Literature Review

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Optic Neuritis or Inflammatory Optic Neuropathy

N. M. Moyseyenko

Ivano-Frankivsk National Medical University;
Ivano-Frankivsk (Ukraine)

According to the literature, there are two equivalent terms "optic neuritis" and "inflammatory optic neuropathy". Classification, pathogenesis and clinical manifestations are ambiguous. However, the growing interest in the problems of demyelinating and infectious diseases contributes to detailing the data on the mechanisms of certain forms of optic nerve inflammation.

Purpose. *To study the current views on the pathogenesis of optic nerve inflammation.*

Methods. *The literature search in Ukrainian and foreign scientific sources was performed. Modern diagnostic methods such as optical coherence tomography (OCT), magnetic resonance imaging (MRI), immunological and virological tests allow studying i) the role of factors, individual and in combinations, in the development of neuritis, ii) the changes in visual functions, iii) damage to individual structural elements of the visual system, and iv) recovery from the damage received.*

Conclusion. *The analysis of literature data on optic neuritis and/or inflammatory optic neuropathy showed a high topical interest of the scientific community. Further studies are likely to improve the current classifications of optic nerve inflammation and develop a differentiated approach to the treatment of optic nerve inflammation.*

Keywords:

optic neuritis, inflammatory optic neuropathy, OCT, MRI, demyelinating diseases

Optic neuritis [1] and inflammatory optic neuropathy [2] are two terms which can be found in the literature and which explain a large group of inflammations of the optic nerve. The discussion on the correct use of the terms and the understanding of the nature of damage requires more detailed research and literature search.

Purpose. To study the current views on the pathogenesis of optic nerve inflammation.

Methods. The literature search in Ukrainian and foreign scientific sources (32 sources).

The classification of neuritis, theories of pathogenesis and approaches to their treatment in Ukrainian ophthalmology and in the world societies of neuro-ophthalmology (NANOS and EUNOS) are different. In Ukraine, the most commonly used classification is based on localization (papillitis and retrobulbar neuritis) [3], while abroad they prefer the classification based on pathogenesis (typical and atypical neuritis).

Until recently, up to 2016, the difference between typical neuritis, which is considered a consequence of demyelinating diseases, and atypical neuritis, which has a different nature, was clearer (Table 1). [4].

On the other hand [5], the diversity of manifestations of atypical forms, in which both papillitis and retrobulbar neuritis variants are possible (Fig. 1), shows, in our opinion, the imperfection of the Ukrainian neuritis classification system.

Now, a more thorough study of multiple sclerosis and its early manifestations has shown the heterogeneity in the group of demyelinating diseases. The occurring optic neuritis also has a different course (recurrent or monophasic), different visual functional outcomes (with full recovery or with the development of atrophy) and different treatment approaches (use of corticosteroids, monoclonal antibodies or plasmapheresis).

An important cause of optic neuritis is a type of demyelinating disease, neuromyelitis optica (NMO) or Devic disease [6], which is characterized by unilateral neuritis, brainstem, cerebral and diencephalic syndromes. [7]. NMO is often associated with positive tests for antibodies to oligodendrocyte glycoprotein (MOG) and/or aquaporin-4 (AQP4-IgG) [8].

Due to modern research, the difference between typical and atypical neuritis (Table 2) is less pronounced, but this interpretation becomes the key to successful treatment, since it prevents the transformation of multiple sclerosis into more aggressive forms. [9].

Pathogenesis of nervous tissue inflammation or inflammatory neuropathy development

Systemic activation of T cells is observed at the onset of symptoms and precedes changes in the cerebrospinal fluid, which is considered the basis of demyelinating processes. [10]. In typical optic neuritis, there is also activation of B

cells against the myelin basic protein in the cerebrospinal fluid. [11].

