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Neuro-ophthalmic Disorders

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Current Practices in Ophthalmology

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Neuro-ophthalmic Disorders

Springer

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ISSN 2523-3807 ISSN 2523-3815 (electronic)
Current Practices in Ophthalmology
ISBN 978-981-13-8521-6 ISBN 978-981-13-8522-3 (eBook)
https://doi.org/10.1007/978-981-13-8522-3

This Springer imprint is published by the registered company Springer Nature Singapore Pte Ltd.
The registered company address is: 152 Beach Road, #21-01/04 Gateway East, Singapore 189721, Singapore

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Emerging Trends in Optic Neuritis and Associated Demyelinating Diseases

1

Prem S. Subramanian

Introduction

Optic neuritis often is the first neurological symptom that heralds the onset of systemic demyelinating disease, although there are numerous other causes that must be considered as well. The initial evaluation and treatment of optic neuritis is guided by the clinical presentation and, in particular, whether the condition results in papillitis or solely retrobulbar inflammation. Treatment may be offered both to reduce the period of disabling vision loss and to improve visual outcomes in some cases. Identification of optic neuritis related to viral or other infections also must be done to institute appropriate therapy in such cases. Risk of further neurological events is based upon any prior neurological symptoms as well as MRI findings at the time of vision loss. Systemic medical therapy may be indicated to prevent progression to full-blown demyelinating conditions such as multiple sclerosis (MS) or neuromyelitis optica (NMO), and the treatment strategies for these two conditions is quite different. Both the ophthalmologist and neurologist should be familiar with the acute and chronic care of individuals with optic neuritis and their long-term prognosis, as both play an important role in the short- and long-term assessment of their visual and neurological health.

Clinical Presentation

Patients with vision loss from optic neuritis tend to be in the second to fourth decade of life, with women affected more frequently than men [1]. Subacute vision loss occurs over the course of days and is typically accompanied by pain

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_1

that is worse with eye movement. Although pain is not required to make the diagnosis of optic neuritis, it is present in over 90% of patients with the condition [1], and the absence of pain should be considered atypical and raise suspicion for an alternative diagnosis being the cause of the visual loss [2]. In adult patients, unilateral vision loss is characteristic, although bilateral disease may occur; however, bilateral disease occurs with greater frequency in the pediatric population, especially in the first decade of life [3]. Pain may also be less common in children. A visual field defect typically is present when automated perimetry is performed. Presenting visual acuity ranges from normal (20/20 or equivalent) to no light perception [1], with recent data suggesting that worse presenting visual acuity is associated with particular systemic disorders and pathogenic mechanisms (see below). In most cases, a preceding or concurrent systemic illness is not present, and accompanying neurological symptoms such as numbness, weakness, or tingling may help to establish the nature of an underlying disease process or infectious disorder.

Incidence of optic neuritis varies depending on geographic area and population ethnicity. In a study of a largely white population in the USA, an incidence of 5.1 per 100,000 persons was noted, and prevalence was estimated at 115 per 100,000 [4]. A more recent study of Chinese patients from Hong Kong reported 30 cases in 1 year from a catchment area of 1.8 million persons, suggesting a much lower incidence of 1.7 per 100,000 although the authors acknowledge that milder cases may not have presented for treatment and thus may have been missed [5]. Presenting signs and symptoms also vary across populations, and these differences may be related to differing underlying causes of the condition. For example, about 2/3 of patients in the Optic Neuritis Treatment Trial (ONTT, see below for more details) presented with vision loss and retrobulbar optic nerve involvement [1], while over half of patients in an Indian cohort of optic neuritis patients had papillitis (optic disc swelling) at presentation [6].

Other exam findings on presentation include infrequent vitreous cells, particularly when papillitis is present, and tenderness to palpation of the globe. Intermediate uveitis, although it has been associated with multiple sclerosis, does not have a specific association with the development of optic neuritis, and it is important that the clinician not confuse vision loss, usually painless, from uveitic macular edema with optic neuritis. Furthermore, patients with uveitis and demyelinating disease such as multiple sclerosis typically are older than optic neuritis patients, and their vision loss often is more chronic in nature [7].

Visual field testing by perimetry or even tangent screen often is helpful in establishing the diagnosis of optic neuritis. The most common visual field deficits in optic neuritis patients are a central scotoma or diffuse depression, although any deficit may be found, and the foveal threshold on automated perimetry correlates most closely with visual acuity both acutely and during the recovery phase of the disease [8]. Subtle visual field deficits in patients with normal visual acuity at presentation may be missed with standard threshold perimetry and may be better detected with a supraluminal threshold strategy [9].

Lab Findings and Neuroimaging

Barring an absolute contraindication to the study, patients presenting with an acute attack of optic neuritis should undergo magnetic resonance imaging studies with and without contrast to assess the integrity of the visual pathways and the broader central nervous system (CNS). MRI orbits can demonstrate hyperintensity in the affected optic nerve(s) on T2 and/or STIR sequences, and contrast enhancement is usually observed on fat-suppressed T1 sequences. In cases where there is diagnostic uncertainty in the presence of optic disc swelling (i.e., absence of pain), orbital MRI may be helpful, as most cases of optic neuritis have optic nerve enhancement [10], and lack of abnormal optic nerve signal should steer the clinician away from an optic neuritis diagnosis. The optic nerve enhancement should resolve after several weeks, and if it does not, then an alternative entity such as tumor must be considered [11]. In most cases, the clinical diagnosis is quite secure, and the orbital MRI findings are merely confirmatory, although the location and extent of optic nerve signal abnormalities may be related to the underlying cause of the optic neuritis (see below). Rather, it is MRI of the brain and/or spinal cord that is more valuable in the detection of specific lesions related to systemic disorders such as MS and NMO, and the interpretation and application of neuroimaging results to diagnosis and therapy is detailed in a subsequent section.

Laboratory investigations, including serologies and cerebrospinal fluid analyses, are generally restricted to patients presenting with papillitis rather than retrobulbar optic neuritis, as the ONTT showed that few clinically relevant abnormalities were discovered via such studies [12]. Patients with papillitis should have serologies drawn for Lyme disease (in endemic areas), syphilis, angiotensin converting enzyme (for sarcoidosis), and tuberculosis (via Quantiferon Gold testing). Additional tests for local viruses (Zika, dengue fever, Chikungunya) may be indicated and should be considered along with a careful travel history, and tuberculin testing may be performed with the recognition that cross-reactivity with non-tuberculous mycobacterial species may occur [13].

Differential Diagnosis

Painful, subacute vision loss may occur with optic perineuritis, and it may be mistaken for retrobulbar optic neuritis. MRI orbits can help to distinguish these conditions, since gadolinium enhancement of the optic nerve sheath and not the nerve itself is a hallmark of perineuritis. Neuroretinitis often causes subacute vision loss with optic disc swelling that mimics anterior optic neuritis (papillitis). The characteristic macular star (Fig. 1.1) may not be evident for 2–3 weeks after the onset of disc swelling [2]. Thus, repeat examination at 2–3 weeks post presentation should be performed in patients with disc swelling and suspected optic neuritis. There is limited demographic and symptomatic overlap between patients who develop optic neuritis and nonarteritic anterior ischemic optic neuropathy (NAION), as the latter

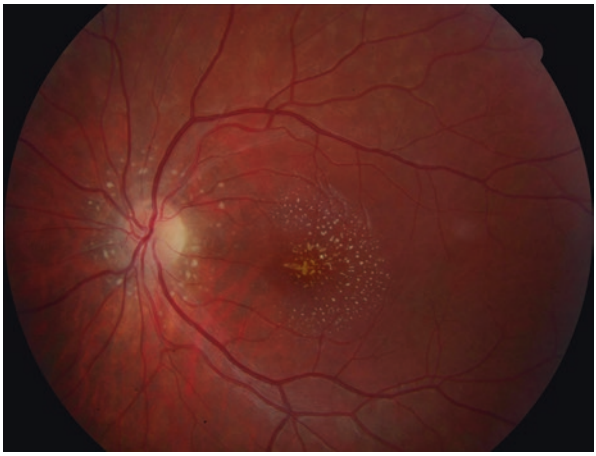

Fig. 1.1 Macular star associated with neuroretinitis in the left eye of a patient who developed painless vision loss in the left eye. She initially had mild left optic disc swelling, decreased vision, and a left relative afferent pupillary defect. The macular star seen in this image was not evident until 3 weeks after the onset of visual symptoms

patients tend to be older, have a male predominance, and experience sudden, painless, unilateral vision loss. Sectoral rather than diffuse optic nerve swelling is more typical in NAION, and peripapillary hemorrhages are common. MRI may be used to distinguish NAION from optic neuritis in many cases (see above), although this is usually not necessary. Vision loss from compressive optic neuropathy usually is more indolent than from optic neuritis, but MR imaging studies should be reviewed to exclude the presence of a mass lesion affecting the anterior visual pathways.

Initial Treatment and Management

Optic neuritis treatment has been guided by the results of the ONTT [1], which demonstrated that patients treated with intravenous methylprednisolone for 3 days followed by an 11-day course of oral prednisone 1 mg/kg/day had more rapid improvement in visual acuity than did patients given an oral placebo. A third group was treated with oral prednisone 1 mg/kg/day alone for 14 days, and this treatment is not recommended because an increased risk of recurrence was observed [12]. Final visual outcome was not statistically different among the three groups. Subsequent studies suggest that it is the initial high dose of corticosteroid, rather than the route, that is important to avoid the increased risk of relapse as was seen in the ONTT with lower dose oral prednisone treatment [14]. Similarly, the efficacy and necessity of the oral steroid treatment given after the initial IV pulse has been debated, and many physicians do not prescribe this treatment, instead choosing to treat patients with 5 days of intravenous therapy alone. A study is ongoing to compare the efficacy of self-administered ACTH injections with standard intravenous pulsed steroid therapy; ACTH gel also has been used by some physicians to treat patients with various types of demyelinating disease, although this practice is not widespread. The ONTT excluded patients with vision loss >8 days from presentation and included patients aged 18–45; thus, the results can be applied strictly only

to such a population. In practice, many physicians will treat patients of all ages with optic neuritis who present within 2 weeks of onset of symptoms.

Typical demyelinating optic neuritis does not improve dramatically or immediately upon starting steroid therapy, and if there is very rapid recovery of vision in the first 24–48 h, then the ophthalmologist should be concerned that the vision loss may be caused by a steroid-dependent process, such as sarcoidosis. Continued worsening of vision after steroid treatment is finished may occur but is unusual, and in cases where there is profound vision loss (counting fingers or worse visual acuity), additional acute treatment with plasmapheresis/plasma exchange has been advocated, although there is a paucity of data to support this practice.

Final visual outcomes, as reported in the ONTT, did not vary statistically among the three treatment groups, although contrast sensitivity was worse in subjects who received placebo therapy [15]. The characteristic pain with eye movement often subsides quickly with steroid treatment, and failure for pain to improve is unusual. Steroid therapy may be withheld or delayed in patients with a secondary identifiable cause of the optic neuritis, such as TB or syphilis, and management should occur with the assistance of an infectious disease specialist.

Neurological Prognosis

MRI and Risk Stratification

MR imaging of the brain and spinal cord should be performed in all patients with acute optic neuritis. Doing so is considered standard practice in more developed nations, and as MRI becomes more accessible to greater portions of the population in other countries, its use should become more standardized there as well. Extensive research has shown that the number, extent, and location of white matter abnormalities are highly predictive of later risk of demyelinating disease. In the absence of neurological symptoms of any type, patients may be diagnosed with high risk for MS if they have white matter lesions that meet defined criteria. The MAGNIMS working group has proposed that MRI abnormalities in two or more CNS areas may comprise radiologic evidence for MS as follows: >3 periventricular lesions, >1 infratentorial lesion, >1 spinal cord lesion, >1 optic nerve lesion, >1 cortical or juxtacortical lesion [16]. Patients with an abnormal MRI in the ONTT (defined as a single >3 mm WM lesion in a typical periventricular location [Fig. 1.2]) had a 72% risk of developing MS after 15 years, while patients with optic neuritis and normal imaging of the brain were estimated to have a 25% risk [17]. For patients undergoing MRI in 2017, the risk associated with a normal MRI study is almost certainly lower, since MRI used in the ONTT did not employ FLAIR sequences (which are much more sensitive for detection of WM lesions) or gadolinium contrast and was performed on instruments with lower field magnets than are commonly used at present. The predictive value of an abnormal MRI also is less, and this fact has impacted the outcomes of clinical trials assessing the ability of pharmacotherapy to delay or prevent the onset of MS (see below).

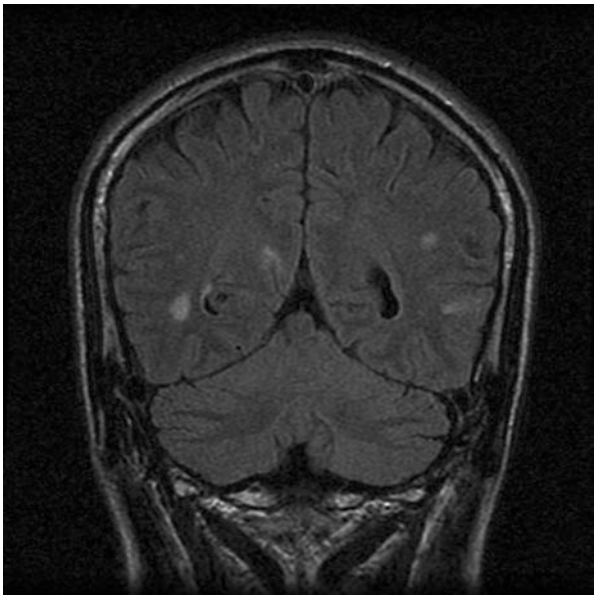

Fig. 1.2 Coronal FLAIR MRI brain without contrast showing periventricular white matter hyperintensities more prominent on the right side of the brain

MS vs NMO(SD)

Orbital MRI is not required for optic neuritis diagnosis, but the extent of optic nerve enhancement on T1-weighted MRI may help to determine subsequent risk for MS or NMO. Posterior or chiasmal involvement may increase risk for NMO rather than MS (see below), although some studies do not support the idea that chiasmal optic neuritis has a different course than other types of the disorder [18]. Other MRI changes that are associated with NMO rather than MS include longitudinally extensive (spanning three or more vertebral segments) spinal cord lesions on FLAIR sequences, lesions in the dorsal medulla or area postrema, the periependymal tissues, and the thalamic region, and extensive or large subcortical white matter abnormalities [19]. The revised diagnostic criteria for NMO (Table 1.1) demonstrate that the presence of WM lesions within the brain, previously thought to be incompatible with NMO, does not exclude the diagnosis, but that the location and size of these lesions must be evaluated carefully. Furthermore, patients may be diagnosed with incomplete NMO, also called NMO spectrum disorder (NMOSD) if they fulfill some but not all of the criteria. A crucial element of this diagnosis can be the detection of serum antibodies against aquaporin-4, an astrocyte footplate water channel that is selectively targeted in NMO [20]. The NMO-Ig is pathogenic in animal models and is highly specific but moderately sensitive for the diagnosis of "full-blown" disease [21]. Its sensitivity in NMOSD is lower but with high specificity nonetheless [22].

Another imaging modality that can be helpful for prognosis and risk stratification is optical coherence tomography (OCT), as it may be able to predict irreversible

Table 1.1 Diagnostic criteria for neuromyelitis optica and neuromyelitis optic spectrum disorder

Diagnostic criteria for NMOSD with AQP4-lgG 1. At least one core clinical characteristic 2. Positive test for AQP4-lgG using best available detection method (cell-based assay strongly recommended) 3. Exclusion of alternative diagnoses
Diagnostic criteria for NMOSD without AQP4-lgG or NMOSD with unknown AQP4-lgG status 1. At least two core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements a. At least one core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome b. Dissemination in space (two or more different core clinical characteristics) c. Fulfillment of additional MRI requirements, as applicable 2. Negative tests for AQP4-lgG using best available detection method, or testing unavailable 3. Exclusion of alternative diagnoses
Core clinical characteristics 1. Optic neuritis 2. Acute myelitis 3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting 4. Acute brainstem syndrome 5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions 6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions
Additional MRI requirements for NMOSD without AQP4-lgG and NMOSD with unknown AQP4-lgG status 1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm 2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis 3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions 4. Acute brainstem syndrome: requires associated periependymal brainstem lesions

From Wingerchuk DM, Banwell B, Bennett JL, et al. Neurology 2015;85:1–13
Abbreviations: *AQP4* aquaporin-4, *IgG* immunoglobulin G, *LETM* longitudinally extensive transverse myelitis lesions, *NMOSD* neuromyelitis optica spectrum disorders

optic nerve damage and indicate a greater likelihood of NMOSD. Axonal swelling on OCT of the retinal nerve fiber layer (RNFL) is seen in the acute phase with all types of optic neuritis, both with papillitis and retrobulbar disease. However, comparison of the RNFL >3 months later between those with MS and NMO shows much greater RNFL loss, on average, in patients with NMO [23–27]. Furthermore, the advent of macular ganglion cell-inner plexiform layer (GCIPL) complex analysis with spectral domain OCT has led to the earlier identification of possible NMOSD patients in the acute phase, since early loss of the GCIPL is associated with later RNFL thinning and thus more characteristic of NMO [25, 28, 29].

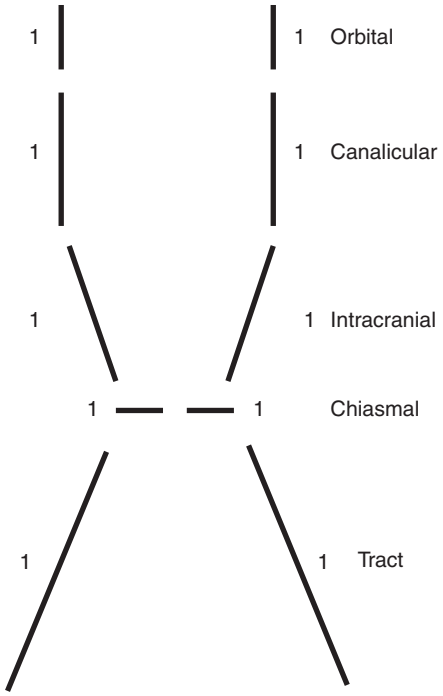

Fig. 1.3 Grading scheme to quantify the extent of optic pathway signal abnormalities on MRI in patients with acute optic neuritis. A higher score (more segments involved) is associated with an increased risk of NMO rather than MS as the underlying cause. Reprinted with permission from Storoni M, Davagnaman I, Radon M, Siddiqui A, Plant GT. Distinguishing Optic Neuritis in Neuromyelitis Optica Spectrum Disease from Multiple Sclerosis: A Novel Magnetic Resonance Imaging Scoring System. J Neuroophthalmol 2013;33:123-127

Other testing modalities, such as visual evoked potentials [30], may be more sensitive diagnostically for optic neuritis than is RNFL OCT, although macular GCIPL changes may be seen within a few weeks of disease onset.

The location and extent of optic nerve enhancement also may differ between MS and NMO-associated disease. In a small, masked analysis of 17 patients in whom an underlying diagnosis of either NMO or MS was known, optic nerve enhancement intracranially or at the chiasm was seen only in patients with NMO [31]. While these authors did not find a correlation between the extent of enhancement and the underlying disease process, others have proposed a grading scheme (Fig. 1.3) that quantifies the amount of anterior optic pathway enhancement, as they found that patients with NMO had, on average, twice the lesion extent as did patients with MS-associated optic neuritis [32]. Based on these and other data, the 2015 NMO diagnostic criteria indicate that, in the absence of NMO-Ig positivity, optic nerve enhancement of greater than half the length of the nerve and/or chiasmal enhancement may be used to support a diagnosis of NMOSD in concert with other clinical, radiologic, and laboratory data [19].

Visual Outcomes

Visual recovery after typical demyelinating optic neuritis occurs in most patients. Long-term visual prognosis has been studied systematically in patients with

demyelinating optic neuritis associated with both MS and NMO and has been reported more anecdotally for patients with other systemic associations. In the ONTT, about 85% of patients recovered visual acuity of >20/40, and over 65% achieved >20/20 [1]. Visual field recovery also was likely to occur at 6 months after presentation, and barring a recurrence, both visual acuity and visual field remained stable for several years of follow-up [15].

Recovery from other types of optic neuritis, in particular, that which is associated with NMO, is much more variable. In fact, failure to recover good visual function after optic neuritis has been suggested to help differentiate NMO-associated disease from other causes [33, 34]. For example, in a series of 128 Chinese patients with optic neuritis, AQP-4 antibody positivity was found in 45, and patients in this group were significantly more likely to have final visual acuity of 20/200 or worse ($p < 0.001$) [35]. They also had a greater chance for recurrent disease and bilateral involvement [35]. A meta-analysis of the effect of AQP-4 positivity on visual outcomes disclosed a 3.16-fold greater risk of visual impairment in subjects who were antibody positive, especially when more sensitive assay methods were used to maximize the sensitivity of the test [36]. Nonetheless, Brody and colleagues found that 11 of 12 patients with NMOSD retained adequate vision to qualify for a driver's license and experienced only mild, if any, visual disability per WHO criteria over a mean follow of 9 years [37]. Since outcomes may vary based on patient age and ethnicity, it is appropriate to have a guarded prognosis for visual recovery in NMOSD, particularly with AQP-4 seropositivity.

Long-Term Treatment

MS Prevention

Patients at high risk for conversion to MS by ONTT criteria may be classified as having clinically isolated syndrome (CIS) and should be considered for prophylactic treatment to reduce their risk of future MS. Several large, randomized studies have demonstrated the benefit of this treatment strategy for patients with CIS; these studies have included patients with a first demyelinating event that may include optic neuritis or other neurological symptoms. The first of these studies (CHAMPS) enrolled 383 patients, 192 of whom had optic neuritis as their neurologic event. In this study, treatment with weekly intramuscular interferon beta-1a reduced the risk of developing MS by 51%, and the study was terminated early with all patients transitioned to open-label drug from placebo because of the dramatic effect [38]. Efficacy in the subgroup of patients with optic neuritis also was demonstrated, with a 50% risk reduction when an adjusted model accounting for MRI lesion burden and age was applied [39]. Later studies showed similar risk reduction with the use of interferon beta-1b [40] and glatiramer acetate [41], although in the latter study, the study endpoint had to be changed from time to MS development in 25% of patients rather than 50%, as even in the placebo group, fewer than 50% of subjects had progressed to definite MS [41]. The lower rate of MS progression even without

treatment may reflect the increased sensitivity of modern MRI for white matter lesion detection. Lifelong therapy with MS drugs is expensive and carries potential side effects, and it has been argued that MS after optic neuritis is less severe than MS after other first demyelinating events [42–44]. For this reason, some neurologists do not advocate prophylactic treatment for CIS after optic neuritis. However, because CNS axonal loss occurs before onset of MS symptoms, others strongly favor early treatment in all CIS patients [45].

Long-Term MS Treatment

Most ophthalmologists will not manage the long-term care of MS patients, but familiarity with treatment agents and their side effects will assist in their care. Patients with relapsing-remitting MS (RRMS) may be treated with injections of beta-interferon, daclizumab, or glatiramer acetate, oral agents such as dimethyl fumarate, fingolimod, or teriflunomide, or infusions of natalizumab, alemtuzumab, or mitoxantrone. In addition, ocrelizumab may be used in the management of patients with progressive MS; data supporting the efficacy of other MS agents in the treatment of progressive disease are poor. Treatment is maintained indefinitely in most patients, as data suggest functional worsening may occur upon halting therapy [46]; however, there is ongoing research to identify those patients for whom discontinuation of therapy may be appropriate.

The ophthalmologist plays a critical role in the co-management of patients on MS therapies. New onset of visual symptoms in a previously stable patient could indicate new MS disease activity, and an alternative therapeutic strategy may be instituted by the neurologist. However, it is equally important that the ophthalmologist ensure that unrelated eye conditions are not present to avoid inappropriate therapeutic changes being made [47], as the neurologist often lacks the diagnostic equipment and experience to identify many ophthalmic diseases. Patients who are being treated with fingolimod may develop macular edema and should be screened by an ophthalmologist at baseline and again after 3–4 months of drug use [48]. Patients with a history of uveitis are at highest risk for this drug-related side effect [49].

NMOSD

Acute treatment of NMO and NMOSD patients includes use of corticosteroids and possibly plasmapheresis as noted above. Long-term immunosuppression may prevent relapses and/or progression to transverse myelitis and severe disability. Patients with AQP-4 seropositivity are at particular risk for disease progression [22, 50, 51]. In patients with definite NMO, long-term immunosuppression should be instituted, with azathioprine being somewhat less effective at relapse prevention than either mycophenolate mofetil or rituximab [52–56], to reduce long-term disability. Infused eculizumab also may be effective in preventing NMO relapse [57], but its cost has limited its widespread use. For patients with NMOSD and not full

NMO, immunosuppression often is not recommended until or unless relapse or new symptoms occur in seronegative patients, while seropositivity alone may be adequate reason to start therapy. Patients with NMO or NMOSD should not be treated with immunomodulatory MS therapies, as these agents are not only ineffective but may be harmful to them by causing disease progression [58, 59]. As in MS, the treatment of NMO may be lifelong, and there is no well-defined endpoint or time at which stopping therapy should be considered. As in patients with MS, the treatment is usually directed by a neurologist, with the ophthalmologist remaining an important member of the care team by evaluating patients for evidence of new or recurrent vision loss and excluding the presence of other eye diseases that also may cause new visual symptoms.

Visual Disability and Rehabilitation

While patients with MS-associated optic neuritis usually recover normal or near-normal visual acuity, decreased contrast sensitivity will impair their ability to perform tasks such as driving at night or in poor weather [60]. Reduced scores on clinical color vision testing with pseudoisochromatic plates is associated with worse disease severity in MS patients [61], and this may be a surrogate measure for contrast sensitivity [62]. Decreased overall quality of life has been correlated with reduced RNFL thickness as measured by OCT [63], but a direct or linear relationship between RNFL and the degree of visual dysfunction does not appear to exist. Similarly, although NMO patients will, on average, have lower RNFL thickness on OCT than MS patients after their acute optic neuritis resolves [25, 35], this difference is not enough to distinguish the two disorders in a given patient [24]. Furthermore, visual function does not correlate directly with RNFL or macular GCIPL thickness in NMO patients as well. Nonetheless, because of evidence that visual quality of life is reduced in both MS and NMO patients [64–66], rehabilitation should be offered to all patients, to include mobility training, driving assessment, and household safety evaluations as appropriate.

Conclusions

Our knowledge of the presentation and time course of optic neuritis has evolved with better understanding of the molecular and immunological mechanisms underlying the disorder. In the western world, the majority of cases are related to demyelination in a spectrum often associated with multiple sclerosis. In non-Caucasian populations, other types of optic neuritis including those that are typical for NMO must be considered, since both the acute and chronic management will differ significantly from other optic neuritis. Visual outcomes can vary but may be worse with NMO-associated disease. Long-term care is directed at prevention of recurrent episodes and neurological disability from involvement of structures outside of the optic pathways.

Acknowledgements This work is supported in part by a Challenge Grant to the Department of Ophthalmology, University of Colorado, from Research to Prevent Blindness, Inc.

Disclosure Dr. Subramanian has no relevant financial disclosures.

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2 Recent Advances in the Management of Idiopathic Intracranial Hypertension (IIH)

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Idiopathic intracranial hypertension (IIH) is one of the most frequently seen conditions in the Neuro-ophthalmology clinic. However, the exact pathophysiology of this condition is still not well understood. Over the last few years, there have been advances about the understanding, treatment, systemic associations in IIH in general, and in children with IIH. This chapter focuses on these aspects.

