Peer Review File

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Reviewer A

This case illustrates a girl with epilepsy and multiple organ failure which might be associated with a NEXMIF variant or sodium valproate. This is an interesting case and suitable for Translational Pediatrics. However, I have many concerns in this paper.

Major comments

1. Title. This variant has been previously reported from Webster et al., as the authors mentioned (2017 Clin Gent). Therefore, the title could lead the misunderstanding for the readers. Please delete 'Novel' from the title.

Reply: Thanks for your comment,we had deleted 'Novel' from the title

Changes in the text: Page 1,Line 2

2. Page 2, Line 63. If the patient had nodding spasm (infantile spasm?), the authors should describe how the patient had been treated before.

Reply: Thanks for your comment,we had added treatment.

Changes in the text: Page 2,Line 64

3. Page 3, Line 68-70. The authors performed EEG and showed many abnormalities on it. Adding the result of EEG would give more information to the readers, so please show it as figures including chest X ray showing pulmonary hemorrhage (Page 3, Line 115).

Reply: Thanks for your comment,we had added the result of EEG

Changes in the text: Page 3,Line 68-70

Reply: Thanks for your comment,pulmonary hemorrhage was diagnosed because of blood pouring in the catheter after endotracheal intubation,there was no sufficient evidence of the chest X ray

4. Page 3 and 5. There are many laboratory data in the manuscript and table. It is so difficult to understand, please add the normal range in the manuscript and table. Also, some units are not written. Please pay attention in detail.

Reply: Thanks for your comment,we had added the normal range and units.

Changes in the text: Page 6

5. Page 8 Line 173-198. There are no citations in the discussion. Also, the other sentences in the discussion are as well. Please cite appropriate papers in the discussion.

Reply: Thanks for your comment,we had added the citations.

Changes in the text: Page 8,Line 178 and Line 184

6. In discussion. Taking sodium valproate in patients with NEXMIF mutations is very important. Please summary (additional table is also good) and discuss all the patients

with NEXMIF mutations who have taken sodium valproate before. Are there any patients with NEXMIF mutations who have side effect in sodium valproate?
Reply: Thanks for your comment,this is a very good suggestion.
Changes in the text: Page 8,Line 188-193

7. There are many grammatical errors in this paper. Proofreading by Native English Speakers should be necessary.
Reply: Thanks for your comment,this is a very good suggestion. We had corrected grammatical errors

Minor comments
1. Page 1, Line 28. 'Kidney injury 3' is a little bit difficult to understand for the readers. I could not find the same words in the other papers related renal diseases. I assume that '3' would be the disease stage, please make the words more clearly.
Reply: Thanks for your comment,we had changed the Kidney injury 3 to kidney injury-Grade 3
Changes in the text: Page 1,Line 29;Page 8,Line 202;Page 10,Line 255;

2. Page 2, Line 55. A period is missing here.
Reply: Thanks for your comment,we had corrected errors.

3. Page 3, Line 73. How much sodium valproate did the authors prescribed? It is very important information because the authors suspected that sodium valproate might be related her death.
Reply: Thanks for your comment,we had added the dose of sodium valproate
Changes in the text: Page 3,Line 73;

4. Page 3, Line 83. Please write SD in her height and weight.
Reply: Thanks for your comment,we had added the SD in her height and weight
Changes in the text: Page 3,Line 83;

5. Page 3, Line 83. I am afraid 'The pharynx congestion, diminished heart sounds and hepatomegaly.' might confuse the readers. Please rewrite the sentence.
Reply: Thanks for your comment,we had changed the sentence to 'The positive physical examination of the patient is that pharyngeal congestions, cardiac sounds low and dull and hepatomegaly.'
Changes in the text: Page 3,Line 83-85;

6. Page 3, Line 87. I think that pro-BNP is missing 'NT'.
Reply: Thanks for your advise,we had changed the pro-BNP into NT-proBNP.
Changes in the text: Page 3,Line 83;

7. Page 9, Line 232. Please do not use two ways such as c.C937T, p.R313X and c.937C>T, p.R313* as these words are the same.
Reply: Thanks for your advise,we had changed the c.C937T, p.R313X into c.937C>T, p.R313*
Changes in the text: Page 9,Line 237;Page 10,Line 249

8. Page 4, Line 128. Whole exon sequencing should be described 'whole exome sequencing'.
Reply: Thanks for your advise,we had changed the exon into exome
Changes in the text: Page 4, Line 128.

Reviewer B
This article presents a case report: pathogenic variant in NEXMIF in a epileptic female patient with a multiple organ failure.
I consider this article of interest. However, I recommend the revision of the paper and the correction/clarification of some points.

