CASE REPORT

Optic perineuritis: an important differential diagnosis of optic neuritis

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Abstract

We report a case of idiopathic optic perineuritis presenting akin to optic neuritis. Characteristic appearance on magnetic resonance imaging can differentiate between the 2 conditions. The patient was successfully treated with high-dose oral corticosteroids so as to avoid permanent visual loss. The diagnosis is difficult and requires a high index of suspicion, comprehensive systemic enquiry and workup, and appropriate imaging. The literature on various types of optic perineuritis was also reviewed.

Key words: Optic atrophy; Optic neuritis; Orbital pseudotumor

Introduction

Optic perineuritis (OPN), also known as perioptic neuritis, was first mentioned by Edmunds and Lawford[1] in 1883 as a histopathologic description of inflammatory infiltration loosely organized around the optic nerve, whose function was presumed to be preserved. Recently, however, this term was used to describe a form of orbital inflammatory disease primarily affecting the optic nerve sheath (ONS) and surrounding tissues. The diagnosis was based on a combination of clinical and radiographic findings. We herein report on a patient with idiopathic OPN treated with high-dose steroid therapy.

Case report

A 47-year-old Chinese man with good past health presented with subacute left eye visual loss and dyschromatopsia for few days, together with ipsilateral dull retro-orbital pain exacerbated by ocular movement. There was no history of trauma, fever, or weight loss. Visual acuity was down to hand movement in left eye, 6/6 in right eye. Goldmann perimetry found extensive visual field loss in the left eye with only a temporal island remaining (**Figure 1a**). The right eye visual field was full. Relative afferent pupillary defect (RAPD) was present in left eye. The anterior segment was unremarkable each eye, with normal intraocular pressure. No proptosis or ptosis was observed. Ocular motility was normal, and no other neurological deficit was detected. Fundoscopy revealed mild temporal pallor of the left optic disc with no swelling or abnormal vessels. The posterior segment was otherwise unremarkable.

Baseline investigations including complete blood count, liver and renal function test, blood pressure and blood glucose were all normal. The erythrocyte sedimentation rate was 14 mm/hour, the C-reactive protein level was normal; the anti-nuclear antibody (ANA) test was negative, as was the *Treponema pallidum* enzyme immunoassay (TP-EIA). The chest X-ray revealed no pulmonary or hilar opacity typical of sarcoidosis or Wegener's granulomatosis. The presumptive diagnosis was retro-bulbar optic neuritis (ON). Subsequent magnetic resonance imaging (MRI) of the brain and orbit with gadolinium-diethyltriaminepentaacetic acid (Gd-DTPA) contrast demonstrated subtle T2-weighted hyperintensities within posterior part of left ONS at the orbital apex with mild contrast enhancement. Similar enhancement was noted on a post-contrast T1-weighted axial scan with fat suppression. The coronal scan demonstrated doughnut-shaped enhancement of the left ONS (**Figure 2**). The left optic nerve was otherwise unremarkable. No other focal intracranial mass, abnormal signal or contrast enhancement was detected, nor was there thickening of extraocular muscles. The finding was suggestive of left-sided OPN. Oral prednisolone 70 mg daily was started around 3 weeks after onset of symptoms. On day 8 of treatment, the retro-orbital pain resolved and Goldmann perimetry showed near-normal visual fields but an enlarged blind spot on left side (**Figure 1b**). Visual acuity was down to counting fingers. Prednisolone was maintained at around 40 mg daily for 3 months and slowly tapered off over next 3 months. The

