

Long QT syndrome induced by elevated dose of Fluoxetine Cloridrato: case report

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Abstract: Long QT syndrome is a clinical condition that affects cardiac repolarization with an increased risk for the development of severe ventricular arrhythmias. The acquired form can be induced by drugs, such as selective serotonin reuptake inhibitors. An 83-year-old female patient, previously diagnosed with major depressive disorder in use of Fluoxetine 80mg/day, was admitted in the emergency department after a syncopal event. An important widening of the QT interval was observed, with a corrected value of 580ms. A 24-hour Holter monitoring showed increased ectopic ventricular activity (18% of beats), prolonged QT interval (up to 630 ms), and high-complexity ectopic ventricular beats. Non-sustained ventricular tachycardia was also observed (1030 episodes). The prolonged QT interval was associated to an elevated dose of Fluoxetine. We believe that the coexistence between a high dose of Fluoxetine and other risk factor such as female sex and increased age contributed to the development of the case presentation. The rising prevalence of depression in the geriatric population and the indiscriminate use of antidepressive agents such as selective serotonin reuptake inhibitors may contribute to an increase in potentially severe cardiovascular complications.

Keywords: Ventricular tachycardia; Fluoxetine; Long QT syndrome.



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1. Introduction

Long QT syndrome (LQTS) is an uncommon clinical condition that is characterized by QT interval prolongation with effects on cardiac repolarization. This disorder is generally triggered by adrenergic activity and leads to an increased risk in the development of severe ventricular arrhythmias, especially torsades de pointes (TdP). It can be divided in congenital and acquired. The estimated prevalence of the inherited form is estimated in 1:2500 in the general population, with an annual rate of sudden cardiac death of 5% in symptomatic patients [1]. There is a probable connection among these two variants with a hereditary component as a predisposing factor for clinical manifestations of the inherited form. Among pharmacological classes implicated in the process, serotonin reuptake inhibitors (SSRIs) are amongst the most associated drugs in the acquired form. Fluoxetine is traditionally considered a low-risk drug for the development of LQTS [2].

Electrolyte abnormalities such as hypokalemia, hypo/hypercalcemia, hypomagnesemia and bradycardia are also associated to increased risk at developing this condition, although the most common risk factor is medical therapy. The diagnosis is typically established with a corrected QT interval (QTc) ≥ 480 ms or a risk score >3 [3]. The LQTS

diagnostic score also comprises electrocardiogram (EKG), clinical history, family history and genetic testing. The clinical presentation of the disease includes an increased risk of severe arrhythmias, especially polymorphic ventricular tachycardia and TdP. Other signs and symptoms may include palpitations, syncope, and sudden cardiac death. Guideline-directed medical therapy includes beta-blockers as first-line for the management of this disorder, regardless of the heart rate [1].

Non-selective drugs such as Nadolol and Propranolol have shown better efficacy in reducing adrenergic activation and thus arrhythmic risk. Therefore, the aim of this case report is to describe a relatively uncommon disorder in its acquired form. The unique clinical presentation and association with SSRIs as a triggering factor in a high-risk elderly female patient raises concern about the condition and stimulates further research in the field. A brief literature review was conducted in order to highlight the diagnostic criteria, pathophysiology, and medical management.

2. Case Report

An 83-year-old female patient previously diagnosed with major depressive disorder, type 2 Diabetes Mellitus and hyperlipidemia was admitted at the emergency department after an episode of syncope. There was no mention to palpitations, chest pain, relation to effort or prodromes. In terms of previous medical therapy, prescription consisted in Fluoxetine 80mg/day, Simvastatin 20mg/day and Metformin 850mg twice daily. Vital signs on admission were stable (Blood pressure 197x114mmhg | Heart rate 76bpm) and there was rapid return to basal conscious level. Physical examination was unremarkable, including cardiac auscultation and regular heart rhythm. Initial investigation included a chest radiography (Figure 1) and an EKG, that demonstrated a possible cause for the current presentation: normal sinus rhythm with a pronounced widening of the QT interval (QTc of 580ms).



Figure 1: Chest x-ray (No major abnormalities).

At the occasion, risk and prognostic scores were calculated: OESIL (*Observatorio Epidemiologico sulla Sincope nel Lazio*) [4] with 34.7% mortality risk and EGSYS (*Evaluation of Guidelines in Syncope Study group*) [5] with a possible cardiogenic syncope diagnosis. Inpatient admission for further investigation was indicated. Electrolytes, including sodium, potassium, calcium, and magnesium were within the normal laboratory range. Transthoracic echocardiogram and cardiac magnetic resonance were also performed. Considering

the absence of structural heart disease, we decided to proceed with 24-hour Holter monitoring (Figure 2). The results included: increased high complexity ventricular ectopic activity (18% of beats), widening of the QT interval up to 630ms and non-sustained ventricular tachycardia (Figure 3).



Figure 2: 24h Holter-monitoring. Normal sinus rhythm, HR 60bpm, corrected QT interval: 630ms – highlighted in the image above.

