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Dear Editor

Thank you for the opportunity to resubmit this paper. We have addressed all the points raised by the reviewers on a point-by-point basis below. We hope you find this in accordance with the reviewer's comments.

We look forward to hearing from you.

Best Regards,

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Comments to the Reviewer(s):

Reviewer 1: "This is an interesting case report addressing the possible pathophysiological relation between hypothyroidism and hepatic encephalopathy. However, the manuscript needs English edition as there are many mistakes in text and tables. The discussion part needs to be shortened and omitting unnecessary repeated phrases. Table 1 needs major revision. Correct abbreviations should be used and all abbreviations should be defined properly".

We appreciate the comments and we agree with them.

- English has been revised and polished.
- Discussion has been shortened, omitting redundancy and incorporating some other 2 paragraphs as suggested by other reviewers.
- Table 1 has been revised and edited according to the comments.

Reviewer 2: "The case is interesting and provide some interesting observations on the association of hypothyroidism and refractory HE. The authors propose that hypothyroidism may result in decreased hepatic ammonia clearance which again could enhance brain exposition to ammonia. However, other precipitating factors could also

contribute and these need to be commented on in more detail: 1) the patient had macrocytosis at admission, this could be due to hypothyroidism but an alternative explanation could be reintroduction of excessive alcohol intake - do you have any data to support that the patient was actually abstaining from alcohol at admission? 2) The patient was constipated at admission which could be secondary to hypothyroidism, did the patient normalize defaecation during lactulose treatment? 3) It is difficult to understand that decreased hepatic ammonia clearance induced by hypothyroidism is the principal cause of HE in this patient where a large shunt is demonstrated - much of the blood from the GI tract will likely never reach the liver but shunt directly into the systemic circulation and reach the brain - this needs commenting and alternative mechanisms should be discussed - direct toxic effect on the brain secondary to hypothyroidism? Decreased cerebral ammonia metabolism? Overall the case should be shortened to improve readability and major language revision is needed. The case needs language polishing and should be shortened as there is a lot of redundancy in the discussion."

We thank the reviewer for his criticism:

- A detailed description of the searched precipitating factors has been added: Infections, gastrointestinal bleeding, recent alcohol abuse has been ruled out. A clarification regarding the laxative effect of lactulose also was added.
- Potential mechanisms by which hypothyroidism induce hyperammonemia are detailed in the discussion. They mention the potential impact of thyroid hormone on the activity of glutamine synthetase enzyme in extrahepatic organs.
- English has been revised and polished
- Discussion has been shortened.

Reviewer 3: "This is an excellent case report describing an incidence whereby hypothyroidism was a precipitating factor that contributed to a recurrence of hepatic encephalopathy in a patient with liver cirrhosis. Overall, the report was very well written, with a clear description of the time line of events followed by a thorough discussion of the literature and known interactions between hypothyroidism and hepatic encephalopathy. There are only very minor corrections: Page 6, line 2: "stablished" should be "established"? Page 6, line 2: sentence "She had no ascites neither hepatocellular carcinoma and primary prophylaxis with propranolol because of Oesophageal varices grade II-III/IV was started" doesn't make sense. Should it be "She had no ascites nor hepatocellular carcinoma and primary prophylaxis with propranolol because of Oesophageal varices grade II-III/IV was started Page 7: 3rd paragraph, spelling "hyperammoniemia" (also found on page 9 2nd paragraph, and other places throughout) and "Encephalopaty" Table 1: Spelling error "amonia".

We thank the reviewer for his revision:

- All these corrections were implemented in the revised version of the paper.

Reviewer 4: "In the paper of Diaz-Fontenla et al an interesting case of a patients with refractory hepatic encephalopathy and hypothyroidism is described. This paper might

benefit by implementing the following suggestions. MINOR: #1 Please shorten the paper by approximately 20-30%. #2 Tables 1+2, and figure 1 are of importance, however figure 2 might be omitted. #3 Please mention also Hashimoto's encephalopathy in your discussion as it might present with high TSH, low fT4, elevated liver enzymes and severe neurological symptoms. #4 Please check your manuscript for grammatical and language errors. Some passages are difficult to read and there are some typos. e.g.: - Then, she recognized a history of alcohol abuse for years, other causes of liver disease were rule[d] out and a diagnosis of alcoholic cirrhosis Child-Pugh B7 was stablished. - She had no ascites neither hepatocellular carcinoma and primary prophylaxis with propranolol because of [O]esophageal oesophageal varices grade II-III/IV was started. - The question [,] whether the neurological impairment was cause[d] by the hypothyroidism or [it] was attributable to the large portosystemic shunt [,] was very important [in order] to make [further] therapeutic decisions."

We thank the reviewer for his/her comments:

- The paper has been shorten as suggested.
- Figure 2 has been deleted
- Hashimoto's encephalopathy has been included in the discussion as an entity to consider when facing a patient with refractory cognitive impairment.
- English language has been revised.
- All the gramma and typo errors were corrected as suggested.