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Absence of Decussation in Optic Pathway Inflammation in Neuromyelitis Optica and Its Implications for Astrocyte Localization

Joshua P. Harvey, MA (Oxon), BM, BCh, Jonathan Hart, MA (Oxon), BCh, MRCS, FRCR, Jacqueline Palace, BM, FRCP, DM, Eoin P. O'Sullivan, MD, MRCP, FRCOphth

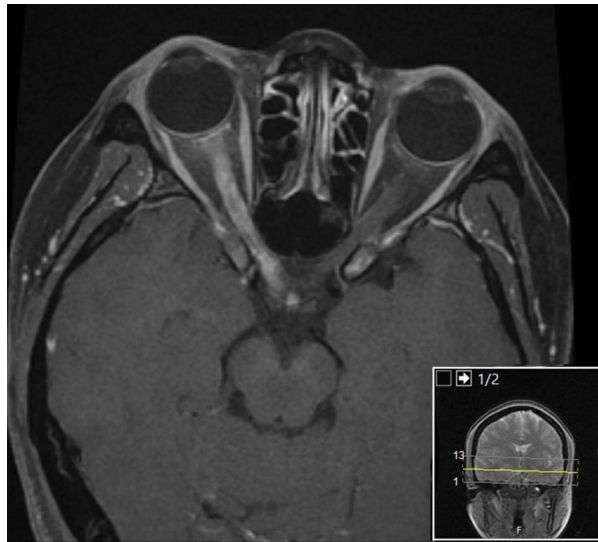


FIG. 1. Axial image from a contrast T2 head MRI demonstrating long unilateral tract inflammation.

Abstract: A 39-year-old woman presented with acute visual loss in her right eye. Brain and orbit MRI demonstrated T2 hyperintensity along a long section of her right optic nerve, chiasm, and tract with no evidence of decussation of the inflammation. Subsequent seropositivity for the aquaporin 4 antibody confirmed a diagnosis of neuromyelitis optica. Posterior pathway involvement is typical in neuromyelitis optica and supports the hypothesis that the condition is an astrocytopathy. Furthermore, the absence of decussation in the condition may be a function of astrocyte localization within the chiasm.

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King's College Hospital NHS Foundation Trust (JPH, JH, EPOS), London, United Kingdom; King's College Hospital (JPH), Denmark Hill, Brixton, London, United Kingdom; and Nuffield Department of Clinical Neurosciences (JP), Oxford, United Kingdom.

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The authors report no conflicts of interest.

Address correspondence to Joshua P. Harvey, MA (Oxon), BM BCh, King's College Hospital, Denmark Hill, Brixton, London SE5 9RS, United Kingdom; E-mail: joshua.harvey@doctors.org.uk

A 39-year-old Chinese woman awoke with acute loss of vision in the right eye accompanied by retro-orbital pain, which worsened on eye movement. Before this, the patient reported intermittent pain as well as positive visual phenomena. The patient had no other neurological symptoms. The patient otherwise had no medical history, no ocular history, was not taking any regular medications, and had recently traveled to China 3 months previously but had been living in the United Kingdom for 12 years. She was a nonsmoker, did not report recreational drug use, and worked in a restaurant.

On initial examination, the patient had no perception of light in the right eye and vision was 6/6 in the left eye. There was a right relative afferent pupillary defect and the left eye had normal pupillary reactions, visual fields, and color vision. There was mild right disc edema with a normal disc appearance in the left eye. The rest of the neurological examination was normal.

Blood tests including ESR, CRP, electrolytes, liver profile, ferritin, ANCA, ANA, rheumatoid factor,

dsDNA, and serum protein electrophoresis were all normal. Additional serological testing for *Toxocara*, *Mycoplasma*, *Brucella*, *Bartonella*, *Toxoplasma*, CMV, HIV, Lyme, Mumps, EBV, *Treponema*, Measles, and acid-fast bacilli were all normal. Lumbar puncture demonstrated a normal opening pressure of 12 cm H₂O with normal white cells, glucose, and protein. An MRI of the brain and orbits showed a T2 high signal change in the intraorbital and prechiasmatic right optic nerve, the right optic chiasm, and right optic tract. The left optic nerve, chiasm, and tract were otherwise normal.

