Answering Reviewers

Reviewer's code: 05078668

SPECIFIC COMMENTS TO AUTHORS

Authors have titled the mansucript as NCPHT. But they have discussed the new entity of PSDV. Hence the title is not appropriate to the content. Are the authors interested in highlighting vascular liver disorders that cause portal hypertension? Some aspects of the manuscript are not agreeable 1)1st para: Budd chiari syndrome can be classically categorised as NCPHT as late stages of BCS can progress to cirrhosis (post sinusoidal cause of cirrhosis) 2)2nd para: Commonly EHPVO is not difficult to diagnosis from cirrhosis. A portal cavernoma on imaging differentiates the two. In rare cases (10%) a cirrhosis may have a portal vein thrombosis due to abnormal coagulation or concomitant HCC. Conversely <5% of EHPVO may progress to behave like cirrhosis or be complicated by secondary biliary cirrhosis in symptomatic cholangiopathy (10%) 3)The word "Imagistic examination" throughout the text is not clear 4)Authors should clarify PSDV vs "cryptogenic cirrhosis" and PSDV vs "non-cirrhotic portal fibrosis" (with references to pediatric/young population) 5)Remove the entity on VOD..not pertinent to this review 6)Spelling and grammatical errors need attention 7) Table 2 endoscopy finding comparison is not impressive. 8) comment on splenic vein status in the entities described with respect to EHPVO and NCPF

Author's reply: Thank you for your comments that allowed us to improve our manuscript. Indeed, we have mostly discussed the diagnostic challenges in PSVD, therefore we agree that the title should be changed accordingly. We agree with your comments regarding BCS and EHPVO, that sometimes can lead to cirrhosis, therefore we have clarified our arguments in the introduction. We also have added a paragraph concerning non-cirrhotic portal fibrosis in the pediatric population (see paragraph "PSVD in the pediatric population), as suggested and commented on the splenic status in EHPVO and PSVD (see paragraph "Differentiation between PSVD and EHPVO").

We, however, decided to keep the paragraph concerning the challenges between PSVD and SOS since both entities could be the consequence of oxaliplatin and azathioprine toxicity. Since little is known about the pathophysiological mechanism and natural history, we believe that it is important to address these issues.

Regarding the comments on Table 2 , although it may appear not impressive, it resumes the main findings of different diagnostic tools. Thus, we believe that readers could obtain an integrative and comparative picture of the entire diagnostic progress.

Reviewer's code: 01426451

SPECIFIC COMMENTS TO AUTHORS

In general, this manuscript is well written and reviews an important area with some new definitions and clinical handling of a difficult patient group I have a few specific comments, please see below. In addition, I think there need a section on treatment of complications in this patient group or discussion on the use of terlipressin for variceal bleeding, betablockers as prophylaxis, ascites etc. Diagnostic sections are relevant and well described bu need a few references, see below Comments: Regarding hemodynamic investigations the measurement of spleen pressure should be mentioned and two important publications cited. Combined liver vein and spleen pulp pressure measurements in patients with portal or splenic vein thrombosis. Keiding S, et al Scand J Gastroenterol. 2004 Jun;39(6):594-9. PMID:15223686; β-Blockers Improve Presinusoidal Portal Hypertension. Sørensen M, et al. Dig Dis Sci. 2018 Nov;63(11):3153-3157. doi: 10.1007/s10620-018-5186-1. Epub 2018 Jul 12. PMID: 30003386. They showed that the gradient may be estimated as shown in the first paper and that beta-blockers may reduce this gradient Minor comments: Page 2, line 1: "the prognostic is relatively good, in the case of cirrhosis the outcome is completely different." Prognostic changed to prognosis Page 2, 2nd paragraph: It should be noted that ascites develops after a trigger factor, and is usually transient[1],[2]. May develop? Prefer imaging in opposition to imagistic, please change throughout the manuscript table 2: "predominat vascular" should be predominant

Author's reply: Thank you for your comments. We agree that further discussions should be focused on the hemodynamic changes in PSVD; therefore, we added your suggestions in the corresponding paragraph (page 4/5) as well as the suggested references (no 35 and 36). Regarding the need for a section dedicated to the treatment, we agree that it would be interesting. However, since the treatment is not the main focus of this review and for reason of space restriction, we decided not to reserve a whole paragraph on this matter but instead mention that NSBB are effective in these patients too (page 4/5).

Reviewer's code: 04761926

SPECIFIC COMMENTS TO AUTHORS

The authors present a very clear and exhaustive review on non-cirrhotic portal hypertension and report data in line with the most updated guidelines on the management of vascular liver disease. In particular they underline the difficulty of suspect and diagnose PSVD and the more difficulty challenge to differentiate between PSVD and other liver disease such as compensated cirrhosis, chronic portal vein thrombosis, SOS, or healty population that may share different aspects/characteristics of the disease. The paper is well written and well argumented, I have only few comments: 1. Title: it reflects the major contents of the article, and is comparable to the aim of the work. 2. Core tip: ok 3. Introduction: ok 4.1. Differentiation between PSVD and hepatic cirrhosis: please correct "hepatic cirrhosis" simply in "cirrhosis" 4.2. Differentiation between PSVD and EHPVO: ok 4.3. Differentiation between PSDV and healthy population: -In this section the authors correctly mention the case of patients with OPV at histology but without portal hypertension that now are contemplated in the last definition of PSVD. Due to the absence of clinical signs of portal hypertension such as splenomegaly, esophageal varices, thrombocytopenia etc., it results very difficult to suspect the presence of PSVD. However, as descripted in literature, most of patients with OPV have not normal liver tests. In fact, the principal indication to realize a liver

biopsy is the presence of elevated transaminases or cholestasis with no evident causes. The authors are invited to mention concept that is an important and useful data to differentiate PSVD and healthy population. 4.4. PSVD and Sinusoidal obstruction syndrome: The mechanism which whom this drugs toxic to vascular liver system and in particular oxaliplatin and azathioprine is not well understood. As the authors state is probably related to the depletion of glutathione transferase leading to toxic insult to sinusoidal endothelial cells. However, the description of the mechanism of NRH provided to the authors ("obstruction is caused by erythrocytes sloughing, and blebs, characterized by free fragments of cytoplasmic processes, occasionally containing cellular organelle") seems to correspond more properly to the pathogenetic mechanism of SOS, not of NRH/PSVD. Please verify and modify the abovementioned statement. 5. Illustrations and tables: ok 6. Biostatistics: not required. 7. Units: ok 8. References: ok 9. Quality of manuscript organization and presentation: please correct the typo "PSDV" in "PSVD" in the title of the paragraph "Differentiation between PSDV and healthy population". 10. Ethics statements: not required.

Author's reply: Thank you for your comments on our manuscript. We agree that most of the patients with OPV without clinical signs of PHT undergo liver biopsy because of the unknown causes of elevated liver enzymes. Therefore we underlined this fact in the corresponding paragraph (page 9). Concerning your comments regarding the differentiation between PSVD and SOS, we agree that the mechanism we have presented is mostly related to the development of SOS. Both the obstruction of the sinusoids and NRH occur in patients taking Oxaliplatin. The mechanisms could be intricated since NRH can be a single anomaly but also a consequence of long-lasting alterations produced at the level of sinusoids. We have rewritten the paragraph in hopes of making it more explicit.

Reviewer's code: 02527808

SPECIFIC COMMENTS TO AUTHORS

Well written manuscript covering most of the important challenges in the diagnosis of NCPH and their difficult differentiation from cirrhotics -some minor comments : - A Table listed all causes of NCPH is important and needed some points of differentiation like immunohistochemistry is mentioned in the table only while not mentioned in the text

Author's reply: Thank you for your interest in our manuscript. Indeed, a table listing all causes of non cirrhotic portal hypertension could be illuminating, however the reason why we did not include it in this manuscript is because these type of tables have already been published in several papers and one more would be unnecessary. Moreover, we mostly focused on diagnostic challenges in PSVD and we decided to change the title accordingly, as suggested by other reviewers.

We agree that the immunohistochemistry analysis is reported in the table but not in the text. Because it is not pathognomonic, we have decided to eliminate it form the table and to let the discussion only in the text (see paragraph regarding the biopsy changes in PSVD, page 5).