Dear Editors and Reviewers:

Thank you for giving us the opportunity to submit a revised draft of the manuscript "A Case Report of a 7-Year-Old Boy with Recurrent Cyanosis and Tachypnea" (Manuscript NO.: 72120) for publication in the Journal of World Journal of Clinical Cases.

Those comments are valuable and very helpful for revising and improving our manuscript. We appreciate the time and effort that you and the reviewers dedicated to providing feedback on our manuscript and are grateful for the insightful comments on and valuable improvements to our paper.

We have incorporated most of the suggestions made by the reviewers. Those changes are highlighted within the manuscript. Please see below, for a point-by-point response to the reviewers' comments and concerns. All page numbers refer to changes in the revised manuscript file.

Reply to Reviewer 1

Question 1: Workup of pulmonary exam on spirometry was incomplete. You find small airway obstructive pattern but didn't continue with broncho-dilators to confirm reversibility; DLCO was not reported; especially considering a potential diagnosis of interstitial lung disease (dyspnea, cough, exercise intolerance and characteristic CT images); a proper discussion of the entity and how you ruled it out is recommended.

Reply: Thank you very much for the suggestions given by the reviewer. The spirometry mainly revealed mild restrictive ventilation disturbance with decreased FVC, the patient's value of FEV1 and FEV1/FVC were normal. In China only when FEV1/FVC under 70% necessitate bronchodilation test (BDT). In this case the FEV1/FVC value was 97.6% so the BDT was not performed. DLCO should be performed in patients suspected to have ILD. But the DLCO test requires the patient to hold the breath for at least 10 seconds. This patient could not complete this test because of young age and dyspnea. So the DLCO test was not performed in this boy.

Question 2: Elevated liver enzymes, without further workup of liver diseases and hepatitis; a potential differential diagnosis in this case could be hepatopulmonary syndrome; which I suggest you discuss and try to rule it out.

Reply: Thanks for the suggestion. We add Hepatopulmonary syndrome (HPS) as a differential diagnosis in discussion. （see line275, Page 12~ line 294, Page 13）

Question 3: Arteriovenous shunts is another differential diagnosis which needed discussion. The patient has reportedly chest wall pain; that could explain much of the constellation of signs/symptoms and tests; It also needed to be properly discussed and ruled out

Reply: Thanks for the suggestion. We add arteriovenous shunts as a differential diagnosis in discussion. （see line295, Page 13~line 305, Page 13）

Question 4: Cyanosis during exercise is not suggestive of central hypoventilation (Ondine's Curse) syndrome. In fact, an improvement during the exercise & REM sleep is characteristic to the diagnosis. Tachypnea is also against this diagnosis

Reply：Thanks for the suggestion. We realize that Ondine's Curse syndrome, a congenital disease, does not fit the manifestations of the boy. We modify this point in the manuscript. （see line306, Page 13 to line312, Page 14）

Question 5: The patient's severe obesity as well as snoring suggests obesity hypoventilation syndrome together with obstructive sleep apnea

Reply: Due to the elevated CO2 level during sleep (PaCO2 was 59.7mmHg), Secondary central hypoventilation or obesity hypoventilation were most suspected. But obstructive components could not be ruled out without PSG examination. The specific type of the breathing disorder was not certain because in the ICU ward the PSG examination could not be performed. We discuss this point in the revised manuscript. （line230, Page 10 to line 274, Page 12）

Question 6: Data needed: Sputum production? Presence of clubbing? Orthopnea? Polysomnography; cardiac catheterization

Reply: Thanks for the suggestion. The patient coughed with little sputum production; sputum culture was performed without positive findings. He had orthopnea but no clubbing. We add that information in the revised manuscript. Polysomnography should be performed, but the patient was critically ill, and MRI revealed the etiology, so polysomnography and cardiac catheterization were not done during hospitalization.

Reply to Reviewer 2

Question 1: Differential diagnosis: Is hepatopulmonary syndrome excluded? Is the liver ok? Is there no portosystemic shunt? There are some reports about patients with hypoxia and brain tumor, of which fatty liver, obesity, and hepatopulmonary syndrome are combined. In addition, in case of portosystemic shunt, interstitial lung disease with pulmonary hypertension and cyanotic changes also occur and mimic hypoventilation type a little bit. I am a pediatric gastroenterologist. Occasionally we see these combinations of symptoms in patients with brain tumor + fatty liver or portosystemic shunts.

Reply: Thanks for the suggestions. The congenital portosystemic shunts (CPSS) are rare vascular malformations that create an abnormal connection between portal and systemic veins resulting in complete or partial diversion of the portal flow away from the liver to the systemic venous system. The main complications include hepatic encephalopathy, liver tumors, portopulmonary hypertension, and pulmonary arteriovenous shunts. If the pulmonary hypertension of this patient was caused by the CPSS then it would not relieve without a radiologic or surgery correction. In this case the pulmonary artery pressure decreased from 62mmHg on admission to 30mmHg after 3 days of conservative medical treatment and respiratory support. And the level of liver enzyme decreased to normal shortly after treatment. These responses are not supportive for the CPSS diagnosis.

Question 2: Outcome: What was the outcome of the patient? Did the patient had surgery and the cyanosis was cured?

Reply: Thanks for the suggestion. After neurosurgery the patient's symptoms including cyanosis resolved transiently but relapsed gradually. Six months later the boy died of respiratory failure.

Question 3: Clinical message: The etiology of Ondine's curse is already well known. The detailed differential steps to final diagnosis would be informative.

Reply: Thanks for the suggestion. Congenital central hypoventilation syndrome (CCHS), used to known as the Ondine's curse syndrome, is a rare disorder defined by a failure in autonomic control of breathing caused by mutations of the PHOX2B gene. We realize that CCHS does not fit the manifestations of the boy. We modify this point in the manuscript. （line306, Page 13 to line312, Page 14）