Neuromyelitis optica spektrumu hastalıkları ve AQP4-Ab pozitif/negatif hastalıkların klasifikasyonu ve patogenezi

Dr. Münife Neyal

SANKO Üniversitesi Tıp Fakültesi Nöroloji AbD

Uluslararası Türk Dünyası Multipl Skleroz Kongresi
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Aquaporin → su kanalları

- AQP4 → astrosit bacaklarında yerleşmiş su kanalları
  - Yutak, tükürük bezleri, mide, toplayıcı kanallar, kaslar vb farklı yapılarda da gösterilmiştir
- Anti- AQP4 antikorları serumda ↑↑↑ / BOS'ta (±) → AQP4- IgG ölçümleri serumda yapılır
- Serum AQP4-IgG düzeyleri ataklar sırasında klinikle korelasyon gösterir ama remisyonda aynı ilişki gösterilememiştir
- Tedaviyle serum düzeyleri düşebilir → kan tedavi başlamadan önce alınmalıdır
- Tekrarlayan ölçümlerde pozitifleşebilir (nedeni?)

Nöromyelitis optika (Devic hastalığı)

- Bilateral optik nöropati

- Uzun segment (>3) transvers myelit

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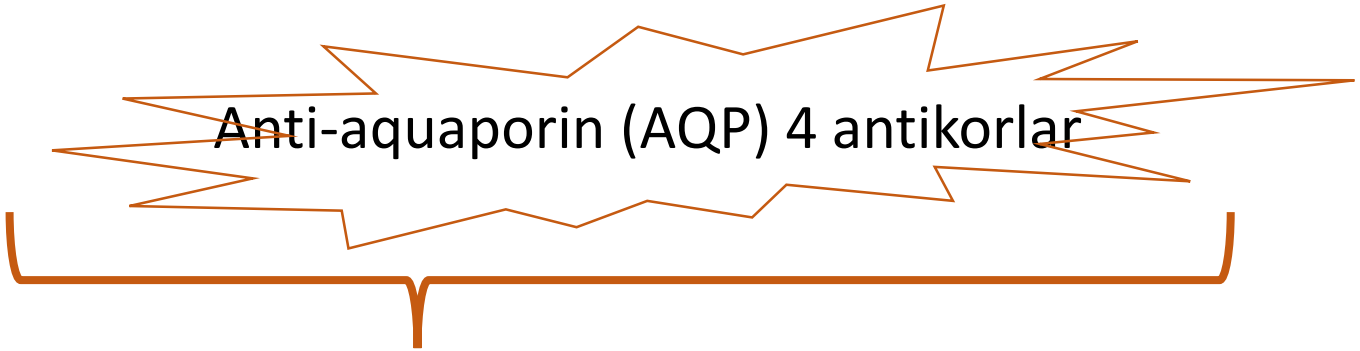

✓ NMO’nun MS’ten ayrılması

Nöromyelitis optika (Devic hastalığı)

- Bilateral optik nöropati
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Anti-aquaporin (AQP) 4 antikorlar

✓ NMO'nun MS'ten ayrılması

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- Bilateral optik nöropati
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Anti-aquaporin(AQP) 4 antikorlar

✓ NMO'nun MS'ten ayrılması

- Anti-AQP4 ab (+) ilişkili farklı klinik sendromlar → NMOSD

Anti-AQP4 ab (-) NMO hastaları (≅ %10-20)

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Anti-aquaporin(AQP) antikorlar

✓ NMO'nun MS'ten ayrılması

- Anti-AQP4 ab (+) ilişkili farklı klinik sendromlar → NMOSD

Anti-AQP4 ab (-) NMO hastaları

Anti-myelin oligodendrosit glikoprotein (MOG) antikor (+) hastalar

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Anti aquaporin (AQP) antikorlar

✓ NMO'nun MS'ten ayrılması

- Anti-AQP ab (+) ilişkili farklı klinik sendromlar → NMOSD

Anti-AQP ab (-) NMO hastaları

Anti-MOG antikor (+) hastalar

Anti- AQP4 (+) ve anti-MOG antikor (+) hastalar

Anti- AQP4 (-) ve anti-MOG antikor (-) hastalar

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Anti akuaporin (AQP) 4 antikorlar

✓ NMO'nun MS'ten ayrılması

- Anti-AQP4 ab (+) ilişkili farklı klinik sendromlar → NMOSD

Anti-AQP4 ab (-) NMO hastaları

Anti-MOG antikor (+) hastalar

Anti- AQP4 (+) ve anti-MOG antikor (+) hastalar

Anti- AQP4 (-) ve anti-MOG antikor (-) hastalar

± Diğer antikorlar (+)

NMOSD hasta popülasyonu →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

NMOSD hasta popülasyonu →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

- Anti-AQP4 ab (+)
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± Anti-MOG ab (+) NMOSD

- Anti-AQP4 ab (+)
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± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

NMOSD hasta popülasyonu (prevalans (?) → 0.3-4.4/100000) →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

NMOSD hasta popülasyonu →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

- Anti-AQP4 ab (+)
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± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

NMOSD hasta popülasyonu →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

Esas patojen Anti-AQP4 ab

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

Patogenez?

Patogenez

Journal of the Neurological Sciences 355 (2015) 7–17

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Review article

Epidemiological, clinical, and immunological characteristics of neuromyelitis optica: A review

Wildéa Lice de Carvalho Jennings Pereira [a,b], Edna Maria Vissoci Reiche [c,*], Ana Paula Kallaur [a], Damacio Ramón Kaimen-Maciel [b,d]

[a] Health Sciences Postgraduate Program, Health Sciences Center, State University of Londrina, Londrina, Paraná 86038-440, Brazil
[b] Outpatient Clinic for Demyelinating Diseases, University Hospital, State University of Londrina, Londrina, Paraná 86061-335, Brazil
[c] Department of Pathology, Clinical Analysis and Toxicology, Health Sciences Center, State University of Londrina, Londrina, Paraná 86038-440, Brazil
[d] Department of Clinical Medicine, Health Sciences Center, State University of Londrina, Londrina, Paraná 86038-440, Brazil

Epidemiological, clinical, and immunological characteristics of neuromyelitis optica: A review

