Three “red lines” for pattern recognition based differential diagnosis using OCT in clinical practice

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Optical coherence tomography, retinal layer atrophy, oedema, Acute Zonal Occult Outer Retinopathy (AZOOR), Alzheimer disease, branch retinal artery occlusion (BRAO), Disorders of Cognitive Impairment, epilepsy, Foster-Kennedy syndrome, glaucoma, motor neuron disease (MND), mouche dormant, multiple sclerosis, neurodegeneration, neuroretinitis, ischemic optic neuropathies, optic neuritis, Parkinson disease, retrochiasmal lesions, stroke.
Abstract

Background: Optical coherence tomography (OCT) devices for imaging of the eye are broadly available. The test is non-invasive, rapid and well tolerated by patients. This creates a large number of OCT images and patient referrals. Interpretation of OCT findings at the interface between neurological and ophthalmological conditions has become a key skill in the neuro-ophthalmology service. Similar to the interpretation of visual fields a vertical and horizontal median are helpful. A third red line is added which will be reviewed here.

Evidence: Levels 1a to 5 evidence.

Acquisition: Literature research.

Results: There is level 1a evidence that neurodegeneration of the brain is associated with inner retinal layer atrophy. Predominantly this is driven by retrograde (trans-synaptic) axonal degeneration from the brain to the eye. This process typically stops at level of the inner nuclear layer (INL). Anterograde (Wallerian) axonal degeneration from the eye to the brain can trespass the INL. The geography of atrophy and swelling of individual macular retinal layers distinguishes pre- from post-chiasmal pathology. The emerging patterns are a Front-Back “red line” at the INL; a vertical “red line” through the macula for chiasmal / post-chiasmal pathology; a horizontal “red line” through the macular for pathology pointing to the optic disc. This is summarized by illustrative cases vignettes.

Conclusion: The interpretation of patterns of individual retinal layer atrophy (three “red lines”) needs to be combined with recognition of localized layer thickening (edema, structural) at the macula. Certain macular patterns point to pathology at the level of the optic disc. This requires revision of the optic disc OCT and will guide need for further investigations. The three “red lines” proposed here may be found useful in clinical practice and the related mnemonics (“half moon”, “sunset”, “rainbow”) for teaching.
Introduction

This review will first start with an overview of the recent literature on the association between the retina with neurodegeneration and neuroinflammation. This will cover key findings from research in multiple sclerosis (MS) and optic neuritis (ON). In this context neuroretinitis and an new easily overlooked, benign finding at the vitreoretinal interface (“mouche dormant”) are discussed as well as glaucoma. Special focus is given to Alzheimer's Disease (AD). This is followed by other CNS degenerative conditions including Parkinson disease (PD) and motor neuron disease (MND) or amyotrophic lateral sclerosis (ALS). There patterns of retrograde trans-synaptic axonal degeneration (RTD) in epilepsy and stroke which suggest a window or opportunity for treatment. Taken together the literature reveals patterns of OCT changes which can be readily recognized.

For didactic reasons case vignettes will be used to discuss in great detail the OCT findings. The patterns discussed can be broken down into macular inner retinal layer atrophy resulting in three “red lines”. For illustration “red lines” will be used in the Figures. For bedside teaching I found an unconventional mnemonic approach helpful (Figure 1). The “half moon” sign indicate need for potentially urgent brain imaging as primary neurological pathology is likely (Figure 1A). The “sunset” sign is more common with opthalmological pathology (Figure 1B). Finally, the “rainbow” sign (Figure 1C) aids to distinguish primary neurological from ophthalmological pathology in case of a “sunset” or more complex patterns of inner retinal layer atrophy. The proposed system of three “red lines” is internally consistent.

OCT protocols

The OCT data in this review are from the macula and optic disc. Most commonly a volume scan of the macula is combined with a peripapillary ring scan [1]. Additional information can be obtained from a optic nerve head volume scan, B-scans placed through the region of interest (ROI) and autofluorescence. The reader should bear in mind that it can be very challenging to obtain reliable quantitative OCT data in patients who cannot easily sit still, are disabled, and/or cannot visually fixate. A simple trick to overcome at least the latter is to make use of proprioception. One always can move, for example, a patients finger and ask to look at where the patient thinks her/his finger tip is. This works reliably even in a blind person.