MAJOR COMMENTS
The relation of the NEXMIF variant with the multiple organ failure in this case has not been proved. As reported in the paper, could be due to the antiepileptic drug treatment. Without taking into consideration the multiple organ failure, the clinical description of the patient includes epilepsy without intellectual developmental disorder nor developmental language delay, compatible with mild phenotype in females.
Reply: Thanks for your comment. As you said, we can't confirm the relation of the NEXMIF variant with the multiple organ failure in this case. But it may also be relevant.

MINOR COMMENTS
- OMIM code should included * (for gene) or # (for disease).
Reply: Thanks for your advise,we had added for gene after OMIM
Changes in the text: Page 4, Line 128.

- No other variants were reported in the WES? As supplementary material the list of VUS, PP or P variants should be reported.
Reply: Thanks for your comment. WES reported other variants. Because it involved the privacy of patients, we did not release this result. We have emailed the results in Chinese to the editorial department, and we can translate them into English if needed later.

- Since it is an X-linked gene X-inactivation could be tested. Even more, since the patient died x-inactivation pattern in different tissues could be measured.
Reply: Thanks for your comment. We did not do this examination because the patient died, but this is a very good suggestion, which is very helpful for our future research.

- a revision of other cases affected by pathogenic variants in NEXMIF should be better developed. Literature review (line 226-236) is poor and unconnected. A table summary of phenotype-genotype in these cases could be of help.
Reply: Thanks for your comment. We had added a summary table.
Changes in the text: Page 9, Line 232.

- Finally, although English is not my mother tongue either, some English errors/typos have been detected. Therefore, the text should be proof-read by a fluent English-speaking person.

RE-review comments

Reviewer A
The manuscript is now much improved and the authors made relevant changes in the manuscript and followed the reviewer recommendations, but there remain some minor comments.

In abstract, sodium valproate appears in the last sentence. It is a little bit strange. If you would like to say the relevant of VPA and multiple organ failure, the authors should put the word "sodium valproate" in around line 21-23. Also, please mention that the duration from taking sodium valproate to the onset of multiple organ failure in the abstract.
Reply: Thanks for your very good comment. We have corrected the last sentence.
Changes in the text: Page 1, Line 31-33.

Line 52, As I mentioned before, please do not use "novel". This variant has been reported previously. The authors cannot use "novel" in the manuscript.
Reply: Thanks for your very good comment. We have deleted the "novel".
Changes in the text: Page 2, Line 51.

Line 126 and 216 "exon" should be exome.
Reply: Thanks for your very good comment. We have corrected the word "exon" to exome.
Changes in the text: Page 4, Line 125 and Page 9, Line 215.

Line 233- 242; The authors should be aware of that writing of genetic variants are messy. If the authors want to write the amino acid as a single letter, please do not use "Arg" and "R" in the same manuscript. Also, if the authors want to write the termination "*", please do not use "X" and "*" in the manuscript. As I mentioned before, this manuscript has not been checked by native English speaker. There are many typos in the manuscript. Please attach the file of certification proofread by native English speaker.
Line 234. G1018Dfsx2 should be G1018DfsX2 or G1018Dfs*2.

Line 240. “Ser” should be “S”…. etc. Please see your manuscript and “Table” carefully.
Reply: Thanks for your very good comment. We have corrected the Line from 232 to 240.
Changes in the text: Page 9, Line 232-240.
As to the certification proofread by native English speaker, we have entrusted the editorial office to send our manuscript to language editing.

Figure1 and 2. There are no figure legends here. Please write figure legends.
Reply: Thanks for your very good comment. We have added the figure legends.
Figure1 Electroencephalogram showed sharp slow waves, multi-sharp slow waves, generalized spike waves, dominant rhythm slowing down in occipital region.
Figure2 Myoclonic seizures were detected.

Reviewer B
This article presents a case report: pathogenic variant in NEXMIF in a epileptic female patient with a multiple organ failure.
I consider this article of interest. However, I still find some correction that need to be done:
- Supplementary material is not entirely in English, as proposed by the authors it should be translated into English.
Reply: Thanks for your very good comment. We have translated supplementary material into English.

- Although the patient died, I assume there's still peripheral-blood DNA left, so at least X-inactivation could be tested on this sample.
Reply: Thanks for your very good comment. Unfortunately, it's been too long, and the specimen can't be found.

- According to the text “Previously reported patients with NEXMIF gene pathogenic variants showed that most males were severely affected, while most females had a milder phenotype or were asymptomatic (9,10,11)” [line 47-49]. In table 2, however, where “Clinical data of previously described patients with NEXMIF variant” are reported, these references are not included.
Reply: Thanks for your very good comment. As we list the literature of the past five years, so literature 9,10 and 11 are not included.