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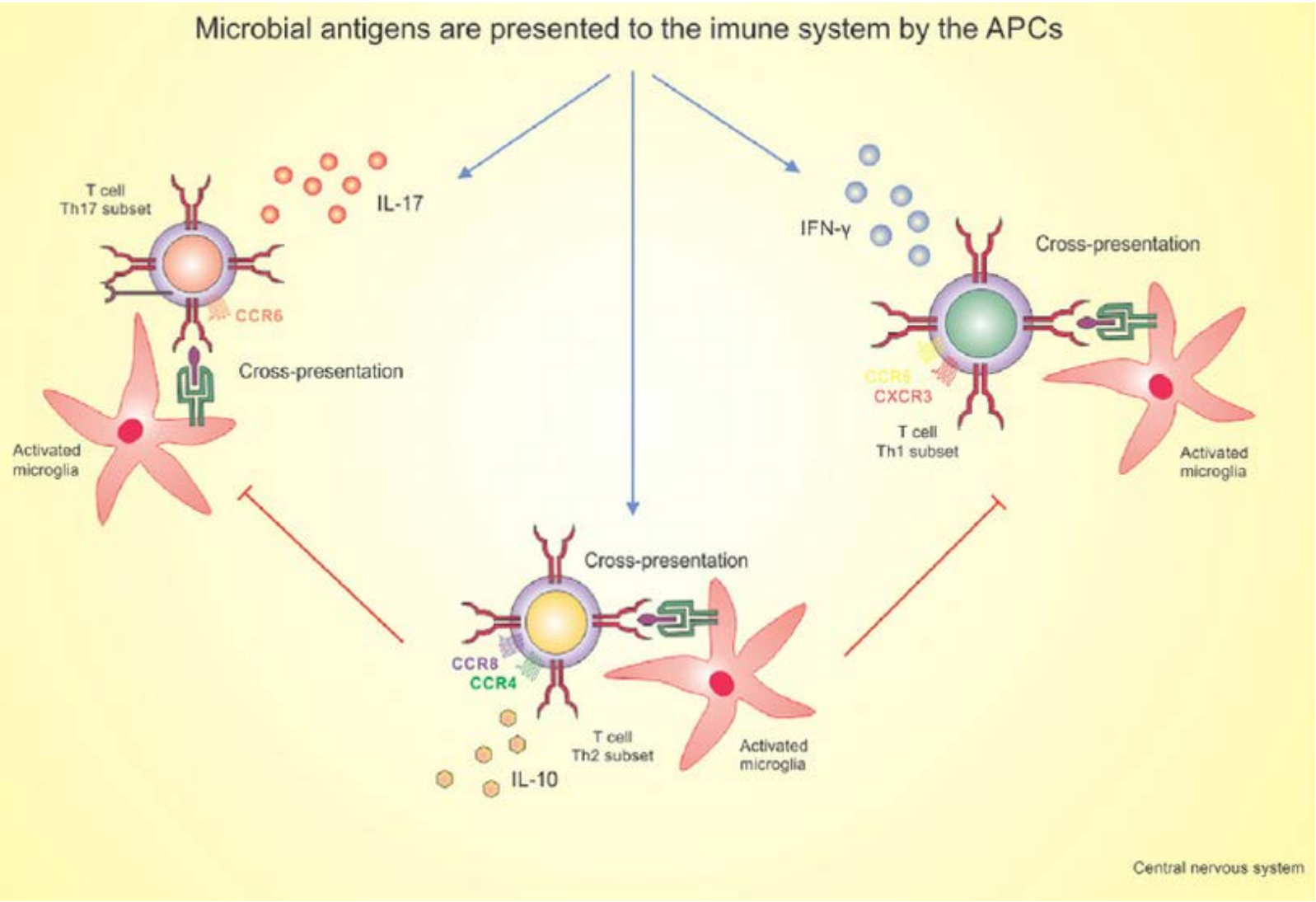

Neuromyelitis optica pathogenesis mechanisms mediated by in fl ammatory cytokines and chemokines. In the periphery, environmental factors, such as virus and bacteria, induce an innate immune response. The activated microglia presents antigens to the adaptive immune response with activation of T helper (Th) 1, Th2, and Th17 lymphocytes. The Th1 and Th17 cells secrete in fl ammatory cytokines, such as interferon gamma (IFN-γ) and IL-17, respectively, which activate other in fl ammatory cells and amplify the innate immune response. The Th2 cells secrete IL-10, an anti-in fl ammatory cytokine that modulates the Th1 cells. Moreover, these cells express different chemokine receptors that contribute to the recruitment of other in fl ammatory cells to the central nervous system.

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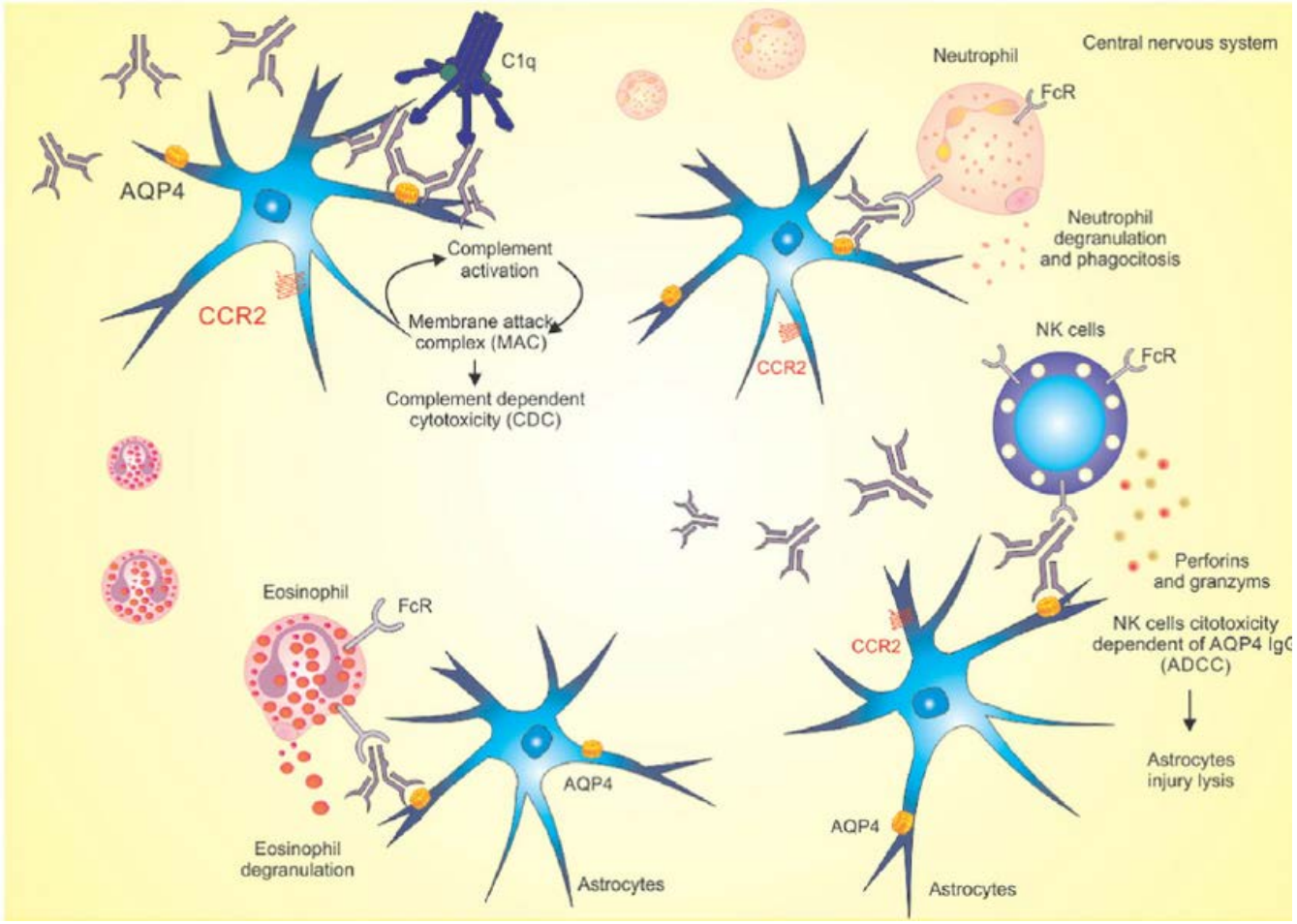

