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Original Article

Clinical and radiologic manifestation B-cell mediated autoimmune diseases of central nervous system

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Abstract: B-cell mediated autoimmune diseases of central nervous system (CNS) put a heavy burden on different aspects of society and economy. Taken together, there are different types of autoimmune diseases in which B-cells play an important role and affect CNS in a pattern of inflammation. These diseases have some similarities in clinical presentations and radiological findings and some similarities with other diseases in different aspects such as treatments with each disease having its own characteristics. In this review article, we had a survey on some different types of B-cell mediated autoimmune diseases of CNS and explained how they can be distinguished from each other and how distinct they are according to radiological findings. The aim of this study is to distinguish B-cell mediated autoimmune diseases of CNS from other non-B-cell diseases in order to choose the best anti-B-cell treatments. At the end of this article we briefly explain different types of treatments being utilized and the role of corticosteroids in acute phases of different diseases.

Keywords: Central nervous system, radiology, B-Cell, clinical

Introduction

B-cell mediated autoimmune diseases of central nervous system (CNS)s consist of different types of diseases, each having its own clinical presentations and radiological findings but in some diseases no specific lesions are observed in radiological findings and clinicians should diagnose the disease by ruling out other diseases. These diseases are caused due to the inflammatory responses mediated by T-cells and B-cells, leading to mitochondrial injury and oxidative burst. The key aspect of these diseases are production of inflammatory cytokines (i.e. INF-g, TNF, IL-4 and IL-6), exacerbating autoimmune condition and production of antibodies by B-cells [1-3]. T-cells are divided into different subtypes. T-helper (Th) cells that mediate the responses of B-cells by cytokine productions and B-cells that contribute to inflammatory responses by presenting the antigens to Th-cells so they produce more inflammatory cytokines [4]. There are different specific and non-specific markers on the surface of B-cells and the most important of all is CD-20 which is targeted by specific monoclonal antibodies such as rituximab as a highly effective and new therapeutic method for most of B-cell mediated diseases. Other therapies also include systemic corticosteroids which are considered effective but are associated with different systemic side effects [5]. At the acute phase of B-cell mediated disease, systemic pulse of corticosteroids especially methylprednisolone is considered as one of the best therapeutic methods [6] but most of B-cell mediated disease require a maintenance therapy which is determined by the physician. Other treatments include plasma exchange and immunosuppressive agents. Taken together, B-cell mediated diseases of CNS have some common clinical manifestations that might not be helpful for diagnosing the disease but can help physicians to distinguish them from other diseases and choose the best treatments based on radiological findings. In this article, we have reviewed some of the most important B-cell mediated diseases of CNS and explained their clinical characteristics, radiological findings and a number of ways to distinguish them from

each other and from other non-B-cell diseases. At the end of the article, we briefly reviewed different treatments that are mostly accompanied by corticosteroids in acute phases. This review article was made by searching for studies and review articles in PubMed, Google Scholar, and EMBASE using the key terms for each disease such as Neuromyelitis Optica Spectrum Disorder, Myelin oligodendrocyte glycoprotein IgG, Chronic relapsing inflammatory optic neuritis, Recurrent isolated optic neuritis, Multiple sclerosis, Acute disseminated encephalomyelitis, Recurrent transverse myelitis, Anti-*N*-methyl-d-aspartate (NMDA) receptor encephalitis, Glial fibrillary acidic protein (GFAP) astrocytopathy, B-cell, imaging, treatment and rituximab.

Neuromyelitis optica spectrum disorder (NMOSD)

NMOSD is a rare autoimmune disorder of central nervous system (CNS) which is typically characterized by myelitis and demyelination in the brain or spinal cord along with optic neuritis (ON) [7]. A patient with NMOSD is affected by episodes of remission and exacerbation and may suffer from different stages of disability. NMOSD onset is mostly in the third to fourth decades of life and the incidence rate of the disease is reported to be 0.05-4.4 per 100,000 [8]. In order to diagnose NMOSD and distinguish it from other B-cell mediated CNS-autoimmune diseases, a highly disease specific serum immunoglobulin G (IgG) autoantibody against astrocyte water channel aquaporin-4 (AQP4) is used which has also led to diagnosing more complicated forms of the disease [9, 10]. The diagnostic criteria for NMOSD was first developed by Wingerchuk and colleagues in 1999 [11] but it has been progressed and revised through the time. The current criteria of NMOSD diagnosis is divided into two groups of patients [12]. One with positive results for NMO-IgG and the other group with negative or unknown status of NMO-IgG. In patients with seropositive results, presence of one of the core clinical characteristics are enough for diagnosis of NMOSD [13]. Clinical presentations of NMOSD are based on the area involved in disease. For example, ON presents mostly with altitudinal visual field defect, or causes severe residual visual loss. On the other hand, an area postrema clinical syndrome (16%-43% incidence) consists of intractable hiccups or nausea and vomiting and Spinal cord syndrome is presented with paroxysmal tonic spasms [12]. Diagnostic characteristics of NMOSD are: ON, transverse myelitis (TM), area postrema syndrome, other brainstem syndromes, symptomatic narcolepsy or acute diencephalic syndrome and symptomatic cerebral syndrome with magnetic resonance imaging (MRI) lesions. For those patients with seronegative results of NMO-IgG, presence of two episodes of such core clinical characteristics which one of them must be ON, TM or area postrema syndrome along with potential radiologic findings. Recently there have been growing numbers of studies putting emphasis on the role of B-cells in pathogenesis of NMOSD. Furthermore, the efficacy of anti-CD20 (a protein expressed on B-cells) drugs such as Rituximab signifies this theory that NMOSD has a B-cell basis [14]. Radiologic findings of NMOSD is closely resembles those of multiple sclerosis (MS) but the most important difference is presence of longitudinally extensive transverse myelitis (LETM) of more than three vertebral segments [7]. More specific MRI findings are divided based on clinical features of patients. For example, in a patient with ON, brain MRI is almost normal or with changes restricted to optic chiasm such as unilateral or bilateral increased T2 signal or T1 gadolinium enhancement. In patients with brain involvement, lesions are detected in dorsal medulla, hypothalamus, fourth ventricle, and corpus callosum [14]. In those with presentation of TM, a central medullary lesion or focal atrophy involving at least 3 contiguous vertebral segments and in area postrema syndrome, a lesion in dorsal medullary region is observed [13]. These radiologic findings along with clinical presentations and laboratory data are very helpful in diagnosing the disease. Another characteristic of NMOSD which help to distinguish the disease from MS is cerebrospinal fluid (CSF) data. CSF examination in NMOSD patients reveals protein increase (> 1 g/L), high cell count (> 50 or 100 cells/mm^3) and lack of oligoclonal bands which are observed in only 30% of NMOSD patients against 90% of patients with MS [7]. All these clinical, radiological and lab data help to diagnose NMOSD.