Retinal layers and neurodegeneration

The anatomy of the retina is hierarchical and already clearly described by Santiago Ramón y Cajal who also performed detailed investigations on the progression of anterograde and retrograde axonal degeneration through retinal layers [1]. Retinal OCT does permit for an in vivo approximation of retinal layers as summarised in detail [2]. For this review relevant is the retinal nerve fiber layer (RNFL). This layer is clearly visible as a highly reflective band shown in Figure 2. Loss of axons in the RNFL impress as thinning of this layer also shown in Figure 2. All axons of the RNFL converge at the optic disc. After the axons passed through the cribiform plate they become myelinated and form the optic nerve. Next, these axons synapse in the dorsolateral geniculate nucleus (LGN) to become the optic radiations.
(Meyer's loop) which reach the primary visual cortex in the occiput. Damage to the visual cortex, optic radiations or optic nerve sets off a process called retrograde axonal degeneration (RTD). The first case vignette discussed introduces the retinal layer anatomy [2] and abbreviations used in this review in great detail (Figure 2 A-Z).

There is direct RTD and trans-synaptic RTD [3]. Direct RTD is due to damage of the axons originating from the retinal ganglion cell layer (GCL). Clinically, this is most frequently due to pathology of the optic nerve. As will be reviewed here, this is a rapid process. In contrast, trans-synaptic RTD is due to damage to the visual posterior pathways, that is after the LGN. It takes more time for neurodegeneration due to trans-synaptic RTD to cause atrophy in the retina than for direct RTD [3]. Both processes cause atrophy of the RNFL as shown in Figures 2-4. Important for this review is to remember that the atrophy progresses to involve the inner plexiform layer (IPL) and the GCL. Generally progression of atrophy due to RTD stops at level of the inner nuclear layer (INL) as illustrated Figure 2. Therefore the first “red line” introduced in this review to help with pattern recognition of OCT in neurological disorders is at level of the INL.

**Selection and sequence of diseases selected for this review**

In order to illustrate the point made above on RTD further the OCT findings of trans-synaptic RTD are reviewed in multiple sclerosis, followed by a review of direct RTD in optic neuritis. Because of the clinical relevant differential diagnosis in the post-infectious setting also OCT findings in neuroretinitis are discussed. Neither of these conditions permits to describe anterograde axonal degeneration for which reason an acquired large blind spot syndrome is reviewed. Bespoke “red line” at the INL is trespassed in this example. Clinically another, benign, condition can be confused with optic neuritis, but is easily recognized by OCT.

The second section reviews primarily neurodegenerative conditions. Glaucoma was chosen not only because it is so frequent, but also because it permits to return to the “red line” at level of the INL from a primarily ophthalmological perspective. And importantly, introduce the second “red line” as a red flag for longterm monitoring of these patients. Next in the neurodegenerative section, Alzheimer disease was chosen because of frequency and the opportunity to make a point about the importance of high quality OCT. This point is further enforced by a review of OCT data from two other neurodegenerative conditions, Parkinson disease and amyotrophic lateral sclerosis. In none of the neurodegenerative conditions there is validated progression of retinal layer atrophy beyond the INL, which is the first “red line”.

In contrast, to the more easily timed events due to brain surgery and stroke were pivotal to introduce the concept of RTD to OCT and deserve their own, the third, section.
1. Demyelination and selected differential diagnosis

Multiple Sclerosis

Contemporary understanding is that the primary pathology in MS is demyelination with a neurodegenerative component due to axonal loss [4]. High frequency, longitudinal quantification of axonal loss in vivo was challenging until OCT filled this void. Over the last two decades OCT has become a surrogate marker of CNS neuroaxonal integrity in MS patients [5; 6]. Patterns of atrophy in MS can be seen in the inner retinal layers. The RNFL, GCL and IPL are all reduced in thickness. The INL can be increased in thickness. The underlying mechanisms depend on location and age of the MS lesion. MS lesions located in the area of the visual cortex or Meyer’s loop set off slow RTD [7]. Much quicker in contrast is direct retrograde axonal degeneration due to MS lesions in the dorsolateral LGN, optic tract or optic nerve [8]. In general retrograde axonal degeneration in the visual system of patients with MS stops at the INL (“rainbow”) [9].

Thickening of the INL in MS is not yet fully understood. There are indications that INL edema is related to increased inflammatory disease activity [10; 11]. Even more pronounced thickening can present as microcystic macular edema (MME) [12]. Interestingly recovery of INL edema has been observed in patients with MS who are treated successfully [13]. The transient nature of INL edema and MME in many can be explained by inner retinal fluid transport through the retinal glymphatic system [14], which has just been shown to exist experimentally [15].

There is a large number of correlative studies underpinning and cross-validating the value of OCT as an outcome measure for neurodegeneration in MS. There is also potential for measures of retinal asymmetry in MS and MS optic neuritis (MSON) to be considered as a supportive diagnostic test [16-19].

Part of the success of OCT in MS is due to a network approach on early development of quality control criteria [20; 21] which were followed by validation steps [22] and made it into reporting guidelines [23]. The key point is that the amount of annual inner retinal layer atrophy rates (~0.5 um/year) is below the spacial resolution of the OCTs used in clinical routine (~3-7 um). Therefore it is paramount to reduce measurement noise to permit for meaningful statistical analyses on a group level. Confidence in the group level data is justified by two meta-analyses covering two generations of OCT technologies [24; 25].

