

July 12, 2021

Dear Editor,

Thank you for your valuable comments for our paper “Ethambutol-induced optic neuropathy with rare bilateral asymmetry onset: a case report” (N0: 68865). We have carefully revised the paper and listed the corresponding replies to the comments from the reviewers as follows:

**Reply for comments from reviewer #1 (03816788)**

1. Incorporate the rationale of reporting this particular case in Introduction.

Reply: Thanks for your valuable comment. We have incorporated the rationale of reporting this case in Introduction as follows:

There are few reports on bilateral asymmetry onset and manifestation of EON cases. Here we present a case of EON with bilateral asymmetry manifestation over 19 months. A full battery of objective and subjective tests was performed. These tests show how the condition changes in detail.

2. Thoracic tuberculosis- there are many types, be specific which organ was involved.

Reply: Thanks for your valuable comment. We are very sorry for this low-level error, this patient was diagnosed with tuberculosis of thoracic vertebrae. We have corrected it in the paper.

3. He received 3 anti-tubercular drugs. Can authors distinguish between the intensive and continuation phase here?

Reply: Thanks for your valuable comment. The standard anti-tuberculosis treatment plan should be HRZE (isoniazid, rifampicin, pyrazinamide, ethambutol) for 3 months of intensive treatment, and then changed to HRE maintenance treatment for 9 months. Because this patient suffered from renal failure, the tuberculologist did not use an intensive treatment plan. They treated him with a combination of ethambutol, isoniazid, and rifampicin. After half a month, the patient had an allergic rash and drug-induced liver damage, so rifampin was discontinued. Therefore, the patient was finally treated with ethambutol and isoniazid for 10 months, until the vision loss appeared and came to the ophthalmology clinic. After an ophthalmological diagnosis of toxic optic neuropathy, we recommend stopping ethambutol and isoniazid.

We added the patient's medication status in the history of present illness.

4. Exact dates not needed, the timeline should be clear.

Reply: Thanks for your valuable comment. We deleted the exact dates .

5. “History of renal dysfunction and renal hypertension”- Provide value of Kidney function and BP.

Reply: Thanks for your valuable comment. We supplemented the value of Kidney function and BP in the History of past illness.

6. Ethambutol dose adjustment was done or same dose was given over the entire period ?

Reply: Thanks for your valuable comment. This patient was given the same dose of ethambutol and isoniazid over the entire period, because the dose had been considered to be safe.

7. “rat nerve growth factor” Rationale of its use, is it standard treatment in such conditions ?

Reply: Thanks for your valuable comment. Mouse nerve growth factor has the effect of promoting nerve recovery, which is used for the treatment of optic nerve injury. Considering that the right eye of the patient is in the early stage of the disease at the time of diagnosis, we used this drug in order to better improve the optic nerve function. This is not the standard treatment drug for toxic optic neuropathy, and We only used the drug for 1 week and then stopped. So we decided to delete this drug in the treatment part.

8. Duration of treatment by the ophthalmologist ??

Reply: Thanks for your valuable comment. This patient had a treatment by the ophthalmologist for 6 months. We have supplemented this in the treatment part.

9. “time-dependent adverse effect” What is the average time of development of Ethambutol-induced optic neuropathy?

Reply: Thanks for your valuable comment. Regarding how long after taking the drug ethambutol, toxic optic neuropathy may occur, the time mentioned in different literatures is different, and most literature believes that it occurs within 2 to 10 after taking the drug.

10. “In >60% of patients with EON, ocular examination reveals bilateral, painless, and typically symmetric loss of visual acuity and abnormal color vision” Does the author means, rest (40%) are asymmetric? If it is this much, then it is common. Elaborate further.

Reply: Thanks for your valuable comment. We have not found specific information for the time between the onset of the two eyes in the case of asymmetric onset. The feature of this case is that the time between the onset of both eyes is long (approximately 6 months). Secondly, the degree of disease and recovery of the two eyes are also asymmetric, and through the OCT macular high-definition scan, we found that the two eyes were different in the macular structure. These characteristics make this case seem relatively rare. In addition, the follow-up data is relatively complete and lasts as long as 19 months. It shows the visual function of the eyes from the early onset, the advanced stage, and the recovery stage, as well as the changes in the retinal RNFL, GCIPL, and macular high-definition structure. The report is relatively rare at present, so we believed that this case had the value of being reported

11. OCT full form must be listed once in manuscript.

Reply: Thanks for your valuable comment. We have listed the full form of OCT in the Abstract.

12. Discussion is essentially about this case only. Some more asymmetric cases and their pattern or comparison with current case should be added. It also lacks on various treatment options.