Myelin oligodendrocyte glycoprotein IgG (MOG-IgG)

Recently there has been a focus on serum immunoglobulin G (IgG) in patients with inflammatory CNS diseases. The role of B-cell in

pathogenesis of these types of CNS diseases and secretion of such immunoglobulins cannot be ruled out. An important example is MOG-IgG. Recently, there have been documentations with focus on the so called MOG-IgG associated Optic Neuritis, Encephalitis, and Myelitis which is a CNS demyelinating syndrome associated with MOG-IgG [15]. According to the studies, MOG-IgG has been detected in seronegative NMOSD patients. Evidence suggests that the presence of MOG-IgG seropositive NMOSD can be very helpful to distinguish this disease from MS [16]. All these data indicate a possible pivotal role of B-cell lymphocytes in production and secretion of such immunoglobulins and pathogenesis of diseases. MOG-IgG is reported to be found in patients with ON, encephalitis and also demyelinating lesion in CNS [15]. Taken together, MOG-IgG is found in the so called MOG-IgG-associated encephalomyelitis (MOG-EM) [16]. MOG-EM has many overlaps with MS [16, 17] such as occurrence of relapses, meeting McDonald's criteria for MS in 33% of patients, being previously diagnosed with MS or responsive for B-cell targeted treatments such as rituximab. Clinically, patients with MOG-IgG might experience ON, LETM, NMO and encephalomyelitis [15]. But patients with positive results for AQP4-IgG, NMO and LETM have much more occurrence than in MOG-EM (60% and 30% in AQP4-IgG positive against 6-24% and 29-31% in MOG-EM) [18, 19].

Chronic relapsing inflammatory optic neuritis (CRION)

CRION was first described in 2003 [20] as an inflammatory autoimmune disease of optic nerve, which increases the risk of blindness. Mostly CRION is presented with unilateral or bilateral subacute or chronic vision loss with different severity, pain in one eye or both and its response to systemic steroids [21]. Another clinical manifestation of CRION is painful eye movements. The patient also experiences recurrent attacks of such clinical presentations and the episodes between these attacks vary from weeks to years [22]. It must be also noted that neurological deficits, sarcoidosis or systemic autoimmune diseases must be ruled out. A review article reported bilateral visual loss with more than one episode the most important clinical presentation of the disease. Pain was also present in about 35% of patients and uveitis in 7% [23]. They also conclude that diagnosis of CRION is basically by ruling out other diseases based on clinical manifestation, laboratory tests and imaging. Another study performed by Petzold and colleagues demonstrated that 95% of patients with CRION are seronegative for NMO-Ig which can be helpful to distinguish these two autoimmune diseases [24]. Moreover, glial fibrillary acidic protein (GFAP) is elevate in over 98% of patients with NMO which is also helpful [25]. There is evidence of effective treatments with anti-CD20 drugs that target B-cells such as rituximab and atumumab which indeed signify the role of B-cells in pathogenesis of CRION [26]. Imaging studies revealed normal brain MRI in almost 40% of cases [23] and a multi-site consortium with expert MRI neuro-radiologists may be helpful. It has been suggested that high signal abnormalities which enhance, might be observed in optic nerves in brain MRI of patients with CRION [20].

Recurrent isolated optic neuritis (RION)

RION is another inflammatory and autoimmune of CNS which affects optic pathway. As it was mentioned, ON is observed in some CNS diseases such as NMO and MS [11]. It is important to highlight the fact that recurrent isolated optic neuritis can also occur. Based on a report by Beck et al. [27], about 30-50% of patients with ON may experience at least one recurrent attack which is known as RION. It should be noted that based on McDonald's criteria, recurrence of ON affecting both optic nerves could also be considered MS [28]. In a study by Pirko and colleagues [29], they had a survey on patients with RION and suggested that rapid succession of severe ON events in patients, are more possible to develop to a generalized demyelinating disease such as MS or NMO. Such changes in disease forms are almost due to the nature of B-cell mediation of these diseases. It has also been suggested that in patients with RION with absence of any specific radiological findings for MS, other diagnostics such as NMO should be considered [30]. Another important differential diagnosis in a patient with recurrent ON is CRION. It has been reported that taking glucocorticoids is a risk factor in developing RION [31] since steroid dependency is a characteristic sign in CRION [21]. Clinical presentation of RION is not very

particular to this disease. It is consisted of signs and symptoms of ON including visual loss along with at least two of the following criteria: afferent pupillary defect, color vision abnormalities, pain on eye movement, abnormal visual evoked response, and cecocentral field defect [29, 32]. Radiological findings in RION are almost unspecific and might change during time if any other CNS inflammatory disorders appear but mostly, brain MRI of patients with RION is normal or it indicates enhancement of chiasm and both optic nerves [30].

