Chapter 8
Clinical Updates and Recent Developments in Neuro-Ophthalmology

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Updates in Diagnostic Criteria/Clinical Presentation

The ability to diagnose efficiently and accurately neuro-ophthalmic conditions is imperative to guiding timely intervention. In this section, we introduce new neuro-ophthalmic diagnoses and review updates to the diagnostic criteria for previously described conditions. These updates are intended to guide clinicians in accurate examination, identification and management of commonly encountered neuro-ophthalmic conditions. The updates are outlined by subspecialty to help the reader think in terms of a differential diagnosis for conditions with similar presentations.

Updates in Neuro-immunology

Perhaps one of the most exciting areas in neuro-ophthalmology at the present time are neuro-ophthalmic diagnoses pertaining to neuro-immunology. Over the years, with the invention of magnetic resonance imaging (MRI) and the discovery of new antibodies, two of the most well-known autoimmune conditions causing optic neuritis, multiple sclerosis (MS) and neuromyelitis optica (NMO), were delineated as separate entities. The diagnostic criteria for these conditions include guidelines for clinical and imaging features as well as serum and cerebrospinal fluid (CSF) testing. Revisions to these criteria have been designed to increase the sensitivity and

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specificity for diagnosis; the most recent criteria for MS and NMO are described below. The mystery remains as to why some patients with clinical presentations similar to MS or NMO are seronegative. More recently, the clinical significance of previously described antibodies including those to myelin oligodendrocyte glycoprotein (MOG) and glial fibrillary acidic protein (GFAP) have been identified as separate, unique pathologies with presentations that may present with optic neuritis and clinically may appear to be similar to MS and/or NMO. This section will review the current literature regarding these new antibodies, the associated clinical presentations and the recommended medical management.

Multiple Sclerosis (MS)

Multiple Sclerosis (MS) is a well-known inflammatory demyelinating disease and is the single most common cause of disability in young adults, with age at onset strongly influencing the course of progression [1]. In the 1970s, when MS was first being diagnosed, there were no treatment options, and diagnosis was limited to autopsy and direct tissue examination [2]. Since then, our ability to diagnose MS has changed dramatically with the use of MRI in 2001 and subsequent updates in the clinical diagnostic criteria. In the same way, disease-modifying therapies (DMTs) have multiplied, with over a dozen DMTs currently approved worldwide over the past 25 years [2]. With an improved ability to delay or halt clinical progression, the need to diagnose and treat patients with MS earlier has become paramount [3].

The McDonald Criteria for diagnosing MS were first established in 2001 [4] but have been revised many times over the last 17 years, resulting in an increase in the number of patients diagnosed with the condition. The most recent revision of the McDonald Criteria for diagnosing MS occurred in 2017 [5]. This revision included three major changes. The first was related to the inclusion of symptomatic supratentorial, infratentorial and spinal cord lesions on MRI to meet the criteria for dissemination of lesions; previously, only asymptomatic lesions could be used. Second, if enhancing and non-enhancing lesions are found on an MRI at one point in time, this can be considered dissemination in time. Finally, a patient meeting the criteria for a clinically isolated syndrome may be diagnosed with MS if oligoclonal bands are present in the cerebrospinal fluid [5, 6].

Neuromyelitis Optica (NMO)

NMO is a rare autoimmune disease of the central nervous system (CNS) that primarily affects the spinal cord and optic nerves, leading to optic neuritis and longitudinally extending transverse myelitis. Onset is typically in the third to fourth decade of life. There is a strong female predominance with a female:male ratio as high as 9–10:1 [7]. Clinical attacks may be recurrent as is the case with MS and anti-MOG disease (see below); however, unlike MS and anti-MOG disease, it may take only one attack of NMO-related optic neuritis and transverse myelitis to leave

a patient blind and paraplegic. In other words, the disability risk with NMO is extremely high [8]. It was not until 2004 when NMO-IgG was identified as a specific marker autoantibody that can be used to distinguish MS from NMO [9]. These autoantibodies target the most abundant water channel in the CSF: aquaporin-4 (AQP4), located on the astrocytic foot processes of the blood-brain barrier [10]. Over time, it was discovered that the range of clinical presentations associated with AQP4 autoimmunity was much broader than just optic neuritis and longitudinally extending transverse myelitis [10, 11]. Subsequently, Wingerchuck et al. outlined new criteria and described NMO spectrum disorder (NMOSD). The new criteria take into account the serum status of AQP4-IgG (present, absent or unknown) and add additional requirements for patients with absent or unknown AQP4-IgG status. These requirements include specific core clinical characteristics of optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic syndrome and/or symptomatic cerebral syndrome with typical brain lesions. There also are additional MRI requirements for this group of patients [12].

New information regarding AQP4 antibody status and its relation to prognosis also has become available. A large, retrospective cohort study evaluating the efficacy of immunotherapy in NMOSD suggests that several factors, including age, antibody status and the presence of previous attacks, may predict further attacks in patients diagnosed and treated for NMOSD [8]. Indeed, the presence of AQP4 in the serum of patients with NMOSD may predict future recurrent disease as opposed to patients with seronegative presentations of NMOSD who are more likely to have a monophasic course [13].

Myelin Oligodendrocyte Glycoprotein (MOG-IgG)

Myelin oligodendrocyte glycoprotein (MOG) is a glycoprotein that is expressed on the outer membrane of myelin. This glycoprotein is specifically found within the CNS, including the brain, optic nerves and spinal cord [14]. MOG antibodies bind to extracellular glycoprotein on the myelin sheath and to oligodendrocytes [15]. First identified in the 1990s, MOG antibodies initially were identified in patients with relapsing autoimmune illness who were presumed to have MS [16, 17]. After studies revealed low sensitivity of MOG in larger MS populations, skepticism arose regarding the validity of MOG-IgG as a reliable biomarker for MS [18]. Shortly thereafter, MOG-IgG was identified in several pediatric cases of acute disseminated encephalomyelopathy (ADEM) and by 2011, the first report of MOG antibodies in NMOSD was reported [19]. Recent studies have concluded that the presence of MOG-IgG antibodies in a patient with an acute neurologic syndrome is indicative of an entity separate from both MS and NMO [20, 21]. In one study, it was stated that up to 42% of NMOSD patients who tested negative for AQP4 worldwide tested positive for MOG-IgG [14]. In another study, MOG-IgG was found in 20% of patients with a demyelinating illness that did not fit the criteria for MS or NMOSD [6].

The clinical manifestations of patients presenting with MOG-IgG are extremely variable. Perhaps because of this, several studies have reported different findings in regards to age and sex predilections as well clinical phenotype for MOG-IgG disease. MOG-IgG likely affects both men and woman equally or has a very slight female predominance and age of onset is 20–30 years of age [22, 23]. Clinically, the majority of MOG-IgG patients present with optic neuritis, with or without other accompanying neurologic symptoms. The optic neuritis may be unilateral; however, simultaneous bilateral optic neuritis can occur and may occur with higher frequency than in NMOSD [21]. Anti-MOG antibody-related optic neuritis attacks may be recurrent, with the reported number of attacks ranging from one to eight [23]. Patients who develop anti-MOG antibody-related optic neuritis tend to have an anterior optic neuritis: the fundus exam typically reveals optic disc swelling, sometimes with associated flame hemorrhages (Fig. 8.1).

Other neurologic manifestations include atypical cerebral inflammatory lesions (that may have been characterized as relapsing steroid-responsive autoimmune encephalitis in the past), ADEM, atypical MS or CNS vasculitis. Aseptic meningitis and pseudotumor cerebri (PTC)-like presentations (with elevated opening pressure) also have been reported [24]. Finally, patients with anti-MOG-IgG-associated disease are more likely to have seizures and encephalitis as part of the presentation compared with patients with AQP4-IgG-associated disease [20].

Data from several cohorts suggest that both visual and neurological outcome are favorable in the majority of cases of MOG-IgG disease; only a small number of patients are left with severe visual deficits, cognitive impairment or are wheelchair bound [22]. Phenotype at onset may predict long-term outcome including likeli-

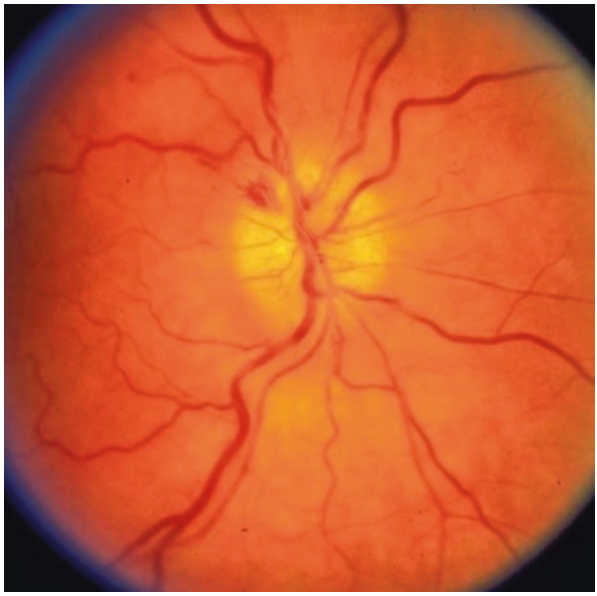

Fig. 8.1 Right optic disc of a patient with MOG-IgG-associated anterior optic neuritis. Note diffuse swelling associated with a single flame-shaped hemorrhage

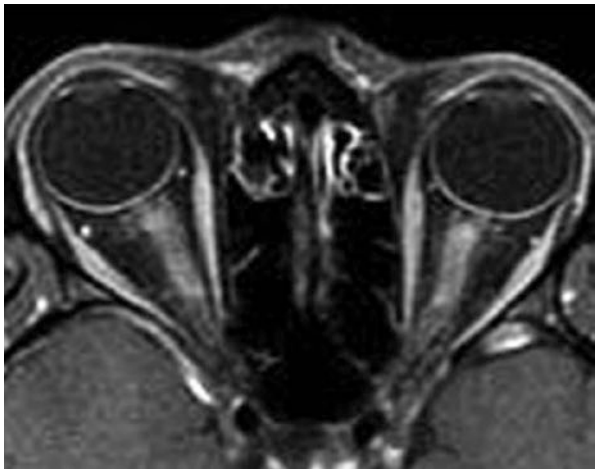

Fig. 8.2 T1-weighted, post-contrast axial MRI of a patient with bilateral, simultaneous anti-MOG antibody-related optic neuritis. Note marked enhancement of the orbital portions of both optic nerves. This is not typical of the findings in idiopathic or MS-related optic neuritis

hood for relapse; however, a large number prospective studies will be needed to determine if this is the case [22]. CSF studies in the majority of cases reveal a pleocytosis that may be mild (>5 white blood cells) to significant (≥50 white blood cells), and the CSF protein concentration may be increased.

Neuroimaging findings in patients with anti-MOG antibody-related optic neuritis include a long enhancing segment of the optic nerve including its orbital and intracranial portions (Fig. 8.2).

Some patients have perineural enhancement with extension of the enhancement into the surrounding orbital tissues [3]. In a cohort of 246 patients with recurrent optic neuritis, no patient with positive MOG-IgG showed MS-like MRI lesions [21].

In general, treatment of patients with anti-MOG antibody-related disease with systemic corticosteroids provides rapid and robust clinical improvement; however, relapse upon withdrawal of steroids is not uncommon [25]. Thus, it is recommended that treatment include a prolonged steroid taper to minimize chances of an early relapse from steroid withdrawal and that close monitoring be performed once the steroids are discontinued [14]. The finding of optical coherence (OCT) retinal nerve fiber layer (RNFL) changes in patients with anti-MOG antibody-associated transverse myelitis who have not experienced an attack of acute optic neuritis supports the need for early and sustained immunosuppression [26].

Glial Fibrillary Acidic Protein (GFAP)

GFAP auto-antibody-positive meningoencephalitis is a newly described entity for which the clinical phenotype has been described in only a small number of patients. The presentation may be subacute or chronic and is characterized by encephalitis or meningoencephalitis accompanied by bilateral optic disc swelling at initial presentation, although some variations in this presentation have been observed [27].

The cause for the bilateral optic disc swelling is unknown; however, the majority of patients do not have an elevated opening pressure on lumbar puncture. The underlying pathophysiology for GFAP autoantibody-positive meningoencephalitis is unknown but may be related to venous inflammation based on fluorescein angiography showing prominent venular leakage in one patient with this entity and the presence of radial perivascular enhancement on MRI in several patients [27]. Knock-out studies of GFAP in mice revealed local impairment in the blood brain barrier and disruption in normal white matter architecture with late onset CNS dysmyelination [28]. Patients with GFAP antibody-related neurologic disease typically have evidence of inflammation and GFAP-IgG in their CSF.

