Peer Review File

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Reviewer A

This is very well written article presenting the differential diagnosis of hepatic WD, however according to multiorgan damage presented in WD as well as pathognomonic symptoms,

We are grateful for the helpful and detailed comments provided and we have addressed each statement separately as recommended.

Comment 1: I recommend to include in description of diagnostic methods in WD differential diagnosis ocular findings in WD: K-F ring pathognomonic for WD and current methods (AOCT) which let us perform differential diagnosis of K-F ring (with other pathological conditions with hyperbilirubinemia or hyper estrogenism) also in liver disorders. It is difficult to write completely separately about WD and other disorders, the ophthalmologic examination is safe, non-invasive (contrary to liver biopsy) that's should be performed as standard differential diagnostic in WD diagnosis.

Reply 1: We agree with this comment about the importance of KF rings assessment and added a section which includes mention of the anterior segment optical coherence tomography (AOCT) (page 7, line 3-11).

Comment 2: Further discussing the WD differential diagnosis it is worth to mention just few sentences according to neurological or psychiatric symptoms in WD (40% of patients had them) that is helpful to NASH, or AIH and WD? In neurological differential diagnosis of movement disorders always the movement disorders with/or liver injury is taken into account when we discuss about WD (not only neurologlcal symptoms)

Reply 2: we have expanded the section on diagnostic criteria and provided a description of the neurological and psychiatric manifestations (page 7, line 12-22). This comment is shared with reviewer B (comment 5, reviewer B).

Comment 3: Finally, discussing the copper metabolism in liver disorders the radiocopper test is used in differential diagnosis in the past as well as in some of the countries, what's is helpful in diagnosis in doubtful for WD patients.

Reply 3: We have added a section on ^{64}Cu radioactive tracer (page 6, line 1-7).

Comment 4: Also I propose to correct the title of article as: .....differential hepatic diagnosis.... because the differential diagnosis of WD described in paper is only hepatic, not neurological nor general, I recommend to revise this manuscript.

Reply 4: the title was modified as recommended to highlight the hepatic focus of the

review.

Reviewer B

Although this review is intended to assist readers in distinguishing between Wilson's disease (WD) and other liver disorders by describing the clinical, laboratory and histologic features of WD and these conditions, the review is rather weighted towards histologic features and relatively limited in its descriptions of clinical and laboratory features.

Comment 5: Essentially no description of helpful findings on the history and physical examination of WD patients such as their younger age, family history, presence of Kayser-Fleischer rings, tremor, hyper salivation and other neurological features of WD.

Reply 5: We agree with this comment which is also similar to comment 2 from reviewer A. We expanded the description of WD clinical manifestations to include age, family history and neuro-psychiatric signs and symptoms (page 7, line 12-22).

Comment 6: In terms of laboratory features, there is no mention of the falsely normal ceruloplasmin levels that can occur in WD patients with acute inflammatory responses and no discussion of the various genetic WD mutations that are employed for diagnostic and screening purposes.

Reply 6: Falsely normal ceruloplasmin levels are now mentioned in page 4, line 5-9. Genetic studies are described in page 6, line 8-17.

Comment 7: The authors should consider shortening the histopathology section to only describing the differences that exist between WD and each liver condition rather than an extensive description of WD histology followed by that of the liver condition followed by common and distinguishing features between the two (which tends to be the present format).

Reply 7: We agree that the overview of WD liver histology may be somehow redundant, although we also think it is important to give an initial summary for the reader. Regardless, the section on WD liver histology (page 9, line 9-19), although still present, has been shortened. We also have shortened the description of hepatic steatosis.

There are also more specific concerns:

Comment 8: The authors should qualify their statement that it is "crucial" that clinicians list Wilson's disease in their differential diagnosis by adding the statement; in those 'presenting with a hepatocellular pattern of liver injury'.

Reply 8: we have modified the text as recommended (abstract, page 1, line 25).

Comment 9: In the first paragraph of the Introduction the authors should present data

indicating that Wilson's disease typically presents as hepatocellular rather than cholestatic liver injury.

Reply 9: Reference added #17 (page 3, line 5-6).

17. Vieira Barbosa J, Fraga M, Saldarriaga J, et al. Hepatic manifestations of Wilson's disease: 12-year experience in a Swiss tertiary referral centre. Swiss Med Wkly 2018;148:w14699.

Comment 10: In the section on serum ceruloplasmin levels, the authors need to elaborate on the levels of ceruloplasmin (i.e. the extent of decreases) in patients with other chronic liver disease versus those with WD.

Reply 10: Additional language added as recommended (page 4, line 5-10).

Comment 11: Urinary copper concentration, line 14. This sentence needs to be reworded.

Reply 11: Sentence was reworded (page 4, line 14-17).

Comment 12: Laboratory and liver histopathological features……of Wilson's disease, line 19. What is being described here is an inflammatory infiltrate rather than hepatocellular necrosis.

Reply 12: Language has been modified to reflect this comment (page 8, line 22-23).

Comment 13: Laboratory and liver histopathological features…..of Wilson's disease, line 7. The authors should describe what proteins the rhodanine and rubeanic acid stains are actually staining.

Reply 13: Rhodanine and rubeanic acid bind directly to copper. We add a sentence about this (page 9, line 9) and 2 new references (# 50 and # 51).

Comment 14: Nonalcoholic fatty liver disease and elsewhere. Somewhere in this review the authors should make the point the AST/ALT ratio >1 often reflects advanced fibrosis/cirrhosis regardless of the underlying etiology.

Reply 14: We agree with this comment and we added a comment to "Laboratory and liver histopathological features…" (page 8, line 16-17).

Comment 15: Nonalcoholic fatty liver disease, second paragraph. This paragraph appears out of place in that it describes WD features without a comparison to NAFLD.

Reply 15: The paragraph has been removed allowing for a shorter but still detailed description.

Comment 16: Nonalcoholic fatty liver disease. In the second paragraph of this discussion there are two conflicting statements dealing with the correlation between hepatic steatosis and copper content (line 1-2 and 18-20). This discrepancy should be

discussed.

Reply 16: We edited the text to reflect high frequency ("primarily") of macrovesicular steatosis in WD (page 10, line 3).

Comment 17: Alcohol-associated liver disease, line 19. Did the authors intend to state that the findings are non-specific and distinguish alcohol-associated liver disease….from Wilson's disease or do not distinguish alcohol-associated liver disease from WD?

Reply 17: The language was updated to reflect non-specific findings that do not distinguish alcohol-associated liver disease from WD (page 12, line 4-5).

Comment 18: Autoimmune hepatitis, line 6-7. It is unclear whether the reference to acute and chronic presentations represents patients presenting with WD or AIH.

Reply 18: The language was updated to reflect WD overlap with acute and chronic manifestations of AIH (page 13, line 16-18).