Multiple sclerosis (MS)

MS is an autoimmune disease of CNS which is believed to have inflammatory basis [33-35]. Clinical presentations of MS are due to MS plaques in the CNS. Most patients are reported to experience visual signs such as recurrent episodes of blindness or double vision. Other presentations include weakness and sensation problems [36]. Although the exact pathogenesis of MS still remains unknown, but the important role of different immune cell cannot be ruled out [37]. Inflammation, demyelination, axonal loss and gliosis are morphological manifestation of MS in which different immune cell types and inflammatory cytokines play important roles [38]. Recent data have proven that B-cells have an important and vital role in pathogenesis and etiology of MS [39, 40]. There have been large body of researches on the role of B-cells in MS disease and a very important evidence of this issue is the effectiveness of anti B-cell therapies in MS patients [41]. It must also be noted that some documents indicate the presence of oligoclonal band (OCB) pattern in CSF of MS patients even after anti-lymphocytes therapies which might show the role of other immune cells like plasma cells in pathogenesis of MS [42, 43]. MS disease is divided into five types based on clinical signs and symptoms [44]. The first type is clinically isolated syndrome [45] which is characterized by loss of myelin and neurological signs at the beginning of the disease which must also last at least for 24 hours. The second type is relapsing remitting MS (RRMS) which accounts for 80-85% of diagnosed cases. This type is known by episode of so called attacks following full of partial remission periods between attacks. Primary progressive MS (PPMS) is also another type of MS with continuously impaired neurological functions and no remission. This group consists of 10-15% of known patients. It is also important to notice that these patients experience disease plateaus. The forth type of MS is secondary progressive MS (SPMS) which is almost the next step of MS in RRMS patients in which there will be no more remission periods. Progressive relapsing MS (PRMS) is another MS type in which patients will experience relapses over time with no plateau or remission. Different lines of evidence have revealed important function of T lymphocytes and inflammatory and anti-inflammatory cytokine balance. For years the role of B-cells in MS pathogenesis was ignored but recent evidence put emphasis on pivotal role of B-cells in MS disease. As Magliozzi and colleagues reported, B-cell follicles were detected in 41.4% of SPMS patients [46]. Another important evidence for role of B-cells in MS is the efficacy of anti B-cell therapies such as rituximab, ocrelizumab [47] and presence of oligoclonal immunoglobulins in CSF of more than 90% of MS patients [48, 49]. There has also been a review article on the effectiveness of anti-B-cell therapies preventing formation of new lesions in T2-weighted MRI and of course the relapse of the disease [50]. In this article, Xie and colleagues also indicated that anti-B-cell treatments have no serious adverse effects. Demyelination spots in brain MRI of patients with MS are related to their signs and symptoms which exacerbate with each relapse as it has been observed in radiological findings [51]. Such radiologic findings and clinical characteristics made up the diagnostic criteria of McDonald's [52] by which dissemination in space and/or time is paid attention. There are also some image findings that are more commonly observed in those MS patients with dominant role of B-cells such as the so called tumefactive MS. These findings include prominent GAD enhancing lesions, meningeal enhancement and subpial demyelination which are called tumefactive lesions in MS [53-55]. Some clinical data such as recurrent neurological symptoms like ON, TM and Ataxia along with long standing lesions in visual pathway, spinal cord and corpus callosum and encephalopathy are mostly reported in patients with B-cell prominent MS [55-57]. Based on such clinical findings and radiological data, we suggest that patients who suffer from B-cell prominent MS, might respond very well to anti-B-cell therapies such as rituximab. However,

further clinical trials and studies are still required.

Acute disseminated encephalomyelitis (ADEM)

ADEM is also another autoimmune disease of CNS which is associated with inflammation and demyelination and is also age related with higher incidence among children. The exact etiology of the disease remains unknown however, there is evidence that it might be related to viral diseases, probably preventive vaccination and rarely application of immune sera [58, 59]. The exact mechanism of the disease is not yet clarified but it could be due to activation of different types of B-cell lymphocytes and production of different antibodies. As a result, this disease is also a B-cell mediated inflammatory disease of CNS. It has been also documented by histological studies that perivascular infiltration of lymphocytes along with plasma cells and monocytes are histological characters of ADEM [60]. Clinical manifestation of ADEM is consisted of fever, headache and meningeal signs and neurological signs after the onset of the disease. The most important clinical feature of ADEM is Encephalopathy [61]. Such signs are reported to be seizure, speech disturbance and tremor. The mortality rate of ADEM is reported to be 10-15% which decreases after intensive care procedures [59]. Although, the exact clinical signs and symptoms of ADEM differ based on the potential previous viral disease, they mostly include the mentioned signs. Incidence rate of ADEM is unfortunately not very clear through data because of variability among studies. For instance, Torisu and colleagues reported an incidence rate of 0.64 per 100,000 among children under the age of 15 years [62] but Tselis and Lisak [59] report different incidence rates based on the fundamental disease which ADEM occurs afterwards. They report post-measles ADEM 1:1000, postvaricella ADEM 1:10,000, and post-rubella ADEM 1:20,000. It has also been not clear if ADEM and MS are two distinct diseases or variant of the same disease. Poser and Brinar [63] suggested that sharp edged plaques in brain MRI do not occur in MS. Also the most important thing to distinguish the two diseases is reported to be the occurrence of relapses observed in MS [64]. We also suggest that based on clinical manifestations i.e. neurological signs following fever and viral infection, age of patients and presence of relapses, these two diseases can be separated.

Recurrent transverse myelitis (RTM)

RTM is a recurrent inflammation in spinal cord with autonomic dysfunction, weakness and sensory alterations as its characterized clinical manifestations [65]. It has also been reported that recurrent transverse myelitis can be a part of CNS diseases such as MS or a separate disease on its own. The mechanism of RTM is suggested to be mediated by autoreactive T-lymphocytes which in turn, activate B-cells and humoral immune system. It is reported that IgE, hypereosinophilia and autoantibodies have been detected in spinal cord of patients with RTM [66]. Due to similarities in clinical presentation of RTM with other CNS involving inflammatory diseases such as MS, distinguishing the two diseases is very important. Clinical manifestations of the disease depend on involved spinal segments. Some patients might suffer from sensory loss and ascending paresthesia while others might suffer from urinary retention, hyperreflexia, and bilateral Babinski signs [67]. On one hand, some reports proclaim that RTM signifies the presence of MS disease [68, 69]. On the other hand, other reports of patients with idiopathic RTM [67]. As kim and colleagues [70] report, only 15-20% of patients with transverse myelitis experience recurrent episodes while the rest have just one episode. They also report that RTM can be distinguished from MS caused transverse myelitis by paying attention to clinical characteristics and MRI findings. They reported that RTM occurs mostly in male patients, oligoclonal bands are absent and they face multiple relapses. It should also be noticed that despite the similarities in spinal lesions in T2W1 MRI between RTM and MS [71, 72], in almost all of idiopathic RTM patients, no abnormalities can be detected in brain MRI.