Pathogenic mechanisms mediated by complement system. NMO pathogenesis involves binding of anti-aquaporin 4 (AQP4) to AQP4 on astrocyte end- feet, which activates complement, leading to formation of membrane attack complex (MAC) and astrocyte injury. This event is followed by recruitment of in fl ammatory cells, fi rst neutrophils and eosinophils (granulocytes), and then macrophages, which further disrupt the blood – brain barrier. Astrocyte injury and an in fl ammatory reaction are thought to damage oligodendrocytes and neurons secondarily. Anti-AQP4 can cause antibody-dependent cellular cytotoxicity (ADCC) when effector cells are present, such as neutrophils, eosinophils, and natural killer (NK) cells, and complement-dependent cytotoxicity (CDC) when complement is present. The ability of AQP4-bound anti-AQP4 IgG to cause CDC and ADCC is explained by the fact that IgG Fc region binds to complement protein C1q and to effector cell receptor FcR. IgG1 subtype of anti-AQP4 IgG is the predominant antibody in NMO, which strongly activates complement and binds all classes of FcR involved in ADCC.

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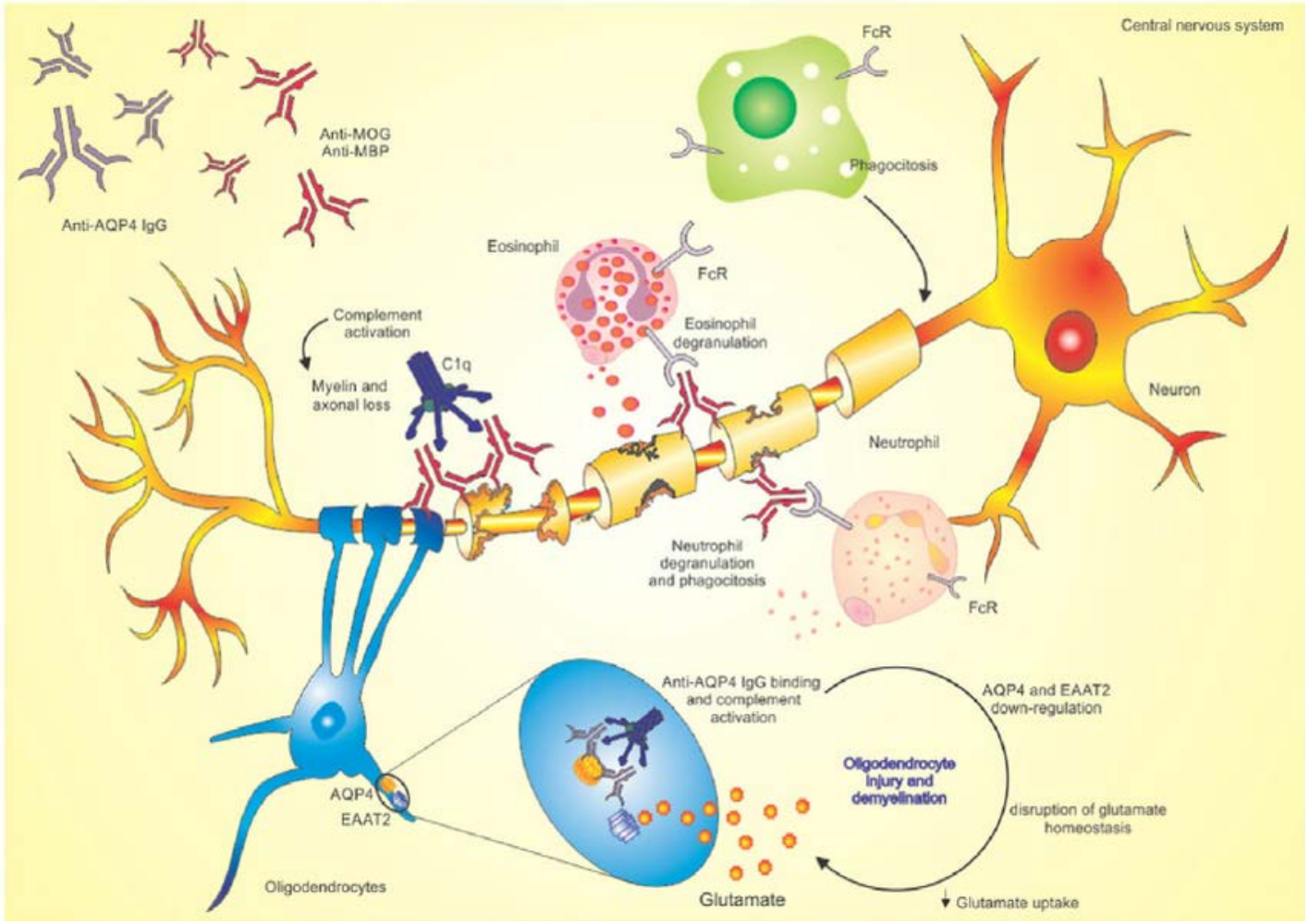

Neuromyelitis optica (NMO) pathogenic mechanisms mediated by complement dependent cytotoxicity (CDC), antibody dependent cellular cytotoxicity (ADCC), and glutamate excitotoxicity. In the normal central nervous system, AQP4 is expressed at astrocyte end-feet facing the blood – brain barrier (BBB) formed by endothelial cells connected by tight junctions. In NMO, by unknown mechanisms, circulating anti-AQP4 IgG crosses the BBB and binds to AQP4 on astrocytes. This event leads to recruitment and activation of complement system proteins and deposition of the membrane attack complex (MAC), producing astrocyte damage by CDC.

