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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 61494

Title: Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report

Reviewer's code: 00722213
Position: Editorial Board
Academic degree: MD, PhD
Professional title: Academic Research, Chief Doctor, Full Professor, Research Dean
Reviewer's Country/Territory: Romania
Author's Country/Territory: China

Manuscript submission date: 2021-01-01

Reviewer chosen by: AI Technique

Reviewer accepted review: 2021-01-03 19:32

Reviewer performed review: 2021-01-03 20:04

Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[ ] Grade A: Priority publishing [ ] Grade B: Minor language polishing [Y] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

In this paper teh authors presented the genetic profile of a patient with torsades des points, a severe arrythmia. The case is interesting but some points need to be addressed, as follows: 1. The manuscript was not typed based on Baishideng criteria. Please adapt it. 2. Laboratory examination - the authors mentioned "Cervical lymph node biopsy revealed T cell significant proliferation. Bone marrow biopsy indicated infectious imaging". Please add the pathologist in the authors team and add a detailed description of the lymph node and bone marrow, with relevant figures. This is mandatory to sustain the diagnosis. 3. In Introduction, diagnostic criteria for Still disease need to be presented, to can sustain the present case. Please move the diagnostic criteria from Discussion to Introduction. 4. Can be Still disease reversible? 5. Treatment - the authors mentioned "The genetic analysis verified the patient and her father with QTc interval of 490 ms had heterozygous mutations of KCNH2 (c.1370C>T) and AKAP9 (c.7725A>C) while her mother had normal QTc interval and had no mutations ". Please add technical data. How these mutations were detected? Which technique was used for detection? 6. If the authors chose to discuss the gene profile, this part should be significantly enlarged. In Discussion, please add more literature data regarding these gene profile. Which might be the evolution of the case? It is indeed congenital/ Please argue....

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PEER-REVIEW REPORT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 61494

Title: Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report

Reviewer's code: 02750589
Position: Peer Reviewer
Academic degree: MD

Professional title: Doctor

Reviewer's Country/Territory: Italy

Author's Country/Territory: China

Manuscript submission date: 2021-01-01

Reviewer chosen by: Ya-Juan Ma

Reviewer accepted review: 2021-01-05 09:27

Reviewer performed review: 2021-01-14 12:55

Review time: 9 Days and 3 Hours

Scientific quality	[ ] Grade A: Excellent [ ] Grade B: Very good [Y] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [Y] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

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SPECIFIC COMMENTS TO AUTHORS

The authors report the case of a 30-year-old female with adult-onset Still's disease (AOSD) who developed marked QTc prolongation complicated by Torsades de Pointes (TdP). In particular, the authors highlight as TdP occurred in the patient in presence of several QT-prolonging risk factors, specifically drugs (macrolids, fluoroquinolones, azole antifungals) and genetic mutations (heterozygous mutations in both KCNH2 and AKAP9 genes), in the absence of any evidence of cardiac injury. The authors conclude that the risk of drug-induced long-QT syndrome (LQTS)/TdP should be carefully considered when selecting antibiotics for unexplained fever. Although the report is potentially important, the paper has important limitations that the authors must address before that it may be considered for publication. 1. The most important limitation is that the authors completely disregarded the potential pathogenic role of high-grade systemic inflammation and fever present in the patient at the moment of LQTS/TdP. In fact, mounting data in the literature are demonstrating the key role of systemic inflammatory activation in promoting LQTS and TdP development [Systemic inflammation as a novel QT prolonging risk factor in patients with torsades de pointes. Heart. 2017;103(22):1821-1829] via direct electrophysiological effects on cardiac repolarization [Systemic inflammation and arrhythmic risk: lessons from rheumatoid arthritis. Eur Heart J. 2017;38(22):1717-1727]. Many basic experimental studies demonstrated that inflammatory cytokines, mainly tumor necrosis factor-α (TNFα), interleukin-1 (IL-1), and interleukin-6 (IL-6), can directly cause the dysfunction of several cardiac ion channels particularly K+ channels, leading to ventricular APD prolongation [Impairment of HERG K(+) channel function by tumor necrosis factor-alpha: role of reactive oxygen species as a mediator. J Biol Chem 2004;279:13289-13292 - Effects of human recombinant interleukin-1 on electrical properties of guinea pig ventricular cells.

