

## OPTIC NEURITIS

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## ABSTRACT

Acute optic neuritis (ON) is the most common optic neuropathy affecting young adults. Exciting developments have occurred over the last decade in understanding optic neuritis pathophysiology and these have been translated to recent treatment trials. In its typical form it presents as an inflammatory demyelinating disorder of the optic nerve, which can be associated with multiple sclerosis (MS). Atypical forms may occur in association with other inflammatory disorders or in isolation. Differential diagnosis includes various optic nerve and retinal disorders. Diagnostic investigations may include magnetic resonance imaging (MRI), visual evoked potentials (VEPs) and CSF examination. Optical coherence tomography (OCT) can demonstrate retinal axonal loss, which correlates with measures of persistent visual dysfunction. Treatment of typical forms with high dose corticosteroids shortens the period of acute visual dysfunction but not final visual outcome. Atypical forms may require prolonged immunosuppressive regimes. OCT and VEP measures are suitable for detecting neuroaxonal loss and myelin repair following ON. Clinical trials are underway to identify potential neuroprotective or remyelinating treatments for acutely symptomatic inflammatory demyelinating CNS lesions.

## INTRODUCTION

The term optic neuritis (ON) indicates inflammation of the optic nerve (panel 1). It occurs throughout the world and has multiple aetiologies. In temperate latitudes and Caucasian populations it is commonly associated with multiple sclerosis (MS). However, there is an extensive differential diagnosis, with the prognosis and treatment depending on the cause. There have been significant recent developments in diagnostic workup, understanding pathophysiology and treatment approaches in ON. This review provides an update of these developments for clinicians and scientists with an interest in ON.

## EPIDEMIOLOGY – INCIDENCE, GENETIC AND ENVIRONMENTAL FACTORS

The incidence of unilateral ON around the world ranges from 0.94 - to 2.18 per 100,000.<sup>1-4</sup> Rates in Japan (1.6/100,000) are similar to those in Sweden (1.46 per 100,000) and UK (1/100,000).<sup>5,6</sup> Incidence studies universally show a female preponderance although the ratio of male to female in Japanese (1:1.22) is less than in Northern European cohorts (3:1), suggesting that racial differences exist.<sup>5-7</sup> Meta-analysis of optic neuritis in the Northern hemisphere found rates to be greater at higher latitudes, during spring and in those of Northern European ancestry.<sup>8</sup> Similar findings have been reported in Australia.<sup>3</sup> There is also an association with serological evidence of past Epstein-Barr virus infection and an additive interaction with HLA *-DRB1\*1501* status,<sup>9</sup> suggesting an association between risk factors for MS and aetiology, in areas of the world where MS is common. Conversely, in regions of low MS prevalence, it is likely that ON is less frequently associated with MS and possesses different risk factor profiles.

In adults the incidence of bilateral simultaneous optic neuritis in Western populations is low<sup>10</sup> and as in children the risk of developing multiple sclerosis low.<sup>11</sup> In recurrent ON both visual recovery and neurological prognosis is more variable. This probably reflects the broader differential diagnosis (see below) and the background population risk of these conditions.

## ON AND THE RISK OF MS

ON is the presenting symptom of MS in 25% of cases and occurs during the disease in about 70%, usually in the relapsing remitting phase. Long term follow up studies before MRI reported conversion to clinically definite MS in 34-75% of subjects presenting with ON in the United Kingdom<sup>12</sup> and United States.<sup>13</sup> MRI studies in the same regions identified disseminated white matter lesions suggestive of demyelination in 50%<sup>14</sup> and 62%<sup>15</sup> of subjects. Clinically silent MRI lesions predispose to future clinical events leading clinically definite MS: in the North American Optic Neuritis Treatment Trial (ONTT), conversion to MS was seen after 15 years in 72% with an abnormal brain scan and in 25% with a normal scan.<sup>16</sup> Brain MRI abnormalities in ON are less frequent where MS is uncommon, for example Japan<sup>17</sup> and in such regions, ON is more likely to be associated with other disorders, e.g., neuromyelitis optica (NMO). MRI criteria have been developed that predict the conversion to clinically definite MS with a high sensitivity and specificity in ON and other clinically isolated syndromes.<sup>18,19</sup> MRI evidence of dissemination in space and time can now enable a diagnosis of MS at presentation in some patients with acute ON (panel 2).<sup>20</sup>

## DIAGNOSIS, DIFFERENTIAL DIAGNOSIS AND INVESTIGATIONS

### CLINICAL FEATURES OF TYPICAL OPTIC NEURITIS

Typical ON presents with subacute monocular visual loss associated with pain on eye movement. Visual loss usually develops over hours to days.<sup>21</sup> Most patients report diffuse blurring or fogging of vision. Severity varies widely and tends to reach its nadir within two weeks. Dyschromatopsia occurs early and has a variable spectral pattern. The ONTT described mostly mixed defects (red-green and blue-yellow) but blue-yellow defects were slightly more common in the acute phase and red-green more common at six months.<sup>22,23</sup> Defect type was not associated with severity of visual loss. Other studies have tended to show both red-green and blue-yellow colour defects with neither type dominating.<sup>24-26</sup> One study found greater foveal field depression more likely to be associated with red-green defects.<sup>24</sup> Peri-ocular pain, exacerbated by eye movement, is usually mild and present in most subjects. It may precede or begin with the onset of visual dysfunction and settles after days. ON lesions posterior to the orbit are less likely to cause pain.<sup>27</sup> Other described symptoms include phosphenes,<sup>21,28</sup> Uhthoffs phenomenon and the Pulfrich effect (panel 3).

Early clinical signs include reduced visual and contrast acuities. The ONTT found variable visual field deficits with static perimetry (panel 3) that included focal and diffuse deficits, central, centrocaecal, altitudinal, arcuate, nasal step defects and even hemianopic defects.<sup>29</sup> Central defects were more common than peripheral ones.<sup>30</sup> Other studies using kinetic or higher resolution static perimetry have shown central scotomata to be prevalent,<sup>31,32</sup> the discordance in findings from the ONTT potentially explained by methodological differences e.g. a diffuse defect assigned in the ONTT (testing the central 30 degrees of vision) may actually have been a large central scotoma if tested with larger field perimetry. A relative afferent pupillary defect is usually seen, although involvement of the fellow optic nerve may mask it. Diffuse optic disc swelling is present in a third of cases and is normal in two-thirds (retrobulbar ON).<sup>21</sup> Retinal periphlebitis (perivenous sheathing) is occasionally seen and may indicate a greater risk of conversion to MS.<sup>33</sup>

Asymptomatic concomitant fellow eye visual dysfunction may occur<sup>21,34</sup>. In the ONTT, these abnormalities were not associated with a previous MS history or brain MRI lesion load, but did recover over several months, suggesting that subclinical acute contralateral optic nerve demyelination could be responsible.<sup>34</sup>

Recovery of typical ON usually begins within the first few weeks of symptom onset. An initial rapid recovery is followed by a slower improvement that can continue up to a year after onset, with more than 90% of patients making a good visual recovery (20/40 or better).<sup>35,36</sup> A final 15-year ONTT analysis of 294 patients (although a large number, only 65% of the original cohort) reported 72% of patients had acuities 20/20 or better whilst 8.7% had acuities 20/40 or worse in the affected eye. Six patients (2%) had a visual acuity 20/40 or worse and only 3 (1%) had a visual acuity 20/200 or worse in both eyes.<sup>37</sup> Visual improvement is modestly correlated with initial degree of visual loss,<sup>21</sup> although severe visual loss can still recover well. In the ONTT, 64% of patients, with perception of light only or worse, recovered to 20/40 or better.<sup>35</sup> Poor acuity (20/200 or worse), contrast sensitivity (<1.0 log units) or visual mean deviation ( $\leq$ -15dB) at one month, but not baseline, can predict poor vision at six months.<sup>38</sup>

Although recovery is usually good, persistent residual deficits may include disturbances of visual acuity (15-30%), contrast sensitivity (63-100%), colour vision (33-100%), visual field (62-100%), stereopsis (89%), pupillary reaction (55-92%) and visual evoked potentials (VEPs) (63-100%).<sup>39</sup> Psychophysical studies have found variable contributions of parvo- and magno-cellular pathway damage to visual deficit<sup>40,41</sup> and persistent deficits in motion perception.<sup>42</sup> Optic disc pallor, especially involving the temporal aspect, often develops even when recovery is excellent.