Anti-N-methyl-d-aspartate (NMDA) receptor encephalitis (NMDARE)

NMDARE is a CNS disorder described by Dalmau et al. [73] in which patients suffer from neuropsychiatric symptoms with presence of anti-NMDA receptor antibody in their CSF. The role of B-cells in pathogenesis of this disease still remains unknown but the presence of B-lymphocytes are proven. Clinical manifestation of NMDARE consist of changes in mood,

behavior, and personality, resembling acute psychosis progressing to motor dysfunctions such as seizures, dyskinesias, decreased level of consciousness, and autonomic instability such as cardiac dysrhythmia [74, 75]. These clinical manifestations were observed mostly in young women with teratomas of the ovary [76]. Such Diagnosis of NMDARE is by presence of antibodies to the NMDA receptor in serum or CSF of patients which also correlates with clinical symptoms [77]. Lymphocytes pleocytosis and CSF-specific oligoclonal bands are also detected in CSF of most these patients. These data along with effective responses to anti-B-cell therapies are evidence of B-cell lymphocytes presence [78]. Dyskinesias, seizures and catatonia are the most important psychiatric differential diagnosis of NMDARE and it has been suggested that NMDARE should be ruled out in patients with such symptoms and no previous history of psychiatric disorder. Radiological findings can be a great help in patients with psychiatric and motor dysfunction suspected to have NMDARE but brain MRI is reported to be normal in about 70% of patients. Other 30% will have implicated areas include the hippocampi, cerebellar and cerebral cortex, basal ganglia, brainstem, frontobasal and insular regions [75, 79].

Glial fibrillary acidic protein (GFAP) astrocytopathy

Glial fibrillary acidic protein (GFAP) is a protein found in astrocytes of CNS and is thought to play a pivotal role in maturation and shaping of astrocytes following any brain trauma, inflammation or other CNS diseases [80]. GFAP astrocytopathy is another autoimmune disease of CNS associated with meningitis, encephalitis or myelitis. This disease is usually associated with presence of antibodies against GFAP. In a study, it was indicated that 25% of patients were diagnosed with a range of neoplasms and additional astrocytic or neural antibodies such as anti-AQP4 or NMDAR [81]. The pivotal role of antibodies in pathogenesis of GFAP astrocytopathy along with poleocytosis and presence of oligoclonal bands in CSF of patients are strong evidence of the role of B-cell lymphocytes in pathogenesis of this disease. Clinical manifestation of the disease is variable but most of patients experience seizures, meningitis, encephalitis, multi-organ failure, skin rash, colitis, and heart failure [81, 82]. Brain MRI is also reported to show a linear perivascular radial pattern of gadolinium enhancement in half of patients which might not be very helpful. Due to the important role of serum antibodies against GFAP for diagnosis of this disease, they should be measured. As it was discussed, It should also be noted that serum GFAP levels also increase in NMOSD [25].

Acute hemorrhagic leukoencephalitis (AHL) (Weston-Hurst syndrome)

AHL is known as a rapidly growing hemorrhagic and inflammatory demyelinating disease of CNS which is often diagnosed after the death of the patient [83]. An important differential diagnosis of AHL is ADEM disease and some neurologists believe that AHL is a hyperacute variant of ADEM. Clinical presentation of AHL is similar to ADEM but an important difference is that AHL leads to mortality within days due to brain edema. The patients may suffer from headache, seizures, multifocal or asymmetrical neurologic deficits, and rapid progression to coma [84]. The exact role of B-cells in AHL is still not fully known but there have been documents of neutrophilic and lymphocytic infiltrations in the brain [85]. Imaging studies of AHL indicate hemorrhagic lesions in white matter and brain edema. There have been reports of focal hemorrhages in the white matter of the bilateral posterior frontal and parietal lobes [86]. Such radiological findings along with a history of previous illness or viral disease and rapidly improving clinical manifestations must lead the physicians to AHL diagnosis.

Treatments

All of these diseases are inflammatory diseases and have B-cell mediated autoimmune basis. There are some common as well as specific treatments for each of them. Almost all of these diseases respond very well to administration of corticosteroids in acute phase of the disease but for long term treatments, some specific anti B-cell therapies have been evaluated. For NMOSD, early treatments with corticosteroids play a pivotal role in early attacks. It has been suggested that intravenous (IV) administration of 1 g methylprednisolone for 3-5 days followed by 20 mg oral prednisolone for two weeks can be an effective treatments in NMOSD relapses [7]. Five times plasma exch-

Table 1. Pathogenesis, clinical manifestation and imaging finding of autoimmune diseases of central nervous system

