CLINICAL AND NEURORADIOLOGICAL FEATURES IN PATIENTS WITH NEUROMYELITIS OPTICA SPECTRUM DISORDER: A NARRATIVE LITERATURE REVIEW

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Abstract
Neuromyelitis optica spectrum disorder (NMOSD) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS), characterized by severe clinical involvement of the brain, spinal cord and optic nerves. The diagnostic approach is based on magnetic resonance imaging and testing for antibodies against aquaporin-4 in the serum, categorizing patients as seropositive or seronegative. Due to the uniqueness of the pathogenesis of the disease, specific clinical-imaging patterns usually emerge in NMOSD in comparison with other autoimmune or demyelinating diseases of the CNS. Sufficient knowledge of these characteristics is now deemed necessary for a correct and early diagnosis of the disease, thereby enabling the use of appropriate targeted immunotherapies. In the present narrative review, we summarize the existing literature focusing mainly on the clinico-radiological characteristics and diagnostic criteria of NMOSD patients, with a brief description of the current therapeutics of the disease. We also provide characteristic examples of NMOSD cases from our own clinical experience that focus on the diagnostic approach of the disease based on current neuroimaging and clinical diagnostic criteria.

Key Words: *Neuromyelitis Optica Spectrum Disorder, NMOSD clinical evaluation, Νευροαπεικόνιση NMOSD, NMOSD diagnosis.*

ΚΛΙΝΙΚΑ ΚΑΙ ΝΕΥΡΟΑΠΕΙΚΟΝΙΣΤΙΚΑ ΧΑΡΑΚΤΗΡΙΣΤΙΚΑ ΑΣΘΕΝΩΝ ΜΕ ΔΙΑΤΑΡΑΧΗ ΤΟΥ ΦΑΣΜΑΤΟΣ ΤΗΣ ΟΠΤΙΚΗΣ ΝΕΥΡΟΜΥΕΛΙΤΙΔΑΣ: ΒΙΒΛΙΟΓΡΑΦΙΚΗ ΑΝΑΣΚΟΠΗΣΗ

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Περίληψη
Η διαταραχή του φάσματος της οπτικής νευρομυελίτιδας (NMOSD) ανήκει στις αυτοάνοσες φλεγμονώδεις απομυελινωτικές νόσους του κεντρικού νευρικού συστήματος (ΚΝΣ), χαρακτηριζόμενη από βαρείες κλινικές προσβολές του εγκεφάλου, του νωτιαίου μυελού και των οπτικών νεύρων. Η διαγνωστική προσέγγιση βασίζεται στη μαγνητική τομογραφία και στην αναζήτηση των αντισωμάτων έναντι της ακουαπορίνης-4 στον ορό, κατηγοριοποιώντας έτσι τους ασθενείς σε οροθετικούς ή οροαρνητικούς. Λόγω της μοναδικότητας στον παθογενετικό μηχανισμό της νόσου, συνήθως προκύπτουν συγκεκριμένα ειδικά κλινικο-απεικονιστικά πρότυπα στην NMOSD σε σχέση με άλλα αυτοάνοσα ή απομυελινωτικά νοσήματα του ΚΝΣ. Η επαρκής γνώση αυτών των χαρακτηριστικών κρίνεται πλέον αναγκαία με στόχο τη σωστή και έγκαιρη διάγνωση της νόσου, δίνοντας κατ' επέκταση τη δυνατότητα εφαρμογής καταλλήλως στοχευμένων ανοσοθεραπειών. Στο παρόν άρθρο πραγματοποιείται ανασκόπηση της υπάρχουσας βιβλιογραφίας εστιάζοντας κυρίως στα κλινικο-απεικονιστικά χαρακτηριστικά και διαγνωστικά κριτήρια των ασθενών με NMOSD, με συνοπτική περιγραφή της σύγχρονης

θεραπευτικής της νόσου, παρέχοντας παράλληλα παραδείγματα με περιστατικά με διάγνωση NMOSD από τη δική μας κλινική εμπειρία. Η διαγνωστική προσέγγιση με βάση τα κλινικά και απεικονιστικά χαρακτηριστικά των ασθενών αναλύεται με βάση τα σύγχρονα υπάρχοντα κριτήρια.

