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OPEN PEER REVIEW

Liver Transplantation in Progressive Familial Intrahepatic Cholestasis with Normal Gamma-Glutamyl Transferase: Evaluation of Post-transplant Steatosis and Steatohepatitis

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

3 comments · 8 Aug 2021 – 13 Aug 2021

Referee 1 Reviewer

MINOR REVISION 8 Aug 2021

This is a valuable study, but I have some comments:
1- In the abstract section, the conclusion part is not written clearly.
2- One of the most prominent post-transplant complications is pancreatitis. What about pancreatitis in patients in this study, pre- and
post-transplant?
3- A significant number of patients died after transplant (29.1%) because of liver transplant complications. Can we
conclude that liver transplant is an option if other nonsurgical management fails?
4- In the discussion section, the author revealed that liver transplant can correct the genetic defect. How can this make
such a change?
5- Some sentences and paragraphs do not have references.
6- The text and grammar need editing.

Emna Barkaoui Reviewer

MAJOR REVISION 12 Aug 2021

The Title: PFIC1, but the diagnosis is not certain
I PROPOSE TO CHANGE THE TITLE TO PFIC with normal GGT without specifying the Type

Background:
1- The methodology for diagnosing PFIC1 was not described: the authors didn't specify how PFIC1 was diagnosed.
2- The management of these patients with steatohepatitis or steatosis was not clear.
Introduction:
1- The authors must update the classification of PFIC: to date, 5 types of PFIC have been identified, and there may be more: PFIC1, 2, 3, 4, 5. Each one is secondary to a defect in a gene.
2- Steatosis after liver transplantation for PFIC1 is different from NASH, and the mechanisms are also different.
Patient and METHODS
1- The diagnostic criteria include PFIC1, but other forms of cholestasis could have the same presentation, so the 111 cases cannot be confirmed as PFIC1 without genetic confirmation.
2- In cases lacking genetic confirmation, the authors must perform all examinations, such as Alphafoetoprotein ++, BER, and lipasemia for pancreatitis…
Even without extrahepatic symptoms, the authors can't be certain that the patients have PFIC1.
3- Growth retardation and diarrhea before LT were not specific to PFIC1.
4- The exclusion of other diseases: the authors must specify which diseases.
5- Medical treatment must be detailed: ursodesoxycholic acid and others
6- Importance of specific nutrition
7- The indication for LT was not defined: liver failure? Intense pruritus? Hepatocarcinoma?
8- The monitoring of parameters after LT was not defined: clinical and biological parameters, such as transaminases, gammaglutamyltransferasis, alkaline phosphatasis, etc. These are very important in patients with steatosis secondary to PFIC1 after LT.

Results
Post-LT findings
1- Growth retardation was seen in 35 (31.5%) 143 patients and diarrhea in 41 (36.9%): the authors didn't specify when these outcomes occurred: after one month, 2 months, etc.
2- NAS: abbreviation of?
3- The authors presented the results but didn't report cases treated with biliary diversion followed by LT?
Discussion
1- For steatosis, even severe steatosis, the first study was by the authors from Bicêtre: Lykavieris et al.
2- The authors refer to PFIC in some places and PFIC1 in others.
3- Steatosis was reported in 30% in this study: the authors must emphasize that, in the absence of genetic confirmation, the proportion of patients with PFIC1 may be about 30%.
4- All results could be questioned because genetic confirmation was not done.
5- In the tables and discussion, the authors can't compare studies with confirmed PFIC1 to their patients without confirmed PFIC1. There can be many other types of PFIC with normal GGT that are not PFIC1, such as PFIC4 and PFIC2.
References
The authors may add new articles on type 4 (related to a mutation in the gene TJP2) or 5, etc., and articles on PFIC2 AND REPORT THE DIFFERENCES between each form and PFIC1.

In conclusion

I highlight this study
I propose changing the strategy from PFIC1 to PFIC with normal GGT. Then the authors can report their results despite the lack of genetic studies or confirmed cases, and they can discuss the possibility of PFIC1 in cases with steatosis. But in cases without pruritus, the authors couldn't discuss PFIC.

Associate Editor

MAJOR REVISION 13 Aug 2021

Dear author
- Please define the indication for LT: liver failure? intense pruritus? Hepatocarcinoma?
-Please correct and define all abbreviations. All results must be discussed.
Some references were old and must be replaced with newer ones.
Authors may add novel articles on type 4 (related to a mutation in the gene TJP2) or 5, etc., and articles on PFIC2 AND REPORT THE DIFFERENCES between each form and PFIC1.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

Dear Prof. Vahid Ziaee
Hi,
Enclosed is a revised version of our submitted manuscript (117380). I thank the reviewers for taking the time to evaluate our manuscript and provide us with their valuable suggestions. We have carefully studied the comments and tried to implement the suggestions to improve the quality of our manuscript. The corrections are highlighted in the revised manuscript. We are looking forward for your final decision and we really appreciate it.

Reviewers' Comments:
Reviewer 1:
The Title : PFIC1 but not certain
I PROPOSE TO CHANGE THE TITLE TO PFIC with normal GGT withpit specifying the Type
Author response: The title was changed.

Bacground :
1- There was no methodology of the diagnosis of PFIC 1: the authors didn’t precise how the diagnosis of PFIC1 was done ?
Author response: we explained the criteria for diagnosis of PFIC with normal GGT in the method section (pages 5 and 6), and we emphasized that PFIC types with high GGT were excluded.

2- The management of these patients with steatohepatitis or steatosis was not clear.
Author response: In our center we prescribed antioxidants like vitamin E in these patients with follow up and conservative therapy (mentioned in page 16, first line).