GFAP antibody-positive neurologic disease tends to be very steroid responsive, with the majority of patients showing improvement in their optic disc swelling and MRI lesions after a course of high-dose intravenous corticosteroid treatment followed by a prolonged oral steroid taper. The optic disc swelling in these patients has been reported to be visually asymptomatic, although arcuate visual field deficits after treatment and resolution have been observed [27]. It is not yet known if GFAP-IgG occurs in isolation or if it co-exists with other demyelinating diseases such as MS and NMO.

Recurrent Optic Neuritis

MS previously was recognized as a major cause of recurrent optic neuritis [21]; however, more recently, the glial antibodies AQP4 and MOG-IgG also have been recognized as important contributors. AQP4 IgG has been reported to be present in the serum in 8.3–25% of patients with recurrent optic neuritis [29, 30]. In addition, it is known that patients with anti-MOG antibody-associated optic neuritis tend to experience recurrent attacks. One cross-sectional cohort study of 246 patients with recurrent optic neuritis reported that one-third of all patients had a positive glial antibody (either MOG-IgG or AQP4) [21]. The same study concluded that that AQP4-IgG seropositivity predicts a worse visual outcome than MOG-IgG seropositivity, double seronegativity (ie, idiopathic recurrent optic neuritis), or MS. Interestingly, although the relapse rate of recurrent optic neuritis is higher in MOG-IgG-positive patients compared with patients with MS and NMO, the visual prognosis is better [21, 31]. Recurrent optic neuritis may behave differently in the glial antibody diseases compared with MS-related recurrent optic neuritis. Although recurrent optic neuritis in patients with MS tends to attack the same optic nerve that initially was affected, glial antibody-associated recurrent optic neuritis appears to be randomly distributed between the two optic nerves [32].

Chronic relapsing inflammatory optic neuropathy (CRION) is a recurrent optic neuritis that is steroid responsive and is a rare cause of subacute and recurrent painful vision loss unrelated to demyelinating or connective tissue disease [33]. This diagnosis should be made with extreme caution and only after extensive testing and imaging. In the previously discussed cohort of 246 patients with recurrent

optic neuritis (see above), 4/14 patients with CRION tested positive for MOG-IgG, whereas no patient tested positive for AQP4 or had an MS-like phenotype. Patients with recurrent optic neuritis who have negative MOG-IgG and AQP4 but who also do not fulfill criteria for MS pose a diagnostic and management challenge, especially as the probability of permanent vision loss is higher in this group compared with MS or MOG-IgG-positive patients. Unfortunately, there are no specific treatment recommendations for this subset of patients. Most are treated with systemic corticosteroids, with other immunosuppressive agents used when necessary.

Conclusion and Recommendations

The differentiation of these various entities causing optic nerve and CNS inflammation and demyelination remains crucial due to the difference in optimum treatment approach and both visual and neurological outcomes. Especially in the case of MS and NMO, incorrect management can potentially lead to worsening of the disease course. At this time, our recommendation would be to start with the diagnostic criteria for MS and NMO. If the presentation is atypical or does not fulfill the above criteria, proceed with MOG testing. MOG testing has a 98.5% specificity but 1.5% of healthy controls testing positive for MOG-IgG [34]. The sensitivity for MOG testing is much lower, ranging from 5% in MOG to about 36% in ADEM cases [14]. International guidelines for diagnosis and testing in MOG were published in 2018 and recommend testing for MOG-IgG in patients in whom at least minimal clinical criteria are met. The minimal criteria include an attack of optic neuritis, transverse myelitis or brainstem lesion; objective evidence of a demyelinating process detected by MRI or optical coherence tomography (OCT); and other typical findings of MOG-IgG disease, including a longitudinally extensive lesion in the optic nerve or spinal cord [35]. These guidelines also give recommendations for "red flags" if the result comes back positive in atypical presentations.

Complete neuro-ophthalmologic evaluation, MRI brain and orbits (and in appropriate cases cervical and thoracic spine) with and without contrast and optical coherence tomography also should be performed for all patients. Treatment appropriate for the diagnosis should be initiated early.

In regards to monitoring, we recommend that all of these patients be followed with OCT. Optic neuritis causes substantial retinal damage and vision loss independent of the underlying disease. Ganglion cell/internal plexiform layer damage begins close to clinical onset and, thus, the structure-function correlations between OCT and vision make OCT an important tool for monitoring acute optic neuritis [36]. The utility of OCT to differentiate among MS, NMOSD, and anti-MOG antibody-related optic nerve disease is still poorly understood. Various studies have presented controversial results including equal RNFL thinning in both anti-MOG-IgG and AQP4-related disease [37, 38], increased thinning of the RNFL in AQP4 compared with MOG disease [39]. A recent study showed RNFL thinning to be similar in MS, MOG, and idiopathic optic neuritis [36].

Neuro-Degenerative Diseases

Parkinson Disease

The clinical diagnosis of Parkinson disease (PD) emphasizes the motor manifestations and cardinal signs of tremor, bradykinesia, rigidity and postural instability. Perhaps because of this, visual signs and symptoms have been under-recognized. In fact, non-motor symptoms, including visual complaints, impact a patient's quality of life significantly and may predict progression and disease outcomes [40].

Ophthalmic findings in PD are likely related to the loss of dopaminergic neurons with accumulation of alpha synuclein in the retina [41], or related to a disturbance of cortical visual processing from intracranial loss of dopaminergic neurons and accumulation of alpha synuclein. Visual impairment has been suggested as a marker for early diagnosis of PD [42] and can be recognized by neuro-ophthalmic exam. Thus, the role of a neuro-ophthalmologist is very important in the early identification of PD and other parkinsonian presentations. Below is a summary of the visual problems seen in PD with clinical implications and influence of levodopa therapy.

Color Vision—Color vision deficiencies have been reported in PD patients who are not treated with a dopaminergic drug [43]. The gold standard test for assessing color deficiencies is the Farnsworth-Munsell 100 Hue Test; however the results are influenced by cognitive difficulties and motor deficits [44, 45]. Interestingly, color vision impairment also is present in patients with Rapid Eye Movement (REM) sleep behavior disorder (RBD), an early manifestation of alpha synucleinopathies, In the case of RBD, color vision deficiency is a risk factor for disease conversion to PD [46] and also may predict rapid disease progression [44]. Patients with the LRRK2 gene mutation of PD have more color impairments compared with patients with idiopathic PD [47]. Levodopa therapy may improve color vision in PD patients [48].

Visual Contrast Sensitivity—PD patients may experience problems with contrast sensitivity in relation to both static and moving stimuli [49]. Worsening contrast sensitivity is related to disease progression [50] and is partly reversible with levodopa therapy [51, 52].

Saccades—Patients with PD often make hypometric reflexive (visually guided) and voluntary (memory-based) saccades [53, 54]. Clinically, instead of making accurate saccades to a target, the patient makes several small saccadic movements to reach it [55]. Such patients also may have difficulty initiating memory-guided saccades [56] and performing anti-saccades [57, 58]. The amplitude of voluntary more than reflexive saccades is reduced with PD disease progression [54], whereas the latency of visually guided saccades worsens in early disease stages but then stabilizes [54]. Levodopa therapy has little to no effect on changing saccadic amplitude. Although levodopa may shorten the latency for voluntary saccades, it also prolongs the latency of reflexive saccades [54].

Smooth Pursuit Eye Movements—Smooth pursuit may be impaired in healthy elderly patients in general [59] but also in patients of all ages with PD [60, 61]. Reduced pursuit gain has been identified in early and untreated patients with PD [62]. The efficacy of dopaminergics in improving smooth pursuit is unclear, with

some authors suggesting improved pursuit gain [59, 63] and others finding no improvement [64].

Convergence Insufficiency—Reduced convergence amplitude is a common finding in PD [65, 66]. Such patients often have horizontal binocular diplopia when attempting near tasks such as reading and sewing. Convergence amplitude and near point of convergence measurements are better when evaluated in PD patients during the "on" state compared to the "off" state, possibly suggesting that dopaminergic therapy may be useful for this symptom [67]. Other patients may benefit from convergence exercises, converging (base-in) prisms, extraocular muscle surgery, or simply occluding the lower portion of one of their spectacle lens with tape.

Stereopsis—PD patients with abnormal stereopsis show worse motor functions, supported by higher scores on the unified PD rating scale (UPDRS) compared with PD patients with abnormal stereopsis [40]. Depth perception deficits correlate with color deficiencies in patients with PD [68]. Stereopsis impairment in PD has been associated with a faster cognitive decline [69] and suggests disease progression [68]. It is also a predictor for dementia in PD patients at 24 months [69].

Ocular findings in PD for which there are no data regarding the utility in determining progression or prognosis include square-wave jerks and ocular tremor (ocular oscillations in antiphase to the direction of a head tremor during fixation) [70]. Visual hallucinations in PD previously were thought to correlate with levodopa therapy; however, minor hallucinations have been reported in PD patients naive to levodopa therapy and in premotor phases of PD as well [71]. Because visual hallucinations have been associated with abnormalities in color vision and contrast sensitivity [72], they may suggest disease progression and also may reflect impending dementia or even impending psychosis later in the course of the disease [40]. Nevertheless, caution is warranted in attributing visual hallucinations to worsening disease, as they may be a medication side effect.

Progressive Supranuclear Palsy (PSP)

In 2017, the Movement Disorder Society put forth a new set of recommendations for diagnostic criteria of PSP [73]. These criteria identified four functional domains, with ocular motor dysfunction being one of the four along with postural instability, akinesia and cognitive dysfunction. The ocular motor domain refers to several clinical findings related to eye movements, including vertical supranuclear gaze palsy, slowed velocity of vertical saccades, frequent macro square-wave jerks and apraxia of eyelid opening. Although definitive diagnosis of PSP requires pathology, the new PSP criteria suggest categories for probable, possible and suggestive PSP based on clinical features alone. By identifying these eye movement abnormalities, neuro-ophthalmologists can play an important role in helping to facilitate the early diagnosis of PSP. However, it also should be emphasized that many patients with pathologically confirmed PSP do not have eye movement abnormalities early in their disease course. Thus, the lack of eye movement abnormalities does not exclude the diagnosis of PSP [74].

Space Flight-Associated Neuro-Ocular Syndrome (SANS)

Both subjective and objective changes in visual function with associated structural changes in the optic nerve are recognized to occur in astronauts spending long periods of time in space. Previously described as visual impairment and intracranial pressure (VIIP) syndrome, scientists at the National Aeronautics and Space Exploration Administration (NASA) have more recently termed this phenomenon "spaceflight-associated neuro-ocular syndrome" (SANS). Clinical findings associated with this syndrome include optic disc swelling of varying severity (unilateral and/or bilateral), flattening of the posterior globe, refractive error (hyperopic shifts), choroidal and retinal folds and nerve fiber layer (NFL) infarcts with cotton-wool spots and, rarely, hemorrhages [75, 76]. Patients with SANS have structural changes that can be appreciated on various imaging studies including MRI, ultrasonography and OCT. For example, globe flattening may be appreciated on MRI on earth and by ultrasound in space, and OCT reveals changes in the NFL.

The pathophysiology for SANS is unclear. Lumbar punctures performed on a few astronauts with persistent optic disc swelling after their return to earth from long-duration space flight reveal mildly elevated opening pressures (22–28.5 cm H_2O), suggesting that the optic disc swelling represents papilledema, similar to that observed in patients with terrestrial pseudotumor cerebri (PTC). However, the demographics are quite dissimilar in that SANS occurs in non-obese, middle-aged men rather than obese young women of child-bearing age. In addition, SANS often is characterized by asymmetric disc swelling whereas most patients with PTC have symmetric disc swelling. Another difference is that choroidal folds are commonly seen in SANS and often are associated with very mild optic disc swelling, whereas choroidal folds are an uncommon finding in PTC and usually are associated with significant disc swelling. Thus, although raised ICP may be a factor in some cases of SANS, the most widely accepted mechanism for SANS is prolonged exposure to a microgravity environment, with resultant microgravity fluid shifts and jugular venous distention [75, 77, 78]. Another suggested mechanism for SANS includes compartmentalization of CSF within the orbital subarachnoid space; however, this hypothesis has not been confirmed. The role of lymphatics and venous flow is unknown.

Ongoing efforts to understand the pathophysiology of SANS include the use of OCT and OCTA to study structural changes in the optic nerve, retinal tissue and choroid. ICP measurements thus far have been limited to pre- or post-flight terrestrial lumbar punctures. Researchers currently are trying to find a way to measure the ICP inflight using various techniques [79].