Λέξεις ευρετηρίου: *Φάσμα της Οπτικής Νευρομυελίτιδας, Κλινική εικόνα NMOSD, Νευροαπεικονιστικά χαρακτηριστικά της NMOSD, Διαγνωστικά κριτήρια της NMOSD.*

INTRODUCTION

Neuromyelitis Optica Spectrum Disorder (NMOSD) is anautoimmune inflammatory demyelinating disorder of the central nervous system (CNS), characterized by clinical attacks usually affecting the optic nerves (unilaterally or bilaterally), spinal cord and brainstem. Initially, neuromyelitis optica (NMO) was considered a subtype of multiple sclerosis (MS), frequently termed "opticospinal MS"[1]. In 2004 Lennon et al. recognized a serum IgG antibody binding to astrocytic foot processes in most NMO patients and specifically to aquaporin-4 (AQP4) water channel; thus a new biomarker for NMO emerged[2,3]but optimum treatments differ. The relation of neuromyelitis optica to optic-spinal multiple sclerosis in Asia is uncertain. We assessed the capacity of a putative marker for neuromyelitis optica (NMO-IgG. The neuropathologic studies in NMO lesions also showed thata primarily astrocytopathic process associated with complement deposition was present, with a secondary demyelination effect, therefore NMO was distinguished from MS[4–6]. Currently, according to the 2015 Revised diagnostic criteria for NMOSD[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG (Table) patients with NMOSD phenotype are categorized into seropositive (AQP4(+)NMOSD) or seronegative (AQP4(-)NMOSD) based on the presence of AQP4-IgG in serum. In a small percentage of AQP4(-)NMOSD patients with NMOSD-like clinical and radiological features, serum MOG-IgG can be detected, consistent with myelin oligodendrocyte glycoprotein antibody-associated disease\(MOGAD)[8–12]. MOGAD nowadays is considered a distinct clinicopathological entity from AQP4(+)NMOSD, histopathologically characterized by grey and white matter demyelination in brain and spine[13].

The use of cell based assays (CBA) is considered the gold standard method for the detection of both antibodies[12,14,15]a universally accepted CBA has not been adopted yet. We aimed to analyze the clinical and radiological features of patients with anti-MOG IgG1-antibodies detected with a live-cell CBA and to compare the three most popular MOG-CBAs. We screened sera from 1300 Greek patients (including 426 patients referred by our 8 clinics. Interestingly, dual seropositivity for AQP4-IgG and MOG-IgG in adult and paediatric patients is considered to be extremely rare.[16,17]This phenomenon could possibly reflect the different immunopathogenic mechanisms involved in AQP4(+)NMOSD and MOGAD. Regarding the epidemiology of NMOSD, its prevalence and incidence depends on geographical location and ethnic origin. More specifically, the prevalence range is estimated to be 0.5–4/100,000[18,19], but it can be higher in the island of Martinique (11.5/100,000)[20]and in patients of African origin[8]. The annual incidence (per million population) of NMOSD is reported to be 0.5-0.8 in Whites[21–23]and up to 7.3 in Blacks[20].Sex differences are also present in NMOSD patients; specifically, the female to male ratio is 10:1 in seropositive and 3:1 in seronegative patients[18-23]. It is typically an adulthood disorder. AQP4(+)NMOSD patients tend to have a mean age of 40 years at onset, and likewise 38.5 years for the AQP4(-)NMOSD patients, though it can affect any age.[24,25] Accordingly, NMOSD cases have also been observed in childhood[26] but also at a late age.[27]to compare the outcome with that of early-onset (EO-NMOSDAlso of note is the further characterization of NMOSD as late-onset (≥50 years)[27]to compare the outcome with that of early-onset (EO-NMOSD and very late-onset (≥75 years in several studies[28,29],reporting also poor prognosis of these patients.Even though NMOSD is considered to be mainly sporadic, there is gathering evidence of a familial clustering component indicating a genetic predisposition to the manifestation of the disease[30].

