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Review

Diagnosis and classification of autoimmune optic neuropathy

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ABSTRACT

The spectrum of autoimmune optic neuropathies (ON) is extending. The phenotypic spectrum includes single isolated optic neuritis (SION), relapsing isolated optic neuritis (RION), chronic relapsing inflammatory optic neuropathy (CRION), the neuromyelitis optica (NMO) spectrum disorder, multiple sclerosis associated optic neuritis (MSON) and unclassified optic neuritis (UCON) forms. Epidemiological data suggests a slight female predominance. The ethnic heritage is relevant as Caucasian patients are more likely to suffer from MSON, whilst SION, RION, CRION and NMO are more frequent in non-Caucasian patients. Importantly, prognosis for recovery of visual function is good in MSON, but poorer in NMO and CRION which also have a high chance for recurrent episodes. Testing for serum anti-AQP4 autoantibodies is advised in all patients with severe, atypical or recurrent ON because of the high diagnostic specificity. The diagnostic specificity may be aided by testing for glial biomarkers in the CSF and prognostic accuracy by testing for biomarkers for neuroaxonal degeneration. Optical coherence tomography is a highly accurate tool to document the final outcome. The current clinical classification criteria rely on the phenotype, response to treatment and presence of anti-AQP4 autoantibodies.

Contents

Abbreviations: ADEM, acute demyelinating encephalomyelitis; AION, anterior ischaemic optic neuropathy; AQP4, aquaporin-4; AZOOR, acute zonal occult outer retinopathy; CF, count fingers; CRION, chronic relapsing inflammatory optic neuropathy; CSF, cerebrospinal fluid; CT, computed tomography; GBS, Guillain Barré Syndrome; GCA, giant cell arteritis; GCL, ganglion cell layer; GFAP, glial fibrillary acidic protein; HM, hand movement; INL, inner nuclear layer; ION, isolated optic neuritis; IVIG, intravenous immunoglobulin; IVMP, intravenous methylprednisolone; LETM, longitudinal extensive transverse myelitis; LHON, Leber hereditary optic neuropathy; LP, lumbar puncture; MMO, microcystic macular oedema; MMC, microcystic macular changes; MRI, magnetic resonance imaging; MS, multiple sclerosis; MSON, multiple sclerosis optic neuritis; NMO, neuromyelitis optica; NPL, no light perception; OCT, optical coherence tomography; ON, optic neuritis; ONTT, optic neuritis treatment trial; DOA, dominant optical atrophy; PE, plasma exchange; PION, posterior ischaemic optic neuropathy; PPMS, primary progressive multiple sclerosis; RION, relapsing isolated optic neuritis; RNFL, retinal nerve fibre layer; RRMS, relapsing remitting multiple sclerosis; SLE, systemic lupus erythematosus; SPMS, secondary progressive multiple sclerosis; UCON, unclassified optic neuritis; VA, visual acuity.

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1. Introduction

Autoimmune optic neuropathies are rare, but potentially blinding conditions if not diagnosed and treated appropriately. This review on autoimmune optic neuropathies is focused on the diagnostic criteria, including some information on history, epidemiology and biomarkers as appropriate for the clinical diagnosis and classification criteria. Crucially, there have been important discoveries on the autoimmune pathology of the optic nerve. These recent observations substantially extend on the description of optic neuritis beyond the phenotype that is a presenting symptom or a relapse in multiple sclerosis (MS). Particularly, the increased risk for progressive loss of vision seen with some autoimmune optic neuropathies was not necessarily recognised in the literature on MS associated optic neuritis (MSON) at the turn of the century.

2. Diagnostic criteria

In brief, the published diagnostic criteria distinguish patients phenotypically. Autoimmune optic neuritis may remain isolated as an optic neuropathy or be associated with more wide-spread central nervous system (CNS) or systemic disease [38,41,44,64].

The phenotypic classification of autoimmune optic neuropathies includes single episode of isolated optic neuritis (SION) [38], relapsing episodes of isolated optic neuritis (RION) [38], chronic relapsing inflammatory optic neuropathy (CRION) [41], optic neuritis in multiple sclerosis (MSON) [44] and optic neuritis as seen in the neuromyelitis optica (NMO) spectrum disorder [64] and other forms of suspected autoimmune ON not covered by the above.