Updates on Toxic and Nutritional Optic Neuropathies

Toxic-nutritional optic neuropathies (TNON) may occur in the setting of various offending agents including medications, poisonous environmental exposures, illicit substances, metabolic derangements and nutritional deficiencies [80]. The classic

clinical presentation for this group of optic neuropathies includes subacute, progressive, bilateral, painless vision loss. Visual field testing often reveals bilateral central and cecocentral scotomas due to loss of the papillomacular bundle [81]. Patients also may experience significant deficient of color vision and contrast sensitivity. Depending on when in the course of the optic neuropathy the patient is evaluated, the optic discs may appear normal, there may be mild optic disc swelling and hyperemia that mimic that sometimes seen in patients with Leber Hereditary Optic Neuropathy (LHON), or the optic discs may be pale, particularly temporally [82]. The mechanism of injury is at least in some of these cases is thought to be related to disruption of normal physiologic processes in the retinal ganglion cells and synapses in the afferent visual pathway [83]. This hypothesis has been confirmed by recent OCT studies showing thinning of the retinal ganglion cell/inner plexiform layer in patients with toxic optic neuropathies [84]. It is important to note that some patients have a combination of insults; e.g., both a toxic process and a nutritional deficiency, resulting in a compounding injury to the optic nerve. This is referred to as a toxic-nutritional optic neuropathy (TNON). Many TNONs share a mechanism of injury similar to that which produces mitochondrial optic neuropathies, particularly LHON, and, thus, careful evaluation should include testing for LHON in the appropriate clinic setting, such as those patients who do not improve or worsen despite repletion of the deficient nutrient or cessation of the toxic substance [85].

Toxins

The most commonly reported causes of toxic optic neuropathies include methanol, ethylene glycol and toluene [85]. Methanol toxicity typically occurs in patients consuming alcoholic beverages that contain excessive methanol rather than ethanol. Toxicity in this setting is related to the accumulation of toxic metabolites (formaldehyde and formic acid), leading to metabolic acidosis and cellular dysfunction. Acute demyelination of the optic nerve secondary to toxic formic acid may cause axon degeneration [86]. Treatment includes hemodialysis, ethanol and fomepizole. These antidotes are meant to inhibit alcohol dehydrogenase. The problem with ethanol is that it is not readily available in developing countries, and given the pharmacokinetics of ethanol, it is difficult to maintain adequate plasma concentrations. Serial monitoring of ethanol levels is required. Ethanol also may cause liver injury and hypoglycemia. There is no evidence for superiority of ethanol versus fomepizole in the treatment of methanol toxicity; however, fomepizole may have fewer adverse effects despite being very expensive [87, 88]. It has been suggested that treatment with steroids (IV methylprednisolone) may inhibit the demyelination process caused by methanol and also may prevent blindness and retinal atrophy [89]; however, this is a controversial issue and has not been proven in clinical trials [90]. There is also recent research suggesting that erythropoietin (EPO) may be useful for methanol poisoning, with reports of improved visual acuity after treatment with IV recombinant human EPO, but this, too, remains unsubstantiated by prospective clinical trials [91].

Medication-Induced

As novel oral and injectable pharmacologic agents emerge for various disease processes, the need to monitor for visual and ocular side effects becomes increasingly important. Medication-induced optic neuropathies typically are related to the dose of the offending agent and the length of time the patient was consuming it. We briefly review some updates in the literature for various medications and provide a table for commonly encountered medications causing optic neuropathy by category (Table 8.1).

Although it was previously thought that ethambutol causes an optic neuropathy at high doses (25 mg/kg/day), recent reports suggest that an optic neuropathy may occur at lower doses closer to the recommended dose of 15 mg/kg/day. Particularly in patients with renal dysfunction, progressive visual field deficits have been reported, even in the setting of concurrent hemodialysis [93]. Aside from immediate cessation of the medication, there are no new treatments for ethambutol-induced optic neuropathy. Rigorous monitoring with visual acuity, visual fields, color vision, and OCT thus remain important. In particular, it has been suggested that assessment of the thickness of the retinal ganglion cell/inner plexiform layer (rather than the peripapillary retinal nerve fiber layer) can be used to diagnose ethambutol-induced optic neuropathy at its earliest stage [94].

Linezolide is an antibiotic used to treat complicated, multidrug-resistant, gram-positive skin infections and pneumonia. It is generally well tolerated when used for up to 28 days [95]; however, it is known to cause a bilateral optic neuropathy in some patients. Dempsey et al. recently suggest a new screening protocol for linezolid use in adult patients, with screening beginning within 1 month after initiating linezolid, followed by a subsequent evaluation every 30–60 days beginning 3 months from initiation if needed for long-term use [96].

Amiodarone is a commonly used antiarrhythmic drug used to treat atrial fibrillation in cardiac patients around the world. Amiodarone-associated optic neuropathy (AAON) is a somewhat controversial diagnosis in that most patients receiving amiodarone have significant cardiac disease as well as other vascular risk factors for NAION, which AAON mimics. The difference between the two conditions is that AAON tends to be bilateral and mild, with optic disc swelling resolving over

Table 8.1 Commonly encountered medications causing optic neuropathy

Antimycobacterials/ antimicrobials	Ethambutol, Isoniazid, Linezolid, Ciprofloxacin, Cimetidine, Chloramphenicol, Erythromycin, Streptomycin, Dapsone, Quinine, Clioquinol
Antidepressants	Pheniprazine
Reversal agents	Disulfiram
Chemotherapeutic agents	Methotrexate, Cisplatin, Carboplatin, Vincristine, cyclosporine, tamoxifen, Infliximab, Clomiphene
Cardiovascular medications	Amiodarone, PDE-5 inhibitors, Blood pressure medications causing hypotension such as amlodipine may cause bilateral optic neuropathy [92]

4–6 months, whereas NAION tends to be unilateral, ranges in severity of optic disc swelling from mild to severe, and generally resolves in 6–11 weeks [97]. The exact mechanism of injury is unclear, although ultrastructural changes within in the optic nerve axons and disruption of axoplasmic flow have been suggested [98]. Most cases of AAON occur within the first year of taking the medication. Thus, it is recommended that patients undergo regular evaluations during the first year of treatment, followed by annual evaluations thereafter [99]. Treatment is cessation of the medication, assuming that there are other cardiac regimens available for the patient. Thus, the decision regarding management of patients with presumed AAON should be made in conjunction with the patient's cardiologist.

Phosphodiesterase-5 (PDE-5) inhibitors, including sildenafil, tadalafil, and vardenafil, commonly are used to treat erectile dysfunction and pulmonary arterial hypertension in both the pediatric and adult populations. Although it is clear that some patients taking PDE-5 inhibitors can develop an optic neuropathy, it is unclear if there is a cause-and-effect relationship. Favoring such a relationship are the fact that PDE-5 inhibitors are vasodilators and, thus, may cause systemic hypotension. Also, several challenge cases have been reported [100]. Finally, a study involving 102 centers found a twofold increased risk of an acute NAION-like optic neuropathy occurring within five half-lives of the use of a PDE-5 inhibitor compared with use in a prior time period [101] and a similar multicenter study involving 279 men reported similar results [102]. On the other hand, a retrospective cohort study of four million male patients prescribed PDE-5 inhibitors showed no difference in the rate of development of an optic neuropathy compared with published rates of NAION [103]. In addition, a pharmaco-epidemiological nested case-control study in which 1109 cases of NAION were matched to 1,237,900 controls found no significant association with the use of PDE-5 inhibitors [104]. Having said this, there was a report of the development of an acute optic neuropathy in a child using sildenafil for chylothorax [105]. Other visual side effects of PDE-5 inhibitors include dose-dependent, reversible color vision problems (cyanopsia) and photophobia [106].

Nutritional Deficiencies

Nutritional optic neuropathies often are considered a subset of toxic optic neuropathies, with the clinical presentation being very similar; i.e., bilateral, subacute, and characterized by central or cecocentral scotomas. True nutritional optic neuropathies are rare and occur more commonly in developing countries. In the Western world, nutritional deficiencies often occur in the setting of chronic alcoholism, following bariatric surgery, and even in patients with severe depression resulting in a poor diet. Once identified, replacing the deficient nutrient and removing other offending agents may result in visual improvement, assuming that the patient does not have contributing genetic factors or other toxic insults [82] or that there has not been irreversible damage to the optic nerves. Vitamins B12, B1 (thiamine), and B2 (riboflavin), as well as folic acid (particularly in chronic alcoholics) and copper are commonly encountered deficiencies that can produce an optic neuropathy. Deficiencies

in zinc and other fat-soluble vitamins (A, D, E) may also be seen, particularly after gastric bypass surgery, and have the potential to result in various neuropathies, including optic neuropathy [107]. When determining if a vitamin deficiency is the cause of an optic neuropathy, the clinical history is of critical importance. Vitamin levels in the serum may not be reliable in all cases. In particular, serum vitamin B12 levels may be falsely normal due to B12 binding transcobalamin [85], and red blood cell folate is a better indicator of folate levels than serum folate [108].

The Role of Alcohol and Tobacco

Patients who consume large quantities of alcohol are, as noted above, at risk for developing a bilateral optic neuropathy [83]. Although previously termed "tobacco-alcohol amblyopia," this term is inappropriate. Firstly, the pathology is related to optic nerve injury and, thus, is not an "amblyopia" [109]. Secondly, there is absolutely no evidence to suggest cigarette smoking causes an optic neuropathy in otherwise healthy individuals who do not also consume alcohol heavily. In fact, the bilateral optic neuropathy that occurs in patients who abuse alcohol almost always is due not to the toxic effects of the alcohol (unless the individual is consuming methanol, see above) but to the vitamin deficencies that occur when alcohol abusers do not have an appropriate diet. Treatment thus is alcohol cessation combined with vitamin and folate supplementation. As in the case of other toxic and nutritional deficiencies, the prognosis for visual recovery is good it the diagnosis is made and treatment is commenced before irreversible damage to the optic nerve occurs.

Glaucoma and the Role of Cerebrospinal Fluid Pressure

Primary open-angle glaucoma (POAG) is a leading cause of blindness worldwide [110]. Although elevated intraocular pressure (IOP) is commonly encountered and can be modified, not all patients with what appears to be typical POAG have elevated IOP [111]. Accordingly, other mechanisms for optic nerve damage that is consistent with POAG have been hypothesized. In particular, the role of CSF flow on the optic nerve in patients with so-called "normal-tension glaucoma" (NTG) has been raised. Three main mechanisms have been proposed to describe the role of ICP in NTG: (1) a barotraumatic phenomenon, (2) failure of CSF dynamics and (3) ocular glymphatic system dysfunction.

The barotraumatic theory of NTG hypothesizes that low ICP causes a clinical picture of glaucoma by inducing a high pressure gradient across the lamina cribrosa, ultimately damaging the optic nerve head [111]. Several studies using swept-source OCT indicate that the lamina cribrosa is the principal site where retinal ganglion cell axon insult occurs [112]. The lamina cribrosa provides structural and functional support to retinal ganglion cell axons as they go through the high-pressure environment in the eye to the low-pressure environment of the subarachnoid space

surrounding the orbital optic nerve [113]. It is postulated that significant pressure changes in the intraocular space or the subarachnoid space has a potential to biomechanically injure the nerve through deformation of the laminar and optic nerve head biomechanics.

Another proposed mechanism for NTG includes that of failed CSF flow dynamics. The theory in this case is that low ICP leads to inadequate clearance of toxic substances from the CSF, causing optic nerve damage [114]. It is well-known that CSF circulation and turnover play an important role in the elimination of toxic substances from the CNS [115]. Because CSF turnover rate is directly proportional to the formation but inversely related to the volume, decreased CSF production may lead to decreased CSF turnover and, thus, allow for accumulation of biologically highly active toxic substances and ultimate neurotoxicity [110].

The third and most common proposed mechanism used to explain the development of what appears to be typical glaucomatous field and disc changes despite normal IOP involves the ocular glymphatics. The ocular glymphatic system consists of channels around the optic nerve and retina through which CSF is recirculated and neurotoxic metabolites are cleared. These channels have been found paravascularly, around the central retinal vein and central retinal artery [116]. A paravascular channel of the optic nerve has also been suggested and confirmed in studies of the optic nerves of mice [117]. It has been suggested that CSF flow along the perivascular space surrounding the central retinal artery into the anterior optic nerve and retina and then back along the perivascular space surrounding the central retinal vein into the subarachnoid space surrounding the optic nerve removes potentially toxic metabolites. If ICP is too low, CSF flow may stop or decline due to an increased pressure barrier. This, in turn, hinders paravascular flow from the optic nerve to retina, resulting in suppression of the glymphatic fluid system and toxin accumulation followed by glaucomatous optic neuropathy [110].