Terminology

Idiopathic intracranial hypertension (IIH) is a disorder characterized by symptoms of elevated intracranial pressure (ICP) in the absence of an underlying intracranial disorder, a meningeal process, or cerebral venous thrombosis. Therefore, diagnosis of IIH necessitates evaluation to rule out these conditions, and demonstration of elevated CSF opening pressure with normal CSF constituents. Diagnosis of IIH is established using modified Dandy criteria as described below [1].

In the past, it was referred to as 'benign intracranial hypertension' (BICH), as it was believed to have a benign course. However, it can cause permanent visual loss and disability, and hence this term is no longer recommended. It was also called 'pseudotumor cerebri' (PTC), as no true tumor was seen on neuroimaging; however, studies have shown features suggestive of elevated ICP on CT and MRI brain [2, 3]. Therefore, the most accepted term currently is idiopathic intracranial hypertension. However, over the last few decades there are reports of idiopathic intracranial

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hypertension without disc edema [4, 5], IIH secondary to cerebral venous sinus thrombosis [6], and other causes of secondary intracranial hypertension [7], etc.

Therefore, some authorities [8, 9] have proposed that it is better to designate the disease by the term 'pseudotumor cerebri' syndrome (PTCS) and subclassify as 'primary' or 'secondary' pseudotumor cerebri (PTCS) depending on absence or presence of secondary causes of elevated intracranial pressure.

Epidemiological Features

Gender, Age, and Body Weight

Many prior reports have shown [10–15] that idiopathic intracranial hypertension most frequently affects young to middle aged, obese women of childbearing age. This was endorsed further by the idiopathic intracranial hypertension treatment trial (IIHTT), which was a large multicenter prospective clinical trial developed by the NORDIC (Neuro-Ophthalmology Research Disease Investigator Consortium) to evaluate the clinical, epidemiological features, and outcomes in IIH [16].

In the IIHTT [16], mean patient age was 29.0 (SD: 7.4) years, and 97.6% of the patients were women. The average (SD) body mass index (BMI) was 39.9 (8.3) kg/m [2], thereby reiterating that majority of the patients were *obese females of childbearing age*.

The reported incidence of the idiopathic intracranial hypertension is one case per 100,000 population per year in general population, and about 19.3 per 100,000 in obese women aged 20–44 years [14].

Although there is limited literature from India, it also supports similar patient profile. Ambika et al. [17] reported that 80% of patients in their study were women with a mean age of 32.89 (range: 3.5–49) years. Although they did mention that majority of the patients were obese, details regarding the mean BMI of these patients were not provided. In another study, Agarwal et al. [18] reported that the mean body mass index (BMI) of the patients was 28.1 ± 5.5 kg/m^2. In this study, while only 33% of the patients were obese using the WHO criteria (BMI > 30 kg/m^2), over 67% of the patients had BMI >24.9 kg/m^2 (overweight). These reports suggest that overall IIH patients from Indian population might be overall thinner than the patients from the western population, majority of these patients do tend to be overweight, and obese as per the Indian criteria [19].

Role of Weight Gain, Higher BMI in the Pathogenesis, Recurrence, and Visual Outcomes

In addition, studies have shown that recent moderate weight gain of 5–15% of their baseline weight might increase the risk of development of IIH among the non-obese patients (BMI < 30), and in these patients the risk of IIH is almost equivalent to the obese [20]. It is also reported that higher BMI might also contribute to an increased risk of recurrence. In a study by Ko et al., they reported that among 26 women with recurrent IIH, BMI was higher at the time of the recurrence than at the time of initial

diagnosis [21]. Further in a study on relation between obesity and visual outcome in IIH, Szewka et al. found that a 10-unit increase in BMI increased the odds of severe visual loss by 1.4 times [22].

Therefore, these studies suggest a definite role of obesity in increasing the risk of developing IIH, risk of recurrence, and possible worse visual outcomes. The mechanism of increased risk of IIH in obese patients is not clearly understood. It might be related to elevated central venous pressure, reduced venous return, and/or various endocrinological and hormonal changes induced by obesity [23]. In addition, IIH might occur in non-obese individuals as well [24]. A recent study by Manfield et al. showed that bariatric surgery is beneficial not only in weight loss but also in reducing papilledema and improving the visual function of the patients [25]. The authors suggest that obesity might be related to the development of IIH due to increase in the intra-abdominal pressure [26] and therefore reduced central venous return, and reduced CSF compliance in the spinal canal [27], leading to a change in the CSF hemostasis. They suggest that obesity might lead to mineralocorticoid receptor activation [28] and increased CSF secretion, and increased adiposity might lead to microthrombosis [29], leading to occult cerebral venous sinus thrombosis and reduced rate of CSF outflow.

Role of Exogenous Substances

There are many reports in the literature that describe increased risk of IIH with various exogenous substances such as tetracyclines (especially doxycycline and minocycline) [30–32], systemic corticosteroids use and withdrawal [33, 34], nalidixic acid [35], nitrofurantoin [36], vitamin A [37], lithium [38], and danazol [38]. However, evidence emanating from the more recent case control studies have shown that many of these (especially multivitamins, oral contraceptives, oral corticosteroids, antibiotics) might be mere chance associations [39, 40], but some substances such as tetracyclines (especially doxycycline and minocycline) and vitamin A may precipitate the onset of IIH [32, 37, 41–43]. Furthermore, while prolonged use of oral steroids does not appear to be associated, sudden withdrawal of the drug might precipitate IIH.

Role of Vitamin A

Ingestion of high doses of vitamin A has been implicated to precipitate the development of IIH. It is hypothesized that elevated levels of vitamin A might lead to alternation in the gene expression in CSF resorption pathways causing decreased CSF absorption and elevated intracranial pressure [44, 45]. However, these changes are believed to be transient, and stopping vitamin A/retinoids intake often leads to normalization of the equilibrium [44].

A recent report by IIHTT looked at the metabolism of vitamin A and its metabolites (retinol, retinol-binding protein, all-trans retinoic acid (ATRA), alpha- and beta-carotenes, and beta-cryptoxanthin) in the serum and CSF of 96 IIH patients and 25 controls at baseline, and at 6 months after treatment [45]. The study found

that the IIH patients had lower levels of serum ATRA (median 4.33 nM) as compared to the controls (median 5.04 nM, $p = 0.02$). At the same time, serum levels of all the other vitamin A metabolites were similar in the two groups. Following treatment, levels of all the vitamin A metabolites increased in the serum and CSF, and among patients treated with oral acetazolamide, the levels of alpha-carotene ($p = 0.02$) and CSF ATRA ($p = 0.04$) were greater than the patients treated with placebo. This study contradicted the widely held belief that vitamin A toxicity may be contributory to the causation of IIH.

Role of Pregnancy and Fertility Drugs

As IIH usually occurs in young, obese women of the childbearing age, it is often speculated that the weight gain during pregnancy might contribute to the precipitation/onset of IIH in pregnancy. However, controlled studies have shown that the prevalence of IIH during pregnancy is like that in non-pregnant women [46, 47]. These reports showed that IIH might be diagnosed anytime during pregnancy; however, it is diagnosed most often during the first half of the pregnancy. A study by Huna-Baron et al. [48] reported outcomes in 16 pregnancies in 12 women and found that IIH symptoms and disc edema improved in most patients following lumbar puncture and salt-restricted diet; however, two patients needed continuous spinal drainage for 2 days, and one patient required acetazolamide and medical termination of pregnancy. In their series, only one patient had permanent visual field loss despite optic nerve sheath fenestration, lumbo-peritoneal shunt, and corticosteroids. Furthermore, these reports suggest that IIH does not appear to alter the obstetric outcomes in these patients.

Role of Obstructive Sleep Apnea

Existing literature suggests that obstructive sleep apnea may lead to or precipitate intracranial hypertension by leading to reduced venous return [49]. However, many of these patients also are obese, and it is unclear if obesity or obstructive sleep apnea is causative. Thurtell et al. compared the polysomnography data from 24 patients with IIH with a sample of 1741 controls from population [50]. They found that eight patients with IIH also had OSA, but their polysomnography results (apnea-hypnea index, AHI) were not different from those of controls after adjusting for their baseline age, gender, BMI, and menopausal status. It remains unclear if detection/treatment of obstructive sleep apnea influences the course of IIH. At the same time, there are case reports that suggest improvement in patient symptoms following surgical procedures for treatment of OSA [51, 52]. Therefore, the current understanding suggests that while it might be useful to screen the patients for OSA and offer treatment apart from the routine management of IIH, it is unclear if OSA alone can lead to development of intracranial hypertension.

Pathophysiology

Although idiopathic intracranial hypertension has long been studied, the exact pathophysiology remains unclear. Various hypotheses have suggested increased CSF production [53], reduced CSF outflow via the cerebral venous sinuses [54], or reduced CSF absorption either through the arachnoid granulations or through the extracranial lymphatics [55]. Prior studies have proposed that for any hypothesis to be true, the proposed pathophysiological mechanism should be able to explain the epidemiological features such as increased predisposition of young obese women of childbearing age to develop IIH, reduced CSF outflow, normal-sized ventricles, and absence of hydrocephalus, and effect of exogenous substances/hypercoagulable states to the development of elevated intracranial pressure [42, 43, 56–58].

Although a detailed description of the pathophysiological considerations is beyond the scope of this chapter, however, there is increased interest in the role of aquaporin channels and lymphatic pathways in the pathogenesis of IIH.

Aquaporin-4 proteins are water transport channels, present primarily in the foot processes of astrocytes, which contribute to several physiological functions in the CNS such as CSF circulation, interstitial fluid regulation, waste and metabolite clearance, electrolyte homeostasis (potassium and Calcium), and synaptic plasticity [59]. Few studies have found a role of aquaporin-4 as an alternative CSF drainage route if the other channels of CSF drainage are dysfunctional [60, 61]. However, anti-aquaporin-4 is not detectable in either blood or CSF in patients with IIH [62]. Another study evaluated the genetic association, expression of aquaporin-4 gene on chromosome 18, and did not find any significant association between IIH and aquaporin-4 gene expression; however, these authors proposed further studies looking at the tissue levels of aquaporin-4 in these patients with IIH [63]. Hence, the exact role of aquaporin-4 in IIH still remains doubtful.

Another interesting development in the possible pathogenesis is the proposed role of lymphatics in the central nervous system. Traditionally, the CNS is believed not to have a lymphatic drainage system; however, newer studies have suggested a possible lymphatic system that flows along the paravascular spaces and is termed as ‘Glymphatics’. Bezerra et al. have proposed the role of this alternate lymphatic circulation in IIH [64]. Some of the prior studies using the tracers injected into the brain have shown that the CSF outflow occurs along the paravascular spaces [65, 66]. A dysfunction of this proposed glymphatic system is responsible for the increased interstitial fluid. This may occur secondary to either increased inflow or reduced outflow of the fluid into the paravascular space and ultimately leads to the accumulation of the fluid in the interstitium and paravascular spaces. This pathway is linked to obesity, which might be associated with increased inflammatory activity and the aquaporin-4 pathway [7, 67]. They have even suggested that the neuro-radiological features of IIH are possibly influenced by the glymphatic pathways.

Another important consideration is the possible role of predisposing anatomic factors such as cerebral venous sinus stenosis, and hypercoagulable states that might also predispose to the development of IIH. Although cerebral venous stenosis is seen in up to 30–93% of the patients, it remains controversial if this is a cause or effect of the elevated ICP as there are reports of improvement in the venous sinus narrowing after lumbar puncture, suggesting that it might occur secondary to the elevated ICP [68, 69]. Furthermore, these might be incidentally found in normal population without elevated ICP [70]. Despite this, there are many reports of improvement in the CSF outflow and reduction in disc edema following placement of venous stents (see below). Despite this, exact role of venous sinus stenosis in the development of elevated ICP remains controversial. It might be hypothesized that in patients who have stenosis of the dominant right-sided venous sinus (see below), and in whom venous sinus stenosis persists even after lumbar puncture, it might be contributory to the development of IIH.

Finally in patients with thrombophilic disorders [58], it is believed that the development of microthrombi within the cerebral venous sinuses might lead to the development of microthrombi, and thereby increased resistance to the CSF outflow. Fortunately, these are rare conditions, and a work-up for an underlying hypercoagulable state is proposed in patients with a strong personal history, and/or demonstrated cerebral venous sinus thrombosis.

Diagnostic Criteria

The diagnosis of idiopathic intracranial hypertension is based on the modified Dandy criteria [1] which essentially include high-pressure headache and papilledema, elevated CSF opening pressure of ≥250 mm water, awake and alert patient, no localizing signs other than lateral rectus paresis, normal CSF constituents, normal brain imaging with no evidence of venous obstruction, benign clinical course apart from visual deterioration, and no other cause of raised intracranial pressure.

The IIHTT used the similar diagnostic criteria for the diagnosis of IIH; however, they defined increased CSF pressure as >200 mm water for non-obese patients and >250 mm H_2O for obese patients [71].

In children, CSF opening pressure may be abnormal if >280 mm of H_2O if sedation is used, and >250 mm of H_2O if no sedation is used [72]. CSF opening pressure tends to increase with the concomitant use of the sedation secondary to increased end-tidal carbon dioxide levels in the blood [73].

Furthermore, there are some patients who might have all features of elevated intracranial pressure in the absence of disc edema. These patients are often classified as ‘IIH without papilledema’.

Given these considerations, Friedman et al. proposed that IIH be better called as ‘pseudotumor cerebri syndrome’ and proposed the following diagnostic criteria for the diagnosis in both typical patients with papilledema and those without papilledema (Table 2.1) [74].

Table 2.1 Most recent proposed diagnostic criteria for the diagnosis of pseudotumor cerebri (reproduced with permission from Friedman D, Liu G T, Digre K. Revised diagnostic criteria for pseudotumor cerebri in adults and children. Neurology 2013;81: 1159–1165)

1. Required for diagnosis of pseudotumor cerebri syndrome[a]
a. Papilledema
b. Normal neurological examination
c. Neuroimaging: Normal brain parenchyma without evidence of hydrocephalus, mass, or structural lesion and no abnormal meningeal enhancement on MRI, with and without gadolinium, for typical patients (female and obese), and MRI, with and without gadolinium, and magnetic resonance venography for others; if MRI is unavailable or contraindicated, contrast-enhanced CT may be used
d. Normal CSF composition
e. Elevated lumbar puncture opening pressure (≥250 mm CSF in adults and ≥280 mm CSF in children (250 mm CSF if the child is not sedated and not obese) in a properly performed lumbar puncture)
2. Diagnosis of pseudotumor cerebri syndrome without papilledema
In the absence of papilledema, a diagnosis of pseudotumor cerebri syndrome can be made if b–e from above are satisfied, and in addition the patient has a unilateral or bilateral abducens nerve palsy
In the absence of papilledema or sixth nerve palsy, a diagnosis of pseudotumor cerebri syndrome can be suggested but not made if b–e from above are satisfied, and in addition at least three of the following neuroimaging criteria are satisfied:
– Empty sella
– Flattening of the posterior aspect of the globe
– Distention of the perioptic subarachnoid space with or without a tortuous optic nerve
– Transverse venous sinus stenosis

Note: A diagnosis of pseudotumor cerebri syndrome is definite if the patient fulfills criteria a–e. The diagnosis is considered probable if criteria a–e are met but the measured CSF pressure is lower than specified for a definite diagnosis

Recommended Workup of a Patient with IIH

IIH remains a diagnosis of exclusion, and the final diagnosis is based on the constellation of clinical findings and investigations that exclude any intracranial neoplasm, diffuse inflammatory process, and any CSF flow abnormalities.

Ophthalmological Evaluation

Recommended ophthalmological evaluation includes:

1. Formal visual fields (usually automated perimetry and could include manual kinetic perimetry, Goldmann perimetry for patients who fare poorly on automated perimetry)
2. Fundus (optic disc and posterior pole) photography, and
3. Optical coherence tomography (OCT) of the retinal nerve fiber layer (RNFL) to document the disc edema and macular ganglion cell layer (mGCL) which might be more sensitive to the ganglion cell damage than the RNFL protocol itself.

Serial optic disc photographs help us compare the change in the disc edema at subsequent follow-ups, and visual fields provide a measure of the visual function. In fact, the visual field examination remains the most sensitive test for detecting any worsening of the function in these patients and often dictates the need for the medical vs. surgical management.

OCT can be a reliable marker of monitoring the changes in the optic disc edema [73]. In addition, the changes in the ganglion cell thickness might enable us to detect neuronal loss despite the presence of optic disc swelling [75]. Spectral domain OCT is a sensitive tool in detecting, comparing, and monitoring the retinal and choroidal changes (folds) in patients with papilledema in IIH [74]. Sibony et al. showed that there could be three kinds of folds in patients with papilledema (peripapillary wrinkles, retinal and choroidal folds), and a higher number of patients showed presence of wrinkles/folds on OCT than on fundus photographs [76, 77]. These peripapillary wrinkles/folds are helpful in distinguishing true papilledema vs. pseudo-papilledema [78].

Kupersmith et al. showed that OCT was helpful in showing a greater reduction in these folds in the patients treated with acetazolamide vs. placebo in IIHTT [74]. Kupersmith et al. also showed that high definition OCT is useful in distinguishing the optic nerve swelling among patients with papilledema as in IIH where it is more likely to show an inward deflection of the RPE–choriocapillaris as compared to patients with optic neuritis and NAION [78].

Recommended Neuroimaging of the Patients

1. MRI brain with contrast and MR venogram to rule out intracranial pathologies and cerebral venous sinus thrombosis as discussed above.

   However, if the MRI is contraindicated or is not economically feasible, computed tomography (CT Brain) with contrast and CT venogram may be performed.

   Although changes suggestive of elevated intracranial pressure (empty sella, flattening of the posterior sclera, optic nerve head protrusion, distension of the optic nerve head, and vertical tortuosity of the optic nerve) have long been described in patients with IIH [2, 3], there is greater stress in utilizing these in making a diagnosis of IIH especially in patients with borderline CSF opening pressure, mild disc edema, and patients who do not meet all the diagnostic criteria of IIH [9, 79]. Newer imaging features that have been described in patients with IIH which may provide clues to diagnosis of IIH are [79–86]:

   Features relating to effect of elevated ICP on bony remodeling: increased incidence of meningoceles, meningo-encephaloceles, and increased size of the foramen ovale [80, 81].

   Features that possibly explain increased risk of spontaneous CSF leaks: thinning of the cribriform plate/presence of associated meningocele/meningoencephalocele along the skull base [82].

Features that possibly explain uncommon presentations such as asymmetric/unilateral disc edema in IIH (described below) and tonsillar descent [83, 84].

Asymmetric papilledema in IIH: Bidot et al. [83] compared the radiological features among patients with IIH with asymmetric (≥grade 2 difference in the Frisen scale) or unilateral (Frisen grade 0) papilledema versus those with bilateral symmetrical disc edema. They reported that the optic canal diameter was significantly larger (14.9%, range: 2.5–31.0%; $p = 0.008$) on the side of the worse disc edema. They also reported that it was also associated with a smaller perioptic CSF space, lesser flattening of the globe and lesser protrusion of the optic nerve head on the side of less severe disc edema.

Tonsillar descent in IIH: Although tonsillar descent might occur secondary to many conditions, significant downward displacement (>5 mm below the foramen magnum) of the cerebellar tonsils raises concern for Chiari malformation type 1 (CM1) [84–86]. Reports have shown that patients with chronically elevated ICP might show downward displacement of the cerebellar tonsils secondary to the changes in the foramen magnum, or secondary to chronically elevated ICP [84, 86]. This might cause difficulty in distinguishing between the primary etiology being CM1 or IIH, or co-existence of both.

However, CSF opening pressure and radiological findings on MRI may not correlate [87].

Figure 2.1 shows examples of MRI changes seen in patients with IIH.

2. *Lumbar puncture*: Lumbar puncture holds the key for the diagnosis of IIH. An elevated CSF opening pressure (>250 mm H_2O for adults and children without sedation, and >280 mm H_2O for children under sedation) [9] with normal CSF constituents in the absence of any structural/cerebral venous outflow abnormalities confirms the diagnosis of IIH.

   Although the technique of lumbar puncture is a well-established practice, few developments regarding the CSF analysis in relation of IIH are worth mentioning:

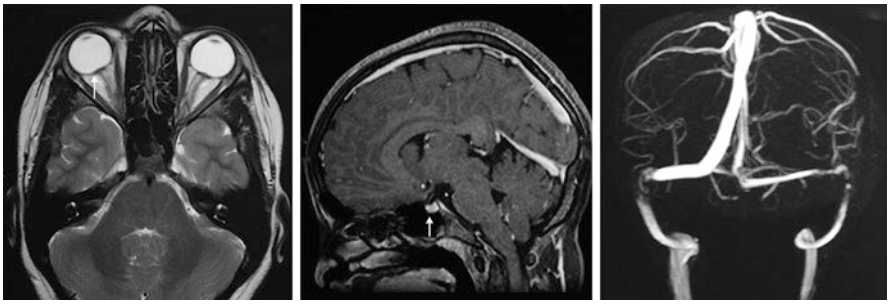

Fig. 2.1 Neuroimaging in IIH. The first panel shows a T2-weighted axial MRI scan showing posterior globe flattening (white arrow) with protrusion of the optic papilla into the globe. The middle panel shows a T2-weighted sagittal MRI scan showing a partially empty sella (white arrow). The third panel shows an MR Venogram demonstrating narrowing of both transverse sinuses

Effect of the patient positioning on the lumbar puncture: There are many studies that have studied the effect of the body position on the CSF opening pressure [88, 89]. Despite some conflicting results, majority of the studies recommend lateral decubitus position with legs extended for determining the CSF opening pressure. In addition, further studies especially in children have shown that there is no much difference in the CSF opening pressure being measured with legs flexed or extended [90].

Management Options

The primary objective of management of IIH centers around the lowering of ICP, which leads to amelioration of symptoms (such as headaches, tinnitus, and visual obscuration), and more importantly helps in the preservation of the visual function.

The principles of management revolve round three basic principles: weight loss, medical management, and surgical treatment.

Weight Loss

It is reported that about 6–10% weight loss from the baseline goes a long way in the long-term management of IIH [91]. Therefore, it is prudent to stress to all the IIH patients the need for long-term weight reduction. Patients should be encouraged to take low sodium diet, restrict fluid intake, and increase their physical activity. Although weight loss alone has been shown to be beneficial, but it is a long-term measure, and patients with visual dysfunction need simultaneous medical/surgical management. For patients with mild disc edema, headache, and near normal visual function, weight loss and headache control measures might be instituted with careful visual function monitoring.

While dietary modification and regular exercise help majority of the patients, patients with morbid obesity might require bariatric surgery for appropriate weight reduction.

Medical Management

The mainstay of the medical management has been acetazolamide. Although it has been used for long, evidence regarding its benefit has been established only recently in the idiopathic intracranial hypertension treatment trial (IIHTT) [92].

In IIHTT, patients with IIH and mild vision loss were treated with dietary modification, and either escalating doses of acetazolamide or placebo. It was observed that at 6 months follow-up, treatment with acetazolamide (69 patients) had greater improvement in the pointwise monitoring of the visual fields as compared to the placebo group (63 patients), with greater improvement in the nasal and pericecal

areas (around the blind spot). Furthermore, this improvement in the visual function was more marked among patients with moderate and severe disc edema. Also, improvement in the pattern mean deviation in the visual fields was greater in the acetazolamide group (1.61 dB vs. 0.94 dB), but it was not statistically significant. Overall, IIHTT showed that there was modest improvement in the visual function of the patients. The IIHTT also showed that treatment/acetazolamide group had greater weight loss as compared to placebo (average 7.5 kg vs. 3.45 kg, treatment effect 4.05, $p < 0.01$) [92], but improvement in visual function was independent of weight loss effect of acetazolamide.

As regards tolerance and adverse effects of acetazolamide, results from the IIHTT suggest that even though patients treated with acetazolamide had more incidence of adverse events such as gastritis, paraesthesia, and dysgeusia, but overall majority of the patients tolerated even high doses of acetazolamide. In the IIHTT, the benefits of treatment outweighed its side effects and majority of the patients reported better quality of life as compared to the placebo [93].

However, it should be remembered that this study was not designed to assess the beneficial effect of acetazolamide without weight loss [92]. Lastly, it is important to remember that acetazolamide provides little benefit for headaches; therefore, it has limited role in the patients who do not have significant visual dysfunction and primarily have headaches [94]. It is also important to exercise caution in its use in pregnancy (see below) and in patients who have a tendency for renal stones [95].

Other treatment options include topiramate [42, 43, 96], and diuretics like furosemide [42, 96, 97]. There are no large studies comparing the efficacy of topiramate in the management of IIH, but an open label study comparing acetazolamide vs. topiramate in 40 patients found significant improvement in the visual fields in both groups [67]. The improvement in visual fields was reportedly similar in both groups, while topiramate group had greater weight loss.

Therefore, topiramate is useful in the management of IIH patients:

- Patients who primarily have headaches as the presenting complaint
- Patients who have intolerance to acetazolamide
- As an adjunct to acetazolamide in the control of headaches and promoting weight loss

There are some reports that suggest beneficial effect of diuretics such as furosemide and chlorothiazide, in the management of IIH by promoting diuresis and reducing intracellular transport of sodium to the brain. It is believed that this leads to reduced CSF volume [42, 96, 97]. However, again there are no controlled studies demonstrating the benefits of diuretics over placebo or vs. acetazolamide. At present, furosemide might be recommended in patients who have acetazolamide intolerance, sulfa allergy, family history of renal stones, and possibly in the first trimester of pregnancy, where there might be a possible teratogenic effect of acetazolamide.

Surgical Management

As is well described in the literature, the primary management in IIH is medical, the surgical management of IIH is recommended for the patients who are refractory to medical management with severe visual dysfunction, rapidly progressive course (fulminant IIH), and those intolerant to the medical therapy. Surgical management of IIH again revolves around three specific interventions: Optic nerve sheath fenestration (ONSF), CSF diversion procedures (ventriculoperitoneal (VP) shunt; lumboperitoneal (LP) shunt; or thoraco-peritoneal shunt), and venous stenting procedures. Generally optic nerve sheath fenestration (ONSF) is indicated when visual function is threatened and is not controlled by medical treatment and when headache is not the very significant. Shunt procedure are considered if the main symptom is headache refractory to or partially relieved by medical treatment with/without visual function impairment.

Although there have been many short case series in literature, however, there are not enough prospective comparative studies comparing the various surgical procedures. However, the following generalizations can be made:

Optic Nerve Sheath Fenestration (ONSF) Procedures

Optic nerve sheath fenestration (ONSF) procedures are indicated primarily for the patients with advanced visual field damage, fulminant course, and mild headaches [98]. Although the exact mechanism of ONSF remains unknown, two mechanisms has been proposed—creation of fistulous tract allowing transdural egress of CSF and second is obliteration of subarachnoid space following fibrosis and thus blocking the transmission of raised CSF pressure to optic nerve distally [99]. In a long-term study, Obi et al. described the 7-year outcomes in 31 patients. They reported that following ONSF, visual acuity (VA) improved in 24.1%, remained stable in 62.1%, and worsened in 13.8% of operated eyes. Similarly, visual fields (VF) improved in 33.4%, remained stable in 55%, and worsened in 13.3% [100]. However, there is a potential for damage to the adjoining structures, with potential for vision loss, bleeding, injury to pupillary fibers, and corneal innervation. Fortunately, these are rare [101].

Also, it requires the expertise to perform the procedure, and might fail over time. Therefore, even if the patients improve, it might be prudent to monitor the visual function carefully followed by further CSF diversion procedures as a definitive procedure.

