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Review Article

Neuromyelitis Optica and Differential Diagnosis (mimics)

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Abstract

Neuromyelitis Optica is an inflammatory neurodegenerative demyelinating autoimmune channelopathy affecting brain and spinal cord, for which Aquaporin-4(AQP4) water channels are the main target.

Discovery of the AQP4 immunoglobulin (IGG) antibody in 2004 was a major step for understanding the disease which helped to distinguish from multiple sclerosis and other demyelinating diseases.

Aquaporin -4 (AQP4) is a water channel protein expressed in two major isoforms which includes a short isoform M1 and a isoform M23 , AQP4 is expressed heavily on astrocyte endfeet end process at blood brain barrier, nodes of Ranvier and neuronal synapses processes in spinal cord, optic nerves , brain stem, thalamus ,hypothalamus, dorsal medulla at area postrema, diencephalon, subcortical white matter, gray and white matter in spinal cord, periaqueductal and periventricular region.

Keywords: neuromyelitis; optica; diagnosis; channelopathy; cerebrum

Introduction

Neuromyelitis Optica is an inflammatory neurodegenerative demyelinating autoimmune channelopathy affecting brain and spinal cord, for which Aquaporin-4(AQP4) water channels are the main target [1].

Discovery of the AQP4 immunoglobulin (IGG) antibody in 2004 was a major step for understanding the disease which helped to distinguish from multiple sclerosis and other demyelinating diseases [2].

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Binding of NMO-IGG to AQP4 cause downregulation of NMO-IGG mainly IGG subclass causing classical complement cascade activation which result in impairing the water flux directly independent of the AQP4 dawn- regulation, binding of the NMO-IGG to Astrocyte AQP4 in a astrocyte has isoform specific outcome,

M1 is completely internalized but M23 is resistant to internalization and activate the complement more effectively than M1,

Autoimmune attack is believed to cause astrocyte damage, this caused disruption of blood brain barrier by increasing the permeability resulting in influx of eosinophils and neutrophils into the Central nervous system, this result in death of astrocyte. oligodendrocyte and neurons, [4].

AQP4-IGG levels had been found to fluctuate during the disease course and treatment, usually escalated during relapse and decrease during remission, AQP4 is found in abundance in optic nerves, spinal cord, area postrema in dorsal medulla, brain stem, diencephalic region includes

Thalamus, hypothomes and cerebrum,

Glial Fibrillary Acid Protein (GFAP) is highly sensitive biomarker for astrocytes and gliosis, during relapse attack of NMO, GFAP increases in CSF due to astrocyte damage and correlate with the Expanded disability Status Scale (EDSS), in contrast with serum GFAP which remains without change [50] or occasionally decreased

Neuromyelitis Optica was published in the late 19 century by Eugen's Devices where he diagnosed a monophasic disease characterized by bilateral optic neuronitis (simultaneous or sequential) and long extensive

spinal cord myelitis, spanning three contiguous vertebrae or more which was called devic's disease [6].

Devic's NMO cases and other reports of the same disease were also published,

Since the clinical concept had broadened and changed after the discovery of AQP4 IGG antibody,

Many organs specific autoimmune antibodies had been found in association with NMO including acetylcholine receptor antibodies, Anti RO, anti-LA, anti SM, thyroid antibodies, DNA binding, ANA, parietal cell antibodies, in addition to association with non-organ specific autoimmune disease like pernicious anemia, SLE and sjogren's syndrome

The concept had been broadened from neuromyelitis Optica to Neuromyelitis Optica spectrum disorder due to its association with autoimmune diseases, and different phenotypes,

In 2006 requirements for Diagnose NMOSD are seropositivity of the serum for AQP4 IGG antibody and two core criteria (optic neuritis, longitudinal extensive transvers myelitis or area postrema syndrome, acute brain stem disease) and exclusion of any alternative disease including any silent demyelination in the cerebrum

In 2015, consensus diagnostic criteria by international NMOSD panel concluded

Either seropositivity of the serum and one core criteria which could be

Optic neuritis, extensive longitudinal myelitis, (lesion spanning more than three continues vertebra)

Area postrema syndrome

Acute brain stem syndrome (opthalmoparesis, involvement of corticospinal tract, ataxia, encephalitis)

Panel was reluctant to call seropositive and sero negative after the discovery of another antibody called Myelioligodendrocyte Glycoprotein (MOG) antibodies,

We looked at the NMO cases from the literatures before the discovery of AQP4 and we found that NMO cases whith relapse resemble very much AQP4 seropositive and monophasic cases are quite different phenotype similar to ADEM and most of them had element of encephalitis and very similar to seronegative NMO acute demylenating encephalopathy, these findings are reported before by Wingerchuk et al [6],