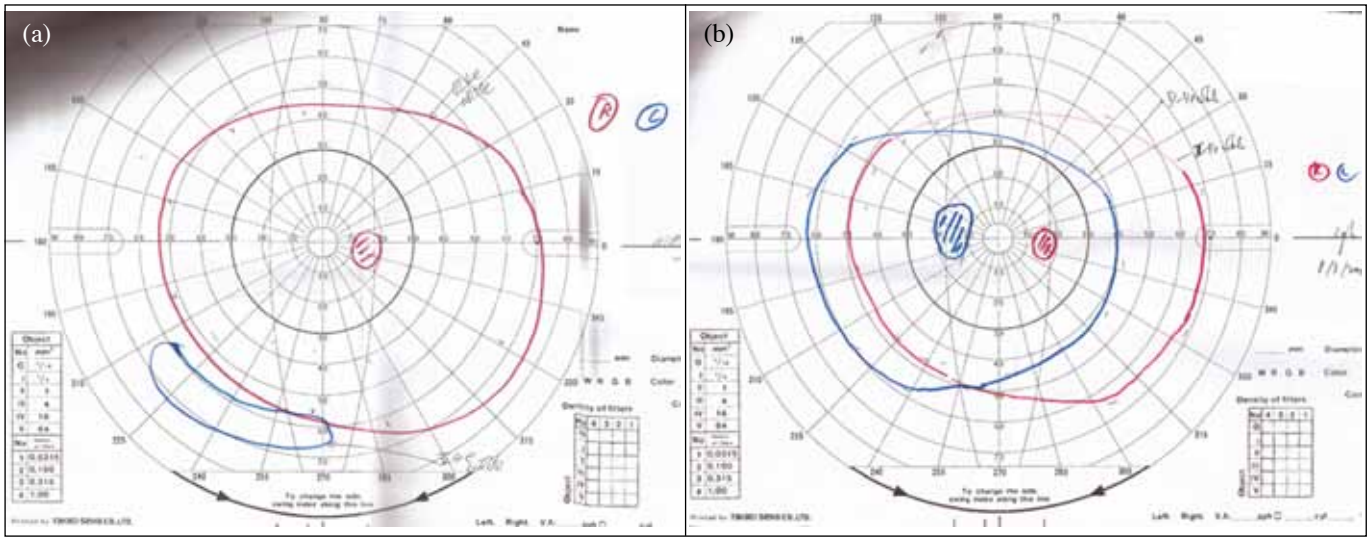

Figure 1. (a) Visual field on presentation showing a temporal island only. (b) After high-dose oral steroids, the visual field shows dramatic improvement with residual enlargement of blind spot.