Feature / Disease	Possible known Pathogenesis	Clinical manifestation	Major imaging finding
NMOSD	myelitis and demyelination in the brain or spinal cord along with optic neuritis	altitudinal visual field defect, intractable hiccups or nausea and vomiting, paroxysmal tonic spasms	Mostly changes are restricted to optic chiasm such as unilateral or bilateral increased T2 signal or T1 gadolinium enhancement
MOG-IgG	CNS demyelinating syndrome associated with MOG-IgG	ON, LETM, NMO and encephalomyelitis	unspecific
CRION	inflammatory autoimmune disease of optic nerve	unilateral or bilateral subacute or chronic vision loss with different severity, pain in one eye or both and its response to systemic steroids	revealed normal brain MRI in almost 40% of cases, high signal abnormalities which enhance might be observed in optic nerves
RION	inflammatory autoimmune disease of optic nerve	visual loss, afferent pupillary defect, color vision abnormalities, pain on eye movement, abnormal visual evoked response, and cecocentral field defect	unspecific and might change during time
MS	Inflammation, demyelination, axonal loss and gliosis	visual signs such as recurrent episodes of blindness or double vision, weakness and sensation problems	prominent GAD enhancing lesions, meningeal enhancement and subpial demyelination which are called tumefactive lesions
ADEM	might have relations to viral diseases and probably preventive vaccination and rarely following application of immune sera	Encephalopathy, fever, headache and meningeal signs and afterwards neurological signs appear	sharp edged plaques in brain MRI
RTM	IgE, hypereosinophilia and autoantibodies detected in spinal cord	autonomic dysfunction, weakness, sensory loss, ascending paresthesias, urinary retention, hyperreflexia, and bilateral Babinski signs	Unspecific spinal lesions in T2W1
NMDARE	presence of antibodies to the NMDA receptor in serum or CSF of patients	mood, behavior, and personality, resembling acute psychosis progressing to motor dysfunctions such as seizures, dyskinesias, decreased level of consciousness, and autonomic instability such as cardiac dysrhythmia	brain MRI is reported to be normal in about 70% of patients, 30% will have implicated areas include the hippocampi, cerebellar and cerebral cortex, basal ganglia, brainstem, frontobasal and insular regions
GFAP astropathy	presence of antibodies against GFAP, a protein thought to play a role in maturation and shaping of astrocytes	meningitis, encephalitis or myelitis	Brain MRI is also reported to show a linear perivascular radial pattern of gadolinium enhancement in half of patients
AHL	hemorrhagic and inflammatory demyelinating disease of CNS	headache, seizures, multifocal or asymmetrical neurologic deficits, and rapid progression to coma	hemorrhagic lesions in white matter, brain edema, focal hemorrhages in the white matter of the bilateral posterior frontal and parietal lobes

anges within 5-10 days are also recommended in those nonresponsive to IV steroid therapies [87] but based on B-cell basis of the disease, anti-CD20 drugs such as Rituximab which target B-cells have proven their efficacy [88]. Furthermore, some MS drugs are reported to worsen the disease course such as interferon-beta and Fingolimod [89-91]. Other suggested therapies for NMOSD are Azathioprine (AZA), Rituximab [88], Mitoxantrone and Methotrexate [7]. Rituximab and Mitoxanthrone are also used in treatment of MS. Rituximab that acts as an anti-CD-20 antibody, is now under lots of attention due to its well proven efficacy and lack of documented serious adverse effects. Infusion related reactions and infections such as nasopharyngitis, upper respiratory tract infection and urinary tract infection are the most common adverse effects of rituximab in the two trials on the drug [92, 93]. An important feature of rituximab is that this drug affects both peripheral and central B-cells and decreases the CSF [94]. It has been also indicated that treatments with rituximab can be associated with reduction in gadolinium [25]-enhanced lesions in brain imaging of MS patients [95]. Administration of IV steroids such as 1 g methylprednisolone for 3-7 days is a choice in attack episodes of almost all of the inflammatory diseases as it is also used in CRION [23]. In CRION disease, oral corticosteroid therapy is reported to have an acceptable role in stabilizing the vision after an attack period. Other long term treatments are somehow similar to those in NMOSD but there have been reports of other treatments too [20, 96, 97]: AZA, methotrexate, cyclophosphamide and IVIG. In patients with RION, administration of corticosteroids was a risk factor for development of CRION but such result may not be very liable due to limited population of studied cases. MS is also an inflammatory disease and the patient may experience attacks during the disease period. Different line of evidence put emphasis on the important role of IV corticosteroid administration (1 g methylprednisolone for 3-7 days) [98, 99] and some suggest plasma exchange (5 times within 5-10 days) [100]. Moreover, different immunosuppressant therapies for long term immunosuppression in order to modify the progression have been developed including beta interferones (250 microg every day as standard dosage) [101, 102], ocrelizumab (600 mg every 6 months) [103], Glatiramer acetate (mostly 40 mg three times per week) [104], Fingolimod (0.5 mg daily) [105], Natalizumab (Tysabri) [106] and Alemtuzumab [107]. Each type of treatment has its own efficacy and adverse effects. ADEM and RTM are also treated by using high doses of corticosteroids and plasmaphresis [59]. NMDARE, GFAP astrocytopathy and AHL are also benefited by corticosteroids, plasma exchange and of course anti-B-cell therapies such as rituximab [75, 81] with same dosages used for other diseases. But it should also be noted that immediate psychological treatments in NMDARE with clonidine (0.1 mg orally 2 times a day), trazodone (150 mg orally per day) and benzodiazepines such as alprazolam (0.5 mg orally administered 3 times a day) are also effective in order to control the primary psychological signs and symptoms [75]. Treatments of AHL may include corticosteroids such as intravenous (IV) administration of 1 g methylprednisolone for 3-5 days followed by 20 mg oral prednisolone and also plasma exchange (5 times within 5-10 days) [84]. **Table 1**.

Taken together, almost all of the discussed inflammatory diseases of CNS, except for RION, are treated by using corticosteroids in their acute phase of attack and the long-term treatments can differ from one to another. However, most of them benefit from anti-B-cells treatments including rituximab. Physicians can choose the treatments based on clinical evaluations and imaging studies which help to distinguish such B-cell mediated diseases of CNS.

Disclosure of conflict of interest

None.

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References

[1] Bar-Or A, Fawaz L, Fan B, Darlington PJ, Rieger A, Ghorayeb C, Calabresi PA, Waubant E, Hauser SL, Zhang J and Smith CH. Abnormal B-cell cytokine responses a trigger of T-cell-mediated disease in MS? Ann Neurol 2010; 67: 452-461.

