2019-6-30
Dear editor Li-Jun Cui
Science Editor, Editorial Office
Baishideng Publishing Group Inc,

We are grateful for the opportunity to revise our paper (Manuscript No. 46553) entitled “Wilson disease associate with immune thrombocytopenia: A case report and literature review”, and the helpful comments of your reviewers.

We feel that the comments have allowed us to improve the paper and hope you convey our gratitude to the reviewers.

We attach a version showing the tracked changes in blue words and, separately list our point-by-point responses.

We also had the manuscript edited by a professional scientific-editing service.

Yours sincerely,

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Reviewer reports:

For Reviewer 00722122

The manuscript titled "Immune thrombocytopenia may be a hematological presentation of Wilson disease: a case report and literature review" is an interesting case report however it require some major and minor corrections before its publication Minor corrections there are few spelling mistakes such as on page 3, line 13- check spelling of 'cleare' should be "clear" and on page 4, line 2 spelling "sing" is incorrect it should be "sign" .

Answer: Apologies for the English language issues. We have corrected the spelling mistakes.

The sentence "The manifestations of WD are quite variable" is actually a repitition of previous sentence in different words and can be merged with earlier sentence. The sentence "but there no evidences to show major contribution" require language editing the symbol " " need correction.

Answer: Thank you for reviewing our manuscript. We have revised the part and eliminated repetitive information, and corrected the " " to "μ".

Major corrections：The entire case report needs to be rewritten in a clear case report format and not as the clinical notes written in hospital file. May be authors should seek help from the expert for case reporting and language polishing.

Answer: Thank you for reviewing our manuscript. We have revised the parts according to the guidelines of the journal, and the manuscript has been edited by a professional scientific-editing service.

The bone marrow report is not written correctly. What lens power was used and how many fields were observed etc. what is meant by platelet forming megakaryocytes not found. these cells are meant to produce platelets. Authors have written 56 megakaryocytes on bone marrow examination so what is the significance of this number. Please get the correct reporting with interpretation done by a hematologist.

Answer: Thank you for reviewing our manuscript. The part was revised after consulting with a hematologist. We removed the descriptions of the bone marrow examination, and revised to the clinical conclusions as “normal granulocytic and erythrocytic series

with immature megakaryocyte series".

The authors stated that "The child was not treated with glucocorticoids because her platelet count was greater than 50×109/l and she had no signs of hemorrhagic tendency" however at this platelet counts, only platelet transfusion is hold but not the specific treatment such as glucocorticoids so please check again and correct it.

Answer: Thank you for your suggestions. In our hospital, platelet transfusion was not performed if the platelet count was over 25×10^9/l and there were no hemorrhagic signs. For the patient, she had no signs of hemorrhagic tendency when the platelet count was 34-43$\times10^9$/l, so platelet transfusion was not performed. If the platelet count was decreasing less than 25×10^9/l during surveillance, we usually gave intravenous immunoglobulin 400mg/Kg·d for three days and methylprednisolone of 1-2 mg/Kg·d for about two weeks or longer. But for the patient, intravenous immunoglobulin was not given because of lack of hemorrhagic signs, and glucocorticoids were not given after we evaluated the possible risks of glucocorticoids for the patient.

The authors wrote "Antibodies for autoimmune hepatitis (including anti-ds-DNA, Sm, SS-A, SS-B, and ENA-Jo-1) were negative", This is not the autoimmune hepatitis panel. please check the diagnostic criteria of autoimmune hepatitis and re-write. Also mention titer and pattern of ANA.

Answer: Sorry for the omission. The examination of panels for autoimmune hepatitis and connective tissue diseases had been performed, and some antibodies were omitted when the manuscript was built. We have corrected the part. ANA was positive with the titer 1:40 for the first-time examination, but was negative by reexamination soon after and during the follow-up, so we think that ANA was false positive. And we considered that ANA should be recorded as negative.

The authors have given a good explanation of anti-platelet autoantibody formation in patients with WD however either it should be substantiated with references/evidence or a further study should be suggested to look at these antibodies in such patients. In this regard the recommendation given by the authors is case report to investigate children with thrombocytopenia without an obvious cause for WD is not evidence based and further studies should be suggested.

Answer: Thank you for your suggestions. We have revised the parts to “anti-platelet autoantibodies should be tested in WD patients with thrombocytopenia in future to verify the association.”