These published, phenotypic diagnostic criteria partly overlap with the ICD10 Medical Coding system [65]. Optic neuritis was described anatomically under H46. First, with regard to the location of the inflammation with regard to the optic disc, optic papillitis was listed under H46.0 and retrobulbar neuritis under H46.1. Second, the ICD10 classification clarifies if the side of the affected eye was not known (subitems 46.00 and 46.10), on the right (subitems 46.01 and 46.11), on the left (subitems 46.02 and 46.12), or bilateral (subitems 46.03 and 46.13). Next, there are "other optic neuritis" listed under the billable ICD10 code H46.8 which can be used to specify a diagnosis. Following the ICD10 system MSON comes under H46; ION, RION and CRION under H46.8 and NMO under G36.0. All types of unspecified ON not covered by above are under H46.9. Of note, whether the right or left optic nerve is involved is not of diagnostic significance whereas bilateral simultaneous optic neuritis has a very different differential diagnosis from purely unilateral case. Chiasmitis is a particular instance not covered by this classification which prior to contemporary would often have been classified as bilateral simultaneous retrobulbar optic neuritis. From the point of view of differential diagnosis "papillitis" is not helpful except that it indicates involvement of the orbital portion of the optic nerve but this can occur without disc swelling.

Next, there is the approach of the World Health Organisation (WHO) which interprets optic neuritis in the context of the diagnostic criteria for MS [44]. The WHO separates the Western type of MS from the Asian variant with the latter have more frequent "restricted recurrent optic nerve and spinal cord involvement." [66]. The precise nosology of the "optic–spinal" form of MS seen in East Asia is not clear as some cases have serological evidence indicating that they are a form of NMO while others more resemble MS.

Finally, there are important differences according to the age of onset between children and adults [7,20]. Because of restricted space, this manuscript is focused on adult onset autoimmune optic neuritis.

As with any diagnostic classification it is relevant to exclude mimics. The here relevant differential diagnosis of subacute visual loss is summarised in Table 1.

3. History

Historically, the ophthalmologists von Graefe (1828–1870) [18] and Nettleship were jointly credited for the objective description of the symptoms and signs of optic neuritis: "They are characterized by failure of sight limited to one eye, often accompanied by neuralgic pain about the temple and orbit and by pain in moving the eye; many recover but permanent damage and even total blindness may ensue; there is at first little, sometimes no, ophthalmoscopic change, but the disc often becomes more or less atrophic in a few weeks, and occasionally there are slight retinal changes." [34]. These observations were only possible with aid of the ophthalmoscope which had been introduced to wider clinical practise by von Helmholtz (1851).

There are earlier, anecdotal descriptions of possible optic neuritis. The most frequently cited case is probably of Auguste D'Este whose diary suggests episodes of relapsing bilateral optic neuritis in 1822 and 1826 [15]. The writer and poet Heinrich Heine (1797–1856) may have suffered from at least ten episodes of relapsing optic neuritis in September 1837, December 1837, June 1838, end of 1839, June 1838, April 1843, three times in 1844 and again in 1845 [24]. Heine wrote: "Depuis dix jours mon mal d'yeux est revenue et de nouveau ej souffre des éblouissements qui font vaciller à ma vue les objects, et leur prêtent une couleur moité grisâcre, moité argentine."[1] Then there is the case of Lidwina from Schiedam (1380–1433) who suffered from symptoms suggestive of multiple sclerosis and lost sight in one eye [32].

4. Epidemiology

The difference between Caucasian and Oriental optic neuritis was already described in a series of papers between 1970 and 1978 [1]. Notably, recent studies added weight to the argument of ethnic differences on the association between ON and MS [3,6,12,22,29,47,61,68]. The association between ON and MS appears to be lower in Asian patients compared to Caucasian patients. Likewise CRION and NMO were reported to be more frequent in patients with African or African-Caribbean heritage [37,52]. None of these studies were population based, most were retrospective and neither an inclusion bias nor referral bias can be excluded.

There is some evidence from Australia that the earlier reported association between latitude and MS is also found for MSON [58]. The overall incidence of MSON in Australia was less than 2/100,000 with about a 3:1 female predominance. But this study was focused on MSON and we do not know about other forms of autoimmune optic neuropathies. A slight female predominance was also noted in the Asian studies [3,6,12,22,29,47,61,68].

A seasonal association was reported for MSON [25]. Again, care needs to be taken to control for false positive findings related to type I error rates [14].

5. Prognosis

The prognosis for recovery of visual acuity is good following MSON. Despite the difference in follow-up time between studies a comparison of outcome visual acuity is informative because of the speed of recovery within 2–6 months [21], which did fall in the time-frame of the studies cited [3,4,6,12,13,19,22,29,30,41,47–49,54,61,68].

From the 294 of the originally 457 participants of the ONTT VA had recovered to ≥ 1.0 in 77% at the 15-year follow-up visit [19]. Only 2% had a VA ≤ 0.5 [19]. These data contrast with the poorer visual outcome in other forms of autoimmune optic neuropathies (Table 2). Visual outcome was worst in NMO and CRION [41,43].

[1] For 10 days my eye trouble has returned and I suffer giddy turns which make objects vacillate in my sight, and gives them partly a greyish and partly a silvery colour [translated by Jellinek [24]].

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