Finally, swept source OCTA now permits for imaging of the retinal and choroidal vasculature alike. This permits for a more detailed analysis of the increasingly recognized contribution of vascular pathology in MS. In addition to the documentation of reduced density of the microvasculature this may serve to investigate the “virtual hypoxia hypothesis” as a cause for neurodegeneration [26].

Optic neuritis

The evidence to date indicates that peripapillary RNFL (pRNFL) damage in ON is substantial
and that it takes about three months for pRNFL damage to manifest [27]. The three months rule has informed the design of longitudinal cohort studies and clinical trials in ON [28]. It was not until introduction of spectral domain OCT, that the much earlier degeneration of the macular GCIPL (mGCIPL) was recognized [29]. There are data which suggest that mGCIPL atrophy can be detected within eight to eleven days after onset of visual loss and can precede reliable detection of pRNFL atrophy [30; 31]. As with MS RTD stops at the INL (“rainbow”) as illustrated in the second case vignette (Figure 3 H-I). There is also scope for OCTA and functional assessment of outer retinal layers to contribute [32]. It should be investigated if high frequency OCT/OCTA imaging in a cohort of patients with acute optic neuritis permits to capture subgroups without optic disc swelling, mGCIPL atrophy preceding pRNFL atrophy and electrodiagnostic features of early retinal ganglion cell dysfunction [33; 34]. Comprehensive analysis of the time course of these variables will help to advance our knowledge on the timing and progression of neurodegeneration in optic neuritis.

Neuroretinitis

Optical coherence tomography provides an imaging correlate to the classic macular star in neuroretinitis [34; 35]. Reports on OCT findings in neuroretinitis remain anecdotal [36-38]. In my own experience I have seen the reported hyper-reflective dots migrate through the retina. The migrating hyper-reflective dots are clearly distinct to those hyper-reflective dots we come now to recognize as retinal capillaries using OCTA [32]. The dynamic of this process in an own case is shown in a short video (see supplementary material). It is suggested that this represents a phenomenon related to migrating inflammatory pathology in the retina.

AZOOR spectrum

The large blind spot syndromes include the Acute Zonal Occult Outer Retinopathy (AZOOR) [39]. The OCT features in AZOOR have are well recognized and consist of disruption of the inner outer segment and changes on auto-fluorescence [40; 41]. For OCT research AZOOR provides a model for the study of acquired anterior axonal degeneration in the retina which starts distal to the INL. This is relevant because, in contrast to RTD which generally stops at the INL, anterior axonal degeneration appears to be more aggressive [42]. Anatomically, this is thought to be related to convergence and divergence of the visual pathways. The more axons converge to one neuronal layer (e.g. the INL), the more likely this layer is affected by propagation of anterior trans-synaptic axonal degeneration.

Mouche dormant – a not uncommon pitfall

There are pitfalls to the interpretation of symptoms and sings in patients which result in unnecessary referrals. One example is a mouche dormant (pre-foveal floater). A tiny mouche dormant can readily be recognized on OCT, but not by slit lamp examination [43]. For a patient to be symptomatic there needs to be a shadow cast dense enough to cause a scotoma. If the scotoma reduces visual acuities than this will also change the ERG and VEP signal. It is precisely because this combination of VEP/ERG data with visual symptoms that a misdiagnosis of optic neuritis can be made.
2. Neurodegenerative conditions

Glaucoma

The distinguishing feature of glaucoma to other optic neuropathies is the pattern of visual field loss associated with the characteristic image of the excavated optic nerve head [44]. With around 65 million people affected worldwide, glaucoma is likely the most prevalent neurodegenerative condition [44]. The optic nerve head appearance is so characteristic that the first international consensus classification for global epidemiological studies incorporated this as the first criterion (see Box 33.1 in [44]). The two main risk factors for glaucoma are age and an increased Intraocular pressure (IOP, i.e. > 21 mmHg) [45; 46]. There is primary open-angle glaucoma (POAG) and primary angle-closure glaucoma (PACG), as well as a long list of secondary glaucoma which includes treatment with corticosteroids, uveitis and other inflammatory conditions, tumors, trauma and pigment dispersion. The most common for is POAG accounting for about 86% of all glaucoma cases [44]. Glaucoma can also present with normal IOP which opens up a discussion on the pressure gradient between the IOP and intracranial pressure [47]. All types of glaucoma result in trans-synaptic axonal degeneration which can be depicted by OCT and magnetic resonance imaging (MRI). The signal changes of the optical pathways in the MRI brain scans from patients with glaucoma are generally a sign of anterior axonal degeneration. For quantification of structural disease progression in glaucoma there is a role for OCT [48]. There is also an emerging role for OCTA and AI in glaucoma [49]. Because of the pattern of progression a region of interest (ROI) approach has important advantages over more global OCT metrics [50]. Because glaucoma is chronic most patients are followed up lifelong accounting for an estimated 23% of all follow-up attendances in a UK hospital eye service [44]. In a small proportion of these patients a vertical “red line” will emerge in the macular OCT (see Figure 4). In these cases a “half moon” shall always prompt for further investigations including prolactin levels and MRI brain imaging. This is an important role the neuro-ophthalmology services can fulfill working together with the glaucoma service.