MOG-specific and AQP4-specific antibodies (Ab) target two different populations of resident cells of the central nervous system (CNS), oligodendrocytes (Olig.) or astrocytes (A), respectively. The data indicate that antibodies are produced outside of the CNS in both MOG Ig1 AQP4-seronegative opticospinal inflammatory disease (Fig. 2, A) and AQP4-seropositive neuromyelitis optica spectrum disorder (NMOSD) (Fig. 2 B). AQP4-specific antibodies interact with antigen-specific follicular T helper (Tfh) cells when B cells differentiate into plasma cells. [12].

Serum antibodies to MOG or AQP4 separately are not considered pathogenic in the absence of a cell-mediated inflammatory response. MOG-specific T effector cells (Teff) (which are detected in experimental autoimmune encephalitis (EAE), in multiple sclerosis (MS) [13]) or AQP4-specific Teff cells can initiate CNS inflammation, which in AQP4-seropositive NMOSD is characterized by the accumulation of neutrophils (Neutro.) and eosinophils (Eosin.).

In both cases, inflammation can compromise the integrity of the blood-brain barrier, allowing the penetration of antibodies. MOG-specific antibodies are likely to bind MOG expressed on myelin-forming oligodendrocytes and the myelin layer surrounding axons which extend from the neuronal body (N) [14].

The pathogenesis of atypical, infectious forms of neuritis is much less studied. However, inflammation of the optic nerve against the background of activation of herpesvirus [15] and cytomegalovirus infection [16] is increasingly common.

Immunological and virological studies of cerebrospinal fluid become mandatory in the diagnosis of neuritis forms [17]. In particular, the detection of antibodies [18] and oligoclonal plates [19] is the current standard for the diagnosis of multiple sclerosis, as it is many years ahead of the appearance of MRI foci [20]. Virological tests of cerebrospinal fluid can diagnose rare neuritis [21, 22].

Hemodynamic disorders in neuritis are studied by determining the thickness of the peripapillary choroid using optical coherence tomography (OCT) and magnetic resonance imaging (MRI). It was found that edema observed in papillitis leads to cerebral hypoperfusion in multiple sclerosis and optic neuromyelitis [23].

Some MRI studies indicate a decrease in perfusion and ischemia. Ischemia itself is classified as primary, which is associated with inflammation, and secondary, which occurs as a result of hypoperfusion after axonal degeneration [24].

On the other hand, hypoperfusion potentiates mitochondrial energy deficiency and oxidative stress, which also leads to axonal degeneration [25].

Impaired blood circulation in the extraocular vessels in multiple sclerosis has also been described. It leads to an increase in the concentration of endothelin-1 in the blood, which activates astrocytes around the disc head in optic papillitis and impairs surrounding perfusion [26].

It is also believed that hypoperfusion of the choroid is positively correlated with the degree of edema of the nerve fiber layer and their compression due to edema of the anterior part of the optic nerve [27].

Under the influence of ischemia, erythropoietin is also activated, which, in turn, activates signaling cascades. These cascades increase brain resistance to ischemia-reperfusion stress by stabilizing mitochondrial membranes and, thus, limit the formation of active intermediate oxygen and nitrogen compounds. The production of pro-inflammatory cytokines and neutrophil infiltration is suppressed. Therefore, if vascular hypoperfusion is part of the pathophysiology of acute optic neuritis, then erythropoietin may provide neuroprotection [28].

OCT in inflammatory neuropathy. This question is raised in case of chronic inflammatory processes such as neuromyelitis optica or multiple sclerosis. It is reported that in recurrent neuritis there is an increase in the thickness of the nerve fiber layer and a decrease in the thickness of the ganglion cell layer [29].

In MOG-associated acute neuritis, the nerve fiber layer is thinner compared to that in acute neuritis with multiple sclerosis [30, 31].

In acute neuritis, there is also an increase in the thickness of the outer and inner nuclear layers of the retina. Although some authors also report a decrease in the thickness of the ganglion cell layer in acute neuritis [32].