The current narrative review aims to highlight NMOSD clinical features and recapitulate the main neuroimaging patterns of the disease, providing also real-world clinical insights. Magnetic resonance imaging (MRI) examples from seropositive NMOSD patients diagnosed and therapeutically managed in our Departments of Neurology in tertiary care centers in Athens are also displayed.

CLINICAL PRESENTATION IN NMOSD

The typical presentation of NMOSD is characterized by recurrent attacks of optic neuritis (ON), myelitis and symptoms arising from brainstem involvement. ON can manifest with blurred vision, retrobulbar pain and/or pain during eye movements, phosphenes, non-central scotoma, altitudinal defect, color desaturation; on examination reduced visual acuity, relative afferent pupillary defects and sometimes papilledema may be found. Nevertheless, the latter is more commonly detected in MOGAD patients.[7,8,31]which is stratified further by serologic

testing (NMOSD with or without AQP4-IgG Even though bilateral ON can be encountered in AQP4(+) NMOSD patients, it is more common in MOGAD cases, with the paradox that contralateral ON might present in the primarily non-affected eye within a few weeks after the initial attack, a fact that warrants to repeat ophthalmologic examinations to assess the full extent of the attack[8]. Additionally, NMOSD-associated ON tends to lead to severe visual deficits (20/200 for high contrast visual acuity).

Another common presentation in NMOSD, encountered in approximately 10-15% of the patients, is the area postrema syndrome (APS) including uncontrollable bursts of nausea, vomiting or hiccups that can possibly lead to an initial misdiagnosis of a pure gastrointestinal cause/ disorder. Consequently, specific diagnostic criteria have been proposed by Shosha et al.[32]duration, and severity of intractable nausea, vomiting, or hiccups in aquaporin-4-immunoglobulin G (AQP4-IgG for APS: 1) acute or subacute onset of nausea vomiting and hiccups, which may be episodic or constant, 2) persistent symptoms for ≥ 48 hours with incomplete resolution after symptomatic therapy, 3) the exclusion of any other etiology. Duration shorter than 48 hours is deemed sufficient when MRI reveals abnormalities in the area postrema. The differential diagnosis of the APS is quite broad, including metabolic etiologies, CNS tumors, stroke, migraine and psychiatric disorders[8]. Moreover, the differential diagnosis from MS is always clinically relevant. However, brainstem involvement without symptomatology consistent with APS has been described in NMOSD as well, such as facial palsy, hearing loss or oculomotor disturbances. Of note, initial presentation with APS, male sex and age over 45 years-old are considered risk factors for tumor association in NMOSD patients, even though the disease is not tumor-associated[33]. Another clinical manifestation of NMOSD, usually overlooked, is pain; it is mainly neuropathic and commonly associated with paroxysmal tonic spasms, pruritus, allodynia, and hyperalgesia[34–36].Acute cerebral syndrome (ACS) with NMOSD-typical brain lesions on MRI is part of the core clinical features of the disease as well;it includes a variety of symptoms such as headache, encephalopathy and epileptic seizures.[37] However, memory deficits are also quite commonly reported in up to 44% of NMOSD patients, a clinical finding that has been associated with the white matter lesion load.[38]

The diencephalic syndrome is another rare presentation in NMOSD cases, detected in approximately 3.4% of thems according to Etemadifar et al[39]. It is characterized by narcolepsy, hypotension, hypo or hyperthermia, anorexia, anhidrosis, amenorrhea and syndrome of inappropriate antidiuretic hormone secretion[15]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG. Additionally, neuropsychiatric manifestations of NMOSD have been described rarely, even in cases with absence of cortical lesions[40]. They include hallucinations, agitation, speech disturbances and lethargy/confusion. These symptoms do not abate with antipsychotic medications.

