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LETTER TO THE EDITORS

Retrograde degeneration of visual pathway: hemimacular thinning of retinal ganglion cell layer in progressive and active multiple sclerosis

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Dear Sirs,

Afferent visual pathway extends from retinal ganglion cells (GC) to the primary visual occipital cortex. Anterodegeneration of visual pathway, known as Wallerian degeneration (dying forward) is exemplified by glaucoma [1] and optic neuritis (ON) affecting visual pathway [2, 3] and visual cortex [4]. Retrograde degeneration (dying back) has recently been recognized in multiple sclerosis (MS) [5–7] as result of accessibility of optical coherence tomography (OCT) on monitoring first-order neurons in the retina, and magnetic resonance imaging (MRI) to examine second- and third-order neurons in the brain [8]. Here we report longitudinal studies on two patients to illustrate retrograde degeneration and translate the concept into clinical practice.

Case 1 is a 33-year-old woman who at age 26 developed visual hallucinations, paresthesia, allodynia and weakness in the left leg. Brain MRI revealed 10 supratentorial demyelinating lesions bilaterally including one in the left optic radiation (OR). Eight of the lesions were gadolinium enhanced. Cerebrospinal fluid (CSF) showed mononuclear pleocytosis and oligoclonal IgG bands (OBs). Ophthalmological examination including fundus, inner eye pressure, visual acuity, color vision, perimetry and visual-evoked potential (VEP) was normal. After five years on natalizumab without clinical relapse or new MRI lesion, positive JC-virus motivated switch to fingolimod. One year later, perimetry revealed right homonymous hemianopia (Fig. 1). MRI showed >10 non-enhanced lesions including one in the left OR (Fig. 1) and 3 new subcortical lesions. OCT demonstrated bilaterally reduced GC layer (GCL) of left homonymous hemimacula (Fig. 1) consistent with right homonymous hemianopia and lesion in left OR. Bilateral retinal nerve fiber layer (RNFL) thinning was also registered by OCT. Six months later, additional thinning of hemimacular GCL (right 4 μm; left 3 μm) and RNFL (right 6 μm; left 2 μm) was registered. Ophthalmological examination revealed no sign of ON.

Case 2 is a 49-year-old woman who in 1988 had ON in the left eye. In 1998 she developed diplopia, numbness and weakness in both legs. Brain MRI revealed multiple demyelinating lesions in the cerebral hemispheres and brain stem. CSF showed mononuclear pleocytosis and OBs. Treatment with interferon-beta was started. She had relapse in 2013 with increased spasticity in the left leg and bilaterally blurred vision. EDSS had increased from 1 to 2.5. MRI revealed bilateral demyelinating lesions supra- and infratentorially including two Gd-enhanced lesions and one new lesion in the left OR (Fig. 2). OCT before relapse showed normal GCL in the right eye (Fig. 2) and diffuse GCL thinning in the left eye, reflecting previous ON. During relapse, hemimacular GCL thinning in right eye developed successively over 4 months, followed by plateau at four examinations over next 12 months. Fundus, perimetry and VEP of right eye were normal. Natalizumab therapy was started in March 2014.

