



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 05040484

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor, Doctor, Professor, Research Scientist

**Reviewer's Country/Territory:** Russia

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2021-01-11 10:04

**Reviewer performed review:** 2021-01-12 17:25

**Review time:** 1 Day and 7 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input checked="" type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

This case is very interesting and worthy of publication, but I have some comments: 1) the normal value of laboratory indicators should be given, especially such as D-dimer; different clinics use different methods, which makes it difficult to evaluate the data; 2) if the authors have already used abbreviations, then they should apply them further in the text, and not write the words completely



### PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 05326882

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Doctor

**Reviewer's Country/Territory:** Japan

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** AI Technique

**Reviewer accepted review:** 2021-01-12 01:50

**Reviewer performed review:** 2021-01-13 10:38

**Review time:** 1 Day and 8 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input checked="" type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input checked="" type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

The authors described the newly diagnosis of TMA due to sodium valproate. Case presentation was written well, however this manuscript included several problems.

First, the basis of TMA diagnosis was described not enough. In the diagnosis of TMA, fragmented erythrocytes in the peripheral blood smear was needed ([https://www.uptodate.com/contents/drug-induced-thrombotic-microangiopathy?topicRef=88648&source=see\\_link](https://www.uptodate.com/contents/drug-induced-thrombotic-microangiopathy?topicRef=88648&source=see_link)). However, the authors described "but there were no fragmented erythrocytes on the peripheral blood smear" in Laboratory examinations section. Similarly, severe thrombocytopenia was needed. Why didn't the authors explained the data on ADAMTS13 activities and ADAMTS13 inhibitors? I considered that this patient couldn't diagnosed with TMA. Second, because this manuscript was based on wrong diagnosis, there were no novelty. For example, "therefore, sodium valproate in combination with carbapenem antibiotics may increase the risk of hemolysis" was written in Discussion section, this consideration was syllogism. Third, limitations of this study was out of my hands. Minor revision The author used the abbreviations at the wrong time. The abbreviation was used when the words were first used in your manuscript. For example, in line 12, Introduction section, "thrombotic microangiopathy" was not used the abbreviation.



**PEER-REVIEW REPORT**

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer’s code:** 02549939

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Attending Doctor, Surgeon

**Reviewer’s Country/Territory:** Switzerland

**Author’s Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2021-01-13 13:38

**Reviewer performed review:** 2021-01-18 15:40

**Review time:** 5 Days and 2 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input checked="" type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input checked="" type="checkbox"/> Rejection
<b>Re-review</b>	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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#### **SPECIFIC COMMENTS TO AUTHORS**

Dear authors I have reviewed your manuscript dealing about a male patient after neurosurgical procedure and valproic acid induced lethal liver failure. Although it is an interesting report I have some relevant comments. You postulate a novel pathway of valproic acid and drug-induced liver failure: thrombotic microangiopathy. But there is no imaging or further diagnostic tools mentioned which support your hypothesis. The characteristic features of thrombotic microangiopathy as you mentioned are not different to parameters of liver failure (anemia, thrombocytopenie, organ dysfunction). You do not discuss other causes or pathways for liver failure (e.g. rhabdomyolysis which has been previously postulated, this would be an explanation for the increase of creatine kinase) in this setting. What makes you sure that this is the pathway of liver failure. Did you measure other lab parameters (e.g. ammonia) or did you perform a liver biopsy to reveal histological changes. Did you treat your patient with N-acetylcysteine or other symptomatic or supportive treatment? There are some language and editorial issues which should be revised (delete all dates within the text: e.g. November 9, 2019....). Best regards.



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 03290510

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Associate Professor

**Reviewer's Country/Territory:** United States

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2021-01-12 02:20

**Reviewer performed review:** 2021-01-18 21:06

**Review time:** 6 Days and 18 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

Thank you for submitting your interesting case report. It highlights a number of important issues, including valproic associated toxicity. While this is a known association, it is still a unique case worth highlighting. There are many excellent points throughout the article. We appreciate your clear timeline throughout the article. Our minor recommendations for ways to improve are as follows: (1) Your abstract could be shortened by not including all of the laboratory data and summarizing the highlights. (2) Additional details regarding the staging of the meningioma and pre-operative work-up would be useful to provide context to the reader. (3) An explanation of the antibiotic choices would be useful. (4) You state that since he did not have active alcohol use or Hepatitis B, it was presumed to be secondary to Valproic acid, but were there any other findings that suggested this. While you state there is no correlation between serum level and hepatotoxicity, it would still be worthwhile to note. (5) Any details regarding imaging during this post-operative period of the liver or abdomen would be useful (such as CT scans). (6) It would be worth clarifying when the patient developed renal failure and was this simply shock liver or secondary to another cause. (7) Discussion: I recommend clarifying the sentence "Carbapenem antibiotics can reduce the plasma concentration of sodium valproate by inhibiting its transmembrane transport in erythrocytes[37]; therefore, sodium valproate in combination with carbapenem antibiotics may increase the risk of hemolysis." It is not clear how inhibiting the transmembrane transport of valproate impacts a reduction in the plasma concentrations of the drug. (8) Two additional relevant articles to review include are: -Thrombocytopenic purpura and anemia in a breast-fed infant whose mother was treated with valproic acid. Stahl MM, Neiderud J, Vinge E. J Pediatr. 1997 Jun;130(6):1001-3. doi: 10.1016/s0022-3476(97)70292-0. PMID: 9202628 -Thrombopenia



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and erythroblastopenia in a 1-month-old infant treated with valproate. Nathan D, Guillon JL, Chevallier B, Gallet JP. *Ann Pediatr (Paris)*. 1987 Feb;34(2):149-50. PMID: 3107456



## PEER-REVIEW REPORT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 01467363

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Full Professor

**Reviewer's Country/Territory:** Slovenia

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Jia-Ping Yan

**Reviewer accepted review:** 2021-01-22 13:39

**Reviewer performed review:** 2021-01-24 10:23

**Review time:** 1 Day and 20 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input checked="" type="checkbox"/> Grade B: Very good <input type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Re-review</b>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No



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## **SPECIFIC COMMENTS TO AUTHORS**

Title and “running” title: accurately reflects the topic and content of the paper.