An important differential diagnosis to glaucoma and optic neuritis are the ischemic optic neuropathies [51]. Two of the “red lines” are helpful for pattern recognition in this context. Both, a branch retinal artery occlusion (BRAO, Figure 5 A-G) and an anterior ischemic optic neuropathy (NAION, Figure 6 A-F) can produce the “sunset” sign. The difference between the two is that the INL is atrophied with a BRAO, but not NAION where pathology occurs at the optic disc.

The other addition in this age group relates to impaired higher visual function in patients in whom there is a substantial mismatch between the structural appearance of the optic nerve head and the visual fields due to a dementia.

Alzheimer Disease and Disorders of Cognitive Impairment

In clinical practice referrals to a neuro-ophthalmology service of people suspected to suffer from cognitive impairment are due to a mismatch between structure and function. There is a body of literature showing that difficulties with visual fields can be due to a neurodegenerative dementia. The textbook example is posterior cortical atrophy (PCA) or
Benson’s disease. Most people with PCA will develop Alzheimer disease in the long term. Of course Alzheimer disease can co-exist with glaucoma and indeed there is a genetic overlap in common genetic variants associated with an increased risk [44]. The resulting overlap in care for these patients has contributed stimulating early research on OCT in AD [52]. One intriguing hypothesis is that of amyloid deposition in the retina of patients suffering from AD [53]. In addition, and similar to what has been described in PD interest on OCT in AD has also been influenced by melanopsin driven hypotheses on neurodegeneration [54]. A critical appraisal of the early, mainly time domain dominated OCT literature and subsequent spectral domain OCT reveals however a publication bias [55]. Because the effect size is very small there is need for making use of big data. The large United Kingdom Biobank study suggests that is likely that the association between progressive inner retinal layer atrophy and progression of cognitive decline is associated with a wider clinical spectrum than pure AD alone [56]. In contrast to the research published in the field of MS which makes use of OCT quality control criteria [20], such a rigorous approach has yet to be adopted by OCT research in the dementia field. The degree of inner retinal layer atrophy in dementia [55] is much less than in MS [25; 57] and high quality scans even more important.

Parkinson disease
A stimulating discovery in the field was a novel opsin in the eye, melanopsin [58; 59]. Melanopsin is related to melanin, which is deficient in patients suffering from Parkinson disease (PD). Therefore a hypothesis is that lack of melanopsin may be associated with retinal layer atrophy similar to the association between melanin and the substantia nigra [60]. The effect size is small as demonstrated in a recent meta-analysis [61]. There is more to vision in PD than OCT alone [62] and cognitive impairment is relevant [63].

Amyotrophic Lateral Sclerosis / motor neuron disease
There is interesting, statistically correlative work on inner retinal layer atrophy in MND / ALS [64-66]. More research is needed as it is difficult to understand what the underlying biological mechanism should be. Why should the macular RNFL thickness correlate with the forced vital capacity percent predicted and forced expiratory volume as suggested [66]? Whilst more research is needed, in our own experience, patients with ALS are not easy to image because of the rapid disease progression. Frequently, re-positioning of the patients head at the OCT chin rest already difficult early in the disease course. Therefore follow-up imaging can be extremely challenging.

3. Insights on onset and progression of RTD

Epilepsy
There are two reasons for changes to the OCT in epilepsy: drug toxicity and surgery. Neurotoxicity of vigabatrin on retinal ganglion cells had been demonstrated by OCT [67; 68]. Epilepsy surgery can damage Meyer’s loop [69]. It is impossible to completely prevent this complication. As part of their routine assessment patients have a visual field examination
and OCT before and after surgery [3]. Longitudinal data shows the presence of truly acquired RTD in humans. By matching the visual field with the macular OCT highly accurate ROI specific OCT atrophy analysis becomes possible [3]. This permits to extract three patterns of axonal degeneration: (a) direct retrograde axonal degeneration which is very quick; (b) rapid RTD which is self-terminating within less than one year; (c) prolonged RTD which persists for more than one year [3]. The difference between the two last patterns relates to the size of the lesion to Meyer’s loop. Larger lesions trigger a mechanism of RTD which cannot be captured by a short equation because the underlying biological process is most likely governed by spatial cellular stoichiometric relationships between glia, neurons and axons. It is possible that there is a potentially salvageable ‘penumbra’ area [3]. The challenge for future research in the field is to now demonstrate that there are successful neuroprotective strategies to rescue this ‘penumbra’. If shown as a ‘proof of principle’ in patients with epilepsy surgery, the approach may be expanded to other diseases such as MS.