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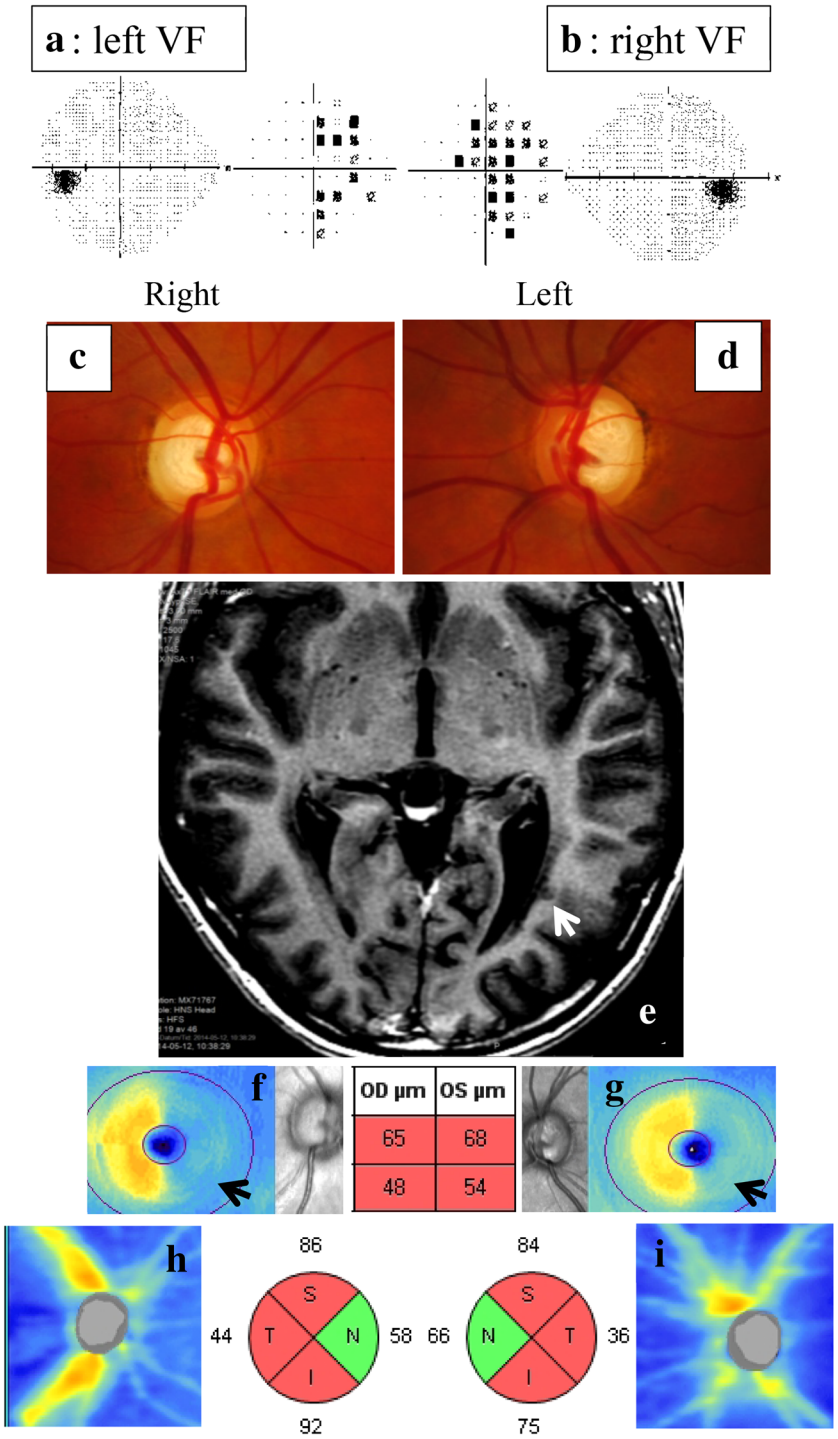

Fig. 1 Images from case 1. Humphrey-automated visual fields (VF) show right homonymous hemianopia (**a**, **b**). Fundus view shows normal optic disk (**c**, **d**). Three tesla (3 T) axial T1 MRI (**e**) reveals a hypointense lesion in the left optic radiation (white arrow). Retinal imaging was performed using SD Cirrus HD-OCT (model 4000). Ganglion cell layer (GCL) thickness is the sum of GCL and inner plexiform layer (IPL) and obtained using Macular Cube 512 × 128 protocol. Peripapillary retinal nerve fiber layer (RNFL) thickness was obtained using optic disk cube 200 × 200 protocol. Color-coded GCL thickness map (bright = thicker, dark = thinner) reveals initial left homonymous hemimacular GCL thinning (**f**, **g**; *black arrows*) which is in progress 6 months later. Color-coded RNFL thickness map reveals initially thinned RNFL in both eyes, most marked temporally (**h**, **i**) which is also in progress

OR damage is frequently detected in MS by ultra-high-field MR and associated with RNFL thinning [8]. Longitudinal monitoring of retinal GCL and RNFL by OCT in our two MS patients enabled us to follow development of retrograde degeneration of visual pathway in relation to clinical relapse, and occurrence of new and Gd-enhanced lesions on MRI. GCL thinning associated with posterior visual pathway lesions has unique pattern of homonymous hemimacula on OCT corresponding to lesions in retrochiasmal visual pathway, and is consistent with clinical homonymous hemianopia contralaterally [9, 10]. Hemimacular GCL thinning can accelerate during progressive MS or develop parallely with new OR lesion.

