Chapter

Atypical Optic Neuritis

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Abstract

Optic neuritis (ON) is defined as inflammatory optic neuropathy. In its initial clinical appearance, ON can have unilateral or bilateral manifestation and anterior (papillitis) or retrobulbar localizations. Traditionally, they are divided into typical and atypical ON. In the western hemisphere, most optic nerve inflammations are associated with multiple sclerosis, in their typical form. However, ON can be associated with a series of disorders of unknown or known origin. Atypical ON has a somewhat different clinical picture from typical and encompasses neuromyelitis optica spectrum disease (NMOSD), idiopathic recurrent neuroretinitis (NR), chronic relapsing inflammatory optic neuritis (CRION), ON within systemic autoimmune diseases, and neuritis during or after infectious diseases or vaccination. Their cause should be meticulously worked up, because of the therapeutic and prognostic challenges that they present.

Keywords: NMO spectrum disease, systemic autoimmune diseases optic neuropathy, neuroretinitis, infectious and postinfectious optic neuritis, postvaccination optic neuritis

1. Introduction

Optic neuritis (ON) is an optic nerve inflammatory neuropathy. Diagnosis is based on the disease history and basic ophthalmological examination. Further clarification and monitoring of the disease include more detailed ophthalmological, neurological, and radiological examinations, including visual field test, pupils reactions [relative afferent pupillary defect (RAPD)], color and contrast sensitivity tests, optical cocherence tomography (OCT) of ganglion cells layer and retinal nerve fiber layer recordings, magnetic resonance imaging (MRI) of brain, optic nerves and spinal cord and lumbar puncture with cerebrospinal fluid analysis. Although not necessary for optic ON diagnosis, electrophysiological testing [visual evoked potentials (VEP), pattern electroretinogram (PERG), photopic negative response electroretinogram (PhNRERG), and sometimes other electroretinographies (ERG)] can aid in differential diagnoses and further monitoring of the disease [1, 2]. Additional laboratory tests are used to rule out or confirm the suspicion of certain etiologies of ON. For the same reason, consultations with other specialists may be required.

Traditionally, ON is divided into typical and atypical.

2. Typical optic neuritis

Typical ON is the most common presentation of the disease and manifests as a clinically isolated syndrome (CIS). It can take the form of unclassified optic neuritis, as single or relapsing isolated neuritis (SION, RION), or can occur as part of newly diagnosed or previously recognized multiple sclerosis (MS). It most often occurs in younger women. Patients have an acute or subacute decline in visual acuity, pain in moving the eyes, scotoma in the visual field, and dyschromatopsia. The disease occurs in one eye, usually as a form of retrobulbar neuritis. Relative afferent pupillary defect (RAPD) is present. MRI is needed to examine the presence of demyelinating plaques and to diagnose multiple sclerosis or assess the risk of its development. OCT assessment, particularly of the ganglion cell layer, may have a similar function [3]. Retinal ganglion cell layer thinning, seen on OCT, may exist even without previous clinically evident episode of ON. Further neurological evaluation includes lumbar puncture and cerebrospinal fluid analyses for oligoclonal bands.

Neuritis usually responds well to corticosteroid intravenous therapy and also has the property of spontaneous recovery after several weeks [4]. In patients with MS, positive RAPD and extended p100 latencies on VEP last several months after improvement in visual functions.

3. Atypical optic neuritis

Atypical ON has a more diverse clinical picture than typical ON. Atypical ON includes etiologically, pathogenically, pathoanatomically, and clinically diverse neuropathies and diseases. The manifestations are often bilateral, in the form of papillitis, sometimes without pain in eye movements, and occur in all age and sex groups. The disease may have a progressive course and show only temporary improvement on corticosteroid therapy. The causes and pathogenic mechanisms are diverse and should be examined at several levels. A diverse therapeutic approach is likely to be required.

Atypical neuritis includes neuromyelitis optica spectrum disease (NMOSD), autoimmune optic neuropathy, chronic relapsing inflammatory optic neuropathy (CRION), idiopathic recurrent neuroretinitis (NR), optic neuropathy associated with systemic autoimmune diseases and related to infectious disease and vaccination [5]. Because atypical neuritis affects different parts of optic nerve, with varying causes and clinical courses, its forms often overlap, depending on the mentioned factors. Other optic neuropathies can also mimic inflammatory neuropathies [6].

3.1 Neuromyelitis optica spectrum disease

3.1.1 Ayuaporin-4-positive-antibodies NMOSD

Neuromyelitis optica spectrum disorder (NMOSD) is usually known for the best described Devic's disease. It is an autoimmune demyelinating disorder where inflammation of the optic nerve and inflammation of the spinal cord (longitudinally transverse myelitis extending across three or more vertebral segments) can be accompanied by brainstem or brain symptoms (area postrema syndrome, diencephalic syndrome or other brainstem disorders). Cases are more frequent in people who are not of European descent. Most patients meeting the current criteria for NMOSD experience repeated attacks separated by periods of remission.

Damage of the afferent pathway at the starting point, at the level of ganglion cells (retina, examined by OCT or n95 wave on PERG and phnr wave on PhNRERG), is prominent but does not appear before optic neuritis, unlike in MS [7].

The interval between attacks may be weeks, months, or years. It occurs in all ages, but mean age of onset is in early 40s, and there is high female-to-male predomination rate [8]. A blood test for antibodies against astrocyte water channel protein aquaporin-4 (AQP4-IgG) is highly specific and moderately sensitive for NMOSD. These antibodies are found in the cerebrospinal liquid, and testing is frequently positive at the time of the very first symptom, even before a confident clinical diagnosis is possible.