The patient was initially treated with IV methylprednisolone 500 mg daily for 3 days, commencing on day 2 of admission, followed by 60-mg oral prednisolone. Aquaporin 4, AQP4 antibodies were subsequently found to be positive. After steroid treatment, vision improved to hand movements in the right eye and the retro-orbital pain resolved. Repeat MRI brain and orbits on day 20 of admission demonstrated a reduction in T2 hyperintensity. The patient was subsequently started on long-term azathioprine.

F1–F3

This patient's initial MRI (Figs. 1–3) demonstrated involvement of the right optic nerve, chiasm, and tract without any involvement of the contralateral tract. A radiographic 12-patient case series, which mapped optic pathway involvement in NMOSD, supports the notion that the absence of decussation of optic pathway inflammation is typical in neuromyelitis optica spectrum disease, NMOSD (1). Of these cases, 2 cases replicated our patient with ipsilateral nerve, chiasm, and tract involvement. Seven cases showed only nerve and chiasm involvement and the remaining 3 cases demonstrated bilateral nerve, tract, or chiasm involvement. No cases demonstrated involvement of the optic nerve with unilateral

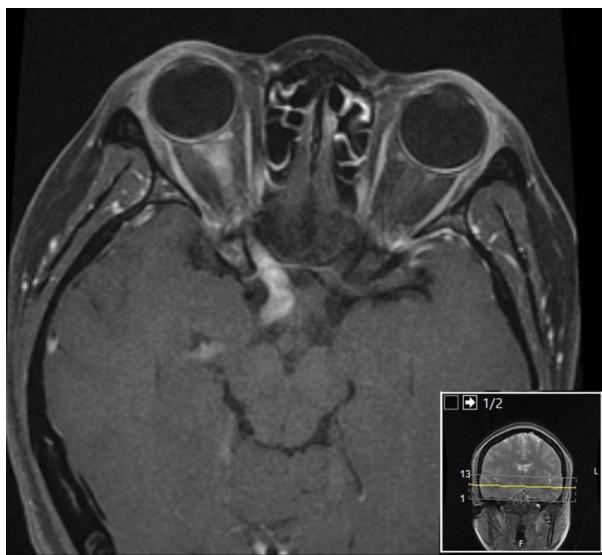


FIG. 2. Axial image from a contrast T2 head MRI demonstrating long unilateral tract inflammation.

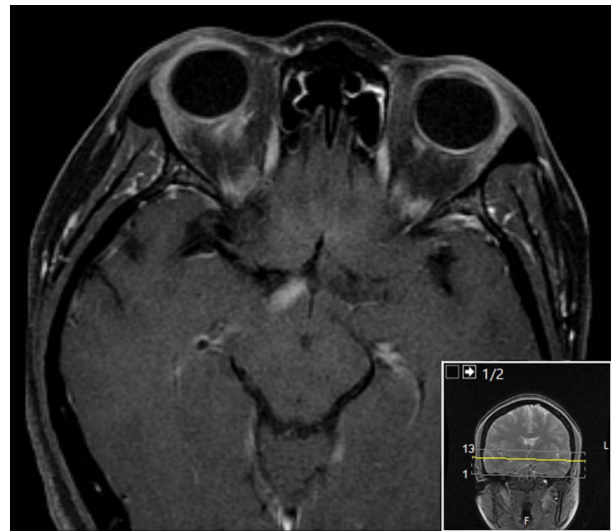


FIG. 3. Axial image from a contrast T2 head MRI demonstrating long unilateral tract inflammation.

contralateral tract involvement. Furthermore, we could not identify any reported cases of apparent decussation of inflammation. We hypothesize that this pattern of anterior optic pathway inflammation, typical in NMOSD, is due to astrocyte localization within the chiasm.

In 75% of NMOSD patients, there is seropositivity for IgG binding AQP4 (2). AQP4 is a transmembrane protein that regulates transmembrane water flux. AQP4 is highly expressed in astrocytes found in the brain, spinal cord, and optic nerves. Astrocyte localization within the optic tract is therefore likely to influence the localization and pattern of inflammation (2). This hypothesis is supported by the observation that the anatomical localization of AQP4 within the brain and spinal cord correlates with patterns of disease involvement (3). We believe that the localization of astrocytes within the anterior optic pathway explains both the pattern of nerve involvement and the absence of decussating neuroinflammation seen in our case report.