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Cardiovasc Res 1993;27:525-530 - SHP2 mediated signaling cascade through gp130 is essential for LIF dependent I CaL, [Ca2+]i transient, and APD increase in cardiomyocytes. J Mol Cell Cardiol 2007;43:710-716 - Interleukin-6 inhibition of hERG underlies risk for acquired long QT in cardiac and systemic inflammation. PLoS One.2018;13(12):e0208321]. For this reason, the term of inflammatory cardiac channelopathies has been recently coined and it is now increasingly recognized [Emerging Arrhythmic Risk of Autoimmune and Inflammatory Cardiac Channelopathies. J Am Heart Assoc. 2018;7(22):e010595 – Cardioimmunology of arrhythmias: the role of autoimmune and inflammatory cardiac channelopathies. Nat Rev Immunol. 2019;19(1):63-64]. Moreover, besides the direct effect, systemic inflammation might also favour LQTS/TdP indirectly, by several additional mechanisms, including the induction of fever and related temperature-mediated changes in cardiac ion channel biophysical properties, particularly of the hERG-channel [Febrile temperature facilitates hERG/IKr degradation through an altered K(+) dependence. Heart Rhythm. 2016;13(10):2004-11 - Fever accentuates transmural dispersion of repolarization and facilitates development of early afterdepolarizations and torsade de pointes under long-QT Conditions. Circ Arrhythm Electrophysiol. 2008;1(3):202-8 - Exaggerated block of hERG (KCNH2) and prolongation of action potential duration by erythromycin at temperatures between 37 degrees C and 42 degrees C. Heart Rhythm. 2005;2(8):860-6]. All these aspect should be highlighted and carefully discussed by the authors and related references included in the manuscript. 2. Based on the above consideration, it is important that the authors provide more detailed information regarding the extent of the systemic inflammatory activation in this patients. In particular, they reported that C-reactive protein (CRP) levels were markedly elevated at the initial laboratory test (>160 mg/L), but no data are provided regarding CRP when TdP occurred (even if the concomitant presence of high fever and chill strongly suggests

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that systemic inflammatory activation was elevated). In this regard, if available, additional information on cytokine blood levels (particularly IL-6) may be very insightful. 3. Accordingly, the title should be changed from "Torsades de pointes episode in a female with high-grade fever: A case report" to "Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report". Moreover the potential role of the inflammatory activation and fever should be highlited also in the Abstract. 4. The presence of other concomitant risk factors probably favoring TdP should be also more accurately discussed. In fact, multiple concomitant risk factors are usually necessary for TdP occurrence, as normal action potential duration in ventricles is preserved by numerous often-redundant ion channel mechanisms (repolarization reserve) (Repolarization reserve: a moving target. Circulation. 2008;118(10):981-2); thus, multiple QT-prolonging factors need to be simultaneously present to significantly disturb ventricular repolarization (multi-hit theory) (Emerging Arrhythmic Risk of Autoimmune and Inflammatory Cardiac Channelopathies. J Am Heart Assoc. 2018;7(22):e010595). Accordingly, in a cohort of 40 unselected patients with TdP, on average >4 QT-prolonging risk factors per subject were detectable (Heart. 2017;103(22):1821-9). Please expand this aspect in the discussion at the light of the above fundamental references. 5. Genetics: the authors reported that the patient (and her father) had heterozygous mutations of KCNH2 (c.1370C>T) and AKAP9 (c.7725A>C). Are these specific mutations already descrive in the literature as pathogenic for LQTS? More information regarding this point should be provided. 6. In the discussion, the authors correctly stated that "The difference in the sex hormones is considered to be the main reason for this gender difference of lethal arrhythmias. It is now becoming clear that sex hormones play an important role in cardiac repolarization and the control of QT intervals". Please provide specific key references to substantiate this statement [for example: Sex, hormones, and repolarization. Cardiovasc Res. 2002;53(3):740-51 -

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Influence of steroid hormones on ventricular repolarization. Pharmacol Ther. 2016;167:38-47]. 7. At the beginning of the discussion, the authors stated that "Here, we present a case of AOSD showing TdP accompanied with long QTc". In order to better reflect the pathogenic sequence of the events, please change to "Here, we present a case of AOSD showing long QTc complicated with TdP".

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RE-REVIEW REPORT OF REVISED MANUSCRIPT

Name of journal: World Journal of Clinical Cases

Manuscript NO: 61494

Title: Torsades de pointes episode in a female with high-grade fever and inflammatory activation: A case report

Reviewer's code: 02750589
Position: Peer Reviewer
Academic degree: MD
Professional title: Doctor
Reviewer's Country/Territory: Italy
Author's Country/Territory: China

Manuscript submission date: 2021-01-01
Reviewer chosen by: Han Zhang (Part-Time Editor)
Reviewer accepted review: 2021-02-08 08:29
Reviewer performed review: 2021-02-08 08:58
Review time: 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[Y] Accept (High priority) [ ] Accept (General priority) [ ] Minor revision [ ] Major revision [ ] Rejection
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

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The authors did a good job. The revison has significantly improved the quality and significance of the manuscript.