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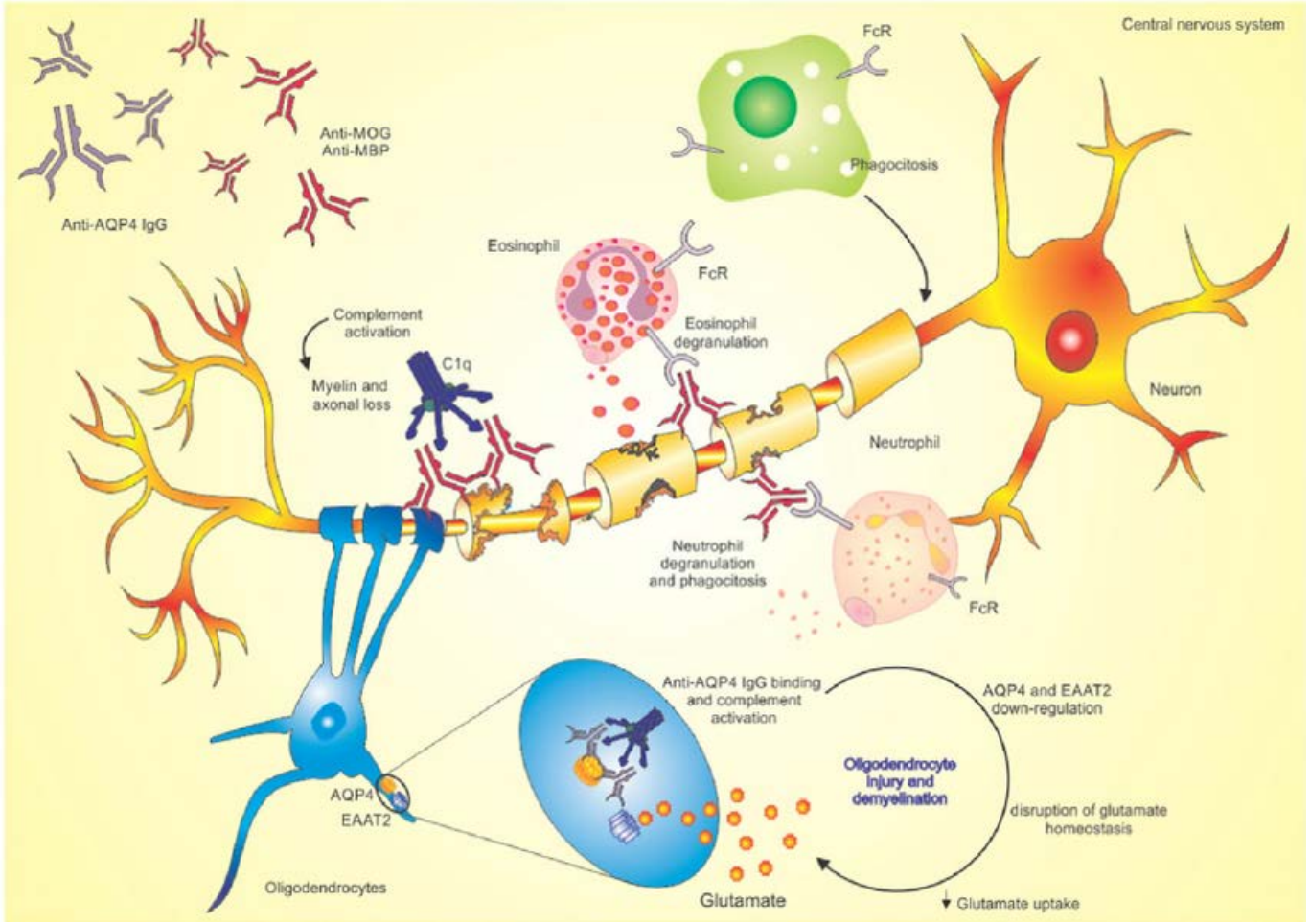
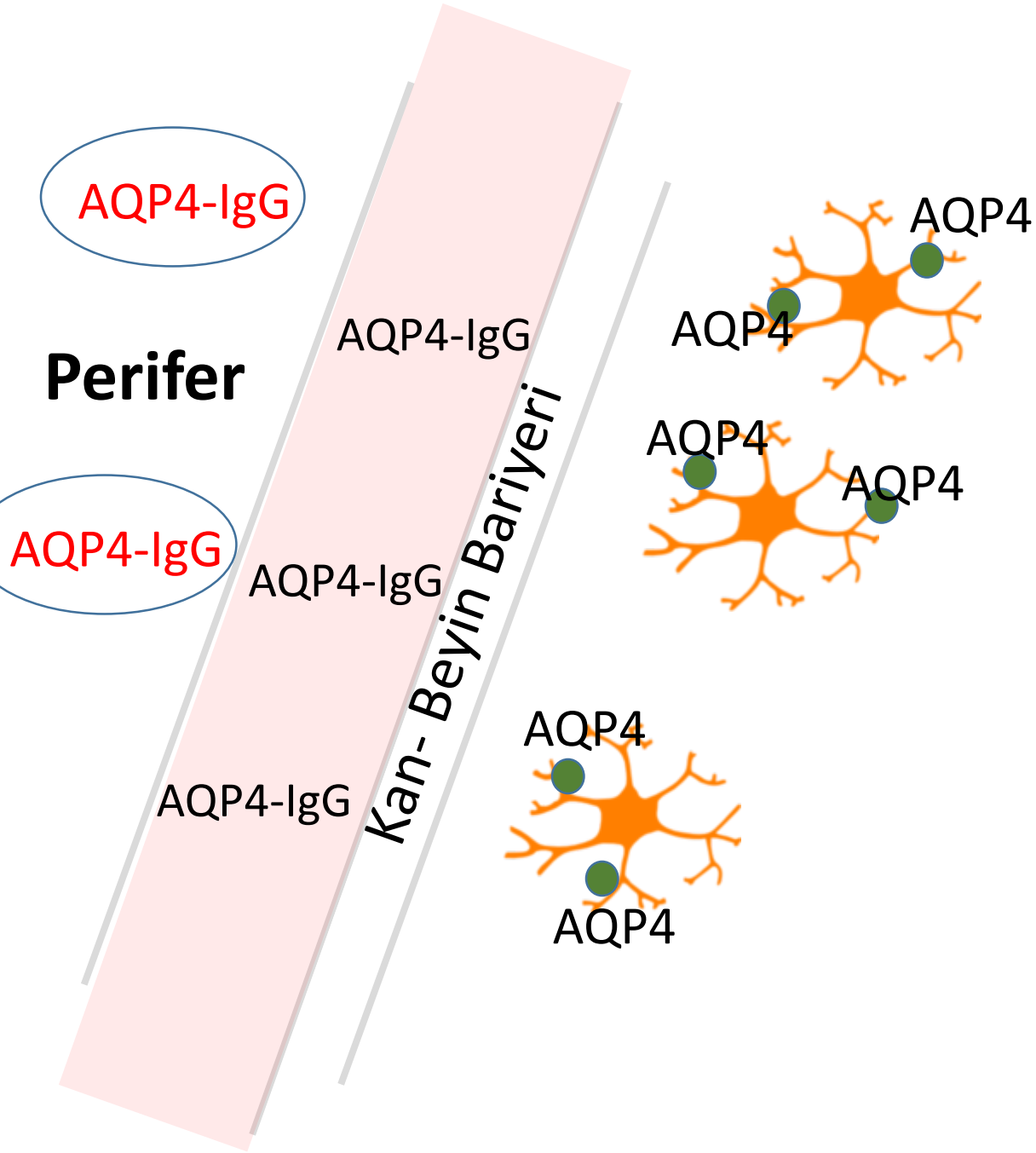