AQP4 –IGG- AB is very disease specific if tested by the right assay methods, it is very unlikely to be find it healthy person or other neurological disease, also seropositivity of AQP4 IGG antibody can predict the long-term prognosis and response to medication (7), and residual disabilities

AQP4 AB can be detected by the following method

Enzyme linked immunoassay (ELISA)

Indirect immunofluorescences (IIF)

Flow Cytometry

Assay (FACS -assay)

Cell- based Assay (CBAs)

Strong recommendation from the panel on 2015 for CBAs as it is very accurate, sensitive and specific,

Sensitivity up to 70% and specificity close to 100%

CBA can be done using either live cells expressing Human M23-AQP4 or a commercial kit expressing human M1 -AQP4

The advantage of the fixed one is it is easy to use, not expensive and have good accuracy, good sensitivity and specificity,

The live CBA is more accurate but more expensive and require technical experience and time consuming,

The consensus from the panel is, if the result of fixed BCA is not consistent with the clinical signs, it is reasonable to retest with the live CBA,

Recently Scientists found that FACS assay have the advantage of providing quantitative and cutoff discriminator with a good accuracy [8].

Immunofluorescence is a rapid test and can be used as a screening,

Ethnicity and race are important factors for disease phenotype, response to treatment and prognosis

It is a rare disease among Caucasian, prevalence ranged up to 0.5to 4 cases in 100000 population [9].

Most of the cases reported in Indian, black African and Asian population, in studies performed in south East Wales, found that disease is frequent in populations of Northern European non-Caucasian [10].

Studies in Latin America found high prevalence of NMO in non-white descendants,

Disease is common in females, disease predilection in female is stronger than MS with a gender ratio varies from 2; 1 to 8;1 female to male ratio

females with NMO have a high ratio of miscarriage due to imbalance in TH1and TH2 cytokines [11].

AQP4-IGG NMO is a serious acute relapsing disease with severe disability, common manifestation is optic spinal phenotype in Asian people, it was diagnosed previously as optical-spinal multiple sclerosis

Seronegative for AQP4 -IGG antibodies with seropositivity to MOG has different phenotype characterized by,

Monophasic disease, Male to female ratio is equal 1:1,

Disease is more common in children, has element of encephalitis, similar to (ADEM) acute disseminated encephalomyelitis and association with autoimmune diseases are very rare

Spinal cord lesion mainly in the lumbar region including conus medullaris,

Relapse is less common than NMOSD,

More commonly to involve bilateral optic nerves in the same time, rather than spinal cord

Patient usually have a poor visual acuity and even loss of vision and a thinner peripapillary retinal nerve fiber layer with optical coherence tomography (OCT) 12

Myelin oligodendrocyte antibodies titer is elevated in patient with sever impairment of visual acuity ,affecting mainly anterior compartment of optic nerve , and involve perineural fat which enhance with contrast in T2 weighted MRI , diagnosis on MOG-NMOSD is confirmed if MOG IGG antibodies is positive in CSF during relapse even if negative in serum(14), this is in contract with AQP4 – IGG seropositive which involve posterior compartment and extend to optic chiasma and optic tract

Study of optic neuritis in patients with MOG NMO in Africa showed that optic neuritis was retrobulbar in 20 cases out of 23 cases and the rest has papillitis. [14].

And involvment of optic nerve wether unilateral or bilateral, associated by pain during eye movement,

decreased acuity of vision, impaired colored vision, and altitudinal defects,

most patients will be blind in 5 years if not diagnosed or treated, MRI in the acute phase showed hyperintensity in T2 and enhancement with gadolinium in T1, in chronic stages atrophy of the optic nerve with variable intensity in T2

Neuromyelitis Optica spectrum disorder without AQP4 antibody had been called seronegative for AQP4 IGG antibody, this includes NMOSD positivity for Myleene oligodendrocyte antibody [12].

Longitudinal Extensive transverse myelitis (LETM) usually include central grey matter and lateral cord Causing anterolateral cord syndrome, mostly involve thoracic and cervical cord, causing motor, sensory and sphincteric disturbance,

area postrema syndrome affecting dorsal medulla manifested by intractable nausea, vomiting, hiccough, and sometimes intractable pruritis, acute brainstem syndrome is a core criterion in AQP4 -IGG NMOSD manifested by

Oculomotor dysfunction, facial palsy, vertigo, hearing loss, vestibular and trigeminal neuralgia, Intractable vomiting, [3,14] and even death due to respiratory failure due to involvement of respiratory center in brain stem, absence of cortical lesion in the neuroimage is considered a red flag and needs to revise the diagnosis

Epileptic seizures are common in MS and not in NMOSD

Cutaneous manifestations in the form of Erythematous rash, sclerodactyly, bilateral oedema of hands, Reynaud's phenomenon, cutaneous, manifestations of dermatomyositis had been reported in patients with NMOSD [15].