Stroke
A stroke causes trans-synaptic axonal degeneration [70]. The changes observed for the pRNFL are clearly visible on OCT and progress over time [71]. Since it has become easier to demonstrate patterns and progression of RTD in stroke by analyzing the mGCIPL [72]. Similar to the data from epilepsy a time window of progression of RTD is emerging which might be relevant for future treatment strategies.

The risk of a cerebrovascular disease and stroke is increased in patients with vascular pathology of the retina [73]. The risk of stroke is substantially increased in patients with a retinal artery occlusion (RAO) [74]. Clinically the challenge is to separate embolic from non-embolic etiologies of monocular visual field loss [75]. Pattern recognition in OCT is helpful to do so as was illustrated already in the two case vignettes with vascular pathology (Figures 5 and 6).

Perinatal pathology
There are very important insights from the association of perinatal damage to the visual pathways and the resulting OCT findings [76]. Generally speaking the degree of RTD quantified is more profound compared to RTD brain lesions acquired later in live. The final case vignette 4 in this review is one example where the “half moon” is shown to persist for life (Figure 7 A-G). There is a an opportunity to study the pattern of retinal atrophy in the context of perinatal pathology in much more detail as the literature remains largely anecdotal [76-78]. Yet, OCT findings in this context almost always result in a patient referral.

Three red lines for clinical practice
This literature review at the interface between neurology and ophthalmology suggested that the INL acts as a tight barrier for RTD and a more permissive barrier for anterograde axonal degeneration. The understanding of the different dynamics of these pathologies is relevant. For the daily clinical practice there are three red lines which had been illustrated in detail in the case vignettes. The patterns reviewed were all due to a individual retinal layer atrophy.
The three red lines are aligned in a 3D space with respect to the macular. The first red line is vertically through the macula (Figure 1A), the second red line is horizontally through the macula (Figure 1B) and the third red (front-back) aligned to the INL (Figure 1C).

Summary
It is concluded that in clinical practice there are three red lines through the macular which indicate patterns of atrophy aid with the differential diagnosis, reviewed here, as presented in summary table (Table 1).

Acknowledgments
I want to apologies to those colleagues who I was unable to cite due to space restrictions, but who have made important contributions to the field, either directly or indirectly.

References


Table 1
Overview on how three red lines help with the interpretation of the macular OCT. The relevant differential diagnosis discussed in this review is presented. The spectrum of the differential diagnosis can readily be expanded using the same approach. The OCT of the macular always needs to be interpreted together with the OCT of the optic disc. Recommended investigations in support the differential diagnosis are listed for consideration. As a mnemonic and for bedside teaching “beware of the half moon” (Figure 1).

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<th>Recommended</th>
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<td>(N)AION, Glaucoma, pathology at disc</td>
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<td>“Rainbow”</td>
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<td>Above INL</td>
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<td>BRAO, PAMM</td>
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Figures

Figure 1

Anatomy and mnemonics for the three “red lines” used in this review. (A) The “half moon” sign which if recognized should trigger (urgent) brain imaging. This is because lesion to the visual pathways at the chiasma or retro-chiasmal will cause atrophy of the inner retinal layers (RNFL to GCIPL) which leaves the impression of a vertical line on the macular OCT thickness map in both eyes. (B) The “sunset” sign which leaves the impression of inner retinal layer atrophy through the macular which is distributed horizontally. This generally points to vascular pathology leaving an altitudinal pattern or other pathology at the optic disc. (C) The “rainbow” sign which helps to separate inner retinal atrophy due to retrograde trans-synaptic axonal degeneration as can be seen with a range of primary neurological pathologies from more likely retinal pathology. This “red line” stops at level of the INL in all neurological conditions reviewed.
Figure 2

**Patterns of retinal layer changes in a patient with Pseudo Foster-Kennedy Syndrome.**

A 49 year old man presented with slowly progressive loss of vision in his left eye (OS). On examination visual acuity was count finger only on the right (OD), there was complete dyschromatopsia and a right relative afferent pupillary deficit (RAPD). Fundus examination showed a pale optic disc (OD) and a swollen optic disc (OS). An urgent computed tomography (CT) scan of the head revealed a colloid cyst in the third ventricle causing raised intracranial pressure. A diagnosis of a pseudo Foster-Kennedy syndrome was made, a ventriculo-peritoneal shunt was inserted and septum pellucidotomy performed. Disc swelling (OS) resolved and visual function was preserved (logMAR -0.2, Ishihara 17/17, normal visual fields). Post-surgical OCT testing demonstrated near complete atrophy of the RNFL, GCL and IPL with a preserved INL (“rainbow” sign).