Introduction:
1- Author must up to date the classification of PFIC until now we found 5 PFIC and may be more PFIC1, 2, 3, 4, 5, and each one was secondary to a defect in a gene.
Author response: The new types of PFIC were added in the introduction section.

2- Steatosis in post liver transplantation of PFIC 1 is different from the NASH and the mechanisms are different also.
Author response: It is true; the data about NASH was omitted.

Patient and METHODS
1- Criteria OF DIAGNOSIS include PFIC1 but other cholestasis could have the same expression so 111 case could not be PFIC1 without genetic confirmation.
Author response: The study population was changed to PFIC patients with normal GGT.

2- In the cases of luck of genetic confirmation authors must do all exams

such Alphafoetoprotein ++, BER, lipasemia for pancreatitis….
Even without extrahepatic symptoms the authors can’t be certain to have PFIC1.
Author response: These examinations were done for the patients to exclude other possibilities.

3- Growth retardation and diarrhoea in pre LT were not specific of PFIC1.
Author response: It is true; this subject was not concluded in the manuscript.

4- The elimination of other diseases: authors must precise witch diseases.
Author response: The other diseases were added in the method section (page 5).

5- Medical treatment to detail: ursodesoxycholic acid and others
Author response: Our pre-transplant medical management was described in the discussion section (page 13, paragraph 2); we did not repeat them in the method section.

6- Importance of specific nutrition
Author response: This subject was not available.

7- The indication of LT was not defined: liver failure? intense pruritus? Hepatocarcinoma?
Author response: It was defined in the method (page 6, paragraph 1) and discussion (page 13, paragraph 2) sections.

8- The monitoring of parameters post LT was not defined: clinic and biologic as transaminases, gammaglutamyltransferasis, alkaline phosphatasis etc. They are very important in steatosis secondary to PFIC1 patients after LT.
Author response: The post-transplant laboratory findings in steatotic and non-steatotic groups were added in Table 3. Also, Table 4 with laboratory data at the time of liver biopsy in steatotic group was added.

Results
Post LT finding
1- Growth retardation was seen in 35 (31.5%) 143 patients and diarrhea in 41 (36.9%) : the authors didn’t precise the interval of outcome : after one month 2 months etc.
Author response: This subject was not available.

2- NAS: abbreviation of?
Author response: It was corrected.

3- Authors Developed results but didn’t report cases treated by Biliary diversion then LT?

Author response: We had 15 cases with biliary diversion then LT, but in this study we did not assess their precise results. Our plan is their assessment with larger population in another study.

Discussion
1- For steatosis even severe the first study was of the authors from Bicêtre: Lykavieris et al
Author response: It was corrected in Table 6.

2- The authors report in a time PFIC and in the other PFIC1
Author response: It is corrected.

3- Steatosis as reported in this study in 30% : the authors must insist that in luck of genetic confirmation the proportion of patients with PFIC1 may about 30%
Author response: It was emphasized that this rate is in PFIC patients with normal GGT without genetic subtyping (page 15, paragraph 2).

4- All results could be discussed because the genetic confirmation weren't done.
Author response: We think that these subjects have discussed.

5- In tables and discussion, the authors can't compare studies with confirmed PFIC1 to theier patents not confirmed. We can have many others PFIC with normal GGT not PFIC1 as PFIC4 and PFIC2.
Author response: We only collected all the reported PFIC patients in Table 6, and the specific types if specified were mentioned in a column. Also, in the discussion section, we mentioned the specific type of each paper.

References
Authors may add novel articles for type 4 (related to mutation in the geneTJP2) or 5 etc and articles for PFIC2 AND REPORT THE DIFFERENCES each form from PFIC1.
Author response: The references 6 and 7 were added.

In conclusion
I highlight this study
I propose to change the strategy from PFIC1 to PFIC with normal GGT then authors can report theirs results despite luck of genetic study or confirmed cases then they can discuss the possibilities of PFIC1 in cases with steatosis. But in cases without pruritis the authors couldn't discuss PFIC.

Reviewer 2:
This is valuable study but I have some comments:
1- In the abstract section , conclusion part is not written clearly

Author response: The conclusion of abstract was revised.

2- One of the most prominent post transplant complications is pancreatitis. What about in patients in this study, pre and post transplant.
Author response: we did not have pancreatitis in our cases according to patients' file reviews.

3- The significant numbers of patients died after transplant (29.1%) because of liver transplant complications, can we conclude that liver transplant is an option if other non- surgical managements fails?
Author response: The mortality rate in our study was relatively high, so we concluded that the LT is the final option for the patients that not responded to other therapies. It was added in the conclusion section.

4- In the discussion section the author revealed that liver transplant can correct the genetic defect. How can this make such a change?
Author response: It was about PFIC type 1, so it was omitted.

5- Some sentences and paragraphs do not have references.
Author response: It was corrected.

6- The text and grammar need edition.
Author response: This manuscript has edited for proper English at NedMedica.

Associate Editor's Comments:
Associate Editor 1:
Dear author
- Please define the indication of LT: liver failure? intense pruritus? Hepatocarcinoma?
Author response: It was defined in the method (page 6, paragraph 1) and discussion (page 13, paragraph 2) sections.

-Please corrected and define all abbreviations. All results must be discussed.
some refrences were old and must be with a newer one.
Authors may add novel articles for type 4 (related to a mutation in the geneTJP2) or 5 etc and articles for PFIC2 AND REPORT THE DIFFERENCES each form from PFIC1.
Author response: The abbreviations were defined. The new references were added.

Best regards

2 Revision 1

2 comments · 23 Sep 2021 – 24 Sep 2021

Referee 1 Reviewer

ACCEPT 23 Sep 2021

Dear editor
Convincing answers were given to my suggestions. Thank you.

Associate Editor

ACCEPT 24 Sep 2021

Accept
Thanks for the correction.