Moreover, it has been recently reported by Liu et al. that headache presenting with characteristics of trigeminal autonomic cephalalgia could be the first manifestation of in the context of an NMOSD-associated brainstem attack.[41] Moreover, sudomotor dysfunction was commonly reported in approximately half of the patients with NMOSD in a cohort published by Habek et al.[42] NMOSD patients can experience symptoms of myeloradiculitis[43] including motor, sensory, bowel and bladder dysfunction. Interestingly, motor symptoms tend to indicate an AQP4(+)NMOSD etiology, whereas orthocystic, sexual and conus medullaris disorders are in favor of MOGAD diagnosis.[44,45]

NMOSD-associated myelitis consists a key feature of the disease and is typically manifested as longitudinally extensive transverse myelitis (LETM) extending over ≥3 complete vertebral segments[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG. NMOSD-myelitis may present with severe para- or tetraplegia, sensory deficits and bladder symptoms, thus being a main contributor to accrual disability and poor outcomes[46]. Meanwhile, spinal atrophy is also common in the NMOSD phenotype, resulting also in severe clinical disability and mortality[7,47]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG.

NMOSD PROGNOSIS

Regarding NMOSD prognosis, the majority of these patients (approximately 90%) exhibit a relapsing course with clinical attacks, with a high risk for accrual disability after a clinical episode[48]. In general, AQP4(+)NMOSD-related attacks are usually more severe than the ones encountered in MS-related attacks. According to a recent study of Lana-Peixoto et al. on NMOSD, only a 3% of these patients follow a benign course[49] that has been associated with low annual relapse rate, Caucasian race and lack of spinal lesions at disease onset.

Moreover, it should be clarified that according to the 2015 IPND (International consensus diagnostic criteria for neuromyelitis optica spectrum disorders) criteria[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG, the definition of a relapse is a new attack that follows after ≥4 weeks after the initial attack. This is important regarding the management of the initial attack and the severity of the disease in each patient since

symptoms emerging within 4 weeks after the initial attack should be considered part of the same attack. NMOSD attacks may present with a vast variety of symptoms, from ON and mild paresthesias, to tetraplegia and respiratory distress due to cervical myelitis[48]. Notwithstanding the provided treatment, it is reported that in 80-85% of NMOSD cases neurologic disability accumulates during the disease course.[50]In another study, 8 years after symptom onset, two thirds of the patients were blind and half of them were mono- or paraplegic[46]. Even though chronic progressive deterioration without well-defined clinical episodes is considered atypical for NMOSD, silent disease activity with asymptomatic new lesions should not be excluded[51–53]"

Mortality has always been an important issue in NMOSD patients; specifically, before the advent of current treatments high mortality rate was observed (approximately 2–30%)[48,54,55], whereas under immunotherapies and with earlier diagnosis mortality rate was significantly reduced (approximately 3-15%)[25,56–59]. Infections and respiratory failure in the context of extensive cervical myelitishave been reported as the main causes of mortality in NMOSD[59].

NEUROIMAGING FEATURES IN NMOSD

Brain and spinal imaging with MRI is an essential component in the diagnosis of NMOSD and are incorporated in the 2015 IPND criteria[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG(Table). With regards to NMOSD

Table. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders (modified from Wingerchuk et al., 2015)[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG

DIAGNOSTIC CRITERIA FOR SEROPOSITIVE AQP4-IgG NMOSD PATIENTS:
≥ 1 **core clinical characteristic**
Exclusion of alternative diagnoses

CORE CLINICAL CHARACTERISTICS
Optic neuritis
Acute myelitis
Are postrema syndrome: episode of otherwise unexplained hiccups or nausea and vomiting
Acute brainstem syndrome
Symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions
Symptomatic cerebral syndrome with NMOSD-typical MRI lesions

