

## Brugada type 1 pattern and lithium therapy

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Dear Editor,

Brugada syndrome is a genetic disorder characterized by specific dynamic electrocardiographic patterns in the right precordial leads and an increased risk of ventricular tachyarrhythmia and sudden cardiac death. Lithium, a drug commonly prescribed for psychiatric disorders, may unmask the Brugada ECG pattern in patients with the genetic disease. We report the case of a 50-year-old man with a psychiatric disorder treated with lithium who was admitted for septic shock. The ECG revealed right bundle branch block and ST segment elevation in V1-V3 consistent with Brugada type 1 ECG pattern.

## Case Report

A 50-year-old man with a history of schizoaffective disorder treated with lithium, clozapine, and citalopram was admitted to the hospital for septic shock of abdominal origin. He presented impaired general condition with disorientation, hypotension, and axillary temperature 37.8°C. The blood tests revealed metabolic acidosis with pH 7.29 and bicarbonate 16.5 mEq/L, as well as creatinine 4.5 mg/dL, sodium 140 mEq/L, potassium 3.1 mEq/L, C-reactive protein 24.6 mg/dL, leukocytosis with neutrophilia, and high lithium level 1.89 mEq/L (therapeutic range 1–1.2 mEq/L). The initial electrocardiogram (ECG) showed sinus rhythm with pseudo-right bundle branch block (RBBB) and coved ST elevation  $\geq 2$  mm in V1–V3, all consistent with an electrocardiographic pattern of Brugada type 1 (BrP) (Figure 1). The patient was treated energetically with vasoactive support, antipyretics, and antibiotics. His metabolic imbalance was corrected and all psychoactive treatment was discontinued. Rapid clinical improvement and prompt correction of all the laboratory abnormalities was achieved, but normalization of ECG repolarization was observed only after blood lithium levels fell to 0.32 mEq/L (Figure 2). For this reason, lithium was finally considered responsible for the BrP Type 1 observed in this patient at admission. The patient did not report personal or family history of syncope, palpitations, arrhythmias, or sudden cardiac death (SCD).



Figure 1

ECG of the patient at admission to the hospital (with toxic levels of lithium) consistent with Brugada type 1 ECG pattern

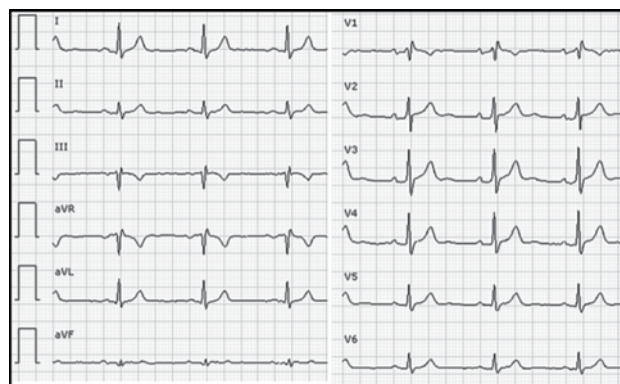


Figure 2

Patient control ECG (without lithium treatment)

His echocardiogram was normal so, after considering all the data and based on current recommendations, outpatient cardiology follow-up (clinical and electrocardiographic) and modification of the patient's psychotropic treatment was prescribed. On subsequent follow-up visits, the ECG showed only incomplete RBBB and the patient remained asymptomatic.

### Discussion

Brugada syndrome (BrS) is a genetic disorder, generally of autosomal dominant inheritance with variable penetrance, which is characterized by a specific electrocardiographic pattern in the right precordial leads and increased risk of ventricular tachyarrhythmia (polymorphic ventricular tachycardia or ventricular fibrillation) and SCD, which may even be the first clinical event. However, BrS usually manifests with syncope or cardiac arrest, at rest or during sleep, usually in the third or fourth decade of life. However, BrS is considered responsible for 4% to 12% of all sudden deaths, and for at least 20% of deaths that occur in patients with structurally normal hearts.<sup>1</sup> Many mutations cause the syndrome but they mainly affect the SCN5A gene that encodes a subunit of the sodium channel in cell membranes and they occur in the absence of structural heart abnormalities.

Two electrocardiographic BrPs have been described,<sup>2</sup> which are sometimes dynamic and consist of RSR' or pseudo-RBBB in V1–V2 (sometimes only detectable if the leads are recorded in the second or third intercostal space) in addition to: a) BrP type 1 or coved ST elevation  $\geq 2$  mm, with a rapid concave or straight downslope and a symmetrical negative T wave, or b) BrP type 2, or saddle-back, consisting of R'  $\geq 2$  mm in amplitude followed by a concave ST elevation  $\geq 0.05$  mm and a positive or flat T wave. The prevalence of BrPs in the general population ranges from 0.1% to 1%, being 8 to 10 times more common in males than in females. The prevalence of BrS (clinical BrP) is unknown. BrP type 1 defines the existence of the genetic disorder and can be either spontaneous or unmasked by challenge with sodium channel blockers (procainamide, flecainide, and ajmaline) or fever. In both cases, whether spontaneous or unmasked, it is necessary to identify the patients who are at high risk of presenting SCD, such as patients with spontaneous BrP type 1 and history of nonvagally syncope or ventricular tachyarrhythmia or prior SCD, and those with a family history of SCD before the age of 45 years (not caused by an acute coronary syndrome) or BrP type 1. In all these high-risk cases, implantation of an automatic defibrillator is indicated. In addition, the screening of first-degree relatives should not be overlooked.

