Case Report

Retrograde trans-synaptic visual pathway degeneration in multiple sclerosis: A case series

Omar Al-Louzi, Julia Button, Scott D Newsome, Peter A Calabresi and Shiv Saidha

Abstract

Background: Trans-synaptic degeneration (TSD) describes the propagation of neuronal injury through synaptic pathways in the human nervous system and may be linked to the accelerated retinal atrophy seen in multiple sclerosis (MS).

Results: We report six cases where homonymous, hemi-macular ganglion cell + inner plexiform (GCIP) thickness reduction was seen in conjunction with posterior visual pathway lesions. Macular microcystoid changes of the inner nuclear layer (INL) were seen in a subset of three subjects.

Conclusion: Our findings highlight the utility of assessing regional GCIP changes to identify potential retrograde TSD in MS and demonstrate that INL changes may be an accompaniment in such instances.

Keywords: Relapsing/remitting, T2 lesions, MRI, atrophy, retina, optical coherence tomography

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Introduction

A putative mechanism of neuronal injury is trans-synaptic degeneration (TSD); a term referring to degeneration of neurons connected through a synaptic cleft to a distant primary degenerating neuron. Retrograde TSD of the visual axis has been described following occipital lobe damage due to stroke.1 In patients with multiple sclerosis (MS), prior studies have described a trend of association between retinal axonal degeneration and posterior visual pathway white matter (WM) lesions,2 as well as visual cortex gray matter (GM) volume.3 The integrity of the retinal ganglion cell layer, which harbors the neuronal bodies of optic nerve axons, can be estimated with optical coherence tomography (OCT) through the composite thickness of the ganglion cell + inner plexiform (GCIP) layers.4 We have previously described that homonymous hemi-macular thinning of the GCIP can be seen in relation to thalamic lesions involving the lateral geniculate nucleus (LGN).4 However, depictions of retrograde TSD in individual cases stemming from lesions beyond the LGN, involving the optic radiation or visual cortex, with objective retinal hemi-macular atrophy are limited. Furthermore, whether such possible patterns of TSD are limited to the innermost layers of the retina or may extend beyond the ganglion cell layer remains undetermined. Herein, we report six cases with evidence of neuroinflammatory injury to the posterior visual pathway on routine brain magnetic resonance imaging (MRI) demonstrating likely retrograde TSD characterized by a homonymous, hemi-macular pattern of GCIP thickness reduction on OCT, with evidence of macular microcystoid pathology (MMP) of the inner nuclear layer (INL) over a similar topographic distribution in a subset of eyes.

Cases

A total of six cases consistent with possible retrograde TSD of the visual pathway were identified. A diagnosis of relapsing–remitting multiple sclerosis (RRMS) was made in all six cases. The demographic and clinical characteristics are summarized in Table 1. No prior history of optic neuritis (ON) in either eye was present for any of the cases. The majority of patients reported visual symptomatology. Patients 1 and 2 described intermittent episodes of bilateral visual blurring that were insidious in nature and not categorized as an acute relapse. In contrast, patients 3–6 reported an acute onset of visual field difficulties consistent with homonymous hemianopia that was characterized as a relapse of inflammatory disease activity. This was confirmed by neuro-ophthalmological assessment and automated perimetry testing.

Correspondence to:
Shiv Saidha
The Division of Neuroimmunology and Neurological Infections, Department of Neurology, The Johns Hopkins Hospital, Pathology 627, 600 North Wolfe Street, Baltimore, MD 21287, USA.
ssaidha2@jhmi.edu
Omar Al-Louzi
Julia Button
Scott D Newsome
Peter A Calabresi
Shiv Saidha
The Division of Neuroimmunology and Neurological Infections, Department of Neurology, The Johns Hopkins hospital, Baltimore, MD, USA
Brain MRI revealed multifocal, WM T2 hyperintensities (including variable involvement of the posterior visual pathways) with a distribution and morphology consistent with a clinical diagnosis of RRMS (Figure 1 and Table 1). OCT demonstrated topographically matching patterns of homonymous, hemi-macular GCIP thickness reduction. Patients 1–3 also exhibited lacunar areas of hyporeflectivity within the INL (characteristic of MMP) in a similar retinal distribution (Figure 1), which did not cross the vertical meridian of the macular cube scans (Videos 1 and 2).