Updates in Imaging

New Imaging Sign in Multiple Sclerosis

The most recent imaging criteria by the Magnetic Resonance Imaging in MS (MAGNIMS) committee was published in 2015 [118]. Although brain MRI is a very sensitive test for diagnosing MS as well as for monitoring disease activity and treatment response, MRI spine is less sensitive [119, 120]. The typical MRI findings in MS include the presence of multiple focal white matter lesions and three or more of these lesions should involve the periventricular white matter [121]. In addition, however, an addition MRI sign, the central vein sign, has been suggested to differentiate MS from MS mimics [122, 123]. Pathologically, white matter lesions in MS correspond with inflammatory infiltrates that develop around venules. Using susceptibility-based MRI sequences, the association between brain white matter venules and perivenular lesions can be visualized. It has been found that the

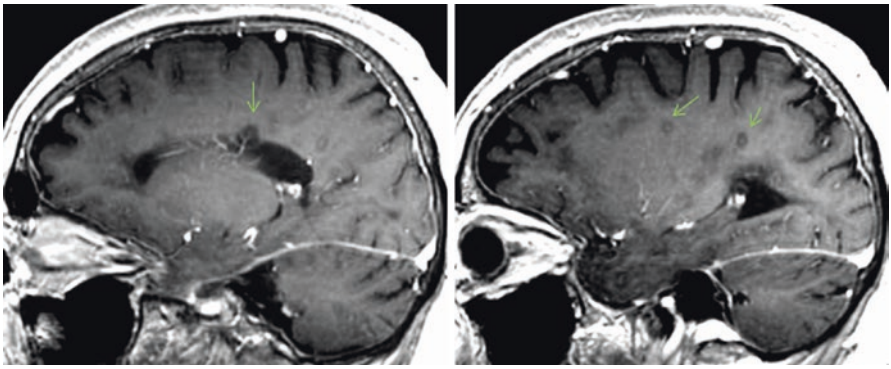

Fig. 8.3 T2-FLAIR sequence showing the central vein sign in periventricular lesions in a patient with multiple sclerosis (Both images courtesy of Dr. David Poage, MD)

proportion of MS lesions with a central vein is high [122, 124] and when compared against other pathologies including CNS vasculopathies, the high frequency of perivenular lesions on MRI is pathologically specific for MS and, thus, important for improving the accuracy with which MS can be diagnosed [122, 123] (Fig. 8.3). It is important to note that the frequency of the central vein sign is the same for 1.5 and 3 T MRI machines and can be applied across the various phenotypes of MS [122].

Imaging Updates in Giant Cell Arteritis (GCA)

Evidence-based recommendations for imaging in GCA (and other large vessel disease such as Takayasu Arteritis) were suggested by the European League against Rheumatism in May 2018 [125]. In particular, the League recommended that imaging with ultrasonography, MRI or both should be performed in patients in whom GCA is suspected, followed by temporal artery biopsy if the diagnosis is still in question after imaging and clinical examination. Imaging should be performed as early as possible after the initiation of therapy as glucocorticoid use may reduce the sensitivity of imaging [126, 127]. Ultrasonography is recommended as the first imaging test of choice in patients with GCA and predominantly cranial symptoms. The League specifically recommended imaging of the superficial temporal and axillary arteries; however, other authors also have included examination of the carotid, vertebral, occipital and subclavian arteries when possible [128]. The two imaging findings seen on ultrasound in patients with GCA include the "hypoechoic halo" and the "compression sign." The halo sign is due to homogenous, hypoechoic vessel wall thickening that is delineated toward the luminal side and visible in longitudinal and transverse planes [129]. The hypoechoic halo is thought to represent inflammation of the vessel wall. This sign was found to have a sensitivity of 77% and specificity of 96% in a systemic literature review where data was pooled from 43

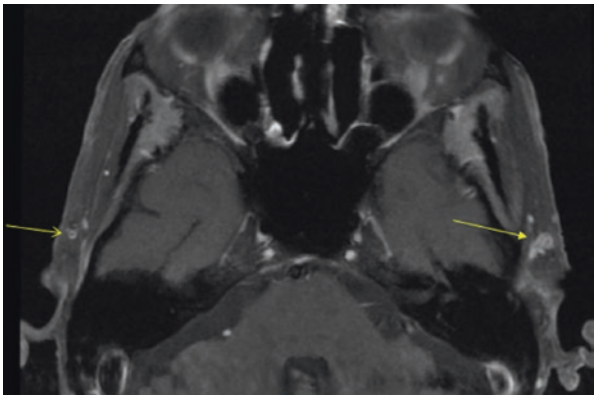

Fig. 8.4 High-resolution, T1-weighted, post-contrast MRI showing vascular mural enhancement in a patient with biopsy-proven giant cell arteritis (arrows). Note the central arterial flow void and the ragged infiltrative appearance around it. (Image courtesy of Dr. Andrew G. Lee and colleagues)

different studies [130]. The compression sign refers to continued visibility of the hypoechoic vessel wall while the ultrasound probe is used to apply pressure to the artery. This sign has been found to have a sensitivity of 77–79% and a specificity of 100% [125, 131]. In the event that ultrasound is inconclusive or simply is not available, the League recommended high-resolution scalp MRI of the cranial arteries—specifically, the temporal and occipital arteries—to assess for mural inflammation manifesting as mural contrast enhancement and arterial wall thickening (Fig. 8.4) [125]. One prospective cohort study of 170 patients with suspected GCA found MRI to be 93.6% sensitive and 77.9% specific in diagnosing patients with GCA [132]. It should be noted, however, that accurate identification of abnormal ultrasonographic and MRI findings is highly dependent on the individual performing the study in the case of ultrasound and on the individual interpreting the study in both cases. Other authors have raised the question as to what to do when imaging shows inflammation but temporal artery biopsy at the same location is negative. To date, there is no recommendation for how to handle this situation [128, 133].

New consensus criteria for the classification and diagnosis of GCA is expected to come out in 2019 via the Diagnostic and Classification Criteria in Vasculitis Study (DCVAS) and will replace the initial criteria created by the American College of Rheumatology in 1990s [134].

Updates in Testing and Diagnostic Modalities

Myasthenia Gravis (MG) Antibodies (MuSK and LRP4)

MG is an autoimmune disorder in which antibodies, primarily those to acetylcholine receptors, result in disruption of neuronal transmission at the neuromuscular junction. Clinical symptoms include skeletal muscle weakness and fatigability [135]. Ocular myasthenia gravis (OMG) refers to isolated involvement of the extraocular muscles and typically presents as double vision, ptosis, or both.

Approximately 60% of patients with MG have ptosis and/or diplopia at onset, and almost all patients with MG experience ocular symptoms at some point during their disease course [136]. In some cases, it is difficult to make the diagnoses of OMG based on clinical examination alone due to the potential for OMG to mimic ocular motor nerve palsies or brainstem motility deficits (eg, internuclear ophthalmoplegia) or even an ocular myopathy [137]. When the diagnosis cannot be made from the examination alone, the role of serum antibodies becomes important. For decades, antibody testing in MG was limited to the acetylcholine binding, blocking and modulating antibodies, with the binding antibody being the most frequently detected in both ocular and systemic MG [137]; however, although the presence of an elevated acetylcholine receptor antibody is highly specific for diagnosing OMG, these antibodies are typically positive in only half of all patients presenting with OMG [138]. This is in stark contrast to cases of generalized MG where seropositivity is reported to be as high as 85–90% [139–141]. Now, two new antibodies, LDL-related receptor-related protein 4 (LRP4) and Muscle-specific tyrosine kinase antibodies (MuSK) have been identified that may help to increase the diagnostic sensitivity of OMG.

LRP4 antibodies are thought to play a role in maintenance of the neuromuscular junction. During formation of the neuromuscular junction, LRP4 binds with agrin to form a complex that promotes acetylcholine receptor clustering and differentiation on the postsynaptic membrane by activation of MuSK. LRP4 antibodies have been found in 1–5% of all patients with MG and 7–33% of patients who are negative for acetylcholine antibodies and MuSK [136, 142, 143]. LRP4 positivity is more common in women than men and is associated with a mild disease course with only rare escalation to myasthenic crisis. Most importantly for the ophthalmologist, it can be present in patients with isolated ocular symptoms [136, 144–146]. The prevalence of OMG is similar in patients with acetylcholine antibodies and LRP4 antibodies [147]. Thus, an assay for LRP4 antibodies should be performed in patients for whom OMG is highly suspected but in whom acetylcholine receptor antibodies are negative [137].

MuSK antibodies cause a reduction in the postsynaptic density of acetylcholine receptors by binding to an extracellular domain [143, 148]. MuSK antibodies are present in 1–10% of all patients with MG [149, 150], with higher prevalence in the female gender and patients of Mediterranean descent [139, 145]. From 20 to 40% of patients with generalized MG but negative acetylcholine receptor antibodies will test positive for MuSK [143, 148]; however, they are rarely found in patients with OMG. One study found MuSK antibodies in only three of 82 patients with OMG [151, 152]. Nevertheless, in patients with MuSK-positive OMG, the ocular manifestations appear to be more symmetric and less fluctuating than typical MG [152]. Given the low diagnostic yield of MuSK in isolated OMG, it is recommended that this testing be reserved for patients with suspected MG despite negative acetylcholine receptor and LRP4 antibody testing [137]. A positive assay for MuSK antibody in patients with OMG has been associated with a high risk for early generalization [152, 153].

Optical Coherence Tomography (OCT)

The use of OCT has rapidly escalated over the years since its initial invention in the 1990s [154]. This increased usage is directly correlated with improved knowledge of how OCT can be used for diagnosis and monitoring of various ophthalmic and neurologic conditions. By providing high-resolution structural information about the retina and optic nerve, OCT has become an imaging procedure that is routinely performed in ophthalmology clinics worldwide. Below, we review OCT findings in various neuro-ophthalmic disorders.

OCT can be useful in discerning the etiology of an optic neuropathy in a patient with glaucoma and other comorbidities. Glaucomatous optic neuropathy typically causes thinning in the superior and inferior quadrants of the disc, with temporal sparing, whereas many non-glaucomatous optic neuropathies tend to affect the papillomacular nerve fiber bundle, ultimately causing more temporal thinning in addition to super or inferior thinning [155]. In a patient presenting with an optic neuropathy and no visual acuity or field change, thinning on the OCT may be the only indication that there has been damage to the optic nerve.

OCT in Optic Disc Elevation

Measurement of the RNFL by OCT may be useful in patients with PTC or other etiologies of disc swelling such as non-arteritic anterior ischemic optic neuropathy (NAION) to monitor improvement of the thickened RNFL [156] (Fig. 8.5). In addition, assessment of the position of the lamina cribrosa (bowed out vs bowed in) may be useful in differentiating local swelling from papilledema. Finally, in patients who present with an apparently elevated disc, OCT may help differentiate true disc swelling from congenital elevation (eg, pseudopapilledema). No change in OCT for several months after initial examination may provide reassurance that the disc elevation is congenital rather than acquired.

OCT in Neurodegenerative Disease

Thinning of the RNFL and the ganglion cell/inner plexiform layer has been reported in various neurodegenerative diseases such as Alzheimer disease (AD), PD, Mild Cognitive impairment syndrome, and MS.

Alzheimer Disease: Although it has been established that there is some thinning of the RNFL in patients with AD and that progressive thinning correlates with disease progression, it is unclear if a specific quadrant of the nerve or specific layer of the retina is particularly susceptible [157] (Fig. 8.6). In OCT studies in patients with AD, the AD was not confirmed with pathology, thus giving room for similar diagnoses like vascular dementia or other dementia subtypes to be included, confounding the reported findings [157]. The future of OCT in patients with dementia is to learn

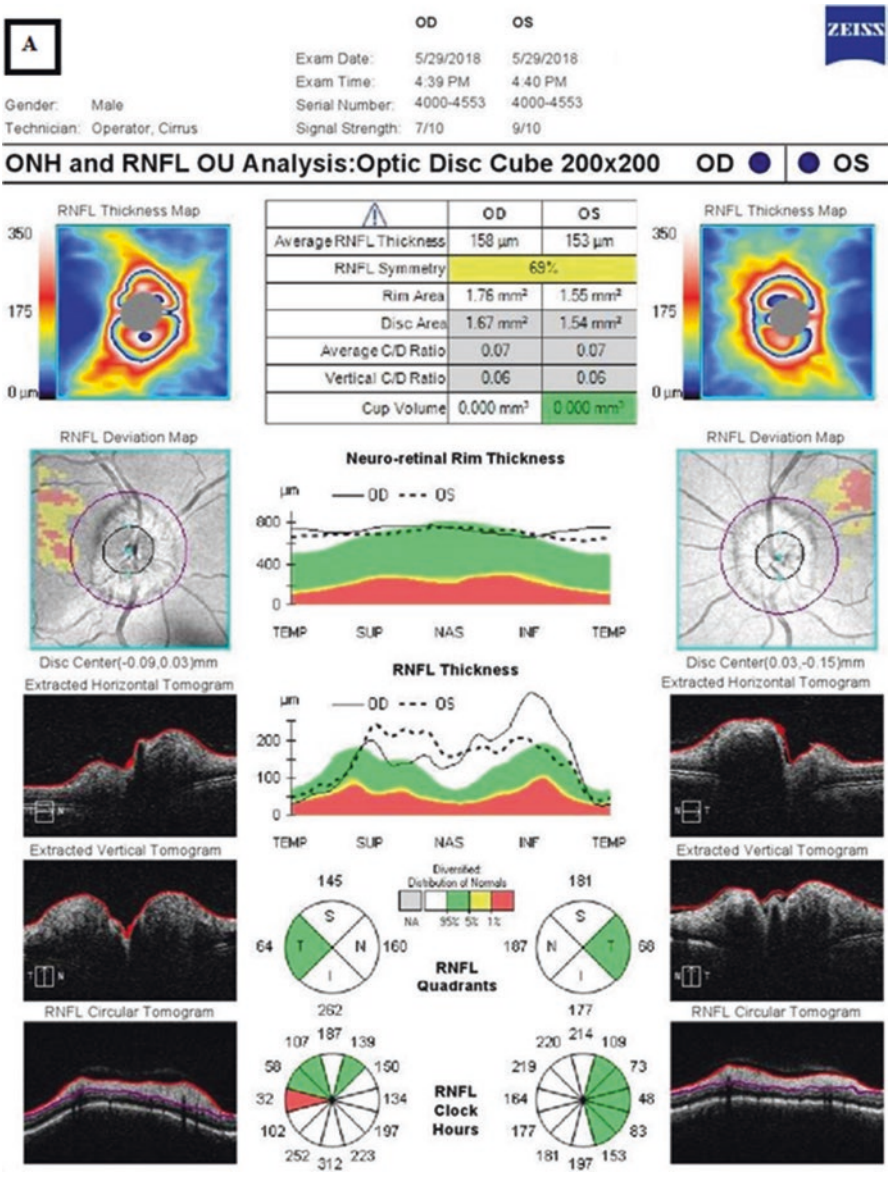

Fig. 8.5 OCT in optic disc elevation before (**a**) and after (**b**) treatment with Diamox (Acetazolamide). The coinciding fundus photos showing significant papilledema before treatment (**c**), with improvement after treatment (**d**) are also shown