DIAGNOSTIC CRITERIA FOR NMOSD WITH UNKNOWN OR NEGATIVE AQP4-IGG STATUS
≥2 core clinical characteristics occurring as a result of ≥1 clinical attacks, meeting **ALL** of the following requirements: ≥1 core clinical characteristic must be ON, LETM or area postrema syndrome Dissemination in space (≥ 2 core clinical characteristics) Fulfillment of additional MRI requirements, as applicable
Negative testing for serum AQP4-IgG using the best detection method or testing unavailable
Exclusion of alternative diagnosis

ADDITIONAL MRI REQUIREMENTS
Acute ON: brain MRI with (a) normal findings or nonspecific white matter lesions, *OR* (b) optic nerve MRI with T2-weighted hyperintense lesion or T1-weighted gadolinium enchancing lesion extending > ½ of the optic nerve length or involving optic chiasm
Acute myelitis: requires associated intramedullary MRI lesion extending ≥ 3 contiguous segments (LETM) OR (b) (as defined previously) OR > 3 contiguous segments of focal spinal cord atrophy in patients with history compatible with acute myelitis
Area postrema syndrome with dorsal medulla/ area postrema lesions
Acute brainstem syndrome with periependymal brainstem lesions

patients presenting with ON, high signal on the optic nerves may be evident on T2-weighted (T2w) or Fluid attenuated inversion recovery (FLAIR) images,with or without gadolinium contrast enhancement on T1-weighted (T1w) images. A longitudinally extensive optic nerve lesion can be found involving more than half of the length of the optic nerve, commonly extending posteriorily into the optic chiasm.[8,64–66] Additionaly, residual optic nerve atrophy can be depicted on follow-up MRIs[67]. Nevertheless, brain MRI in the context of NMOSD optic neuritis can be normal or with only non-specific white matter lesions as well. If available, a fat-suppressed MRI sequence is recommended for more efficient evaluation of the optic nerves[8].

MRI findings of NMOSD-associated myelitis include usually longitudinally extensive lesions (≥ 3 continuous vertebral segments) with high signal on T2w/ short tau inversion recovery (STIR) images; spinal edematous appearance can be present in the acute phase; upper cervical lesions might also extend to the medulla showing commonly a linear shape[7,68]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG. Spinal lesions in NMOSD are more located centrally in the axial plane, but may extend to full transverse myelitis. Interestingly, shorter lesions can also be depicted in NMOSD-related myelitis (7–14%)[25,69–71]some patients with otherwise typical NMO have additional symptoms not attributable to optic nerve or spinal cord inflammation or have MS-like brain MRI lesions. Furthermore, some patients are misclassified as NMO by the authors' earlier proposed criteria despite having a subsequent course indistinguishable from prototypic MS. A serum autoantibody marker, NMO-IgG, is highly specific for NMO. The authors propose revised NMO diagnostic criteria that incorporate NMO-IgG status. METHODS: Using final clinical diagnosis (NMO or MS. Gadolinium enhancement (Gd+) on T1w sequences of myelitis is common but with variable patterns of Gd+; a lens-shaped Gd+ pattern on saggital images is detected in up to 1/3 of patients with NMOSD diagnosis[71–73]. We assessed the frequency and characteristics of ring-enhancing spinal cord lesions in neuromyelitis optica spectrum disorder (NMOSD.

After the acute myelitis phase, spinal atrophy may be detected on follow-up MRI, so the timing of MRI is important.[67,68]Another new neuroimaging feature with high specificity (89-94%)for AQP4(+) NMOSD is the "bright spotty lesion"(BSL). BSLs are defined as T2-weighted hyperintensities with similar or increased signal compared to the CSF and also hypo- or iso-intense on T1w images[74–76]and to determine whether the \"bright spotty lesions\" (BSLs. BSLs are more likely to be non-gadolinium-enhancing lesions.[77]