## DIFFERENTIAL DIAGNOSIS

The diagnosis of ON can be made clinically. A thorough history and neuro-ophthalmic examination will look for other causes of acute monocular visual loss (table 1). After diagnosing ON a clinical distinction should be made between typical and atypical forms (table 2). Atypical ON can be classified into those with systemic disease and those without (table 3). The latter group includes NMO-ON (panel 4) and corticosteroid dependent CRION.<sup>43</sup> Systemic conditions associated with atypical ON include sarcoidosis, connective tissue diseases (e.g. lupus) and vasculitis (e.g. Wegener's granulomatosis). A substantial number of patients may have isolated ON without systemic or neurological disease that are not corticosteroid dependent. They are diagnosed retrospectively after extended follow up as solitary (SION) or recurrent (RION) ON.<sup>44</sup> SION has a rare association with NMO seropositivity (about 5%) and tends to be a common retrospective diagnosis in the presence of a normal MRI brain.<sup>45</sup> Studies have reported 20-30% of RION cases developing seropositivity for NMO over variable follow up periods up to 12 years.<sup>46,47</sup> A retrospective case analysis reported findings from 74 patients with recurrent or bilateral ON. For the recurrent unilateral group (n=47) final diagnoses were MS in 29, CRION in 11, NMO in four and thyroid eye disease in three.<sup>48</sup> Bilateral ON (n=23) was divided into recurrent (n=15) and non-recurrent types (n=8). Final diagnoses for the recurrent group were vasculitis or connective tissue disease in 13 (including lupus, Sjogren's syndrome and polyarteritis nodosa) and MS in two and for the non-recurrent group were post-infectious in four, sarcoid in two and MS in two.<sup>48</sup>

## INVESTIGATIONS

For **typical ON**, basic investigations such as erythrocyte sedimentation rate (or C-reactive protein), syphilis serology and chest X-ray can be considered.<sup>49</sup> Optic nerve MRI with gadolinium, although usually not required for diagnosis, shows the intrinsic ON lesion in 95%.<sup>50</sup> T2-weighted optic nerve signal change on MRI is also seen. MRI brain in typical ON can help stratify the future risk of converting to MS (see earlier). Visual evoked potentials (VEPs) can diagnose optic nerve involvement but do not robustly distinguish between different acute optic neuropathies, although a delayed but well preserved P100 waveform is characteristic of demyelination.<sup>51-53</sup> VEPs with pattern electroretinograms (pERGs), can distinguish between optic nerve and macular pathology. Optical coherence tomography (OCT) is used to exclude macular pathology in appropriate cases.

For **atypical ON**, further investigations are performed including MRI orbits/optic nerves with gadolinium (figures 1 and 2) and usually lumbar puncture.

MRI may reveal compressive lesions, nerve sheath enhancement in granulomatous conditions, orbital inflammation, meningeal or brain parenchymal enhancement (e.g. with sarcoid) as well assessing the degree of optic nerve involvement. In NMO-ON, white matter lesions may be seen but are atypical for MS. Periaqueductal gray matter and hypothalamic abnormalities have also been described, corresponding to sites of high aquaporin-4 (AQ4) antibody expression.<sup>52,54</sup>

Lumbar puncture may show CSF pleocytosis, elevated protein and sometimes low glucose in atypical inflammatory infectious or infiltrative disorders. CSF serology can detect certain infectious aetiologies. Matched oligoclonal bands in CSF and serum may indicate a systemic condition (although the absence of oligoclonal bands does not exclude this). A relatively high CSF pleocytosis is extremely unusual in MS-ON and would reinforce an atypical aetiology.

Other investigations include chest X-ray, blood tests such as full blood count, erythrocyte sedimentation rate (or C-reactive protein), renal function, liver function, bone profile, B12, folate, serum angiotensin converting enzyme, auto-antibodies (anti-nuclear, double-stranded DNA, anti-neutrophil cytoplasmic antibodies), syphilis serology, TB quantiferon testing and AQ4 antibody.<sup>55,56</sup> The latter has high sensitivity (68-91%) and very specificity (85-99%) for NMO<sup>55,57</sup> and is positive in about 5-6% of unilateral ON.<sup>44,45</sup> Its presence is likely to

reflect a more severe relapsing disease course and clinical conversion to NMO.<sup>45,58,59</sup> Myelin-oligodendrocyte glycoprotein (MOG) antibodies in AQP4-negative NMO spectrum disorder patients have been recently identified in a small study but further research is required to elucidate their clinical value.<sup>60</sup> Other specialized tests may depend on the diagnosis being sought but include genetic testing for Leber's hereditary optic neuropathy, viral or atypical infection serological screening. A body positron emission tomography scan can reveal avid localized soft tissue uptake amenable to biopsy (figure 2). After early investigations are performed, appropriate treatment can be instituted.

## INSIGHTS INTO PATHOPHYSIOLOGY

The pathophysiology of MS-ON has been studied in humans and animal models.<sup>61,62</sup> The optic nerve lesion is pathologically very similar to MS brain lesions. In the acute phase, inflammatory demyelination<sup>63</sup> occurs, resulting in varying degrees of conduction block<sup>64</sup> and visual loss. Predominant T-cell activation occurs in the acute phase with release of pro-inflammatory cytokines,<sup>65</sup> although there may also be B-cell involvement<sup>66</sup> and microglial activation.<sup>67</sup>

Resolution of inflammation and visual recovery occur over the next few weeks.<sup>64,68,69</sup> Remyelination occurs<sup>70</sup> though tends to be incomplete<sup>71</sup> and sodium channels are redistributed over demyelinated segments. The latter improves conduction but may make surviving axons vulnerable to damage.<sup>72</sup> Visual recovery can be incomplete and this probably reflects effects of persistent demyelination<sup>73</sup> and axonal loss.

Advances in OCT, VEPs and MRI have provided insights into the pathophysiological processes and clinical correlations for ON.

