Title: BRUGADA PATTERN IN HEROIN ADDICTION: SYNDROME OR PHENOCOPY?

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Abstract

Introduction: Brugada phenocopies (BrPs) are clinical entities that differ in etiology from true congenital Brugada syndrome (BrS) but have identical electrocardiographic (ECG) patterns.

Methods: Our Manuscript reports a interesting case of BrP in a young man with heroin overdose who developed Acute Kidney Failure secondary to rhabdomyolysis. His initial ECG showed Brugada type 1 pattern with elevation "Coved-Type" of the ST segment in V1 and V2. The Brugada ECG pattern resolved upon hemodialysis treatment. Provocative testing using sodium channel blockers was performed, and failed to reproduce a BrS ECG pattern, confirming the diagnosis of Brugada's phenocopy.

Conclusion: Several clinical conditions can imitate a true Brugada Syndrome and Brugada Phenocopies are a part of those conditions. A systematic approach and a prompt recognition of this clinical and electrocardiographic entity may avoid diagnostic errors and may promote the initiation of appropriate treatments.

Key words: Brugada syndrome, Brugada phenocopy, drug addiction, rhabdomyolysis, acute renal failure.

Abbreviations: AKI: Acute Kidney Injury; **BrP:** Brugada Phenocopy**; BrS**: Brugada Syndrome**;; ECG:** Electrocardiogram**; SCN5A:** Sodium Voltage-gated Channel Alpha Subunit 5;

Introduction

Brugada phenocopies (BrP) are clinical entities that are etiologically distinct from true Brugada syndrome (BrS). They form a group of heterogeneous conditions that are perhaps the most difficult to differentiate from true congenital BrS due to identical ECG patterns and are elicited by various underlying clinical conditions such as electrolyte disturbances, drugs or myocardial ischemia.

In this report, we describe the case of BrP occurring in a man with heroin addiction who developed hyperkalemia for acute renal failure due to rhabdomyolysis.

Case presentation

We describe a clinical case of a 41-year-old Caucasian man, who presented to the Emergency room of a hospital in the province of Palermo for dyspnea and general discomfort following use of heroin. The family history was negative for cardiovascular and congenital heart diseases or sudden cardiac death. He has a long history of drug addiction, initially cocaine addiction, until October 2019, then alcohol, cannabis and heroin abuse. He was in methadone maintenance treatment for opiod addiction and on therapy with a fixed combination of Zofenopril/Hydrochlorothiazide 30/12.5mg day for arterial hypertension.

The patient reported lumbosacral trauma two days before the hospitalization and he took heroin for analgesic purpose.

On admission, in our hospital, the patient was afebrile (Temp. 36 ° C), its blood pressure was 180/138 mmHg, the heart rate 61bpm and oxygen saturation 89%. He was in a state of psycho-motor excitement, and presented profuse sweating, cold extremities, miotic pupils, shallow and frequent breathing. He complained widespread muscle pain. Neither cardiovascular murmurs nor pathological breath sounds were detectable at chest auscultation. The weight was 126 Kg; the height: 180 cm, the resulting body mass index 37 Kg / m2.

Acute kidney injury (AKI) was diagnosed for the presence of anuria, increased azotemia (102 mg / dl), serum creatinine (6.56 mg / dl) and potassium levels (8.5 mmol / L) along with a severe metabolic acidosis (pH = 7.27, pO2= 83 mmHg, pCO2= 29 mmHg, HCO3 = 13.6 mmol/L, Base deficit=-13.9 mmol/L, Lactate 4.3 mmol/L). The increased levels of CreatinePhosphokinase (CPK> 2000 U / L) and of transaminase (AST / ALT 5684/4305 U / L) and the presence of myoglobinuria revealed a rhabdomyolysis that was the very likely responsible for the AKI.

The electrocardiogram (ECG) performed in the emergency room of the hospital he came from showed: sinus bradycardia, left axis deviation, elevation of the ST "Coved-Type" segment in V1 and V2 (**Figure 1)**. The troponin I at the admission was 356 ng / ml (normal values <14 ng / ml).

The patient was treated by a intravenous infusion (10 ml) of 10% calcium gluconate and 10 IU rapid insulin in a 500 ml glucose intravenous solution 10 %. In addition, 60 mEq of 1 mEq / ml sodium bicarbonate and one intravenous injection

of Naloxone (4 mg) were administered to reduce the symptoms of heroin intoxication. The absence of defects in kinesis cardiac segmental echocardiogram and the stability of troponin I values, allowed to exclude a coronary acute syndrome. Due to the persistence of serious general clinical conditions, the patient was moved to our Unit of Nephrology, where he underwent urgent hemodialysis treatment , after placing a central venous catheter in his right jugular vein, to be continued in the following days. There has therefore been a gradual improvement in rhabdomyolysis indices and a recovery in diuresis and a complete normalization of the ST segment alterations with the disappearance of the typical Brugada ECG-graphic pattern **(Figure 2)**.

Toxicological screening in serum and urine tested positive for opioids and cannabinoids. For the appearance of symptoms related to the withdrawal syndrome, methadone hydrochloride 10 mg / day was used.