Other core criteria which occur less often is acute diencephalic syndrome, symptomatic narcolepsy, and acute cerebral syndrome characterized by asymptomatic demyelination disseminated in space,

Autoimmune diseases had been reported with NMOSD commonly SLE, sjogren's Syndrome, dermatomyositis, polymyositis, pernicious anemia, scleroderma and celiac disease,

Patient with NMOSD reported to have subacute combined degeneration of the cord and have low B12 due to inhibition of intrinsic factor and gastric acid secretion by partial cells due AQP4 antibody in the stomach which result in low vitamin B12 causing subacute degeneration of the cord, neuroimaging of the brain during a symptomatic attack showed that abnormalities which are quite unique, usually lesions involving corticospinal tracts, posterior limb of internal capsule and cerebral peduncle periependymal lesions surrounding the aqueduct, third and fourth ventricles, medullary lesions extending to the cervical cord, extensive hemispheric white matter involvement are often edematous and have the appearance of tumefactive lesions.

These brain lesions are typically represented vasogenic edema as confirmed by diffusion -weighted and apparent diffusion coefficient maps causing

Lesions to be similar to posterior reversable leukoencephalopathy (PRES), and ADEM,

Cerebral demyelinated lesions inAQP4 -NMOSD are characterized by absence of central vein sign (very common in MS) which is the perivenous localization of demyelinated lesions in the white matter of the brain and spinal cord, APQ4 IGG was found in lungs, kidney and stomach in Autopsy with no significances

NMOSD with seropositivity for myelin oligodendrocyte antibody has a different phenotype,

By being mostly monophasic rather than relapsing remitting affecting mainly optic nerve, and not uncommonly spinal cord, had prediction to affect the lumbar cord and conus medullaris, less likely to be associated with autoimmune diseases, affect males and females equally, unlike in AQP4 positive which affect mainly females,

monophasic disease is less likely to have relapse, more likely to involve brain stem and cerebellum and less likely to involve supratentorial region,

few studies had shown a monophasic disease had no sex predilection, not associated with autoimmune disease, not relapsing up to 5 years, presented with simultaneous optic neuritis and transvers myelitis, occurring in a relatively young age, seronegative for both AQP4and MOG antibodies. [15].

findings in MRI brain which is not compatible with the diagnosis of AQP4 NMOSD but needs to rule out multiple sclerosis, Characteristic MRI findings in multiple sclerosis includes,

Lesion involving U – fiber Juxtacortical region,

Dawson fingers in periventricular area,

White matter involvement of inferior temporal lobe,

Lesion adjacent to lateral ventricles [16].

CSF during relapse in AQP4 NMO usually show pleocytosis with lymphocytes, neutrophils more than 50 cells /mm and elevated protein, CSF oligoclonal band could be detected in 6% of patient but usually transiently and not sustained, unlike MS which characterized by sustained oligoclonal, in 90% of patients, IL6 was found to be elevated during relapse [17].

Level of neurofilament light chain protein and glial Fibrillary acidic protein (markers of axonal and astrocyte destruction) are higher in NMOSD patients [18].

Patients tested seronegative for AQP4 -IGG antibody from the serum, should have repeated test from CSF [19].

Patient tested positive for AQP4 -IGG antibodies, has a predictive value for relapse and having more sever disease [20]. patient can convert to sero negative during remission (21)

Mortality rate is higher than multiple sclerosis and most commonly due to acute brain stem syndrome causing acute respiratory failure [22]. most recent studies showed drop-in mortality rate from 30 to 10% due to awareness of the disease and early diagnosis [22]. diagnosis of autoimmune diseases in the same patients are very common, some studies reported high ratio up to 50%, common autoimmune disease coexisting with AQP4 NMO like SLE, Myasthenia gravis, Sjogren syndrome [23].

Explanation for co-existence of both autoimmune diseases could be genetic susceptibility to autoimmunity [24].

Differential diagnosis and mimics of AQP4 NOMSD

Accurate diagnosis is of paramount importance as disease can be brought under control during acute stage and prevent relapse with immunosuppressive medication, Failure to diagnose AQP4 NMOSD and add instead treatment of disease modifying agents for Multiple sclerosis

like interferon beta, fingolimod and Natalizumab are not effective and even harmful [25].

Also correct diagnosis and treatment was found to decrease mortality and disability, mainly paraplegia and blindness.