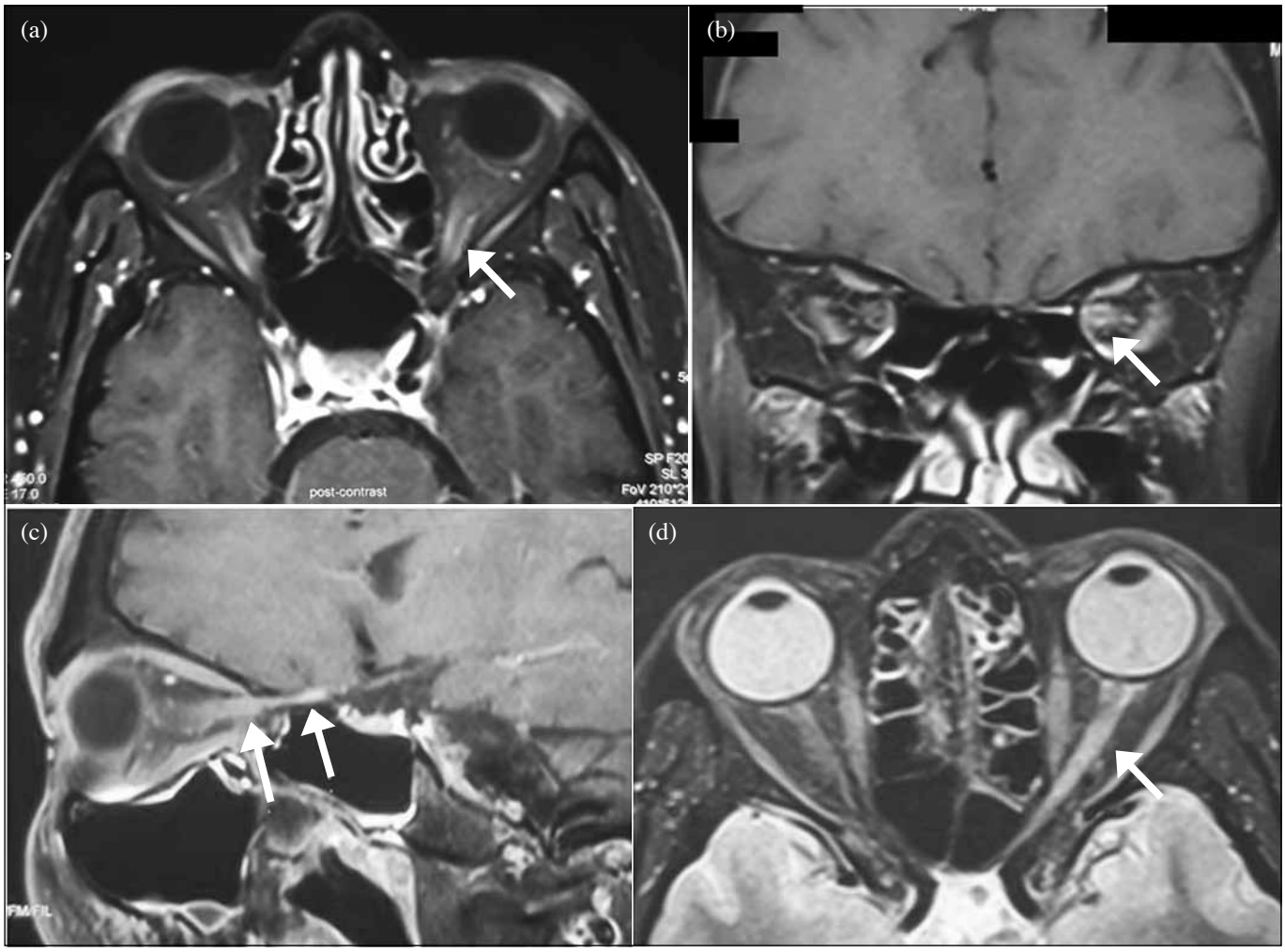

Figure 2. (a) T1-weighted fat-suppressed axial image showing tram-track enhancement of the left optic nerve sheath. (b) T1-weighted fat-suppressed coronal image showing ring-shaped enhancement of the left optic nerve sheath. (c) T1-weighted sagittal image showing intra-orbital and intra-canalicular optic nerve sheath enhancement. (d) T2-weighted axial image showing left optic nerve sheath enhancement.

visual acuity stabilized at 6/90, with further improvement of visual field and color vision returned to normal, but left optic disc pallor persisted. Optical coherence tomography of the retinal nerve fiber layer in left eye confirmed the presence of extensive peripapillary nerve fiber loss in all quadrants (**Figure 3**).

Discussion

OPN was used in the early literature to describe a syndrome of optic disc swelling in the absence of optic nerve dysfunction, except for enlargement of the blind spot. It was later reserved for cases with enhancement of ONS evident on contrast MRI. The condition was described in a variety of circumstances, including secondary syphilis,[2-10] post-influenza vaccination,[11] sarcoidosis,[12] and Wegener's granulomatosis,[13] whilst some cases were labelled idiopathic.[14-17] However, a histopathologic diagnosis was established only in a minority of cases. In the early literature most were diagnosed based on clinical features, relevant