In AQP4(+)NMOSD the pattern of brain lesions is believed to be related to the sites where AQP4-IgG binds to AQP4, and especially where AQP4 is abundant, thus causing regional astrocytic damage[78–80]. Accordingly, typical-NMOSD brain lesions[15]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG[81] are observed as high signal on T2w/FLAIR sequences including the following localization (Table): 1) dorsal medulla (mainly area postrema), 2) peri-ependymal areas of the 4th ventricle and 3rd ventricle, 3) thalami, 4) hypothalamus, 5) corpus callosum, 5) periaqueductal grey matter, 6) corticospinal tracts (long lesions contiguously with the internal capsule and cerebral peduncle)**.** Of great interest is the corpus callosum NMOSD, wherelong lesions having also in some cases edematous appearance have been described[15]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG. Interestingly, Nakamura et al. have described the "marbled pattern"[82] in acute callosal lesions i.e. a specific pattern of heterogeneous intensity in T2w/FLAIR images.

Regarding brain hemispheric lesions in NMOSD,when both the posterior limb of the internal capsule and the corticospinal tract are involved and vasogenic edema is present the pathology might result in the temporal lobe presenting in a trident shaped way.[83] Brain MRI lesions that are perpendicular to the ventricles, strictly cortical or juxtacortical lesions including the U-fibers or temporal lobe lesions should raise the suspicion of a different diagnosis than NMOSD. Additionally, large hemispheric/tumefactive brain lesions (>2cm), confluent, in the subcortical or deep white matter can also occur in NMOSD[8,81]

On post-contrast-T1w images, different Gd+ patterns have been described in NMOSD patients including 1) cloud-like Gd+, 2) thin periventricular Gd+, 3) pencil-thin linear ependymal Gd+, 4) meningeal Gd+[67,68,80]. It has been estimated that Gd+ is present in 9-36% of NMOSD patients.[68]The classic "ring" and "open ring" gadolinium enchancing pattern of MS is rarely seen in NMOSD.

Of great interest as a neuroimaging biomarker is the detection of leptomeningeal contrast enhancement (LMCE) on specially designed MRI protocols. Specifically, in NMOSD patients brain and spinal LMCE has been visualized on post-contrast-T1w images[84–86]; nonetheless, LMCE is not specific for NMOSD and can occur in other chronic neuroinflammatory diseases too[87]. Interestingly,brain LMCE has been also observed in MS[88,89]fluid-attenuated inversion recovery (FLAIR and MOGAD[90] patients using post-contrast-3D-FLAIR sequences. Examples of AQP4(+) NMOSD-associated myelitis and optic neuritis/atrophy are shown in Figures 1-4.

NMOSD DIAGNOSIS

Currently, the 2015 published IPND criteria are

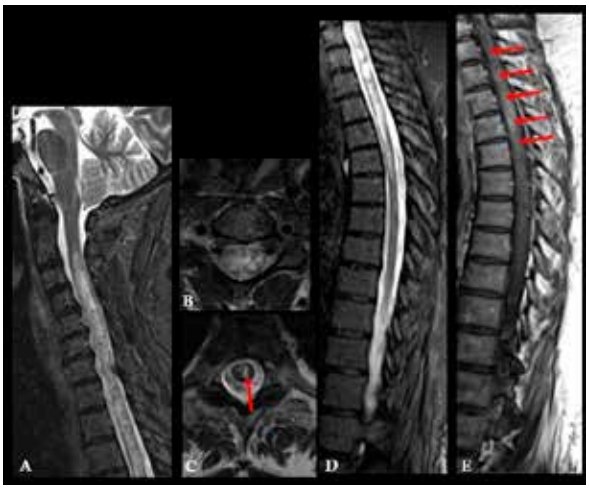

Figure 1. Longitudinally extensive transverse myelitis in an AQP4(+)NMOSD 47-year-old female patient presenting with paraplegia. A long lesion extending from the cervical (A) to the upper thoracic cord (D) is demonstrated on saggital STIR image. Axial T2-weighted images demonstrate the involvement of almost the entire cross-section of the cord (B) and a "bright spotty lesion" (arrow C). Lesion enhancement is also seen on saggital T1-weighted contrast-enhanced images (arrows E).