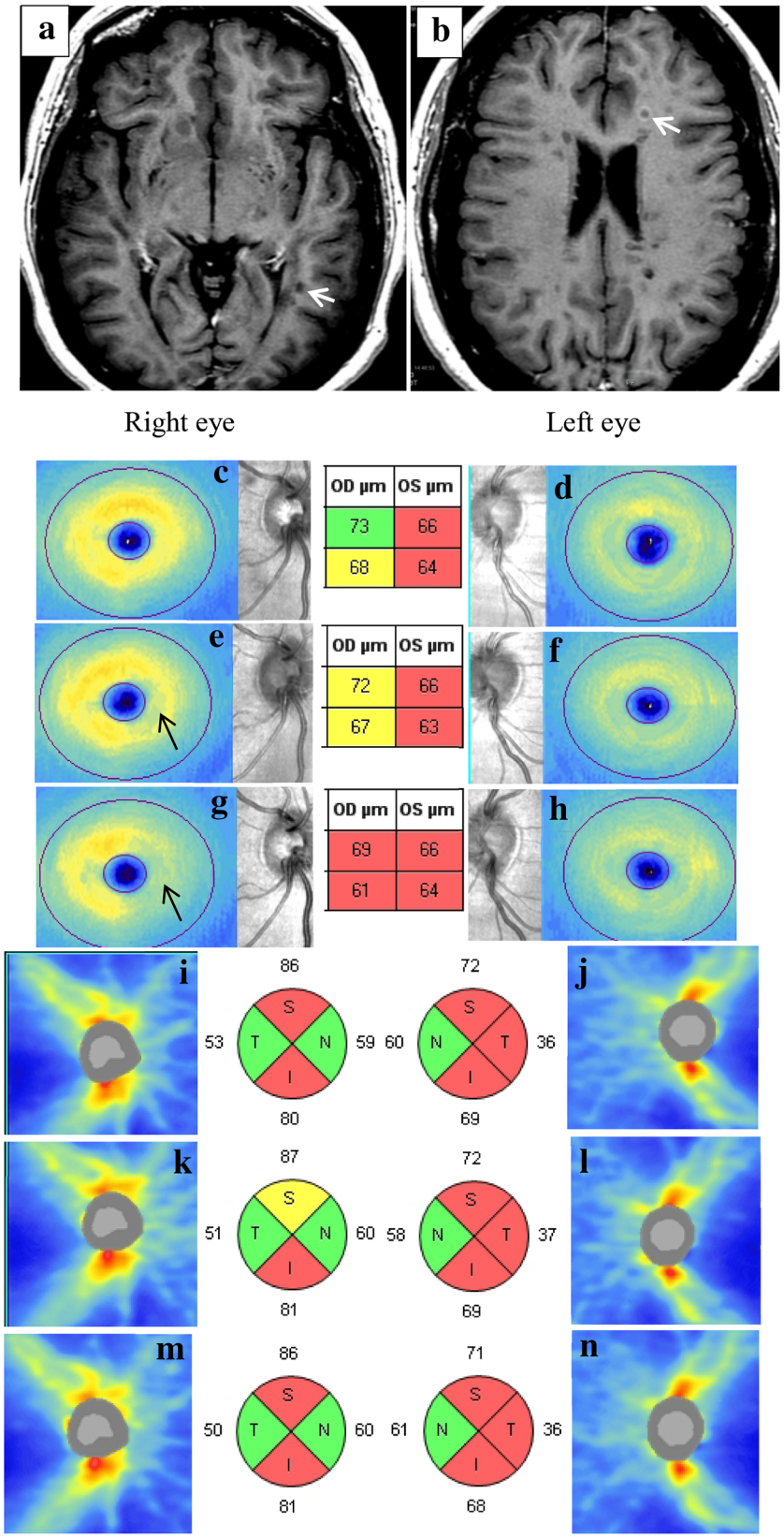

Fig. 2 Images from case 2. 3 T axial T1 MRI reveals one lesion (*black hole*) (**a**) in the left optic radiation (*arrow*) and one left-side subcortical Gd-enhanced lesion (**b**). Using SD Cirrus HD-OCT (model 4000), color-coded thickness map of ganglion cell layer (GCL) and peripapillary retinal nerve fiber layer (RNFL) (bright = thicker, dark = thinner) initially shows normal GCL thickness in the right eye (**c**) and diffusely thinned GCL in the left (**d**) due to previous ON. Within 2 months of MS relapse with increased EDSS and new lesion in the left optic radiation on MRI, thinning of nasal hemimacular GCL thickness was observed in the right eye (**e**, *black arrow*), and continued up to 4 months (**g** *black arrow*). Diffuse thinning GCL thickness in the left eye remained unchanged 2 and 4 months after MS relapse (**f**, **h**). Slightly thinned RNFL in the right eye (**i**) and markedly thinned RNFL in the left eye (**j**) are initially registered. RNFL thickness in both eyes remains unchanged (**k**–**n**). Stable OCT parameters are thereafter observed at next four examinations over following 12 months (data not shown)

Although retrochiasmal lesions often cause non-persistent visual field defects or asymptomatic homonymous hemianopia [11, 12], insidious retrograde trans-synaptic degeneration with acceleration can relate to progressive, active MS subclinically and clinically. With the help of OCT, retrograde degeneration can be monitored in the retina at micrometer level and performed more frequently, especially in clinical trials.

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Conflicts of interest The authors declare no conflict of interests.

Ethical standard The study was approved by the Ethical Committee of the Linköping University, Sweden, study number is 2013/141-31.

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