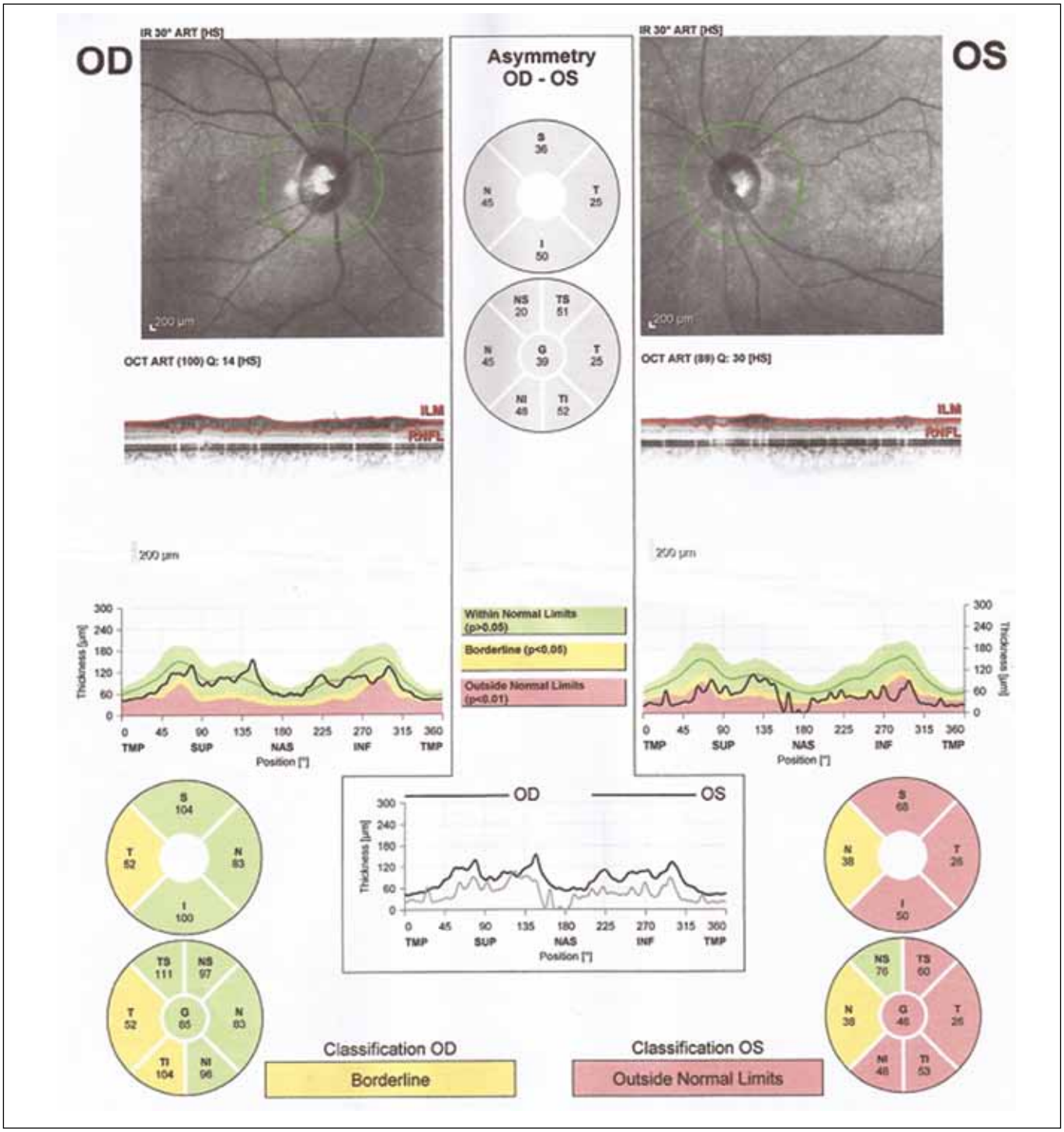

Figure 3. Optical coherence tomography scans of retinal nerve fiber analysis after steroid therapy showing circumferential thinning of peripapillary nerve fibers on the left side.

history, blood tests, and cerebrospinal fluid (CSF) analysis.