[2] Zadeh AR, Askari M, Azadani NN, Ataei A, Ghadimi K, Tavoosi N and Falahatian M. Mech-

anism and adverse effects of multiple sclerosis drugs: a review article. Part 1. Int J Physiol Pathophysiol Pharmacol 2019; 11: 95-104.
[3] Zadeh AR, Ghadimi K, Ataei A, Askari M, Sheikhinia N, Tavoosi N and Falahatian M. Mechanism and adverse effects of multiple sclerosis drugs: a review article. Part 2. Int J Physiol Pathophysiol Pharmacol 2019; 11: 105-114.
[4] Janeway CA, Travers P, Walport M and Shlomchik MJ. Immunobiology: the immune system in health and disease. 2005.
[5] Goodin DS. Glucocorticoid treatment of multiple sclerosis. Handbook of Clinical Neurology. Elsevier; 2014. pp. 455-464.
[6] Kamei K, Okada M, Sato M, Fujimaru T, Ogura M, Nakayama M, Kaito H, Iijima K and Ito S. Rituximab treatment combined with methylprednisolone pulse therapy and immunosuppressants for childhood steroid-resistant nephrotic syndrome. Pediatr Nephrol 2014; 29: 1181-1187.
[7] De Seze J, Kremer L and Collongues N. Neuromyelitis optica spectrum disorder (NMOSD): a new concept. Rev Neurol 2016; 172: 256-262.
[8] Pittock SJ and Lucchinetti CF. Neuromyelitis optica and the evolving spectrum of autoimmune aquaporin-4 channelopathies: a decade later. Ann N Y Acad Sci 2016; 1366: 20-39.
[9] Asgari N, Owens T, Frøkiær J, Stenager E, Lillevang S and Kyvik KO. Neuromyelitis optica (NMO)-an autoimmune disease of the central nervous system (CNS). Acta Neurologica Scandinavica 2011; 123: 369-384.
[10] Franciotta D, Gastaldi M, Sala A, Andreetta F, Rinaldi E, Ruggieri M, Leante R, Costa G, Biagioli T, Massacesi L, Bazzigaluppi E, Fazio R, Mariotto S, Ferrari S, Galloni E, Perini F, Zardini E, Zuliani L, Zoccarato M, Giometto B and Bertolotto A. Diagnostics of the neuromyelitis optica spectrum disorders (NMOSD). Neurol Sci 2017; 38: 231-236.
[11] Wingerchuk DM, Hogancamp WF, O'brien PC and Weinshenker BG. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 1999; 53: 1107-1114.
[12] Wingerchuk DM, Banwell B, Bennett JL, Cabre P, Carroll W, Chitnis T, de Seze J, Fujihara K, Greenberg B, Jacob A, Jarius S, Lana-Peixoto M, Levy M, Simon JH, Tenembaum S, Traboulsee AL, Waters P, Wellik KE and Weinshenker BG; International Panel for NMO Diagnosis. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 2015; 85: 177-189.
[13] Sahraian MA, Moghadasi AN, Azimi AR, Asgari N, Hajiakhondi F, Abolfazli R, Alaie S, Ashtari F, Ayromlouh H, Baghbanian SM, Moghadam NB, Fatehi F, Foroughipour M, Langroodi HG, Majdinasab N, Nickseresht A, Nourian A, Shayganejad V and Torabi HR. Diagnosis and management of Neuromyelitis Optica Spectrum Disorder (NMOSD) in Iran: a consensus guideline and recommendations. Mult Scler Relat Disord 2017; 18: 144-151.
[14] Etemadifar M, Salari M, Mirmosayyeb O, Serati M, Nikkhah R, Askari M and Fayyazi E. Efficacy and safety of rituximab in neuromyelitis optica: review of evidence. J Res Med Sci 2017; 22: 18.
[15] Dos Passos GR, Oliveira LM, da Costa BK, Apostolos-Pereira SL, Callegaro D, Fujihara K and Sato DK. MOG-IgG-associated optic neuritis, encephalitis, and myelitis: lessons learned from neuromyelitis optica spectrum disorder. Front Neurol 2018; 9: 217.
[16] Jarius S, Paul F, Aktas O, Asgari N, Dale RC, de Seze J, Franciotta D, Fujihara K, Jacob A, Kim HJ, Kleiter I, Kümpfel T, Levy M, Palace J, Ruprecht K, Saiz A, Trebst C, Weinshenker BG and Wildemann B. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J Neuroinflammation 2018; 15: 134.
[17] Jarius S, Ruprecht K, Kleiter I, Borisow N, Asgari N, Pitarokoili K, Pache F, Stich O, Beume LA, Hümmert MW, Ringelstein M, Trebst C, Winkelmann A, Schwarz A, Buttmann M, Zimmermann H, Kuchling J, Franciotta D, Capobianco M, Siebert E, Lukas C, Korporal-Kuhnke M, Haas J, Fechner K, Brandt AU, Schanda K, Aktas O, Paul F, Reindl M and Wildemann B; in cooperation with the Neuromyelitis Optica Study Group (NEMOS). MOG-IgG in NMO and related disorders: a multicenter study of 50 patients. Part 2: epidemiology, clinical presentation, radiological and laboratory features, treatment responses, and long-term outcome. J Neuroinflammation 2016; 13: 280.
[18] Sepúlveda M, Armangue T, Martinez-Hernandez E, Arrambide G, Sola-Valls N, Sabater L, Téllez N, Midaglia L, Ariño H, Peschl P, Reindl M, Rovira A, Montalban X, Blanco Y, Dalmau J, Graus F and Saiz A. Clinical spectrum associated with MOG autoimmunity in adults: significance of sharing rodent MOG epitopes. J Neurol 2016; 263: 1349-1360.
[19] Höftberger R, Sepulveda M, Armangue T, Blanco Y, Rostásy K, Calvo AC, Olascoaga J, Ramió-Torrentà L, Reindl M, Benito-León J, Casanova B, Arrambide G, Sabater L, Graus F, Dalmau J and Saiz A. Antibodies to MOG and AQP4 in adults with neuromyelitis optica and suspected limited forms of the disease. Mult Scler 2015; 21: 866-874.
[20] Kidd D, Burton B, Plant GT and Graham EM. Chronic relapsing inflammatory optic neuropathy (CRION). Brain 2003; 126: 276-284.