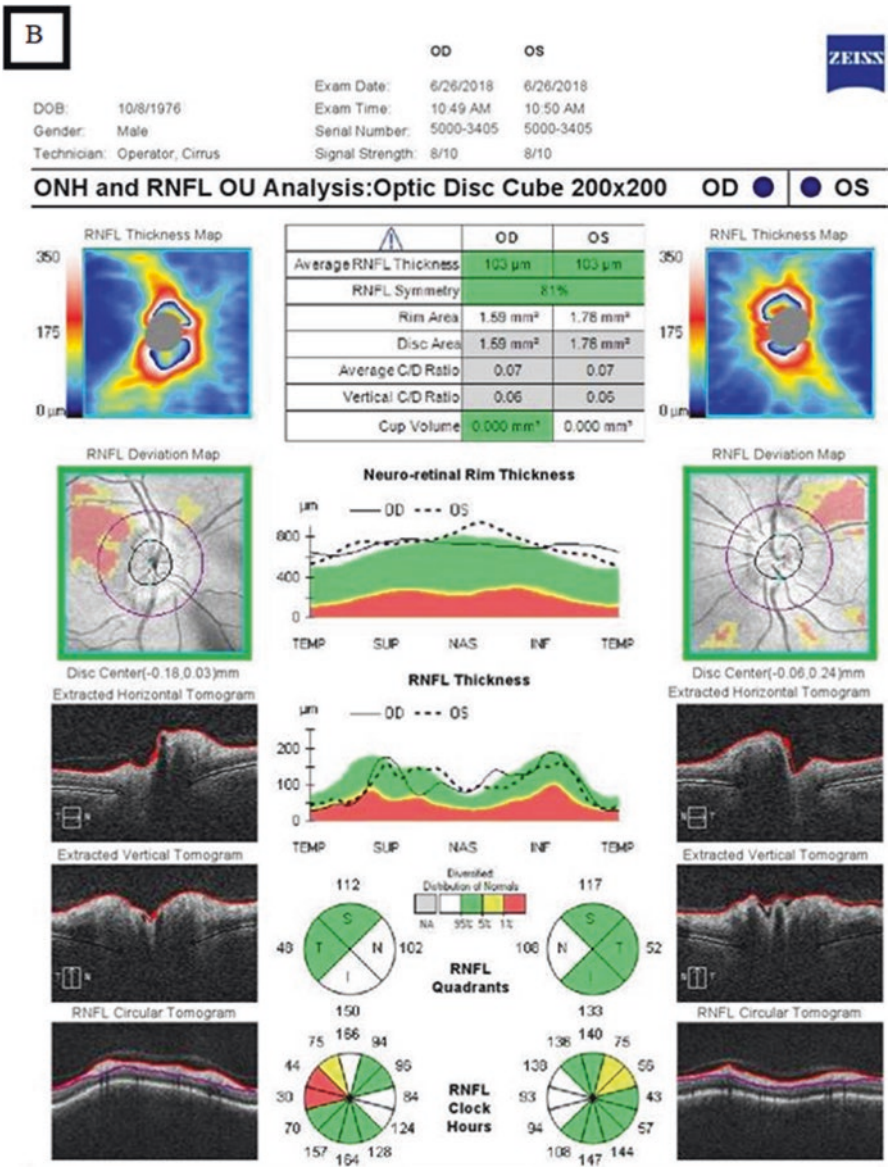

Fig. 8.5 (continued)

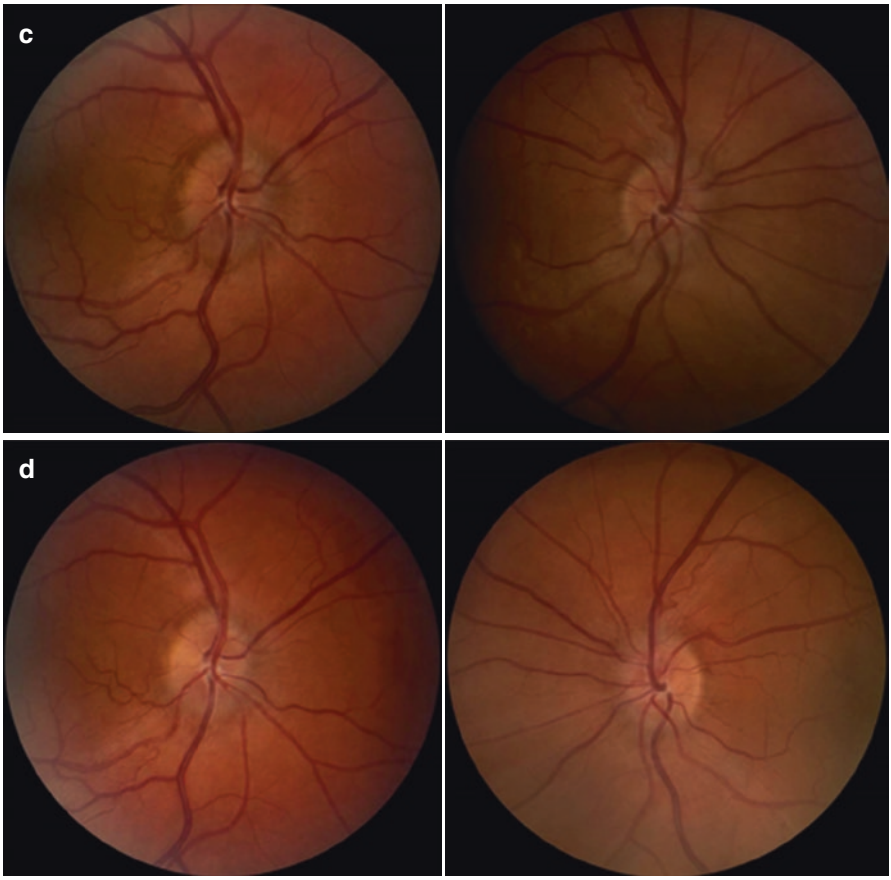

Fig. 8.5 (continued)

if specific retinal or optic nerve changes point to a specific etiology. If this proves to be the case, it will allow OCT to be used as a diagnostic tool for patients with cognitive impairment.

MS: RNFL thinning and resultant optic nerve atrophy is a well-known and accepted marker of disease burden in patients with MS, even in cases in which there is no reported history of prior optic neuritis [158, 159]. There also have been reports of reduced macular volume at baseline without any reduction in RNFL thickness in patients with MS [160] as well as reduced central foveal area, all suggesting involvement of outer retinal layers [161]. OCT thus has become an important monitoring tool for MS and other etiologies of optic neuritis, helping to determine progression, prognosis, and need for modification of therapy. Its utility to differentiate MS from NMO, MOG and GFAP autoantibody disease remains poorly understood.

PD: Some studies have shown thinning of the RNFL contralateral to the side of motor symptoms in patients with PD [162], although this finding is controversial as there are other studies that have not shown thinning [163, 164]. Nevertheless,

macular retinal thickness and the total macular volumes are reduced in PD, and the degree of macular thinning may correlate with disease progression and severity [165, 166], although further studies are needed to confirm this finding. Increased choroidal thickness on OCT was also observed in PD patients compared with unaffected controls [167]. The significance of this finding is unclear.

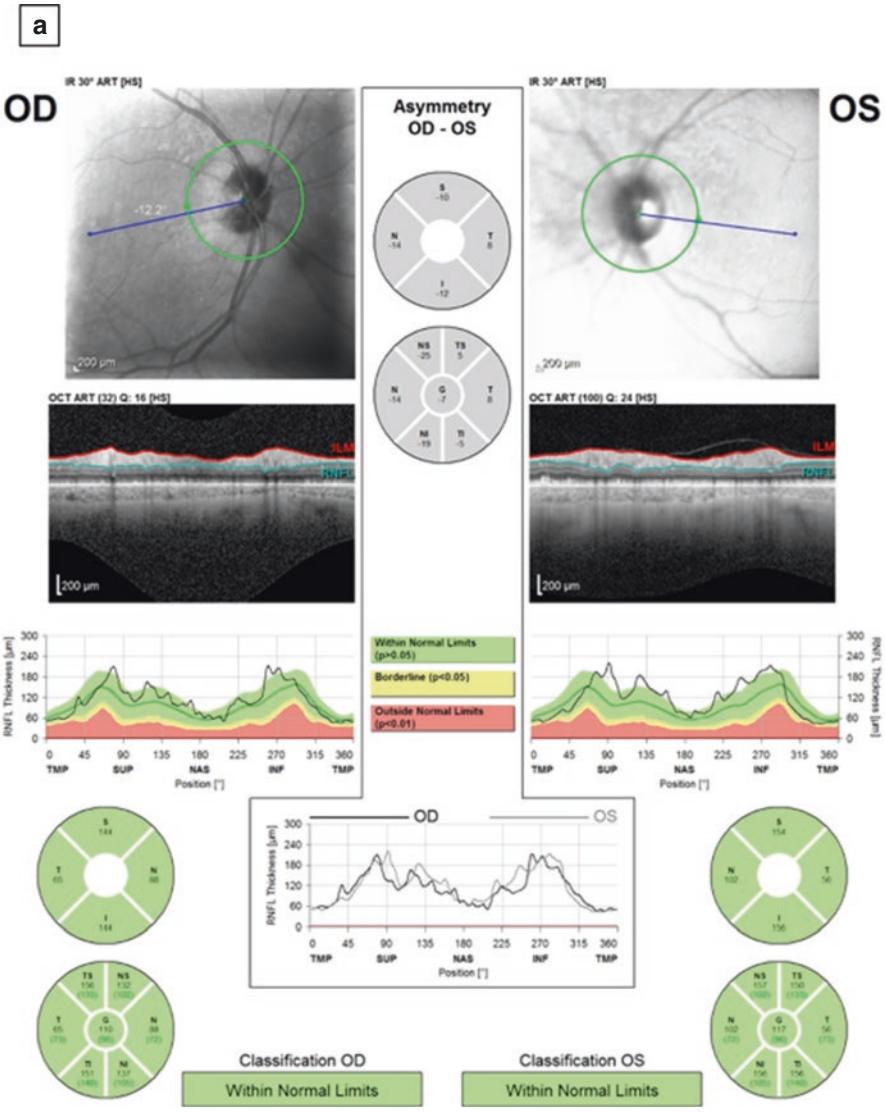

Fig. 8.6 OCT in a patient with mild/moderate Alzheimer disease (AD). Compared with the OCT from a normal individual (**a**), the OCT in a patient with AD (**b**) shows mild but definite thinning of the peripapillary retinal nerve fiber layer in both the right and left eyes. (Images courtesy of Dr. Elizabeth Couser)