used for the diagnosis of NMOSD.[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG For AQP4-IgG seropositive patients at least one core clinical characteristic and the exclusion of alternative diagnosis are required. For the detection of serum AQP4-IgG live cell-based assay is considered to be the gold standard and is also strongly recommended)[60,]as mentioned before, but nowadays fixed cell-based assays are almost as specific and sensitive. Immunofluorescence methods are less sensitive but present with good specificity;enzyme-linked immunosorbent assays (ELISA) are the least sensitive and specific, but permit ready estimation of an antibody

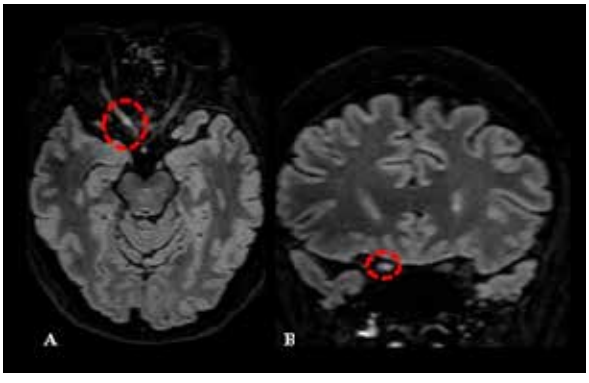

Figure 3. Right optic nerve involvement in a 48-year-old female with AQP4(+)NMOSD. The patient had an acute attack of right optic neuritis 19 months before the MRI, resulting in permanent loss of sight to the right eye. On axial (A) and saggital (B) 3D-FLAIR images a longitudinally extensive right optic nerve lesion with high signal is shown (red circle), involving more than half of the length of the optic nerve.

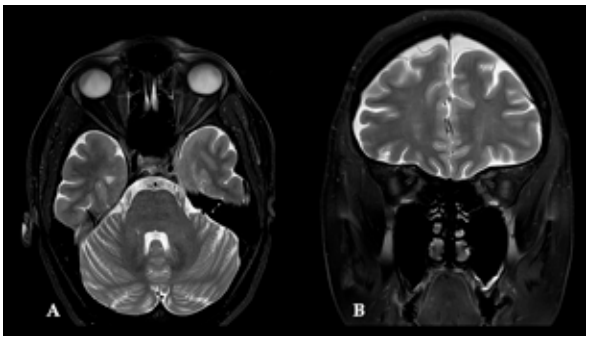

Figure 2. Chronic bilateral optic nerve atrophy in an AQP4(+) NMOSD 45-year-old female. The patient had a history of recurrent bilateral optic neuritis episodes over the last 30 years, resulting in bilateral blindness. Axial (A) and coronal (B) T2-weighted images depicting bilateral optic nerve atrophy.

titre when positive[60],[61.Noteworthy,] neurofilament light chain and glial fibrillary acidic protein , in serum and cerebrospinal flud (CSF),are emerging new biomarkers of neuronal and astroglial damage respectively in NMOSD.[5,6,62,63] There are specific diagnostic challenges for patients with NMOSD phenotype but seronegative or with unknown status for AQP4-IgG, thus requiring additional characteristics for the diagnosis. The IPND criteria are summarized in Table.

Lumbar puncture is usually performed in patients suspected of suffering from NMOSD; CSF findings include pleocytosis usually greater than the ones observed in MS, with neutrophils and eosinophils present in some cases;oligoclonal bands (OCBs) are detected less frequently than in MS, with OCB posi-