The OCT at presentation shows (A) a pale disc on confocal scanning laser ophthalmoscopy (cSLO). The green ring indicates the location of the OCT B-scan shown in (B). The OCT B-scan has been segmented with the red line located at the border between the inner limiting membrane (ILM) and the top of the peripapillary RNFL (pRNFL). The horizontal green line indicates the border between the pRNFL and the GCL. The vertical green line in the OCT image is located in the papillomacular bundle (PMB) and also seen as a small line crossing the circle in the cSLO image. Blood vessels are seen as a vertical black shadow traversing all retinal layers in the OCT. There is thinning of the pRNFL. The degree of pRNFL atrophy is expressed in absolute numbers in (C). The global average from the ringscan is 75 µm (black number in red central inset). The normal average value is 97 µm (green number in brackets). In the left eye there is a (D) swollen optic disc which shows dark on the cSLO image. The disc margins are blurred, capillaries buried by swollen axons and veins engorged. The swollen axons of the (E) are also shown in the OCT. The pRNFL is thickened compared to (B) and the layer colouring becomes more greyish. There is less image contrast between the pRNFL and GCL. This explains why automated segmentation at the lower border of the pRNFL becomes unreliable. The diameter of the engorged veins (yellow asterix) is larger than in (B). The increased global average (F) pRNFL thickness of 246 µm is still an underestimate of the algorithm. Within one hour the patient had urgent brain imaging. The (G) coronal and (H) sagittal CT brain scans revealed hydrocephalus due to a colloidal cyst (yellow arrow). After neurosurgery the (I) cSLO in the left eye looks similar to (A).

**Progression of pRNFL atrophy** is much better seen in (J) the follow OCT with (K) a mean global average of only 51 µm. In contrast to the right eye, for the left (L) the cSLO clearly shows resolution of disc swelling. This is corroborated by the (M) OCT with thinning of the pRNFL, improved image contrast at the pRNFL/GCL border, normalisation of blood vessel diameters (yellow asterix) and (N) a normal global average thickness of 98 µm. On second glance however the PMB appears thinned and the pRNFL thickness in the temporal quadrant is reduced to 45 µm (red shaded area, normal value 73 µm).

The **first red line for OCT** is located at the border between the inner plexiform layer (IPL) and inner nuclear layer (INL) of the macula (O) of the right eye. The green line in the cSLO goes through the centre of the fovea. The foveola is seen as a central depression (yellow asterix) in the corresponding OCT B-scan (P). The INL is the dark layer below the brighter RNFL and IPL (yellow arrows). Within the INL there are almost black microcystic spaces (arrow heads) called ‘microcystic macular edema’ (**MME**). Retinal layer atrophy stops at the
INL (horizontal red line) In the left eye (Q) the cSLO and (R) OCT of the INL are comparable to the right with exception of absence of MME. Quantitative analysis of the macular volume scan from the right eye (S) provides evidence for severe GCL atrophy. The total volume is reduced to 0.16 mm$^3$. Absolute values are shown for volume (red numbers) and vertical thickness in μm (black numbers). The even distribution of macular GCL (mGCL) atrophy over the entire area is also appreciated visually as darker colours in the (T) heat map. As anticipated from the PMB atrophy in the left eye there is also (U) macular GCL atrophy on the left. The volume is reduces to 0.29mm$^3$. In absence of FDA approved normal values, I would have expected for this age a normal value of around 0.46 mm$^3$. Visual comparison of (V) the heat map from the left with the right eye (T) easily reveals that mGCL atrophy is more severe on the right. Finally, for the (W) INL there is a high normal absolute volume of 0.53 mm$^3$ on the right, with a (X) bright coloured heat map for the INL (red line). Likewise for (Y) the left eye the the INL volume 0.45 mm$^3$ is normal. (Z) The bright coloured INL heat map (red line) on the right is almost indistinguishable from the right or a normal healthy control subject.