### A) IMAGING OF PRE-GENICULATE VISUAL PATHWAYS

#### RETINAL NERVE FIBRES

OCT relies on interferometry of near-infrared light to construct very high resolution images of the retinal layers. The most visible layer is the retinal nerve fibre layer (RNFL), comprising unmyelinated axons in a supportive connective tissue framework. The RNFL axons originate from retinal ganglion cell bodies, and continue through the optic nerve, chiasm and tract (where they are myelinated) to synapse in the lateral geniculate bodies. The RNFL measurements using OCT are typically made from a circular arc through the RNFL 3.4mm from the centre of the optic disc. In acute ON, RNFL thickness increases occur with optic nerve swelling.<sup>74</sup> Subsequent reductions in RNFL thickness indicate significant axonal loss after acute ON (figure 3).<sup>75,76</sup> Two serial OCT studies identified a median 20% decrease in RNFL thickness after 6 months in cohorts recruiting 54 and 23 ON patients respectively,<sup>76,77</sup> although there was large inter-subject variability in the amount of RNFL loss (0-50%).<sup>77</sup> Consistent with these findings, a study of 90 MS subjects identified a mean 20% decrease in RNFL thickness in eyes previously affected by optic neuritis.<sup>78</sup> RNFL thinning has been correlated with visual dysfunction in several studies<sup>75,76,79</sup> and with optic nerve MRI-detected atrophy<sup>80</sup> and radial diffusivity (water diffusivity perpendicular to the main axis of diffusion along the nerve).<sup>81</sup> Impaired colour vision is particularly correlated with thinner RNFL in both cross-sectional and prospective cohorts.<sup>82,83</sup>

Supported by data - obtained in an animal model of optic neuritis - showing a relationship of VEP latency with demyelination,<sup>53</sup> clinical studies have acquired both VEP and OCT measures to investigate the relationship between myelination and axonal loss. Both VEP amplitude and latency were correlated with OCT measures of axonal loss in a clinical cross-sectional post-acute ON study.<sup>84</sup> In another clinical study, sectoral RNFL thickness correlated with the multifocal (mf) VEP amplitude from the corresponding part of the visual field suggestive of a structural-functional correspondence, e.g. the largest reductions in RNFL thickness and mfVEP amplitude

affected the temporal disc and central field respectively.<sup>85</sup> A longitudinal clinical study showed that the improvement in latency delay in acute optic neuritis tends to be greatest in the first six months.<sup>70</sup> From one to three years, an ongoing small reduction in RNFL thickness did not correlate with mfVEP latency change, suggesting no association between optic nerve demyelination and ongoing axonal loss.<sup>85</sup>

Recent clinical OCT studies have performed intra-retinal layer segmentation to examine the retinal ganglion cell (RGC) and inner plexiform layers (IPL). RGC (or RGC+IPL, as the two layers are difficult to discriminate) measurements are not affected by disc swelling and should be more specific to axonal pathology. Thinner RGC+IPL values have been found in MS patients especially those affected by previous ON and correlate with visual function.<sup>86</sup> RGC+IPL thinning has also been observed in longitudinal studies of ON.<sup>87</sup>

Greater RNFL thinning is seen in NMO-ON eyes than in MS-ON eyes<sup>88,89</sup> with a predilection for superior and inferior RNFL quadrants.<sup>89,90</sup> One study suggested that RNFL thickness loss greater than 15 microns in non-MS patients should prompt a search for NMO spectrum disorder.<sup>88</sup> Early administration of high dose steroids was found to preserve RNFL thickness albeit in an uncontrolled, retrospective study.<sup>89</sup> Longitudinal reductions in RGC-IPL thickness have also been observed in NMO-ON eyes.<sup>87</sup> There may be increased thickness of the inner nuclear layer (INL) in NMO<sup>91,92</sup> although *in vivo* quantification of the INL has also included the outer plexiform layer, thus the specificity of the observation for the INL *per se* is uncertain. A qualitative abnormality called microcystic macular oedema (MMO) has also been observed in the INL of the retina in 20% of subjects with NMO<sup>93</sup> and about 5% with MS.<sup>92,94</sup> MMO has been defined as “cystic, lacunar areas of hyporeflexivity with clear boundaries, evident on at least two contiguous B scans, or visible in a comparable region on at least two separate acquisitions” and has been associated with more severe MS<sup>95</sup>. It has been speculated that MMO may reflect a greater degree of neuroinflammation rather than being more specific to NMO, An alternative mechanism for the cystic spaces might be tissue loss due to neurodegeneration.

## OPTIC NERVES

The acute inflammatory lesion is detectable on MRI by gadolinium enhancement.<sup>50,64,96</sup> Optic nerve atrophy often develops and has been associated with disease duration and visual function (figure 3),<sup>80,97</sup> thinner RNFLs and lower VEP amplitude.<sup>80</sup> Two recent studies reported that the NMO-ON lesion is more likely to affect the posterior optic nerve, including the chiasm,<sup>98,99</sup> although the distinction is not absolute and chiasmal involvement may be seen in MS-associated ON.

Optic nerve diffusion tensor imaging (DTI) measures water diffusion, providing microstructural information.<sup>100</sup> DTI markers of tissue disruption are seen in the affected optic nerves post-ON and correlate with visual function and VEP.<sup>101,102</sup> Lower axial diffusivities in the acute phase (suggesting greater axonal damage) are associated with worse vision at six months.<sup>103</sup>

Magnetization transfer imaging distinguishes between free and macromolecular bound macromolecules and the resulting magnetization transfer ratio (MTR) is influenced by myelination and axonal loss and is altered in ON<sup>104-106</sup> and MS.<sup>107</sup> A time dependent association between VEP latency and MTR suggests a potential for lesional MTR to detect remyelination following ON<sup>106</sup>, and post-mortem pathology-MRI studies have shown higher MTR in remyelinated than demyelinated lesions.<sup>108,109</sup>

## B) IMAGING OF POST-GENICULATE VISUAL PATHWAYS

### OPTIC RADIATIONS

DTI metrics have identified abnormalities in the optic radiations in post-acute ON.<sup>110</sup> A reported significant association between an mfVEP measure of anterior visual axonal dysfunction (reduced amplitude) and reduced optic radiation axial diffusivity (which correlates with axonal injury in animal studies<sup>111</sup>) suggests possible

anterograde trans-synaptic axonal degeneration, i.e., degeneration of retrogeniculate fibres secondary to primary degeneration of anterior visual pathway axons.<sup>110</sup>

## VISUAL CORTEX

Lower grey matter MTR within the visual cortices after ON has been found suggesting cortical structural changes.<sup>112</sup> A longitudinal study found that early peri-calcarine atrophy predicts later conversion to MS at one year after acute ON.<sup>113</sup>

Functional MRI (fMRI) studies have shown reduced visual cortex activation after ON, sometimes associated with visual dysfunction<sup>114</sup> and more recently with RNFL thickness.<sup>115</sup> Longitudinal studies have implicated several brain regions that may help visual recovery, including the lateral occipital complexes,<sup>116,117</sup> cuneus<sup>118</sup> and lateral geniculate nuclei.<sup>119</sup> Some degree of neuroplasticity would help to explain the discordance seen between good visual recovery and persistent structural optic nerve damage after acute ON.<sup>120</sup>

## ACUTE TREATMENT OPTIONS OF OPTIC NEURITIS

Several treatment options have been investigated in acute ON.