Pathology

Early reports on syphilis-related OPN described chronic inflammation of the surrounding meninges, particularly around blood vessels.[2,4,5] It was most frequently noted in secondary syphilis, but detailed pathological descriptions were lacking as most reported cases were treated successfully based on clinical grounds and without resorting to biopsy.[6-10]

More recent literature on idiopathic OPN described pathologies in greater details. Chronic granulomatous inflammation of the ONS is the hallmark of idiopathic OPN.[18] Margo et al[19] found chronic inflammation of ONS with vasculitic changes and necrobiotic granulomas in a full-thickness biopsy of the optic nerve. Fay et al[16] described a hypocellular, polymorphous lymphoid infiltrate consisting of lymphocytes, plasma cells, macrophages, and polymorphonuclear cells, involving both the neural sheath and perineural fat. Purvin et al[15] described thickening of perioptic meninges, pia mater, and pial septa due to chronic inflammatory infiltration and fibrosis. Vasculitic changes may be present.[19] Visual loss is attributed to secondary ischemic infarction of optic nerve due to circumferential compression by the thickened neural sheath,[15,16,19] or to vascular occlusion due to vasculitis.[16]

For OPN associated with other etiologies,[11-13,20] optic nerve histology was lacking. Diagnosis was made either on clinical grounds or radiologic appearance of the optic nerve, considered together with other systemic features.

Epidemiology

For OPN associated with syphilis and other secondary causes, only isolated reports are available. Syphilis-related OPN was described in 2 patients with positive human immunodeficiency virus (HIV) serology.[6,7] Regarding idiopathic OPN, the largest series by published by Purvin et al[15] consisted of 4 men and 10 women ranging from 24 to 60 (mean, 41 and median, 40) years. The mean age of such patients was greater than that of demyelinating ON (mean age, 32 years) as reported in the Optic Neuritis Treatment Trial (ONTT).[21]

Clinical characteristics

Clinical manifestations vary according to the etiology, most having been described as syphilis-related and idiopathic OPN (**Table**).

Most cases of syphilis-related OPN present with minimal symptoms.[8] Some present with transient blurring,[9] floaters,[6] seeing stars[10] or cobweb images,[7] epiphora, and conjunctival congestion.[10] This could be related to the definition of syphilitic OPN in the early literature as inflammation without nerve-fiber dysfunction and visual impairment[8,10]; cases with optic nerve dysfunction were therefore classified as syphilitic optic neuropathy. Patients could also have systemic features such as generalized skin rash, malaise, lymphadenopathy, headache, orogenital ulcer, and weight loss. The skin rash is usually typical of secondary syphilis. A few cases were HIV-positive.[6,7] Ocular findings included optic disc swelling, enlarged blind spot, and lack of RAPD. The disc appearances are described as elevated, hyperemic, swollen, and peripapillary flame-shaped hemorrhages were often noted. Usually both eyes are affected but asymmetrically. Ocular inflammation, if any, is minimal and visual acuity is usually normal. Color vision is not affected. The diagnosis of syphilis usually depends on blood test results and CSF analysis (positive serology or CSF findings based on Venereal Disease Research Laboratory [VDRL] tests).[6-10]

Cases of idiopathic OPN present with various symptoms.[14-17] The commonest is acute-onset unilateral dull pain in the retro-orbital region or the eye itself, which is constant and aggravated by palpation or ocular movement. Most reported cases are unilateral, except for one described by Purvin et

Table. Clinical features of optic perineuritis due to various etiologies.