For Reviewer 02627036

Please delete from your article the following words: "future", "may be" and rebuilt the sentence without these words.

Answer: Thank you for your suggestions and we revised the related sentences.

For Reviewer 05088164

The paper presents an interesting case of WD associated with ITP in a child. This is a rare association in WD, but there is not clear enough if this could be a manifestation of WD or just an association. The title should be change - literature review is too much said for what was presented in the Discussion chapter. Also I would say that this is an association not a hematological presentation, as there were from the beginning clinical symptoms of a neurological WD.

Answer: Thank you for your suggestions. We have revised the title, and it is really better to consider that WD associate with ITP, but not as a manifestation of WD. We observed that PLT counts ceased to decrease after the treatment of WD, the observation may also support the association of WD with ITP.

In the Introduction paragraphs I would correct the info from line 3 - gene or protein? also in line 10-11 probably is better to use compound heterozygous status; in line 15-16 I would not present the definition of thrombocytopenia as is well known. In line 23-24 you present that the diagnosis of ITP was made before WD confirmation, but is clear that the WD was diagnosed in the same time with ITP as the signs and lab results were obvious for WD diagnosis; just the genetic confirmation was delayed. I would say that WD was present and ITP was only the moment for revealing the WD... as the drooling, dysarthria were already present from the onset.

Answer: Thank you for your suggestions. We have revised the related parts.

In the laboratory results I would include also other: ASAT, total bilirubine. Somewhere (page 9 line 8) you said that the AIH was excluded as autoantibodies were negative, but in line 15 page 6 - positive for antinuclear antibodies - in what titer? It is well known

that autoimmunity could be a manifestation of WD in a part of the patients.

Answer: Thank you for suggestions. We added the values of AST and total bilirubin. The antibodies for autoimmune hepatitis and connective tissue disease were corrected. ANA was positive with the titer 1:40 for the first-time examination, but was negative by reexamination soon after and during follow-up, so we think that ANA was false positive and should be recorded as negative.

I would explain in more details what were the findings an ultrasound examinations- and to say that these changes were compatible with liver cirrhosis. There is no Fibroscan or Fibrotest results in order to sustain the liver cirrhosis? Also in page 9 line 26-27 I would make more clear that the US image was stable, that could be equivalent to cirrhosis

Answer: Thank you for your suggestions. We added the ultrasound findings of the liver. We did not do some examinations for liver fibrosis because we considered that liver fibrosis should exist because liver cirrhosis had developed. We revised the part (page 9 line 26-27) to show there were no marked changes in the US images.

In the Treatment paragraph I would explain the dose also for Zinc and I would present the way of administration. Did you give directly the full dose of d-penicillamine? or you increased the dose over a period of time, in order to prevent the neurological deterioration? There was no treatment for ITP?

Answer: The dose of Zinc sulfate was added. We ordered d-penicillamine after the negative penicillin skin test and increased the dose to 1000mg/day in one week, anaphylaxis and neurological signs was under surveillance at the same time. Because the counts of PLT was over 25×10^9/l and she had no signs of hemorrhagic signs, ITP was not treated.

In Discussion paragraphs (page 8 line 13) you said that this association of mutations was not presented, but there is a paper presented this association in a patient with WD and albinism (doi: 10.1097/MD.0000000000013744) and another one in Human Pathobiochemistry 2019 (https://doi.org/10.1007/978-981-13-2977-7_13). As those mutations are frequent in Asian population I would think that are more cases. This part should be revised.

Answer: Sorry for the omission of the lectures, we have revised the part and added the

lectures into the references. In the two reported cases with the compound heterozygous mutation, no thrombocytopenia was found.

Based on this case presentation I consider that the idea of screening for WD in all thrombocytopenia cases would be too much. As also was in this case, there are other signs that could direct the diagnosis of WD not just thrombocytopenia. In fact, the child was in cirrhosis stage, with neurological signs, not only thrombocytopenia that revealed WD. Maybe this conclusion should be changed to something related to the possible association of ITP in WD patients also with an emphase on autoimmunity (positive ANA). The paper need some English language review, better by a native English speaker... just an example - excessive use of "her" in physical examination paragraph... After the revision of these aspects, I would consider that the paper could be published.

Answer: Thank you for suggestions and we revised the part. Because the ANA was considered to be false positive, we did not add the association of ITP and autoimmunity in WD. And apologies for the English language issues. The manuscript has been edited by a professional scientific-editing service.