### CORTICOSTEROIDS

Several studies have evaluated acute corticosteroid treatment for ON providing level 1<sup>121</sup> evidence.<sup>122-124</sup> The ONTT (a prospective randomized placebo-controlled study) showed no benefit in visual acuity (P=0.66) six months after three days of high-dose (1g/day) intravenous methylprednisolone (IVMP) followed by 11 days of low-dose oral prednisolone versus placebo, although visual recovery was faster.<sup>122,125</sup> Mild benefits were seen for some secondary outcomes - visual fields (P = 0.054), contrast sensitivity (P = 0.026), and colour vision (P = 0.033). Standard-dose (1mg/kg) oral prednisolone did not differ from placebo in visual outcomes but unexpectedly increased the risk of ON recurrence for reasons that remain unclear. IVMP also delayed the onset of clinically definite MS at two years<sup>126</sup> but this difference abated over time.<sup>16</sup> A recent Cochrane review reported no long-term benefit for corticosteroid treatment for visual acuity, visual fields or contrast sensitivity.<sup>127</sup> Most participants in these studies were likely to have typical ON, and the relative lack of efficacy of corticosteroids is concordant with studies investigating their effects on non-ON MS relapses i.e. hastening recovery but not affecting final outcome.

A few studies suggest that timing of corticosteroid administration may be important, but more research is warranted. In the rat model of MS, corticosteroids given prior to induction of experimental allergic encephalomyelitis reduced the incidence of ON and relatively preserved the RGCs after ON.<sup>128</sup> In humans, poor evidence exists and only uncontrolled studies examining very early treatment (within days) have been published. In a case series, steroids administered hyper-acutely to eight patients with previous ON (including MS, CRION and NMO), who reported a relapse of their pain, resulted in no visual loss and resolution of their pain.<sup>129</sup> MRI confirmed ON in five out of five patients. A retrospective analysis of NMO cases reported that early administration (within three days) of intravenous methylprednisolone for ON relapse was associated with more preservation of RNFL thickness.<sup>89</sup> Oral high-dose methylprednisolone may be an alternative to the intravenous form. A randomized, controlled trial (n=60) showed that oral 500mg/day methylprednisolone was superior to placebo at one and three weeks although final visual outcome was unaltered after ON.<sup>124</sup>

Randomized controlled trials devoted to atypical ON are lacking and evidence is observational or retrospective (mainly level 4).<sup>121</sup> NMO-ON appears to respond to IVMP especially if administered early.<sup>89,129</sup> Similarly, for sarcoid-related ON, high dose corticosteroids are indicated, although visual recovery may be hard to



induce.<sup>130,131</sup> Lupus-associated ON is also thought to benefit from steroids<sup>132</sup> although cyclophosphamide in combination or as an alternative may be more effective.<sup>133</sup> Vasculitic ON is very rare but some patients may respond to corticosteroids.<sup>134</sup> High-dose corticosteroid treatment for atypical ON is usually followed by an oral weaning dose. Patients with CRION may have a granulomatous optic neuropathy which is very steroid sensitive but also steroid dependent and can relapse on weaning.<sup>43</sup>

## PLASMAPHERESIS

Plasmapheresis has been tested in steroid-unresponsive demyelinating ON in observational cohorts. Early treatment, within weeks, is more likely to be beneficial.<sup>135,136</sup> In a case series of 23 patients (10 relapsing-remitting MS, one NMO and 12 isolated ON) 70% improved with plasmapheresis, given after two cycles of IVMP.<sup>137</sup> Another case series of 20 MS patients reported good benefit in three-quarters of those with ON.<sup>135</sup> A pooled review of plasmapheresis in NMO<sup>136,138</sup>, together with the authors' data for steroid-refractory-ON with severe visual loss, analysed 39 eyes. People who improved received plasmapheresis a median of 19 days after onset compared with 41 days for those who did not. Finally, plasmapheresis in addition to corticosteroids, when compared with corticosteroids had better visual outcome in NMO-ON.<sup>139</sup> Plasma exchange may be considered a viable option in demyelinating ON unresponsive to steroids.

## INTRAVENOUS IMMUNOGLOBULINS

Studies with intravenous immunoglobulins have produced mixed results. An open-label, non-randomized, prospective study found a good improvement in visual acuity in 18 out of 23 MS-ON steroid-refractory subjects who had treatment, compared with 3 out of 24 subjects who did not.<sup>140</sup> However, two earlier randomized, double-blinded, placebo-controlled studies recruiting a combined total of 123 acute ON subjects showed no significant beneficial effect.<sup>141,142</sup> Overall evidence for a beneficial effect is weak.

## RECOMMENDATIONS

For typical ON, the affected patient is counselled regarding the benefits, limitations and potential side effects of corticosteroids and is offered treatment if visual loss is functionally disabling or if there is pre-existing visual impairment of the fellow eye. We tend to prescribe high-dose methylprednisolone (either 500mg/day oral for five days or 1g/day intravenous for three days) with no oral tail and follow up the patient clinically, regardless of treatment, within the next few weeks to check recovery. If atypical features develop or recovery does not begin then the atypical pathway for investigations and treatment is immediately followed. The patient is also counselled about the future potential to convert to MS and is offered an MRI brain for risk stratification.

For atypical ON, after appropriate and urgent investigations, treatment is instigated with IVMP (1g/day for three to five days) followed by a prolonged oral tail, weaning over 4-6 months. If patients relapse after initial treatment then oral corticosteroids can be increased or a further course of IVMP can be given and a steroid-sparing immunosuppressant considered (panel 5). If initial high dose steroids are not effective at improving vision and the aetiology is demyelinating, plasmapheresis can be considered. For lupus-related ON, cyclophosphamide can be considered.

## LONG TERM MANAGEMENT OF TYPICAL ON

### DISEASE MODIFYING TREATMENTS (DMDs) USED IN MS

Several placebo-controlled trials of the MS-DMDs beta interferon and glatiramer acetate have investigated CIS patients (including isolated ON) with positive MRI scans.<sup>143-146</sup> All have shown delay of subsequent relapse and conversion to clinically definite MS. A follow-up study of one of the trial cohorts treated with beta interferon

showed that this delaying effect persisted up to five years, although there was no difference in long-term disability between early and late treatment arms.<sup>147</sup> A 10-year follow-up of another beta interferon trial cohort found similar effects.<sup>148</sup> Despite the modest long term clinical efficacy, advocates for early versus delayed treatment of CIS patients argue that many will otherwise accumulate new MRI lesions, which may increase the chances of for future disability.

## RECOMMENDATIONS

We tend to monitor patients with typical, isolated ON. They are counselled about the risk of MS conversion, based on their MRI brain result, if it was performed. Although the most recent prescribing guidelines<sup>149</sup> from the Association of British Neurologists suggest that DMDs can be considered for CIS with demyelinating brain scans, funding for this can be, in practice, problematic to secure in the UK, and the potential long-term benefits are still uncertain. If the patient converts to MS, with a further relapse within two years, then DMDs are often prescribed. Interval MRI scanning can be offered during monitoring to make an earlier diagnosis of MS.