In summary, this case illustrates that RTD in the setting of post-papilledema optic atrophy to the optic nerve does not progress beyond the INL. Therefore the red line is placed in plane at the upper border of the INL. This is the “rainbow” sign in Figure 1C.
**Figure 3**

**Recurrent inflammatory ON.** A 54 year old woman experienced retrobular pain OD which worsened with eye movements. She developed subacute vision loss OD (visual acuity was 20/16) over several days, which progressed to hand motion vision. Further examination revealed profound right dyschromatopsia with Ishihara plate testing, a RAPD (OD) and a central scotoma. Fundus examination showed a swollen optic disc (OD). She was started on a 3-day course of oral methylpredisolone 1,250 mg (with taper) for presumed right optic neuritis. Her retrobular pain stopped within hours after the first dose of corticosteroids and within four days visual acuity on the right recovered to 20/20. Macular OCT showed GCIPL atrophy on the right and presence of MME, whereas findings were normal OS. MRI of the brain and orbits revealed an isolated right optic neuritis (ION). She relapsed again within a week after corticosteroids were tapered off, with worsening vision OD. Again, visual acuity OD normalized to 20/20 within one week of oral predisolone treatment (1 mg per kilogram). Serology testing was positive for myelin oligodendrocyte glycoprotein (MOG) autoantibodies confirming a diagnosis of MOG-ON. She was started on long term immunosuppression with methotrexate 7.5 mg once weekly. She had one further relapse of MOG-ON on the left eye three years after first presentation. At her last follow up there was bilateral atrophy of the GCIPL with preservation of the INL and outer retinal layers (“rainbow” sign).

**The long term OCT pattern in this patient with MOG-ON shows.** (A) The macular volume scan of the right eye shows severe GCIPL atrophy between onset (volume 0.49 mm$^3$) of symptoms and four year follow-up (0.28 mm$^3$, highlighted by red). The distribution of the total loss of GCIPL volume of -0.21 mm$^3$ is indicated by the green area. Essentially all of the damage had happened in the first year. (B) The INL volume remained preserved over the four year follow up period (“rainbow”). (C) On the left the GCIPL remained stable until she experienced a relapse three years after onset. Treatment was hyperacute and GCIPL atrophy on the left much less severe than on the right (-0.11 mm$^3$). (D) Captured acutely there was mild oedema of the INL (+0.02 mm$^3$) indicated by the red shaded area. (E) The acute relapse of the left eye is captured by OCT B-scan and shows segmental swelling of the nasal and superior border of the superior pRNFL. This is appreciated on cSLO by a darker signal around the disc (yellow arrows). There is already a small amount of pRNFL atrophy visible at the inferior border (red arrow). (F) At her next follow-up the swollen superior border has normalised. There was mild increase of the segmental atrophy inferiorly. This qualitative assessment of the OCT is further explained quantitatively in (G) the thickness graph (y-axis in um) reveals the degree of pRNFL swelling (bold black line, yellow arrows) compared to her last, asymptomatic, scan (thin black line). (H) At follow-up, the quantitative output shows the extend to which the inferior border of the pRNFL (bold black line, red arrows) as atrophied compared to her last, asymptomatic, scan (thin black line) in um. Hyper acute corticosteroid treatment partly prevented extend axonal degeneration of the acutely inflamed (black arrows), swollen pRNFL seen in (E). The sequential longitudinal four year follow-up pRNFL values capturing the acute episode of MOG-ON are shown in (I). These data indicate that the pRNFL remained stable until she relapsed (yellow arrow).

In summary, this case shows that also with recurrent inflammatory pathology of the optic nerve, there is no progression of RTD beyond the INL. Again, red line is placed at the upper border of the INL ("rainbow").
Figure 4

The “Half moon” sign in a patient with glaucoma. A 56 year old gentleman with a seven year history of PAOG was referred with progressive worsening of his visual fields with normal IOPs (13 mmHg) under treatment with Latanoprost eye drops. His retinal OCT showed a “half moon”. Urgent brain imaging revealed a large, non-functioning (prolactin low at 72 mIU/L) pituitary macroadenoma. He underwent transsphenoidal surgery. Visual function remained stable over the a year follow-up period. Note that in his case hemimacular atrophy of the mGCIPL had already progressed to an extend which crosses the vertical meridian (vertical red line). Yet, the visual impression of a “half moon” (Figure 1A) looking at the yellowish coloring of the thickness map is still preserved.
Figure 5

*Differentiating Ischemic Insults of the Retina from the Optic Nerve. The case of a branch retinal artery occlusion (BRAO).* A 50-year-old woman reported a prior episode of sudden, painless loss of vision OS. Visual acuities were 20/20 in both eyes (OU). There was no RAPD. Confrontation testing showed a dense altitudinal superior visual field defect, and normal findings OD. Color vision was normal OU with Ishihara plate testing. Fundus examination showed a normal appearing optic disc OD and segmental optic disc pallor OS. Her macular OCT showed altitudinal inferior GCL and INL atrophy (“sunset”) corresponding to the superior visual field defect OS, with no retinal thinning beyond the INL (“rainbow”). Branch and central retinal arteries supply the inner retina, and retinal artery occlusions cause thinning of the entire inner retina, including the INL, in the chronic setting. In contrast, optic neuropathies will cause thinning that is limited to the RNFL and GCIP layers of the inner retina. The OCT pattern in this case localized the diagnosis of a BRAO OS, as opposed to remote anterior ischemic optic neuropathy (AION). Because of the anatomically distinct separate vascular innervation of the inner retina by the superior and inferior retinal vasculature the second red line is placed horizontally through the macular (“sunset” Figure 1B).