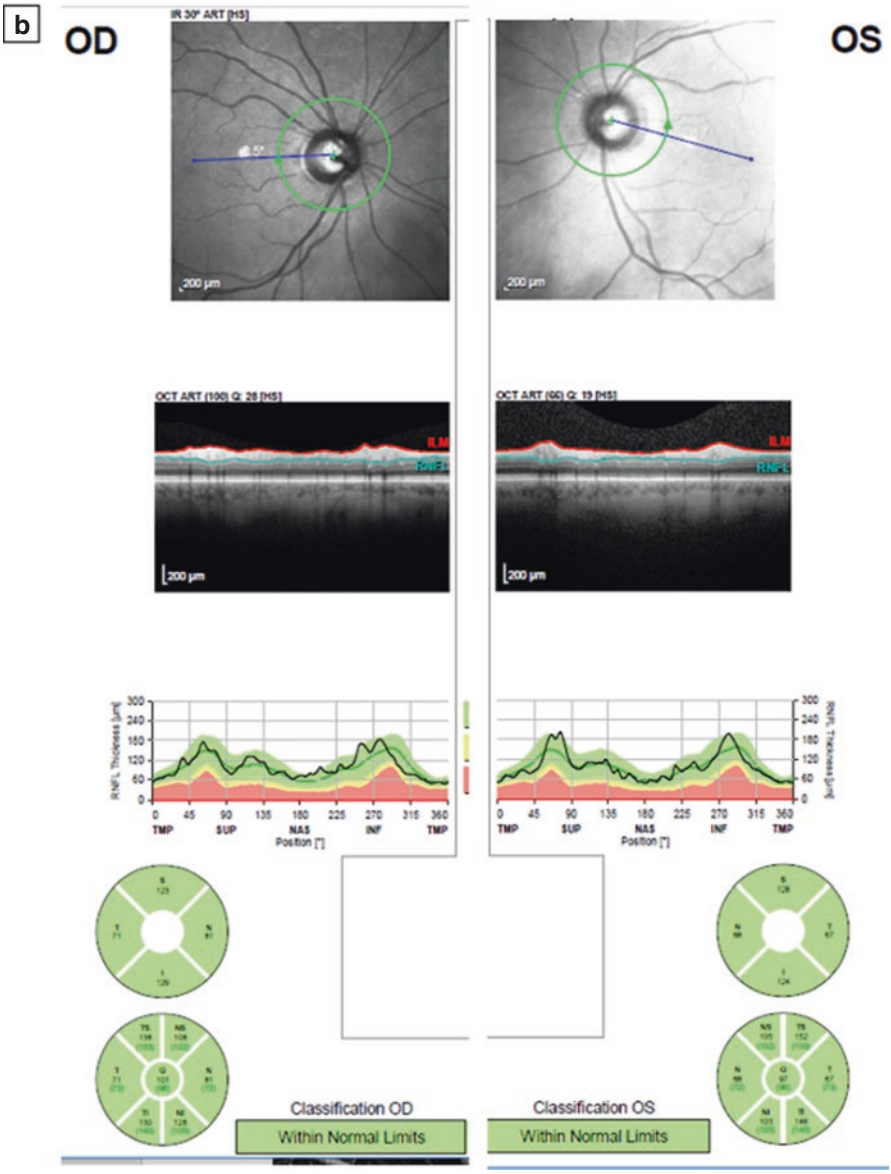

Fig. 8.6 (continued)

Optical Coherence Tomography Angiography (OCTA)

The addition of angiography to standard OCT (OCTA) has become a new area of interest in the evaluation of patients with optic neuropathies as well as neurologic conditions since it was introduced commercially in 2014 [168]. Although Doppler

OCT has been used to measure retinal blood flow in the past, it assesses only the axial component of blood flow velocity and is not sensitive to the slow, transverse blood flow in retinal, choroidal, and optic disc capillary networks as is possible with OCTA [169]. OCTA provides a three-dimensional motion-contrasted, cross-sectional image that is produced by the backscattering of light in the retinal vascular and neurosensory tissue as moving red blood cells are contrasted against static neurosensory tissue. Because OCTA uses the intrinsic contrast of moving red blood cells, no dye is needed [168]. The benefit is that one may obtain quantitative information about retinal vasculature using a non-invasive test. It also has been suggested that the imaging resolution obtained by these photos are "histology level" [170]. Clinical applications of OCTA in relation to neuro-ophthalmic conditions are discussed below:

OCTA in Optic Neuropathies

Decreased peripapillary capillary density that correlates with RNFL thinning has been found using OCTA in patients with optic neuropathies. Although this may seem like an obvious observation in patients with ischemic optic neuropathies where circulation is the direct cause of the insult, decreased peripapillary capillary density also has been identified in patients with optic neuritis, traumatic optic neuropathy, autoimmune optic neuritis, compressive optic neuropathy (chiasmal compression) and Leber hereditary of optic neuropathy (LHON). In these cases, although ischemia is not the underlying cause, it has been suggested that optic nerve injury leads to subsequent RNFL loss with associated decrease in capillary flow. The suggested mechanism is that chronic injury to an optic nerve leads to a reduction in the number of nerve fibers that results in a decrease in metabolic demand and subsequent reduced capillary blood flow. The decreased peripapillary capillary density is a secondary consequence [171]. Clinically, OCTA may be helpful in differentiation of various etiologies of chronic optic neuropathy. Significant and profound peripapillary capillary loss relative to RNFL thinning may suggest an ischemic etiology such as anterior arteritic ischemic optic neuropathy (AAION) or NAION as opposed to, for example, optic neuritis (Fig. 8.7). Other causes of optic nerve compression and injury including chiasmal compression and optic disc drusen have been found to have decreased retinal perfusion on OCTA [171]. Studies are still lacking to determine if OCTA can be used to determine etiologies of optic neuropathy in an acute setting. Data regarding the influence of optic disc swelling on the measurements in OCTA remain poorly described.

OCTA in Multiple Sclerosis

OCTA of the optic disc has revealed reduced flow index and vessel density in eyes of patients with MS, with and without a prior history of optic neuritis compared with normal subjects [172, 173]. Reports regarding macular OCTA changes in MS are inconsistent and inconclusive [174].

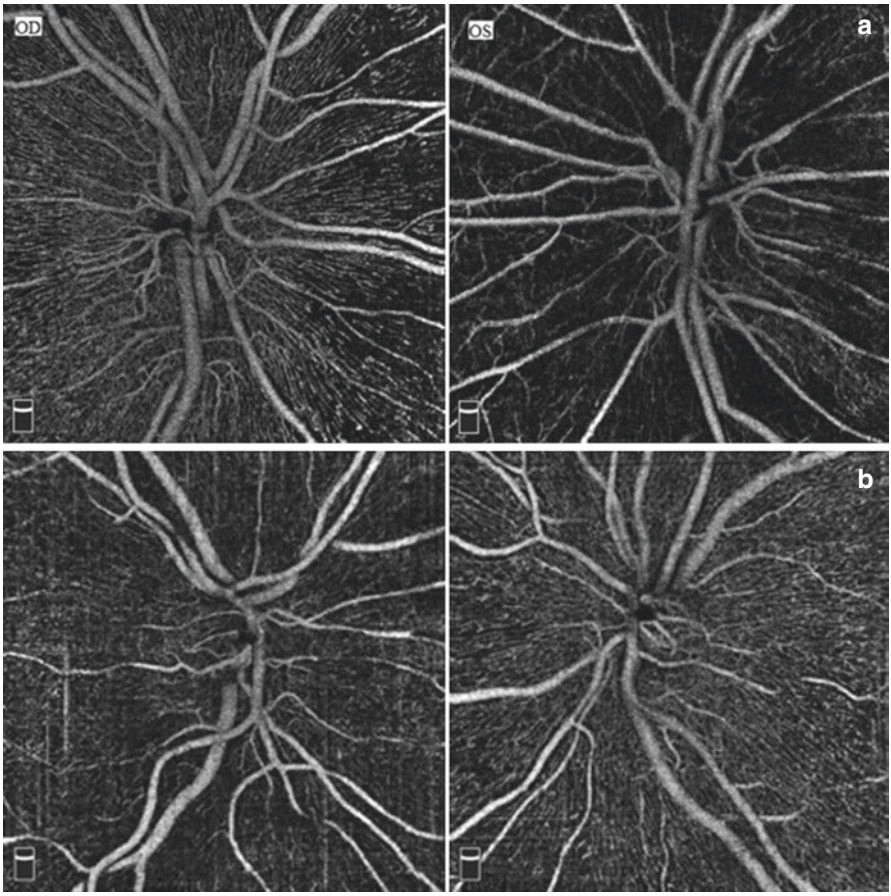

Fig. 8.7 OCTA in non-arteritic ischemic optic neuropathy (NAION) in the **left eye** (**a**) and in chronic optic neuritis involving the **right eye** (**b**). Note that there is reduction in the disc and peripapillary vessel density in both pathologies. Although there is a reduction in peripapillary vascular density in all optic neuropathies, significant and profound peripapillary capillary loss relative to RNFL thinning may suggest an ischemic etiology. (Images courtesy of Dr. Amanda Henderson)

OCTA in LHON

In some patients, OCTA has shown peripapillary telangiectatic blood vessels that were not visualized with fluorescein angiography [175]. A recent small study of six patients with LHON evaluated with OCTA (total 12 eyes) concluded that the peripapillary microvascular network in these patients is very abnormal, thus suggesting that there may be a contribution of microangiopathy to the vision loss in this population [176]. More recently, a study of optic nerve head and macular OCTAs in 15 patients with LHON (20 eyes compared with 20 controls) showed that changes in superficial and deep capillary plexi occur nasal and inferior to the optic disc, corresponding with the papillomacular bundle [177] (Fig. 8.8). The same study showed a significant correlation between reduction in the superficial capillary plexus vessel

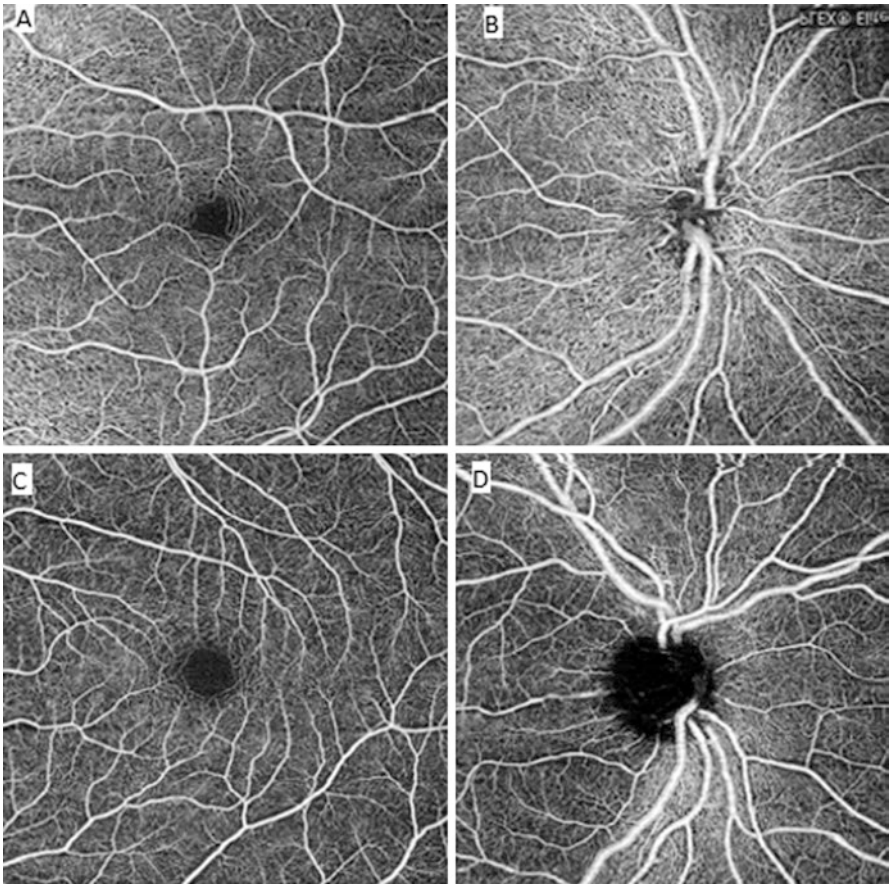

Fig. 8.8 OCTA of the macula (**a**) and optic nerve head (**b**) in a 27-year-old woman with acute genetically proven LHON (11,778 mutation) 4 weeks after symptom onset. Note the increased perfusion of the vessels at the disc and macula, particularly on the nasal aspect which corresponds to the papillomacular bundle. This is in contrast to the OCTA in chronic LHON (6 months after symptom onset), where there is microvascular drop out in the macula (**c**) and atrophy of the superficial plexus of the optic disc (**d**). Pictures (**c**) and (**d**) are from a 15-year-old boy with LHON associated with the 14,484 mutation. (Images courtesy of Dr. Alfredo Sadun and Dr. William Sultan)

density an severity of vision loss measured by visual acuity. Of note, the authors also found no association between OCT-assessed structural changes (thinning of the retinal nerve fiber or ganglion cell layers) and best-corrected visual acuity.

Updates in Treatment

Unfortunately, large-number, prospective, controlled studies are significantly lacking for many of the treatment and management updates in neuro-ophthalmology. Below we review several of the updated recommendations for various

neuro-ophthalmic problems that are based primarily on systemic reviews and meta-analyses, with a few exceptions.

Treatment in Giant Cell Arteritis

Giant Cell Arteritis (GCA) is a vasculitis that affects medium-to-large vessels and is an important cause of acute vision loss in neuro-ophthalmic patients over the age of 50. Previously, GCA was diagnosed by clinical examination, serum inflammatory markers (erythrocyte sedimentation rate, C-reactive protein, and platelets), and temporal artery biopsy (the gold standard for diagnosis). Although temporal artery biopsies may be used to may confirm the presence of GCA, a negative biopsy does not definitively exclude it due to the potential for inflammatory lesions to skip certain arteries or segments [128, 178].