Etiology	Ocular features	Systemic clues
Idiopathic	Retro-orbital pain on ocular movement Acute optic neuropathy Extraocular muscle dysfunction, ptosis Chemosis, conjunctival injection Variable visual field defect	Unremarkable
Wegener's granulomatosis	Similar to idiopathic optic perineuritis Peripheral ulcerative keratitis Uveitis, scleritis	Polymyalgia rheumatica Upper and lower respiratory symptoms Renal failure
Syphilis	Mostly asymptomatic Floaters Transient visual disturbance Enlarged blind spot	Characteristic skin rash Sexual history Human immunodeficiency virus status
Sarcoidosis	Asymptomatic Anterior uveitis Enlarged blind spot	Generalized malaise Other systemic features of sarcoidosis
Post-vaccination	Asymptomatic Normal visual function	History of influenza vaccination Encephalomyelitis

al.[15] Mild photophobia may be present. Typically, blurring of vision is present and described as dimming, foggy vision, or spots. Less commonly, diplopia, ptosis, conjunctival injection, or chemosis may be present.[15] Visual acuity is better than 20/40 in over half of the cases,[14-17] but others have significant visual loss. In the case series by Purvin et al,[15] the presenting visual acuity was worse than 20/200 in 3 of the 14 patients. Two of 3 cases reported by Tatsugawa et al[14] and 1 case by Ohtsuka et al[17] also had visual acuity worse than 20/200. Visual field defects are present in nearly all cases,[14-17] and mostly consist of para-central or central scotomas followed by arcuate scotomas, enlarged blind spots, peripheral constriction, and altitudinal loss. As in our case, some may even present with temporal islands only. Disc swelling was evident in over half of the reported cases, usually hyperemia and splinter hemorrhages were also present. The remainder had normal optic discs or disc pallor. Associated ptosis and paralytic strabismus have also been reported.[15] The overall clinical picture closely resembles demyelinating ON; the presence of ptosis and paralytic strabismus could suggest orbital apex syndrome. These patients therefore present a diagnostic challenge in which imaging has an important role.

Only isolated reports are available for OPN associated with other etiologies. In 2000, Vilain et al[11] reported a case after influenza vaccination, who presented with headache, arthralgias, urinary retention, constipation and unsteadiness, but without any ocular symptom. He was found to have bilateral disc swelling with a flame-shaped hemorrhage 2 months after vaccination. He had no RAPD, and visual acuity and color vision were grossly normal. Goldmann perimetry revealed bilaterally enlarged blind spots. The diagnosis of OPN was made based on disc swelling with relative absence of ocular symptoms or signs, as in cases of syphilis-related OPN.

In 2003, Wals et al[20] reported a case of neuroretinitis and OPN occurring simultaneously with unilateral visual loss with pain on ocular movement. Fundoscopy revealed disc swelling and macular star formation. OPN was diagnosed based on an MRI showing enhancement of the ONS and perineural fat. No specific etiology including cat scratch disease was found.

Regarding OPN associated with sarcoidosis reported by Yu-Wai-Man et al[12] in 2007, the patient was asymptomatic except for general malaise in the past 3 months. Visual acuity was normal. Visual field assessment revealed slight enlargement of blind spots bilaterally. Fundoscopy yielded bilateral but asymmetrical optic disc swelling with peripapillary hemorrhages. MRI revealed no abnormal enhancement. Thus, the diagnosis was made on clinical grounds, constant with the early definition of OPN used in syphilitic cases.

In 2009, Purvin and Kawasaki[13] reported 3 cases of OPN associated with Wegener's granulomatosis, all of whom presented with unilateral painful optic neuropathy. Additional features included scleritis and diplopia with vertical deviation. Other systemic symptoms were consistent with polymyalgia rheumatica (proximal muscle stiffness and aching), fatigue, serous otitis, and other features of small vessel vasculitis. OPN was diagnosed based on MRI findings showing contrast enhancement around the intra-orbital optic nerve but sparing the nerve itself.