## LONG TERM MANAGEMENT OF ATYPICAL ON

Atypical ON often requires long term immunosuppression especially if the risk of relapse is high or relapses occur. The specific choice of immunosuppressant may be influenced by the underlying aetiology. This section will mainly focus on agents used for relapse prevention in NMO-ON.<sup>56,150</sup>

### NMO-ON RELAPSE PREVENTION

Maintenance of remission is crucial, as the accumulation of disability is related to relapses. Several agents have been studied retrospectively and observationally in NMO, its limited forms and spectrum disorders, providing mainly level 4 evidence.<sup>121,151</sup>

#### AZATHIOPRINE

A small prospective study of seven patients with NMO reported a relapse-free follow up over 18 months and with azathioprine plus prednisolone treatment.<sup>152</sup> Two retrospective studies of patients with NMO spectrum disorder<sup>153,154</sup> found that azathioprine, with or without prednisolone, reduced the annualized relapse rate by about three-quarters. Doses larger than 2mg/kg and increases in mean corpuscular volumes were possibly related to greater reductions in relapse rate.<sup>153</sup> Beneficial effects on disability scores and/or visual acuities have also been found.<sup>153,154</sup> A target dose of 2.5-3.0 mg/kg/day is recommended and the first few months of treatment should be in combination with oral prednisolone whilst awaiting treatment effect. This is followed by a slow steroid wean. Some patients may require low steroid maintenance doses.<sup>155</sup>

#### METHOTREXATE

This can be considered an alternative first line agent to azathioprine, especially in those who are intolerant to the latter. A recent report described 14 patients on long term methotrexate and found an 85% reduction in annualised relapse rate (1.39 to 0.18,  $P < 0.005$ ) with disability improvement or stabilization in 79%.<sup>156</sup>

#### RITUXIMAB

Although EFNS guidelines suggested this a potential first-line treatment,<sup>151</sup> in practice it is usually considered second line.<sup>155</sup> It is an anti-CD20 chimeric monoclonal antibody administered by intermittent infusion with the CD19 count being monitored.<sup>151,155</sup> The three largest retrospective studies (recruiting 23, 35 and 30

patients)<sup>157-159</sup> all described reductions in median annualized relapse rate by at least 90% and stabilization or improvement of disability in at least 80% of cases.

## MYCOPHENOLATE

Mycophenolate is gaining favour as an effective immunosuppressant despite the relative lack of evidence in NMO.<sup>151</sup> A retrospective analysis of 24 patients reported an improvement in median annualized relapse rate by 93% (1.3 pre-treatment to 0.09 treatment,  $P < 0.001$ ) and a stabilization or improvement of disability in 91% of cases.<sup>160</sup>

## OTHER TREATMENTS

**Eculizumab** has recently shown promising results albeit in a small open-label pilot study.<sup>161</sup> Median annualized relapse rate fell from 3 (range 2-4) to 0 (range 0-1) after a year's treatment in 14 patients ( $p < 0.001$ ). Median EDSS improved from 4.3 to 3.5 ( $p = 0.0078$ ). Further studies are warranted.

Low dose maintenance **corticosteroids** may play a role in maintaining remission.<sup>162</sup> There is limited or mixed evidence for other treatments used in relapse prevention - these include **mitoxantrone**,<sup>163</sup> **cyclophosphamide**,<sup>164</sup> **pulsed plasmapheresis**,<sup>165</sup> **cyclosporine A**,<sup>166</sup> **tacrolimus**,<sup>155</sup> **intravenous immunoglobulins**<sup>167</sup> and **tocilizumab**.<sup>168</sup>

**Interferon-beta**, **fingolimod** and **natalizumab** should be avoided in NMO and NMO-spectrum disorders as there is some evidence that clinical disease does not improve or can worsen.<sup>169-173</sup>

## ON WITH SYSTEMIC DISEASE (E.G. SARCOID, CONNECTIVE TISSUE DISORDER, VASCULITIS) OR CRION

Most immunosuppressants used to maintain clinical remission in systemic inflammatory disease tend to be the same as those described for NMO. Specific treatments should be tailored towards the underlying condition, individual clinical course and the degree of multi-organ involvement. Available evidence again tends to be level 4.<sup>121</sup>

A retrospective analysis together with a literature review by Myers et al reported a total of 48 patients with corticosteroid-dependent atypical ON.<sup>174</sup> Seventeen had lupus, 12 had sarcoid, three had other conditions and 16 had no identifiable systemic disease. About 80% of patients demonstrated clinical benefit with a variety of immunosuppressive agents.

Lupus-associated ON is reported rarely but some case reviews suggest that it responds to cyclophosphamide,<sup>133,175</sup> azathioprine or low-dose maintenance corticosteroids.<sup>132</sup> Sarcoid-associated ON has a variable clinical course (including acute monosymptomatic, relapsing-remitting and progressive)<sup>176</sup> and may improve with azathioprine,<sup>177</sup> methotrexate,<sup>178</sup> cyclosporin,<sup>179</sup> mycophenolate and infliximab.<sup>130,180</sup> CRION may respond to low-maintenance dose corticosteroids, azathioprine and methotrexate.<sup>43</sup>

## RECOMMENDATIONS

For NMO, a recent guide has been published, suggesting steroid-sparing agents for first and second line treatment, with dosing and monitoring regimes.<sup>155</sup> This could be transferred across to guide relapsing NMO-ON management. First line treatments would therefore include azathioprine, methotrexate or mycophenolate (panel 5). A relapse whilst on treatment of sufficient dose and duration would indicate treatment failure. It may be helpful to monitor AQ4 antibody titres, if available.<sup>181</sup> Second-line treatment would be rituximab followed by other options which include mitoxantrone.

For non-NMO ON (systemic conditions or CRION), similar first line agents can be considered i.e. azathioprine, methotrexate or perhaps mycophenolate. Treatment should be disease oriented although there will be overlap with second line agents as well. For example, cyclophosphamide may be useful in lupus ON or infliximab in sarcoid ON.

## EXPERIMENTAL NEUROPROTECTION AND REMYELINATION TRIALS

After ON the degree of neuroaxonal loss correlates with quantitative measures of visual dysfunction.<sup>75</sup> Corticosteroids do not prevent axonal loss<sup>182</sup> or improve visual outcome. Therefore a key avenue of therapeutic research is to identify neuroprotective agents that can prevent long term axonal loss and hopefully lead to better visual outcomes.

Developing effective neuroprotection in ON also has implications for MS. Acute CNS inflammatory-demyelinating exhibit axonal transection,<sup>183</sup> and effective neuroprotectants should reduce axonal loss in all CNS lesions, not only optic nerve. ON is a suitable clinical “model” for neuroprotection studies. Firstly, there are quantitative tools for measuring visual function, including low contrast acuity, visual fields, and colour discrimination. Secondly, OCT provides an *in vivo* measure of axonal loss secondary to ON: because axons in the retina are not myelinated, a decrease in RNFL thickness is direct evidence for axonal loss, and sample size calculations indicate that RNFL loss is a sensitive outcome measure for proof-of-concept trials of neuroprotection following ON.<sup>77</sup> Thirdly, VEPs can measure optic nerve conduction. A well preserved P100 wave form with prolonged latency provides evidence for demyelination and subsequent shortening of latency is expected with remyelination.<sup>70</sup> Remyelination is an important therapeutic aim as well: it may enhance conduction, thereby improving visual function, and may also be neuroprotective in reducing vulnerability of axons to adverse effects associated with inflammation and demyelination.<sup>83</sup>

Some trials have recently investigated neuroprotection or remyelination in the anterior visual pathway in ON and MS (table 4). A placebo-controlled trial of erythropoietin showed smaller decreases in RNFL thickness in the affected nerve<sup>184</sup> but was complicated by the presence of RNFL swelling during the acute phase of ON. Swelling reflects acute inflammation and the decrease in RNFL thickness represents a combination of axonal loss and resolution of inflammation. More specific evidence for axonal protection should be obtained by comparing the final thickness of the affected optic nerve with that of the unaffected nerve.<sup>77</sup> Another randomized, controlled trial investigated simvastatin in acute ON.<sup>185</sup> Significant benefits were seen with VEP amplitude (P=0.01) and latency (P=0.01) and borderline effects for contrast sensitivity (P=0.06). A small baseline crossover trial of autologous stem cells in secondary progressive MS identified shortening of VEP latency and increase in optic nerve area following treatment that could reflect remyelination.<sup>186</sup>

## CONCLUSIONS

We have presented a summary of the current state of knowledge regarding ON. It is crucial to clinically distinguish typical from atypical forms in the acute phase. This will then guide further management. The most common form is typical ON, likely to be demyelinating and closely associated with MS though also not infrequently occurring in isolation. Typical ON resolves spontaneously and provides researchers with a useful *in vivo* model to study mechanisms of localized damage and recovery due to inflammatory demyelination in the central nervous system, including the study of neuroprotective and remyelination strategies. If untreated, atypical ON can lead to irreversible visual loss and often requires urgent corticosteroids with slow wean and, sometimes, chronic immunosuppression.