Complement activation and cytokine secretion by astrocytes recruit in fl ammatory cells, such as eosinophils, neutrophils, and macrophages, which further disrupt the BBB, allowing more entry of anti-AQP4 IgG. Degranulating in fl ammatory cells and astrocytes damage secondarily cause oligodendrocytes injury, myelin loss, and axon damage by ADCC. The presence of anti-AQP4 in the oligodendrocyte decreases glutamate uptake in astrocytes and internalization of the glutamate transporter excitatory amino acid transporter 2 (EAAT2) together with AQP4. NMO pathogenesis involves glutamate excitotoxicity by a mechanism involving anti- AQP4 IgG-induced internalization of EEAT2 on astrocytes and consequent injury in glutamate uptake from the extracellular space following neuroexcitation, leading to oligodendrocyte impairment and myelin loss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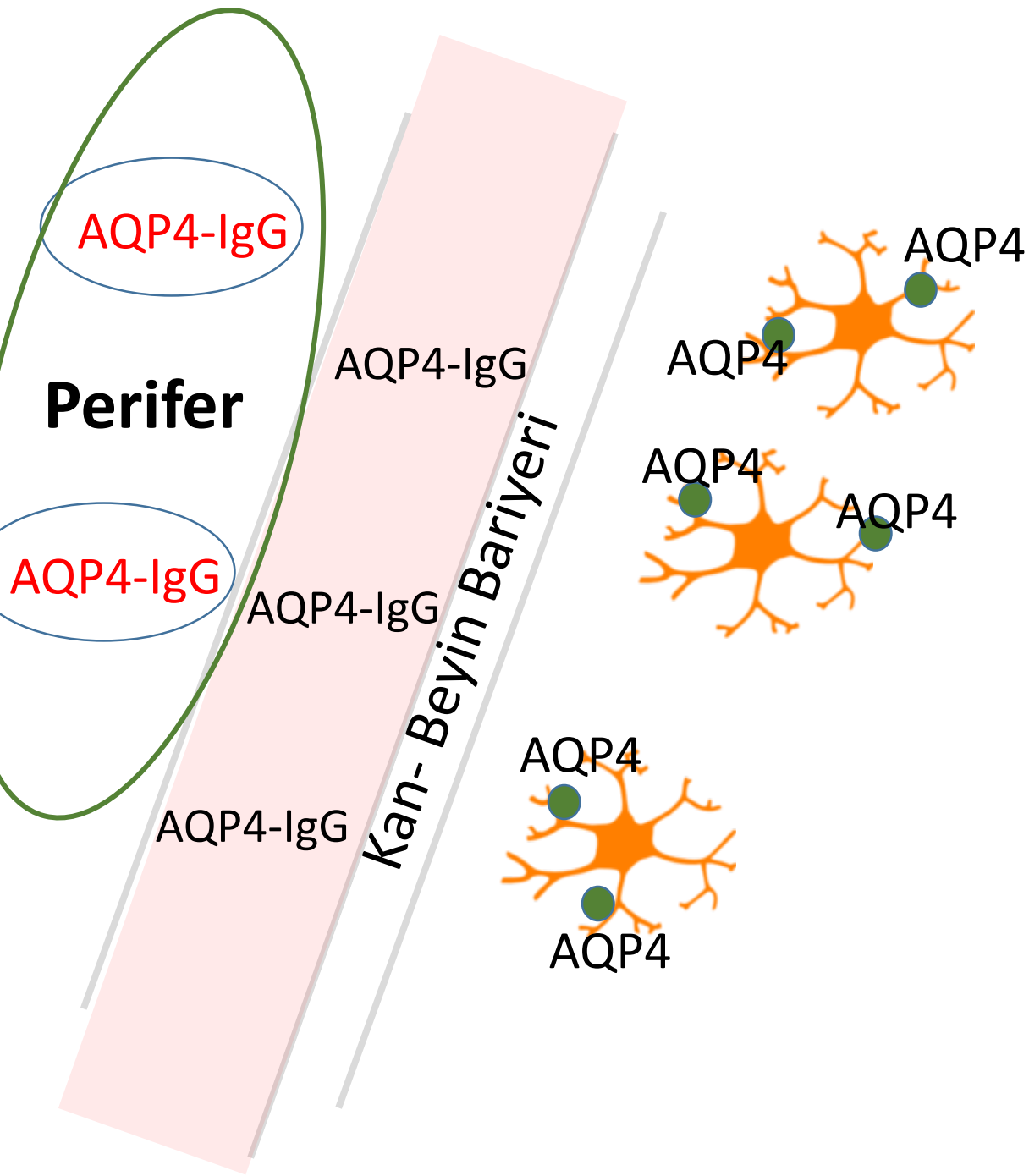
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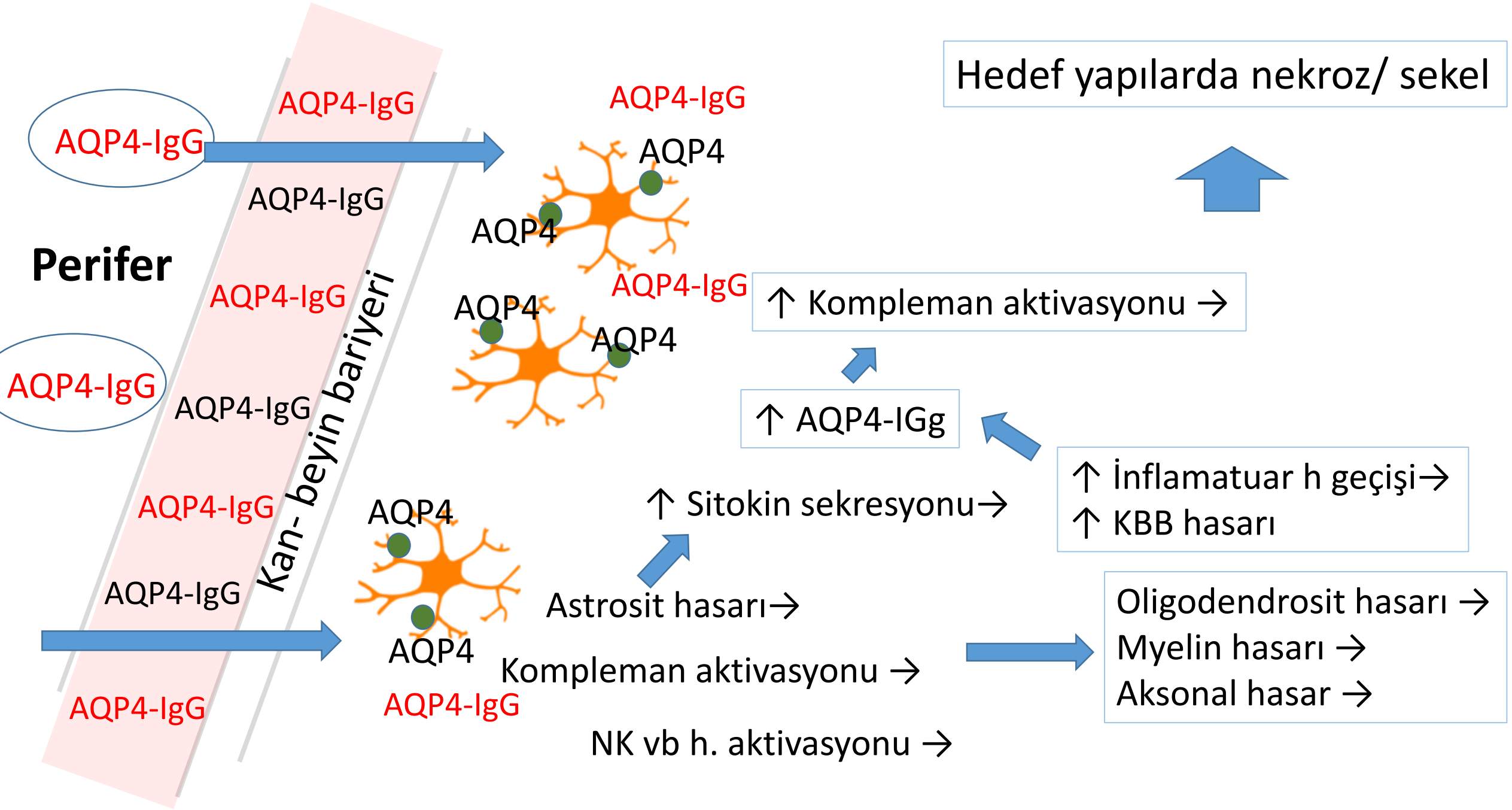
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↑ Kompleman aktivasyonu →
↑ AQP4-IGg
↑ İnflamatuar h geçişi→
↑ KBB hasarı
↑ Sitokin sekresyonu→
Astrosit hasarı→
Kompleman aktivasyonu →
NK vb h. aktivasyonu →
Oligodendrosit hasarı →
Myelin hasarı →
Aksonal hasar →