Despite our increased ability to recognize GCA, treatment continues to be a challenge. For decades, management of GCA was limited to long courses of steroids and immunosuppressants that have debilitating side effects and do not secure a good outcome. In a landmark clinical trial, the GiACTA Trial, the drug tocilizumab was identified as the first non-corticosteroid agent with good efficacy for management of GCA [179]. Tocilizumab is an IL-6 inhibitor that works by reducing and inhibiting acute phase reactants contributing to inflammation. In the GiACTA trial, 251 patients with newly diagnosed or relapsed GCA were treated with either tocilizumab and steroids or placebo and steroids. This study was a double-blind, randomized controlled trial. The patients were divided in a 2:1:1:1 ratio among the following treatment regimens: weekly subcutaneous tocilizumab (162 mg) plus a 26-week prednisone taper, every-other-week subcutaneous tocilizumab (162 mg) and 26-week prednisone taper; weekly placebo +26-week prednisone taper and weekly placebo +52-week prednisone taper. Tocilizumab exhibited a marked steroid-sparing effect with a higher rate of sustained remission at 52 weeks compared with placebo. Of note, weekly dosing of tocilizumab was superior to every-other-week dosing. Overall, the cumulative prednisone dose in the tocilizumab group was significantly less than the amount used in the placebo group. No patient treated with weekly tocilizumab developed any permanent visual deficits, and quality of life measures were improved with tocilizumab compared with placebo. Tocilizumab was approved by the FDA in 2017, shortly after completion of this trial. The downside for the use of tocilizumab is that at this time, long-term follow-up is lacking for its use in GCA. Also, the high cost of this medication has led some physicians to resort to this medication only in cases where patients cannot tolerate long-term corticosteroid treatment or have failed corticosteroid treatment [128]. Of note, and in line with the new recommendations above regarding imaging in GCA, 46% of the patients in the GiACTA trial were diagnosed based on positive imaging rather than temporal artery biopsy. It should also be noted that although tocilizumab clearly has efficacy as an add-on treatment for GCA, no studies have been performed in which it has been used as a first-line treatment.

Abatacept is a CTLA-4 inhibitor that has been shown to be effective in GCA. In a small, randomized, placebo-controlled trial, 41 patients were treated with an induction course of abatacept 10 mg/kg intravenous with a 28-week prednisone taper. The patients were then divided into two groups, one of which went on to receive monthly treatment with abatacept and the other, placebo. The abatacept group showed a statistically higher rate of relapse-free survival (48% compared with 31%). One patient from the abatacept group had a visual event related to GCA that occurred 28 weeks after the initial induction [180].

Ocrelizumab in Multiple Sclerosis

In March 2017, the FDA approved the drug ocrelizumab for the treatment for multiple sclerosis. This medication is the first to be approved for primary progressive MS and also is the first monoclonal antibody approved for use in secondary progressive MS. Ocrelizumab is an anti-CD20 antibody that has been evaluated in phase II and III trials and found to lower disability progression and improve radiologic and relapse-related outcomes compared with placebo in patients with MS [181].

Treatment for Optic Pathway Gliomas and Optic Nerve Sheath Meningiomas

Optic Pathway Gliomas

Falsini et al. performed a randomized, double-masked, phase II clinical trial in 17 patients with optic pathway gliomas and stable visual function and imaging [182]. Patients received either a 10-day course of 0.5 mg murine nerve growth factor (NGF) or placebo (10 NGF/8 placebo). Patients were evaluated clinically (visual acuity, visual field), by imaging (OCT, MRI), and by electrophysiological testing (visual evoked potentials and photopic negative responses) before therapy and at 15, 30, 90, and 180 days after therapy. There were no adverse effects from the treatment and all patients who received NGF showed statistically significant improvements in all parameters.

Optic Nerve Sheath Meningiomas

It has become increasingly clear that the appropriate management of an optic nerve sheath meningioma (ONSM) for patients who require intervention because of progressive visual loss is stereotactic fractionated or conformal radiation therapy (FCRT). Pandit et al. performed a retrospective chart review with prospective follow-up of adult patients treated with FCRT for primary ONSM at four academic medical centers between 1995

and 2007 with ≥10 years of follow-up after treatment [183]. They identified 16 patients with mean post-treatment follow-up of 14.6 years; (range: 10.5–20.7 years). The mean age at symptom onset was 47.6 years (range: 36–60 years). FCRT was performed at a mean of 2.3 years after symptom onset (range: 0.2–14.0 years). At last follow-up, visual acuity had improved or stabilized in 14 of the 16 (88%) patients, and 11 (69%) had retained or achieved ≥20/40. Mean deviation on automated perimetry remained stable (−14.5 dB pre-treatment vs. −12.2 dB at last follow-up; p = 0.68; n = 10). Two (11%) patients had persistent pain, proptosis, or diplopia, compared with seven (44%) pre-treatment (p = 0.11). Two (13%) patients developed radiation retinopathy more than 6 months after completion of therapy, one (50%) of whom had worse VA compared with pre-treatment. No patient developed tumor involvement or radiation damage in the fellow eye. Based on these findings, the authors concluded that FCRT stabilizes or improves visual function in most patients with primary ONSM and is associated with a low risk of significant ocular sequelae. We agree that this treatment should be considered instead of surgery in patients with primary ONSM who require intervention because of significant or progressive visual loss.

Leber Hereditary Optic Neuropathy (LHON)

LHON is a well-known mitochondrial disorder and is an important cause of hereditary optic nerve-related permanent vision loss. LHON should be suspected in a young male with subacute vision loss and a maternal family history of similar vision loss [184]. Clinical examination findings are similar to those of other mitochondrial optic neuropathies and include variably reduced visual acuity, impaired color vision, and central or cecocentral scotomas. At onset, the optic discs may appear normal or hyperemic with telangiectatic vessels on the disc surface and in the peripapillary region. Eventually, optic disc pallor occurs that usually is more profound temporally than nasally Diagnosis is confirmed by gene testing for one of the three most common mitochondrial DNA mutations: 11778G>A/MT-ND4, 3460G>A/MT-ND1 and 14484T>C/MT-ND6. These three mutations account for about 90% of cases, however, if this screen is negative and there is a high suspicion for LHON based on the clinical picture, entire mitochondrial genome sequencing should be pursued to identify other rare mutations [144, 184].

There currently is no consistently beneficial treatment for LHON. The drug idebenone is the main intervention for preventing visual deterioration in LHON when administered in the acute or subacute phase of the disorder. More recent treatment options being evaluated are adeno-associated viral vector-based gene therapy and mitochondrial replacement therapy.

Idebenone

LHON is the first mitochondrial disease for which a treatment has been approved by the European Medicine Agency. The approved treatment is idebenone which has been used empirically since 1992 [185]. Idebenone is a short-chain benzoquinone with

antioxidant properties. It carries mitochondrial electrons to complex III of the mitochondrion and directly promotes ATP production, ultimately activating ganglion cells of the retina with resulting visual recovery [186]. The therapeutic benefit of idebenone has been evaluated through a placebo-controlled randomized clinical trial [187] and a large retrospective case series [186]. In 2016, an international consensus statement on the clinical and therapeutic management in LHON was put forth by a panel of world experts [184]. The consensus recommendation for therapeutic management in LHON is to initiate idebenone as soon as possible at a dose of 900 mg/day in patients with symptom onset of less than 1 year and to continue the treatment for 1 year. They panel did not find evidence to suggest the use of idebenone in patients with chronic disease.

Gene Therapy

The mutations generated in LHON affect mitochondrial genome complex I of the electron transport chain and typically involve a single amino acid exchange [188]. The goal of gene therapy in LHON is to replace the missing protein product. In the case of the LHON 11778G>A mutation, this pertains to missing ND4 (mitochondrial encoded NADH:ubiquinone oxidoreductase core subunit 4). Genetically modified adeno-associated viral vectors (AAV2) have been developed to deliver a mitochondrial ND4 gene construct either into the mitochondrial matrix compartment [189] or into the nuclear genome [190] to compensate for the 11778G>A mutation [191]. It has yet to be determined if these modified ND4 subunits will integrate smoothly into complex 1 and be stable enough to allow the electron transport chain to run efficiently [192]; however, preliminary data from clinical trials have supported the safety of AAV2-based gene therapy vectors and have found some visual improvement in eyes treated by intravitreal injection of the vector [193–195]. Clinical trials to establish efficacy are ongoing.

Mitochondrial Replacement Therapy (MRT)

MRT is being studied with the goal of completely replacing mutated mitochondria with normal mitochondria to prevent maternal transmission of mitochondrial DNA mutations. This is done by reproductive technologies that allow for uncoupling of the mitochondrial DNA from nuclear DNA [196] such that only the mitochondrial part of the DNA comes from a donor [197]. Parental nuclear material is transferred into a mitochondrial donor zygote carrying wild-type mitochondrial DNA to minimize or eliminate carryover of mutant DNA. Preliminary results are promising and may pave the way for eliminating the transmission of mutated maternal mitochondrial DNA in the future [196, 198].

Visual Restoration Therapy

The reported number of patients suffering from vision loss after stroke, either hemorrhagic or ischemic, ranges from 45 to 92% in the acute setting and from 8 to 25% chronically [199–201]. Although both efferent and afferent pathways may be

affected by stroke, homonymous hemianopia is the most common visual field deficit occurring after stroke [200, 202]. Homonymous hemianopias often are debilitating, leaving a patient symptomatic for years [199]. Although 50% of patients with homonymous hemianopia from a stroke may show some degree of improvement, complete resolution is seen in only 8–12% of patients [201].

The benefit of several types of proposed visual rehabilitation after stroke continues to be a controversial topic of discussion among ophthalmologists and neurologists. Proposed interventions for visual restoration include the use of prisms to expand the area of good vision, saccadic exploration to explore the blind hemifield, and restorative therapy to bring attention to the border between the seeing and nonseeing area in an effort to increase the area of vision [202]. Unfortunately, none of the prospective studies evaluating these interventions has been double blind and controlled, and the results have been inconclusive. For example, in patients who have undergone visual restoration therapy, there is no correlation between improvement in visual field and improved ability to perform daily activities. Some patients have reported improved daily activities despite no change in their field defect and some patients with an apparent visual field improvement has reported no improvement in their ability to perform daily activities. In addition, even when patients have reported improvement in quality of life, when asked to draw what they perceive to be the area of their scotoma after visual restoration therapy, there was no statically significant change in the area of vision loss when compared with what was drawn at baseline [203]. On the other hand, functional MRI and magnetoencephalography studies performed after visual stimulation activities (although without a control) have suggested there may be some plasticity contributing to visual recovery and visual training; however, the utility of these imaging findings in the absence of evidence to support retinotopic reorganization is limited [202, 204, 205].

Researchers have suggested various theoretical mechanisms for apparent visual recovery. These mechanisms include activation of uninjured but suboptimally activated occipital cortex, bypassing damaged cortex, changes in neuronal chemistry and sprouting of new connections to name a few [206–208]. Alternatively, it has been suggested that the apparent visual recovery is actually due to unstable fixation. It is hoped that with an increased theoretical understanding of visual rehabilitation, new and reliable clinical therapies are on the horizon.

Endovascular Intervention Updates

Neuro endovascular intervention has become important in the world of neuro-ophthalmology due to intersections in management [209]. This intersection includes strokes, aneurysms, CNS vasculitis, and venous sinus stenting for pseudotumor cerebri (PTC) to name a few. Neuroendovascular intervention provides an additional avenue to aid in diagnosis and management of vision-related problems; however, the treatment itself may cause adverse visual events in some cases. Below we review a few of the scenarios where neuro-ophthalmology and neuro-intervention intersect.