Most patients have relapsing rather than monophasic clinical course. High intravenous corticosteroid doses are used as a first-line treatment of an acute attack [9]. The prognosis for visual recovery is poorer in Devic's disease than in typical form of ON. Neurological monitoring and early intervention with plasmapheresis and other therapeutic immunosuppressive options are needed to alleviate the deficits caused by this disease or even to prevent mortality [10, 11].

3.1.2 Myelin oligodendrocyte protein-positive-antibodies NMOSD

An another form of ON, frequently in the form of papillitis in one or both eyes, in an isolated form or with myelitis or acute disseminated encephalomyelitis (ADEM), makes significant portion of AQP4-IgG negative, but myelin oligodendrocyte protein (MOG) IgG-positive patients [12].

The disease is initiated by damage to the oligodendrocytes, it is followed by demyelination, and meets criteria for NMOSD. It can occur without previously recognized disease, but usually follows a viral infection or inoculation such as a bacterial or viral vaccine [13, 14].

The relatively recently discovered MOG-IgG is present in approximately half of patients with NMOSD who are AQP4-IgG negative. This antibody is not normally found in the cerebrospinal liquid, but is detected in it during the disease.

Myelin oligodendrocyte glicoprotein antibody-associated disease (MOGAD) usually has less severe course than Devic's disease. The optic nerve inflammation is more anteriorly located and affects a longer portion of optic nerve [15]. Spinal lesions tend to be located in toracolumbar region. ADEM is more frequent in children [16]. Frequently, the disease has a course of CRION, including relapsing ON, usually with the first relapses 2 months after corticosteroid therapy and steroid dependency [10, 17]. Treatments for acute attacks involve high intravenous corticosteroid doses. Long-term oral prednisolone therapy, for 3 months or more, has beneficial effect in relapsing disease. The absence of steroid-dependent attacks in the early stages of the disease may predict a long-term non-relapsing disease course and a more favorable outcome [17].

Seroconversion to MOG antibodies negative finding is also a better prognostic sign, which does not have to be the case with Devic's disease [18]. In cases of MOGAD with progressive and damaging potentials, other forms of immunosuppressive therapy are needed [19].

3.2 Idiopathic recurrent neuroretinitis

Neuroretinitis is characterized by acute visual loss with optic disc swelling and hard exudates macular star formation in one eye. The most common causes are

infectious diseases due to *Bartonella hensellae, Borrelia burgdorferi, Leptospires, Macobacterium tuberculosis*, and *Treponema pallidum*. If the infectious cause is detected, antibiotics are included in therapy. The role of corticosteroids in therapy is not entirely clear.

Neuroretinitis may be associated with systemic autoimmune diseases. Some cases remain idiopathic and show good response to intravenous corticosteroid therapy or spontaneous recovery without recurrence.

A subset of patients with neuroretinitis have a different clinical profile characterized by larger visual field defects, moderate to large RAPD, and poor visual outcome. The disease frequently appears on both eyes. It occurs in younger patients (mean age of 28 years) and has no sex bias. Poor therapeutic response and recurrence (two or more attacks) lead to progressive and permanent visual disability. The cause of this disorder has not been identified. Although laboratory testing has revealed no systemic disease in these patients, some researchers suspect an autoimmune disorder involving the optic disc vasculature. Corticosteroid therapy solves optic disc edema, but without visual improvement. Nonetheless, corticosteroids are usually included in treatments for initial attack, and chronic low corticosteroid doses or other modalities of immunosuppressive therapy are needed for the prevention of new attacks [20, 21].

3.3 Infectious and vaccine-associated optic neuritis

Atypical optic neuropathy may be associated with a wide variety of infectious agents. Causative factors can be specific viral, bacterial, parasitic, and fungal diseases. Optic neuropathy may present as papillitis, retrobulbar ON, neuroretinitis, perineuritis, and anterior ischemic optic neuropathy (AION). The disease can manifest as ON alone or show signs and symptoms of involvement of other parts of the nervous system. The mechanism of origin can be a direct pathogen invasion, initiation of an autoimmune demyelination process or vascular and coagulation disorders. Diagnosis is based on detailed history, serology, and additional analyses, which are frequently required (e.g., biopsy, lumbar puncture, polymerase chain reaction (PCR), protein immunoblotting, and X-ray and MRI images).

3.3.1 Viral neuritis

Herpes simplex viruses (HSV) cause a number of ophthalmic diseases. The optic nerve is typically affected within acute retinal necrosis (ARN), during, before or after retinitis, in the form of papillitis, and is responsible for more profound vision damages [22]. Viral neuritis can occur during herpetic encephalitis. Rarely, ON may appear in one eye, and other herpetic eye disease may be present in the other eye [23]. Diagnosis is based on HSV 1 and 2 positive serology, and therapy is based on antiviral agents.

Varicella zoster virus (VZV) can cause bilateral papillitis in varicella in children, before, during, or after the varicella onset. Visual outcomes are generally good. In zoster form, ON mostly presents late, weeks to months after skin rash, and therapy involves a combination of acyclovir and corticosteroids [24]. During active zoster, possible ischemic optic neuropathy and neuritis within ARN or progressive outer retinal necrosis (PORN) have been reported [25]. They are more frequent in immunocompromised patients.

Citomegalovirus (CMV) retinitis and papillitis are described primarily in patients with acquired immunodeficiency syndrome (AIDS) and in patients on

immunosuppressive therapy due to transplanted organs [26]. Several cases have been described in immunocompetent patients, who have shown good recovery after antiviral therapy [27, 28].

