Cardiology and Angiology: An International Journal

Volume 12, Issue 3, Page 78-82, 2023; Article no.CA.98616
ISSN: 2347-520X, NLM ID: 101658392

A Rare Case Report of "Torsades De Pointes" Induced by Fluconazole-Levetiracetam Combined Therapy

P. M. Mulendelé [a], M. Njie [a*], M. B. Charfo [a], S. M. Boutar [a], B. E. Ovaga [a], M. Haboub [a,b++], S. Arous [a,b++], M. Ghali Benouna [a,b++], A. Drighil [a,b], L. Azzouzi [a,b++] and R. Habbal [a,b++]

[a] Department of Cardiology, P37, Ibn Rochd University Hospital, Casablanca, Morocco.
[b] Faculty of Medicine and Pharmacy, Hassan II University of Casablanca, Casablanca, Morocco.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/CA/2023/v12i3327

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/98616

Case Study

Received: 11/02/2023
Accepted: 14/04/2023
Published: 19/04/2023

ABSTRACT

Drugs used to treat cardiovascular disease as well as those used in the treatment of multiple other conditions can occasionally produce exaggerated prolongation of the QT interval on the surface electrocardiogram and the morphologically distinctive polymorphic ventricular tachycardia that results is known as «torsade de pointe». «Torsade de pointe» (TDP) is a characteristic polymorphic ventricular arrhythmia associated with delayed ventricular repolarization as evidenced on the surface electrocardiogram by QT interval prolongation. It typically occurs in self-limiting bursts, causing dizziness and syncope, but may occasionally progress to ventricular fibrillation and sudden

[++]Professor of Cardiology;
**Corresponding author: E-mail: malick1njie@hotmail.com;*

death. This rare case report showed the potential higher risk of the occurrences of «Tdp» when levetiracetam (KEPPRA) was used in combination therapy with fluconazole, which is already a known medication with the risk of causing polymorphic ventricular arrhythmia.

Keywords: Torsades de pointes; prolong QT interval; fluconazole-levetiracetam; magnesium therapy.

1. INTRODUCTION

«Torsade de pointe» (TdP), a rare polymorphic ventricular tachycardia, is characterized by a gradual change in the amplitude and twist of QRS complexes around the isoelectric line on an electrocardiogram [1,2]. TdP is associated with QT interval prolongation, which is the prolongation of the QT interval value adjusted for heart rate. Prolongation of the QT interval is one of the major adverse effects of certain medications, as it can lead to sudden cardiac death [3,4]. Fluconazole is one of many drugs that have the potential to cause QT interval prolongation and/or «torsades de pointes», either alone or in a drug-drug interaction situation [5,6]; we report a case of «torsade de pointe» induced by a combination therapy fluconazole in association with levetiracetam (KEPPRA).

2. CASE PRESENTRATION

A 70-year-old patient with a medical history of pulmonary tuberculosis treated and declared cured 40 years ago, and episodes of convulsive seizures lasting for 2 months was admitted to the intensive care unit for status epilepticus, before tonic seizures - generalized clonic without regaining consciousness between crises. Patient intubated, ventilated with an initial Glasgow score of 11/15, his initial cardiovascular examination findings was normal (Fig. 1).

The complete blood count and the other blood workout assessment were initially normal but with a disturbed cerebral spinal fluid (CSF) balance, which was in favor of bacterial and fungal meningitis (cryptococcus).

The electrocardiogram and echocardiography were also normal and the cerebral MRI was in favor of Creutzfeldt Jakob disease (Fig. 2).

The initial treatment with Imipenem-cilastatine (Tienam) 500mgx4 a day; doxycillin 200mg par day; fluconazole (triflucan), sodium valporote (depakine) 500mgx3 par day; Levetiracetam (keppra)100mgx3 par day was instituted.

Her clinical outcome on the 8th day of Fluconazole and the 21st day of levetiracetam (KEPPRA) treatment was marked by a cardiac complication with the occurrence of torsades de pointes (Fig. 3).

