

# Harmless herbs? A case report of acquired long QT syndrome and torsades de pointes in a patient taking herbal supplements



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## Introduction

Herbal supplements are gaining popularity and are often perceived as harmless because of their “natural” character. Indeed, although available without prescription, these preparations contain mixtures of substances that can have significant physiological effects. The potential negative side effects are often not foreseeable, as the exact composition of the preparation can vary greatly from one distributor to another, and because the pharmacodynamic and pharmacokinetic properties of these molecules are not well known. We describe the case of a 56-year-old woman with acquired long QT syndrome, torsades de pointes, and syncope following the use of herbal supplements.

## Case report

A 56-year-old woman was admitted to the emergency department for syncope without prodromes in a supine position. This was the first episode of syncope, but she had experienced 3 prolonged episodes of dizziness over the past month. Her medical history was unremarkable. There was no familial history of sudden cardiac death. For 4 months, she had been taking hemp oil, containing the cannabinoid derivatives cannabidiol (CBD) (61 mg/mL in 1 supplement and 24 mg/mL in the other) and cannabigerol (CBG) (1 mg/mL in 1 supplement), 3–4 times daily because of a stressful work-life balance. The physical examination was normal, apart from hypotension (86/42 mm Hg). Her blood chemistry showed normal kidney function, a magnesium concentration at the lower limit of normal, and a normal potassium level. A toxicology screen was not performed. A rhythm strip showed short runs of torsades de

## KEY TEACHING POINTS

- Herbal supplements are gaining popularity and are often perceived as harmless because of their “natural” character. However, the use of these supplements may be associated with considerable side effects.
- Data concerning the effectiveness, toxicity, and potential for interactions of herbal supplements are limited.
- Dosing recommendations should always be respected and possible interactions with other medication or supplements should be considered.

pointes (Figure 1). She received intravenous magnesium and saline fluids in the emergency department with stabilization of the heart rhythm. The 12-lead ECG showed normal sinus rhythm at 58 beats per minute and a markedly prolonged corrected QT (QTc) interval of 667 ms (according to the Bazett formula, Figure 2).

A transthoracic echocardiography was normal. She was transferred to the coronary care unit for rhythm monitoring. During 24-hour surveillance, the QTc interval shortened to 560 ms, no more torsades de pointes were noted, and she was transferred to the cardiology ward.

In-depth anamnesis revealed that for about 6 weeks, in addition to the hemp oil, she had started taking extra herbal supplements containing 250 mg of berberine. She also admitted that she had been taking up to 6 times the recommended dose of hemp oil supplements.

During her hospital stay, all supplements were stopped and a gradual decrease of the QT interval was noted until normalization after 5 days (Figure 3). She was discharged 6 days after hospitalization. At 3 months’ follow-up, she reported no new episodes of dizziness or syncope, with an electrocardiogram (ECG) still showing a QTc interval within normal range.

**KEYWORDS** Long QT; Torsades de pointes; Cannabidiol; Cannabigerol; Berberin  
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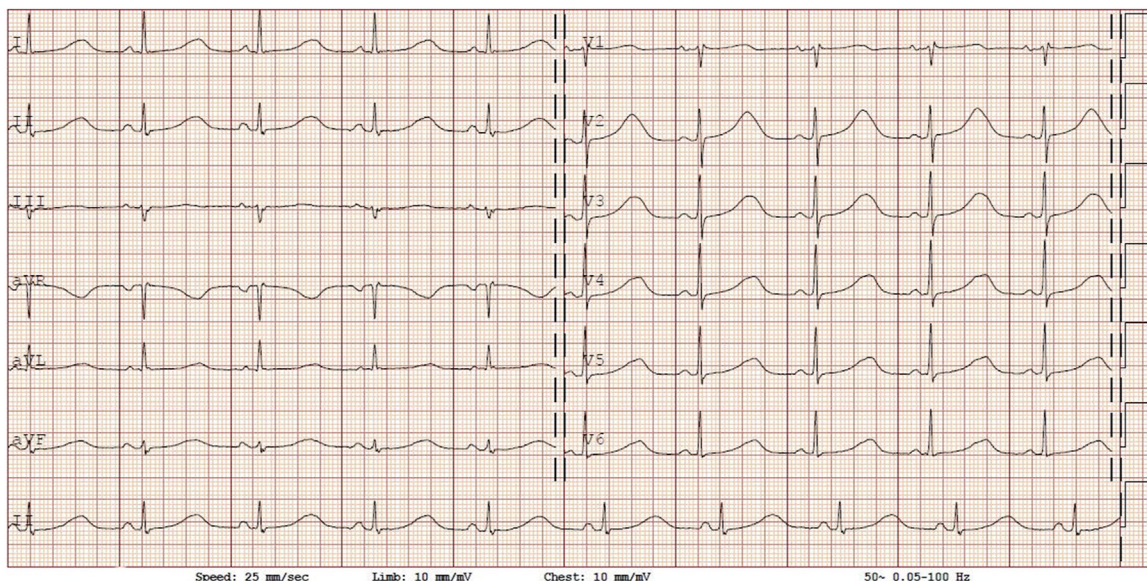
**Figure 1** Rhythm strip showing sinus bradycardia and short runs of torsades de pointes.