CSF Diversion Procedures

These have remained the most popular procedures, and easily available. The choice of the procedure often depends on the expertise of the neurosurgeon. There are limited studies that compare the VP shunts with LP shunts, and these report that VP shunts are slightly more like to fail, while LP shunts are more likely to need repositioning [102]. Kaplan–Meier analysis in a long-term retrospective review by Huang et al. [103] showed a steady reduction of functioning VP shunts over a span of 36 months with 80% (at 1 year), 65% (at 2 years), and 48% (at 3 years) of VP shunts functioning. Overall long-term success of either of these procedures remains similar.

Venous Stenting Procedures

There are many short case series demonstrating the successful resolution of disc edema, and improvement in visual function among patients with bilateral transverse venous sinus stenosis [104, 105]. However, despite advances in this technique, high incidence of complications still precludes its widespread use [106]. Its use is recommended in selected cases with persistent signs of elevated ICP, persistent transverse venous sinus stenosis, and angiographic evidence of stenosis with a pressure gradient of 8–10 mmHg between distal and proximal ends of the stenosis [105, 107].

There is scant data comparing the outcomes of various surgical procedures including optic nerve sheath fenestration and CSF diversion procedures [108]. It has been shown that the visual acuity and visual field improvement are slightly better in CSF diversion procedures, but ONSF surgery also appears to be effective in preserving vision. The complication rate in both the procedures is also comparable with slightly high periprocedural complications in shunt surgery [105].

Bariatric Surgery

Role of weight loss in the management of idiopathic intracranial cannot be overemphasized, since obesity plays a significant role in pathogenesis of IIH. While lifestyle and dietary modification can help achieve weight loss, it remains insufficient in considerable number of cases [109]. Bariatric surgery provides satisfactory results especially in patients with moderate to severe obesity (BMI > 35).

A systematic review [25] on comparison of outcome of surgical and nonsurgical measures of weight loss reported significant improvement in papilledema, headache symptoms, and CSF pressure reduction in both groups, but the reduction was more in surgical subgroup. Bariatric surgery may provide sustainable and optimal weight loss that may lead to long-term relief in IIH symptoms, but its role is still limited to morbid obesity. For milder and commoner forms of obesity, nonsurgical measures, life style modification, and medical management should be tried first as suggested by IHTT [92, 110].

Figure 2.2a, b shows an optic disc edema and visual field changes in a patient diagnosed to have IIH before and after starting treatment with acetazolamide.

Special Situations

Management of IIH During Pregnancy

Medical management of IIH with acetazolamide remains little controversial as there are prior reports of teratogenicity in hamsters in experimental studies [111] and reported case of sacrococcygeal teratoma [112, 113]. Despite this in the prior clinical case reports involving pregnant women in whom acetazolamide has been used, do not show any increased risk of fetal malformations in the usual doses (500–1000 mg/day) used for the treatment of IIH including women during the first trimester [114, 115].

In addition, use of diuretics in pregnancy might lead to a reduction in the maternal blood volume and thus reduced placental blood flow [48, 115]. Therefore, their use should be avoided; however, furosemide and chlorthalidone might be used as alternatives to acetazolamide [116]. Thiazide diuretics are classified as class D drugs in pregnancy and should be avoided [115]. At present, current recommendations for the management of IIH in pregnancy suggest close monitoring with evaluation of completed visual function, including visual fields, papilledema, and cranial nerve dysfunction. Acetazolamide/furosemide/chlorthalidone might be used with caution if warranted. There is limited data regarding the use of topiramate and it should be avoided.

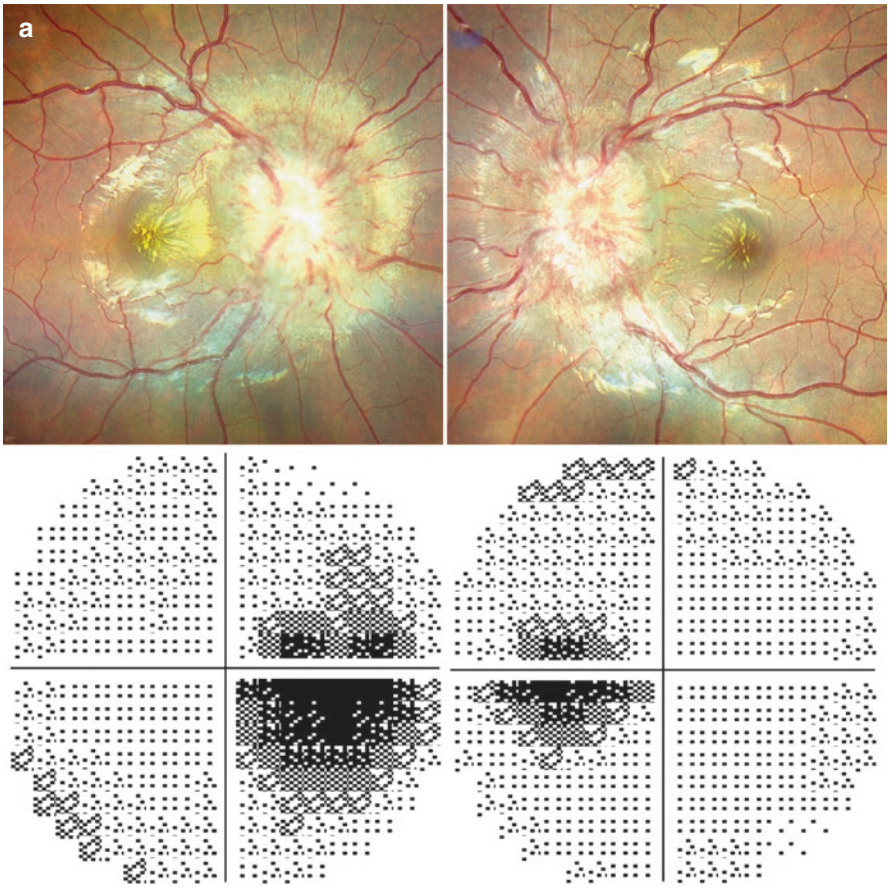

Fig. 2.2 (**a**) A patient with IIH—the top two panels show severe disc edema with accompanying macular edema. The corresponding visual fields show enlargement of the blind spot. (**b**) The same patient—after 3 weeks of oral acetazolamide therapy—the disc edema shows marked reduction, with improvement in the corresponding visual fields

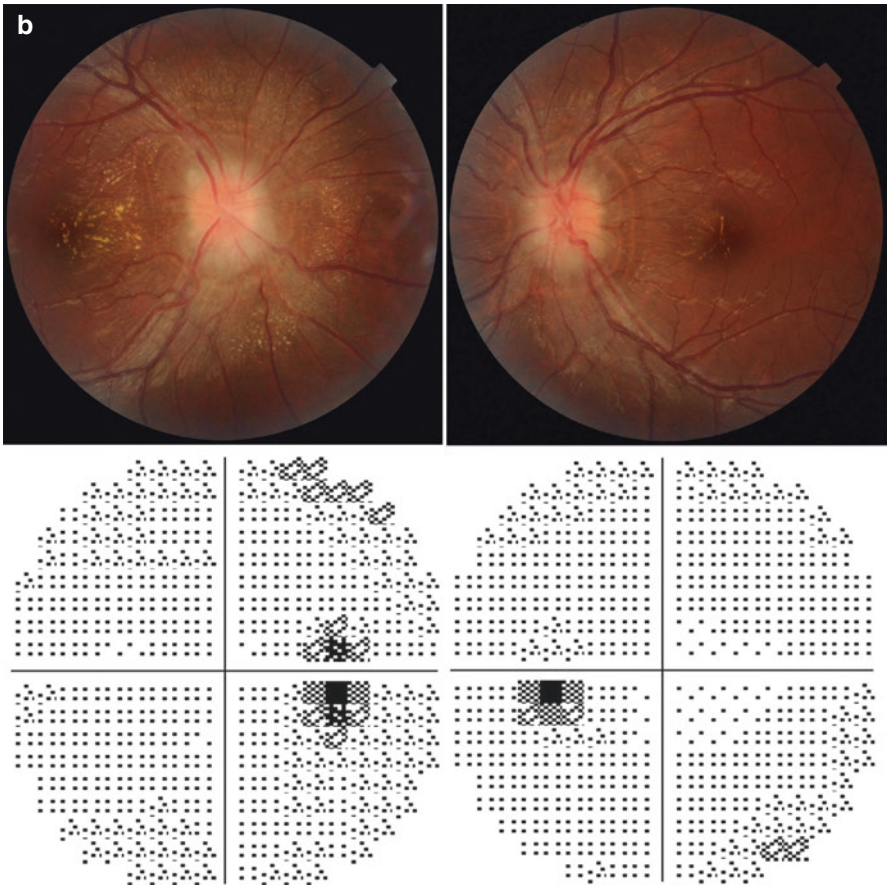

Fig. 2.2 (continued)

Another therapeutic option that is available is close monitoring with repeated lumbar punctures as and when needed. Therefore, management of IIH in pregnancy necessitates close monitoring every few weeks throughout the course of the pregnancy.

Factors Affecting Visual Outcomes

The IIHTT evaluated the subset of patients with poor outcomes, i.e., those who had treatment failure as defined in the protocol [117]. They found that 7/165 participants met criteria for treatment failure. Of these, six were on placebo and one was treated medically. They found that higher grades (grades III to V papilledema) had higher likelihood of treatment failure odds ratio (OR) 8.66 (95% confidence interval [CI] 1.65–*N*, $p = 0.025$). Similarly, males had greater risk of treatment failure 10.59

times higher (95% CI: 1.63–116.83, $p = 0.01$). Also, worse presenting visual acuity, i.e., 1-unit decrease in the number of letters correct on the ETDRS (Early Treatment Diabetic Retinopathy Study) chart at baseline, was associated with an increase in the odds of treatment failure by a factor of 1.16 (95% CI 1.04–1.30, $p = 0.005$). Also, patients with ≥30 TVOs per month were at higher risk of treatment failure: OR, 10.59 (1.63–116.83, $p < 0.010$).

Other Recent Advances

Pediatric IIH

Another area where significant improvement in the understanding of the IIH has occurred is pediatric IIH. It is becoming increasingly clear that IIH might behave differently than adults, with lesser prevalence of female preponderance, obesity [118, 119].

More recent studies suggested significant differences among prepubertal and postpubertal children with IIH [120]. This study reiterated the prior observation that while BMI score and height were like the age-matched children in prepubertal children, postpubertal children were overweight to obese, and taller. This study suggested possible subclassification of the children into three subgroups: prepubescent (age < 11 years), adolescents (age 11–17 years), and adults (>17 years). These studies therefore make the role of secondary endocrine factors to the development of the IIH in prepubertal children a potential area of research.

Differences in the Clinical Presentation

As highlighted above, children with IIH may present first with diplopia and acquired strabismus and visual disturbances are less common. Furthermore, visual complaints are usually overlooked and therefore these patients might present late. In various series 9–25% children were diagnosed to have IIH during evaluation of an incidentally detected disc swelling during routine evaluation [118, 121, 122].

Increased Use of the Optical Coherence Tomography/MRI for the Diagnosis

Studies have shown an increased prevalence of the MRI abnormalities in children with IIH. Lim et al. compared the prevalence of the MRI abnormalities among 23 children (median age: 8 years) vs. age-matched controls and reported higher prevalence of flattening of the posterior sclera (61% vs. 40%), distended perioptic subarachnoid space (65% vs. 35%), optic nerve head protrusion (17% vs. 0%), increased optic nerve tortuosity (30% versus 5%), and empty sella (26% vs. 5%) [122].

Hartman et al. [123] reported the prevalence of imaging characteristics among 50 children with IIH and compared these with the MRI findings from 46 adults. They also subclassified children into prepubertal (<11 years, 10 children), adolescents (11–16 years, 40 children), and adults (>17 years, $n = 50$). They reported that while adolescents and adults (>17 years) had similar prevalence of the imaging abnormalities, prepubescent patients had significantly lower prevalence of scleral flattening, increased perioptic cerebrospinal fluid, optic nerve tortuosity, empty/partially empty sella, and transverse sinus stenosis.

Outcomes in Pediatric IIH

Majority of the patients with IIH are treated medically with acetazolamide as the first line of therapy. A recent study [124] showed good response to acetazolamide with good improvement in headaches over a period of 1 week to 4 months with treatment duration ranging from 1 month to 5 years. Also, 26% had relapse of their symptoms but responded well to retreatment. Female gender, younger age at onset, presence of headaches, and presence of predisposing etiology were predictors of nonresponse to medical therapy, and postpubertal patients were at higher risk of recurrence.

Future Directions

While remarkable progress has been made in the last decade or so, the etiopathogenesis of IIH still remains elusive. There is significant interest in the role of the aquaporin channels, role of vitamin A metabolism, role of other endocrinological risk factors, and glymphatics in the pathogenesis of IIH. Hopefully, some of these factors will help elucidate some mechanisms of IIH.

At the same time, further research is focused at developing *non-invasive methods of ICP monitoring*. In a recent report, Xie et al. [125] showed recorded measurement of the orbital subarachnoid space width (OSASW) at 3, 9 and 15 mm behind the globe using T2 weighted fat supressed MRI of orbits. In this study these measurements showed correlation with the measurement of CSF opening pressure. In another study, Saindane et al. [126] have shown that the use of displacement encoding with stimulated echoes (DENSE) MRI technique showed a good correlation of pontine displacement with the conventionally measured CSF opening pressure. There are other researchers who are developing other methods of non-invasive ICP monitoring and hopefully there will be more progress in this field.

Management

There is active research in the field of medical management with a phase II, double-blinded, clinical trial of the novel drug AZD4017, competitive inhibitor of the

enzyme 11β-hydroxysteroid dehydrogenase underway [127]. The availability of navigation technology is likely to help increase the ease and success of the surgical techniques such as CSF shunts and CSF stenting in patients with IIH [128]. Another interesting development is a multicentric, randomized controlled trial, the VISION study (Venous Intervention versus Shunting in IIH for Optic Disc Swelling) trial that compares radiological venous sinus stenting to surgical intervention (CSF shunting) [129]. Although the authors published the patient perspectives, more details about the outcomes in the two groups will be interesting.

Apart from these, there is increased application of ocular imaging especially optical coherence tomography (OCT), and OCT substudy group of IIHTT has shown way for the increased application of this technique for the monitoring of optic nerve structural loss, and increased scope for structure function correlation in patients with IIH.

In conclusion, idiopathic intracranial hypertension has been a topic of active research over the last two decades. There is modification and expansion of the criteria for the diagnosis of IIH. The NORDIC idiopathic intracranial hypertension trial provided information regarding patient demographics, role of weight loss and medical therapy, OCT characteristics of patients with IIH, and possible factors predictive of poor visual outcomes. Similarly, there is increased understanding of pediatric IIH, and differences as compared to adult IIH. There is increased utilization of ocular imaging in the monitoring of these patients, and neuroimaging in the diagnosis and management of these patients. These advances have set the stage for the further research focused on the underlying etiology, newer modalities of treatment, and maximizing outcomes in IIH.

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Ischemic Optic Neuropathies: Update

3

Elizabeth M. Palkovacs and Karl C. Golnik

Optic Nerve Anatomy and Physiology

The optic nerve can be considered to be an extension of the central nervous system. It consists of 1.2 million axons which are myelinated by oligodendrocytes [1, 2]. The axons of the optic nerve originate from the cell bodies of the retinal ganglion cells. Anatomically, the optic nerve can be divided into four segments: (1) the intraocular portion, (2) the intraorbital portion, (3) the intraosseous portion in the optic canal, and (4) the intracranial portion.

The dimension of the optic nerve head in anterior–posterior dimension is about 1 mm and it widens in the retrolaminar space. The axons are myelinated from the posterior end of the optic nerve head. Blood supply of the ONH is drawn from two distinct sources. The superficial nerve fiber layer derives its supply from the retinal circulation from the branches of the central retinal artery. The deeper section is supplied by the posterior ciliary circulation. The intraorbital segment of the optic nerve is supplied by the pial capillary plexus. It is however important to remember that the ultimate source of blood supply to the optic nerve is from the ophthalmic artery [3, 4].

History and Examination

In patients presenting with vision loss, a detailed history of the chief presenting complaint must be elicited. Details such as laterality of the vision loss and degree and quality of the vision loss must be noted. The timeline of the visual dysfunction

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_3

is also important, including onset, duration of symptoms, chronicity of symptoms, and any associated patterns, intermittent improvement, and progression. A detailed history of the general systemic complaints is a must with particular attention to neurological symptoms that may be associated. For example, for a patient in his 80s, presenting with sudden vision loss, enquiring about the presence of jaw claudication, headaches, weight loss, and malaise, assumes great importance as temporal arteritis needs to be ruled out.

It is important to remember that many neuro-ophthalmic diseases are a part of a larger systemic disorder. Thus, it is extremely important to obtain a complete past medical and surgical history. Of special interest in these cases are diabetes, systemic hypertension, dyslipidemia, obstructive sleep apnea, migraines, prior cerebral vascular accidents, cancers, and rheumatologic conditions. Since a large number of hereditary conditions and environmental factors such as smoking, alcohol, and drug abuse can affect the afferent visual system, a detailed family and social history is a must.

As in any neuro-ophthalmic disorder, a complete ophthalmic assessment is mandatory. This would include visual acuity, color vision testing, visual field assessment, pupillary examination, ocular motility examination, external adnexal examination, evaluation of cranial nerve functions, anterior segment examination with slit lamp, dilated funduscopic examination. Ancillary investigations such as automated perimetry and optical coherence tomography may also be needed.

Best corrected visual acuity with refraction and/or pinhole testing should be recorded. Visual acuity reduction in optic neuropathies is highly variable. Tests such as Hardy-Rand-Ritter plates or Ishihara color plates must be used to evaluate acquired dyschromatopsia. The color vision must be checked uniocularly. Optic nerve dysfunction may show a disproportionate decrease in color vision. The pupillary examination should include pupillary size, reactivity to light, shape of pupils, and the results of the swinging flash light test. A swinging flashlight test should then be employed to assess for the presence of a relative afferent pupillary defect. The presence of a relative afferent pupillary defect is a powerful tool to assist the clinician in determining if an afferent disorder is present anterior to the lateral geniculate nucleus. An ipsilateral RAPD will be present in extensive retinal lesions, lesions of the optic nerve head and optic nerve, and a small contralateral RAPD will be present with optic tract disorders. Cranial nerves should be assessed in a complete neuro-ophthalmic examination. A detailed slit lamp examination, as well as dilated funduscopic examination, is part of a complete neuro-ophthalmic evaluation.

While examining the fundus, it is important to note parameters such as the size of the disc, its appearance, cup-to-disc ratio, presence of swelling or pallor, hemorrhages, and exudates. The most common causes of optic neuropathies that present with swollen optic nerves include ischemic optic neuropathies and optic neuritis. Investigative modalities such as automated visual field analysis and OCT are additional tools for the assessment of these cases. OCT may help in the quantitative analysis of the thickness of the retinal nerve fiber layer and its progress with time.

Anterior Ischemic Optic Neuropathy

Ischemic optic neuropathies refer to optic nerve dysfunction caused as a result of the disruption of vascular supply of the optic nerve. The usual presentation is that of sudden, acute vision loss. Anterior ischemic optic neuropathies can be broadly classified as nonarteritic anterior ischemic optic neuropathy and arteritic ischemic optic neuropathy.

Nonarteritic Anterior Ischemic Optic Neuropathy (NAION)

It is the commonest optic neuropathy in patients who are over 50 years of age. Ninety-five percent of all anterior ischemic optic neuropathies are nonarteritic [5, 6].

Although the typical age range of patients with NAION is 57–80 years old, it may also present in a younger age group [5]. NAION of the young may be more common than previously thought. In a large study which analyzed 848 patients with NAION, Arnold and associates found that 108 (12.7%) were younger than 50 years [6]. NAION is more common in Caucasians as compared to African Americans or the Hispanic population, and both males and females are affected equally [5, 7]. The common risk factors for NAION include diabetes mellitus, systemic hypertension, hypercholesterolemia, and ischemic heart disease [8, 9]. Data from the Ischemic Optic Neuropathy Decompression Trial (IONDT) showed that about half of the patients (47%) had hypertension and 24% had diabetes mellitus [10]. Another important association or risk factor is nocturnal hypotension, which may be exacerbated by some anti-hypertensive medications when taken at bedtime [11, 12]. This could account for the common symptom of vision loss upon awakening [11]. Besides the systemic risk factors, it is believed that local anatomical factors may also be responsible for the development of NAION. The optic nerves with NAION tend to be smaller with smaller cup-to-disc ratios. These small, crowded discs, referred to as "disc-at-risk," are predisposing factors for NAION [13, 14]. Another factor which may predispose to the development of NAION is obstructive sleep apnea. Presence of ipsilateral carotid occlusive disease has not been proven to be an independent risk factor [15, 16].

Recent studies have looked at the relationship between intake of drugs such as phoshodiesterase-5 (PDE5) inhibitors and the development of NAION. These drugs are commonly used to treat erectile dysfunction [17]. In a case-crossover study by Campbell et al. where 43 patients with history of PDE5 inhibitor use were analyzed, the odds ratio for developing NAION within five half-lives of PDE5 use was 2.15 normal [18]. Use of PDE5 inhibitors may result in a drop in the blood pressure, and this systemic hypotension may predispose the optic nerve to ischemia. Also they may cause a disruption in the autoregulation of blood supply in the posterior ciliary artery circulation resulting in NAION [19, 20]. Hence patients with history of NAION in one eye should be cautioned against the use of PDE5 inhibitors, especially in the presence of other associated systemic and anatomical risk factors.

The typical presentation of NAION is painless loss of vision, often noticed upon awakening. Other associated symptoms such as amaurosis, headache, or diplopia are not seen with NAION, and should raise suspicion for arteritic ischemic optic neuropathy (AION). The degree of vision loss in AION is much greater than that in NAION. The commonest visual field defect seen in cases with NAION is an altitudinal visual field defect [21], less commonly central scotomas may be seen. These patients will also show other signs of an optic neuropathy such as relative afferent pupillary defects and loss of color vision.

Pain is usually not associated with the vision loss that occurs as a result of NAION; however, up to 10% of patients may give a history of antecedent pain or discomfort [22]. Fundus examination in patients with NAION characteristically shows a small, crowded disc with segmental disc swelling and splinter disc hemorrhages (Fig. 3.1) [23]. At initial presentation, the ONH edema may be mild, and this segmental edema progresses to pallor, usually after 2 months from onset. In some cases, telangiectatic vessels may be seen on the surface of the optic disc after a few weeks of the acute event. This phenomenon is called "luxury of perfusion" [24].

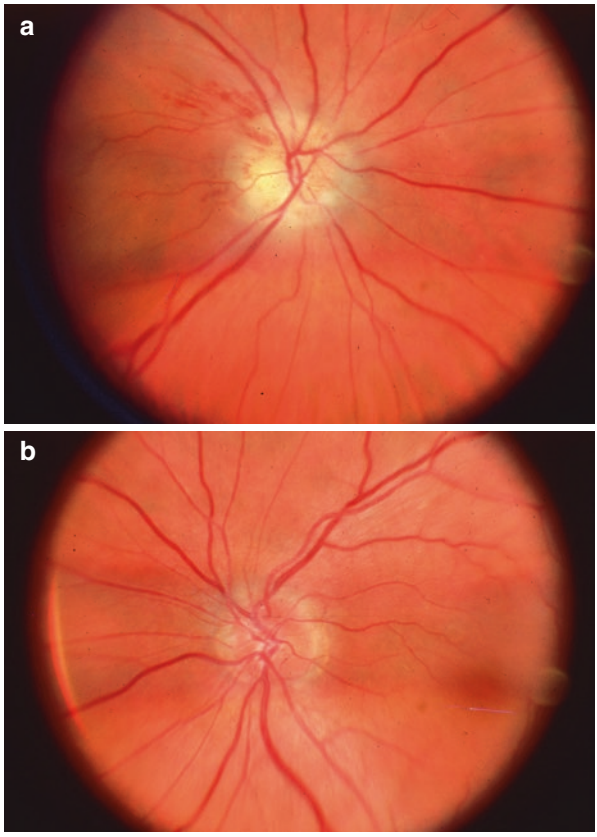

Fig. 3.1 (**a**) Note disc swelling, peripapillary hemorrhage in NAION. (**b**) Note fellow small optic disc with no cup—the "disc-at-risk"

In patients presenting with typical NAION, no further diagnostic work-up is required, but the patient requires a detailed physical evaluation and investigations for the risk factors as mentioned. In certain patients if the age, degree of vision loss, or any other presenting feature arouses a suspicion of temporal arteritis, a complete blood count (CBC) with an erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) is recommended. Visual field testing is helpful in following the stability of the visual field defect with improvement in disc edema. OCT in these cases can be used to document the initial increase in the retinal nerve fiber layer (RNFL) thickness followed by thinning. OCT can also demonstrate subtle subretinal fluid acutely. Neuroimaging (MRI) does not have a diagnostic role in NAION. Vision loss occurring with NAION tends to remain fairly constant over time; however, during the first month, some visual improvement may occur [25]. The second eye is at risk of developing NAION in about 15% of cases as per the IONDT [26]. This risk is greater in older patients, and in those with risk factors such as diabetes and hypertension [27].

Although several theories exist, the exact etiopathogenesis of NAION is still unclear. The most accepted theory remains that of hypoperfusion of the posterior ciliary arteries and choroidal circulation [28]. Several risk factors such as an anatomically crowded optic nerve head, nocturnal hypotension, local thrombosis, or atherosclerosis of the circulation may contribute to the development of NAION, but the exact role of each of these factors is not completely clear [29]. A crowded optic disc may result in the development of a compartment syndrome, and this may further exacerbate the ischemia [30].

Several prothrombotic conditions such as antiphospholipid syndrome have been implicated in the development of NAION in younger patients [31, 32]. Factors such as optic disc drusen and hyperopia which may affect the disc architecture and result in disc crowding are also associated with NAION. A history of migraine and cataract surgery may influence the perfusion of the optic nerve head and have been associated with the development of NAION.

Multiple treatment modalities have been tried in the management of NAION, but no single therapy has been conclusively proven to be beneficial. The IONDT was designed to analyze the effect of optic nerve sheath decompression (ONSD) in NAION and concluded that not only is ONSD ineffective but it may also be harmful in these patients [33]. Oral and intravenous steroids have not been proven effective in the treatment of NAION, but they are used occasionally in clinical practice. Aspirin and hyperbaric oxygen were not proven to be effective treatments [34, 35]. Intravitreal injections have also been tried, and neither intravitreal bevacizumab [36] nor triamcinolone [37] has demonstrated definite benefit. It is believed that recurrence of NAION in the same eye is very rare and that occurrence of NAION may confer protection against a repeat attack; however, this does not protect against the involvement of the second eye. A new drug, QPI-1007, which is a ribonucleic acid caspase 2 inhibitor [38], is currently being evaluated for the treatment of this disease in a large-scale, multicentric, global clinical trial. The drug is supposed to resist apoptosis in cells after acute optic nerve injury and has the potential to provide neuroprotection in acute NAION. This study, the QRK207 NAION study, is

sponsored by Quark Pharmaceuticals Inc., in collaboration with NORDIC and is currently enrolling patients worldwide.