Epstein-Barr virus (EBV) causes infectious mononucleosis, but is also connected with several malignances. EBV-associated neuritis is generally bilateral and in the form of papillitis [29]. It responds well to corticosteroid therapy.

Human immunodeficiency virus (HIV) optic neuropathy may be unilateral or bilateral and may present as retrobulbar optic neuropathy, papillitis, ischemic optic neuropathy, or optic disc pallor [30].

Optic nerve inflammation in measles, rubella, influenza, and infections with West Nile virus, coronavirus and other viruses has been reported [14, 31].

3.3.2 Bacterial neuritis

Mycobaterium tuberculosis (MTB) may affect all ocular tissues [32, 33]. Ocular disease usually occurs without signs of active systemic disease. Hallmarks of tuberculosis infection include caseating granuloma. The clinical spectrum of tuberculous optic neuropathy is broad, including papillitis, neuroretinitis, optic nerve tubercles, compressive optic neuropathy, AION, optic atrophy, papillar edema in posterior scleritis and optic chiasmatic arachnoiditis. Associated posterior uveitis or panuveitis is frequent with inflammatory neuropathy. Multi-month antitubercular treatment leads to cure of disease and favorable visual outcome [34].

Syphilis is a sexually transmitted disease caused by *T. pallidum* spirochete. Its ophthalmic manifestations are numerous. Optic nerve involvement may present as papillitis, perineuritis, chiasmal syndrome, gumma of the optic disc, NR, and optic disc cupping. Optic neuropathy occurs in secondary and tertiary syphilis, and any ocular involvement is considered to indicate neurosyphilis. The disease is known as the "great mimicker," and these ambiguous manifestations are particularly clear in ophthalmology. Numerous tests for the presence of *T. pallidum* are available and not all equally secure [35]. Penicillin is an effective drug when used according to the regimen for neurosyphilis, and corticosteroids can ameliorate the disease.

B. burgdorferi is the causative agent of Lyme disease [36, 37]. Bacteria are transmitted to humans by tick bites, and the disease occurs in three stages. Different ophthalmic manifestations are possible, as with ON forms [36]. The central nervous system is frequently affected. Serology (ELISA) testing for Lyme disease should be followed by immunoblot analysis. The microorganism is sensitive to ceftriaxone or doxycycline treatment.

The most frequent causative agent of NR is *Bartonella henselae*. Cat scratch disease is transmitted by cat scratches or bites, and resultant systemic illness is mild and similar to influenza, with tender lymphadenitis. This stage can go unobserved. The disease may evolve toward Parinaud oculoglandular syndrome or hematogenous spread, when neuroretinal and retinal disease may develop. NR manifests several weeks after the contact with an animal and begins with unilateral optic neuropathy manifestation, which is clinically visible as papillitis. These symptoms are followed by retinitis, and a characteristic macular star composed of exudates develops on the posterior retinal pole 1–2 weeks later [38].

Mild anterior uveal reaction may occur. Diagnosis is based on clinical features and laboratory tests. Doxycycline is beneficial in more serious cases, and corticosteroids use is controversial. The disease typically has favorable outcome, and may even spontaneously resolve, but visual acuity recovery occurs gradually, over several weeks.

Leptospira, *Mycobacterium leprae*, *Tropheryma wippleii* (Wipple's disease), *Brucella*, and other bacteria can rarely cause ON, although they should still be considered as possible causes.

3.3.3 Parasitic and fungal infections

Toxoplasma gondii is a ubiquitous protozoan with feline hosts. The microorganism is transferred to the fetus and characteristic scars are observed later, during childhood. Ocular toxoplasmosis usually involves choroidea and retina from adjacent old retinal scar or can develop as a new retinochoroiditis. Immunocompromised persons are particularly prone. The optic nerve is involved in the form of NR, isolated papillitis or associated with chorioretinitis [39].

Diagnosis is challenging, if characteristic scars are absent, and based on serological testing. Management is combination of antiprotozoal medications and corticosteroids.

Toxocariasis is a zoonosis caused by *Toxocara canis* and *Toxocara cati* nematodes. The typical ocular involvement is retinal granuloma. Several cases of optic neuropathy in the form of papillitis, retrobulbar ON, or NR have been reported [40]. Optic disc granuloma is a possible manifestation, usually with associated vitritis. As in ocular toxoplasmosis, diagnosis is established by serology and rarely by additional aqueous humor or vitreous analysis and Goldmann-Witmer coefficient calculation. Treatment is based on corticosteroids, whereas the role of antihelminitc medications remains controversial.

Mucormycosis is an opportunistic infection caused by fungi *Mucorales*. The fungus is widespread in nature, but infection is uncommon. It happens at immunocompromised hosts, including patients with uncontrolled diabetes mellitus. The disease has lethal potential. Rhino-orbital and rhino-orbito-cerebral mucormycosis includes optic nerve infarction and necrosis. Invasion of the blood vessel walls by the organisms leads to occlusion or thrombosis of the optic nerve sheath, blood vessels, or ophthalmic artery. Direct optic nerve infection by mucormycosis may also occur. The disease has become particularly relevant in the COVID-19 pandemic, in patients with diabetes and those receiving corticosteroid therapy [41]. Treatment involves aggressive surgical debridement of all involved tissues, sometimes including exenteration of involved orbits, with prolonged administration of amphotericin B.

Criptococcus neoformans and other fungi have the ability to cause damage to the optic nerve. Neuroophthalmic manifestations are described within other parasitic infections, as well [31].