**Discussion**

We describe a cohort in which discrete areas of injury to the posterior visual pathway were related topographically to hemi-macular GCIP thickness reduction. Four of the patients exhibited evidence of central nervous system (CNS) inflammatory injury in the optic radiation and/or visual cortex, whereas in two cases, involvement of the LGN was suspected, although the possibility of terminal optic tract involvement cannot be excluded.

There is accumulating evidence from OCT and MRI studies to suggest the presence of TSD in patients with MS. Previous investigations have reported anterograde TSD of the optic radiations following ON. In contrast, our report highlights the capacity for neuroinflammatory lesions in the posterior visual pathway to result in changes suggestive of retrograde TSD at the level of the retina characterized by reduction in hemi-macular GCIP thicknesses. This sheds light on mechanisms underlying the accelerated retinal neuronal loss seen in MS in the absence of ON. We describe how examination of regional, hemi-macular GCIP thicknesses might serve utility in localizing presumably destructive neuroinflammatory pathology in the LGN or the posterior visual pathway, which is in contradistinction to peripapillary retinal nerve fiber layer thickness (RNFL) thickness where hemi-macular axonal segregation is less distinct. A few limitations do exist, however, and may explain why hemi-macular atrophy is not seen as frequently in MS even in the presence of lesions that may seemingly involve the posterior visual pathways. It is plausible that retrograde TSD may be related to the severity of axonal damage, primary neuronal loss, or anatomical location within the optic radiations or visual cortex. In our report, this was exemplified by case 1 in which the occipital lesion was associated with focal atrophy of the GM (implying neuronal loss) and case 2 in which the lesion was T1-hypointense (signifying axonal destruction). It is important to note that the presence of prior history of ON, especially if bilateral, subclinical optic nerve lesions, or local retinal inflammation would hinder the capability of OCT to detect co-existing retrograde TSD due to extensive, diffuse injury to the GCIP layer. Furthermore, the detection of retrograde TSD on OCT relies on differential and relative thinning of adjacent hemi-macular sectors which

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**Table 1. Summary of demographic and clinical characteristics.**

| Case no. | Sex/age, years | Clinical presentation | Disease duration, years | MRI lesion features | Site of GCIP thickness reduction | MMP | Lag timea | Time between MRI and OCT |
|----------|----------------|-----------------------|-------------------------|--------------------|---------------------------------|-----|-----------|--------------------------|
| 1        | M/37           | Intermittent blurred vision | 4                       | Left occipital WM associated with focal volume loss | Left-temporal, right-nasal | Present | 6m       | 6m                       |
| 2        | M/34           | Intermittent blurred vision | 8                       | Right occipital WM involving the juxtacortical U-fibers, T1-hypointense | Right-temporal, left-nasal | Present | 2y 4m   | Same day                 |
| 3        | F/39           | Left homonymous hemianopia | 7                       | Right occipital WM | Right-temporal, left-nasal | Present | 7y 2m   | 5y 9m                    |
| 4        | F/49           | Left homonymous hemianopia | 10                      | Right occipital WM abutting the posterior horn of the lateral ventricle | Right-temporal, Left-nasal | Absent  | 3y 10m  | 3y 10m                   |
| 5        | M/33           | Left homonymous hemianopia | 3                       | Right inferior thalamus | Right-temporal, left-nasal | Absent  | 3y 7m   | 1m                       |
| 6        | F/40           | Left homonymous hemianopia | 1                       | Right thalamus | Right-temporal, left-nasal | Absent  | 3m      | 2m                       |

GCIP: ganglion cell + inner plexiform layer; m: month; MMP: macular microcystoid pathology; OCT: optical coherence tomography; RRMS: relapsing–remitting multiple sclerosis; GM: gray matter; WM: white matter; y: year.