Diabetic Papillopathy

Diabetic papillopathy is thought to be result from ischemia or hypoperfusion of the optic nerve head in young patients with type 1 diabetes [39]. It is thought to represent a milder form of NAION and typically presents with unilateral or bilateral optic disc edema and mild visual dysfunction. The degree of disc edema usually does not correlate with the degree of diabetic retinopathy and may show telangiectatic vessels but true neovascularization is not seen. Visual field defects seen in diabetic papillopathy include enlarged blind spots and arcuate defects. Disc edema and the resultant visual dysfunction are usually self-resolving in weeks to 18 months. Intravitreal or periocular steroid injections [40, 41] may result in a faster visual recovery, but they are not routinely recommended.

Arteritic Anterior Ischemic Optic Neuropathy (AAION)

Temporal arteritis or giant cell arteritis (GCA) is the most common primary vasculitis of the elderly in the Caucasian population [42] and is considered to be a neuro-ophthalmic emergency. Sudden vision loss can occur in 60% of patients [43]. GCA is more common in Caucasian women over 50 years of age [44]. Immediate diagnosis and institution of treatment measures are required to prevent devastating complications such as complete blindness and/or stroke.

Vasculitis occurring as a result of GCA typically affects large and mid-sized arteries and shows a predilection for the branches of the external and internal carotid arteries [45]. It causes inflammation of the branches on the external carotid and hence gives rise to a headache which is one of the most common symptoms in these patients [46]. Involvement of the maxillary artery results in ischemia of the masseter muscle and causes jaw claudication, which has been shown to be the most specific symptom of GCA [47]. In the eye, it results in acute ischemia, and infarction of the retrolaminar portion of the optic nerve occurs at a watershed zone supplied by the short ciliary arteries and the ophthalmic artery [48]. Histopathologic examination demonstrates necrosis of the internal elastic lamina of the vessel wall and granulomas with multinucleated histiocytes and lymphocytes. Occlusion of the affected vessels in patients with GCA is a result of the severe inflammation seen in the condition which leads to direct occlusion or thrombotic occlusion [49].

Loss of vision that occurs as a result of arteritic ischemic optic neuropathy (AAION) is usually sudden and extremely severe. Symptoms such as double vision, pain, or amaurosis may precede the vision loss. Involvement of the fellow eye may occur within days in about 75% of patients who do not receive any treatment [50]. Many patients may have polymyalgia rheumatica, headache, jaw claudication, scalp tenderness, fever, malaise, and unintentional weight loss [51]. Systemic symptoms may be absent in about a fourth of patients with giant cell arteritis (GCA)-associated

vision loss [52]; also the presentation can be very variable and hence a high level of clinical suspicion is required to make a prompt clinical diagnosis.

In addition to AAION, which is the most common neuro-ophthalmological manifestation [53], GCA can cause vision loss due to posterior ischemic optic neuropathy (PION), choroidal infarction, and retinal arterial occlusions [54]. Vision loss in AAION is usually very severe as compared to that seen in NAION [55]. While optic disc edema in present in classic AAION, it may be absent in PION. In AAION, the typical disc edema is 'chalky white' in appearance and may be associated with cotton wool spots (Fig. 3.2). The patient may also present with strabismus due to cranial nerve palsies (ischemic), and the resulting ischemia may also cause a lowering of the intraocular pressure [56, 57].

In patients over the age of 50 years, the diagnosis of GCA is based on the following criteria: (1) evidence of extracranial circulation ischemia (AION, PION, CRAO, ophthalmic artery occlusion), (2) new onset headache, (3) abnormal laboratory results (ESR, CRP, platelets), (4) jaw claudication, (5) abnormal superficial temporal artery (pulseless, localized pain), (6) constitutional symptoms (fatigue, malaise, fever, weight loss), and (7) polymyalgia rheumatica [58].

In those patients where the clinical suspicion is low and there is only one positive criteria fulfilled, one must consider an alternative diagnosis. In cases where the clinical suspicion is moderate and there are at least two positive clinical findings, oral steroids (1 mg/kg/day) must be started and a temporal artery should be performed within 2 weeks of starting steroids, in order to obtain a definitive diagnosis. Intravenous steroids (1 g/day) are necessary in patients with two or more positive clinical findings and cases where the clinical suspicion is high. In these cases also, a temporal artery should be carried out immediately. In case the biopsy is negative and the clinical suspicion for GCA remains high, a repeat biopsy from the contralateral temporal artery is required [58]. While in most cases suspected to have GCA, a

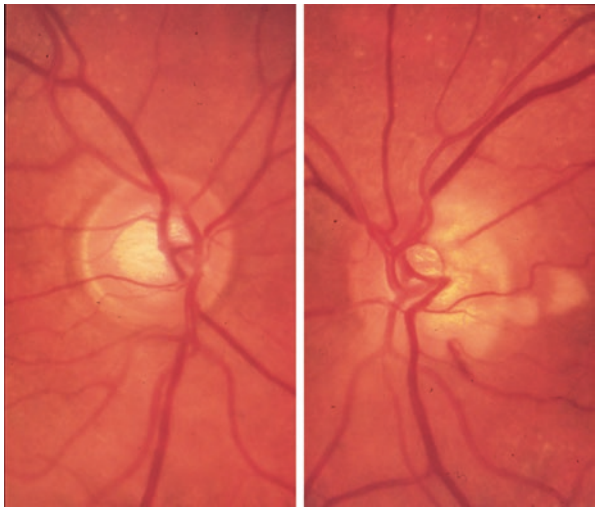

Fig. 3.2 (Left) Fellow eye of a patient with AAION, note large physiologic cup—not the "disc-at-risk." (Right) AAION with mild pale disc swelling and peripapillary nerve fiber layer infarct

biopsy from a single site may be sufficient [59]; in 3–5% of patients, the pathological grade of the disease may be very different on one side compared to the other [60]. Hence, in cases where the clinical suspicion may be moderate, a temporal artery biopsy is a must and in those patients where the clinical suspicion is high, contralateral biopsies should be performed if required.

The risks involved in performing a temporal artery biopsy are minimal compared to the significantly high risk of vision loss that may occur if a diagnosis of GCA is missed. Hence in cases with high clinical suspicion, bilateral simultaneous or sequential biopsies should be considered [61]. However, it is also important to remember that not every patient needs a biopsy and clinical judgment in this regard is important [62]. It is also important to remember that during biopsy the recommended length is at least 3 cm [63], since skip lesions are common in GCA and a shorter biopsy length may result in a missed diagnosis.

Elevated ESR and CRP levels are very important parameters to be considered in the diagnosis of GCA; it is important to remember that the 'normal' ESR levels vary depending upon the age and the sex and can be calculated as (age × 0.5) for men, and ((age + 10) × 0.5) for women. It is also important to note that an elevated ESR is a non-specific test. Higher than normal ESR levels can be seen in renal disease, ESR levels may be lowered in patients taking statins and non-steroidal anti-inflammatory agents, and hence ESR may appear to be within normal range in GCA [64]. An elevated CRP level is considered to be a more sensitive parameter as compared to ESR in the diagnosis of GCA [65], and in cases where both CRP and ESR levels are raised the specificity, there is a 97% specificity for the diagnosis of GCA [66]. Delayed choroidal filling can be seen on fundus fluorescein angiography (FFA) in cases with GCA, and this may be used as an adjunctive test to establish the diagnosis [67]. Doppler studies of the superficial temporal artery is a non-invasive test but does not have enough sensitivity or specificity to be considered for a definitive diagnosis of GCA [68].

The primary treatment modality in GCA remains corticosteroid use. Steroid therapy should be promptly instituted even prior to establishing a definitive diagnosis with temporal artery biopsy. Immediate treatment with corticosteroids helps in preventing vision loss in the second eye and may help to retard vision loss in the affected eye as well. Steroid therapy in these patients may be started via the oral or parenteral route, and an improvement in vision has been demonstrated in some studies (more significant with intravenous steroids as compared to oral) [69]. However, there is still no consensus and not all studies demonstrate superiority of intravenous steroid administration over oral therapy [70, 71], but most authorities agree that in patients presenting with severe vision loss, at least one dose of intravenous steroid should be administered [72]. The usual recommended dosage of IV steroid is 1 gm/day, for 3–5 days, and hospitalization is preferred in elderly patients to minimize the risk of gastrointestinal and cardiac complications. IV administration is usually followed by a course of oral steroids which are tapered over the next 10–12 months. Stability of ESR levels and systemic symptoms must be ensured before the dose of steroids is tapered. Despite careful corticosteroid tapering, there are cases of GCA that are refractory to treatment [73, 74]. Recurrence of an episode of ischemic optic

neuropathy may occur in patients on maintenance doses of prednisone, up to 3 years after initial GCA diagnosis [75, 76]. The immunopathology of GCA is under investigation for the consideration of future targeted therapies [77]. Currently, GiACTA—a Phase III study (conducted by Genentech; https://www.gene.com/media/press-releases/14645/2016-11-12/phase-iii-giacta-study-shows-genen-techs-) evaluating tocilizumab, an IL-6 receptor antagonist, in GCA is underway. The study met its primary and key secondary endpoints, showing tocilizumab, with a 6-month corticosteroid regimen, more effectively sustained remission through 1 year compared to a 6- or 12-month steroid-only regimen in people with newly diagnosed and relapsing GCA.

Prognosis for recovery of vision remains suboptimal in patients with GCA [78], and progression can occur despite treatment with corticosteroids [79]. However, a recent review of quality of life measures in GCA patients showed no significant difference in disability between patients with and without vision loss when only one eye was affected [80].

Posterior Ischemic Optic Neuropathy

Posterior ischemic optic neuropathy (PION) is fairly uncommon in comparison with AION and should immediately be investigated. Vascular risk factors such as diabetes mellitus and hypertension rarely cause PION, and hence this should be considered a diagnosis of exclusion. PION may result from two conditions: (a) giant cell arteritis and (b) peri-operative vision loss [81].

Patients with PION present with acute vision loss and disc edema is absent. In PION, the ischemic insult occurs in the retrolaminar portion of the optic nerve and eventually results in optic atrophy. Since disc edema is absent at presentation, neuroimaging is indicated to rule out compressive or infiltrative pathology. One must rule out GCA in elderly patients presenting with PION [82]. Chronic systemic inflammatory processes in diseases such as herpes, varicella, polyarteritis nodosa, and systemic lupus erythematosus may also cause PION [83, 84]. In patients with perioperative PION, coronary artery bypass and lumbar spine procedures were most commonly associated [85, 86], as well as episodes of hypotension or severe bleeding (further detail given in section below).

Ischemic Optic Neuropathy in the Setting of Hemodynamic Compromise

Systemic hypotension, anemia, or severe blood loss can cause infarction of the optic nerve head. These cases usually present with severe, bilateral vision loss which usually occurs acutely after the event but may sometimes present even days later. Perioperative vision loss is most commonly associated with spine surgery and cardiac surgery [85, 86], and has also been reported with radical neck dissection [87].

Perioperative ischemic optic neuropathy may present with or without optic disc edema—i.e., maybe classified as anterior or posterior ischemic optic neuropathy, respectively. Predisposing risk factors include vasculopathic risk profile, crowded disc, long operative time, prone positioning, anemia, and hypotension. Although no critical blood pressure level has been identified below which ischemic optic neuropathy may occur, a hemoglobin level of less than 8 mg/dl warrants treatment. Chronic anemia and dialysis in patients with renal failure can also cause loss of vision [88]. No definitive treatment has been proven to be effective, and the visual prognosis in these cases is generally poor.

Summary

NAION is by far the most common type of ischemic optic neuropathy encountered. Unfortunately, no proven treatment for NAION exists. One must always consider GCA if AION occurs. Detailed questioning regarding symptoms of GCA and blood tests (ESR, CRP, CBC with platelets) should be considered. If temporal artery biopsy is scheduled, always start corticosteroids immediately. PION usually occurs in either the setting of GCA or perioperatively. One should be very cautious in making this diagnosis in any other setting.

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Hereditary Optic Neuropathies

4

Dan Milea

Hereditary optic neuropathies are a heterogenous group of inherited diseases causing dysfunction of the optic nerves, via retinal ganglion cells (RGCs) and axonal death. Genetically determined optic neuropathies have various patterns of inheritance (e.g. autosomal dominant, mitochondrial, autosomal recessive and X-linked), but they have in common several clinical features: bilateral, irreversible loss of central vision, dyschromatopsia, temporal optic disc atrophy and predominant loss of retinal nerve fibres in the papillomacular bundle [1, 2]. The most common hereditary optic neuropathies are Leber's hereditary optic neuropathy (LHON) and autosomal dominant optic atrophy (ADOA), in addition to other more rare inherited optic neuropathies (i.e. autosomal recessive optic atrophy, or other syndromic hereditary optic neuropathies, occurring in Wolfram syndrome, Charcot-Marie-Tooth, etc.).

A large number of these optic neuropathies share a common mitochondrial background. These disorders may result from mutations in either the mitochondrial DNA or in the nuclear genes encoding for mitochondrial proteins. Primary or secondary mitochondrial dysfunction leads to cellular energetic impairment affecting predominantly the optic nerve, and in particular the retinal ganglion cells. Mitochondria are intracellular organelles and their primary function is the production of ATP, via oxidative phosphorylation. Tissues with high levels of activity such as the brain, muscles, the cardiac conduction apparatus and the optic nerve require a large number of mitochondria for energy generation. Hence these tissues are more likely to manifest effects of depletion of energy due to decreased or improper functioning of the mitochondria.

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_4

About 50% of mitochondrial disorders are associated with visual manifestations. These visual symptoms and signs may sometimes be the presenting features of these disorders, with injury to the afferent visual pathways occurring at various sites from the retina to the occipital cortex [3, 4]. The most common hereditary optic neuropathies are Leber's hereditary optic neuropathy and autosomal dominant optic atrophy.

Leber's Hereditary Optic Neuropathy

Leber's hereditary optic neuropathy (LHON) is the first clinically described, and most common mitochondrial disorder. It is also one of the commonest hereditary optic neuropathies, and the prevalence is greater than 3/100,000. LHON typically affects males more than females (predominance of 80–90%) [4, 5].

LHON is clinically characterised by subacute, painless loss of vision, which is usually unilateral, typically followed by the involvement of the other eye, within weeks or months. In most cases, LHON affects young patients, but loss of vision may occur at ages varying from 4 to 87 years [6]. Although the typical presentation is sequential, simultaneous involvement of both eyes may sometimes occur. The typical visual field defects described are central or centrocecal scotomas, but these are not pathognomonic for optic neuropathies. A reduction in colour vision is also seen. Sparing of melanopsin-expressing RGCs in LHON may be responsible for the visuo-pupillary dissociation seen in this condition [7]. The visual prognosis is usually very poor, but spontaneous recovery may occur in up to 65% of cases, most frequently related to the m.14484T>C mutation, which has the best visual prognosis [8]. In the acute phase of the disease, fundus examination shows the presence of swelling of the peripapillary RNFL, with circumpapillary telangiectatic microangiopathy (Fig. 4.1) Classically, fundus fluorescein angiography does not show any dye leakage. As the disease progresses, non-specific atrophy of the optic disc becomes visible (Fig. 4.2). Evolution of LHON is very different from ADOA: subacute visual loss, due to large central scotomas in the former, and very slowly progressive course, with minimally affected visual fields in the latter (on average, the loss of visual acuity is around 1 Snellen line per decade of life).

A large majority (90–95%) of LHON cases are accounted for by three main mitochondrial DNA mutations (called primary LHON mutations).These are located in the mtDNA at positions m.11778G>A (the most common mutation, with worst visual prognosis), m.3460G>A and m.14484T>C in the *MT-ND4*, *MT-ND1* and *MT-ND6* genes, respectively. Additionally, eleven other mutations, located in the *MT-ND1* gene (m.3635G>A, m.3700G>A, m.3733G>A and m.4171C>A), in the *MT-ND4L* gene (m.10663T>C) and in the *MT-ND6* gene (m.14459G>A, m.14482C>A, m.14482C>G, m.14495A>G, m.14502T>C and m.14568C>T), account for an important fraction of the remaining 10% of LHON cases (http://www.mitomap.org/MITOMAP). As in any other mitochondrial condition, only females can transmit the disease, but never the males. The penetrance of the disease is incomplete: the conversion rate in healthy carriers depends on the type of the

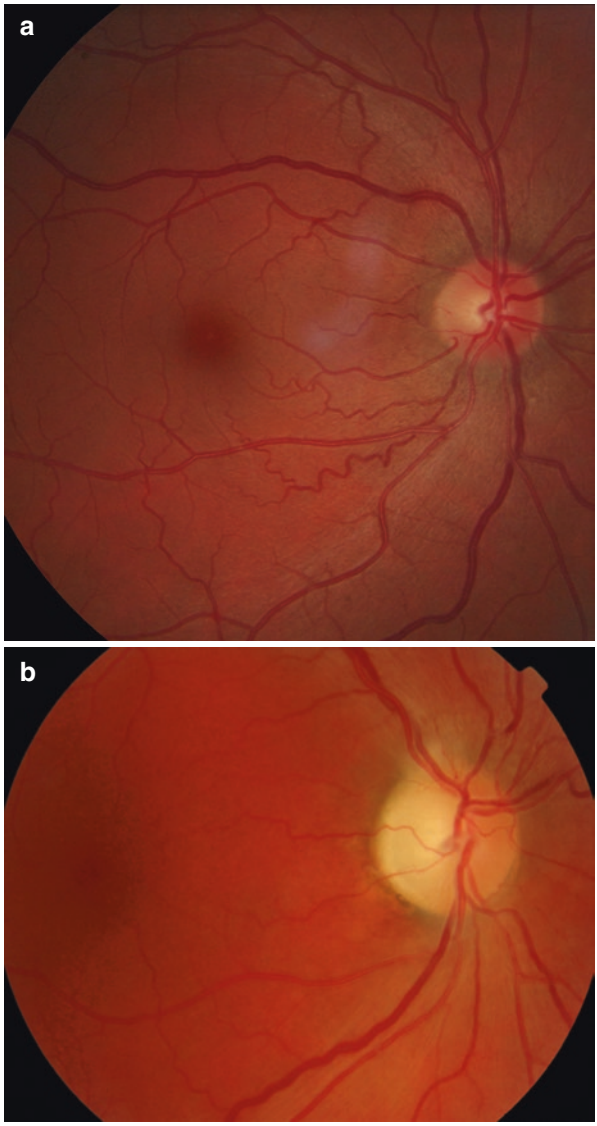

Fig. 4.1 The ocular fundus of a patient with LHON: second eye involvement at the acute phase (**a**). The left eye was previously affected, a few weeks earlier (**b**)

mutation and the age of the patient, but is globally 50% in a male carrier and 20% in a female carrier. De novo mutations are very rare, but a family history of visual loss is missing, according to various cultures, from 40 to 90% of cases. Therefore, absence of a family history of blindness does not rule out LHON.

Consumption of alcohol or tobacco may play a role in precipitating or worsening vision loss in patients with hereditary optic neuropathies. It is postulated that smoking may increase the energy deficit by either reducing complex I activity or limiting oxidative phosphorylation and also increase the penetrance of LHON. Although the

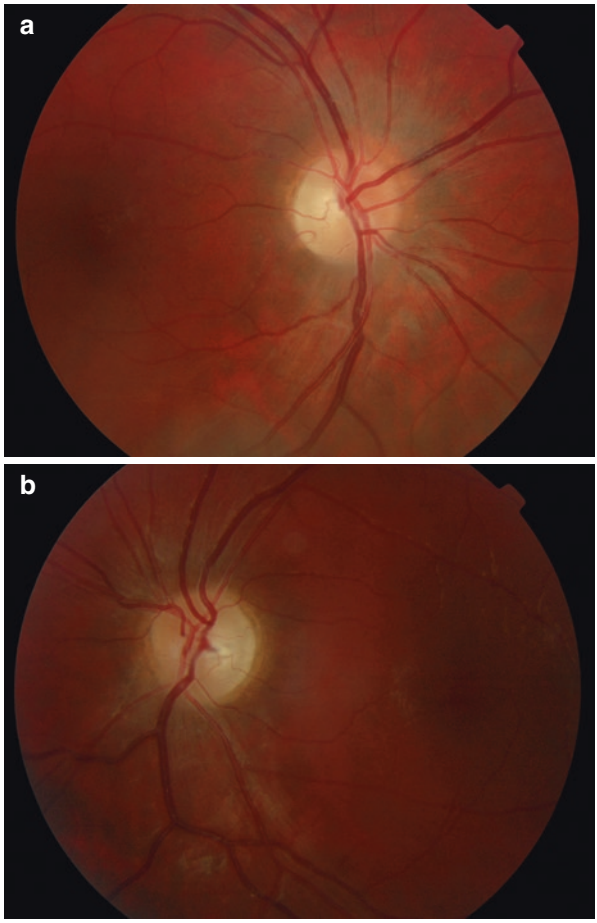

Fig. 4.2 Bilateral optic atrophy (**a** and **b**) in patient with LHON

role of alcohol in worsening the disease progression is not conclusively proven, patients harbouring an mtDNA mutation may be well advised to moderate their alcohol consumption. Therefore, it is reasonable to consider a genetic underlying cause in optic neuropathies initially attributed to toxic causes, which do not recover after cessation of the presumed causal agent.

In a vast majority of LHON patients, vision loss may be the primary symptom or the only manifestation of the disorder. However, a subset of patients may manifest additional clinical features and are referred to as 'LHON plus syndrome'. These features include epilepsy, cardiac conduction abnormalities, spasticity, dystonia, encephalopathy, psychiatric disturbances and a multiple-sclerosis-like phenotype. It is now believed that environmental factors such as smoking, systemic medications and illnesses, consumption of alcohol and genetic factors such as down regulation of the *OPA1* gene and X-linkage may be responsible for the very variable clinical features of the disease, including the asymptomatic form of the condition in maternally related family members [5].

Recent advances in the field of ocular imaging such as optical coherence tomography (OCT) have revolutionised our understanding of the role of the retinal structures and optic nerve involvement in hereditary optic neuropathies. With the help of the OCT, we can now precisely measure the thickness of the retinal nerve fibre layer (RNFL) and the macula and also quantify in vivo the loss of retinal ganglion cells (RGCs). At initial stages, there is thickening of the RNFL, starting preferentially in the superior and temporal quadrants, but ultimately evolving towards atrophy. The pattern of preferential late stage thinning of the papillomacular bundle, visible on peripapillary RNFL, serves as the hallmark of a mitochondrial disorder [9]. Asymptomatic carriers of the disease may at times display retinal nerve thickening, prior of being affected by the disease. Magnetic resonance imaging can show at the late stage T2-hyperintensity of the optic nerve, due to axonal atrophy. At the acute stage of the disease, enhancement of the optic nerves is possible but not common, raising the question of differential diagnosis with an inflammatory optic neuropathy. Multiple sclerosis (MS) has been associated with the presence of optic neuropathy and LHON mutations, in the so-called Harding syndrome.

Autosomal Dominant Optic Atrophy

Autosomal dominant optic atrophy (ADOA) is one of the commonest autosomal inherited optic atrophy. The prevalence of ADOA has been reported to be 1:10,000 in Denmark [10], and varies from 1:34,000 to 1:50,000 in other parts of the world [2]. Vision loss in ADOA is usually slowly progressive and occurs in most cases during the first two decades of life. Fundus examination reveals temporal pallor of the optic disc (Fig. 4.3). ADOA is also characterised by decreased sensitivity in central visual

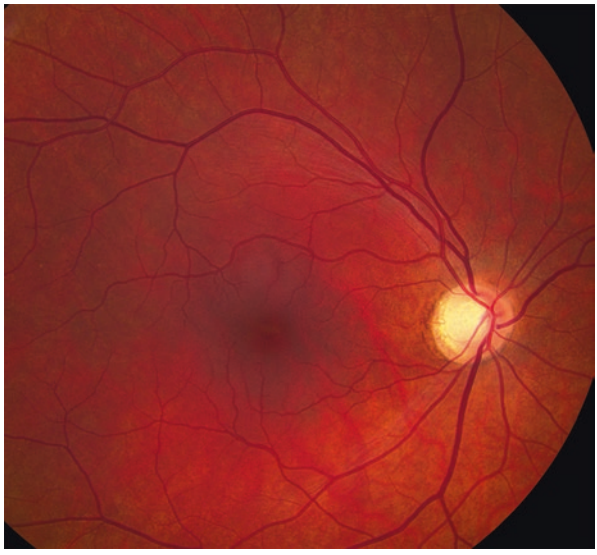

Fig. 4.3 The ocular fundus of a patient with autosomal dominant optic atrophy. There is optic atrophy and optic disc cupping

field or centrocecal scotoma (Fig. 4.4) and colour vision impairment, more specifically in the blue-yellow spectrum. Visual loss is usually very slow, over decades. The functional visual handicap of ADOA patients is often less severe than the quantified visual acuity might suggest, possibly due to cerebral plasticity. Spontaneous visual recovery in ADOA has been reported, but it is exceptionally rare [11].

Although LHON and ADOA demonstrate very different and distinct clinical courses, both conditions have a common morphological end point characterised by end-stage retinal nerve fibre atrophy. Optic disc cupping is more prevalent in ADOA, which may be difficult to differentiate from normal tension glaucoma. OCT can be of use in these cases to document the thinning or atrophy of the RNFL and can also demonstrate thinning of the inner retinal layers [3]. Studies have also

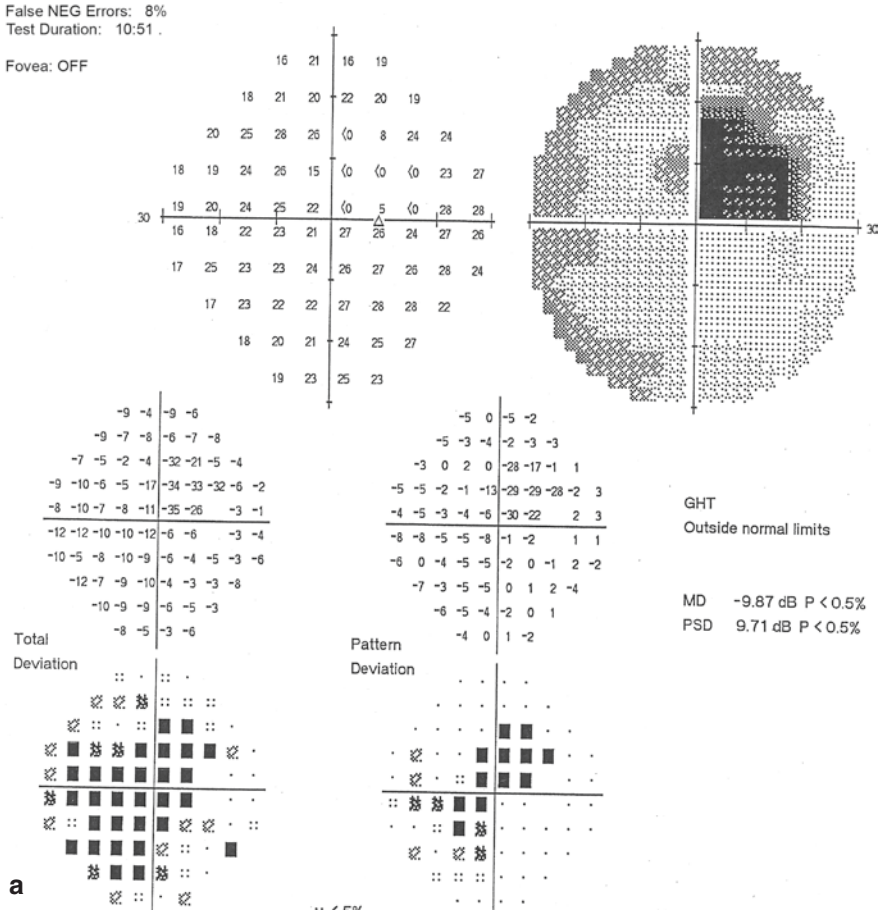

Fig. 4.4 Humphrey visual fields of thr right (**a**) and left (**b**) eye, in a patient with genetically confirmed ADOA, showing paracentral scotomas, displaying and bitemporal deficit pattern

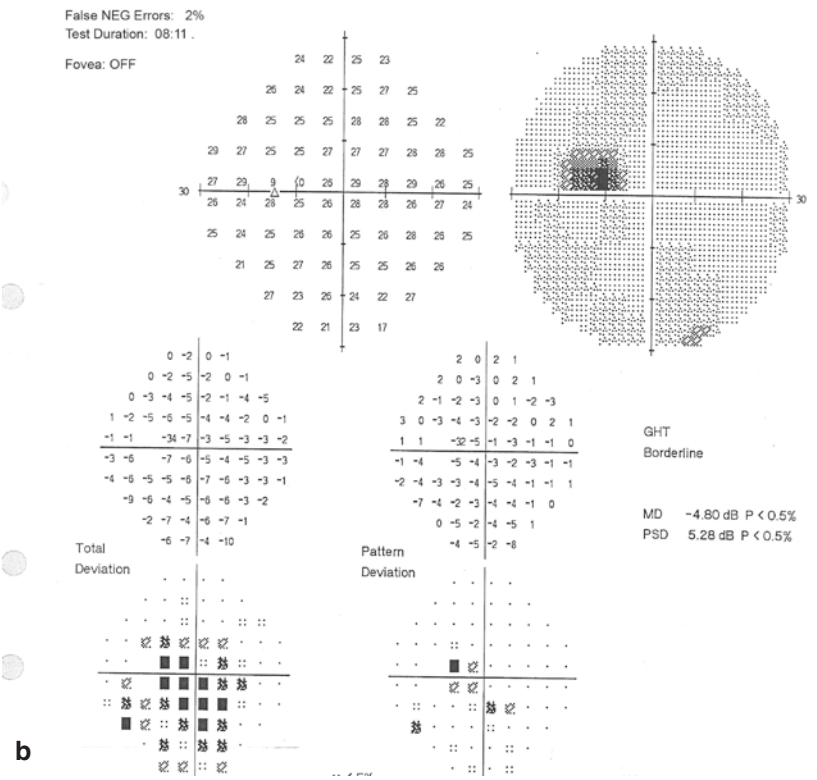

Fig. 4.4 (continued)

described the role of OCT in distinguishing mutation carriers from mutation-free subjects in families with *OPA1* mutations [12].