3.4 Postvaccination neuritis

Postvaccination optic nerve inflammation is rare, but well known. Besides ON, postvaccination inflammations can be ADEM, transverse myelitis, NMOSD in patients with AQP4 and MOG antibodies, and MS, either as a new disease or relapses of previously diagnosed MS. They occur mostly after influenza and human papillomavirus (HPV) vaccination, but also after immunization against other viruses and some bacteria [42, 43]. Suggested mechanisms include molecular mimicry between myelin basic protein and viral proteins, epitope spreading, bystander activation, and superantigen activation.

Since 2019, COVID-19 has been a dominant viral disease, reaching pandemic proportions. Beyond neuro-ophthalmological manifestations of the disease, with the

development and widespread use of vaccines in disease prevention, postvaccination complications have been reported [44]. Postvaccination neuritis usually has a mild course, appears in a period from 1 day to 1 month after vaccination, and may recover spontaneously or with pulse corticosteroid therapy, which accelerates visual recovery.

3.5 Autoimmune diseases

Optic neuropathy can occur in a numerous systemic autoimmune diseases and is often unrelated to lesions in other parts of the nervous system. Its etiology and pathogenesis are not fully understood, and most explanations are based on pathogenic mechanisms of the underlying disease. Sometimes defined as autoimmune optic neuropathy [45], it has diverse emerging forms, which are not specific to certain diseases.

3.5.1 Granulomatosis with polyangiitis or Wegener's granulomatosis

Granulomatosis with polyangiitis (GPA) or Wegener's granulomatosis (WG) is a multisystem autoimmune disease. It affects small and medium-sized blood vessels. The upper respiratory tract and kidneys are the most frequently affected. It can occur at any age, but usually appears in people in their 40s and 50s, and it has no sex bias. Inflammatory indicators, such as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), might be elevated. Diagnosis involves imaging and tests, but a tissue biopsy of the upper respiratory tract or kidney is essential for definitive diagnosis. Positive serology findings for cytoplasmic anti-neutrophil antibodies (C-ANCA or anti-Proteinase3 PR3-ANCA) are highly diagnostic for WG, whereas perinuclear ANCA (P-ANCA, against myeloperoxidase) may exist.

Ocular disease may be the presenting or dominant manifestation in patients with GPA, and it can affect almost all parts of the eyeball, adnexa, and orbit. Thus, the treating ophthalmologist should have a high index of suspicion, particularly in cases in which other features of the disease, such as pulmonary or renal disease, are absent [46].

The optic nerve may be affected in several ways. Optic neuritis, as papillitis or retrobulbar neuritis and perineuritis, ischemic optic neuropathy, and optic nerve compression by granuloma have been described, with or without signs of orbital involvement [46–49]. Optic nerve ischemia is a result of focal vasculitis of small arteries, arterioles and small veins, vascular thrombosis and hemorrhage, granulomatous inflammation, or may be a sequela of chronic inflammation.

Therapy is based on aggressive immunosuppression with high doses of corticosteroids and other immunosuppressants. Prolonged immunosuppression is required.

3.5.2 Systemic lupus erythematous

Systemic lupus erythematous (SLE) is a chronic autoimmune connective tissue multisystem disease. Characteristic manifestations exist on the skin of the face and mucous membranes. The kidneys, and frequently joints and the central nervous system, are affected. The median age of onset is between the late teens and early 40s, and a significantly higher incidence is observed in women than in men [50]. Major histocompatibility complex genes, such as HLA-A1, B8, and DR3, as well as alleles that cause deficiency in complement components C1q, C2, and C4 have been associated with lupus. Numerous autoantibodies are detected in SLE [51]. Specific serology

markers that might be helpful in suspected lupus optic neuropathy are antinuclear antibodies-ANAs, anti-double-stranded DNA (anti-ds DNA)-ANA antibody, anti-Sm, anti-nucleosome, anti-NMDA receptor, and anti-phospholipid antibodies [52].

Optic nerve disease is a rare manifestation of SLE and consists of ON, ischemic optic neuropathy, or NMOSD. However, ON can be the first manifestation of SLE [53, 54].

Optic nerve disease may manifest as a thrombotic, vaso-occlusive event with focal axonal necrosis, usually in one eye and may be associated with antiphospholipid antibodies, or as a general immunological inflammation, such as vasculitis and NMOSD. Poor presenting and final visual acuity and visual field defects are characteristic. The timing of the inflammation treatment is important and usually should occur within first t10 days, because optic neuritis responds well to high-dose corticosteroid treatment. Relapses are possible and require prolonged oral tapering or additional immunosuppressive agents [55].

3.5.3 Sarcoidosis

Sarcoidosis is a multisystem granulomatous disease. Diagnosis is based on chest X-ray, in which hilar lymphadenopathy is present in most cases and on angiotensin-converting enzyme (ACE) levels in the blood. Findings of hypercalcemia and calciuria and changes in the skin in the form of lupus pernio may be helpful. Definitive diagnosis is established by biopsy and a finding of noncaseating granuloma.

Sarcoid granuloma may develop on different parts of the eye and adnexa. Neurosarcoidosis develops in approximately 5–15% of cases, with neuroophthalmic manifestations in half of cases. Visual loss results from visual pathway or optic nerve involvement. Sarcoidosis of the optic nerve can produce a variety of optic disc appearances. The optic nerve is involved as a swollen optic disc with hemorrhages or as retrobulbar neuritis, NR, and optic nerve head granuloma [56, 57]. The optic neuropathy in sarcoidosis is typically painless or associated with mild pain and visual loss is subacute [58]. Involvement can be unilateral or bilateral. Similarly to other autoimmune diseases, optic atrophy, usually in one eye, may be a presenting finding.