[21] Saini M and Khurana D. Chronic relapsing inflammatory optic neuropathy. Ann Indian Acad Neurol 2010; 13: 61-63.
[22] de Seze J. Inflammatory optic neuritis: from multiple sclerosis to neuromyelitis optica. Neuroophthalmology 2013; 37: 141-145.
[23] Petzold A and Plant GT. Chronic relapsing inflammatory optic neuropathy: a systematic review of 122 cases reported. J Neurol 2014; 261: 17-26.
[24] Petzold A, Pittock S, Lennon V, Maggiore C, Weinshenker B and Plant GT. Neuromyelitis optica-IgG (aquaporin-4) autoantibodies in immune mediated optic neuritis. J Neurol Neurosurg Psychiatry 2010; 81: 109-111.
[25] Storoni M, Verbeek MM, Illes Z, Marignier R, Teunissen CE, Grabowska M, Confavreux C, Plant GT and Petzold A. Serum GFAP levels in optic neuropathies. J Neurol Sci 2012; 317: 117-122.
[26] Pescovitz MD. Rituximab, an anti-CD20 monoclonal antibody: history and mechanism of action. American Journal of Transplantation 2006; 6: 859-66.
[27] Beck RW, Gal RL, Bhatti MT, Brodsky MC, Buckley EG, Chrousos GA, Corbett J, Eggenberger E, Goodwin JA, Katz B, Kaufman DI, Keltner JL, Kupersmith MJ, Miller NR, Moke PS, Nazarian S, Orengo-Nania S, Savino PJ, Shults WT, Smith CH, Trobe JD, Wall M and Xing D; Optic Neuritis Study Group. Visual function more than 10 years after optic neuritis: experience of the optic neuritis treatment trial. Am J Ophthalmol 2004; 137: 77-83.
[28] McDonald WI, Compston A, Edan G, Goodkin D, Hartung HP, Lublin FD, McFarland HF, Paty DW, Polman CH, Reingold SC, Sandberg-Wollheim M, Sibley W, Thompson A, van den Noort S, Weinshenker BY and Wolinsky JS. Recommended diagnostic criteria for multiple sclerosis: guidelines from the international panel on the diagnosis of multiple sclerosis. Ann Neurol 2001; 50: 121-127.
[29] Pirko I, Blauwet LK, Lesnick TG and Weinshenker BG. The natural history of recurrent optic neuritis. Arch Neurol 2004; 61: 1401-1405.
[30] Kurne A, Karabudak R, Yalcin-Cakmakli G, Gursoy-Ozdemir Y, Aydin P, Ilksen-Colpak A, Lule S and Kansu T. Recurrent optic neuritis: clues from a long-term follow up study of recurrent and bilateral optic neuritis patients. Eye Brain 2010; 2: 15-20.
[31] Du Y, Li JJ, Zhang YJ, Li K and He JF. Risk factors for idiopathic optic neuritis recurrence. PLoS One 2014; 9: e108580.
[32] Rodriguez M, Siva A, Cross SA, O'Brien PC and Kurland LT. Optic neuritis a population-based study in olrnsted county, minnesota. Neurology 1995; 45: 244-250.
[33] Farrokhi M, Beni AA, Etemadifar M, Rezaei A, Rivard L, Zadeh AR, Sedaghat N and Ghadimi M. Effect of fingolimod on platelet count among multiple sclerosis patients. Int J Prev Med 2015; 6: 125.
[34] Zadeh AR, Farrokhi M, Etemadifar M and Beni AA. Prevalence of benign tumors among patients with multiple sclerosis. American Journal of Experimental and Clinical Research 2015; 2: 127-132.
[35] Farrokhi M, Dabirzadeh M, Dastravan N, Etemadifar M, Ghadimi K, Saadatpour Z and Rezaei A. Mannose-binding lectin mediated complement pathway in autoimmune neurological disorders. Iran J Allergy Asthma Immunol 2016; 15: 251-256.
[36] Vollmer TL, Preiningerova J and Waxman SG. Multiple sclerosis. eLS 2002.
[37] Rafiee Zadeh A, Ghadimi K, Mohammadi B, Naghibi S and Danaeiniya A. Effects of estrogen and progesterone on differ-ent immune cells related to multiple sclerosis. Caspian J Neurol Sci 2018; 4: 39-46.
[38] Payghani C, Khani F, Zadeh AR, Reisi P, Alaei H and Rashidi B. The effect of levothyroxine on serum levels of interleukin 10 and interferon-gamma in rat model of multiple sclerosis. Adv Biomed Res 2017; 6: 118.
[39] Lucchinetti C, Brück W, Parisi J, Scheithauer B, Rodriguez M and Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000; 47: 707-717.
[40] Serafini B, Rosicarelli B, Magliozzi R, Stigliano E and Aloisi F. Detection of ectopic B-cell follicles with germinal centers in the meninges of patients with secondary progressive multiple sclerosis. Brain Pathol 2004; 14: 164-174.
[41] Bittner S, Ruck T, Wiendl H, Grauer OM and Meuth SG. Targeting B cells in relapsing-remitting multiple sclerosis: from pathophysiology to optimal clinical management. Ther Adv Neurol Disord 2017; 10: 51-66.
[42] Solimando A and Tomasicchio A. B-cell therapies in relapsing remitting and primary progressive multiple sclerosis: a short clinical review. Biochem Pharmacol (Los Angel) 2016; 5: 2187-0501.1000218.
[43] Stangel M, Fredrikson S, Meinl E, Petzold A, Stüve O and Tumani H. The utility of cerebrospinal fluid analysis in patients with multiple sclerosis. Nat Rev Neurol 2013; 9: 267-276.
[44] Kira J, Kanai T, Nishimura Y, Yamasaki K, Matsushita S, Kawano Y, Hasuo K, Tobimatsu S and Kobayashi T. Western versus Asian types of multiple sclerosis: immunogenetically and clinically distinct disorders. Ann Neurol 1996; 40: 569-574.

[45] Dieguez-Gonzalez R, Calaza M, Perez-Pampin E, Balsa A, Blanco FJ, Cañete JD, Caliz R, Carreño L, de la Serna AR, Fernandez-Gutierrez B, Ortiz AM, Herrero-Beaumont G, Pablos JL, Narvaez J, Navarro F, Marenco JL, Gomez-Reino JJ and Gonzalez A. Analysis of TNFAIP3, a feedback inhibitor of nuclear factor-κB and the neighbor intergenic 6q23 region in rheumatoid arthritis susceptibility. Arthritis Res Ther 2009; 11: R42.

[46] Magliozzi R, Howell O, Vora A, Serafini B, Nicholas R, Puopolo M, Reynolds R and Aloisi F. Meningeal B-cell follicles in secondary progressive multiple sclerosis associate with early onset of disease and severe cortical pathology. Brain 2007; 130: 1089-1104.

