avoided because they could induce malignant arrhythmias (4; 18). Bupivacaine can cause a QT-interval elongation interacting with sodium current and calcium current, resulting arrhythmogenic (19; 20).

Evidence about the use of lidocaine is contradictory. It appears to be safe (19; 21) but rare cases of induced-lidocaine BrS have been described (16; 22), so it is preferable to avoid using the drug (16; 18).

No data in literature are available to describe the effects of conscious sedation in patients with BrS undergoing oral surgery.

The management of a BrS patient under general anesthesia, however, has been well described (18; 23). Propofol is considered safe when administered in single bolus and with a limited infusion period, even though it is included in the list of drugs to avoid, since cases of induced-propofol BrS have been described (24). Arrhythmic events seem to occur when propofol is administered in patients with other risk factors or comorbidities such as sepsis, traumatic brain injury, critical illness, impaired microcirculation, impaired carbohydrate supply, or increased endogenic or exogenous catecholamine levels (25).

The administration of propofol/fentanyl/atracurium/air and oxygen or propofol/midazolam, or propofol/sevoflurane and fentanyl has shown not to cause BrS arrhythmias (26).

The perioperative management and drugs in the patient with Brugada Syndrome have been described by Theodotou et al. and are summarized in Figure 1 (26).

Temperature changes should be monitored because they can unmask the syndrome (16).

The dentist should be able to handle an emergency
situation by applying Basic Life Support and Defibrillation (BLS-D). In some cases, this may not be sufficient and more specific skills may be necessary, such as Advanced Cardiac Life Support (ACLS). The latter provides several algorithms for cardiac arrest, acute coronary syndrome, PEA / asystole, VF / pulseless VT, bradycardia, tachycardia, suspected heart attack (27).

The tachycardia procedure is summarized in Figure 2. The same protocol should be followed in the BrS patient when a VT/VF occurs during surgical procedure; drug dosage and selection is required. A careful assessment must be made by the anesthesiologist.

An external defibrillator is necessary and must be attached to the patient for the entire duration of the intervention because of the complex pharmacological management (26).

A silent syndrome: proposal guidelines for dentists to raise the suspicion of undiagnosed patient

Many patients with Brugada Syndrome are undiagnosed, due to its polymorphic presentation (28) and because it is often silent. In the everyday dental practice one may thus encounter a BrS patient. During the anamnesis it is thus necessary to suspect a BrS, especially if the patient needs dental anesthesia. When there is the suspicion of Brugada Syndrome, cardiological examinations must be required.

Dental guidelines during anamnesis are proposed to

![Figure 2 Tachycardia algorithm (27)](image-url)
maintain a high clinical suspicion of BrS. Risk factors and their investigation are summarized in Figure 3.

Points 1 to 6, describe the major risk factors; while point 7 to 10 are medium risk factors; and points 11 and 12 are minor ones. Their convergence, summarized as following, should raise the suspicion of undiagnosed BrS:

- at least 2 major risk factors;
- at least 1 major risk factor, 2 medium risk factors;
- at least 1 major risk factor, 1 medium risk factor and 2 minor risk factors;
- at least 3 medium risk factors and 2 minor risk factors.

If these risk factors are verified, a cardiological consultation is necessary and justified.

Conclusion

In conclusion, the management of a patient diagnosed with BrS who requires surgery is complicated and requires the cooperation of various specialists (dentist, cardiologist, anesthetist). It is not recommended to perform the surgery under local anesthesia because the drugs used in dentistry can interact with sodium channel and trigger the VT / VF polymorphic difficult to control (16). It is better to perform the surgery under general anesthesia; data available in literature affirm that propofol is safe when administered in single bolus and with a limited infusion period, despite being included in the list of drug to avoid. Perioperative times must be reduced as much as possible (25).
Brugada Syndrome is considered a rare genetic syndrome; however, it has a prevalence of about 1 in 2000: an early diagnosis is extremely important in order to prevent possible complications or even death.

For this reason, it is important for the dentist to raise the suspicion of undiagnosed BrS particularly in those cases in which the patient needs anesthesia; it is necessary to send the patient to the cardiologist when there is suspicion of BrS.

References