It is observed that the thickness of the complex of ganglion cells and the inner reticular layer reaches its maximum 4 months after acute neuritis, and then decreases; however, it remains thickened for 12 months compared to the baseline [33].

Thus, according to the literature, there are two equivalent terms - "optic neuritis" and "inflammatory optic neuropathy". Classification, pathogenesis and clinical manifestations are ambiguous. However, the increased interest in the problems of demyelinating diseases contributes to detailing the data on the mechanisms of certain inflammatory forms of the optic nerve.

Modern diagnostic techniques, such as OCT, MRI, immunological and virological tests allow to study i) the role of individual factors, as well as their combination in the development of neuritis, ii) the changes in visual functions, iii) damage to individual structural elements of the visual system, and iv) recovery from the damage received.

To conclude, analysis of the literature data on optic neuritis and/or inflammatory optic neuropathy showed a high current interest of the scientific community. Further advanced research is likely to improve the current classifications of optic nerve inflammation and develop a differentiated approach to the treatment of optic nerve inflammation.

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Disclosures

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Table 1. Differential diagnosis of typical and atypical neuritis.

Symptom	Typical neuritis	Atypical neuritis
Clinical manifistation	Female	Male
	Unilateral	Bilateral
	Painful	Painless
	Average age 32 years	Under 18 or over 50 years old
	Normal optic disk (2/3) or moderate swelling of the optic disk (1/3)	Pronounced swelling of the optic disk, vitrite
	Improvement during 1 month	Progressive worsening up to 2 weeks
	Color vision disorders >	Visual acuity 0.1 and below
	Reduced vision > 0,1	
MRI signs	Contrast enhancement of the anterior part of the optic nerve	Extension to > 1/2 of the posterior optic nerve, junction or tract

Table 2. Differential diagnosis of typical and atypical neuritis according to recent data

Symptomes	Typical neuritis	Atypical neyritis *
Visual acuity	Over 0.1	Light sensation and worse
Pain	Up to days	No pain or over 14 days
Optic disc	⅔ normal, ⅓ moderate	Swelling = moderate + hemorrhages, cotton-wool spots
Age	18-35 years old	40 + years old
Race	Caucasian	Negroid, Mongoloid, South Indian
Sides	Uniliteral	Biliteral
Recurrent course	No	Yes
Steroid dependence	No	Yes
Recovery	Good	Minor
Progression	Up to 7 days	Over 10 days

Notes: * neuromyelitis optica, MOG- and AQP-4 positive, chronic recurrent neuritis