aLag time denotes the time between symptom onset and the first OCT scan revealing hemi-macular GCIP thickness reduction.
Figure 1. MRI and OCT findings: (a) case 1: FLAIR imaging showing a lesion in the left occipital white matter (red inset, arrow) associated with focal volume loss (red inset, arrowheads). OCT imaging revealed homonymous, hemi-macular GCIP thinning and MMP (red insets); (b) case 2: MPRAGE image showing a T1-hypointense lesion in the right occipital white matter extending into the adjacent striate cortex, which appears atrophic relative to the contralateral side (red inset). The lesion appeared T2 hyperintense on FLAIR imaging (green inset), while OCT showed homonymous, hemi-macular GCIP thinning and MMP; and (c) case 4: FLAIR image showing a right periventricular T2 hyperintensity extending into the occipital white matter in a patient who presented with left homonymous hemianopia. OCT images performed 4 years after presentation revealed hemi-macular GCIP thickness reduction without evidence of MMP. FLAIR: fluid-attenuated inversion recovery; OCT: optical coherence tomography; GCIP: ganglion cell + inner plexiform layers; MMP: macular microcystoid pathology; MPRAGE: magnetization-prepared rapid-acquisition with gradient echo; N: nasal; T: temporal.

Video 1. Homonymous, hemi-macular microcystoid changes: macular cube video of the left eye of case 1 showing the appearance of hemi-macular right-nasal and left temporal MMP. Of note, the MMP did not cross the vertical meridian. MMP: macular microcystoid pathology.
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would be compromised if the optic radiations were bilaterally and symmetrically involved. It is also plausible that mild posterior visual pathway lesions may cause subclinical degeneration of retinal neurons that may not be accurately captured with gross visual screening of OCT images. However, it must be borne in mind that this study represents a cross-sectional case series suggesting the occurrence of TSD within the visual pathways, which does not encompass the timeline of TSD per se. As a result, longitudinal studies are required to more formally address this in the future.

A growing list of neurological disorders have been purported to result in MMP of the INL, including MS, neuromyelitis optica, and Leber’s hereditary optic neuropathy.\(^6\)\(^-\)\(^9\) In parallel, several theories have been proposed to explain MMP, including retrograde TSD, retinal traction, and/or Müller cell dysfunction.\(^9\) Importantly, the MMP observed in this case series (patients 1–3) was directly underlying areas of hemimacular GCIP thinning without crossing the vertical meridian to the relatively unaffected side (Videos 1 and 2) suggesting a link between the two forms of pathology. Our findings raise the possibility that retinal ganglion cell dropout may instigate MMP development in the pathway undergoing TSD. Theoretically, this may represent a common denominator among a wide variety of neurological disorders that injure the visual system. Another etiology worth considering is that MMP may result from glial or Müller cell activation triggered by ganglion cell death.\(^10\) However, three out of six patients in this cohort demonstrated a manifest pattern of TSD of the GCIP layer without evidence of apparent, concurrent MMP. Therefore, it is conceivable that ganglion cell death solely may be insufficient to explain the occurrence of MMP in neurological conditions and that other temporal and susceptibility factors may play a role.

In summary, our findings illustrate that retrograde TSD stemming from posterior visual pathway lesions may be detected on OCT as hemimacular GCIP thinning with or without MMP in a proportion of RRMS patients. The cascade of events separating GCIP pathology from MMP development remains unclear, and future research might help uncover cellular mediators behind this finding. Ultimately, a comprehensive understanding of the mechanisms of TSD and neuronal death in MS will help elucidate the neuronal circuitry’s response to axonal injury guiding novel targeted interventions and neuroprotective strategies.

**Author contribution**

Dr Al-Louzi: data collection, drafting, and concept of manuscript. J. Button: data collection, drafting, and revision of manuscript. Dr Newsome: data collection, drafting, and critical revision of manuscript for important intellectual content. Dr Calabresi: drafting and critical revision of manuscript for important intellectual content. Dr Saidha: concept of manuscript, drafting and critical revision of manuscript for important intellectual content.
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Commentary on retrograde trans-synaptic visual pathway degeneration in MS: A case series

Ahmed Toosy

Keywords: Trans-synaptic degeneration, visual pathways, optic radiations, optical coherence tomography

Neurodegeneration in multiple sclerosis (MS) is an important determinant of the accrual of clinical disability. Many mechanisms are thought to interact and contribute to this phenomenon.1,2 There has been recent interest in MS in investigating trans-synaptic degeneration. The visual system, in principle, lends itself as an informative model to study this phenomenon across the lateral geniculate nucleus (LGN) synapses.

Most in vivo imaging studies in MS or clinically isolated syndrome (CIS) have performed cross-sectional