Systemic corticosteroid therapy remains the most rapid and effective initial treatment. Corticosteroids must be tapered over months to years. Steroid-sparing agents should be considered.

3.5.4 Sjögren's syndrome

Sjögren's syndrome (SS) is a chronic autoimmune disease characterized by periductal lymphocytic infiltration of the secretory exocrine glands, particularly the salivary and lacrimal glands [59]. The disease can exists alone as primary SS or on a background of other autoimmune diseases as secondary SS.

Optic neuritis is not frequent, but may be the first symptom of the disease. The clinical course is acute or chronic one. Relapses are frequent on one or both eyes. NMOSD can be another manifestation of SS. In suspected cases of neuritis, signs and symptoms of keratoconjunctivitis sicca and screening of the blood anti-Ro/SSA, anti-La/SSB should be done, and in the context of NMOSD anti-aquaporin-4 (AQP4) antibody testing may be helpful. Biopsy of small salivary glands usually confirms the diagnosis [60]. Patients show minimal to moderate response to systemic corticosteroids or steroid dependence. Plasmapheresis in the acute phase and immunosuppressive agents for maintenance therapy are usually required.

3.5.5 Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disorder affecting the joints. It can occur with other autoimmune diseases [61]. Optic neuritis is rare in patients with RA and usually appears late in the disease course. Approximately one-quarter of patients with RA have vasculitis with involvement in all sizes of veins and arteries. Occlusion of one of the posterior ciliary arteries or its branches produces ischemic optic neuropathy. Milder optic neuropathy can be inflammatory and arise from vascular inflammation mechanisms and demyelination. Those patients respond well to pulse corticosteroid therapy. More severe and irreversible cases of optic neuropathy suffer axonal necrosis [62].

Optic perineuritis within RA, such as in other autoimmune diseases, has also been reported [49].

3.5.6 Behçet disease

Behçet disease (BD) is a rare disorder with blood vessel inflammation in different parts of the body. The eyes are frequently involved. BD can have various manifestations on optic nerve. It can occur alone, or with other CNS involvement, or can be secondary due to other ocular involvement such as uveitis, dural sinus thrombosis with papilledema or obliterative retinal vasculopathy. Sometimes ON can be the first sign of the disease. Neuritis is unilateral or bilateral and can be recurrent. The prognosis of ON related to BD seems to be favorable, particularly if is the first presenting manifestation. Therefore, physician should look for characteristic burdens and changes in the disease (mucus membranes and skin efflorescence, joint pain, and other changes) and immunological analyzes that can lead to a diagnosis. Immunosuppressants should be given along with corticosteroids [63].

3.5.7 Autoimmune-related retinopathy and optic neuropathy

Autoimmune-related retinopathy and optic neuropathy (ARRON) is a rare, autoimmune disorder characterized by painless, progressive, typically bilateral, vision loss and clinical signs of both retinopathy and optic neuropathy. It is found primarily in women and usually appears in their 50s. Detection of antibodies against recoverin protein, which is found in the photoreceptors, as well as against α-enolase, Muller cells, glutamic acid decarboxylase (GAD) in serum, has been reported in cases of presumed ARRON [64, 65].

ERG abnormalities may be seen on full field and multifocal ERG, thus confirming retinopathy. However, the ERG features are not specific for ARRON. OCT shows thinning of the macular retina and photoreceptor cells [66].

ARRON is diagnosed through exclusion, where autoimmune diseases and cancer- and melanoma-associated retinopathy (CAR and MAR) should be ruled out. In cases with dominant optic nerve findings, MRI should be performed. Sometimes are other autoimmune diseases present in patient. Therapy involves corticosteroids and other immunomodulatory agents. The prognosis is moderate improvement of visual functions or gradual worsening over months and years.

3.6 Chronic relapsing inflammatory neuropathy

Chronic relapsing inflammatory neuropathy (CRION) manifestations and its biological markers mostly correspond to NMOSD MOG-IgG positive antibodies ON.

The association between these entities has not been fully evaluated. Both are rare and methodology of MOG-IgG assays is not completely solved. Both are described as isolated disease or in postinfectious and postvaccine course and within systemic autoimmune diseases [13, 67]. CRION is the most often manifestation of the relapsing ON associated with MOG-IgG [17, 68] Patients with relapsing ON who show steroid dependency in the absence of the AQP4-Ab need to be tested for MOG-IgG. Among patients with MOG-IgG-associated ON, the absence of steroid dependency in the early stages of the disease may be a predictor for a favorable outcome. A relapsing course requires prolonged oral corticosteroid therapy or administration of other immunomodulatory drugs. Except optic nerve inflammation, most of them show no MRI lesions or show only nonspecific white matter abnormalities. Relapsing neuropathy results in functional failures and leads to atrophy and morphological changes best shown on OCT.

4. Conclusion

Atypical ON is an optic neuropathy appearing in multiple diseases or in isolated forms. Their clinical features are largely different from those of typical ones. Most are not common and therefore are rarely considered. Moreover, most have been reported as single cases or case series reports. Our goal was to briefly describe the most frequently encountered atypical ON and their characteristics.