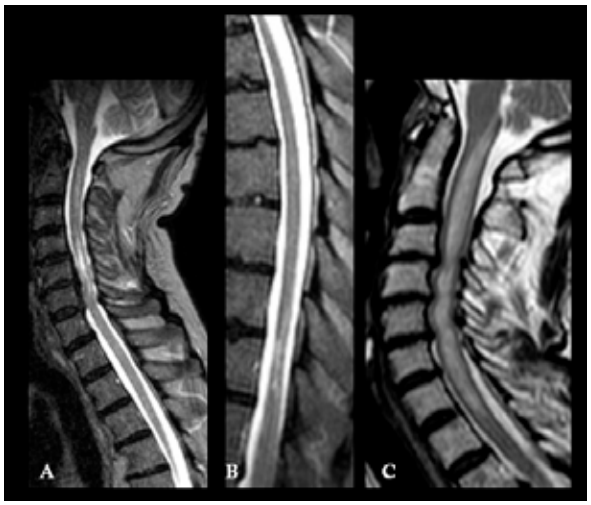

Figure 4. Examples of AQP4(+)NMOSD-associated myelitis. Sagittal STIR images depicting a longitudinally extensive transverse myelitis (LETM) of the cervical cord (A) and also high signal and atrophy of the lower thoracic cord (B) in a AQP4-IgG positive 66 year-old-female. The patient had presented with paraparesis and hypesthesia with a Th3 sensory level. MRI of a 63 year-old-female patient presenting with cervical pain and right hemiparesis; LETM of the cervical cord with edematous appearance and extension of the lesion to the area postrema are demonstrated on saggital STIR image (C).

tiviy of <30%; protein levels are usually slightly elevated[7]which is stratified further by serologic testing (NMOSD with or without AQP4-IgG.Moreover, there are several mimics of NMOSD, including chronic infections (e.g,HIV or syphilis), neoplasms and paraneoplastic diseases, sarcoidosis, non-infectious inflammatory diseases and vasculitic diseases(e.g.systemic lupus erythematosus, CADASIL), metabolic abnormalities and leukodystrophies

THERAPEUTIC STRATEGIES IN NMOSD

Therapeutic strategies in NMOSD can be distinguished into a) treatments of the acute attacks and b) maintenance long-term therapies, aiming the reduction of the number and severityof relapses andthus the progression of clinical disability.Acute NMOSD attacks are usually treated with intravenous high-dose methylprednisolone, whereas plasma exchange is used for corticosteroid-refractory cases[50]are difficult to treat, and leave residual deficits. Here, we analyzed the frequency, sequence, and efficacy of therapies used for NMO attacks. METHODS A retrospective review was made of patient records to assess demographic/diagnostic data, attack characteristics, therapies, and the short-term remission status (complete remission [CR], partial remission [PR], no remission [NR]. With regards to maintenance therapies, few off-label immunosuppressive treatments for NMOSD have shown some effectiveness in relapse prevention, such as low-dose oral corticosteroids, azathioprine, methotrexate, mycophenolate mofetil and rituximab[10,91–96].

Recently, four new biological agents received approval from the European Food Agency (EMA) for the treatment of AQP4(+)NMOSD, based on efficacy data from double-blind randomized-controlled clinical trials; 1) eculizumab, 2) ravulizumab, 3) inebilizumab, 4) satralizumab. These newly approved immunotherapies are analyzed in detail in the position paper of the Hellenic Neurological Society and the Hellenic Academy of Neuroimmunology that has been recently published in the Archives of Clinical Neurology.[97]

CONCLUSION

AQP4(+)NMOSD is a CNS demyelinating disease astrocytopathyusually associated with severe and long-term disability; thus the understanding and deep knowledge of NMOSD characteristics by neurologists is a requisite for timely diagnosis and swift initiation of specific immunotherapies. In the present narrative review, we have analyzed and summarized the main epidemiological, clinical and neuroradiological features of NMOSD patients. Given the importance of MRI findings in the workup of patients with a suspected diagnosis of NMOSD, clinicians must be competent in identifying the typical and atypical imaging characteristics of the disease,since a significant percentage of NMOSD patients (up to 50%) present with non-specific imaging findings[81]. In view of the former considerations, neurologists and neuroradiologists should always bear in mindthe plethora of imaging patterns and diversity of the clinical characteristics of NMOSD patients in order to achieve a swift and accurate diagnosis.

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