Tipik NMO

- Bilateral optik nöropati
- Uzun segment (>3) transvers myelin

Diğer ilişkili klinik durumlar

- Area postrema sendromu (inatçı hıçkırık, bulantı, kusma)
- Akut beyinsapı sendromu
- Semptomatik narkolepsi veya akut diensefalik sendrom + tipik MR bulguları
- Semptomatik serebral sendrom + tipik MR bulguları

- Çekirdek ‘core’ klinik karakteristikler → NMOSD

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

Neurology® 2015;85:177-189

Diagnostic criteria for NMOSD with AQP4-IgG

1. At least 1 core clinical characteristic
2. Positive test for AQP4-IgG using best available detection method (cell-based assay strongly recommended)
3. Exclusion of alternative diagnoses[a]

Diagnostic criteria for NMOSD without AQP4-IgG or NMOSD with unknown AQP4-IgG status

1. At least 2 core clinical characteristics occurring as a result of one or more clinical attacks and meeting all of the following requirements:
   a. At least 1 core clinical characteristic must be optic neuritis, acute myelitis with LETM, or area postrema syndrome
   b. Dissemination in space (2 or more different core clinical characteristics)
   c. Fulfillment of additional MRI requirements, as applicable
2. Negative tests for AQP4-IgG using best available detection method, or testing unavailable
3. Exclusion of alternative diagnoses[a]

International consensus diagnostic criteria for neuromyelitis optica spectrum disorders

Neurology® 2015;85:177-189

Core clinical characteristics

1. Optic neuritis
2. Acute myelitis
3. Area postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
4. Acute brainstem syndrome
5. Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions (figure 3)
6. Symptomatic cerebral syndrome with NMOSD-typical brain lesions (figure 3)

Additional MRI requirements for NMOSD without AQP4-IgG and NMOSD with unknown AQP4-IgG status

1. Acute optic neuritis: requires brain MRI showing (a) normal findings or only nonspecific white matter lesions, OR (b) optic nerve MRI with T2-hyperintense lesion or T1-weighted gadolinium-enhancing lesion extending over >1/2 optic nerve length or involving optic chiasm (figure 1)
2. Acute myelitis: requires associated intramedullary MRI lesion extending over ≥3 contiguous segments (LETM) OR ≥3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis (figure 1)
3. Area postrema syndrome: requires associated dorsal medulla/area postrema lesions (figure 2)
4. Acute brainstem syndrome: requires associated periependymal brainstem lesions (figure 2)

NMOSD hasta popülasyonu (prevalans (?) → 0.3-4.4/100000) →

- Anti-AQP4 ab (+) NMOSD
- Anti-AQP4 ab (-) NMOSD

- Anti-AQP4 ab (+)
- Anti-AQP4 ab (-)

± Anti-MOG ab (+) NMOSD

- Anti-AQP4 ab (+)
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± Anti-MOG ab (+) NMOSD ± Diğer antikorlar

J Neurol. 2017 Oct;264(10):2088-2094. doi: 10.1007/s00415-017-8596-7. Epub 2017 Aug 24.

What proportion of AQP4-IgG-negative NMO spectrum disorder patients are MOG-IgG positive? A cross sectional study of 132 patients.

Hamid SHM[1,2], Whittam D[1], Mutch K[1], Linaker S[1], Solomon T[2], Das K[1], Bhojak M[1], Jacob A[3].

⊕ Author information

Abstract

Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been described in patients with neuromyelitis optica spectrum disorders (NMOSD) without aquaporin-4 antibodies (AQP4-IgG). We aimed to identify the proportion of AQP4-IgG-negative NMOSD patients who are seropositive for MOG-IgG. In a cross sectional study, we reviewed all patients seen in the National NMO clinic over the last 4 years (after the availability of MOG-IgG testing), including clinical information, MRI, and antibody tests. 261 unique patients were identified. 132 cases satisfied the 2015 NMOSD diagnostic criteria. Of these, 96 (73%) were AQP4-IgG positive and 36 (27%) were AQP4-IgG negative. These 36 patients were tested for MOG-IgG and 15/36 (42%) tested positive. 20% (25/125) of the patients who did not satisfy NMOSD criteria had MOG-IgG. Approximately half of seronegative NMOSD is MOG-Ig seropositive and one in five of non-NMOSD/non-MS demyelination is MOG-IgG positive. Since MOG-associated demyelinating disease is likely different from AQP4-IgG disease in terms of underlying disease mechanisms, relapse risk and possibly treatment, testing for MOG-IgG in patients with AQP4-IgG-negative NMOSD and other non-MS demyelination may have significant implications to management and clinical trials.

J Neuroinflammation. 2016 Sep 26;13(1):279.

MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 1: Frequency, syndrome specificity, influence of disease activity, long-term course, association with AQP4-IgG, and origin.