[47] Rahmanzadeh R, Weber MS, Brück W, Navardi S and Sahraian M. B cells in multiple sclerosis therapy-A comprehensive review. Acta Neurol Scand 2018; 137: 544-556.

[48] Link H and Huang YM. Oligoclonal bands in multiple sclerosis cerebrospinal fluid: an update on methodology and clinical usefulness. J Neuroimmunol 2006; 180: 17-28.

[49] Lehmann-Horn K, Kinzel S and Weber MS. Deciphering the role of B cells in multiple sclerosis-towards specific targeting of pathogenic function. Int J Mol Sci 2017; 18.

[50] Xie Q, Li X, Sun J, Yuan B, Li Y, Wang L and Wang M. A meta-analysis to determine the efficacy and tolerability of anti-B-cell monoclonal antibodies in multiple sclerosis. Exp Ther Med 2017; 13: 3061-3066.

[51] Barkhof F, Filippi M, Miller DH, Scheltens P, Campi A, Polman CH, Comi G, Ader HJ, Losseff N and Valk J. Comparison of MRI criteria at first presentation to predict conversion to clinically definite multiple sclerosis. Brain 1997; 120: 2059-2069.

[52] Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M and Kappos L. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011; 69: 292-302.

[53] Lucchinetti CF, Gavrilova RH, Metz I, Parisi JE, Scheithauer BW, Weigand S, Thomsen K, Mandrekar J, Altintas A, Erickson BJ, König F, Giannini C, Lassmann H, Linbo L, Pittock SJ and Brück W. Clinical and radiographic spectrum of pathologically confirmed tumefactive multiple sclerosis. Brain 2008; 131: 1759-1775.

[54] Jitawatanarat P, Tingpej B and Deringer P. Tumefactive multiple sclerosis. BJMP 2011; 4: a419.

[55] Selkirk SM and Shi J. Relapsing-remitting tumefactive multiple sclerosis. Mult Scler 2005; 11: 731-734.

[56] Pilz G, Harrer A, Wipfler P, Oppermann K, Sellner J, Fazekas F, Trinka E and Kraus J. Tumefactive MS lesions under fingolimod: a case report and literature review. Neurology 2013; 81: 1654-1658.

[57] Pittock SJ and Lucchinetti CF. The pathology of MS: new insights and potential clinical applications. Neurologist 2007; 13: 45-56.

[58] Tenembaum S, Chitnis T, Ness J and Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. Neurology 2007; 68 Suppl 2: S23-36.

[59] Wender M. Acute disseminated encephalomyelitis (ADEM). J Neuroimmunol 2011; 231: 92-99.

[60] Dale RC, de Sousa C, Chong WK, Cox TC, Harding B and Neville BG. Acute disseminated encephalomyelitis, multiphasic disseminated encephalomyelitis and multiple sclerosis in children. Brain 2000; 123: 2407-2422.

[61] Alper G, Heyman R and Wang L. Multiple sclerosis and acute disseminated encephalomyelitis diagnosed in children after long-term follow-up: comparison of presenting features. Dev Med Child Neurol 2009; 51: 480-486.

[62] Torisu H, Kira R, Ishizaki Y, Sanefuji M, Yamaguchi Y, Yasumoto S, Murakami Y, Shimono M, Nagamitsu S, Masuzaki M, Amamoto M, Kondo R, Uozumi T, Aibe M, Gondo K, Hanai T, Hirose S, Matsuishi T, Shirahata A, Mitsudome A and Hara T. Clinical study of childhood acute disseminated encephalomyelitis, multiple sclerosis, and acute transverse myelitis in Fukuoka Prefecture, Japan. Brain Dev 2010; 32: 454-462.

[63] Poser CM and Brinar VV. The nature of multiple sclerosis. Clin Neurol Neurosurg 2004; 106: 159-171.

[64] Tardieu M and Mikaeloff Y. What is acute disseminated encephalomyelitis (ADEM)? Eur J Paediatr Neurol 2004; 8: 239-242.

[65] Krishnan C, Kaplin AI, Deshpande DM, Pardo CA and Kerr DA. Transverse myelitis: pathogenesis, diagnosis and treatment. Front Biosci 2004; 9: 1483-1499.

[66] Kerr DA and Ayetey H. Immunopathogenesis of acute transverse myelitis. Curr Opin Neurol 2002; 15: 339-347.

[67] Tippett DS, Fishman PS and Panitch HS. Relapsing transverse myelitis. Neurology 1991; 41: 703-706.

[68] Ropper AH and Poskanzer DC. The prognosis of acute and subacute transverse myelopathy based on early signs and symptoms. Ann Neurol 1978; 4: 51-59.

[69] Berman M, Feldman S, Alter M, Zilber N and Kahana E. Acute transverse myelitis incidence and etiologic considerations. Neurology 1981; 31: 966-971.

[70] Kim KK. Idiopathic recurrent transverse myelitis. Arch Neurol 2003; 60: 1290-1294.

[71] Campi A, Filippi M, Comi G, Martinelli V, Baratti C, Rovaris M and Scotti G. Acute transverse myelopathy: spinal and cranial MR study with clinical follow-up. AJNR Am J Neuroradiol 1995; 16: 115-123.
[72] Dalecky A, Pelletier J, Cherif AA, Levrier O and Khalil R. Acute myelopathies in young patients and multiple sclerosis. Prospective study of 20 cases. Rev Neurol (Paris) 1997; 153: 569-578.
[73] Dalmau J and Bataller L. Limbic encephalitis: the new cell membrane antigens and a proposal of clinical-immunological classification with therapeutic implications. Neurologia (Barcelona, Spain) 2007; 22: 526-537.
[74] Tonomura Y, Kataoka H, Hara Y, Takamure M, Naba I, Kitauti T, Saito K and Ueno S. Clinical analysis of paraneoplastic encephalitis associated with ovarian teratoma. J Neurooncol 2007; 84: 287-292.
[75] Barry H, Byrne S, Barrett E, Murphy KC and Cotter DR. