Peer Review File
Article information: https://dx.doi.org/10.21037/amj-22-24.

Reviewer A:

This is interesting review about WD and copper metabolism, however several issues should be clarified and extended.

Dear reviewer,

Many thanks for reviewing our paper. We are grateful to your thoughtful comments that helped to improve the overall quality of our work. In the revised version, we have marked all changes in red letters.

Comment 1:

Chapter Clinical presentation

Page 5 line 128 this chapter is Clinical presentation; the neurological presentation should be described with more details, chorea is not common neurological symptom of WD

Reply 1:

As suggested we have added some more information about the neurological symptoms of Wilson disease and referred to a summarizing article in the revised version of our article (Ref 41).

Comment 2:

Brain iron accumulation in WD seems to be secondary to tissue damage (Dusek, et al Brain iron accumulation in WD: a post mortem 7Tesla study; 2017) not primary

Reply 2:

We fully agree with your concern and added the mentioned references by Dusek and colleagues (Ref 44).

Comment 3:

There is a lack of psychiatric WD manifestation (in clinical presentation part)
Also please extend the other organs involvement in WD

Reply 3:

Thanks for this comments. We have added psychiatric manifestations in Wilson disease, added a respective reference (Ref 42) and added information about other organs affected by Wilson disease with a respective reference (Ref 45).

Comment 4:

Line 135 page 5 aim of therapy is to suppress urinary copper below 60 µg/day - is true for zinc, in case of chelators urinary excretion in treated patients is between 200-500 µg/24h

Reply 4:

Thanks for this hint. According to your advice we have added the sentence “Therefore in case chelator therapy is continued, values of 200-500 ug/day are desirable” and added a reference for this statement (Ref 68).

Comment 5:

Page 6 - the factors affecting the WD phenotype - the gender impact should be added

Reply 5:

In the revised version, we have added some information about potential gender effects in Wilson disease and added respective references (Refs 52 and53).

Comment 6:

Page 8 Diagnosis: the free copper calculation should be: 3.15 x ceruloplasmin in mg/L equals the amount of ceruloplasmin-bound copper in µg/L

Reply 6:

We agree and corrected the formula.

Comment 7:

Further there are several papers describing the false negative value of "free" copper - please discuss it. Currently all studies (CUFENCE, CHELATE, ALXN1840) use direct free copper assessment - the explanation of this method would be interesting. Also the Exchangeable Copper is proposed as biomarker of copper metabolism - could You add it?

Reply 7:

This is a good suggestion. Accordingly, we have added the respective information including references (Refs 64-66).

Comment 8:

The K-F ring is present in almost 100% of neurological WD, but less frequently in hepatic and presymptomatic patients

Reply 8:

We have added the information that the K-F are almost present in 100% of neurological Wilson disease., but not necessarily in hepatic or pre-or asymptomatic cases.

Comment 9:

Currently in diagnosis ATP7B peptide assessment is proposed (please add)

Reply 9:

We have added this information and the reference for this test (Ref 75).

Comment 10:

Radiocopper test (or PET) is also proposed in WD diagnosis (please discuss)

Reply 10:

We have added this information and the reference for this test (Ref 76).

Comment 11:

Discussing the place of LT in neurological WD patients treatment, apart French group (Poujois, et al) the systematic review about it was published this year presenting the results - please discuss it.

Reply 11:

Yes this is correct. Liver transplantation is a potential rescue therapy. According to your advice, we have added the respective reference by Poujois and coworkers (Ref 89).

Comment 12:

Article is interesting and provide data about WD - treatable inherited disorder of copper metabolism, but should be corrected and updated according to suggestions

Reply 12:

Again many thanks for reviewing our paper. We have addressed the things that you mentioned.

Reviewer B:

Comment 1:

The article presents subjective opinions of the Author rather than current knowledge on this disease. The structure of sections is chaotic. There are repetitions throughout the manuscript.

Reply 1:

Many thanks for your critical evaluation. As suggested, we have restructured the review and deleted repetitions. We think that the sequence of chapters is now much better.

Comment 2:

There are false information like: liver biopsy is a gold standard in WD diagnosis (line 228), opinion on pathomechanism of brain involvement (lines 124-129) sounds like speculation based on unproven arguments, results of current studies are in opposite to- similarly speculations on genotype-phenotype-severity are false (lines 1343-145). Line 150-158 unexpected description of two Wilson disease cases.

Reply 2:

We are grateful for your open words and tried to correct the mentioned critical passages. In addition, we have now better explained the description of the two Wilson disease cases. We think that the restructuring of the manuscript that you suggested is indeed helpful for the reader.

Comment 3:

Free copper (line 219) is not calculated anymore. Non ceruloplasmin copper (NCC) or relative exchangeable copper are using instead but the Authors did not mention it.... TTM (line 269) is an approved for treatment worldwide not " under investigation" etc.

Reply 3:

According to your advice, we have removed/corrected the mentioned passages in the revised article.

Reviewer C:

This is an excellent analysis on the current knowledge about Wilson disease and the potential mechanisms involved in copper toxicity. I have some suggestions to the authors hoping to improve the revision:

Comment 1:

The organisation of the review might be changed for a better readability: Physiology of copper metabolism, Copper overload conditions, Cholestasis, Idiopathic Childhood cirrhosis, Wilson disease, Clinical presentation-pathophysiology, Diagnosis, Therapy, Conclusion

Reply 1:

Many thanks for your critical evaluation. As suggested, we have restructured the review.

Comment 2:

Page 3: I am not sure about the meaning of the sentence in Line 57: "Cu2+ in blood is shuttled between histidine for cellular uptake and release and on the other hand albumin for transportation, both constituting the non ceruloplasmin bound "free" Cu fraction".

Reply 2:

We agree that the sentence was a little bit confusion. In the revised version we have rephrased the mentioned sentence.

Comment 3:

Page 7, Line 191: "Despite the knowledge of normal Cu metabolism, the exact pathophysiological processes in Wilson disease are only partially understood"

Reply 3:

We have taken out this sentence.

Comment 4:

Page 10, Line 274. It will be nice to know author's opinion about the mechanism involve in TTM toxic effect. Why Cu redistribution occurs and how it damages mitochondria.

Reply 4:

As suggested we have added our opinion about the mechanism that provokes TTM toxic effect.

Comment 5:

Line 289: The authors should indicate that gene therapy is now at initial phases of clinical development with two phase I/II clinical trials open and recruiting patients.

Reply 5:

We have added the information that gene therapy is presently at initial phases of clinical trials.

Comment 6:

It will be nice to mention the promising data obtained in preclinical animal models.

Reply 6:

As suggested, we have added information about this topic at the end of our review (before the

conclusion section).

Comment 7:

Line 290: For clarity rephrase the sentences “Thus, it was suggested also in patients with this fulminant neurologic course. However, critics argue since the neurologic disorder is manifested, it is an irreversible damage and also liver transplantation would be of no cure.”

Reply 7:

Thanks for this comments. We have changed the respective sentence.

Comment 8:

Page 11, Line 302: a space is missing.

Reply 8:

We have added the missing space.

Reviewer D:

Comment 1:

The topic of Wilson's disease is highly relevant; however, this review does not add anything new to the field and missed several important issues discovered in the last few years. The review is not a systematic one or a meta-analysis of the literature. It is a mere description of some of the studies that the authors deemed relevant. The text needs to be completely re-written as the many typos, grammatical errors, ambiguous sentences, and others make it almost impossible to read and understand. In addition, the review mixes WD with copper overload...which in reality WD is a fraction of the "copper overload" umbrella. Several scientific concepts are misquoted such as "free copper in plasma or serum" which do we know this metal travels bound to relevant and specific proteins.

Reply 1:

Many thanks for your open words. According to your fulminant critique we have restructured our review, corrected errors, and modified several statements about the scientific concepts that were misquoted. Please note, that it was necessary to add several more references. All changes are marked in red letters.