## Discussion

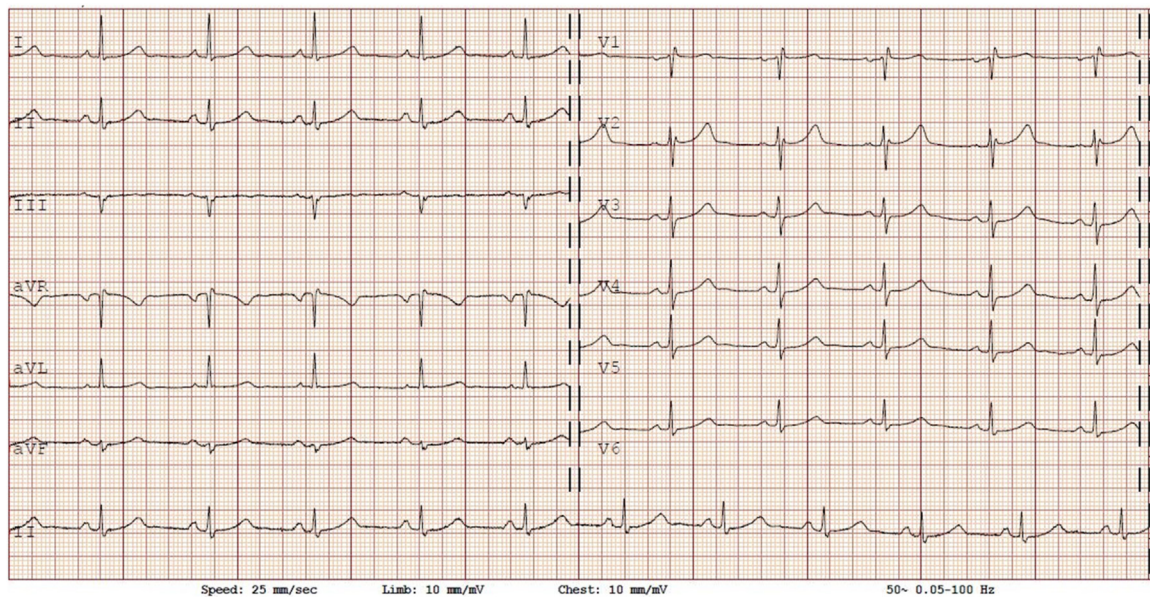
We report the case of acquired long QT syndrome with torsades de pointes secondary to hemp oil and berberine supplements. The normalization of the ECG after stopping all supplements, without any other causative factors, strongly indicated these as being responsible for the prolonged QTc interval. As a reminder, a prolonged QTc interval is defined by a QTc >450 ms in men and >460 ms in women, with QTc >500 ms being considered at risk for immediate arrhythmic complications.<sup>1</sup>

CBD is a chemical present in the cannabis plant (*Cannabis sativa* or *Cannabis indica*), which contains over 90 so-called cannabinoids. The most important and most thoroughly investigated cannabinoid is tetrahydrocannabinol (THC), the substance responsible for the psychotropic effect of cannabis.<sup>2</sup>

Acquired long QT syndrome and torsades de pointes have been described after consumption of THC.<sup>3</sup> To our knowledge, long QT syndrome after CBD ingestion has not been reported to date. Unlike THC, CBD has no psychoactive effect and therefore it is not subject to the Narcotics Act. Products containing CBD are gaining popularity. They are supplied as raw material (in the form of substances or preparations) or as ready-to-use products (cosmetics, tobacco substitutes, chemicals such as scented oil, etc). CBD has been shown to have anti-inflammatory, antiepileptic, analgesic, anxiolytic, antipsychotic, and immunomodulatory properties.<sup>2</sup> Several studies with cannabinoids have shown effects on various transmembrane ion channels, such as inward sodium and calcium channels and outward potassium channels.<sup>4</sup> In guinea pigs CBD has been shown to be an inhibitor of the cardiac human



**Figure 2** Twelve-lead electrocardiogram after administration of intravenous magnesium, showing normal sinus rhythm and a markedly prolonged QTc interval of 667 ms (Bazett).



**Figure 3** Twelve-lead electrocardiogram 5 days after stopping all herbal supplements, showing normalization of the QTc interval, measured at 413 ms (Bazett).

Ether-à-go-go-Related Gene (hERG) channels at concentrations between 1 and 5  $\mu\text{M}$ .<sup>5</sup> These channels conduct the rapid delayed rectifier potassium currents ( $I_{kr}$ ) and play a central role in the third phase of the cardiac repolarization. Inhibition of these channels lengthens repolarization and significantly lengthens the QT interval. In this study, an at least 30-fold margin between hERG's half maximal inhibitory concentration ( $\text{IC}_{50}$ ; indicates the quantity of substance needed to inhibit a given biological process in vitro by 50%) and the maximal concentration after 1 dose of cannabidiol ( $C_{\text{max}}$ ) has been proposed to be an acceptable degree of safety from arrhythmogenesis.<sup>5</sup> There are human pharmacokinetic data showing that the  $C_{\text{max}}$  values for CBD can reach 0.35–0.58  $\mu\text{M}$  after smoking (19.2 mg) and oral intake (400 mg), respectively.<sup>6</sup> Based on Orvos and colleagues,<sup>5</sup> who showed that CBD had an inhibitory effect on hERG channel activity with an  $\text{IC}_{50}$  value of 2.07  $\mu\text{M}$ , the ingestion of 400 mg of CBD results in a ratio of 3.57 ( $<30$ ), thus suggesting the potential of proarrhythmic side effects in humans, especially in case of interactions with the metabolism of CBD.<sup>6</sup> In vitro, CBD inhibits CYP isozymes (mainly CYP3A4 and CYP2C19),<sup>7</sup> but it is unclear whether this occurs at concentrations achieved with doses used clinically.

CBG has been shown to be a very potent alpha-2 adrenoceptor agonist in vitro and, as a consequence, might thus cause bradycardia or hypotension.<sup>8</sup> In vitro, CBG inhibits CYP1A2 activity.<sup>7</sup>

Berberine is an active alkaloid component found in the root, rhizome, and stem bark of many medicinal plants, frequently used in traditional Chinese and ayurvedic medicine to treat infections, diarrhea, type 2 diabetes mellitus, hyperlipidemia, and hypertension.<sup>9</sup> As a supplement it is commercialized to support a normal glucose and lipid metabolism. Berberine has been shown to promote the degradation of

and directly inhibit the cardiac human hERG channels, and may thus prolong the QT interval.<sup>10</sup> In vitro, berberine is a substrate of the CYP1A2, CYP2D6, and CYP3A4 enzymes, and may therefore be prone to drug interactions.<sup>11</sup>

In summary, according to the (in vitro) data in the literature, berberine exhibits a proarrhythmic effect by inhibiting the hERG channels. CBD in itself also has a proarrhythmic potential and CBG, owing to its alpha-2-adrenergic action, could have promoted hypotension and bradycardia. Pharmacokinetically, berberine concentrations could also have been increased by inhibition of CYP1A2 (CBG) and CYP3A4 (CBD). We therefore conclude that the concomitant intake of the berberine supplements and hemp oil caused significant QTc prolongation.

## Conclusion

Herbal supplements are gaining popularity and are available as over-the-counter medicine. To our knowledge, this is the first description of an acquired long QT interval and torsades de pointes following the use of CBD/CBG-containing supplements. These products should be used with caution, as data concerning their effectiveness, toxicity, and potential for interactions are limited. In addition, there are variations in the concentrations of the active substances. Therefore, the use of these supplements should not be taken lightly, dosing recommendations should be respected, and possible interactions with other medication or supplements should always be considered.

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