In recent years, it has been observed and reported how diverse drugs can induce BrP type 1 through different mechanisms. This has led to the creation of a website for doctors and patients that can be freely accessed and is regularly updated, where a list of unsafe drugs, grouped by their degree of dangerousness,<sup>3</sup> can be consulted. It is estimated that the clinical significance of these induced BrPs is similar to that of Brugada patterns induced by sodium channel blocking agents during diagnostic tests. In this regard, lithium and various other psychotropic drugs are listed in the group of drugs that have been associated not only with the appearance of BrP type 1, but also with the production of arrhyth-

mias. Avoidance of these drugs is energetically recommended in patients with known or suspected BrP or BrS (although the degree of evidence is IIb because there is conflicting evidence and/or divergence of opinions). Today, there are very few case reports relating lithium with BrS.<sup>4–7</sup> Such interactions can even occur with blood levels within therapeutic range,<sup>8,9</sup> and they seem to derive from the ability of lithium to block sodium channels in a dose-dependent way.<sup>4</sup>

The clinical case reported here highlights the importance of all physicians being familiar with BrS and BrP, and the need for ECG recordings before and during lithium treatment. Given the well-known cardiovascular adverse effects of lithium, it has the potential to unmask the Brugada genetic disorder and may induce fatal events.

### CONFLICTS OF INTERESTS

None.

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### The question of metabolic syndrome X

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## Letter to the editor

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Dear Editor

Metabolic alterations in the psychiatric patient have ended up becoming a controversial and debated subject in recent years. In the center of this controversy, the so-called metabolic syndrome has been object of a lively debate.<sup>1-7</sup> Five years have passed since the 2010 publication in *Diabetologia* of the clear conclusions of the expert's committee consulted by the World Health Organization (WHO) of: "The metabolic syndrome should not be used as a clinical diagnosis" (8, p.604). However, the concept has been successful and in successive years, we have been able to read works in the same journal.<sup>9-11</sup> In this way, we have been driven once again to raise the issue of whether it makes sense to continue referring to said syndrome.

### Criticism of the metabolic syndrome

The main stumbling block denounced by the critical tendency regarding the metabolic syndrome is precisely it being called a syndrome. Two requirements have been proposed<sup>5</sup> to allow it to be considered as such: capacity to predict adverse events and identification of a common pathological process. Regarding these, the opponents of the concept understand that its cause is unknown and that it does not have greater usefulness than that of labeling and medicating the population.

However, a common pathological process is not the same as its cause, and may be supported by a physiopathological pathway of unknown etiology (strictly speaking, it is really the absence of cause that defines the syndrome versus the disease). Nonetheless, there is no consensus regarding the physiopathology of the metabolic syndrome since the dominant hypothesis of insulin resistance must be understood along with the inflammatory atherogenic role,<sup>12</sup> and the relationships postulated with hepatopathies, sleep apneas or neoplastic processes must also be considered, so that the consolidation of all the syndrome becomes complicated.

Due to this uncertainty, the nosological criterion has relinquished a large part of protagonism to «the interests or purposes of each one».<sup>5</sup> This has led to changing criteria in the definition of the «syndrome».<sup>13</sup> While in 1999, the WHO chose a definition that has come to be called "glycocentric," in 2001, the Adult Treatment Panel based its definition on central obesity and the determination of abdominal circumference, guided by clinical pragmatism versus the laborious measurement of the euglycemic clamp. Thus, based on the interests of each school, the different elements of the semiological combination has been recombined: shifting the pathologically defined limits of lipids in blood and blood pressure or adding cutoffs to the abdomen circumference. Finally, in 2010, the WHO experts publically

condemned the redefinition of the «syndrome». Then, what should be done; should we return to the first definition?

At first, the «metabolic syndrome» was not defined by clinical signs (characteristic of a syndrome or disease) but rather by the risk factors of (true) cardiovascular disease. The tendency of these risk factors to occur together in an individual above the likelihood of an isolated appearance of each one of them led to the hypothesis of a common pathophysiological pathway supported by insulin resistance.<sup>14</sup> However, as this and the subsequent hypotheses were not sufficiently convincing, the discussion returned to the capacity of risk prediction, which is where it began, although now hampered by the pursuits of specialty.

### A metabolic model of risk

Free of etiological aspirations, the risk model may well rest on specific interests, in this case, on the prediction of cardio- and cerebrovascular adverse events, and on defending its utility.

The declared purpose of identification and prevention of risk factors could be compared with other reputable studies, for instance, read the conclusions based on the American Framingham study or on the European SCORE (Systematic Coronary Risk Evaluation). A comparable predictive capacity can only be achieved if corporatism is renounced; and this is the only way that it will be possible to accept the essential non-semiological variables of age, gender and smoking habit. This cannot occur if the focus continues to be placed on "causes" that were never own.

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## Letter to the editor

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