Jarius S[1], Ruprecht K[2], Kleiter I[3], Borisow N[4,5], Asgari N[6], Pitarokoili K[3], Pache F[4,5], Stich O[7], Beume LA[7], Hümmert MW[8], Trebst C[8], Ringelstein M[9], Aktas O[9], Winkelmann A[10], Buttmann M[11], Schwarz A[12], Zimmermann H[2], Brandt AU[2], Franciotta D[13], Capobianco M[14], Kuchling J[2], Haas J[12], Korporal-Kuhnke M[12], Lillevang ST[15], Fechner K[16], Schanda K[17], Paul F[4,5], Wildemann B[12], Reindl M[17]; in cooperation with the Neuromyelitis Optica Study Group (NEMOS).

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Abstract

BACKGROUND: Antibodies to myelin oligodendrocyte glycoprotein (MOG-IgG) have been suggested to play a role in a subset of patients with neuromyelitis optica and related disorders.

OBJECTIVE: To assess (i) the frequency of MOG-IgG in a large and predominantly Caucasian cohort of patients with optic neuritis (ON) and/or myelitis; (ii) the frequency of MOG-IgG among AQP4-IgG-positive patients and vice versa; (iii) the origin and frequency of MOG-IgG in the cerebrospinal fluid (CSF); (iv) the presence of MOG-IgG at disease onset; and (v) the influence of disease activity and treatment status on MOG-IgG titers.

METHODS: 614 serum samples from patients with ON and/or myelitis and from controls, including 92 follow-up samples from 55 subjects, and 18 CSF samples were tested for MOG-IgG using a live cell-based assay (CBA) employing full-length human MOG-transfected HEK293A cells.

RESULTS: MOG-IgG was detected in 95 sera from 50 patients with ON and/or myelitis, including 22/54 (40.7 %) patients with a history of both ON and myelitis, 22/103 (21.4 %) with a history of ON but no myelitis and 6/45 (13.3 %) with a history of longitudinally extensive transverse myelitis but no ON, and in 1 control patient with encephalitis and a connective tissue disorder, all of whom were negative for AQP4-IgG. MOG-IgG was absent in 221 further controls, including 83 patients with AQP4-IgG-seropositive neuromyelitis optica spectrum disorders and 85 with multiple sclerosis (MS). MOG-IgG was found in 12/18 (67 %) CSF samples from MOG-IgG-seropositive patients; the MOG-IgG-specific antibody index was negative in all cases, indicating a predominantly peripheral origin of CSF MOG-IgG. Serum and CSF MOG-IgG belonged to the complement-activating IgG1 subclass. MOG-IgG was present already at disease onset. The antibodies remained detectable in 40/45 (89 %) follow-up samples obtained over a median period of 16.5 months (range 0-123). Serum titers were higher during attacks than during remission ($p < 0.0001$), highest during attacks of simultaneous myelitis and ON, lowest during acute isolated ON, and declined following treatment.

CONCLUSIONS: To date, this is the largest cohort studied for IgG to human full-length MOG by means of an up-to-date CBA. MOG-IgG is present in a substantial subset of patients with ON and/or myelitis, but not in classical MS. Co-existence of MOG-IgG and AQP4-IgG is highly uncommon. CSF MOG-IgG is of extrathecal origin. Serum MOG-IgG is present already at disease onset and remains detectable in the long-term course. Serum titers depend on disease activity and treatment status.

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Mult Scler Relat Disord. 2018 Oct;25:66-72. doi: 10.1016/j.msard.2018.07.025. Epub 2018 Jul 24.

MOG antibody disease: A review of MOG antibody seropositive neuromyelitis optica spectrum disorder.

Narayan R[1], Simpson A[2], Fritsche K[2], Salama S[3], Pardo S[2], Mealy M[2], Paul F[4], Levy M[5].

⊕ Author information

Abstract

MOG antibody disease is an autoimmune disease of the central nervous system associated with a serological antibody against MOG, myelin oligodendrocyte glycoprotein. MOG is a glycoprotein expressed on the outer membrane of myelin and solely found within the central nervous system, including in the brain, optic nerves and spinal cord. Clinically, the disease resembles neuromyelitis optica spectrum disorders in the predilection for relapses of optic neuritis and transverse myelitis. In addition, acute disseminated encephalomyelitis (ADEM) is a well-recognized phenotype of MOG antibody disease in children. In recent studies around the world where MOG testing is available, up to 42% of NMOSD patients who test seronegative for the AQP4 antibody test positive for MOG antibodies. MOG antibody disease has thus recently emerged as a distinct entity carved out of the patient population diagnosed with NMOSD. In this review, we examine the history of the MOG antibody and its relevance to demyelinating disease, as well as compare the clinical, radiographic and serological profiles of patients with MOG antibody with patients with AQP4 antibody.

NMOSD	**Anti- MOG (+)**	**Anti-AQP (+)**
Yaş	↓	↑
Kadın/erkek	↓ (2/1)	↑ (9/1)
Eş zamanlı bilateral ON	+++	++
Atak şiddeti	↑↑↑	↑↑↑
Mesane/barsak tutulumu	↑↑↑	↑
Spinal kord- motor tutulum	↑	↑↑↑
Conus tutulumu	+++	±
Rekürrens	↓↑	↑
Eşlikçi otoimmün hast	+	+++
Ataktan iyileşme	+++	+/++

J Clin Neurosci. 2018 Jan;47:14-19. doi: 10.1016/j.jocn.2017.10.005. Epub 2017 Oct 21.

Infections in neuromyelitis optica spectrum disorder.

Zhong X[1], Zhou Y[1], Lu T[1], Wang Z[2], Fang L[1], Peng L[1], Kermode AG[3], Qiu W[4].

Author information

Abstract

Neuromyelitis optica spectrum disorder (NMOSD) is an inflammatory astrocytopathy that has both genetic and environmental causes. A growing body of evidence suggests that the presence of several infectious agents correlates with the development of NMOSD. In this review, we summarize studies that either support or present evidence against the hypothesized association between infection and NMOSD. We will also present an overview of potential mechanisms underlying the pathogenesis of NMOSD. Finally, we provide some beneficial properties that infectious elements may have based on "hygiene hypothesis". It is of great clinical significance to further investigate the complex mechanisms by which infections may affect autoimmune diseases to develop better strategies to prevent and treat them, although so far no causal link between infectious agents and NMOSD has been established.

Mult Scler Relat Disord. 2019 Jan;27:289-293. doi: 10.1016/j.msard.2018.11.014. Epub 2018 Nov 13.

HIV infection associated neuromyelitis optica spectrum disorder: Clinical features, imaging findings, management and outcomes.

Mathew T[1], Avati A[2], D'Souza D[2], Therambil M[2], Baptist AA[2], Shaji A[2], Nadig R[2], Rockey SM[3], Parry G[2].

Author information

Abstract

INTRODUCTION: HIV Infection associated NMOSD (HIV-NMOSD) is a recently recognized entity. Management of patients with HIV-NMOSD is a challenge. Here we report our own experience of HIV-NMOSD along with a complete review of all the cases of HIV-NMOSD reported in literature.