The blood workout assessment marked a hypokalemia at 2.6 mEq/l, and normal magnesium level. This cardiac complication was resolved after discontinuation of the offending drugs (fluconazole and levetiracetam), correction of the hypokalemia, magnesium sulphate attack dose of 3g in intravenous followed by maintenance dose of 6g/24h in continuous IV electric syringe perfusion; the evolution being marked by a return to sinus rhythm, the echocardiography carried out concomitantly as well as the troponin were normal.

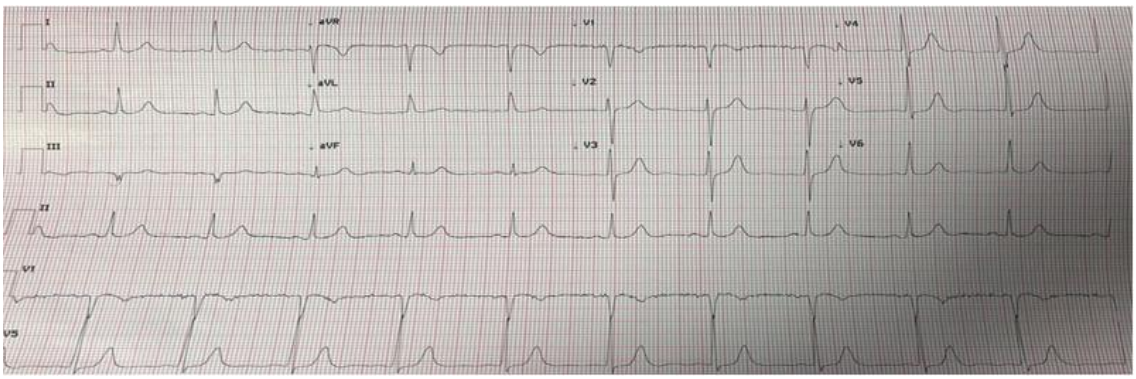

Fig. 1. 12 leads Electrocardiogram (ECG): Regular sinus rhythm with no conduction disorder

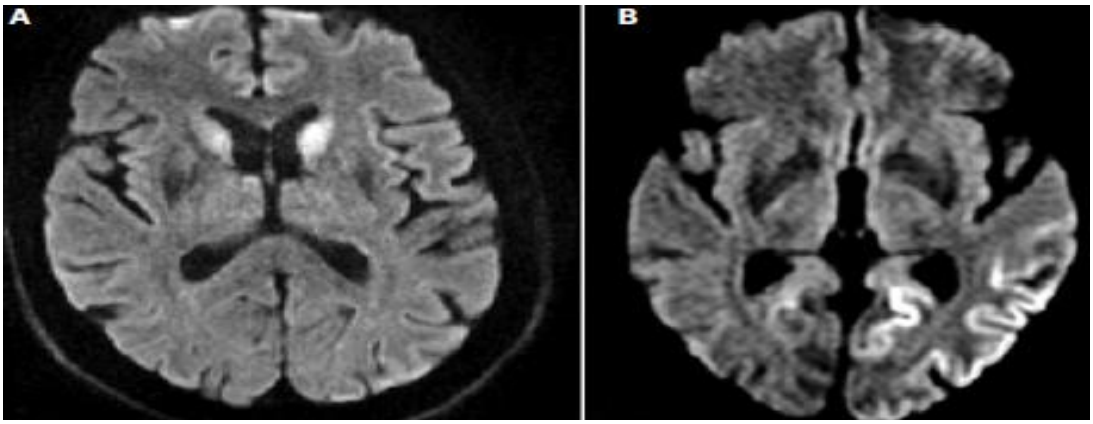

Fig. 2. Cranial MRI. Hypersensitivity T2 signals located in the caudate nucleus on both sides of the brain tissues (A) and in the occipital lobe (B)

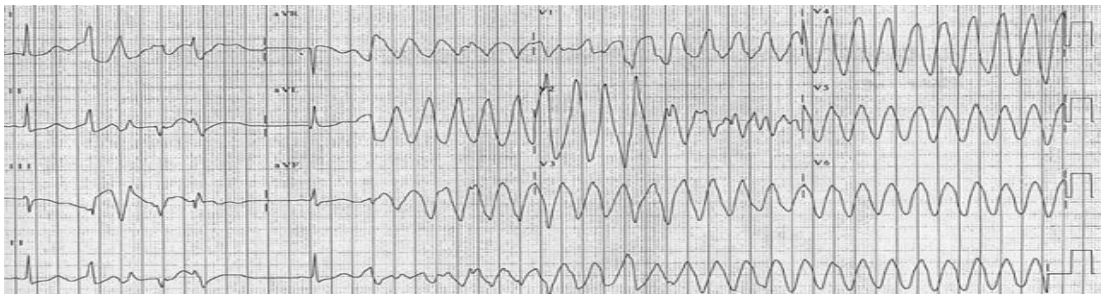

Fig. 3. 12-leads Electrocardiogram: Polymorphic ventricular tachycardia "torsades de pointes"

3. DISCUSSION

Torsade de pointes, a rare polymorphic ventricular tachycardia, described in 1996 by François Dessertenne, and associated with prolongation of the QT interval on a surface ECG, either congenital or induced by drugs [7]. Many drugs, such as antiarrhythmics, antifungals, different classes of antibiotics, can induce torsade de pointes, alone or in combination [5,6]. Anti-infectious combination drugs used in several situations that includes treating bacterial and fungal infectious diseases, sometimes combined with antiepileptic drugs in patients with epilepsy. However, some of the agents have the potential to prolong the QT interval and increase the risk of torsade de pointes [8]. Although cases of torsade de pointes have been reported during treatment with fluconazole alone or in combination therapies such as in combination with antibacterial drugs [6,9,10]. To our knowledge, there are no known reported cases of «torsades de pointes» in the literature induced by fluconazole-levetiracetam combination therapy [11].

Levetiracetam (Keppra), a new generation of multi-acting antiepileptic drug, which binds to the SV2A protein, can induce QT interval prolongation, when taken concomitantly with drugs known to prolong the QT interval or in the event of electrolyte disturbances [12,13,11]. Electrophysiological studies have demonstrated that the main mechanism by which drugs prolong individual action potentials and which manifests itself on the baseline ECG as an elongation of the QT interval is the blockade of potassium channels specific to the heart [14]. These potential effects are increased by drug interactions linked to the inhibition of cytochrome P450 [14,15] as well as other risk factors predisposing patients on these drugs to develop ventricular arrhythmia, these factors include female sex, advanced age, electrolyte disturbances, congenital long QT syndrome, cardiac pathologies and of course the use of other potentially arrhythmogenic drugs [16,17].

Our patient presented hypokalemia under the treatment of imipenem-cilastatine side effects which is similar to some reported cases in the literature [16]; her age, her sex and especially the electrolyte disorder places her at a higher risk and fluconazole combination therapy with levetiracetam increased her risk more in

developing ventricular arrhythmias. Magnesium treatment is the best option in cases of «torsade de pointes» induced by drugs which should be administered effectively in patients [18-20] like in our case.

4. CONCLUSION

Although the prevalence of QT interval prolongation in patients using fluconazole is low, clinicians should be cautious in patients with risk factors and especially when taking concomitant medications known to prolong QT interval, like fluconazole. A surface ECG should always be performed before drug combination therapy known to increase the risk of QT-interval prolongation. Adequate magnesium therapy should be appropriately administered to reduce recurrences and sudden death.

CONSENT

As per international standard or university standard, patient(s) written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

ACKNOWLEDGEMENT

I thank the whole Department of Cardiology P37 at university teaching hospital Ibn Rochd, Casablanca for their outstanding collaboration in the support of this work.

COMPETING INTERESTS

Authors have declared that they have no known competing financial interests or non-financial interests or personal relationships that could have appeared to influence the work reported in this paper.