## CONTRIBUTORS

ATT, DFM and DHM were involved in planning, writing, critical reviewing and revision of the manuscript. DHM was involved in conception of the manuscript.

## CONFLICTS OF INTEREST

ATT has received honoraria from Sereno Symposia International Foundation and Bayer. DHM has received honoraria through payments to his employer, UCL Institute of Neurology, for Advisory Committee and/or Consultancy advice in multiple sclerosis studies from Biogen Idec, GlaxoSmithKline, Novartis, Merck, Chugai, Mitsubishi Pharma Europe and Bayer Schering Pharma. He has also received compensation through payments to his employer for performing central MRI analysis of multiple sclerosis trials from GlaxoSmithKline, Biogen Idec, Novartis and Merck. DFM has received honoraria from Biogen.

## SEARCH CRITERIA AND SELECTION CRITERIA

We searched PubMed for articles published 1970 to July 2013, with the general search term “optic neuritis” combined with more specific search terms related to the subheadings (e.g. “optical coherence tomography”, “corticosteroid”, “plasmapheresis”, “magnetic resonance imaging”). References from identified studies were checked and included if felt appropriate, relevant and scientifically important. Articles published in English were considered. Non-English articles were also considered if referenced from an identified English article. References from our own files were also searched. More recent publications (within the past 10 years) were preferentially selected, although older references that were important were also included.

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## FIGURE LEGENDS

### FIGURE 1

Examples of NMO-ON in two patients A and B showing left optic nerve enhancement on post-contrast T1-weighted MRI scans. Figure 1A provided courtesy of Dr Lynette Masters, Sydney, Australia.

### FIGURE 2

Two cases (A and B) of sarcoid-related optic neuropathy. A) Shows right optic nerve sheath enhancement from a granulomatous optic neuropathy. B) Patient presented with an acute right optic neuritis.,MRI showed optic nerve sheath enhancement. FDG-PET scan showed hilar/mediastinal avid nodes. Lymph node biopsy non-caseating granulomata. Figure 2A provided courtesy of Dr Lynette Masters, Sydney, Australia.

### FIGURE 3

Left optic neuritis at baseline and after six months. A) T1-weighted MRI optic nerve showing acute swelling at baseline and some atrophy six months later. The nerve is outlined in red. B to D show outputs from OCT. B) Peripapillary optic nerve circular scan with disc swelling at baseline. C and D) Profile of RNFL along circular scan from nasal (N) to inferior (I) to temporal (T) to superior (S) fibres. Respective swelling and atrophy are shown at baseline and six months. OCT images are provided courtesy of Rhian Raftopoulos, UCL Institute of Neurology, United Kingdom.

**Table 1.** Examples of causes of acute monocular visual loss other than immune-mediated optic neuritis. Adapted from Jenkins and Toosy.<sup>187</sup>

Anatomical region	Condition	Clinical clues	
<b>OPTIC NERVE</b>	Ischaemic optic neuropathy	Non-arteritic - Painless, acute, disc swelling invariably during acute episode, altitudinal field defect, poor recovery, vascular risk factors  Arteritic (usually associated with giant cell arteritis) – High ESR, painless, acute disc swelling, altitudinal field loss, severe visual loss, may be bilateral if untreated, systemic symptoms of myalgia, fatigue, temporal headache, jaw claudication	
	Optic nerve compression	Progressive symptoms, usually painless (except aneurysms, mucocoele)	
	Leber’s hereditary optic neuropathy	Usually men, bilateral simultaneous or sequential optic neuropathy, painless	
	Toxic optic neuropathy	Methanol poisoning (sometimes seen in alcohol dependent patients). Tobacco/alcohol amblyopia. Bilateral involvement.	
	Nutritional optic neuropathy	B12 deficiency- risks for malabsorption	
	Drug-induced	Ethambutol in treatment of tuberculosis	
	Diabetic papillopathy	Painless acute disc swelling with signs of diabetic retinopathy and mild visual loss, usually good recovery	
	Infectious		Lyme – tick exposure, erythema chronicum migrans, radiculo-neuropathy, neuroretinitis, vitritis, meningeal involvement, retinopathy, CSF cells
			Syphilis – risk factors, genital ulcers, rash, neuroretinitis, vitritis, dorsal column involvement
			Viral (HIV, EBV, CMV) – viral prodrome, vitritis, CSF cells
	Tuberculosis – history of exposure, vitritis, abnormal CXR		

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		Toxoplasmosis – active chorioretinitis with retinal oedema, disc swelling, HIV positive
		Toxocariasis – Neuroretinitis, eosinophilia
		Bartonella – history of cat scratch, neuroretinitis, lymphadenopathy
	Postinfectious	Bilateral, post-viral, more common in children
	Traumatic optic neuropathy	History of trauma, facial/intracranial injury
<b>RETINA</b>	Central serous retinopathy	Painless central blurring and photopsia, macular abnormalities on fundoscopy, usually good recovery
	Cystoid macular oedema	Painless, central blurring. Risk factors – cataract operation, retinal artery/vein occlusion, diabetes, intraocular inflammation. Macular oedema seen.
	Big blind spot syndrome/acute zonal occult outer retinopathy (AZOOR)	Poorly understood painless enlargement of blind spot, photopsias, sometimes associated with disc swelling, usually self-limiting
	Retinal detachment	Floaters/flashing lights then peripheral field loss (shadow) progressing centrally, abnormal red reflex, retinal separation visible. May have RAPD.
	Central retinal artery occlusion	Painless, sudden severe visual loss, retinal oedema, cherry red spot, retinal emboli.
	Central retinal vein occlusion	Variable central visual blurring, disc swelling, tortuous vessels, multiple retinal haemorrhages, cotton-wool spots.
<b>UVEAL MEMBRANE</b>	Uveitis	Anterior – Painful, blurring of vision with reddening of eye and photophobia. Dilated ciliary vessels, keratic precipitates, cells in anterior chamber.  Posterior – Floaters, blurred vision. Vitreous cells, chorioretinitis seen on examination.