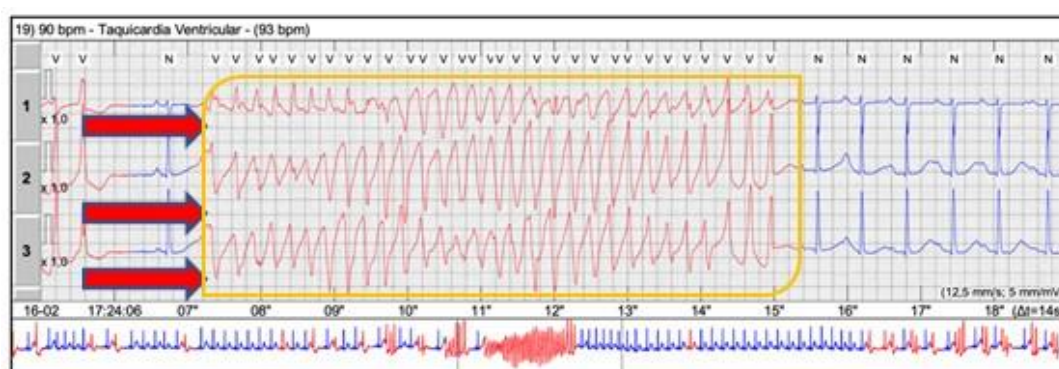


Figure 3: Polymorphic ventricular tachycardia consistent with torsades de pointes registered during 24h monitoring (normal sinus rhythm followed by TdP as indicated by the arrows).

The QT interval widening in this case was associated to an elevated dose of Fluoxetine cloridrate. Although the dosage used by the patient was approved by the current guidelines, we believe that the association of other risk factors like female sex, increased age and drug interaction may have triggered the clinical presentation. The medication was stopped and a control 24-hour Holter monitoring repeated after 2 weeks demonstrated a normal QT interval but remaining elevated ectopic ventricular activity. We opted to initiate Propranolol 20mg twice daily to control both ectopic ventricular beats and to reduce recurrence of LQTS1. During follow-up, the patient remained asymptomatic with good tolerance to beta-blocker therapy and no significant deterioration in quality of life.

Other treatment options were also discussed, including implantable cardiac defibrillators and genotype-specific drugs, but there was no clear indication since the patient remained uneventful with the first-line beta-blocker therapy. The patient continued treatment major depressive disorder with psychotherapy and pharmacologic treatment with other non-SSRI drugs with concomitant QTc monitoring at introduction of new medications, at dosage increases, and on a regular basis at each follow-up appointment.

3. Discussion and conclusion

Drug-induced LQTS is a potentially underdiagnosed lethal condition. Among the most commonly associated drugs with this disorder we can mention: Haloperidol, Amiodarone, Procainamide and Quinidine (Class IA antiarrhythmic drugs), Erythromycin,

antidepressants (including SSRIs), Fluconazol, and Sotalol. Other known triggers include emotional stress, sleep abnormalities and physical exertion. In terms of pathophysiology, the blockade of the IKr mediated by the potassium channel coded by the *KCNH2* gene is the most frequently involved mechanism, accounting for > 50% of the cases [6]. This gene is also associated with the inherited variant.

Although the cardiac potassium channel block is a major cause of acquired LQTS, other mechanisms are also associated with disease development. Adrenergic effects on sodium receptors, especially Ina-L, have implicated in the pathophysiology of LQTS. A prospective trial by Badri et al [6] demonstrated that inhibition of this receptor may lead to a QT interval shortening thus highlighting a major role in receptors other than potassium channels. It is believed that individuals who develop the acquired form are influenced by genetic/hereditary predispositions in this gene and other genetic lines that determine a multivariate clinical phenotype. This phenomenon is described as genetic polymorphism. The gene expression and its interaction with its receptors contributes to the transition between a subclinical spectrum and classical presentation.

The interference of electrolyte abnormalities (most noted hypokalemia and hypomagnesemia), structural heart disease, enzymatic competition, drug interaction, female sex and advanced age also imply a major role in the development of the clinical form [3-5]. In this case report, the elevated dose of Fluoxetine cloridrate was a key component for the installation of symptoms. As expected, withdrawal of the agent was accompanied by resolution of symptoms and electrical conduction system abnormalities [10, 11].

Although considered a safe and effective medication for treatment of psychiatric conditions, Fluoxetine and other SSRIs require caution, especially in high-risk patient populations (elderly, female sex, polypharmacy). In view of the above, we suggest routine EKG monitoring in high-risk groups before initiating treatment with potentially widening QT-interval drugs and whenever dosage changes are made [1, 2, 6]. The key-role of beta-blocker therapy (ideally non-selective agents like Nadolol or Propranolol) is also emphasized in this case report as guidelines suggest its use regardless of heart rate to reduce risk of arrhythmic events [1, 12].

Other treatment strategies such as genotype-specific drugs are implantable cardiac defibrillators are reserved for patients with inadequate response to beta-blockers [10-13]. Therefore, further large-scale research is stimulated in the field, particularly in order to increase awareness regarding this condition, develop better risk stratification strategies and determine guideline specific management.

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Research Ethics Committee Approval: We declare that the patient approved the study by signing an informed consent form and the study followed the ethical guidelines established by the Declaration of Helsinki.

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Conflicts of Interest: None.

Supplementary Materials: None.

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