The *OPA1* gene (Optic Atrophy 1) was the first gene to be identified in ADOA [13, 14]. The *OPA1* gene is located on the long arm of chromosome 3 (3q28 to 29) and encodes a mitochondrial dynamin-related GTPase which plays a role in the regulation of apoptosis and is also needed for mitochondrial fusion.

About 60% of patients with ADOA harbour mutations in the *OPA1* gene. However, this percentage may show significant geographical variation [15]. Over 330 mutations have been reported in the *OPA1* gene till date (http://lbbma.univ-angers.fr/eOPA1) [16]. Additional gene loci have now been identified which may be responsible for less than 1% of cases of ADOA. These include *OPA4* and *OPA5* for pure ADOA, *OPA2* with an X-linked mode of inheritance, *OPA6* and *OPA7* with a recessive mode of inheritance, and *OPA3* and *OPA8* associated with syndromic recessive or dominant forms of ADOA [3]. Although the *OPA1* gene is ubiquitously expressed in the human body, ADOA is specifically causing visual loss due to dysfunction of the RGCs, with very rare extra-ophthalmic involvement. In addition,

melanopsin-expressing RGCs are also involved in non-visual functions such as circadian rhythms, the sleep-wake cycle and the pupillary light reflex. These cells and hence consequently these functions are relatively preserved in those affected with ADOA [17].

Visual dysfunction and optic atrophy are not the only clinical features of patients with ADOA. Mutations in the *OPA1* gene can cause multiple distinct clinical presentations, and about 20% of ADOA patients may demonstrate these features. These include DOA with deafness (ADOAD), multi-systemic syndromes, referred to as 'DOA+' or 'ADOA+' disorders [18]. About 6% of patients have sensorineural hearing loss which is the most frequent extraocular manifestation in 'DOA+' [19].

Wolfram Syndrome

Wolfram syndrome is characterised by diabetes insipidus, diabetes mellitus, optic atrophy and deafness and is hence also referred to as the DIDMOAD syndrome. It is relatively a rare neurodegenerative disorder. The prevalence of DIDMOAD syndrome has been reported to be 1:550,000–1:770,000. More than 400 cases of the Wolfram syndrome have been recently documented [20]. The gene responsible is the *WFS1* gene, which is located on chromosome 4. This gene encodes wolframin, which is an endoplasmic reticulum membrane protein. Wolframin is present in multiple cells such as neurons, pancreatic β-cells, as well as in the heart, placenta, inner ear, lung and liver. It is involved in the regulation of intracellular calcium.

The initial clinical feature to manifest in patients with Wolfram syndrome is diabetes mellitus. It typically appears in the first or second decade of life and is then followed by optic neuropathy. Visual dysfunction and optic neuropathy are definite and prominent features of Wolfram syndrome. Optic neuropathy in Wolfram syndrome has a chronic course and starts insidiously with dyschromatopsia, decreased visual acuity and central and peripheral visual field loss, Vision may decrease to as low as 20/200. It may also result in optic nerve cupping [5]. As in other mitochondrial optic neuropathies, small axons which are predominantly present in the temporal and inferior quadrants of the papillomacular bundle are affected preferentially [9].

Patients with Wolfram syndrome also have other systemic findings such as sensorineural hearing loss, progressive neurological abnormalities, such as ataxia, peripheral neuropathy, dementia, psychiatric illness and urinary tract atonia, and other endocrine abnormalities. Lifespan is usually lesser with the median age of death being 30 years. Other less common ophthalmic features of Wolfram syndrome include pigmentary retinopathy cataract and diabetic retinopathy. The retinopathy is more slowly progressive but less severe as compared to that in type I diabetes mellitus [21]. A 'WFS-like disorder' has also been described in pedigrees showing autosomal dominant inheritance. These patients may develop sensorineural hearing loss, diabetes mellitus, psychiatric illness and variable optic atrophy.

Other Syndromic Hereditary Optic Neuropathies

Optic neuropathy maybe present as an associated secondary feature of several other inherited diseases that are primarily neurologic or systemic. Mitochondrial dysfunction and consequent optic neuropathy is a feature of many disorders with maternal or autosomal inheritance, since the optic nerve is particularly affected by depletion of energy. Optic neuropathy may be seen in association with hereditary spastic paraplegia (HSP). HSP is characterised by progressive and severe spasticity and is caused by mutations in the spastic paraplegia 7 gene (*SPG7*). Structural abnormalities detected by OCT could be a clinical marker of the *SPG7* mutation.

A milder form of optic neuropathy has been seen in patients with spinocerebellar ataxias (SCAs). These are a phenotypically and genetically diverse group of autosomal dominant disorders which are characterised by cerebellar symptoms. Other multi-systemic signs, including a wide variety of ophthalmologic signs and symptoms, are often associated with SCAs. Optic neuropathy maybe a feature of this spectrum of disorders, especially SCA1 and SCA3.

Multiple other mitochondrial disorders may also feature optic neuropathies as a part of their clinical spectrum. These include myoclonic epilepsy with ragged red fibres (MERRF), mitochondrial neurogastrointestinal encephalomyopathy (MNGIE), mitochondrial encephalopathy, lactic acidosis and stroke-like episodes (MELAS), the maternally inherited Leigh syndrome and chronic progressive external ophthalmoplegia, with or without the complete Kearns-Sayre phenotype [5].

Treatment of Hereditary Optic Neuropathies

Treatment of hereditary optic neuropathies is not well defined in spite of major advances in the understanding of the pathophysiology of mitochondrial disorders. A small number of randomised controlled treatment trials have so far been conducted in these conditions [22], but there is no conclusive evidence to establish the efficacy of any specific treatment modality. Multiple treatment options such as Vitamin B, C and E, and folic acid have been attempted. Antioxidants such as coenzyme Q10 have also been tried. An analogue of coenzyme Q called idebenone has been tried in the treatment of LHON. Idebenone facilitates electron transfer along the respiratory chain. In a recent study of 85 patients with LHON, which was designed as a randomised control trial, it was found that in patients with decreased visual acuity and diagnosed at an early stage of the disease and those at the highest risk of visual loss are most likely to benefit from ibedenone treatment [23, 24]. Another study, which was a retrospective analysis of 103 patients with LHON also, recommended an early initiation of treatment [25]. Although idebenone has been approved in some countries in Europe, its therapeutic and negative effects need further study and analysis. There are anecdotal reports demonstrating the efficacy of idebenone in patients with the *OPA1* mutation and in Wolfram syndrome, but there are no controlled trials so far.

Another new therapeutic agent called EPI-743 has been tried in LHON. A study involving five patients showed that two patients had visual recovery without any side effects [26].

Gene therapy may be the way ahead in the management of hereditary optic neuropathies, which occur as a result of mitochondrial mutations. Theoretically speaking, repairing the mutations in the mitochondrial genome should provide a definitive treatment in patients with LHON. Manipulation of the mitochondrial genome is performed by an indirect method, which is based on the nuclear allotopic expression of mtDNA genes that are recoded and adequately engineered. The engineered genes, transduced into the nucleus through the mediation of an adenovirus-associated virus (AVV) vector, produce the proteins normally expressed in the mitochondria. Gene therapy aims at transporting these proteins into the mitochondria by specific targeting sequences.

Many clinical trials involving gene therapy are currently in progress for the treatment of LHON. A recent phase III trial conducted by GenSight has reported visual improvement of 11 ETDRS letters in the treated group as compared with the placebo group. However, the placebo group had better outcomes than those reported in historical cohorts and hence further studies are required to analyse the possible reasons. A newer approach being studied is aimed at preventing the transmission of mtDNA disorders. Replacing the mutated mtDNA in the patient's oocyte with a healthy mitochondrial genome from an oocyte donor using spindle transfer is being tried. The resultant offspring would have healthy mitochondrial genes but would be the genetic child of the patient.

It is important to remember that these patients need supportive and rehabilitative treatment, including low visual aids. Systemic screening to detect the associated features, such as electrocardiograms to detect cardiac conduction defects in LHON patients, or hearing assessment in ADOA patients is also required.

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Cranial Nerve Palsies: What's New?

5

Anita A. Kohli, John Woo, Madhura A. Tamhankar, and Sahil Thakur

Anatomy

The IIIrd, IVth, and VIth cranial nerves innervate the extraocular muscles. The medial, inferior, superior recti and the inferior oblique muscles are supplied by the IIIrd nerve, the superior oblique by the IVth nerve, and the lateral rectus by the VIth nerve. The IIIrd nerve also innervates the levator palpebrae superioris and pupillary sphincter muscle. The extraocular muscles have abduction (lateral rectus), adduction (medial rectus), elevation (superior rectus), depression (inferior rectus), incyclotorsion (superior oblique), and excyclotorsion (inferior oblique) as their primary actions.

The third nerve nuclear complex is found in the midbrain, and is composed of one subnuclei (central caudal nucleus) for the levator palpebrae superioris and paired superior rectus subnuclei that supply the contralateral superior rectus [1, 2].

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_5

The connections from the superior rectus subnuclei pass via the contralateral subnucleus, before joining the IIIrd nerve fascicle. In the event of a unilateral lesion, it causes bilateral superior rectus palsies which may be worse ipsilaterally. The preganglionic fibers from the VIth nerve nucleus in the pons connect to the third nerve nucleus in the brainstem, via the medial longitudinal fasciculus, which is a center for the conjugate horizontal movement of the eyes [3].

The IIIrd nerve fascicles then traverse the red nuclei, the cerebral peduncles, and exit the brainstem into the interpeduncular fossa. Subsequently, they enter the subarachnoid space and the cavernous sinuses, where they travel in the lateral walls, until separating into the superior and inferior divisions in the anterior cavernous sinus [4]. On reaching the orbit, the IIIrd nerve passes via the annulus of Zinn and on to the medial, inferior and superior recti and the inferior oblique. The preganglionic parasympathetic fibers travel along the inferior division of the third nerve from the cavernous sinus into the orbit, eventually synapsing in the ciliary ganglion before supplying the pupillary sphincter (miosis) and ciliary body (accommodation). The fibers run superficially along the third nerve, making them more susceptible to infiltration or compression.

The IVth nerve originates in the dorsal midbrain and has the longest intracranial course of all cranial nerves. It decussates immediately after exiting the brainstem, in the anterior medullary vellum so that each superior oblique muscle is innervated by the contralateral nerve nucleus. The trochlear nerve is thin (0.75–1 mm) and along its incisural course, it is hidden by the tentorium. The nerve then enters the cavernous sinus along the lateral wall, below the IIIrd nerve. It enters the orbit through the superior orbital fissure and runs medially to supply the superior oblique muscle.

The VIth nerve nuclei are located in the dorsal pons. The genu of the VIIth (facial) nerve lies immediately proximal to the VIth nerve nucleus. The VIth nerve fibers pass through the corticospinal tracts before exiting the brainstem ventrally, at the pontomedullary junction (Fig. 5.1). It travels over the clivus and under the petroclinoid ligament to enter the cavernous sinus. This is a narrow space and hence the nerve is susceptible to compression around this area. In the cavernous sinus, the nerve is inferolateral to the cavernous carotid artery, as it courses anteriorly. The postganglionic sympathetic fibers join the VIth nerve for a short course in the anterior cavernous sinus, prior to passing through, but don't synapse in the ciliary ganglion. On entering the orbit, the VIth nerve passes through the annulus of Zinn and supplies the lateral rectus muscle (Fig. 5.2).

Cranial Nerve Palsies

Congenital

While congenital absence or maldevelopment of any cranial nerve nuclei may occur and lead to ocular misalignment, recently the term congenital cranial dysinnervation disorders (CCDD) is being used to describe a wide variety of non-progressive

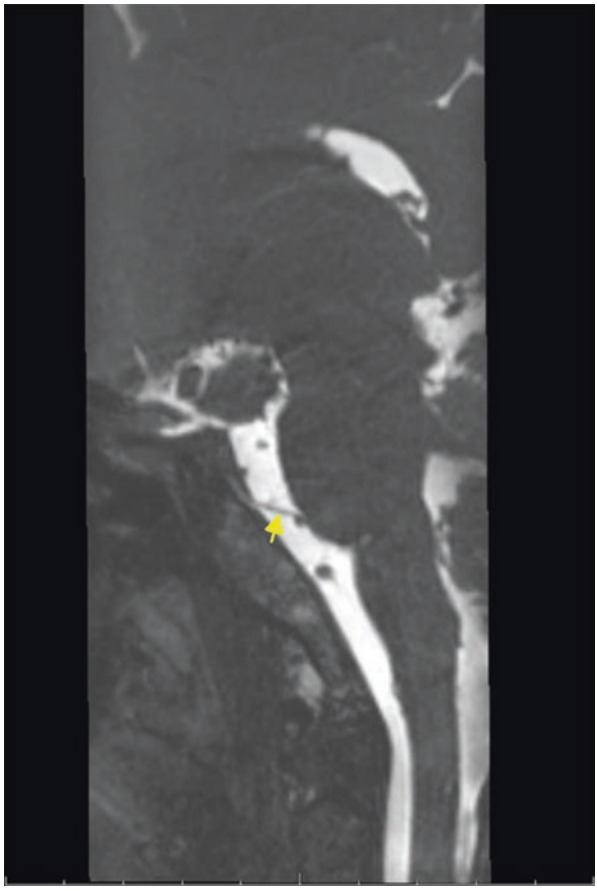

Fig. 5.1 3-T CISS MRI brain: oblique-sagittal view of pontomedullary junction. CISS (based on T2/T1 gradient) reconstruction demonstrating the ventral exit of the VIth nerve from the pontomedullary junction. Pathology involving the VIth nerve often occurs as the nerve courses over the bony clivus, after exiting from the midbrain

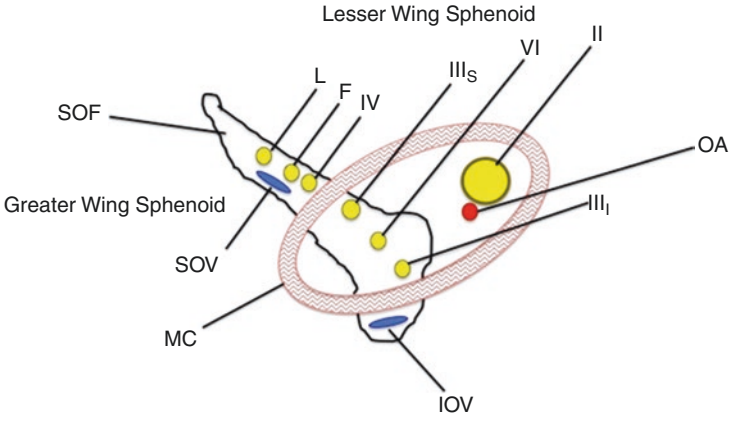

Fig. 5.2 The orbital apex, indicating the passage of the cranial nerves into the orbit. Note that the IVth cranial nerve is outside of the muscle cone (MC). *L* lacrimal nerve, *F* frontal nerve, *IV* cranial nerve IV, III_S superior division of cranial nerve III, *VI* cranial nerve VI, III_I inferior division of cranial nerve III, *II* cranial nerve II, *OA* ophthalmic artery, *IOV* inferior ophthalmic vein, *MC* muscle cone, *SOV* superior ophthalmic vein, *SOF* Superior orbital fissure

neurogenic syndromes. The most common CCDD is Duane syndrome, characterized by limitation of adduction, abduction, or both. Additionally, there is retropulsion of the globe and palpebral fissure narrowing on adduction. Huber classified Duane syndrome into three clinical subtypes: Type 1 is the most common and seen in 85% of the affected individuals and is characterized by limited abduction with or without esotropia, Type 2 with limited adduction with or without exotropia, and Type 3 in which both adduction and abduction are limited [5]. In most patients, there is absence or hypoplasia of the VIth nucleus or fascicle, and the lateral rectus is supplied by a branch of the IIIrd nerve [6, 7]. As opposing muscles are being supplied by the same nerve, co-contraction of both muscles during attempted abduction causes globe retraction and upshoots and downshoots due to tight horizontal recti muscles. Duane syndrome has been studied extensively and has confirmed genetic involvement of SALL4, HOXA1 (nerve development), and CHN1 (axonal guidance) genes. Neuroimaging studies have also showed that the primary cause is maldevelopment of the VIth nerve nucleus. Management of Duane syndrome involves spectacles for refractive correction, prisms for improvement in head position, amblyopia management, and surgical interventions for correction of deviation in primary position.

Moebius syndrome is another rare CCDD characterized by the presence of unilateral or bilateral VIIth nerve palsies along with VIth nerve palsy [8] most commonly, though the IIIrd and/or IVth nerves may also be involved. The syndrome is usually identified in infancy as infants have increased drooling or poor ability to suck [9]. Prenatal hypoxia to the developing fetus and drugs such as misoprostol, thalidomide, and cocaine have been reported to be associated with the syndrome [10, 11]. Genetic studies have shown malformations on chromosomes 1 and 13 with specific deletion of band 13q12.2. Neuroimaging usually demonstrates hypoplasia in the brainstem region around the pons where VIth and VIIth nerve nucleus are located. Congenital fibrosis of the extraocular muscles (CFEOM) is another rare disorder that is classified as CCDD. It is present at birth, is non-progressive, and runs in families. It causes varying degrees of ophthalmoplegia and ptosis. In most cases, the superior recti are dysfunctional, causing the eyes to be infraducted, with a compensatory chin up posture. Genetic studies have identified three types of CFEOM caused by mutations in KIF21A (CFEOM1), PHOX2A (CFEOM 2), and TUBB 3 gene (CFEOM3) [12, 13].

Brown syndrome was first described in 1950 and is thought to be caused by a short superior oblique tendon. Affected individuals exhibit limited elevation in adduction, near normal elevation in abduction, exotropia in upgaze and compensatory chin elevation to avoid diplopia [14].

Structural Intracranial Lesions and Brain Trauma

Structural intracranial lesions can often cause ocular motor palsies which may be isolated or accompanied by other neurological symptoms and signs. Evaluation of a patient presenting with ocular motor palsies is thus dependent on age, presence or

absence of other neurological signs and symptoms, prior history of brain trauma or surgery, and vasculopathic risk factors. Considering the high prevalence of vasculopathic comorbid conditions (diabetes and hypertension), cranial nerve palsies due to a vasculopathic etiology are a common diagnostic occurrence. These palsies typically resolve in 3–6 months from onset. However, in those patients who are <50 years of age or are relatively healthy, it is imperative to evaluate for other etiologies. Reports from case series indicate that in patients aged 21–50 with cranial nerve palsies, mass lesions were seen in 33%, with the majority located in the cavernous sinus [15]. Lee et al. studied the causes of VIth nerve palsies in the pediatric population and found that intracranial lesions or their subsequent surgical removal was the etiology in 45% of cases [16]. In a study of patients older than 50 years, Tamhankar et al. found that in 109 patients, vasculopathic risk factors were found in 61% of those who were identified with other etiologies for the ocular motor palsy, including midbrain infarcts, lymphoma, meningioma, and pituitary apoplexy. These authors also studied the need for early neuroimaging in isolated IIIrd, IVth, or VIth nerve palsies in older adults (>50 years) and reported that contrast-enhanced brain MRI is useful in the initial evaluation of these patients [17]. In a clinic, it is thus imperative to make decisions on a case-by-case basis. The presence of vasculopathic risk factors may point toward a more benign diagnosis, but neuroimaging is essential for a conclusive diagnosis. Additionally, tumors that inherent to the nerves themselves, such as schwannomas and neurinomas [18], should also be considered in the differential diagnosis and can be detected with high-resolution MRI (Fig. 5.3). In patients who have a history of brain trauma, and present with IIIrd nerve palsy, several points should be contemplated. Due to the long intracranial course of the IVth nerve, the proximity of the VIth nerve to the bony clivus, and the possibility of involvement of the IIIrd nerve from herniation or midline shift, involvement of

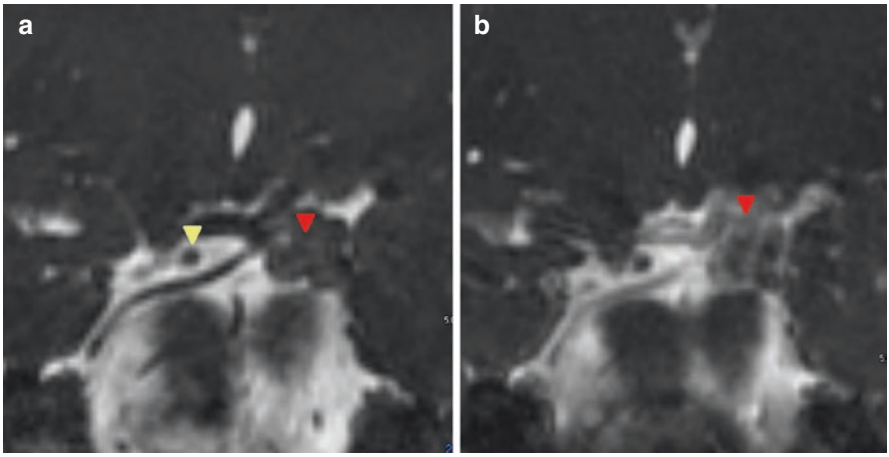

Fig. 5.3 3-T reformatted CISS MRI brain: coronal view of the midbrain demonstrating pre-contrast (**a**) and post-contrast (**b**) IIIrd nerve schwannoma with enhancement (red arrowhead). The yellow arrowhead (**a**) denotes normal IIIrd nerve

multiple cranial nerves is a common occurrence after head trauma. However, the magnitude and type of nerve involvement also depend on grade of head trauma. In a retrospective study of 210 patients with closed head injury, it was found that the severity of head injury was correlated with the type of cranial nerve palsies, such that patients with IIIrd nerve palsies had the highest incidence of severe head injury, those with IVth nerve palsies with an intermediate level of head injury, and those with VIth nerve palsies with the lowest level of head injury [19]. While spontaneous carotid artery dissections can occur rarely, many occur secondary to trauma. It is imperative to this etiology as a differential when the patient presents with diplopia, neck pain, head pain, and symptoms of retinal and cerebral ischemia. Patients with traumatic ocular motor palsies should be followed for at least 6–9 months, as they may have spontaneous resolution, negating the need for surgical intervention. Patching of one eye and prisms may be offered in the interim, but surgical intervention may be needed in those with intractable diplopia.

Inflammation or Infection

A wide variety of infectious and inflammatory etiologies can cause ocular nerve palsies in isolation or in combination with other neurological signs and symptoms. In the younger age group, demyelinating disease should be considered and is the second most common cause after mass lesions, though cranial nerve palsies are an uncommon presentation of demyelinating disease. In a study of 483 multiple sclerosis patients in 7.3%, a cranial nerve palsy was the presenting sign of the disease or of relapse in 3.1% [20]. Another case series found that multiple sclerosis caused 24% of non-traumatic VIth nerve palsies [16]. The patient prognosis in demyelinating disease depends on the early identification of the disease, so early neuroimaging should be considered in all younger patients presenting with ocular motor palsy.

Sarcoidosis is a systemic granulomatous disease that can cause CNS involvement in <5% of the affected patients [21]. The patient with isolated central nervous system sarcoidosis can present with intracranial mass lesions and multiple cranial nerve palsies. Histopathology is required for confirmation of typical epithelioid granulomatous inflammation in sarcoidosis. These lesions usually resolve with intravenous corticosteroids, and it is interesting to note that there may be no hilar adenopathy on chest imaging in these patients [22]. In another case report of undiagnosed neurosarcoidosis, Al-Qudah et al. presented a case of new onset seizure, left VIth nerve palsy, normal erythrocyte sedimentation rate, and MRI revealing dural thickening and enhancement of the left orbital apex. Dural biopsy confirmed sarcoidosis, and this patient also improved with high-dose IV corticosteroids, followed by an oral prednisone taper [23]. Neurosarcoidosis can also affect the IIIrd cranial nerve, as Bansal et al. presented a patient with an acute pupil involving IIIrd nerve palsy. Aneurysm was ruled out with computed tomographic angiogram, but MRI brain with contrast revealed enhancement of the IIIrd cranial nerve and leptomeningeal enhancement. Hilar lymph node biopsy was confirmatory of sarcoidosis, and this patient improved on IV steroids, prednisone taper, and methotrexate [24].