Imaging findings

Computed tomography (CT) is typically unrewarding in the diagnosis of OPN. Notably, CT with contrast is normal in all reported cases of syphilis-related OPN.[7-10] MRI with Gd-DTPA contrast has become the standard in recent years, but was not performed in most cases of syphilis-related OPN. However, it has been the basis for diagnosing idiopathic OPN. Typical findings on T1-weighted images with fat suppression include enhancement of ONS and streaky enhancement of perineural orbital fat. The ONS enhancement occurs in intra-orbital or apical regions, and may resemble a 'tram-track' on axial views and 'doughnut' on coronal views.[15] Occasionally, there may be thickening of the ONS or optic nerve. Less frequently, enhancement of extraocular muscles, sclera, or the optic nerve itself may occur. Brain MRI typically finds no abnormal signal intensities or enhancement to suggest a demyelinating process. Some cases by Purvin et al[15] showed intracranial extension of the lesion, but no white matter abnormality.

Regarding OPN with other etiologies, MRI was normal in the cases related to influenza vaccination[11] and sarcoidosis,[12] and there was ONS enhancement in the case of neuroretinitis.[20] For the 3 cases of Wegener's granulomatosis,[13] in addition to ONS enhancement, there was more extensive intracranial involvement including orbital apex, sphenoid wing, meninges, and cavernous sinus. In 1 case, there were multiple areas of enhancement suggestive of vasculitis.[13]

Fluorescein angiography was performed in selected cases only. In syphilis-related OPN, Gartaganis et al[8] showed dilated and telangiectatic prepapillary capillaries in early arteriovenous phase, mid-phase leakage from disc, and late-phase residual disc hyperfluorescence beyond the optic disc margins. Similar finding was observed in the patient with idiopathic OPN reported by Ohtsuka et al[17] and another with neuroretinitis case by Wals et al.[20] Thus, this finding is not specific enough to suggest any particular etiological factor or pathological process.

Workup

A complete blood count, erythrocytes sedimentation rate, and serological tests for ANA, angiotensin-converting enzyme, and syphilis are commonly performed. The TP-EIA, fluorescent treponemal antibody absorption, and treponemal hemagglutination tests are also performed for syphilis, and in some suspected cases a CSF VDRL test can be considered but is not reported to be particularly helpful.[7-10] HIV antibody testing could be considered in appropriate cases. Typically, these investigations are unrewarding in idiopathic OPN.

In the sarcoidosis case reported by Yu-Wai-Man et al,[12] basic blood tests were unremarkable. However, CT thorax yielded enlarged paratracheal lymph nodes, biopsy of which showed prominent multinucleated giant cells and non-caseating epithelioid granulomas.

In Wegener's granulomatosis, anti-neutrophil cytoplasmic antibodies (ANCA) may be present in 88% to 93% of cases,[13] but is less common if the disease is limited. Cytoplasmic ANCA correlates best with disease activity, while perinuclear ANCA is less commonly present.

In the patient with neuroretinitis reported by Wals et al,[20] blood tests including cat-scratch titer, Lyme disease, and syphilis serology were all negative; only the ANA test (titer 1:320, nucleolar pattern) was positive. No other systemic autoimmune disease was encountered during subsequent follow-up.

Treatment and response

All reported cases of syphilis-related OPN were treated with high-dose penicillin therapy, most commonly 24 million units of intravenous aqueous penicillin daily was given in divided dose (every 2 to 4 hours), with a treatment duration of 10 days[9,10] to 3 weeks.[8] Basta et al[7] described an alternative regimen with intramuscular injection of procaine penicillin 1.8 g with oral probenecid 500 mg 4 times daily for 17 days. All the patients showed complete resolution of ocular and systemic symptoms, as well as optic disc findings, and a significant decline in VDRL titer.

The mainstay of treatment for idiopathic OPN consists of systemic steroid, either orally or by intravenous infusion. The case reported by Ohtsuka et al[17] was treated with intravenous methylprednisolone 1 g daily for 3 days followed by oral prednisone 30 mg daily for 14 days, which was similar to the regimen for ON in the ONTT. Treatment was started around 18 days after onset, with rapid recovery of visual acuity (to 20/20) and disc swelling within 12 days of starting treatment. Repeat MRI 5 weeks later showed disappearance of abnormal enhancement. Similar pulse steroid therapy was mentioned in 2 of 3 cases reported by Tatsugawa et al,[14] also with a dramatic response and no recurrence, but the exact regimen used was not described.