Reply: Thanks for your valuable comments. We have not found other reports of EON cases with asymmetry onset. In the discussion, we added comparison of other disease that may cause similar damages in the macular outer layer.

There is currently no effective treatment for EON. Therapy discontinuation is the only effective management that can halt the progression of vision loss and allow recovery of vision. Some authors recommend treating patients with 100 to 250 mg of oral zinc sulfate three times per day. If vision does not improve 10 to 15 weeks after stopping ethambutol, parenteral administration of 40 mg/day of

hydroxycobalamine (vitaminB12) for 1to 28 weeks has been suggested.

We have added these to the discussion part.

13. Conclusion- Whereas the title and manuscript focusses on “asymmetric” involvement, the conclusion does no justice to “asymmetric involvement”

Reply: Thanks for your valuable comments. We have re-written the conclusion part.

#### **Reply for comments from reviewer #2 (05691230)**

1、 “...EON was most commonly manifested by bilateral...” page 2. I suggest using the present and the term “manifests by”

Reply: Thanks for your valuable comments. We have made changes for this.

2、 “...eyes attacked successively...” page 2 - “...visit to the doctor...” page 12 - “...lots of mitochondria ...” page 8

Reply: Thanks for your valuable comments. We have made changes for these.

3、 “OCT can help us ... determine the prognosis”. page 3. How can OCT determine the prognosis? If so, it should be discussed in the full text. If not, this should be removed

Reply: Thanks for your valuable comments. This part of the content is not the main focus of this case report, so we will not discuss it.

4、 “There was no family history of ocular disease.” page 4. In whom? It would be interesting to better clarify family history (not just the son but also the parents and other ascendants) to help exclude hereditary genetic neuropathies.

Reply: Thanks for your valuable comments. We have supplemented the family history in detail.

5、 “difficulty in reading green color plates” page 4. I recommend specifying which colour plates. Ishihara?

Reply: Thanks for your valuable comments. We have supplemented that we used the Ishihara color plates.

6、 “SATA-FAST” page 4. Do you mean SITA-Fast?

Reply: Thanks for your valuable comments. We have corrected this.

7、 “Color vision examination revealed red and green blindness in both eyes.”

Reply: Thanks for your valuable comments. We changed this sentence to “Color vision examination remained red and green dyschromatopsia in both eyes.”

8、 “...The ellipsoid zone contains lots of mitochondria and may also be susceptible to ethambutol toxicity...”page 8, this is an interesting fact and it should be better explored. I recommend citing a paper that objectively quantify mitochondriae in the external layers.

Reply: Thanks for your valuable comments. We are very sorry that we have not yet found a paper that clearly quantifies mitochondria in the external layers, but we have found cases of similar changes in the external layers of the macula.

We added in the discussion as follows: The ellipsoid zone is composed of inner section of the photoreceptors, the interdigitation zone is the chimera between the tip of the outer section of the photoreceptor and the microvilli on the top of the retinal pigment epithelial cell. Therefore, the macular lesion in the left eye of this patient is located in the outer layer of the macular, especially the photoreceptor layer. There is a rare disease named acute macular neuro-retinopathy (AMNR) has the similar structural manifestations in OCT examination. AMNR is a rare unilateral or bilateral macular disorder. It typically occurs in young women presenting with sudden onset of central scotomas. They correspond to sharp reddish-brown areas in the macular region. OCT images showed focal abnormalities in the photoreceptor outer segments. The pathogenesis of the disease is still unclear. The main related factors reported so far include oral contraceptives, viral infections, adrenergic receptor agonists, trauma, etc. Chronic kidney disease has also been reported.

9、 Figure 4: I recommend showing a scan segmented in the GC+IPL

Reply: Thanks for your valuable comments. We re-take a screenshot of the original picture and supplement this part of the information.

10、 What do you think are the reasons for the asymmetry in this case?

Reply: Thanks for your valuable comments. This patient does not completely rule out

the presence of AMNR-like lesions in the left eye, but AMNR typically occurs in young women presenting with sudden onset of central scotomas. They correspond to sharp reddish-brown areas in the macular region. These were inconsistent with the characteristics of our case.