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References

[1] Behbehani R. Clinical approach to optic neuropathies. Clinical Ophthalmology. 2007;**1**(3):233-246

[2] Zoric L, Stojicevic S, Bukumiric Z. Differential diagnosis of optic neuritis. Sanamed. 2013;**82**(2):131-135

[3] Siger M, Owidzka M, Świderek-Matysiak M, Omulecki W, Stasiołek M. Optical coherence tomography in the differential diagnosis of patients with multiple sclerosis and patients with MRI nonspecific white matter lesions. Sensors (Basel). 2021;**21**(21):7127. DOI: 10.3390/s21217127

[4] Kale N. Optic neuritis as an early sign of multiple sclerosis. Eye Brain. 2016;**8**:195-202. DOI: 10.2147/EB.S54131

[5] Abel A, McClelland C, Lee MS. Critical review: Typical and atypical optic neuritis. Survey of Ophthalmology. 2019;**64**(6):770-779

[6] Voss E, Raab P, Trebst C, Stangel M. Clinical approach to optic neuritis: Pitfalls, red flags and differential diagnosis. Therapeutic Advances in Neurological Disorders. 2011;**4**(2):123-134

[7] Bennett JL, de Seze J, Lana-Peixoto M, Palace J, Waldman A, Schippling S, et al. Neuromyelitis optica and multiple sclerosis: Seeing differences through optical coherence tomography. Multiple Sclerosis. 2015;**21**(6):678-688. DOI: 10.1177/1352458514567216. Epub 2015 Feb 6

[8] Pandit L, Asgari N, Apiwattanakul M, Palace J, Paul F, Leite MI, et al. Demographic and clinical features of neuromyelitis optica: A review. Multiple Sclerosis. 2015;**21**:845-853. DOI: 10.1177/1352458515572406

[9] Volpe NJ. The optic neuritis treatment trial: A definitive answer and profound impact with unexpected results. Archives of Ophthalmology. 2008;**126**(7):996-999. DOI: 10.1001/archopht.126.7.996

[10] Chan KH, Lee CY. Treatment of Neuromyelitis Optica Spectrum disorders. International Journal of Molecular Sciences. 2021;**22**(16):8638. DOI: 10.3390/ijms22168638

[11] Herrero-Morant A, Álvarez-Reguera C, Martín-Varillas JL, Calvo-Río V, Casado A, Prieto-Peña D, et al. Biologic therapy in refractory non-multiple sclerosis optic neuritis isolated or associated to immune-mediated inflammatory diseases. A multicenter study. Journal of Clinical Medicine. 2020;**9**(8):2608. DOI: 10.3390/jcm9082608

[12] Jarius S, Paul F, Aktas O, Asgari N, Dale RC, de Seze J, et al. MOG encephalomyelitis: International recommendations on diagnosis and antibody testing. Journal of Neuroinflammation. 2018;**15**(1):134. DOI: 10.1186/s12974-018-1144-2

[13] Petzold A, Plant GT. Chronic relapsing inflammatory optic neuropathy: A systematic review of 122 cases reported. Journal of Neurology. 2014;**261**:17-26

[14] Žorić L, Rajović Mrkić I, Čolak E, Mirić D, Kisić B. Optic neuritis in a patient with seropositive myelin oligodendrocyte glycoprotein antibody during the post-COVID-19 period. International Medical Case Reports Journal. 2021;**14**:349-355

[15] Salama S, Khan M, Shanechi A, Levy M, Izbudak I. MRI differences between MOG antibody disease

and AQP4 NMOSD. Multiple Sclerosis. 2020;**26**(14):1854-1865. DOI: 10.1177/1352458519893093. Epub 2020 Jan 15

[16] Sato DK, Callegaro D, Lana-Peixoto MA, Waters PJ, de Haidar Jorge FM, Takahashi T, et al. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology. 2014;**82**(6):474-481. DOI: 10.1212/WNL.0000000000000101. Epub 2014 Jan 10

[17] Lee H, Kim B, Waters P, Woodhall M, Irani S, Ahn S, et al. Chronic relapsing inflammatory optic neuropathy (CRION): A manifestation of myelin oligodendrocyte glycoprotein antibodies. Journal of Neuroinflammation. 2018;**15**:302. DOI: 10.1186/s12974-018-1335-x

[18] Hyun J-W, Woodhall MR, Kim S-H, Jeong IH, Kong B, Kim G, et al. Longitudinal analysis of myelin oligodendrocyte glycoprotein antibodies in CNS inflammatory diseases. Journal of Neurology, Neurosurgery, and Psychiatry. 2017;**88**:811-817. DOI: 10.1136/jnnp-2017-315998

[19] Borisow N, Mori M, Kuwabara S, Scheel M, Paul F. Diagnosis and treatment of NMO Spectrum disorder and MOG-encephalomyelitis. Frontiers in Neurology. 2018;**9**:888. DOI: 10.3389/fneur.2018.00888

[20] Viturino MGM, Moura FC. Recurrent idiopathic neuroretinitis as a spectrum of atypical optic neuritis: A case report and literature review. Arquivos Brasileiros de Oftalmologia. 2018;**81**(1):70-72. DOI: 10.5935/0004-2749.20180016. PMID: 29538599

[21] Purvin V, Ranson N, Kawasaki A. Idiopathic reccurent neuritis. Effects of long-term immunosuppression. Archives of Ophthalmology. 2003;**121**(1):65-67

[22] Lau CH, Missotten T, Salzmann J, Lightman SL. Acute retinal necrosis features, management, and outcomes. Ophthalmology. 2007;**114**(4):756-762

[23] Kaur K, Gurnani B, Devy N. Atypical optic neuritis—A case with a new surprise every visit. GMS Ophthalmol Cases. 2020;**10**:Doc11. DOI: 10.3205/oc000138

[24] de Mello VB, Foureaux EC, Porto FB. Herpes zoster optic neuritis. International Ophthalmology. 2011;**31**(3):233-236