Diplopia is an uncommon presentation of giant cell arteritis (GCA), in the older population (>60 years), and occurs in 11.1% of the patients [25]. GCA is an important differential diagnosis, especially when patient presents with symptoms such as temple pain, jaw claudication, scalp tenderness, and unintentional weight loss. Vision loss may accompany or follow diplopia, and the diplopia can be transient. The diplopia is thought to be secondary to ischemia of the nerves supplying the extraocular muscles or the extraocular muscles themselves, along with ischemia of the cranial nerves [26]. In a prospective study by Tamhankar et al., three of the 109 patients studied with isolated ocular motor nerve palsy had GCA. All three had VIth nerve palsies and were diagnosed by positive temporal artery biopsies, after high ESR was detected during laboratory evaluations [18]. In another case series of IIIrd nerve palsy secondary to GCA, one of which had pupil involvement, two patients did not have systemic symptoms consistent with GCA, but had elevated serum inflammatory markers, and in another patient, inflammatory markers were normal, but the patient had systemic symptoms of GCA. All patients had the diagnosis confirmed with temporal artery biopsy and had resolution of the nerve palsy on high-dose oral prednisone [27]. This indicates that GCA can have a myriad variety of presentations; diagnosis, however, is confirmed on temporal artery biopsy and good steroid response. The initiation of prompt steroids for suspected GCA is thus a necessary part of the management of this disease. Liu and Chestnutt demonstrated that contrast-enhanced MRI of the orbits might be helpful in diagnosing GCA where immediate biopsy cannot be taken, as two cases presented with enhancement of the optic nerve sheath(s) in biopsy proven GCA [20]. Liu and Miller showed a case of unilateral anterior arteritic ischemic optic neuropathy with bilateral optic nerve sheath enhancement [21]. Therefore, in atypical presentations of giant cell arteritis, contrast-enhanced MRI may have a contributory role in formulating a working diagnosis. However, optic nerve sheath enhancement may be seen in several common inflammatory causes, such as sarcoidosis, optic neuritis, or nerve-related tumors, thus patient evaluation should be inclusive of these conditions. Patients may also complain of significant retrobulbar pain that may have a relapsing and remitting course.

Tolosa Hunt syndrome should also be considered if there is pain in combination with a IIIrd, IVth, VIth palsy or involvement of first division of the trigeminal nerve. The disease is characterized by inflammation that is exquisitely responsive to steroids, and some contend that its responsiveness to steroids can be used as a diagnostic criterion [28]. Neuroimaging should be undertaken to determine the extent of inflammation and to rule out other causes of painful ophthalmoplegia, such as infection via spread from the sphenoid sinus, especially before systemic steroids are prescribed.

Multiple cranial nerve palsies can also be associated with meningitis. Meningitis itself can be caused via many etiological factors. However, it appears that infectious meningitis by the herpesviridae family may be causative more often. While varicella zoster usually presents with a painful skin rash in the affected dermatome, the skin rash may not accompany cranial nerve palsies leading to diplopia, and the patient may not have encephalitis or meningitis, as shown by Yeh and Liao [29].

Human herpesvirus 6 can also cause cranial neuropathies, including one case of a IVth nerve palsy with concomitant acute retinal necrosis, in an immunocompetent patient [30]. Detection of the virus usually requires polymerase chain reaction of the cerebrospinal fluid or aqueous or vitreous humor. Though more common in children, petrous apicitis secondary to otitis media may lead to a VIth nerve palsy, as only a thin dura separates the VIth nerve and the trigeminal ganglion from the petrous apex. The triad of facial pain, VIth nerve palsy, and otitis media are found, it is termed Gradenigo syndrome [31]. Tuberculous meningitis also has a predilection for the skull base, causing cranial nerve palsies from dense bacterial exudates in the subarachnoid spaces [32]. Due to the involvement of this area, this has been used as a predictive factor to distinguish tuberculous meningitis from acute bacterial meningitis (OR: 1.980) [33]. Lyme disease may cause cranial neuropathy in the absence of Lyme meningitis, and therefore cranial nerve palsies may be seen with normal cerebrospinal fluid studies [34]. In children, Lyme meningitis may cause a pseudotumor cerebri-like syndrome that may lead to VIth nerve palsies [35].

Autoimmune

Myasthenia gravis (MG) is an autoimmune condition that may be localized to the eyes or become generalized to affect larger muscle groups. The disease is B-cell-mediated and is characterized by the presence of autoantibodies against the acetylcholine receptor or, less frequently, against muscle specific kinase (MUSK). Recently, autoantibodies against lipoprotein-related protein 4 (LRP4), titin, or ryanodine receptor have also been implicated [36]. Ocular involvement with myasthenia gravis causes diplopia, which can often mimic any ocular motor nerve palsy. The hallmark of this condition is fluctuating ocular misalignment with or without unilateral or bilateral ptosis. With widespread availability of testing autoantibodies against the acetylcholine receptor, it is desirable to obtain these in patients who complain of transient features of cranial nerve palsies. It has been shown that the binding and modulating antibodies are found with the same frequency in patients with MG, and the diagnostic yield is improved if both modulating and binding antibodies are assayed [37]. Binding and modulating antibodies are found in about 70% of those with ocular myasthenia [38]. Some patients may not be positive for these autoantibodies, even on repeated testing, and are referred to as seronegative. In seronegative patients in whom clinical suspicion for MG is high, single fiber electromyography of the orbicularis oculi muscle should be considered [39]. The first-line treatment for myasthenia gravis is pyridostigmine alone or in combination with other immunosuppressants, such as prednisone, azathioprine, mycophenolate mofetil, or rituximab in more refractory cases [40]. In absence or unavailability of single fiber electromyography, a therapeutic trial with pyridostigmine can be considered, and symptomatic improvement indicates MG. A chest CT should be performed to rule out thymoma, and thymectomy is indicated in patients who have suspected thymoma. Even in patients who do not have thymoma, thymectomy has been proven to be beneficial in patients <65 years old, with generalized myasthenia

gravis, as this may result in decreasing disease severity and less need for immunosuppression [41]. The effectiveness of thymectomy for ocular myasthenia gravis is unproven.

Miller Fisher syndrome is another rare disorder that presents with a triad of ophthalmoplegia, ataxia, and areflexia. The exact pathogenesis of this condition is unknown, although patients may report a preceding illness, and *Campylobacter jejuni* has been implicated in some cases [42]. Clinical features include demyelination of peripheral and central myelin sheaths, with elevated cerebrospinal fluid protein and presence of anti-GQ1B antibodies [43]. Management includes plasmapheresis, intravenous immunoglobulin, and supportive care.

Thyroid eye disease, which is an independent autoimmune process from primary thyroid disease, may mimic cranial nerve palsies due to fibrosis of extraocular muscles. The medial rectus is often involved, and this may mimic a VIth nerve palsy on examination [44]. Thyroid eye disease rarely cause actual cranial nerve palsies, unless there is significant extraocular muscle enlargement leading to orbital apex syndrome.

Evaluation of Patients with Ocular Motor Palsies

History

Patient history is the most important aspect in neuro-ophthalmic evaluation. Mostly patients with an ocular motor cranial nerve palsy complain of double or blurred vision that resolves on closing one eye. It is then important to consider whether diplopia was acute or of insidious onset, horizontal or vertical, worse in any direction of gaze or accompanied with other neurological signs or symptoms. The systemic history of the patient which includes history of vasculopathic risk factors, head trauma, prior ocular surgery, neurosurgery, tumors, or recent infections should be recorded. If the diplopia is binocular, the pattern of misalignment is helpful, as horizontal diplopia indicates the IIIrd or VIth nerve and vertical or oblique diplopia usually implies involvement of IIIrd or IVth nerves. History of strabismus, and prior interventions to manage strabismus should be discussed, as prior patching or surgery can account for a decompensated deviation. It is important to elicit and record history of prior episodes of diplopia, as this is an important clue to guide the neuro-ophthalmological evaluation.

Other associated clinical finding may strongly indicate a particular pathology like:

- New onset diplopia, difficulty swallowing, and ptosis: myasthenia gravis
- History of cardiovascular risk factors: vasculopathic factors
- History of multiple sclerosis and horizontal diplopia: internuclear ophthalmoplegia
- Focal neurological signs, such as confusion, imbalance, vertigo, and gait difficulties: intracranial lesions

The presentation of patient with a IIIrd nerve palsy is usually more subtle than the classical exodeviated and hypotropic eye with a blown pupil. The presentation usually

involves ipsilateral deficits in supraduction, infraduction, and adduction, with ptosis and a dilated, perhaps partially reactive, pupil. A lesion of the IIIrd nerve nucleus may cause bilateral ptosis and bilateral supraduction deficits, due to the paired levator subnucleus and the proximity of the superior recti subnuclei to one another. As the IIIrd nerve splits into the superior and inferior divisions in the anterior cavernous sinus, isolated superior division lesions may cause subtle ptosis and a supraduction deficit only. While it may be tempting to localize a divisional third nerve palsy to the cavernous sinus or orbital apex, it has been shown that divisional palsies may occur from a lesion anywhere along the length of the nerve, due to topographical organization of the nerve fibers prior to the anatomical bifurcation [45]. In a pupil sparing IIIrd nerve palsy, aneurysm and intracranial masses should also be considered, as the pupil may become involved later. Additionally, it is important to consider myasthenia gravis, as this condition may mimic a pupil sparing IIIrd nerve palsy.

Acute IVth nerve palsies are likely to occur after closed head trauma, and will cause vertical diplopia, worse in contralateral gaze and ipsilateral head tilt. In these patients, small degrees of vertical misalignment are quite visually debilitating. In those with >10° of excyclotorsion, measured by double Maddox rod, bilateral IVth nerve palsies should be considered. Congenital IVth nerve palsies occur in about one-third of patients, and examination of childhood pictures for facial asymmetry and head tilt is an important component of evaluation. Additionally, presence of inferior oblique overaction, lack of excyclotorsion, and large vertical fusional amplitudes all suggest a decompensated form of the deviation.

Patients with a VIth nerve palsy will have decreased abduction in that direction of gaze (left VIth nerve palsy leads to a deficit in abduction of the left eye). Occasionally, the extraocular movements will appear full, but there will be a small esodeviation when the eyes are abducted. Therefore, the presentation of a patient with VIth nerve palsy is horizontal binocular diplopia that worsens when looking toward the side of the lesion. Since this causes an esodeviation, the patient will likely be more symptomatic at distance. If there is ipsilateral facial weakness, a nuclear VIth nerve palsy should be suspected, due to the proximity of the VIth nerve nucleus and the genu of the facial nerve [46]. In patients without vasculopathic risk factors who develop a VIth nerve palsy that spontaneously resolves, skull base tumors should still be considered [47]. There is a report of two cases of a recurrent and spontaneously improving VIth nerve palsy in children secondary to skull base chondrosarcoma [48], which reiterates that all children with cranial nerve palsies must undergo neuroimaging. In patients with headaches and blurred vision, with or without optic disc edema, VIth nerve palsies from increased intracranial pressure may result. The differential diagnosis is extensive but includes pseudotumor cerebri, neoplasm, inflammation, infection, and mass lesions.

Examination

Patients require an ophthalmologic and focused neurological examination based on the presenting symptoms. Prior to beginning the examination, it is important to observe the patient's gait as they walk into the examination room and their facial

features for ocular misalignment, ptosis, facial asymmetry, and head position. Pupillary examination should be conducted in light and dark, as subtle differences can be indicative of pathologic states. Color vision is a sensitive indicator of optic nerve function, but familial dyschromatopsia, prior optic neuropathy or optic neuritis, and poor visual acuity may confound this measurement. Patients with shallow orbits may appear to have abduction deficits, but this should be accompanied by an esodeviation in that direction of gaze, if a true deficit exists. Versions and ductions (monocular testing) should be checked, with careful recording of deficits. There are many methods for the evaluation of ocular misalignment, including cover/uncover, alternate cover, Krimsky or Hirschberg techniques. Vertical misalignments can be measured using the Maddox rod in cooperative patients. As mentioned previously, the pattern of misalignment can used to uncover the pathology. However, long-standing deviations may have a spread of comitance, and the ocular misalignments are similar in all directions of gaze. A dilated eye examination should be undertaken on all new patients or known patients with new symptoms so as not to miss retinal or macular pathology.

Laboratory Tests

The laboratory tests are conducted to evaluate specific risk factors. In older patients, evaluation should include metabolic markers, such as hemoglobin A1C, comprehensive metabolic panel, and lipid levels. If GCA is a differential, assessment of the patient's inflammatory status should be undertaken immediately, and lab tests should include erythrocyte sedimentation rate and C-reactive protein. In patients suspected with myasthenia gravis, acetylcholine receptor antibody titers should be requested.

Imaging

Neuroimaging is indicated in patients who present with focal neurological signs, suspicion for multiple sclerosis, new onset headache, or have a complicated clinical picture. Contrast-enhanced MRI is modality of choice in such patients. Orbital imaging with thinner slices can be obtained, and evaluation of orbital structures or cavernous sinuses is required, which may be needed to differentiate actual cranial nerve palsies from mimickers, such as thyroid eye disease [44]. In the prospective study by Tamhankar et al. [18], 5% of patients had true intracranial pathologies, including giant cell arteritis, infarction, and neoplasm. This has been confirmed by other studies, suggesting an incidence of 1–14% of intracranial lesions accounting for cranial nerve palsies in older adults [49, 50]. While it may be argued that imaging one of every 100 patients to determine the prevalence of intracranial pathology [51] is not cost-effective, it has been shown that the actual cost of imaging, when compared to the clinically relevant findings uncovered, is reasonable [52]. It is also difficult to decide if neuroimaging is warranted depending on which cranial nerve palsy is present, as it has been thought that most IVth and VIth nerve palsies are due

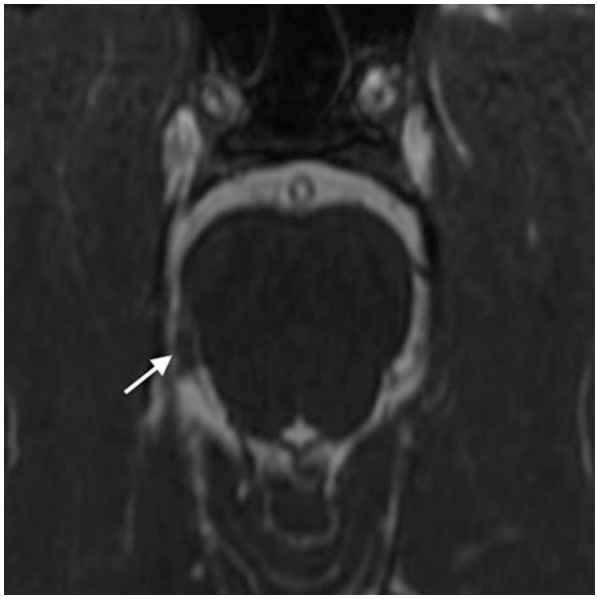

Fig. 5.4 1.5-T FIESTA-C sequence MRI brain: axial view of the midbrain. The fourth cranial nerve exits dorsally and travels through the ambient cistern ventrally. The arrow indicates a schwannoma of the right IVth nerve

to ischemia or demyelination and that neuroimaging may not alter patient management [51]. However, there have been reports of mass lesions causing isolated IVth nerve palsies (Fig. 5.4) [53]. Thus blanket statements suggesting that only certain cranial nerve palsies require neuroimaging should be interpreted with caution. The significantly higher occurrence of intracranial lesions causing cranial nerve palsies in children requires neuroimaging in all cases in this population.

With the advent of 3 Tesla (3 T) MRI scanners and special reconstruction sequences, the course of the cranial nerves can be followed intracranially, and may allow for more accurate localization and diagnosis. Kontzialis et al. found high-resolution 3D skull base MRI imaging for better image quality to image skull base area. In this protocol, 0.6-mm constructive interference in steady-state (CISS) images are obtained before and after gadolinium contrast infusion, based on T2/T1 signal, and the course of the VIth nerve, from brainstem to orbit, can be imaged (Figs. 5.5 and 5.6) [54]. Use of surface coils in a transparent face mask allows visualization of intraorbital motor nerves in a prospective study using high-resolution MRI [55]. The coils allow for 1–2-mm thick sections, and the FIESTA (fast imaging employing steady-state acquisition, analogous to CISS) sequence permits visualization of the cranial nerves against the cerebrospinal fluid background [56]. These images can also be obtained on a 1.5 Tesla scanner, so the additional use of surface coils allows older machines to also produce high-quality images. Similarly, Kau et al. used a similar technique to evaluate 12 patients with IIIrd nerve palsy. In two patients, who were previously stated to have normal MRI imaging, high-resolution MRI found enhancing tumors of the IIIrd nerve in the subarachnoid and intraorbital spaces, with associated atrophy of the extraocular muscles [57].

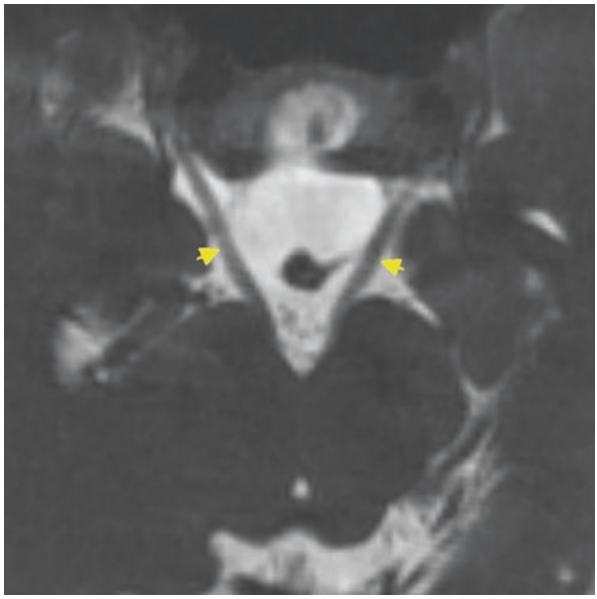

Fig. 5.5 3-T reformatted CISS MRI brain: oblique-axial view of midbrain demonstrating normal IIIrd nerves (arrows) exiting from the ventral midbrain

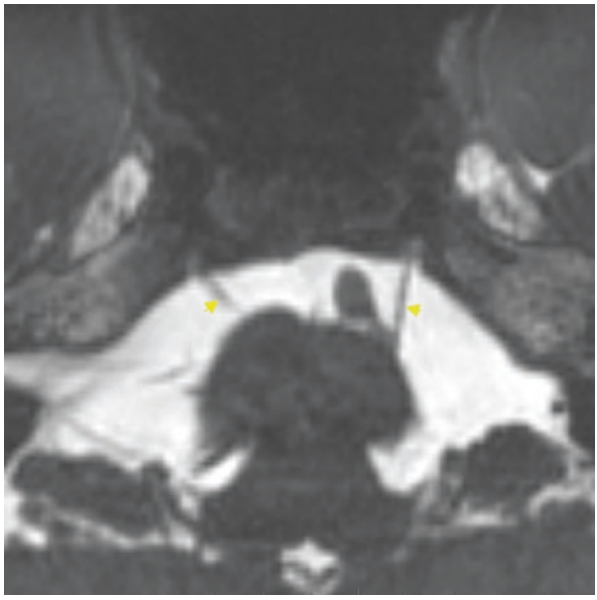

Fig. 5.6 3-T CISS MRI brain: oblique-axial view of pontomedullary junction showing normal VIth nerves (arrowheads) exiting the pontomedullary junction

Ultrahigh field MRI (7 Tesla) has also become available and offers imaging of small structures within and around the brainstem, such as the cranial nerves, with the spatial resolution approaching the sub-millimeter range [58]. When comparing 7 T to 3 T scanners (with head coil), cranial nerves III, V, and the VII/VIII complex can be imaged more readily, but due lack of availability, cost of use and longer scan times of 7 T MRI scanners are largely reserved for research use [59].

Cranial nerve trajectories can be tracked in three dimensions, via the identification of axonal direction using advanced diffusion MRI. Conventional diffusion tensor imaging (DTI) was a major step forward in imaging cranial nerves, but its use was limited by angular resolution, inability to resolve the origins of the cranial nerves, and significant artifact [60]. Newer methods such as high-definition fiber tractography (HDFT) have diminished these artifacts, and using this technology, HDFT can identify the cisternal portions of most cranial nerves in control patients [61]. Overall, these latest imaging techniques have the potential to increase the accuracy of diagnosis and localization of cranial nerve palsies. The cost of neuroimaging is, however, a factor that needs more attention in order to address limitation of availability in resource poor countries.

Treatment

Diplopia resulting from cranial nerve palsies may be managed with prisms or patching one eye. Usually a stick-on Fresnel prism is used initially to give the patient a sense of what prismatic correction will do for them, at the expense of reduced visual acuity. If they are comfortable, then ground-in prisms may be advised.

Fresnel prisms are useful in patients with debilitating double vision with a dynamic course of pathology, as they are inexpensive and easily replaceable. Contrary to the old belief that prismatic correction should not be considered for incomitant strabismus, careful prism selection can help, for example, patients with inferior incomitant vertical strabismus resulting from IVth nerve palsy. Prisms added in reading glasses can help alleviate diplopia in downgaze [62]. In a retrospective study of 64 patients with incomitant, large, and otherwise complex strabismus, it was found that 72% had complete or partial resolution of diplopia, and a larger majority of patients who prescribed vertical prisms reported improvement as compared to those who prescribed horizontal prisms [61]. Satisfaction with prismatic correction was also assessed based on etiology, and it was shown that 100% patients with divergence insufficiency and skew deviation reported improvement in diplopia in contrast to only 64% of those with convergence insufficiency [63]. In those with IVth nerve palsy, 80% of those treated with prism reported symptomatic relief, and a similar percentage reported satisfaction despite prescribing a >10 prism diopters prism [64]. Some patients are intolerant to prismatic correction. For such cases, patching one eye or prescribing fogged glasses provides symptomatic relief. If a patient has had stable strabismus examinations for many months, surgery can be considered. The surgical management of strabismus from cranial nerve palsies is beyond the scope of this chapter.

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Nystagmus

6

Shashikant Shetty and Anshulee Sood

Nystagmus is a rhythmical, involuntary, and repetitive to and fro movement/oscillations of the eyes [1, 2].

Normal Mechanisms of Gaze Stability

As a part of our normal physiology, there are different mechanisms which work in tandem to prevent deviation of the line of sight from the object of regard.

1. *Fixation*:
   To maintain the ability to fix, there are two essential requirements:
   (a) The visual system must be able to generate corrective eye movements to correct any image drift on the retina.
   (b) Any movements—such as any unwanted saccades which may be responsible for moving the eye/visual axis away from the point of fixation must be suppressed/corrected.
2. *Vestibulo-ocular reflex*:
   The vestibule-ocular reflex (VOR) is used to compensate for head movements which are quick—and helps to maintain clarity of vision during natural physiological motion.
3. *Gaze-holding system*:
   The gaze-holding system refers to the central mechanisms which are responsible for maintaining the eyes in an eccentric position in the orbit against the various forces such as the extra-ocular muscles and the elastic pull of the suspensory ligaments, which tend to return it toward a central position.

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_6

Understandably, disruptions of any of these three systems may lead to disorders of steady gaze and to nystagmus.

Physiological Nystagmus

Physiologic nystagmus preserves clear vision during self-rotation. The types of physiological nystagmus are:

1. *Vestibular Nystagmus*:
   As mentioned previously, the VOR is responsible for maintaining a steady line of sight during natural activities. Mostly, the movement of the head during regular physiological activities is minimal/small, and the VOR is able to compensate for these movements by generating remedial eye movements.
   Thus, the line of sight remains pointed at the object of regard.
   However, in case of larger rotations of the body or larger amplitude head movements, the VOR is unable to completely compensate. In these situations, when there are sustained rotations, a "vestibular nystagmus" is generated with fast-phase movements being initiated to reset the eye position and to keep the eyes in their working range.
   Vestibular nystagmus proves useful for assessing vision in young infants—where dampening of the nystagmus should occur about 5–10 s after stopping the rotation. Persistence of nystagmus beyond this time indicates significant visual impairment.
   Caloric testing (response to hot and cold) is performed as an in-office test by ENT surgeons to evaluate vestibular function.
2. *Optokinetic Nystagmus (OKN)*:
   Optokinetic nystagmus is driven visually and compensates for the movement of retinal images upon when one fixates on a repetitive moving target.
   OKN may be utilized for:
   (a) Vision assessment in infants and uncooperative adults.
   (b) Reversal of OKN is seen in infantile esotropia syndrome and congenital nystagmus (now called infantile nystagmus syndrome).
   (c) Asymmetry/disjugacy/Absent vertical OKN is diagnostic of neurological/neurometabolic lesions and warrants neuroimaging in children with nystagmus.
3. *Eccentric gaze Nystagmus*: Comes up as transient nystagmus on extremes of gazes.

Unlike physiological forms of nystagmus, i.e., vestibular and optokinetic nystagmus, nystagmus that occurs as a result of pathology results in an excessive drift of stationary retinal images. This may result in oscillopsia, which refers to an illusory motion of the seen world and hence causes visual degradation.

Congenital Forms of Nystagmus

Older literature described three distinct forms of congenital eye movement disorders: congenital nystagmus, latent nystagmus, and spasmus nutans.

However, in more recent times, the Classification of Eye Movement Abnormalities and Strabismus (CEMAS) Working Group has reclassified eye movement disorders and has recommended that the term infantile nystagmus syndrome (INS) be used for what has previously been called congenital nystagmus, including motor and sensory varieties (https://nei.nih.gov/sites/default/files/nei-pdfs/cemas.pdf).

The primary criteria for defining INS are infantile onset and accelerating slow-phase waveforms on eye motility testing.

As per the new CEMAS classification, latent nystagmus is now referred to as Fusional Maldevelopment Nystagmus Syndrome (FMNS).

Infantile Nystagmus Syndrome

INS refers to eye oscillations which are involuntary, conjugate, rhythmic, and are usually horizontal. In primary gaze, it may have a pendular or jerk quality, and it usually has a torsional component [3].

Various characteristics of infantile nystagmus syndrome are:

(a) INS is usually horizontal in direction. It is conjugate and remains so when tested in vertical gazes. Although a small torsional component maybe present in INS, it is rarely completely vertical [4].

(b) Usually the frequency of infantile nystagmus intensifies on side gazes and INS may become right-beating in right gaze and left-beating in left gaze.

INS does not follow Alexander's law (i.e., the amplitude of the nystagmus increases in the direction of the fast phase and decreases in the direction of the slow phase, but never reverses).

Peripheral vestibular nystagmus obeys Alexander's law, and this may be used in clinics to help differentiate it from INS and also from manifest latent nystagmus (which obeys Alexander's law under conditions of monocular fixation) [5].

(c) INS usually worsens on attempted fixation and also by anxiety or attention, whereas in cases with peripheral vestibular nystagmus, the nystagmus is dampened by fixation and intensifies on ocular occlusion.

A simple clinical test which maybe used to differentiate between these two forms of nystagmus: Use a direct ophthalmoscope and focus on the optic disc of one eye while intermittently occluding the other eye. Increased nystagmus intensity with occlusion suggests a peripheral vestibular nystagmus, while either no change or decrease in nystagmus intensity suggests infantile nystagmus [5].

(d) Induced convergence causes dampening of infantile nystagmus and hence may result in better near visual acuity in comparison to that at distance.
(e) In INS, there is usually a "null zone," i.e., a particular eye position where the amplitude and frequency of the nystagmus are minimum.
(f) Waveform: The waveforms in INS are of a distinctive nature. Most commonly, they are pendular and are characterized by increasing velocity of the slow phase.

Another characteristic feature of INS—is a "foveation period." This refers to a short span of time, usually after a fast phase in each cycle, when the eye is steady and fixed on the object of regard. Foveation periods are usually superimposed on the waveforms.

Waveforms in INS are also dependent upon the age of the patient—for instance "triangular waveforms" with large amplitudes are present in infants and these waveforms may become pendular later.

(g) Oscillopsia is absent in patients with congenital nystagmus—this may be due to the presence of a foveation period.
(h) Almost one-third of patients with INS may have concomitant strabismus. The patients may demonstrate "inverted pursuit" or "reversed optokinetic nystagmus," on testing motility with a handheld optokinetic drum, the direction of the fast phase of the nystagmus is the same as the direction of rotation of the drum [4].
(i) Anomalous head positions are seen fairly commonly in patients with INS. The patient usually adopts a face turn/head posture to align the eyes in the "null zone" and reduce the nystagmus in order to improve the quality of vision.