The outer segment of the retinal photoreceptor contains unsaturated fatty acids and is vulnerable to free radical attack, while the inner segment is rich in mitochondria. Ethambutol poisoning causes mitochondrial dysfunction. While damaging the retinal ganglion cells, it may also cause damage to the retinal photoreceptor. However, we can believe that the onset of drug-toxic optic neuropathy may be unilateral, but eventually both eyes will be affected because the drug will not selectively act on one of the eyes. If there is a significant difference between the eyes, other diagnostic possibilities must be considered. For this patient, the onset of his eyes was 6 months apart, and the right eye subsequently showed the same vision loss, abnormal color vision, visual field changes, GCIPL thinning, and RNFL from mild thickening to temporal thinning, which are the same as those in the left eye. The only difference is the disorder of the outer structure of the macula in the high-definition macular scan. In this regard, we consider that he suffers from nephropathy and high blood pressure, which damage the retinal microcirculation, resulting in insufficient blood supply to the outer layer of the retina, and damage to the outer layer of the retina.

We have supplemented these in the discussion part.

### **Reply for comments from reviewer #3 (06044780)**

- 1、 In the background section, " ... the development of visual function..." may be corrected for " ....the changes of visual function...".

Reply: Thanks for your valuable comments. We have made changes for this.

- 2、 Best corrected visual acuity is described as a ratio (eg. 20/50) followed by a decimal number, (eg 4.6) which is not necessary as the first fractional number appropriately defines visual acuity.

Reply: Thanks for your valuable comments. We have deleted the decimal number.

#### **Reply for comment from reviewer #4 (05937294)**

1. Please add the full term of abbreviations for the first time in the abstract. OCT (line 31), RNFL (line 31), and GCIPL (line 32).

Reply: Thanks for your valuable comments. We have added the full term of abbreviation for the first time in the abstract of OCT, RNFL, and GCIPL.

2. Did the patient have a history of reading green color (like the color of traffic light) or this was the first presentation? I asked it since deuteranopia is the most common type of dyschromatopsia.

Reply: Thanks for your valuable comments. This patient has a motor vehicle driver's license, has no difficulty in identifying red and green in the past, and can correctly distinguish traffic signals. We supplement this in the history of past illness.

3. The authors should explain why their findings make a difference for ophthalmologists around the world and the readers of the World Journal of Clinical Cases? What is your opinion about periodic ophthalmologic follow-up among those who were managed with ethambutol? Or did you suggest the taper to D/C ethambutol in order to prefer the withdrawal-related symptoms?

Reply: Thanks for your valuable comments. Through the long-term follow-up observation of this rare case, we notice that toxic optic neuropathy can occur successively, and there are different characteristics of retinal damage in both eyes. The damage of macular structure may lead to a worse prognosis of visual function. However, after timely withdrawal of the drug and neurotrophic drug treatment, the visual function can be recovered to a great extent. This report highlights the need for identification of patients at risk, adjusting the dose regimen for impaired renal function, regular monitoring for early signs of ocular toxicity, and patient education.

4. What is your recommendation for infectious disease specialists? Do you think informing the patients about the ophthalmological side effects of ethambutol should be made in mind more seriously?

Reply: Thanks for your valuable comments. This case suggests the importance of

identification of patients at risk, adjusting the dose regimen for impaired renal function, regular monitoring for early signs of ocular toxicity, and patient education.

More minor issues that should be addressed include:

1. Case presentation, line 91, the word "examination" doesn't agree in number with other words in this phrase. Change it to "examinations".
2. Case presentation, line 97, the verb "are" doesn't seem to agree with the subject. Consider changing it with "is".
3. Discussion, line 138, the verb "vary" doesn't seem to agree with the subject. Consider changing it with "varies".
4. Discussion, line 146, it appears that the singular verb "was" doesn't agree with the plural compound subject "color vision dysfunction and visual field defects". Consider changing the verb to the plural form of "were".
5. Discussion, line 147, the word "slightly" doesn't seem to fit this context. Consider replacing it with "slight".
6. Discussion, line 152, you are missing a verb before "attributed". Consider adding it and use "was attributed".

**Reply:** Thanks for your valuable comments. We have made these 6 changes.

#### **Reply for comment from reviewer Abdulqadir Jeprel Naswhan 05466290**

This is a case report that highlighted a rare case of EON with very rare asymmetric clinical manifestation of both eyes and observed the development of visual function and retinal nerve fiber structure after drug withdrawal. - The manuscript within the journal's scope. - This study is well designed, executed and presented. It makes important points which are widely applicable. - The conclusion is consistent with the evidence presented - The discussion is relevant - References are up to date and relevant. – Figures are well presented

- 1、 Line no 15: no need for "According to previous studies"

**Reply:** Thanks for your valuable comments. We have deleted it.

- 2、 Lines 31 - 32: please mention the full abbreviation for the terms mentions for the first time such as RNFL, OCT, and GCIPL.



Reply: Thanks for your valuable comments. We have added the full term of abbreviation for the first time in the abstract of OCT, RNFL, and GCIPL.