Abstract: is appropriate, structured, quite long (238 words) – could be shortened! Key

words: 6 key words, define the content of the paper. Core tip: is appropriate, 97 words.

Introduction: is informative, short, 142 words, the reader is very briefly acquainted with the known facts about sodium valproate induced liver injury. Case presentation: informative, 842 words, key data about the patient are presented: chief complaints, history of present and past illnesses, personal and family history, physical examination upon admission, laboratory data, results of imaging procedures (a welcome addition to the presentation would be histology of the liver, autopsy?!), further diagnostic work-up and final diagnosis (including Fig. 1,2 – they should be in better resolution, which will give the reader a better insight into the chronology of treatment and the values of laboratory data), treatment, follow-up and fatal outcome, patient died 12 days after surgery. Discussion: short, 791 words, the discussion is interesting, the authors point out the pathophysiological mechanisms that probably triggered acute liver failure in the described patient, they do not forget to mention the potential interaction with the drug that the patient was receiving also (carbapenem antibiotics) and could affect the fateful course. They also explain the mechanism of thrombotic microangiopathy (TMA), which is defined as a clinical syndrome characterized by thrombocytopenia, hemolytic anemia and multiple organ dysfunction. Drug-induced TMA (DI-TMA) is a type of acquired TMA that is caused by multiple drugs. Explained are two mechanisms of injury: a non-dose-dependent immune reaction or dose- and time-dependent toxicity. The patient presented can be classified as having immune-mediated drug induced DI-TMA. Conclusion: short, 97 words, the authors summarize the key findings of the presented patient and the fatal complication.



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References: 37 (quite a lot), contemporary, references are appropriate. Conflict of interest: the authors declared no conflict of interest. CARE Checklist statement: the manuscript was prepared and revised according to the CARE Checklist. Informed consent statement: was obtained from the patient/family for publication of this report.

Opinion of the reviewer The contribution is interesting, the authors point out an important problem with the use of sodium valproat. I suggest to accept the manuscript after language corrections, the authors should improve the figures.



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 05040484

**Position:** Editorial Board

**Academic degree:** MD, PhD

**Professional title:** Assistant Professor, Doctor, Professor, Research Scientist

**Reviewer's Country/Territory:** Russia

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Man Liu

**Reviewer accepted review:** 2021-02-23 07:16

**Reviewer performed review:** 2021-02-23 10:27

**Review time:** 3 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input checked="" type="checkbox"/> Accept (General priority) <input type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS



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No comments



## RE-REVIEW REPORT OF REVISED MANUSCRIPT

**Name of journal:** World Journal of Clinical Cases

**Manuscript NO:** 62491

**Title:** Acute liver failure with thrombotic microangiopathy due to sodium valproate toxicity: A case report

**Reviewer's code:** 02549939

**Position:** Peer Reviewer

**Academic degree:** MD

**Professional title:** Attending Doctor, Surgeon

**Reviewer's Country/Territory:** Switzerland

**Author's Country/Territory:** China

**Manuscript submission date:** 2021-01-10

**Reviewer chosen by:** Man Liu

**Reviewer accepted review:** 2021-02-23 05:51

**Reviewer performed review:** 2021-02-26 08:26

**Review time:** 3 Days and 2 Hours

<b>Scientific quality</b>	<input type="checkbox"/> Grade A: Excellent <input type="checkbox"/> Grade B: Very good <input checked="" type="checkbox"/> Grade C: Good <input type="checkbox"/> Grade D: Fair <input type="checkbox"/> Grade E: Do not publish
<b>Language quality</b>	<input type="checkbox"/> Grade A: Priority publishing <input checked="" type="checkbox"/> Grade B: Minor language polishing <input type="checkbox"/> Grade C: A great deal of language polishing <input type="checkbox"/> Grade D: Rejection
<b>Conclusion</b>	<input type="checkbox"/> Accept (High priority) <input type="checkbox"/> Accept (General priority) <input checked="" type="checkbox"/> Minor revision <input type="checkbox"/> Major revision <input type="checkbox"/> Rejection
<b>Peer-reviewer statements</b>	Peer-Review: <input checked="" type="checkbox"/> Anonymous <input type="checkbox"/> Onymous Conflicts-of-Interest: <input type="checkbox"/> Yes <input checked="" type="checkbox"/> No

### SPECIFIC COMMENTS TO AUTHORS



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Dear authors I have reviewed your revised manuscript again. Thank you for your comments and answers regarding my concerns. I think the manuscript has improved and you could demonstrate why this case is probably interesting for other clinicians. Unfortunately, you did not include all your answers within the revised manuscript. I would include these comments and references, because other readers will probably have the some questions regarding this case. In addition you should revise the manuscript again regarding language and editorial issues (e.g. spelling errors). Best regards.