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<b>VITREOUS</b>	Vitreous haemorrhage	Painless visual loss, no red reflex. Pre-existing proliferative retinopathy or retinal vein occlusion.
<b>CORNEA</b>	Acute closed angle glaucoma	Blurred vision and haloes. Painful red eye, photophobia, nausea, fixed pupil, corneal oedema, high intraocular pressure, shallow anterior chamber.
	Herpes simplex keratitis	Visual blurring, visible ulcer on fluorescein staining, history of corneal injury, contact lens use, herpetic V1 rash
<b>SCLERA</b>	Posterior scleritis	Severe pain wakes patient from sleep, proptosis, disc swelling
<b>ORBIT</b>	Orbital cellulitis	Proptosis, other cranial nerve involvement
	Optic perineuritis	A type of orbital inflammatory disease. Older age, central vision sparing, severe pain, associated with connective tissue, autoimmune disease or infection (e.g. syphilis, lyme). Good response to steroids.
<b>OTHER</b>	Functional	Variability, no objective signs such as RAPD, normal VEPs

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**Table 2**

Features of typical and atypical optic neuritis

<b>Category</b>	<b>Typical</b>	<b>Atypical</b>
<b>Age</b>	Young adult	Age over 50 or under 12 years
<b>Ethnicity</b>	Caucasian	African, Asian or Polynesian descent
<b>Laterality</b>	Unilateral symptoms	Bilateral simultaneous or rapidly sequential
<b>Pain</b>	Mild peri-ocular pain worse on eye movement	Severe peri-ocular pain waking patient from sleep Painless visual loss Pain persisting longer than 2 weeks
<b>Vision</b>	Mild to moderated unocular visual loss followed by spontaneous improvement	Severe visual loss (worse than 6/60)  No recovery starting within three weeks of onset Progression of visual loss for more than two weeks
<b>Appearance</b>	Normal or swollen optic disc	Severe optic disc swelling Macular star (neuroretinitis) Optic disc haemorrhages Anterior/posterior segment inflammation Marked retinal exudates
<b>Other</b>	Uhthoff's phenomenon Pulfrich effect Previous self-limiting neurological episodes	Family history Neoplastic history

**Table 3.** Main causes of immune-mediated ON

<b>Presence of systemic disease</b>	<b>Aetiology</b>	<b>Features</b>
<b>NO SYSTEMIC DISEASE</b>	Multiple sclerosis associated optic neuritis (MS-ON)	Typical symptoms of optic neuritis usually, disseminated white matter brain lesions suggestive of demyelination, CSF positive oligoclonal bands (unmatched), if first episode may be called demyelinating clinically isolated syndrome (CIS).
	Solitary isolated optic neuritis (SION)	Diagnosed after extended follow-up. Normal brain MRI, isolated optic neuritis.
	Neuromyelitis optic associated optic neuritis (NMO-ON)	Positive antibodies to aquaporin 4 (AQ4) or myelin-oligodendrocytes (MOG), longitudinally extensive cord lesion (myelitis), CSF pleocytosis, negative oligoclonal bands, normal MRI brain or abnormalities atypical for MS (hypothalamus, third ventricle, medulla).
	Chronic relapsing inflammatory optic neuropathy (CRION)	Tendency to relapse off steroids, normal MRI brain, optic nerve sheath enhancement, may become bilateral, requires chronic immunosuppression.
	Recurrent isolated optic neuritis (RION)	Diagnosed after extended follow-up. Normal brain MRI, no other neurological sequelae.
	Acute disseminated encephalomyelitis (ADEM)	Enhancing brain lesions, severe bilateral ON, more common in children.
<b>SYSTEMIC DISEASE</b>	Sarcoid	Other signs of intraocular inflammation, optic nerve sheath enhancement, white matter brain lesions, meningeal enhancement, respiratory symptoms, abnormal chest X-ray, CSF pleocytosis, matched oligoclonal bands.
	Connective tissue disease (e.g. lupus)	Skin rash, arthritis, alopecia, positive autoantibodies (double stranded DNA for lupus), raised inflammatory markers.
	Vasculitis (e.g. polyarteritis nodosa, Wegener's granulomatosis)	Ischaemic presentation if pure vasculitic. Compressive presentation if sino-nasal disease. Positive anti-neutrophil cytoplasmic antibodies.

**Table 4**

Trials of neuroprotection and repair in optic neuritis or the anterior visual pathway in MS

<b>Therapy</b>	<b>Clinical group</b>	<b>Mechanisms</b>	<b>Trial Design</b>	<b>Clinical Outcome</b>	<b>Paraclinical outcome</b>
<b>Erythropoietin<sup>R</sup></b>	Optic neuritis	Neurotrophism	Placebo-controlled	Borderline improvement in vision	Reduced loss of RNFL thickness
<b>Simvastatin</b>	Optic neuritis	Neuroprotection	Placebo-controlled	Borderline improvement in vision	Reduced VEP latency; increased VEP amplitude
<b>Autologous mesenchymal stem cells<sup>R</sup></b>	Secondary progressive MS	Neuroprotection; ?repair	Baseline crossover	Improved visual acuity	Reduced VEP latency; Increased optic nerve area
<b>Phenytoin</b>	Optic neuritis	Neuroprotection (sodium channel blockade)	Placebo-controlled	In progress	In progress (primary outcome: reduction in OCT-measured RNFL loss)
<b>Amiloride</b>	Optic neuritis	Neuroprotection (acid sensing channel blockade)	Placebo-controlled	In progress	In progress (primary outcome: reduction in OCT-measured RNFL loss)
<b>Anti-Lingo antibody</b>	Optic neuritis	Remyelination	Placebo-controlled	In progress	In progress (primary outcome measure: reduction in VEP latency)

## PANEL 1 – TERMINOLOGY FOR OPTIC NEURITIS

There is little consensus on a systematic nosology for ON. Research studies in the field generally adopt different classification systems which can lead to confusion in interpreting their findings. ON is traditionally divided on **clinical** grounds into **typical** and **atypical** forms, with the understanding that typical ON is generally associated with MS or is regarded as a demyelinating clinically isolated syndrome (CIS) at risk of conversion to MS in Caucasians. An alternative method classifies ON on **aetiological** grounds. The content of this review, on this basis, can be said to describe **immune-mediated ON** (see table 2). This itself can be sub-classified into several types including MS associated ON (**MS-ON**), ON associated with Neuromyelitis Optica (**NMO-ON**), ON associated **with systemic conditions** (connective tissue disease, granulomatous disease, infective conditions) and other idiopathic ON **without systemic disease** (recurrent isolated ON [**RION**], chronic relapsing inflammatory optic neuropathy [**CRION**], solitary isolated ON [**SION**]). The term demyelinating ON (**DON**) has been also been used as a **pathological** based definition although this is also not ideal as both MS-ON and NMO-ON cause demyelination and are managed differently. In this review we tend to classify optic neuritis on clinical grounds i.e. typical or atypical, where typical ON is associated with MS and CIS and atypical ON with non-MS immune-mediated causes (e.g. NMO, systemic conditions, etc) as this is highly relevant for dictating clinical management. Where appropriate, i.e. where specific research has been conducted, relevant sections of this review will allude to aetiological based definitions (in particular MS-ON, NMO-ON).

## PANEL 2 – DIAGNOSING MS IN MS-ON (2010 McDONALD MRI CRITERIA)<sup>188</sup>

Requires dissemination in space and time.

- Dissemination in space.
    - At least one lesion\* visible on T2-weighted scan in at least two of the following four locations: juxtacortical, periventricular, infratentorial, and spinal cord
  
  - Dissemination in time
    - A new T2 lesion or gadolinium-enhancing lesion visible on a follow-up MRI scan when this is compared with a previous scan (which is thought to be the baseline scan) obtained at any time after the ON
- OR
- An MRI scan showing both gadolinium-enhancing and non-enhancing lesions that do not cause clinical signs (ie, asymptomatic lesions).