Inflammation in NMOSD seems to have a greater predilection for optic tract involvement in comparison with multiple sclerosis/optic neuritis (1). This clinical observation may be explained by astrocyte localization; studies in the mouse optic tract have shown that astrocytes exist in higher concentrations in the posterior visual pathway (towards the latrogeniculate nucleus). Furthermore, within the optic nerves, tracts, and lateral chiasm, astrocytes are arranged longitudinally, parallel to the nerve fascicles in the interfascicular space (Fig. 4) (5). However, within the medial chiasm, glial cells take on a radial morphology where they form a palisade at the ventral midline. These glia may provide a physical barrier to the spread of inflammation, or they may be resistant to AQP4-mediated disease due to different protein

F4

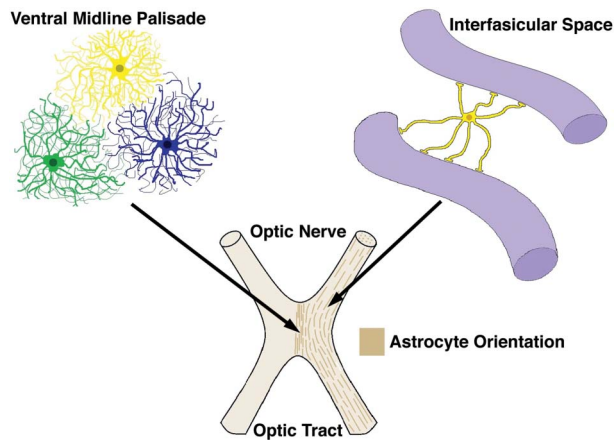


FIG. 4. Schematic demonstrating the differing central and lateral astrocyte morphology within the anterior optic pathway.

expression (5). This patient demonstrated a pattern of long-tract involvement without decussation, which is typical in NMOSD. We hypothesize that the localization of astrocytes within the optic tract explains the absence of decussation seen in NMOSD.

STATEMENT OF AUTHORSHIP

Category 1: a. Conception and design: J. P. Harvey, J. Hart, J. Palace, and E. P. O'Sullivan; b. Acquisition of data: J. Hart and E. P. O'Sullivan; c. Analysis and interpretation of data: J. P. Harvey, J. Hart, J. Palace, and E. P. O'Sullivan. Category 2: a. Drafting the manuscript: J. P. Harvey, J. Hart, J. Palace, and E. P. O'Sullivan; b. Revising it for intellectual content: J. P. Harvey, J. Hart, J. Palace, and E. P. O'Sullivan. Category 3: a. Final approval of the completed manuscript: J. P. Harvey, J. Hart, J. Palace, and E. P. O'Sullivan.

REFERENCES

1. **Storoni M**, Davagnanam I, Radon M, Siddiqui A, Plant GT. Distinguishing optic neuritis in neuromyelitis optica spectrum disease from multiple sclerosis: a novel magnetic resonance imaging scoring system. *J Neuro Ophthalmol*. 2013;33:123–127.
2. **Grabner DJ**, Levy M, Kerr D, Wade WF. Neuromyelitis optica pathogenesis and aquaporin 4. *J Neuroinflammation*. 2008;5: **AU3**
3. **Misu T**, Fujihara K, Kakita A, Konno H, Nakamura M, Watanabe S, Takahashi T, Nakashima I, Takahashi H, Itoyama Y. Loss of aquaporin 4 in lesions of neuromyelitis optica: distinction from multiple sclerosis. *Brain*. 2007;130:1224–1234.
4. **Lee MA**, Sitko AA, Khalid S, Shirasu-Hiza M, Mason CA. Spatiotemporal distribution of glia in and around the developing mouse optic tract. *J Comp Neurol*. 2019;527:508–521. **AU4**
5. **Mason CA**, Sretavan DW. Glia, neurons, and axon pathfinding during optic chiasm development. *Curr Opin Neurobiol*. 1997;7:647–653.