In some patients, the intensity of the nystagmus may be reduced by inducing convergence and hence these patients often induce an esotropia to suppress the nystagmus. This is referred to as nystagmus blockage syndrome (NBS) [6].

(j) Patients with INS may exhibit head nodding or head shaking which is especially noticeable during periods of attempted fixation. The movements of the head are not considered to be an adaptive strategy but are considered to be involuntary movements of pathological origin.
(k) With-the-rule astigmatism may be seen in patients with INS; this has been considered to result from increased application of force on the corneas by the eyelid during ocular oscillations.

Fusional Maldevelopment Nystagmus Syndrome (FMNS) (Latent Nystagmus)

FMNS is characterized by a conjugate horizontal jerk nystagmus that is absent under binocular conditions and manifests on occlusion of one eye. However, most patients also demonstrate a low-amplitude nystagmus under binocular conditions, and this is referred to as "manifest latent nystagmus."

In patients with FMNS, the fast phases of both eyes are directed toward the side of the eye that takes up fixation. Thus the slow-phase drift is directed nasally with respect to the viewing eye.

FMNS obeys Alexander's law, with the nystagmus being greatest on looking in the direction of the fast phases, away from the eye that is occluded. Thus some patients may adopt a head posture to keep the fixing eye in an adducted position, where nystagmus is minimal.

Methods to differentiate FMNS from INS in clinic:

(a) FMNS demonstrates reversal of direction of the nystagmus with alternating fixation
(b) Eye movement recordings: The slow phase of FMNS usually shows a decaying velocity waveform when the eyes are close to central position, in comparison to INS which demonstrates a waveform characterized by increasing velocity of the slow phase.

FMNS is believed to develop as a result of binocular maldevelopment in infancy which may arise due to the presences of monocular amblyopia or strabismus. Another frequent association of FMNS is dissociated vertical deviation (DVD). FMNS is most commonly seen in association with infantile esotropia but may be present in any disorder that results in disruption of binocular fusion in infancy.

Hence, the latest CEMAS classification recommends that the terms latent nystagmus and manifest latent nystagmus be replaced by the etiologic descriptor fusion maldevelopment nystagmus [7].

Spasmus Nutans

Spasmus nutans syndrome is characterized by the triad of nystagmus, head nodding, and torticollis [8].

The onset of the nystagmus usually occurs in the first year of life; however, it may go unnoticed till the child is 3 or 4 years old. It is described as a "shimmering" nystagmus, i.e., it has a high frequency and a small amplitude pendular oscillation. It is largely horizontal in direction; however, it may be disconjugate and often differs in quality between the two eyes and may change and become conjugate or even almost completely monocular over a time span of a few seconds.

The nystagmus in spasmus nutans is accompanied by head oscillations—which may be vertical or horizontal and are more pronounced on attempted fixation.

An anomalous head posture—i.e., a head tilt or face turn may be seen in about two-thirds of patients with spasmus nutans.

Spontaneous resolution is seen in most children with spasmus nutans within 1–2 years after onset, although it may last for over 8 years.

It is important to distinguish spasmus nutans which will resolve over time, from congenital nystagmus (INS), which probably will not. The characteristic "shimmering" quality of spasmus nutans, with its high frequency and low amplitude, helps in differentiating it from INS or FMNS.

Another important management decision that must be taken in cases with spasmus nutans is to determine whether the nystagmus is associated with retinal disease

or a tumor of the visual pathway, particularly an optic chiasmal glioma. Further investigations (e.g., neuroimaging and electroretinogram) are usually warranted in patients with presumed spasmus nutans syndrome to exclude alternative diagnoses.

Acquired Forms of Nystagmus

Peripheral Vestibular Nystagmus

Peripheral vestibular nystagmus results from disorders for the peripheral vestibular system (i.e., labyrinth, vestibular nerve, and vestibular nerve root entry zone). It can occur spontaneously or can even be induced.

It is characterized by a jerk waveform. The slow phases usually have a constant velocity and the fast phase is directed opposite to the side of the lesion [8].

Peripheral vestibular nystagmus is suppressed by visual fixation.

Peripheral vestibular nystagmus follows the Alexander law: that is, it increases in intensity when the gaze is directed in the direction of the fast phase, and decreases when the patient is looking in the other direction.

Since the etiology is often a disease of the peripheral vestibular system, other symptoms such as vertigo and postural imbalance, nausea and vomiting, and auditory symptoms such as hearing loss, tinnitus, and aural fullness may be associated.

Central Vestibular Nystagmus

Central vestibular nystagmus originates as a result of lesions of centers responsible for relaying and processing vestibular information.

Visual fixation does not change or suppress central nystagmus. This type of nystagmus may be unidirectional or bidirectional. Central nystagmus is usually right-beating in right gaze and left-beating in left, i.e., the direction of the quick phase is the same as the gaze of the patient.

Based on the direction of the fast phase—the nystagmus is further classified as downbeat, upbeat, torsional, or horizontal.

Down Beat Nystagmus

It is a type of central vestibular nystagmus where the direction of the fast phase is downwards with upward slow phases [4].

It usually results from an interruption of the pathways connecting the posterior labyrinthine canals through the vestibular nuclei to the ocular motor nuclei. Downbeat nystagmus manifests in straight gaze, but it is generally more pronounced in side gazes and in down gaze. Also, in accordance with Alexander's law is the intensity of the nystagmus is greatest in downgaze and least in upgaze. The nystagmus waveform is generally linear, but it may demonstrate increasing velocity.

Downbeat nystagmus may intensify with convergence and remains unaffected on removal of visual stimulus/fixation. However, changes in head position can modify the nystagmus due to the influence of otolithic inputs. Positioning the patient in a "head-hanging" position can evoke/worsen the nystagmus.

Downbeat nystagmus can be caused by Arnold-Chiari malformation, cerebellar degeneration, and brainstem infarction. However, in about 40% of patients, a clear etiology cannot be demonstrated and it is termed as idiopathic downbeat nystagmus [9].

Most of the affected patients suffer from a disabling vertical oscillopsia.

Several drugs have been tried in the management of downbeat nystagmus, and multiple clinical trials have evaluated medical therapies. Recent clinical trials have demonstrated that 4-aminopyridine can dampen downbeat nystagmus, especially when it is idiopathic or caused by cerebellar degeneration [10, 11]. Clonazepam has also been reported to dampen downbeat nystagmus in clinical trials (Class III) [12].

Upbeat Nystagmus

In contrast to downbeat nystagmus, Upbeat nystagmus is characterized by downward slow phases with upward fast phases and has a jerk waveform. Upbeat nystagmus is always present when looking straight ahead and its intensity does not increase in lateral gaze. Absence of a fixed visual target does not affect upbeat nystagmus, however, like downbeat nystagmus, and it is affected by changes in the position of the head. Convergence is variously reported to enhance, suppress, or convert upbeat nystagmus to downbeat.

Lesions of the regions of the brain which are involved in the regulation of upward eye movements (vestibular, perihypoglossal, and other nuclei in the medial medulla, crossing ventral tegmental tract, brachium conjunctivum, medial longitudinal fasciculus) can result in upbeat nystagmus. Diseases such as Wernicke's encephalopathy, multiple sclerosis, stroke, and tumors may affect these areas and cause upbeat nystagmus.

Common causes of upbeat nystagmus include multiple sclerosis, stroke, tumors, and Wernicke encephalopathy. Most patients with upbeat nystagmus suffer from oscillopsia. Spontaneous resolution is known to occur in cases with upbeat nystagmus although in certain cases it may evolve and change into a downbeating type. In cases where nystagmus is persistent, however, medical treatment can be offered. Memantine (Class II), 4-aminopyridine (Class IV), and baclofen (Class IV) have been observed to dampen upbeat nystagmus in recent clinical trials [13–15].

Torsional Nystagmus

Torsional nystagmus is a type of vestibular nystagmus that is more difficult to recognize in comparison with downbeat or upbeat nystagmus.

It is often subtle and may be difficult to detect on routine clinical examination. Sometimes noting a single conjunctival vessel and looking carefully for its movement may help, also torsional movements maybe noticed during fundus examination and may provide a clue. It is a jerk waveform nystagmus characterized by rotations of the eye about the line of sight when the patient is looking straight ahead. Torsional nystagmus is denoted as clockwise or counterclockwise depending upon the direction of the fast phases. Changes in the position of the head, gravity, or convergence affect the intensity of torsional nystagmus.

Structures in the brainstem—i.e., in the medial longitudinal fasciculus, midbrain, and the lateral medulla—are responsible for mediating torsional eye movements. Any diseases such as stroke, multiple sclerosis, or tumors affecting these areas are likely to result in torsional nystagmus.

When torsional nystagmus persists, it can result in disabling oscillopsia. Recently, a clinical trial, with Gabapentin, has reported modest success in the treatment of torsional nystagmus [13].

Horizontal Nystagmus

Central vestibular lesions can result in a type of an acquired horizontal nystagmus in central gaze. Although this is not very common, it is a known phenomenon. One of the common associated underlying lesions is an Arnold-Chiari malformation. It may be difficult to differentiate this type of nystagmus from INS based on waveforms alone—since the slow-phase waveform has an increasing velocity like in INS, but the presence of an associated vertical component during measurements favors an acquired etiology. Also, in case with acquired nystagmus visual symptoms such as oscillopsia are present.

Nystagmus evaluation and measurements should always be done for a period of at least 2–3 min to exclude the possibility that the nystagmus is actually periodic alternating nystagmus [4].

Periodic Alternating Nystagmus

Periodic alternating nystagmus (PAN) is characterized by a reversal of the direction of the nystagmus every 90–120 s [16]. PAN is predominantly horizontal and has a jerk waveform. A diagnosis of PAN may be missed if one does not observe the patient long enough to detect the reversal of the direction of the nystagmus.

PAN results from a disruption in the velocity storage mechanism. This mechanism is responsible for an improvement of the VOR performance by prolonging the peripheral vestibular signals [17].

Lesions which involve the cerebellum (nodulus, ventral uvula) can result in acquired PAN. Damage to the regions of the cerebellar nodulus and uvula results in an abnormal increase in the duration (velocity storage) of rotationally induced nystagmus. The normal vestibular repair mechanisms reverse the direction of this nystagmus, thus producing the oscillations of PAN. Under normal circumstances,

visual stabilization mechanisms would suppress these oscillations, but disease of the cerebellum that results in PAN usually also impairs these mechanisms.

PAN is not very common in routine clinical practice. Etiology of PAN includes congenital hindbrain anomalies, cerebellar degeneration, multiple sclerosis, and focal lesions (e.g., tumors or stroke) of the nodulus and ventral uvula [4].

Baclofen can be used as a medical therapy in acquired PAN and has shown considerable success.

See-Saw Nystagmus

"See-saw nystagmus" is characterized by a typical combination of torsional and vertical eye movements in which half a cycle consists of elevation and intorsion of one eye and simultaneous depression and extorsion of the other eye, with the vertical and torsional movements reversing during the next half cycle.

The essential characteristic that distinguishes see-saw nystagmus from other types of torsional-vertical nystagmus is that while the vertical component of the nystagmus is disconjugate, the torsional component is conjugate. Most cases of see-saw nystagmus have a pendular waveform. Although the precise site of lesion and mechanism of see-saw nystagmus are not clear, many patients with see-saw nystagmus have large, extrinsic suprasellar lesions (such as craniopharyngiomas) compressing the mesodiencephalon bilaterally.

The pathogenesis of see-saw nystagmus maybe related to loss of crossed visual inputs, i.e., defects in the crossing of the optic nerves may be responsible. Consequently, see-saw nystagmus is often seen in association with lesions of the chiasmal region—which can affect the crossed fibers of the optic nerves and the chiasm. It is usually associated with parasellar lesions, such as pituitary tumors and craniopharyngiomas. Congenital see-saw nystagmus has been reported in patients with achiasmia. Acquired see-saw nystagmus has also been documented in a patient with progressive visual loss due to retinitis pigmentosa. It can be associated with a bitemporal hemianopsia in which the temporal fields are blind.

The genesis of the abnormal "see-saw" movements is thought to be a result of the loss of crossing visual inputs from the temporal fields—which lead to a disruption in the calibration for head movements in a torsional plane (e.g., tilting the head to the right causes the right eye to elevate and incyclotort, whereas the left eye will depress and excyclotort).

Diseases such as Chiari 1 malformation, trauma, brainstem stroke, septo-optic dysplasia, and mesodiencephalic diseases can also cause see-saw nystagmus [4].

Saccadic Intrusions and Oscillations

These are involuntary saccadic eye movements that disrupt visual fixation. Saccadic intrusions may be small intrusions which are infrequent and hence do not result in disturbance in vision or may have a large amplitude and can cause disabling visual symptoms such as oscillopsia.

It is important to distinguish nystagmus from saccadic intrusions—in nystagmus, the primary abnormality is the drifting of the eyes from the primary position of gaze. Another related abnormality is referred to as saccadic dysmetria, in which there is an over- or undershoot while attempting to fix on a target.

Square-Wave Jerks

These are movements which are involuntary and are also seen in healthy individuals but may be exaggerated in patients with diseases such as progressive supranuclear palsy which affect the extrapyramidal system and cerebral hemisphere lesions [8].

Square-wave jerks are horizontal saccades, which are conjugate and move the eyes away from the visual target and are followed by another horizontal saccade, after an intersaccadic interval of about 250 ms, which serves to reposition the eye on the object of fixation. Square-wave jerks, which are very frequent, are called square-wave oscillations and may be mistaken for nystagmus. Cigarette smoking increases the frequency of square-wave jerks.

Macrosaccadic Oscillations

These movements are saccades which are horizontally directed and which occur in bursts. They initially show a buildup with increasing amplitude and then after intersaccadic intervals of about 200 ms show a decrease in amplitude. Macrosaccadic oscillations are seen in patients with cerebellar patients and are considered to be an extreme form of saccadic dysmetria. In these patients, since the saccades toward the object of fixation are hypermetric, they overshoot the target in both to and fro directions and hence the eyes oscillate around the fixation point, and can be very visually disabling. Vertical or torsional components are often present and these oscillations maybe induced by a gaze shift.

Diseases of the cerebellar fastigial nuclei may result in these oscillations. The drug memantine may help to reduce the frequency of the oscillations in these patients [18].

Ocular Flutter and Opsoclonus

Ocular flutter and opsoclonus include consecutive conjugate saccades without an intersaccadic interim. The saccades are absolutely horizontal in ocular flutter, while they are multidimensional (with flat, vertical, and torsional parts) in opsoclonus. Usual reasons for ocular flutter and opsoclonus incorporate viral encephalitis and paraneoplastic disorders (frequently with anti-Ri antibodies), yet they can likewise be caused by medication inebriations (e.g., lithium and organophosphates) and anomalous metabolic states (e.g., hyperosmolar coma). They can be related with other neurologic side effects and signs, for example, myoclonus, as found in the opsoclonus-myoclonus disorder in youngsters with neuroblastoma. Treatment of

ocular flutter and opsoclonus is best coordinated toward the basic reason, in spite of the fact that immunotherapies (e.g., immunosuppressant drugs, IV immunoglobulin, and plasmapheresis) can be considered in patients with a resistant instrument basic the motions (Class IV).

Voluntary Saccadic Oscillations or Voluntary Nystagmus

A few people can willfully initiate high recurrence consecutive even saccades without an intersaccadic interim. Voluntary nystagmus is found in about 5–8% of the population and may happen as a familial quality. These motions can be hard to recognize from ocular flutter; be that as it may, in contrast to ocular flutter, they are frequently started with exaggerated convergence effort, related with eyelid fluttering, and difficult to sustain for more than a few seconds.

Clinical Evaluation

History

- History of oscillopsia—present in acquired forms of nystagmus
- The physician should determine if nystagmus and attendant visual symptoms are worse with viewing far or near objects, with patient motion, or with different gaze angles
- Patients with acquired irregular spontaneous eye movements should be checked for any other neurological and sound-related side effects (e.g., vertigo, ataxia, diplopia, weakness, sensory loss, hearing loss, and tinnitus)
- The patient's medication should be reviewed since some unusual eye movements are drug related (e.g., gaze-evoked nystagmus with anticonvulsant drugs)
- If the patient habitually tilts or turns the head, the physician should determine whether or not these features are evident on old photographs.

Examination

Before evaluating eye movements, the physician must analyze the visual system, searching for indications of optic nerve demyelination or malformation, or ocular albinism, which regularly proposes the determination.

Evaluation of a patient with nystagmus or other abnormal eye movements includes the following steps:

- Evaluate the course and waveform with the patient looking straight ahead at a remote target.
- To decide whether the irregular eye movements are conjugate (i.e., the two eyes moving a similar way), look toward the patient's nasal bridge and note the

relative movement of the two eyes. Some abnormal eye movements are monocular (e.g., superior oblique myokymia), though others are very disconjugate (e.g., see-saw nystagmus). Analyze the nystagmus in each eye, in regard to direction and amplitude of movement, or if there is any asynchrony. If the size of the oscillations differs in each eye, it is alluded to as dissociated nystagmus. In the event that the direction of the movement in each eye varies, it is called disconjugate or disjunctive nystagmus.

- Observe for any intermittent inversion of nystagmus course (e.g., as observed in periodic alternating nystagmus).
- Have the patient look in different gaze directions, as certain types of nystagmus (e.g., gaze-evoked and downbeat nystagmus) might be apparent just with eccentric gaze.
- Evaluate the impact of convergence: A few types of nystagmus dampen with convergence (e.g., infantile nystagmus), while others can alter in force or direction with convergence (e.g., upbeat nystagmus).
- Evaluate the impact of removing visual fixation by looking at the eyes with Frenzel goggles (which comprise of 10- to 20-diopter spherical convex lenses, put in an edge that has its own light source. It amplifies and lights up the patient's eyes, while all the while defocusing the patient's vision) or then again by visualization of the fundus, using an ophthalmoscope, when the other eye is occluded (Note, in any case, that the direction of horizontal or vertical nystagmus is inverted when seen through the ophthalmoscope.) Some types of nystagmus (e.g., peripheral vestibular nystagmus) may possibly be obvious if visual fixation is removed.
- Evaluate the impact of eye closure by gently palpating the eyes when shut; a few types of nystagmus increase in frequency or might manifest just when the eyes are occluded (e.g., oculopalatal tremor).
- Note the impact of occluding one and after that the other eye. In the event that the nystagmus alters course based upon which eye is blocked, latent nystagmus (FMNS) is the conceivable conclusion.
- Assess the patient's eye position, ductions (i.e., capacity to move each eye in the cardinal positions of gaze), and functional eye movements (e.g., vestibular, optokinetic, smooth-interest, saccades, and vergence) for other ocular motor abnormalities.
- Evaluate for anomalous head position, head oscillations, or oscillations of different structures (e.g., palate).

Treatment of Nystagmus

Pharmacological Management

Drug Treatment for Acquired Nystagmus [19]

Topical brinzolamide (1%) eye drops thrice a day is noted to improve foveation by 50%, with a 50% broadening of the null zone.

It has been shown that eye muscle surgery has salutary effects on oscillation characteristics either with or without associated recession or resection (i.e., with only tenotomy and reattachment), in animals and humans with INS. A hypothesis evolved that disruption of the tendino-muscular attachment (enthesis) altered proprioceptive structures near its insertion on the globe that favorably affected the nystagmus oscillation. The enthesial neurons probably provide feedback that assists with ocular alignment and stabilization. Carbonic anhydrase (CA) may play an important role in the neurochemical functioning of the membrane potentials of enthesial nerve endings. A functioning CA system may be involved in facilitating enthesial neuronal feedback to central ocular motor areas and continuing to enhance the developmentally disturbed circuit, thereby resulting in potentiating the ocular oscillation of INS. A carbonic anhydrase inhibitor (CAI) may interfere with the sodium–potassium ATPase membrane-bound system, thus interrupting enthesial neurophysiology (analogous to surgery) and creating a damped circuit, resulting in improvement in the ocular oscillation and enhanced visual function [20, 21]. Nearly 30% patients would experience no change. Topical brinzolamide may be contraindicated in congenital or acquired pathologies of corneal endothelium. The effect commences within 1 week and lasts as long as the drops are continued. There may be an additive effect of the drops when used after the tenotomy and reattachment procedure.

Optical Management

Glasses

Effort should be made to correct any underlying refractive error as children with nystagmus commonly have refractive error, especially with-the-rule astigmatism. This is important even at a young age, as the prevalence and magnitude of with-the-rule astigmatism increases with age, and there is little evidence of emmetropization through age 8. Retinoscopy may be difficult to perform accurately when the nystagmus amplitude is large and should be performed with the eyes in the null zone if such is present. Try to “ignore” the oscillation and start with the distance retinoscopy in a phoropter (in those patients without an anomalous head posture) or trial frame (in those patients who have a significant anomalous head posture).

The next step is to do binocular refraction. This goes against the classic teaching for subjective refraction, but it is the most important step in evaluating these patients because many (over 50%) will have significant changes in their nystagmus under complete monocular conditions (often decreasing their best possible acuity). The best way to do this is to fog the eye that is not being refracted with only enough extra plus to decrease the vision in that eye by 1–3 lines. Many patients with coincidental strabismus (about 50% of the childhood nystagmus population) can fix well enough with one eye at a time, and be subjectively aware of this, so no fogging is necessary. Now your usual routine for subjective refraction can be accomplished [22].

Contact Lenses

Contact lenses have been reported to reduce amplitude and frequency of nystagmus and are helpful in high ammetropias. They have the optical advantage of moving synchronously with the eyes so that the visual axis coincides with the optical center of the lens at all times and shows improvement in visual acuity.

Over Minus Lenses

Adding concave glasses to distant correction induces accommodation that is accompanied with secondary convergence. This induced convergence diminishes amplitude and rate of nystagmus thus enhancing vision. Overcorrection with minus lenses stimulates accommodative convergence and may improve visual acuity at distance fixation by nystagmus dampening.

Prisms

Prisms are used for two purposes in the treatment of nystagmus: (1) to improve visual acuity and (2) to eliminate an anomalous head posture.

(a) *Induced convergence*:
In patients whose nystagmus is suppressed by viewing a near target, convergence prisms will often improve vision. Base-out prisms are prescribed to stimulate fusional convergence, which may be effective in decreasing the amplitude of nystagmus and thus improving visual acuity. The dampening of nystagmus allows "clear vision at a glance" removing the necessity for increased visual concentration and thereby avoiding intensification of the nystagmus resulting from that heightened fixation. Congenital nystagmus (INS) responds well to it. Normal binocular vision is a pre-requisite of the use of base-out prisms since fusional convergence in response to prism-induced temporal retinal disparity cannot be expected in patients without fusion. If the patient has congenital nystagmus and is orthophoric, one can add seven diopters of base-out prism in front of each eye with an additional −1.00 sphere (for the coincidental accommodation) to test the effect of "convergence damping" on acuity at distance. The improvements in acuity, nystagmus intensity, and AHP obtained by this maneuver can be quite impressive in this subset of INS patients without strabismus.

(b) *Induced divergence*:
Some patients with acquired nystagmus and in patients whose nystagmus is worse during near viewing, base-in prisms may help by inducing divergence.

(c) *Moving the null point*:
Prisms with base opposite to preferred direction of gaze may be helpful in correcting the head posture. For example, in a patient with head turn to the left, the null zone is in dextroversion and a prism base-in before the right eye and base-out before the left eye will be helpful in correcting the abnormal head posture.

(d) *Preoperative evaluation*:
The prisms are placed with the base opposite the preferred direction of gaze. For instance, with a head turn to the left, the null zone is in dextroversion, and

a prism base-in before the right eye and base-out before the left eye will correct the head turn. Likewise, a compensatory chin elevation caused by a null zone in downgaze will be improved with prisms base-up before each eye. A combination of vertical and horizontal prisms can be used when the null zone is in an oblique position of gaze. Thus, the results of surgery for head turn in nystagmus can be reasonably well predicted on the basis of the patient's response to prisms, and a postoperative residual head turn may be alleviated further with prisms.

Surgical Management

Indications for surgical intervention:

1. Large face turns—more than 40°.
2. Associated with strabismus
3. Successful prism adaptation

Principles of Surgical Management

(a) To improve head posture—move the eyes toward the null position.
    1. Kestenbaum procedure
    2. Augmented Kestenbaum procedure
    3. Modified Anderson procedure—the two muscle recession.
(b) To improve the visual acuity.
    1. Four muscle recessions

Kestenbaum Procedure

In this procedure, the "rule of 13" is followed wherein each eye the amount of surgery performed is 13 mm including the medial and the lateral recti. In each eye, the yoke muscles are recessed and resected according to the desired shift in position. For example, for a left face turn the left lateral rectus is recessed 7 mm and left medial rectus is resected 6 mm and the right medial rectus is recessed 5 mm and lateral rectus is resected 8 mm, making a total of 13 mm in each eye.

Augmented Kestenbaum Procedure

For larger face turns, there are modifications of the above procedures, which can be followed, by increasing the amount of surgery performed. For example, the Kestenbaum–Anderson procedure can be augmented by 40% or 60% depending upon the extent of the anomalous head posture.

Anderson Two-Muscle Recession Surgery

This is a more conservative procedure where recessions of only two recti are done on the agonist muscles for mild to moderate degrees of face turn.

For vertical head positions:

1. Chin down: bilateral superior recti and inferior oblique recessions.
2. Chin up: bilateral inferior recti and superior oblique recessions.

For head tilts:

1. For moderate tilts: superior oblique and fellow inferior rectus weakening.
2. For severe tilts: weakening of the two incyclotorsional muscle in one eye and the two excyclotorsional muscle of the fellow eye.

For improving visual acuity without null position:

1. Four horizontal recti recessions 12–14 mm.

When there is coexisting strabismus:

1. Best guess dosage.
2. Staged surgery—first correct strabismus and then the null point.
3. Adjustable techniques.

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Paediatric Neuro-Ophthalmology

7

Preeti Patil Chhablani and Jenil Sheth

Introduction

Many of the neuro-ophthalmic disorders which affect adults also affect children; however, paediatric neuro-ophthalmology is now being increasingly recognised as a separate sub-speciality and requires due attention. In this chapter, we focus on some of the common paediatric neuro-ophthalmic diseases that one comes across in the clinic, i.e., paediatric optic neuritis, idiopathic intracranial hypertension in children, cortical visual impairment and congenital optic nerve disorders.

Paediatric Optic Neuritis

Optic neuritis is the inflammation of optic nerve. It may occur as isolated condition be associated with generalised neuro-inflammatory disorders. It is being increasingly recognised that paediatric optic neuritis is different from that in adults in terms of presentation, clinical course, prognosis and association with systemic disorders.

The fundamental characteristics of paediatric optic neuritis are

1. Paediatric optic neuritis is commonly bilateral and has a better visual prognosis.
2. Paediatric neuritis is usually associated with optic disc swelling, whereas adult neuritis is more retrobulbar in nature and has a higher rate of conversion to Multiple Sclerosis (MS).
3. Paediatric optic neuritis can be post-infectious (mumps, measles, chicken pox, infectious mononucleosis, immunizations, etc.) [1–3].

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P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_7

Onset of visual loss in children cannot be accurately determined. Young children may not notice any unilateral vision loss and those with bilateral disease would report only when vision loss becomes incapacitating. Presence of moderate pain during activity of extrinsic eye muscles, dyschromatopsia and presence of relative afferent pupillary defect are some of the other clinical signs. Optic neuritis in children may occur in isolation, as a clinically isolated syndrome, or in association with inflammation of other sites and resulting dysfunction.

The diagnosis is largely clinical. The investigations include neuroimaging, MRI brain with gadolinium contrast, systemic investigations to rule out concurrent systemic infections such as tuberculosis, complete neurological evaluation and lumbar puncture if needed. Figure 7.1 shows a child presenting with bilateral vision loss, with bilateral optic disc edema and MRI (T2 FLAIR axial scan and T2 weighted coronal scan) showing hyperintensities in both optic nerves.