[25] Nakamoto BK, Dorotheo EU, Biousse V, Tang RA, Schiffman JS, Newman NJ. Progressive outer retinal necrosis presenting with isolated optic neuropathy. Neurology. 2004;**63**(12):2423-2435

[26] Cackett P, Weir CR, McFadzean R, Seaton RA. Optic neuropathy without retinopathy in AIDS and cytomegalovirus infection. Journal of Neuro-Ophthalmology. 2004;**24**(1):94-95

[27] De Silva SR, Chohan G, Jones D, Hu M. Cytomegalovirus papillitis in an immunocompetent patient. Journal of Neuro-Ophthalmology. 2008;**28**(2):126-127

[28] Chang PY, Hamam R, Giuliari GP, Foster CS. Cytomegalovirus panuveitis associated with papillitis in an immunocompetent patient. Canadian Journal of Ophthalmology. 2012;**47**(4):e12-e13

[29] Santos-Bueso E, Sáenz-Francés F, Méndez-Hernández C, Garcia-Sanshezet Z. Papillitis due to Epstein-Barr virus infection in an adult patient.

Archivos de la Sociedad Española de Oftalmología. 2014;**89**(6):245-249

[30] Kahloun BK, Murthy KR, Rajagopalan N, Satish B. Vision recovery in human immunodeficiency virus-infected patients with optic neuropathy treated with highly active antiretroviral therapy: A case series. Indian Journal of Ophthalmology. 2009;**57**(4):315-318

[31] Kahloun R, Abroug N, Ksiaa I, Mahmoud A, Zeghidi H, Zaouali S, et al. Infectious optic neuropathies: A clinical update. Eye Brain. 2015;**7**:59-81. DOI: 10.2147/EB.S69173

[32] Albert DM, Raven ML. Ocular Tuberculosis. Microbiology Spectrum. 2016;**4**(6). DOI: 10.1128/microbiolspec.TNMI7-0001-2016. PMID: 27837746; PMCID: PMC5180603

[33] Zoric LD, Zoric DL, Zoric DM. Bilateral tuberculous abscesses on the face (eyelids) of a child. American Journal of Ophthalmology. 1996;**121**:717-718

[34] Gupta V, Gupta A, Rao NA. Intraocular tuberculosis—An update. Survey of Ophthalmology. 2007;**52**(6):561-587

[35] Gaudio PA. Update on ocular syphilis. Current Opinion in Ophthalmology. 2006;**17**(6):562-566

[36] Stanek G, Wormser GP, Gray J, Strle F. Lyme borreliosis. Lancet. 2012;**379**(9814):461-473

[37] Mikkila HO, SeppaHi II, Viljanen MK, Peltomaa MP, Karma A. The expanding clinical spectrum of ocular Lyme borreliosis. Ophthalmology. 2000;**107**(3):581-587

[38] Wade NK, Levi L, Jones MR, Bhisitkul R, Fine L, Cunningham ET Jr. Optic disk edema associated with peripapillary serous retinal detachment: An early sign of systemic Bartonella henselae infection. American Journal of Ophthalmology. 2000;**130**(3):327-334

[39] Vasconcelos-Santos DV. Ocular manifestations of systemic disease: Toxoplasmosis. Current Opinion in Ophthalmology. 2012;**23**(6):543-550

[40] Stewart JM, Cubillan LD, Cunningham ET Jr. Prevalence, clinical features, and causes of vision loss among patients with ocular toxocariasis. Retina (Philadelphia, Pa.). 2005;**25**(8):1005-1013. DOI: 10.1097/00006982-200512000-00009

[41] Singh AK, Sigh R, Joshi S, Misra A. Mucormycosis in COVID-19: A systematic review of cases reported worldwide and in India. Diabetes and Metabolic Syndrome Clinical Research and Reviews; **15**(4). DOI: 10.1016/j.dsx.2021.05.019

[42] Huynh W, Cordato DJ, Kehdi E, Masters LT, Dedousis C. Post-vaccination encephalomyelitis: Literature review and illustrative case. Journal of Clinical Neuroscience. 2008;**15**(12):1315-1322. DOI: 10.1016/j.jocn.2008.05.002. Epub 2008 Oct 30

[43] Kumar N, Graven K, Joseph NI, Johnson J, Fulton S, Hostoffer R, et al. *Case report:* Postvaccination anti-myelin oligodendrocyte glycoprotein Neuromyelitis Optica Spectrum disorder: A case report and literature review of postvaccination demyelination. International Journal of MS Care. 2020;**22**(2):85-90. DOI: 10.7224/1537-2073.2018-104

[44] García-Estrada C, Gómez-Figueroa E, Alban L, Arias-Cárdenas A. Optic neuritis after COVID-19 vaccine

application. Clinical & Experimental Neuroimmunology. 2022;**13**(2):72-74. DOI: 10.1111/cen3.12682. Epub 2021 Nov 22

[45] Goodwin J. Autoimmune optic neuropathy. Current Neurology and Neuroscience Reports. 2006;**6**:396-402. DOI: 10.1007/s11910-996-0020-0

[46] Sfiniadaki E, Tsiara I, Theodossiadis P, Chatziralli I. Ocular manifestations of granulomatosis with Polyangiitis: A review of the literature. Ophthalmology and Therapy. 2019;**8**(2):227-234. DOI: 10.1007/s40123-019-0176-8. Epub 2019 Mar 15