In the series by Purvin et al,[15] most cases were treated with oral prednisone, either 60 or 80 mg daily, subsequently tapered over a few weeks to months. All the patients enjoyed rapid improvement of ocular pain and vision. Relapse occurred in 4 cases upon reduction of the steroid dosage, for which additional therapy was given (intravenous methylprednisolone, peribulbar steroids, azathioprine, and radiation therapy). Most patients (including those who relapsed) retained visual acuity of 20/25 or better. Two of the cases had poor visual outcomes that were attributed to a delayed presentation and initiation of steroid therapy (3 months and 6 months later). Two others were initially treated with oral indomethacin and had good responses and no recurrence. The case by Fay et al[16] was treated with a higher dose of oral prednisone (100 mg daily), tapered over 4 weeks. All symptoms and signs, along with visual field defect, resolved in 1 week and there was no recurrence.

Steroid therapy is also used in OPN due to other etiologies. The post-influenza vaccination case was treated with intravenous methylprednisolone 1 g daily for 3 days with regression of disc swelling.[11] Oral prednisolone 40 mg daily was used to treat the case of sarcoidosis[12]; the disc swelling and gait ataxia resolved with no recurrence. In Wegener's granulomatosis, however, although all 3 patients showed good initial responses to oral prednisone (5 to 80 mg daily), relapse was universal upon dosage reduction.[13] All these patients received additional maintenance immunosuppressants (methotrexate or cyclophosphamide) to maintain the remission.

Differentiation from optic neuritis

It is difficult to differentiate OPN from ON, especially if the former is idiopathic. However, differentiation can be accomplished by considering patient demographics, clinical features, and imaging findings. The mean age of OPN patients was 41 years in the series by Purvin et al,[15] as opposed to 32 years for ON (based on the ONTT). The rate of symptom evolution is also variable (usually within few days to weeks) and cannot differentiate between the 2 conditions. Pattern of visual field defects also varies, and is thus not a good differentiating factor. The most important characteristic in OPN is presence of orbital involvement, such as extraocular muscle dysfunction, paralytic strabismus, ptosis, chemosis, proptosis, which is generally not present in ON. Based on MRI, the characteristic enhancement of the ONS and orbital fat can readily differentiate between the 2 conditions.

It is important to diagnose OPN accurately and promptly. Since the ONTT demonstrated that intravenous pulse steroid may not affect the final visual outcome in ON, many cases of suspected unilateral disease were expectantly managed. In OPN, however, this may cause irreversible visual loss from secondary ischemic infarction. Both intravenous pulse steroid and oral prednisone result in satisfactory outcomes in OPN. Moreover, oral prednisone is contra-indicated in ON due to its association with an increased risk of recurrence. Intravenous steroid treatment durations of 2 weeks (used in ON) are also not sufficient to prevent recurrences in cases of OPN. Furthermore, as ON is associated with a higher risk of subsequent multiple sclerosis, further neurological evaluation and counseling may be necessary, if the diagnosis is not OPN.

Conclusion

OPN is a heterogeneous group of diseases affecting the ONS and surrounding tissues. Its clinical features vary from being asymptomatic to causing acute painful visual loss, resembling a demyelinating ON. Various etiologies are reported and should be ruled out by careful systemic enquiry and examination, combined with appropriate blood tests and other investigations. MRI is important in establishing

the diagnosis, and should enable differentiation from ON. Management is directed towards the cause. In idiopathic OPN, prompt and prolonged high-dose systemic steroid therapy is indicated to prevent irreversible visual loss.

Declaration

The authors declared no financial interest to disclose in this study.

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