The (A) cSLO shows a dark area just below the fovea (yellow arrows). The horizontal green arrow-line indicates the location of the (B) corresponding OCT B-scan. The healthy, dark grey, INL is indicated by the pink arrow. The adjacent yellow arrow point out the large area of the damaged, bright grey, INL. Clinically, it helps to (C) review the cSLO image with an overlay of the heat map of the GCL thickness. The darker colouring of the altitudinal inferior area (yellow arrows) falls within the vascular territory of one branch retinal artery (pink arrow). Within this vascular territory there is severe atrophy of (D) the inferior GCL (pink circle, volumes 9-15 mm³) if compared to the superior GCL (green circle, volumes 42-44 mm³). Separation of the upper and lower macular areas is indicated by the horizontal red line. The strict horizontal altitudinal pattern of GCL atrophy is best appreciated in (E) the thickness heat map (“sunset”). With a BRAO there is also (F) altitudinal atrophy of the INL. The inferior INL (pink circle, volumes 12-13 mm³) is less compared to the superior INL (green circle, volumes 39-40 mm³). The heat map (G) shows a more fuzzy border which is due to difficulties with automated segmentation of the damaged INL. In this case the red line is placed in plane just at the lower border of the INL. That is between the INL and OPL.
Figure 6

Differentiating Ischemic Insults of the Retina from the Optic Nerve. The case of a non-arteritic AION (NAION). A 46 year old man with known diabetes and sleep apnea presented with sudden painless visual loss in his right eye. Visual acuities were 20/125 OD and 20/25 OS. There was a right RAPD. Standard automated perimetry revealed an inferior altitudinal visual field defect OD, and normal results OS. When seen acutely there was swelling of the right optic disc, which evolved into optic atrophy within 2 months. OCT testing showed preservation of the INL in NAION (“rainbow”). (A) The cSLO shows the position of the vertical B-scan adjacent to the foveola. (B) The superior altitudinal atrophy (pink arrows) of the macular RNFL and GCL is clearly visible from the same B-scan. The INL is preserved (yellow arrow). (C) The macular volume scan OD shows severe GCIPL atrophy between onset (volume 0.49 mm³) of symptoms and four year follow-up (0.28 mm³). The distribution of the total loss of GCIPL volume of -0.21 has an altitudinal pattern affecting the superior portion of the macula (“sunset”). (D) The thickness of the INL OD is preserved. (E) For comparison the normal GCL OS and (F) INL OS thickness maps are shown, too. In this case a horizontal red line is again placed through the macular (“sunset”). Note that the difference between this case and case 3 is the other red line (“rainbow”) which is now placed at the upper border of the INL because the INL is preserved.
Figure 7

Retrochiasmal Lesions. A 28 year old woman was incidentally found to have a visual field defect during a routine eye assessment by her optician. This was the first time she ever did a visual field test in her life. She was otherwise asymptomatic. Visual acuities measured 20/20 OU and color vision was normal with Ishihara plate testing. Cranial magnetic resonance imaging (MRI) showed an area of left encephalomalacia in the left occipital temporal region, presumed secondary to an in utero ischemic insult. Macular GC IPL analysis showed a homonymous pattern of left hemi-retinal thinning contralateral to the visual field defect, indicative of RTD from her post-geniculate cortical lesion (“half moon”).

The cSLO of the macula of the (A) right and (B) left eyes are shown. In both images the coloured overlay represents a heat map of the GCL thickness map. The yellow areas indicate the area of the normal GCL thickness of the preserved half of the macula. The pink arrows indicate the area of atrophied GCL. There is a clear vertical line (red line) which demarcates the homonymous hemiatrophy (“half moon”). (C) The same is seen on the horizontally taken OCT B-scan (horizontal green line in A). The normal half of the macular is highlighted by a yellow and the heimiatrophied part by a pink arrow. (D) Identical is observed for the left eye. In both eyes the INL is preserved (horizontal red line, “rainbow”) (E) This is also documented by the heat map of the INL OD and (F) OS. There is no atrophy, but mild thickening of the INL on the side of GCL hemiatrophy OD. There was no MME. (G) The MRI illustrates two areas of encephalomalacia (circles). The one circled in pink extends into the left occipital lobe. The left occipital lobe lesion is responsible for the left macular inner retinal layer hemiatrophy and the resulting right homonymous visual field defect.

In this case a vertical red line is placed through the macular (“half moon”) and a second red line (“rainbow”) at the upper border of the preserved INL.