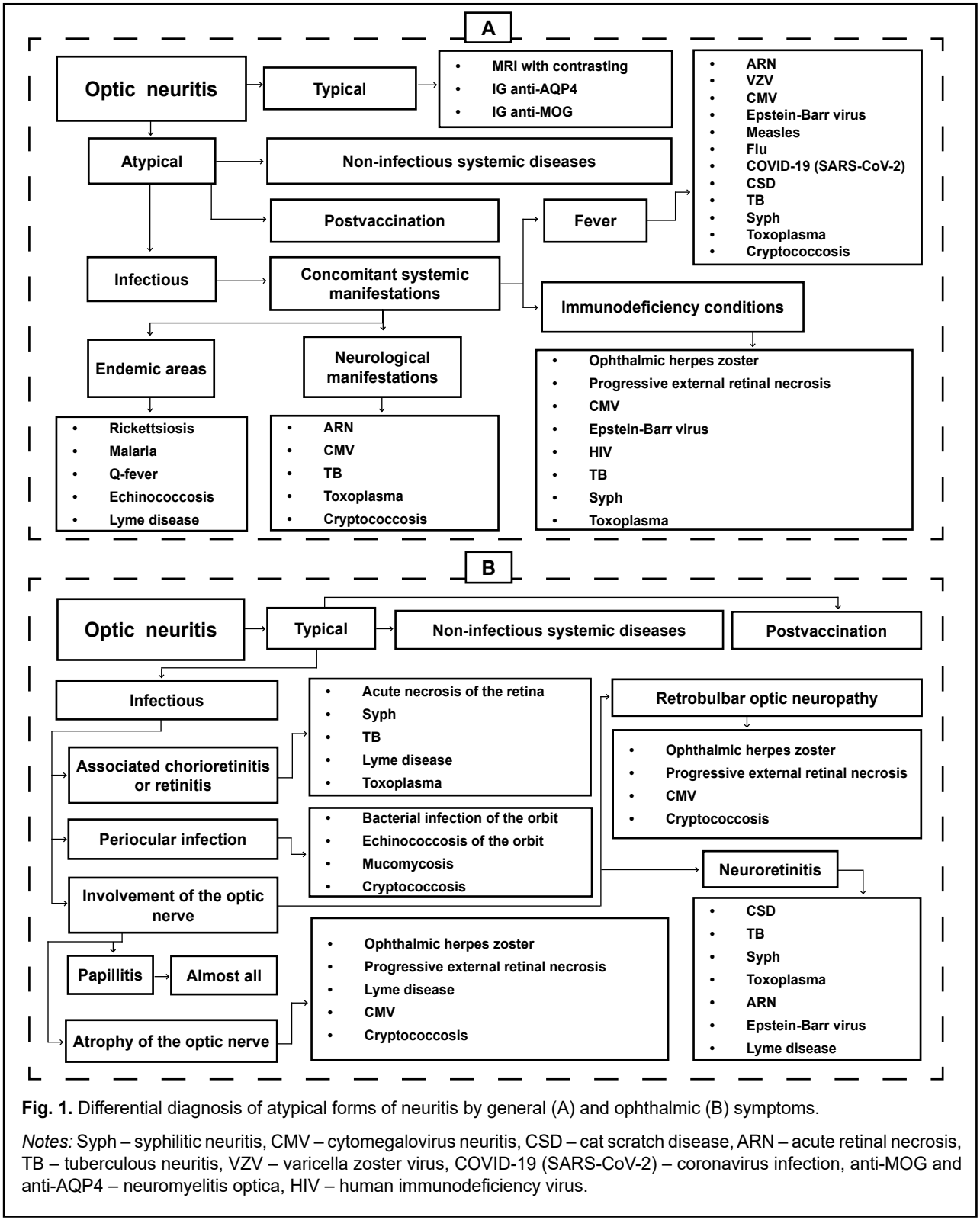

Fig. 1. Differential diagnosis of atypical forms of neuritis by general (A) and ophthalmic (B) symptoms.

Notes: Syph – syphilitic neuritis, CMV – cytomegalovirus neuritis, CSD – cat scratch disease, ARN – acute retinal necrosis, TB – tuberculous neuritis, VZV – varicella zoster virus, COVID-19 (SARS-CoV-2) – coronavirus infection, anti-MOG and anti-AQP4 – neuromyelitis optica, HIV – human immunodeficiency virus.