Differential diagnosis of optic neuritis (core feature of NMOSD)

Acute disseminated demyelinating disease (ADEM)

Commonly affect children, phenotype is mainly polyfocal monophasic phenotype, although it can relapse in 10-18% of cases [26] usually preceded by viral infection or vaccination, encephalopathy is common, although it might be a difficult diagnosis when it does not fulfill all the criteria of acute demyelinating encephalopathy (ADEM),

It affects white matter and deep grey matter [27], it also differs from NMOSD in it does not affect mainly females and more polyfocal and serum is negative for AQP4- IGG AB,

Leber hereditary optic neuropathy,

It is a hereditary disease, commonly affect males, at the age of 20-30, considered as a mitochondrial disease due to mutation in the mitochondrial DNA (28) presented with painless loss of vision in both eyes, it has low penetrance in both males and females, neuroimage characterized by absence of gadolinium enhancement, disease is incurable,

Disease of leber hereditary optic neuropathy plus had been described where posterior column was involved

Idiopathic optic neuropathy

It is a common remitting relapsing disease, all patients with idiopathic optic neuropathy should have neuroimaging and serum for AQP4 – IGG and MOG antibodies to exclude NMOSD, demyelination lesions of MS and longitudinal extensive transverse myelitis,

Multiple sclerosis

Usually smaller longitudinal extension than NMOSD, (30)), usually affect the dorsal and lateral of white matter of the cord, cervical cord is the most commonly affected (44.63), typical Dawson fingers lesions, ovoid and perpendicular to the lateral ventricles. in addition to involvement of inferior temporal lobe and Juxtacortical U – fiber lesion,

Coexistence of autoimmune disease is not common like NMOSD, CSF is positive for oligoclonal band in 90% of patients [31].

Sarcoidosis,

Granulomatous noninfectious, non-demyelinating, remitting relapsing, inflammatory disease which can affect optic nerves and optic chiasma, common in black African females typically indistinguishable from NMOSD causing bilateral optic neuronitis and extensive longitudinal transverse myelitis,

Neurosarcoid can affect cranial nerves causing, bilateral fascial palsy, leptomeninges, hypothalamus, respiratory and lymphoreticular organs are mostly affected and support diagnosis, positive ACE is neither specific nor sensitive, CT-PET scan is highly sensitive to detect highly suspicious areas for biopsy and confirmation of the diagnosis, [32,33]

Dural Spinal A-V fistula,

Not Uncommon vascular disease affecting spinal cord mainly males in their fifth or sixth decades,

Causing decreased arteriovenous pressure which result in decreased perfusion to the spinal cord

Which can cause longitudinal extensive transverse myelitis (LETM), which resembles LATEM due to APQ4-IGG NMOSD, patient usually experience subacute course, symptoms usually occur with exercise or prolonged rest, Spinal MR Angio and catheter angiogram will confirm diagnosis which usually treated with surgical ligation or endovascular embolization (15) conventional MR is not diagnostic (34, 35. 36)

Primary CNS Lymphoma,

Primary CNS lymphoma can cause LATEM and brain lesions can resemble AQP4 NMOSD,

40% of patients with spinal cord lymphoma will have intramedullary lymphoma at presentation,

Both cord lymphoma and NMOSD can respond to steroid [37].

If patient serum is negative for AQP4-IGG and MOG – IGG antibodies,

patients should not be treated with methyl prednisolone or plasmapheresis, pending confirmation of the diagnosis with biopsy, flow cytometry, protein immunoelectrophoresis and and tissue biopsy for cytology [38].

Neuro- Bechet 's disease

Is a vascultic disease affect arteries and veins in addition to other organs which includes optic nerves, cerebrum, brain stem, meninges, skin, peripheral nervous system, it is associated with LATEM which can resemble NMOSD, it is a rare disease, common in the middle east, and very uncommon among Caucasians, from literature, to diagnose neuro Becht, requirements are,

Painful oral ulcer plus two minor criteria which includes, genital ulcers, eye lesion, skin lesion, Positive Pathergy test, (39), neurological manifestation of Bechet's disease includes meningoencephalitis, cerebritis, cerebral atrophy, and LATEM,

Of note, involvement of spinal cord is considered a poor prognostic marker of the disease,

Recent study showed that 70% of spinal cord involvement of Neuro Becht's disease was indistinguishable from LATEM due to NMOSD [40, 41].

Systemin Lupus erythematosus,

Neurological manifestation of lupus is common which includes optic neuronitis, transverse myelitis,

Cognitive impairment, seizure, psychosis, confusion, stroke,

Sometimes it will be difficult to differentiate from multiple sclerosis and NMOSD, most of symptoms related to CNS lupus are distinct from NMOSD which is most probably due to the coexistence of both Neuro lupus and NMOSD in the same patient which could be due to genetic susceptibility of the patient to autoimmunity,

Sjogren Syndrome,

Patient with SS have a similar phenotype disease of the cord, most of myelitis patients in SS have a longitudinal extensive transverse myelitis (LETM) and tested positive for AQP 4 -CSF,

As AQP4, IGG Ab is not found in serum of patients with SS, this strongly support that cord disease in SS is due to NMOSD and not SS, of note, clinical diagnosis including neuroimaging, response to treatment and prognosis did not differ from NMOSD, patients with SS do not have cord disease …

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