REFERENCES

1. Drew BJ, Ackerman MJ, Funk M, Gibler WB, Kligfield P, Menon V, et al. Prevention of torsade de pointes in hospital settings: a scientific statement from the American Heart Association and the American College of Cardiology Foundation. Circulation. 2 mars 2010;121:1047-60.
2. Predicting drug-induced QT prolongation and torsades de pointes. Dan M. Roden Physiol. 2016;594(9): 2459–2468.
3. Yap YG A, Camm AJ. Allongement de l'intervalle QT médicamenteux et torsades de pointes. Cœur. 2003;89: 1363–1372.
4. Torsade de pointes associated with chloroquine, hydroxychloroquine,and azithromycin: a retrospective analysis of individual case safetyreports from Vigi Base. Diego Macías Saint‐Gerons, Rafael Tabares‐Seisdedos. European Journal of Clinical Pharmacology. 2021;77:1513–1521.
5. Tholakanahalli VN, Potti A, Hanley JF, Merliss AD. Fluconazole-induced torsade de pointes.Ann Pharmacother. Avr. 2001;35:432-4. 6.
6. Zeuli JD, Wilson JW, Estes LL. Effect of Combined Fluoroquinolone and Azole Use on QT Prolongation in Hematology Patients. Antimicrob Agents Chemother. Mars 2013; 57:1121-7
7. Dessertenne F. [Ventricular tachycardia with 2 variable opposing foci. Arch Mal Coeur Vaiss. 1966;59:263-72.
8. Li M, Ramos LG. Drug-Induced QT Prolongation AndTorsades de Pointes. Pharmacy and Therapeutics. Juill. 2017;42:473.
9. Tholakanahalli VN, Potti A, Hanley JF, Merliss AD. Fluconazole-induced torsade de pointes. Ann Pharmacother. avr 2001;35:432-4.
10. Drug-induced QT Interval Prolongation in theIntensive Care UnitCecilia Villa Etchegoyen, Guillermo Alberto Keller, Sebastian Mrad, Sixuan Cheng, Guillermo Di Girolamo. CurrClin Pharmacol. 2017;12(4):210-222.
11. QTc prolongation by antiepileptic drugs and the risk of torsade de pointes in patientswith epilepsy. Ashley E. Feldman, Barry E. Gidal. Epilepsy & Behavior. 2013;26:421–426.
12. Gurgul S, Buyukakilli B, Komur M, Okuyaz C, Balli E, Ozcan T. Does Levetiracetam Administration Prevent Cardiac Damage in Adulthood Rats Following Neonatal Hypoxia/Ischemia-Induced Brain Injury? Medicina (Kaunas). 2018 ; 54 :12
13. Lelévétiracétam (KEPPRA) peut entraîner un allongement de l'intervalle. Available:https://pharmacie.ma/article/6795/
14. Roden DM. Predicting drug-induced QT prolongation and torsades de pointes. J. Physiol. 2016;594:2459-68.

15. Prior TI, Baker GB. Interactions between the cytochrome P450 system and the second-generation antipsychotics. J Psychiatry Neurosci. 2003;28:99-112.
16. Drug-drug interactions between COVID-19 treatmentsand antipsychotics drugs: integrated evidence from 4 databasesand a systematic review. Beatriz Oda Plasencia-García, Gonzalo Rodríguez-Menéndez, María Isabel Rico-Rangel, Ana Rubio-García, Jaime Torelló-Iserte, Benedicto Crespo- Facorro, Psycho-pharmacology. 2021;238:329–340.
17. Tosardes de pointes. Cohagen B et al. State Pearls (Internet); 2022. PMID 2908378
18. Magnesium treatment in pediatric patients. Anderson S, et al. J Pediatr Health Care; 2021. PMID:34479684
19. Atrial fibrillation and QT prolongation due to proton pump inhibitor-induced hypomagnesemia. N Noirclercetal. Ann Cardiol Angeiol: 2020;69:201-203.
20. Pharmacological treatment of acquired QT prolongation and torsades de pointe Simon H, L. Thomas & Elijah R. Behr. Br J Clin Pharmacol: 2015;81:420–427.

Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/98616