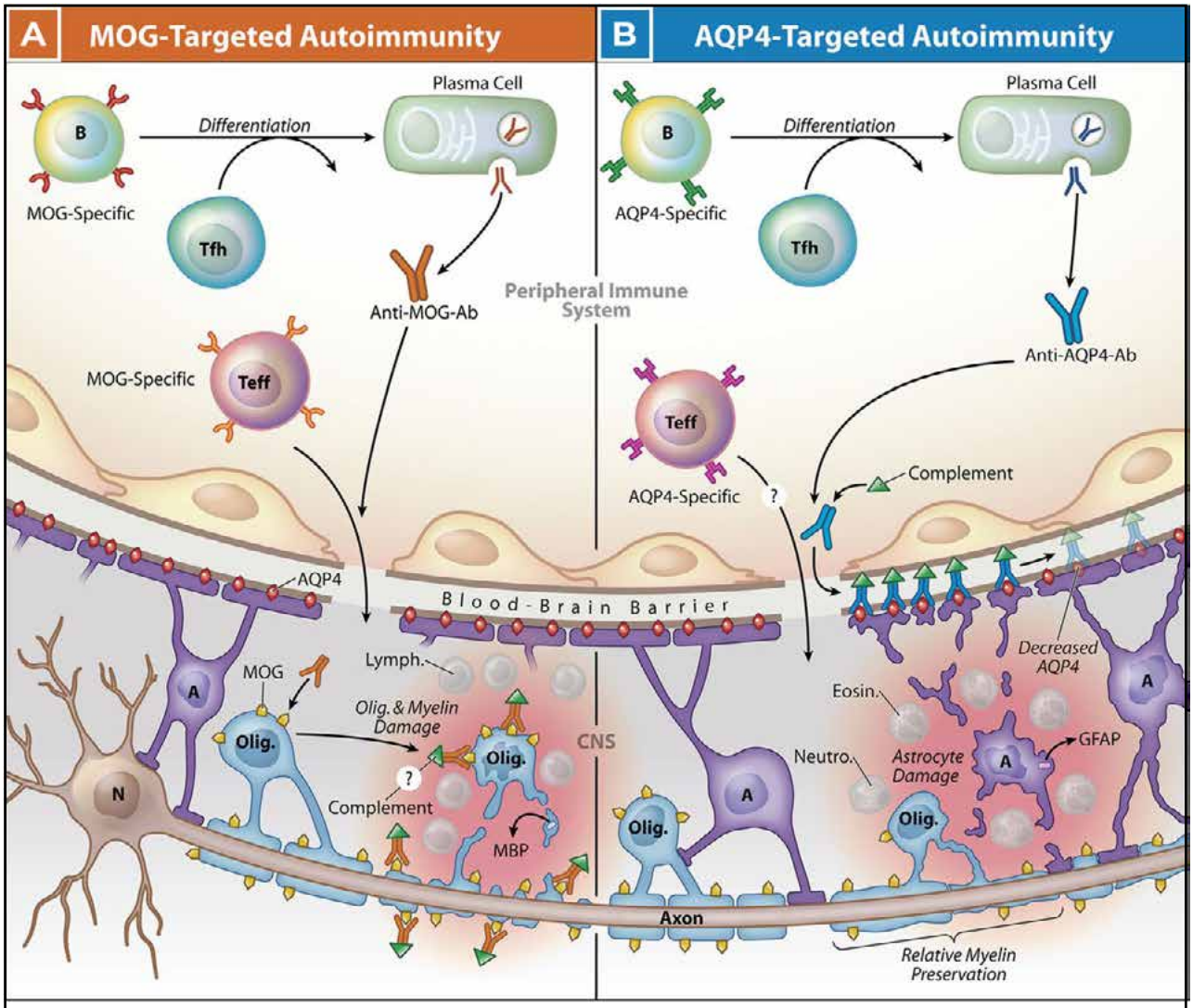

Fig. 2. Model of the potential role of antibodies to myelin oligodendrocyte glycoprotein and aquaporin-4 (AQP4) on the development of optic neuritis (Söderström M. et al., 1993 [11]).

Notes: MOG – myelin oligodendrocyte glycoprotein, AQP4 – aquaporin-4, B – B- lymphocytes, Tfh –MOG-Specific and AQP4-Specific T effector lymphocytes, Anti-MOG-Ab and Anti- AQP4-Ab antibodies against myelin oligodendrocyte glycoprotein and aquaporin-4, respectively, CNS – central nervous system, N – neuron, A – astrocyte, Olig. – oligodendrocyte, Lymph. – lymphocyte, Eosin. – eosinocyte, MBP – myelin basic protein, GFAP – glial fibrillary acidic protein, Olig.&Myelin Damage – damage to oligodendrocytes and myelin sheath, Astrocite. Damage – damage to astrocytes.