[47] Clément M, Néel A, Toulgoat F, Weber M, Godmer P, Hutin P, et al. Inflammatory optic neuropathy in granulomatosis with polyangiitis can mimick isolated idiopathic optic neuritis. European Journal of Ophthalmology. 2021;**31**(1):245-251. DOI: 10.1177/1120672119889008. Epub 2019 Nov 19

[48] Monteiro ML, Borges WI, do Val Ferreira Ramos C, Lucato LT, Leite CC. Bilateral optic neuritis in Wegener granulomatosis. Journal of Neuro-Ophthalmology. 2005;**25**(1):25-28. DOI: 10.1097/00041327-200503000-00007

[49] Li H, Zhou H, Sun J, Wang H, Wang Y, Wang Z, et al. Optic Perineuritis and its association with autoimmune diseases. Frontiers in Neurology. 2021;**11**:627077. DOI: 10.3389/fneur.2020.627077

[50] Palejwala NV, Walia HS, Yeh S. Ocular manifestations of systemic lupus erythematosus: A review of the literature. Autoimmune Diseases. 2012;**2012**:290898. DOI: 10.1155/2012/290898

[51] Yaniv G, Twig G, Shor DB, Furer A, Sherer Y, Mozes O, et al. A volcanic explosion of autoantibodies in systemic lupus erythematosus: A diversity of 180 different antibodies found in SLE patients. Autoimmunity Reviews. 2015;**14**(1):75-79. DOI: 10.1016/j.autrev.2014.10.003

[52] Dema B, Charles N. Autoantibodies in SLE: Specificities, isotypes and receptors. Antibodies (Basel). 2016;**5**(1):2. DOI: 10.3390/antib5010002

[53] Sivaraj RR, Durrani OM, Denniston AK, Murray PI, Gordon C. Ocular manifestations of systemic lupus erythematosus. Rheumatology. 2007;**46**(12):1757-1762. DOI: 10.1093/rheumatology/kem173

[54] Zahid S, Iqbal M. Systemic lupus erythematosus presenting as optic neuropathy: A case report. Cureus. 2019;**11**(6):e4806. DOI: 10.7759/cureus.4806

[55] Lin YC, Wang GA, Yen MY. Systemic lupus erythematosus-associated optic neuritis: Clinical experience and literature review. Acta Ophthalmologica. 2009;**87**(2):204-210

[56] Baughman RP, Weiss KL, Golnik KC. Neuro-ophthalmic sarcoidosis. Eye Brain. 2012;**4**:13-25. DOI: 10.2147/EB.S29401

[57] Malik A, Ahmed M, Golnik K. Treatment options for atypical optic neuritis. Indian Journal of Ophthalmology. 2014;**62**:982-984

[58] Sharma S, Leite MI. Typical and atypical optic neuritis—Diagnosis and initial management. Eye News. 2016;**23**(1)

[59] Tang WQ, Wei SH. Primary Sjögren's syndrome related optic neuritis.

International Journal of Ophthalmology. 2013;**6**(6):888-891. DOI: 10.3980/j.issn.2222-3959.2013.06.26

[60] Bak E, Yang HK, Hwang JM. Optic neuropathy associated with primary Sjögren's syndrome: A case series. Optometry and Vision Science. 2017;**94**(4):519-526. DOI: 10.1097/OPX.0000000000001054

[61] Simon TA, Kawabata H, Ray N, Baheti A, Suissa S, Esdaile JM. Prevalence of Co-existing autoimmune disease in rheumatoid arthritis: A cross-sectional study. Advances in Therapy. 2017;**34**(11):2481-2490. DOI: 10.1007/s12325-017-0627-3. Epub 2017 Oct 24

[62] Chen Y-H, Wang A-G, Lin Y-C, Yen M-Y. Optic neuritis as the first manifestation of rheumatoid arthritis. Journal of Neuro-Ophthalmology. 2008;**28**(3):237-238. DOI: 10.1097/WNO.0b013e318183ca13

[63] Akdal G, Ertaşoğlu Toydemir H, Saatci AO, Uygunoğlu U, Altunrende B, Saip S, et al. Characteristics of optic neuropathy in Behçet disease. Neurology Neuroimmunology & Neuroinflammation. 2018;**5**(5):e490. DOI: 10.1212/NXI.0000000000000490

[64] Adamus G, Brown L, Schiffman J, Iannaccone A. Diversity in autoimmunity against retinal, neuronal, and axonal antigens in acquired neuro-retinopathy. Journal of Ophthalmic Inflammation and Infection. 2011;**1**(3):111-121. DOI: 10.1007/s12348-011-0028-8. Epub 2011 Jul 10

[65] Rahimy E, Sarraf D. Paraneoplastic and non-paraneoplastic retinopathy and optic neuropathy: Evaluation and management. Survey of Ophthalmology. 2013;**58**(5):430-458. DOI: 10.1016/j.survophthal.2012.09.001

[66] Almarzouqi SJ, Morgan ML, Carvounis PE, Lee AG. Autoimmune-related retinopathy and optic neuropathy accompanied by anti-GAD antibodies. Neuroophthalmology. 2015;**39**(4):195-200. DOI: 10.3109/01658107.2015.1050744

[67] Tyndel F, Sundaram A, Bebedjian R, Bookman I, Bookman A, Levin LA. Crohn-related chronic relapsing inflammatory optic neuropathy. The Canadian Journal of Neurological Sciences. 2021;**48**(5):740-741. DOI: 10.1017/cjn.2020.270. Epub 2020 Dec 14

[68] Riedel P, Wall M, Grey A, Cannon T, Folberg R, Thompson HS. Autoimmune Optic Neuropathy. Archives of Ophthalmology. 1998;**116**(8):1121-1124