### PANEL 3 –VISUAL PHENOMENA AND MEASUREMENTS IN OPTIC NEURITIS

- **Phosphenes** are bright fleeting flashes of light, that in ON, tend to be related to eye movement. The symptom of phosphenes should be clinically distinguished from a scintillating scotoma which is usually associated with visual aura of migraine. This tends to appear as a blind region surrounded by margin of sparkling lights which can change shape or move over a period of time, typically 15-30 minutes.
- **Uhthoff's phenomenon** is worsening of vision provoked by small increases in body temperature, typically attributed to exercise, hot baths/showers or hot weather conditions.
- **Pulfrich effect** describes anomalous stereoscopic perception of objects in motion due to asymmetrical conduction between optic nerves.
- **Visual acuity** measures the spatial resolution ability of the visual system. Traditionally it is measured using **Snellen** charts and expressed as in fractional notation with the numerator denoting the actual distance (20 feet or 6 metres) from the chart and the denominator denoting the distance at which a person with normal eyesight can see the line of letters. For example an acuity of 20/40 means that a person viewing the chart at 20 feet can read letters that normal eyesight can distinguish at 40 feet. 20/20 or 6/6 vision is normal; 20/200 or its equivalent 6/60 signifies very poor vision. Research studies such as the ONTT tend to use **logMAR** scores, requiring a retro-illuminated Early Treatment Diabetic Retinopathy Study (ETDRS) chart. A standard ETDRS chart measures the logarithmic (base 10) minimum angle of resolution at four metres and provides a linearly continuous variable amenable to parametric statistics. LogMAR scores can be converted to Snellen equivalent scores and vice versa.
- **Low contrast acuity** charts are more sensitive than standard contrast acuity charts (see above) at detecting visual dysfunction in ON. Several types of charts exist, but the **Pelli-Robson** chart has been commonly used in research studies (including the ONTT). This comprises eight lines of six letters each arranged in two triplets per line. With each successive triplet, the contrast decreases in logarithmic steps by 0.15 log units. The subject is asked to read along and down the chart until the detection limit is reached, scored from 0 to about 2 log units. Higher scores indicate better contrast sensitivity, measured at the peak of the contrast sensitivity function (approx. 1-2 cycles per degree).
- **Colour vision** is conventionally measured in clinical practice with **Ishihara pseudoisochromatic** plates. The subject is asked to distinguish different coloured numbers but this test is designed for deficiencies of the red-green axis. In research, the **Farnsworth-Munsell 100-hue** test provides a more comprehensive assessment (used in the ONTT). The subject is asked to grade 85 coloured caps according to perceived hue, from which an error score is determined. The resulting data is amenable to parametric statistics and indicates the type of spectral deficiency.
- **Visual fields** can be measured with static or dynamic perimetry. The ONTT used **Humphrey field** perimetry (static). This can test different field sizes in an automated fashion but typically tests the central 30 degrees of vision. The subject has to acknowledge luminant stimuli briefly presented in different locations. The stimuli are randomly repeated at various luminances to assess reliability and luminance threshold. The output can be quantitatively summarized as a score ranging usually from 0 to -30 decibels where 0 is normal vision and -30 is severe visual field loss. **Goldmann** perimetry is dynamic and relies on the subject to detect a luminant stimulus moving in from the peripheral field. It is performed by a trained operator who employs targets of different luminances and sizes to create a field map. Its advantages over Humphrey perimetry are that subject compliance can be assessed and the whole visual field can be mapped however its output is more qualitative and scotomata can be missed if not properly assessed for.

PANEL 4 - NEUROMYELITIS OPTICA SPECTRUM (MODIFIED FROM WINGERCHUK ET AL<sup>189</sup>)

- Neuromyelitis optica
- Limited forms of neuromyelitis optica
  - Idiopathic single or recurrent events of longitudinally extensive myelitis ( $\geq 3$  vertebral segment spinal cord lesion seen on MRI)
  - Optic neuritis: recurrent or simultaneous bilateral
- Optic neuritis or longitudinally extensive myelitis associated with systemic autoimmune disease
- Optic neuritis or myelitis associated with brain lesions typical of neuromyelitis optica (hypothalamic, corpus callosal, periventricular, or brainstem)



## PANEL 5 – CONSIDERATIONS FOR IMMUNOSUPPRESSANTS IN ATYPICAL ON (MODIFIED FROM PALACE ET AL<sup>155</sup>)

For the immunosuppressants listed below, the treatment advice is not definitive and the reader is encouraged to refer to local guidelines for more details about monitoring and use. Most will require pre-treatment screening investigations as well.

- **Corticosteroids** can be started at 0.75-1mg/kg/day (after intravenous doses given in an acute relapse) and then tapered slowly over about six months with close clinical monitoring for atypical ON. Many side effects are associated with corticosteroid use. The main ones include mood disturbances, glucose intolerance or diabetes, osteoporosis, proximal myopathy, Cushing's syndrome, adrenal suppression, increased risk of infections (e.g. varicella zoster, tuberculosis reactivation), hypertension, glaucoma, cataracts, electrolyte imbalance, neutrophilia, lymphopaenia, peptic ulceration, avascular necrosis. Patients on long term corticosteroids in the UK should carry a Steroid Treatment Card (providing information on reducing risk and dosage details) and should not discontinue treatment abruptly because of the risk of acute adrenal insufficiency. Local guidelines should be implemented for the prevention and treatment of osteoporosis and patients should be monitored for diabetes and hypertension.
- **Azathioprine** treatment usually aims for a maintenance dose of 2.5-3.0 mg/kg/day assuming that thiopurine methyltransferase levels are normal. It can be commenced at 25mg daily and increased in 50mg steps every week as an outpatient. Side effects include bone marrow suppression, hypersensitivity reactions, gastrointestinal reactions (nausea and vomiting), liver dysfunction, increased infection risk, rarely pancreatitis. Full blood count and liver function tests should be monitored frequently during early treatment whilst dose changes are occurring and less frequently after reaching maintenance dose. A high mean corpuscular volume or a lymphopaenia tends to suggest a treatment effect.
- **Mychophenolate** treatment typically starts at 500mg daily, increasing every week in 500mg steps to a maintenance dose of 1 gram twice daily. Main side effects include hypersensitivity reactions, bone marrow suppression, gastrointestinal reactions, liver dysfunction, renal dysfunction, potential risk of lymphoma and skin malignancy. Blood test monitoring should include full blood count, urea and electrolytes, liver function and should be frequently performed during early treatment phase.
- **Methotrexate** treatment can initially aim for 15mg once weekly. Doses start at 7.5mg weekly (with folate supplementation) and then slowly increase in 2.5mg steps every week. Side effects include bone marrow suppression, liver toxicity, pulmonary fibrosis, gastrointestinal symptoms, hypersensitivity reactions, increase infection risk. Blood test monitoring is mandatory (usually full blood count and liver function tests). Yearly chest X-rays are advised.
- **Rituximab** treatment is usually with 1 gram intravenous on days 1 and 14 repeated every six months or when the CD 19 count begins to rise (which are measure monthly)<sup>190</sup>. Side effects include allergic reactions, hypotension, exacerbation of cardiac disease. Infections can occur in 30% of rituximab treated patients and are severe in 1-2%.<sup>151</sup> Pre-infusion blood tests are recommended (full blood count, urea and electrolytes, liver function).

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