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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54228

Title: Cholesteryl Ester Storage Disease (CESD): Clinical and genetic characterisation

Reviewer's code: 00035033
Position: Editorial Board
Academic degree: MD
Professional title: Associate Professor
Reviewer's country: Italy
Author's country: Denmark
Manuscript submission date: 2020-01-15
Reviewer chosen by: AI Technique
Reviewer accepted review: 2020-01-15 18:13
Reviewer performed review: 2020-01-15 20:57
Review time: 2 Hours

SPECIFIC COMMENTS TO AUTHORS

This is a very accurate and well-presented description of the clinical and genetic characterisation of two adult siblings with cholesterol ester storage disease (CESD). Both subjects presented progressive hepatic failure leading to hepatic transplantation and advanced multiorgan atherosclerosis. Both patients show signs of recurrence of CESD in the liver after transplantation. Moreover, three family members who were LIPA heterozygous had a lysosomal acid lipase (LAL) activity below the reference value. Since analyses of SNPs showed variants with an increased risk of non -alcoholic fatty liver disease and fibrosis for both patients, I suggest that the Authors discuss the clinical case also taking into consideration the following recent publications: Baratta F et al. Reduced

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lysosomal acid lipase activity: A new marker of liver disease severity across the clinical continuum of non-alcoholic fatty liver disease? World J Gastroenterol. 2019 Aug 14;25(30):4172-4180 Baratta F et al. Lysosomal acid lipase activity and liver fibrosis in the clinical continuum of non-alcoholic fatty liver disease. Liver Int. 2019 Dec;39(12):2301-2308 Angelico F et al. Severe reduction of blood lysosomal acid lipase activity in cryptogenic cirrhosis: A nationwide multicentre cohort study. Atherosclerosis. 2017; 262:179-184

Dear Associate Professor,

We would like to thank you very much for your positive review and we are delighted to hear that you found our article interesting. Once again, we would like to thank for your suggested relevant publications which supports our statement that LAL activity could be used as a marker in heterozygote patients and cryptogenic cirrhosis etc.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

Manuscript NO: 54228

Title: Cholesteryl Ester Storage Disease (CESD): Clinical and genetic characterisation

Reviewer's code: 02444978
Position: Editorial Board
Academic degree: MD
Professional title: Professor
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Author's country: Denmark

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Review time: 6 Days and 4 Hours

SPECIFIC COMMENTS TO AUTHORS

This paper describes the case of two siblings affected by CESD who underwent liver transplantation. The siblings were clinically and genetically evaluated, recognizing they were compound heterozygous for the missense variant in LIPA exon 8. Their first-degree family members were also examined. Although this paper does not contains relevant novelty about CESD, the disease is presented in a clear and complete way in the background, with a correct diagnostic and therapeutic conduct. Consequently, the paper offers an example of how to diagnose and manage this rare disease, proposing CESD as a multi-organ disease, the progression of which may occur post-liver transplantation. I have some revisions concerning the exposition of the data. In general, the description of the

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subjects involved in the study is confused. This part needs to be more rigorously and clearly reviewed. There is a discrepancy between table 1 and the other two tables: the number of subjects examined is different. Moreover, it is not easy to identify which subjects the genetic variations correspond to, and what are their clinical characteristics. These aspects need to be better specified. Figure 2 is missing. In table 2 and 3 does not seem to be reported the data of siblings, as stated in the text. In the Family members chapter it is stated that "None of the family members showed evidence of LAL-D in blood tests (Table 1)", but no data on LAL activity is reported in the table. Moreover, two adult family members and one child are mentioned, but in the table appear three adults and three children. Table 3 reports the "Analysis of SNPs in family members of patients with CESD", and not LAL activity. In the discussion, page 11, line 20, it is stated that a "significant correlation between heterozygosity and LAL activity" was found, but no data are reported on this statistical analysis.

Dear Professor,

We would like to thank you for your detailed review and feedback, and we appreciate the positive comments that our article proposes an example of diagnosing patients with LAL-D. We find your feedback outmost relevant and constructive, and we hope that we have revised satisfying according to your comments.

We have corrected the discrepancy between table 1 and other table with regards to number of subjects. However, we were not able to gain blood tests from the seven-year-old child.

- *The references to tables and figures have been revised and corrected.*
- *On page 11, line 20 "significant" has been removed to not be confused with statistical analyze, but rather an quantitate statement.*
- *We have throughout the discussion part tried to precise the references of patients and family members in order to clarify the individual findings and results. (Marked yellow in the*

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