

## Authors' reply

We thank Yi Du and Wenjing Luo and Stefan Gingele and colleagues for sharing their thoughts on the diagnostic criteria for optic neuritis <sup>1</sup>. Both letters raise the important issue of application of the criteria, and particularly testing for a relative afferent pupillary deficit (see video 1) in people with binocular optic nerve pathology.

The criteria allow for a diagnosis of possible optic neuritis can be made based on the clinical assessment alone. We aimed to keep the criteria simple and avoid exclusive reliance on paraclinical measures, firstly because it can be hard to access in low-income countries, and secondly a decision regarding acute treatment may be required before ancillary tests are available.

Our clinical criteria detail three clinical scenarios of increasing complexity (A to C) <sup>1</sup>. Du and Luo highlight that some people with optic neuritis do not experience pain (scenario B in panel 1) and others can have binocular loss of vision (scenario C in panel 1). Figure 1A in our paper shows that a relative afferent pupillary deficit can be unreliable in binocular optic neuritis; this point was explained in more detail in the main text<sup>1</sup> and we elaborate on it further in this reply (see also supplementary figure and video 2).

Gingele and colleagues point out that a relative afferent pupillary deficit was absent in 43/52 (83%) of people previously diagnosed with optic neuritis in their multiple sclerosis cohort. One factor that might contribute to the relative afferent pupillary deficit not being observed, especially in mild cases, is that the test is qualitative, examiner-dependent and has pitfalls (see video 3).

The excellent retrospective analysis performed by Gingele and colleagues is highly informative and precisely what is needed to test the diagnostic criteria and enable their future refinement. Interpretation of such data need to take into consideration that absence of evidence is not evidence for absence. As exemplified clinically for the relative afferent pupillary deficit, this consideration also applies to colour vision testing and taking a history of pain, which is subjective. According to Figure 1 A (e) of the Position Paper<sup>1</sup>, only a diagnosis of possible optic neuritis or exclusion of optic neuritis can be made from Gingele and colleagues cohort because of the retrospective nature. Therefore, to move forward on the suggestion to broaden the diagnostic role of paraclinical tests to reach a diagnosis of definite optic neuritis, cohorts should be reassessed prospectively using our criteria and such a validation study may also consider to include OCT<sup>2</sup> which was not mentioned in either letter. Validation studies must also expand from cohorts of

predominantly White people with multiple sclerosis to include the entire spectrum of people with optic neuritis seen around the world.

We also agree with the other points raised by Du and Luo, regarding the optic neuritis subgroup NMO-ON in relation to ethnicity, need for speedy and accurate of diagnosis, and the benefit of ultra rapid initiation of corticosteroid treatment. The Position Paper elaborates on these points. We also agree that binocular optic neuritis is frequent in the Chinese population, although in our experience, the proportion at first presentation (31/158 people between 01.01. to 31.12.2022, at the Beijing Tiantan Hospital, Capital Medical University, Beijing, China; (Yaou Liu, unpublished) is less (20%) of that quoted by Du and Luo for the Nanning Region (30% of 41 cases between 2003-2009) in China<sup>3</sup>. The high prevalence of aquaporin 4 antibody seropositivity among East Asian populations as compared with White people makes this antibody test an important investigation in both populations, and the difference in acute management emphasises the importance of the bedside assessment<sup>4</sup>.

In conclusion, validation studies will be needed to appraise the sensitivity and specificity of the clinical signs of optic neuritis alongside the paraclinical tests. Specificity was prioritised in the first version of the diagnostic criteria with the aim to improve sensitivity in future revisions.

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## **Declaration of interest**

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Liu, Yaou: has nothing to declare

## References

- [1] Petzold, A.; Fraser, C. L.; Abegg, M.; Alroughani, R.; Alshowaier, D.; et al. (2022). *Diagnosis and classification of optic neuritis*, *The Lancet Neurology* 21 : 1120-1134.
- [2] Oertel FC, Z. H. and MotamediS, e. a. (2022). *Diagnostic value of intereye difference metrics for optic neuritis in aquaporin-4 antibody seropositive neuromyelitis optica spectrum disorders*, *J Neurol Neurosurg Psychiatry* . doi:10.1136/jnnp-2022-330608
- [3] Du, Y.; Li, K.; Yang, J.; Xu, X.; Li, J.-J.; Zhou, R.-W.; Zhang, Y.; Jiang, B.-L. and He, J.-F. (2012). *Disc swelling and mild initial visual acuity loss predict a better short-term visual acuity outcome in bilateral acute optic neuritis.*, *J Clin Neurosci* 19 : 1380-1382.
- [4] Hickman, S. J. and Petzold, A. (2021). *Update on Optic Neuritis: An International View*, *Neuro-Ophthalmology* 46 : 1-18.