To differentiate a Brugada syndrome from a Brugada phenocopy, provocative pharmacological tests were performed with Ajmaline e.v. at 1mg / Kg dose, with negative results, confirming the diagnosis of Brugada's phenocopy**. (Figure 3)**

ECG-graphic monitoring during hospitalization did not detect the presence of arrhythmias and the patient was discharged in improved general clinical conditions, with valid diuresis and partial improvement of the renal function indices (urea 74 mg / dl, creatinine 3.85 mg / dl), while the normalization of the values of CPK, AST and ALT and the absence of myoglobinuria confirmed the resolution of his clinical-lab picture about rabdomiolisis.

Discussion

The case described represents a paradigmatic example of a Brugada phenocopy in a heroin addict with AKI secondary to rhabdomyolysis. The mechanisms leading to rhabdomyolysis in heroin addicts can be manifold: myotoxic effect of quinine, present as an adulterant substance in heroin [1]; direct cyto-toxic effect of narcotics by alteration of membrane conveyors; prolonged immobility or a state of coma following to the inoculation of "dose" [2]. The lack of liquids and food supply during these periods causes a reduction in the production of Adenosine triphosphate, dehydration and consequent increased risk of rhabdomyolysis [3].

Severe renal failure represents the main complication of rhabdomyolysis, that may develop in about 50% of cases, increasing the mortality rate [4].

The mechanisms involved in the induction of AKI during rhabdomyolysis are represented by:

a) Renal vasoconstriction due to both hypovolaemia secondary to the seizure of liquids within the damaged muscle and to the release of vasoconstrictor vascular mediators following muscle injury;

b) Tubular obstruction, mainly at the level of the distal tubules where myoglobin which appears to be in high concentration precipitates following the interaction with the Tamm-Horsfall protein;

c) Direct tubular cytotoxic effect, especially on the proximal tubule level.

Brugada phenocopies are clinical entities with ECG-graphic patterns identical to those of Brugada syndrome but induced by reversible clinical conditions [6]. Baranchuk and colleagues defined this condition in 2012 and since then more than 100 cases have been published in an international on-line register [6]. The criteria for diagnosing Brugada phenocopies can be summarized as follows:

a) Brugada ECG-graphic pattern type 1 and type 2;

b) The patient has an underlying condition

c) The ECG-graphic pattern reults following the resolution of the underlying condition;

d) There is a low pre-test probability of Brugada Syndrome determined by the lack of symptoms and a negative pathological and family history of previous cardiovascular events;

e) The result of provocative tests with Flecainide, Procainamide, Ajmaline (preferred drug for its short action duration) or other sodium channel antagonists is negative;

f) The result of genetic tests is negative (it is not a mandatory criterion, as the Sodium Voltage-gated Channel Alpha Subunit 5 (SCN5A) mutation is identified in only 20-30% of the people to be proved affected by Brugada syndrome).

The causes of Brugada phenocopies are classified into six etiological categories [7]:

1. Metabolic conditions
2. Mechanical compression
3. Myocardial ischemia and pulmonary embolism
4. Myocardium and pericardium diseases
5. Alteration of the ECG from caused by something else
6. Other cause

In our clinical case, Brugada's phenocopy may be due to ECG-graphic alterations induced by the heroin overdose and could be related to a greater risk of sudden cardiac death. Furthermore, heroin-induced ECG alterations have been reported in over 55% of heroin addicts, which are mainly represented by QTc prolongation and bradyarrhythmias [8].

The main etiopathogenetic factor of Brugada phenocopies is represented by metabolic abnormalities, in particular by hyperkalaemia [9].

Hyperkalaemia is believed to determine a reduction in the resting membrane potential of myocardial cells with the consequent temporary inactivation of the voltage-dependent sodium channels responsible for myocardial depolarization. There is therefore an alteration between the flow of sodium ions entering and the flow of potassium ions leaving the myocardiocyte, with the outflow predominance of the potassium ion current (Ito current).

The negative hyperkalaemic effects seem to be more marked in the myocardial cells of the Right Ventricular Outflow Tract (RVOT), involving mainly the epicardial cells than those of the endocardium, as they are more sensitive to the harmful effects induced by the hyperkalemia. This determines a delayed depolarization causing an elevation of the ST segment in the right precordial derivations, simulating the alterations of the sodium channels typical of Brugada Syndrome [10-11]. Data available in literature have shown that typical ECG-graphic Brugada patterns occur when potassium levels are between 6.0 and 8.8 mmol / L [11].

Our patient did not report any heart disease or genetic connection of sudden cardiac death and / or cardiovascular disease and the "coved-type" type 1 ECG-graphic of Brugada resolved after the hemodialysis treatment that led to the resolution of the clinical-lab picture. These characteristics are appealing for a Brugada phenocopy rather than a Brugada syndrome, confirming the negativity of the drug test with ajmaline **(Figure 3)**.

Conclusions

This case allows us to remember the differential diagnosis between a Brugada syndrome and a Brugada phenocopy due to metabolic alterations, which can also simulate a myocardial infarction with ST segment elevation. Hence, a systematic approach is crucial to avoid diagnostic errors and a rapid recognition of this clinical and electrocardiographic entity.

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Legends for figures:

Figure 1: electrocardiogram performed in the emergency room at admission. It shows sinus bradycardia, left axis deviation, elevation of the ST "Coved-Type" segment in V1 and V2.

Figure 2: electrocardiogram performed after hemodyalisis. The elevation of the ST in V1 and V2 completely disappeared.

Figure 3: Negative provocative tests with ajmaline.