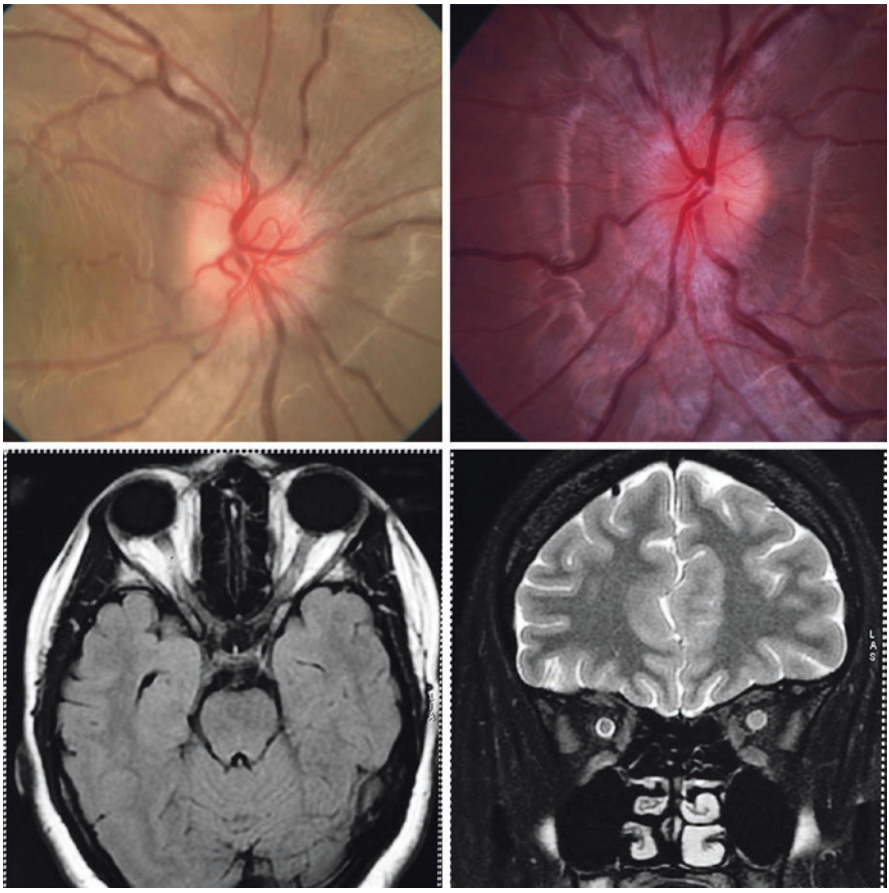

Fig. 7.1 A child with bilateral optic neuritis—the top panel shows bilateral optic disc swelling. The bottom panel shows imaging findings—MRI T2 FLAIR axial scan (bottom right) and T2-weighted coronal scan (bottom left) showing hyperintensities in both optic nerves

Associated Disorders

Acute Disseminated Encephalomyelitis (ADEM)

It is a monophasic, polyfocal, inflammatory, demyelinating encephalitis and myelitis, usually following an episode of viral infection or vaccination. Clinically, presentation usually occurs days to weeks after the inciting event. It has been reported subsequent to infection with Epstein–Barr virus, measles, mumps, rubella and varicella zoster virus.

Children, age, are most commonly affected, presenting with fever, seizures, headache, meningismus, ataxia, hemiplegia or paraplegia and optic neuritis. Despite severity of neurological dysfunction, prognosis for recovery is excellent with appropriate supportive care.

ADEM is believed to result from autoimmune reaction to myelin antigen triggered by virus or live virus vaccine. Neuroimaging shows multiple white matter or deep grey matter lesions in areas of cerebrum, cerebellum, brain stem or spinal cord. These lesions have increased signal intensity on T2 imaging suggesting inflammation and oedema. Lesions are moderately large, poorly demarcated and non-specific and sometimes periventricular in location resembling those in multiple sclerosis. Lesions involving the spinal cord resembling those of Neuromyelitis Optica (NMO) have also been reported [4, 5]. Recent studies have shown thalamic involvement as a useful neuroimaging sign of ADEM as it is rarely seen in children with MS.

Recently, the presence of anti-MOG (myelin oligodendrocyte glycoprotein) antibodies has been noted in cases with ADEM. These cases tend to have a better outcome. However, a relapsing variant of optic neuritis associated with ADEM, unlike the more common monophasic variant, has also been reported to occur with an increased frequency in cases harbouring the anti-MOG antibodies [6, 7].

Systemic corticosteroids is the main stay of therapy. Prognosis for recovery is usually good.

Multiple Sclerosis

Conversion rate to MS in paediatric optic neuritis is unclear. Lucchinetti et al. estimated risk of MS in paediatric optic neuritis as 13% at end of 10 years, 19% at end of 20 years, 22% at end of 30 years and 26% by 40 years. The risk of MS also varies according to age group [8]. Another recent study, from Europe, which looked at 357 children with isolated optic neuritis, found that 40% developed MS at the end of 4 years (median follow-up) [9].

The conversion to MS is more likely in older (post-pubertal) children, those with unilateral optic neuritis and with presence of oligoclonal bands on CSF testing and negative anti-MOG antibodies [1, 9, 10].

Diagnosis of MS in children is based on the McDonald's criteria for dissemination in time and space, as for adults [11]. However, the criteria are more valid in older children.

Neuromyelitis Optica (NMO)

Neuromyelitis optica (NMO) or Devic's disease is a rare acute inflammatory demyelinating condition predominantly affecting the optic nerves and spinal cord segments. It is now believed to be a disease spectrum characterised by typical imaging findings and presence of aquaporin-4 antibodies and is referred to as NMO spectrum disorder (NMO-SD).

Criteria for diagnosis of NMO in adults have been defined and are used in children [12]. These include the presence of optic neuritis, transverse myelitis and at least two of the three supportive criteria:

(a) MRI evidence of contiguous spinal cord segments of three or more in length
(b) MRI brain non-diagnostic for MS
(c) Seropositivity for anti-aquaporin-4 antibody

Children with NMO-associated optic neuritis often have bilateral sequential profound vision loss and transverse myelitis either concurrently or sequentially, but may present only with optic neuritis as well. There is a strong female preponderance, with reported female:male ratio of 9:1. Accompanying symptoms include hemiparesis, seizures and paraesthesias. Paediatric NMO is often aggressive and responds minimally to standard immunomodulatory agents used for MS. [13] Presence of aquaporin-4 antibodies is usually associated with a poorer prognosis and severe visual impairment [14].

Early diagnosis of NMO is critical, since early treatment with immunomodulatory agents may help prevent or minimise disability [14].

Treatment

There has been no prospective controlled study to evaluate the role and efficacy of intravenous corticosteroids or immunomodulator drugs in a typical case of childhood optic neuritis. Recommended dose is 20–30 mg/kg/day (maximum dose of 1 gm/day) of intravenous methylprednisolone for 3 days followed by tapering dose of oral corticosteroids (1 mg/kg/day) for 2–4 weeks, to avoid relapse, which is very common in the paediatric age group [15]. In cases of proven MS, drugs such as interferon beta and glatiramer acetate are used. In NMO, immunosuppressives are generally started early in the course of the disease. Drugs such as rituximab, azathioprine and mycophenolate mofetil have been found to be effective in the management of NMO [15].

Paediatric Idiopathic Intracranial Hypertension

Idiopathic intracranial hypertension (IIH), also referred to as pseudotumor cerebri, is a rare neurological disorder in children and infants. It is characterised by symptoms and signs of raised intracranial pressure without any intracranial mass lesions or hydrocephalus. Though intracranial tension is elevated, it does not alter the consciousness [16].

Though rare, IIH in paediatric population has been well described; however, they differ in their characteristics compared to adult IIH, with lesser prevalence of female preponderance and obesity [17, 18].

Recent studies have suggested significant differences among prepubertal and post-pubertal children with IIH [19]. These reports suggest that while post-pubertal children have a clinical profile like adults (obese and female preponderance), younger prepubertal children are non-obese and have equal prevalence among boys and girls.

A large multicentric study from USA [19] has classified children into three subgroups: prepubescent (age < 11 years), adolescents (age 11–17 years) and adults (>17 years), and reiterated the prior observation that while BMI (Body Mass Index) score and height were like the age-matched children in prepubertal children, post-pubertal children were overweight to obese, and taller.

Based on aetiology of raised intracranial pressure, IIH in children is classified as

1. *Primary IIH*—No recognisable cause for raised intracranial pressure
2. *Secondary IIH*—Raised intracranial pressure secondary to neurological causes other than space occupying lesions, systemic diseases or exogenous agents.

The diagnosis of primary IIH is usually established on basis of *Modified Dandy's* diagnostic criteria [20]:

1. Signs and symptoms of raised intracranial pressure
2. Absence of localising neurological signs
3. Alert and oriented patient
4. Normal neurodiagnostic studies—MRI imaging—no apparent cause of obstruction of ventricular system, displacement or deformity
5. No other cause of raised intracranial pressure present

Clinical Considerations

The clinical presentation of IIH in children varies and may present several hours to years after symptoms begin. Headache is the single most consistent symptom of older children [20]. Headaches in these children are usually vague, frontal in location, severe, pulsatile and worsen on lying down. However, in younger children, asymptomatic IIH is now a recognisable entity, wherein papilledema is recognised incidentally in absence of any symptoms of raised intracranial pressure.

Vision loss in children at the time of presentation is usually mild to moderate and reversible [21]. Estimated 6–20% children with IIH present with visual acuity loss, although 91% have visual field defects at the time of presentation. Like adults, most common visual field defects are enlarged blind spot, inferior nasal field defect, arcuate-type field defects, etc.

Sixth cranial nerve palsy is the only accepted neurological abnormality for the diagnosis of IIH. It is more commonly found in children with IIH than adults. Various studies have shown an estimated incidence of 9–48% of sixth nerve involvement.

The hallmark physical finding in IIH is mild to moderate blurring of disc margins to gross swelling of disc with haemorrhages and hard exudates in peripapillary areas [18, 21]. Disc oedema is often bilateral, symmetrical, though asymmetric disc

oedema can be present [22]. Presence of pallor and cotton wool spot often indicates chronicity of condition and usually correlates with poor visual prognosis. It is very important to differentiate papilloedema from pseudopapilloedema in children as often hyperopes and presence of optic disc drusen cause obliteration of cup and elevation of optic nerve head.

Neuroimaging

Normal neuroimaging studies are mandatory before diagnosing IIH. CT scan is now considered to be sub-optimal, and MRI and MRV with gadolinium contrast is the imaging of choice for diagnosis in suspected IIH [20].

Though none of the neuroimaging abnormalities noted are diagnostic of IIH in children, a number of findings in MRI have been reported with an increased than that seen in the normal population. Studies have reported an increased incidence of typical MRI findings such as flattening of posterior sclera, distension of peri-optic subarachnoid space, optic nerve head protrusion and tortuosity of optic nerves, empty sella in cases of paediatric IIH [23, 24].

Recent studies also suggest lower incidence of imaging abnormalities related to effects of increased ICP in prepubertal children as compared to adults [25].

MR venography is important to rule out cortical sinus thrombosis. Although data regarding the use of MRV in paediatric IIH is limited, narrowing of transverse venous sinus is a consistent finding noted in published literature.

Lumbar puncture is the next most important diagnostic modality after neuroimaging to determine the CSF opening pressures and rule out meningitis. There is lack of reliable published data regarding the normal CSF opening pressure in infants and children. The recommended CSF opening pressures are 180 mm H_2O in children <8 years and with papilledema, and 250 mm H_2O in children more than 8 years or <8 years without papilledema [26].

Treatment

Medical Therapy

There are still no randomised controlled prospective trials on treatment for IIH in children, and hence the treatment is based upon level of vision loss and severity of headache. Most cases respond to medical management, and surgical therapy is limited to only and those with profound vision loss [27].

Acetazolamide has shown to decrease the CSF flow by inhibiting the carbonic anhydrase enzyme in the choroidal plexus. The recommended dose in children is 15 mg/kg/day in 2–3 divided doses until headache, disc swelling and field defects resolve. In case of intolerable side effects of acetazolamide, a dose of 0.3–0.6 mg/kg/day can be used. Data on using acetazolamide in combination with frusemide for additive effect has also been published.

Topiramate in a dose of 1.5–3 mg/kg/day and not more than 200 mg/day has shown to be effective to reduce symptoms in cases not responding to acetazolamide [18, 20, 24, 27]. Topiramate is a secondary carbonic anhydrase inhibitor. In malignant cases presenting with severe headache and profound visual loss, IV methylprednisolone can be used before considering surgical intervention.

Surgical Therapy

The two major types of surgical modalities available for IIH are optic nerve sheath fenestration and CSF shunt surgeries. Indications for surgical interventions are deterioration of visual acuity or visual field defects in spite of maximum medical therapy, intolerance to medical management, poor compliance and intractable headache.

Lumbo-peritoneal and ventriculo-peritoneal shunts have been successful in alleviating symptoms and progression of disc oedema and vision loss [28]. However, the long-term safety and efficacy remains questionable due to risk of shunt obstruction, blockage, migration, meningitis and tonsillar herniation many of which are life threatening.

Optic nerve sheath fenestration is preferred when vision loss is a major issue. Multiple small splits in the nerve sheath or window is made to achieve decompression. A decrease in the rate of progression of vision loss or improvement in field defects is seen in 90% of the patients [27, 28].

In a recent report by Tovia et al. [29], they described outcomes in 60 children (24 prepubertal and 36 pubertal) with IIH. Forty-six (76.6%) patients showed good response to acetazolamide with good improvement in headaches over a period of 1 week to 4 months. While the duration of treatment ranged from 1 month to 5 years, majority of children received treatment for <1 year. Of the 14 (24%) patients who did not respond to treatment, nine required surgical treatment. They reported that 26% had relapse of their symptoms but responded well to retreatment. They also reported that female gender, younger age at onset, presence of headaches and presence of predisposing etiology were predictors of nonresponse to medical therapy, and post-pubertal patients were at higher risk of recurrence.

Cortical Visual Impairment

The term cerebral or cortical visual impairment refers to impairment or dysfunction of the visual system secondary to neural injury [30]. CVI is fast becoming one of the commonest causes of visual impairment in children; however, there is still no clear consensus regarding the terminology and definitions in place to describe the spectrum of disability considered to constitute CVI [30, 31].

The commonest causes of neonatal neural injury are hypoxia, hypoglycemia or a combination of both. The pattern of neural injury shows two distinct patterns depending upon the time of injury. Prenatal and preterm injuries result in damage to the striate and peristriate cortex including the subcortical white matter resulting in

periventricular leucomalacia (PVL) [32, 33]. Whereas, hypoxic damage at term results in infarctions in the watershed areas in the parietal and occipital lobes and parasagittal cortex.

While the diagnosis of CVI remains a clinical one, neuroimaging greatly aids in the confirmation of structural damage to the visual system. Prenatal ultrasound may aid in the detection of large lesions such as intraventricular haemorrhages, cysts and large infarctions [33]. Magnetic resonance imaging (MRI) in infancy is very sensitive in picking up changes such as white matter changes in the periventricular regions, periventricular leucomalacia, gliosis, enlargement of the ventricles, thinning of the corpus callosum and cerebellar atrophy [33].

Whereas the diagnosis maybe relatively straightforward in cases where there is a clear history and imaging evidence of neural damage with poor visual acuity and the relative absence of anterior segment damage, it may not be easy in cases with complex visual processing deficits without obvious loss of visual acuity. Visual acuity in CVI has a very wide range, from perception of light to 20/20. Children with high-functioning CVI may have normal or near-normal visual acuity but may have a range of complex visual processing deficits including processing of crowded scenes, visuomotor control, and route finding [30].

These deficits have now been classified as ‘dorsal stream’ or ‘ventral stream’ dysfunction. Dorsal stream passes between the occipital and posterior parietal lobes and deals with processing of complex visual scenes. Ventral stream passes between the temporal and occipital lobes and deals with recognition of faces, routes, objects, visual memory, etc. Children with CVI may also have a variety of visual field defects such as hemianopia, inferior field loss and Swiss cheese defects, and these may also result in complex visual processing issues.

Since the extent of functional visual deficits are very variable and do not directly correlate with the visible changes on neuroimaging, diagnosis of this condition is not always simple [31, 33]. Diagnostic processes should be based not only on standard ophthalmic and neurological examination but should also include neuropsychological assessment.

Most children show some recovery; however, this may take years [34]. The interventions and management in children with CVI must be done after detailed assessment using a multidisciplinary team approach, including parental interviews, assessment of the child at home and in office and CVI questionnaires. Associated refractive errors, accommodative/convergence insufficiency and amblyopia must also be treated. One must also consider the effect of other preexisting comorbid conditions such as ADHD (attention-deficit hyperactivity disorder), cerebral palsy and autism.

Congenital Optic Disc Anomalies

Congenital optic nerve anomalies are group of structural malformations of optic nerve head and surrounding retinochoroidal tissue causing visual impairment or blindness. Infantile nystagmus or sensory strabismus might be present in such

children due to early sensory deprivation. Amblyopia (unilateral cases) should also be suspected in such cases. Many of the optic disc anomalies are associated with ophthalmologic, neurologic and systemic features like endocrinological abnormalities that will help the ophthalmologist to identify and predict possible outcomes in these patients.

Certain characteristics of congenital optic disc anomalies are:

1. Children with bilateral optic disc anomalies generally present with poor vision and nystagmus and those with unilateral anomalies generally develop severe amblyopia and sensory strabismus by first decade.
2. Small hypoplastic discs are generally associated with CNS malformations, whereas those with large anomalous disc have CNS as well as systemic abnormalities.
3. Colour vision is relatively preserved in contradiction to severe dyschromatopsia in acquired neuropathies.
4. A trial of occlusion therapy should always be attempted in unilateral optic disc anomalies and severe amblyopia.

Optic Nerve Hypoplasia

Optic nerve hypoplasia (ONH) is the most common congenital disc anomaly encountered in paediatric ophthalmologic practice [35]. A small hypoplastic disc is often misdiagnosed as atrophic or may even appear normal to an uninitiated observer.

Clinical Features

Ophthalmoscopically, it appears as abnormally small nerve head. It may appear grey or pale in colour surrounded by a zone of yellowish mottled peripapillary halo, bordered by a ring of increased or decreased pigmentation (double-ring sign). The peripapillary major vessels are dilated and tortuous; however, abnormally straight retinal vessels with decreased branching have also been described [36, 37]. Some evidence of foveal hypoplasia has been found to be associated with this condition. On histopathological examination of optic nerve head and peripapillary tissues, it was found that the outer ring corresponded to normal junction of sclera and lamina cribrosa, whereas the abnormal extension of retinal pigment epithelium over the lamina cribrosa corresponds to inner ring [38].

The visual function in these cases has a wide spectrum and can range from 20/20 to no light perception and does not correlate to the size of the optic nerve head. In addition, visual field defects are often present; these may be localised defects with or without generalised constriction of fields. These eyes are often associated with refractive errors, astigmatism being more common and also may be diagnosed to have amblyopia [39, 40].

Children with ONH may have several neurological and endocrinological associations and need a comprehensive paediatric systemic evaluation. ONH is often associated with septo-optic dysplasia (de Morsier syndrome), which is characterised by absence of the septum pellucidum and agenesis/thinning of the corpus

callosum. These children may also have hypopituitarism—growth hormone deficiency—hypothyroidism, hyperprolactinemia and diabetes insipidus [41]. Children with ONH are also at a risk of sudden death during a febrile illness, likely due to impairment in the corticosteroid responses during fever [42].

Neuroimaging is a must in these cases, since the potential associations include schizencephaly, cortical dysgenesis, periventricular leucomalacia, neurohypophyseal abnormalities such as an ectopic posterior pituitary and absent infundibulum (which is associated with endocrinological dysfunction) [43]. Figure 7.2 shows a child with optic nerve hypoplasia, with the corresponding MRI image showing an absent septum pellucidum.

This optic disc may appear to have segmental hypoplasia—involving either the superior half of the disc (causing inferior field defects) [44], temporal half (in cases with macular colobomas) and band-shaped hypoplasia (in chiasmal hypoplasia) [45]. Periventricular leucomalacia may also be associated with an unusual appearance of the optic disc, with a large cup, which is now considered to be a part of the spectrum of ONH [46].

Many genetic mutations have been described to be associated with optic nerve hypoplasia, both in its sporadic form and in association with septo-optic dysplasia. Mutations in HESX1, SOX2 and SOX3 have been implicated [47].

Morning Glory Disc Anomaly

Morning glory disc anomaly is characterised by a congenital, funnel-shaped excavation at the posterior fundus involving the optic disc.

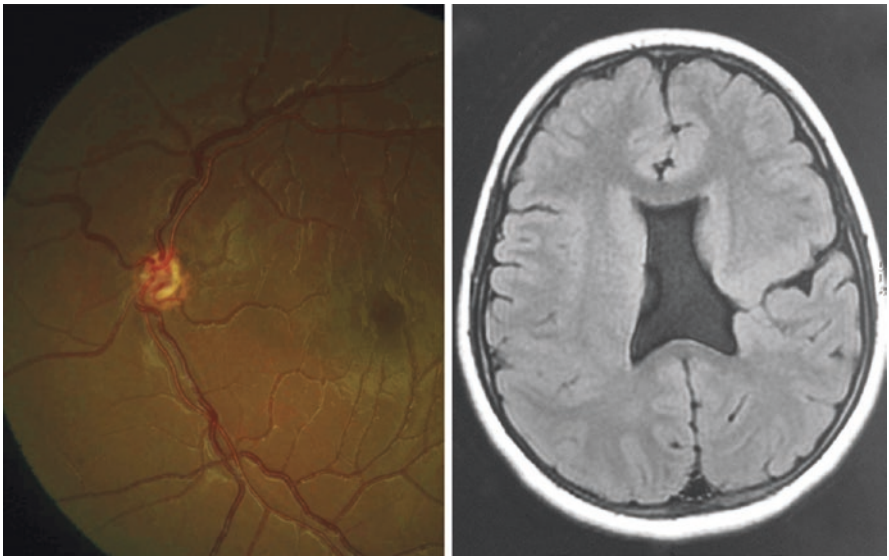

Fig. 7.2 A child with bilateral optic nerve hypoplasia—the left optic nerve—shows a smaller diameter, with a 'double ring' and increased tortuosity of the retinal vasculature. This child was found to have an absent septum pellucidum as seen in the MRI image

Clinical Features

Generally a unilateral condition, however bilateral cases have also been reported. Usually, the optic disc appears larger and lies within an excavation in the central fundus [48]. It may appear pinkish or orange in colour. There is peripapillary excavation, with abnormal retinal pigmentation at the margins of the disc. There is a characteristic central tuft of glial tissue present and the retinal vessels are more in number and appear to emerge in a radial fashion from the borders of the disc (Fig. 7.3).

The visual acuity in these cases may vary—ranging from 20/20 to NLP. In addition to the disc anomaly itself, overlying amblyopia maybe a significant cause of vision loss in these cases. Also, there is an increased predilection to develop a serous retinal detachment in these cases—which can result in further vision loss [49].

Neuroimaging is mandatory in these cases due to the potential neurological associations of his anomaly, some of which maybe life threatening. Morning glory disc anomaly is associated with trans-sphenoidal basal encephalocele [50], which may or may not be associated with other midline defects. Other neurological associations include agenesis of the corpus callosum, absence of the chiasm and dilatation of the lateral ventricles. These children may also have ipsilateral intracranial vascular abnormalities—such as moyamoya syndrome [51], which are detected on MR angiography. Also, children with morning glory discs and infantile hemangiomas have associated PHACE syndrome [52]. Hence, neuroimaging, with MRI and MR angiography, must be a part of the routine workup of these children.

Optic Disc Coloboma

This is a distinct entity which differs from morning glory disc. It is a result of the incomplete closure of the embryonic fissure, which when affecting the optic nerve results in a deep excavation in the substance of the optic nerve. This maybe inferiorly decentered. The presence of a co-existing iris and/or retinochoroidal coloboma

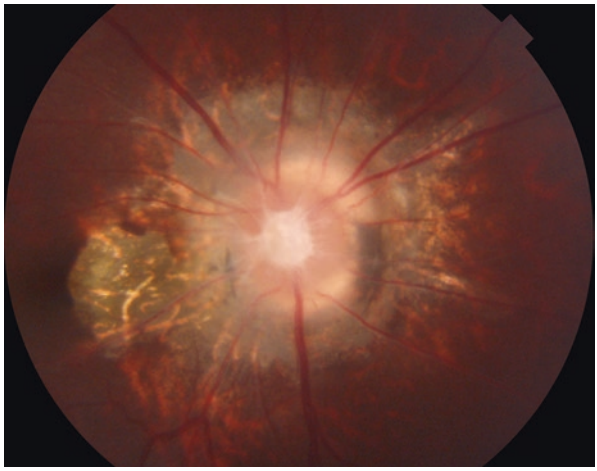

Fig. 7.3 A morning glory disc—with a large optic disc, peripapillary pigmentation, central excavation with a glial tuft and radially emerging retinal vessels

may offer a clue to the diagnosis. Retinal vasculature is usually normal in appearance. An optic disc pit may also be present and may result in a localised serous retinal detachment.

Visual acuity is variable—but is usually impaired. Optic nerve colobomas have multiple ocular and systemic associations. Ocular associations include orbital cysts, retinochoroidal coloboma and retinal detachment [53]. Systemic associations include CHARGE (Coloboma, Heart defects, Atresia choanae, Retarded growth, Genitourinary defects, Ear abnormality) syndrome, Walker-Warburg syndrome, Goldenhar syndrome and Aicardi syndrome [54].

Optic Disc Pit

A pit is a small depression in the substance of the optic nerve, usually present temporally. It may be unilateral (more common) or bilateral. Rarely multiple pits may be present in the same disc. The visual acuity in these cases is generally good (in the absence of serous macular detachment). Variable field defects maybe present. Development of a serous macular detachment complicates a significant proportion of these cases, and the spectrum consists of development of a schisis-like picture to a complete macular detachment requiring vitreoretinal surgery. Optic disc pits and usually not associated with any consistent neurological anomalies.

Papillorenal Syndrome

This syndrome (also called renal coloboma syndrome) is characterised by a distinct optic nerve appearance in association with multiple renal abnormalities such as renal hypoplasia, proteinuria, microhematuria and vesicoureteral reflux. The optic nerve is usually normal in size but has a central excavation and is often referred to as a 'vacant' disc. The central retinal vessels are absent or severely attenuated, and the cilioretinal vessels emerge from the periphery of the disc [55].

Aicardi Syndrome

The optic disc in Aicardi syndrome has a characteristic appearance with multiple chorioretinal patches of atrophy or lacunae surrounding the disc. The CNS associations include absence of the corpus callosum, infantile spasms, mental retardation and developmental delay. Vertebral anomalies, facial dysmorphism, muscular hypotonia and skin lesions may also be present.

Optic Nerve Aplasia

Aplasia of the optic nerve refers to complete absence of the optic nerve. This may present as a complete absence of the optic nerve head on fundus examination, or presence of a depigmented spot in the area of the optic nerve. It is a rare anomaly and is usually unilateral. It may be seen in association with other ocular malformations such as microophthalmos, retinal dysplasia and coloboma. Rarely it may be present bilaterally and may be associated with CNS disorders [56].

Other optic disc anomalies include doubling of the optic disc, megalopapilla and myelinated nerve fibres.

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