OBJECTIVE: Describe the clinical features, radiological findings, treatment patterns and outcomes in patients with HIV-NMOSD.

METHODS: The details of all cases of HIV- NMOSD were searched from our NMOSD registry. A literature search was also done using the terms NMO, NMOSD and HIV infection in PUBMED, Google Scholar and EMBASE. The details of all the reported cases and cases from our registry were collected and analyzed.

RESULTS: Six cases of HIV-NMOSD were identified from the literature and one from our registry. There were four males and three females with age ranging from 8 years to 49 years. Duration of HIV infection ranged from newly detected to 15 years. Optic neuritis followed by myelitis was the commonest presentation, occurring in 5 out of 7 patients. 3 patients were anti-aquaporin 4 antibody positive while 3 were negative and in one anti- aquaporin 4 antibody assay was not done. All patients received immunomodulatory treatment. 5/7 patients had poor recovery from acute attacks but no patient had further relapses while on immunomodulatory treatment and antiretroviral therapy.

CONCLUSION: HIV associated NMOSD is a recently recognized entity. A high index of suspicion is needed to diagnose these patients. In all patients with HIV infection presenting with optic neuritis or/and myelitis, anti aquaporin 4 antibody status should be checked and in all patients of NMOSD, HIV infection should be ruled out.

Mult Scler Relat Disord. 2019 Jan;27:350-363. doi: 10.1016/j.msard.2018.11.008. Epub 2018 Nov 16.

Autoimmune diseases associated with Neuromyelitis Optica Spectrum Disorders: A literature review.

Shahmohammadi S[1], Doosti R[1], Shahmohammadi A[1], Mohammadianinejad SE[2], Sahraian MA[1], Azimi AR[1], Harirchian MH[3], Asgari N[4], Naser Moghadasi A[5].

Author information

Abstract

INTRODUCTION: Neuromyelitis Optica (NMO) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS) which predominantly involves optic nerves and spinal cord. Since the introduction of Neuromyelitis Optica Spectrum Disorders (NMOSD) as a separate entity, there have been many reports on its association with other disorders including systemic and organ-specific autoimmune diseases. Here, we reviewed other immune-mediated diseases associated with NMOSD and tried to categorize them.

METHODS: The present review was conducted using the PUBMED database based on papers from 1976 (i.e., since the first NMO comorbidity with SLE was reported) to 2017. We included all articles published in English. The keywords utilized included Neuromyelitis optica, Neuromyelitis Optica Spectrum Disorders, Devic's disease, in combination with comorbidity or comorbidities.

RESULTS: Diseases with immune-based pathogenesis are the most frequently reported co-morbidities associated with NMOSD, most of which are antibody-mediated diseases. According to literature, Sjogren's Syndrome (SS) and Systemic Lupus Erythematosus (SLE) are the most frequently reported diseases associated with NMOSD among systemic autoimmune diseases. Further, myasthenia gravis in neurological and autoimmune thyroid diseases in non-neurological organ-specific autoimmune diseases are the most reported comorbidities associated with NMOSD in the literature.

CONCLUSIONS: NMOSD may be associated with a variety of different types of autoimmune diseases. Therefore, systemic or laboratory signs which are not typical for NMOSD should be properly investigated to exclude other associated comorbidities. These comorbidities may affect the treatment strategy and may improve the patients' care and management.

Neuropsychiatr Dis Treat. 2017 Oct 20;13:2653-2660. doi: 10.2147/NDT.S147360. eCollection 2017.

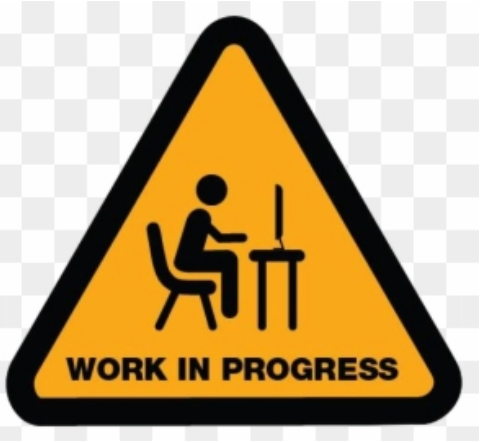
Complexity and wide range of neuromyelitis optica spectrum disorders: more than typical manifestations.

Han J[1], Yang MG[1], Zhu J[1,2], Jin T[1].

Author information

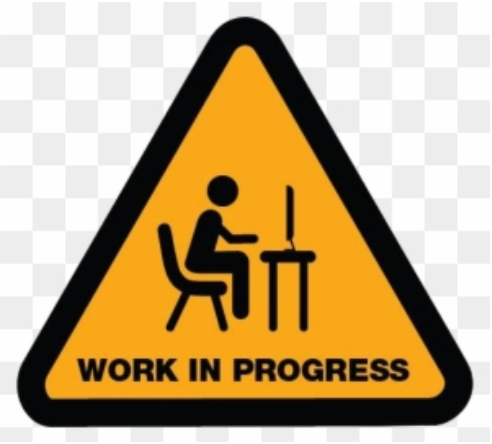
Abstract

Neuromyelitis optica (NMO), considered to be mediated by autoantibodies, often cause severely disabling disorders of the central nervous system, and predominantly cause optic nerve damage and longitudinally extensive transverse myelitis. Remarkable progress has been made in deciphering NMO pathogenesis during the past decade. In 2015, the International Panel for NMO Diagnosis proposed the unifying term "NMO spectrum disorders" (NMOSD) and the updated NMOSD criteria reflects a wide range of disease and maintains reasonable specificity. Moreover, cumulative findings have indicated that NMOSD are frequently associated with multiple autoimmune diseases, thereby presenting complex clinical symptoms that make this disease more difficult to recognize. Notably, most neurologists do not heed these symptoms or comorbid conditions in patients with NMOSD. Whereas previous reviews have focused on pathogenesis, treatment, and prognosis in NMOSD, we summarize the present knowledge with particular emphasis on atypical manifestations and autoimmune comorbidities in patients with NMOSD. Furthermore, we emphasized the identification of these atypical characteristics to enable a broader and better understanding of NMOSD, and improve early accurate diagnosis and therapeutic decision making.



ÖZET?

- Hangisi NMOSD / Hangisi değil?
- Yeni tanımlamalar / Yeni sınıflama



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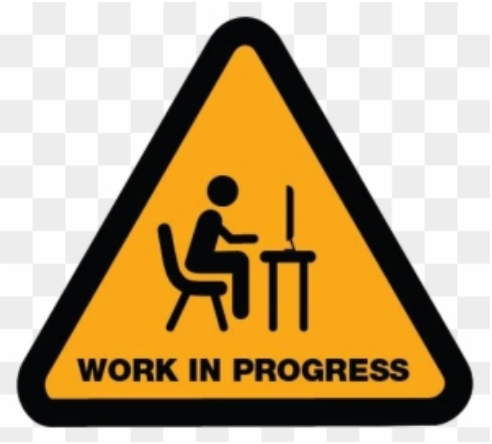

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