Aneurysms

Aneurysms are a common cause of neuro-ophthalmic referrals. Common complaints related to aneurysm compression or rupture include double vision from ocular motor nerve palsy, pupillary changes, visual pathway disorders and compressive chiasmopathy or optic neuropathy [210]. Compression of the structures that comprise the afferent and efferent visual pathways suggests a large and probably unstable aneurysm, the diagnosis and treatment of which is crucial in preventing major permanent visual and/or neurological deficits as well as death [210]. As neuroendovascular intervention evolves as a treatment for aneurysms at risk for rupture, it is important that ophthalmologists and neurologists understand the mechanism of treatment and the potential adverse effects. Neuroendovascular aneurysmal repair involves endoluminal reconstruction. This refers to the use of a stenting devise to redirect flow away from an aneurysmal sac or outpouching while endothelial ingrowth around the stent leads to remodeling of the vessel lumen. In cases where a stent may not be appropriate, usually determined by aneurysm architecture, detachable platinum coils may be used to embolize the aneurysm outpouching [209]. Figure 8.9 below provides an example of a coiled aneurysm, before and after coiling. Adverse events from endovascular treatment include headaches, problems related to compression from mass effect of the thrombosed aneurysm, and intraprocedural rupture [209]. Aneurysms located near the skull base have been noted to swell often which causes stretching of the dura and pain. In one case report, mass effect from a repaired anterior cerebral artery aneurysm caused optic tract edema with unilateral vision loss and a homonymous field cut [211]. In this case, the patient was treated with high-dose steroids with near-complete recovery. A meta-analysis of 13 retrospective studies encompassing 477 patients compared visual outcomes of aneurysm repair by surgical clipping with endovascular coiling [210]. Complete recovery after each procedure reached 78% in the surgical group versus 44% in the endovascular group. Similar findings were observed when comparing recovery rate specifically for cranial neve palsies. Surgical intervention also results in improvement of visual field deficits from anterior visual pathway compression. It must be emphasized, however, that surgical intervention is associated with higher complication rates, longer stays in the intensive care unit, and higher hospital costs compared with endovascular intervention. Decision for neurovascular versus surgical approach is highly influenced by location (experience of the operator in a high volume versus low volume institution) and aneurysm architecture.

Griessenauer et al. treated 127 consecutive patients with 160 ophthalmic segment aneurysms using flow diverters [212]. In this cohort, complete occlusion of the aneurysm was observed in 90 of 101 (89%) cases with a mean follow-up of 18 months. Of ten patients with visual symptoms, one had immediate improvement in visual function. Among 117 patients without visual symptoms, two (1.6%) experienced visual impairment following treatment. There was no mortality related to the procedure, but, in addition to the two patients who experienced visual impairment post-procedure, two developed a permanent neurological deficit (hemiplegia). Based on their experience in this large series, the authors concluded that treatment of

ophthalmic segment aneurysms with flow diversion is a safe and effective procedure compared with clipping. Several of the same authors participated in a two-center retrospective cohort study of consecutively treated ophthalmic segment aneurysms that compared stent-assisted coil embolization with flow diversion [213]. Sixty-two aneurysms were treated with stent-coiling and 106 were treated with flow diversion. The authors found that stent-coiling and flow diversion were equally effective in treating these aneurysms and that there were no significant differences in procedural complications or in angiographic, functional, or visual outcomes. In fact, in this series, no patient with stent-coiling had a permanent visual complication whereas only one patient in the flow diversion series had permanent visual loss.

For the efferent visual system, the issue relates to third nerve palsy recovery after treatment of ruptured and unruptured internal carotid-posterior communicating (PCom) aneurysms. [214] described the effect of endovascular treatment of 34 patients with third nerve palsy associated with a ruptured PCom aneurysm. At 6-month follow-up, 21 (61.8%) had experienced complete recovery of their palsy whereas 8 (23.5%) had incomplete recovery. The mean time to resolution was 24.5 days. As might be expected, there was a trend toward complete recovery among patients with an initially incomplete palsy. No patient in this series had post-operative worsening of an incomplete palsy. Hall et al. described the effect of treatment of unruptured PCom aneurysms on resolution of third nerve palsy [215]. These authors reported their experience with 15 patients and provided a narrative review of 179 patients from 31 case reports or cohort studies. Based on their experience and literature review, they concluded that surgical clipping was associated with a higher rate of recovery than was endovascular treatment. Again, patients who presented with a complete palsy had a lower rate of recovery than did those with a partial palsy.

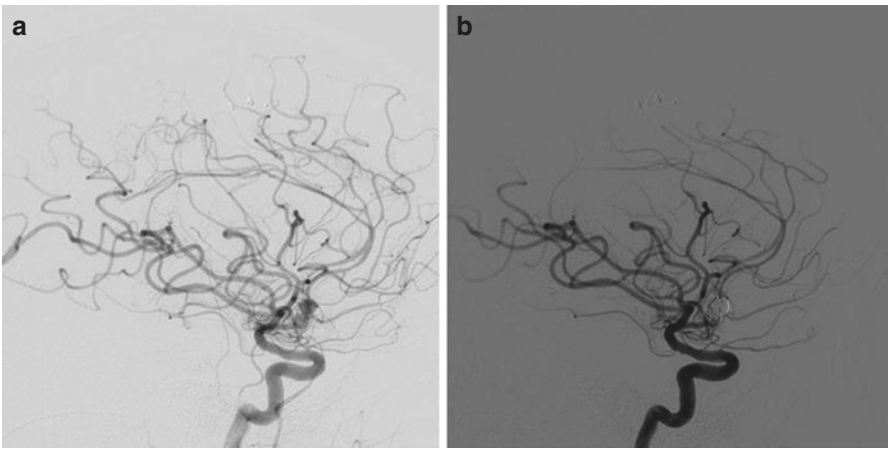

Fig. 8.9 Cather angiogram imaged showing an Anterior communicating artery aneurysm, (**a**) before and (**b**) after coiling. After coiling, there may be compression of neighboring brain tissue or blood vessels from the coil mass. (Pictures courtesy of Dr. Michael Pichler, MD)

Venous Sinus Stenting in Primary Pseudotumor Cerebri (PTC)

Various institutions across the world have begun implementing venous sinus stenting as a therapy for medically refractory pseudotumor cerebri (PTC) and, in some cases, first-line therapy (Fig. 8.10). Liu et al. described ten patients with PTC and venous sinus stenosis with an elevated gradient across the region of stenosis (30.0 ± 13.2 mmHg) and elevated ICP (42.2 ± 15.9 mmHg) for whom medical therapy had failed and who subsequently underwent venous sinus stenting [216]. Following stent placement, all patients had resolution of the stenosis and gradient (1 ± 1 mmHg). More importantly, however, the authors monitored ICP throughout the procedure and noted an immediate decrease in ICP following placement of the stent (17.0 ± 8.3 mmHg) with a further decrease overnight. This publication and another by Matloob et al. confirm the immediate effects of venous sinus stenting on ICP in this group of patients [217]. Another prospective observational study that consisted of 13 patients with venous sinus stenosis, visual field changes, and medically refractory, medically intolerant or fulminant PTC also concluded that venous sinus stenting is a safe and immediately effective method of reducing intracranial pressure (ICP) in PTC [218]. This study also reported improvement in headache and other associated symptoms of PTC, as well as reduction or resolution of papilledema, resolution of RNFL thickness, and improvement in visual field as measured by mean deviation using automated perimetry. A number of other series with smaller groups of patients also have reported successful stenting and resolution of increased ICP and associated symptoms [219]. Several recent retrospective literature reviews, systematic reviews and meta-analyses of patients undergoing venous sinus stenting for medically refractory PTC conclude that stenting has high technical success and low complication rates in appropriately selected patients [220–222]. Recommendations on the appropriate selection of patients also have been suggested based on literature review [222]. This obviously is an important consideration for those patients who present with evidence of optic nerve dysfunction and for whom a decision must be made regarding performing immediate optic nerve sheath decompression, and/or drainage of cerebrospinal fluid.

Despite the enthusiasm for venous sinus stenting for patients with PTC and venous sinus stenosis, a recent single-center case series of 41 patients studied clinical, radiological and manometric outcomes 120 days after venous sinus stenting [223]. Although the results from this study supported prior findings of reduced venous sinus pressure and lower complication rates compared with shunting at 120 days, at least 20% of the patients developed restenosis and only 63.3% of patients showed improvement or resolution of papilledema. This raises a question regarding the long-term viability and clinical outcomes of venous sinus shunting. Ultimately, prospective, randomized controlled studies designed to assess long-term outcomes and complications of stenting for PTC will be required to determine if venous sinus stenting provides sufficient long-term benefit to become the procedure of choice in patients with PTC and venous sinus stenosis.

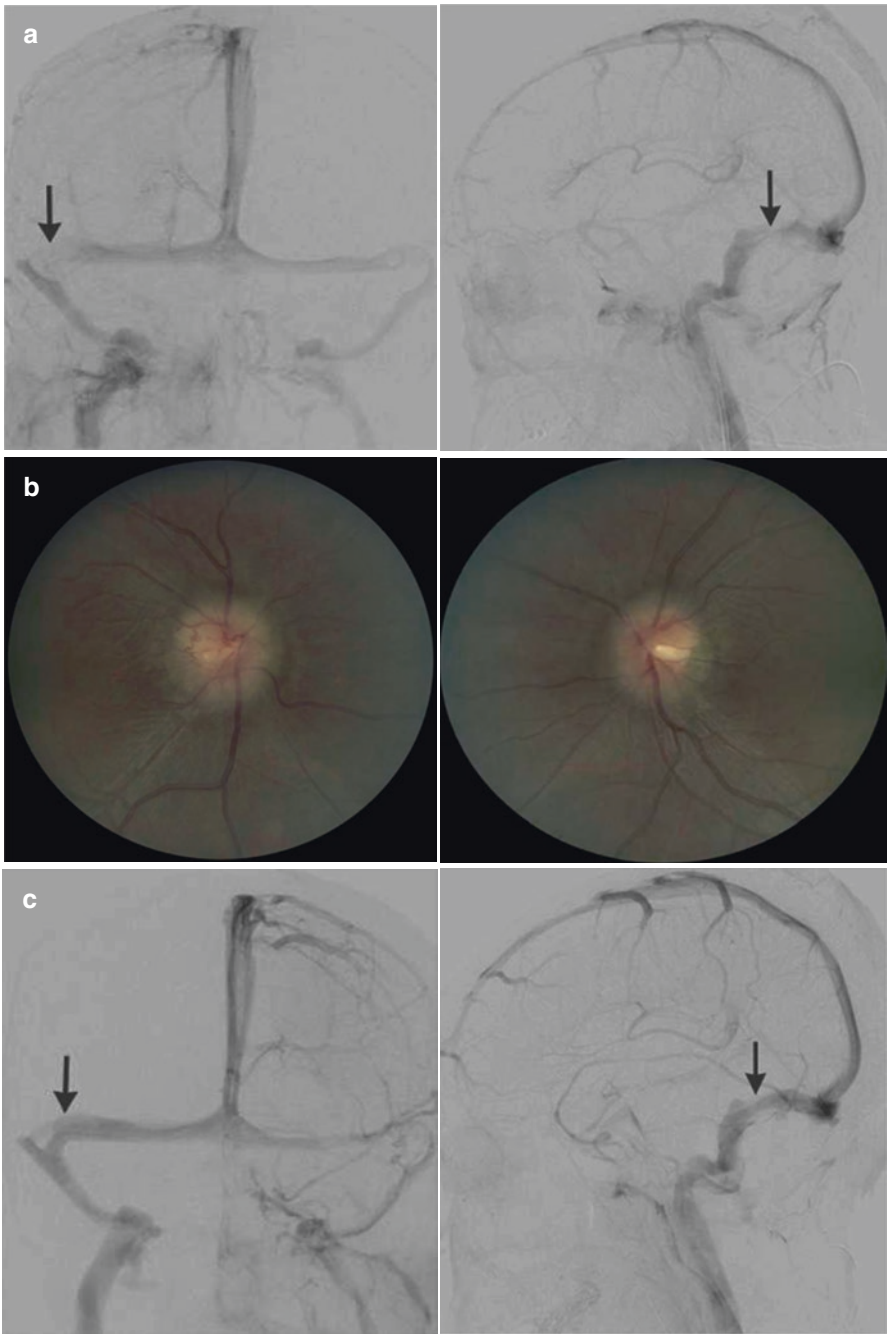

Fig. 8.10 Fundus photos and coinciding MR venogram images in a patient with Pseudotumor Cerebri and venous sinus stenosis; (**a**) venous sinus stenosis seen on MR venogram; (**b**) fundus photos showing papilledema prior to sinus stenting; (**c**) venous sinus now open after endovascular stenting; (**d**) improved papilledema

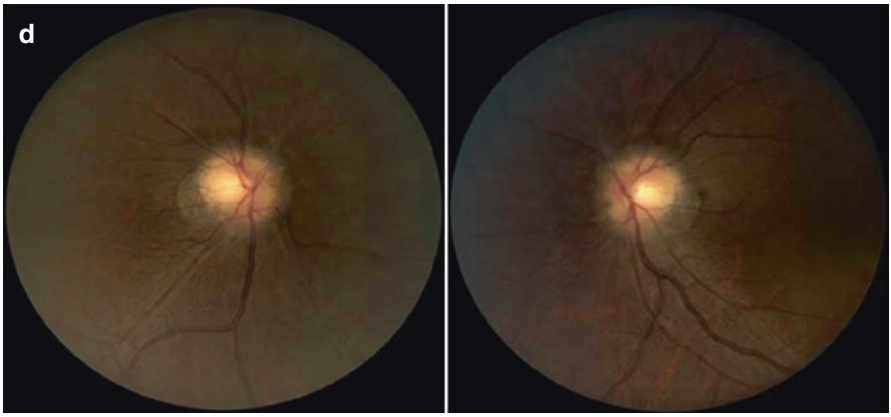

Fig. 8.10 (continued)

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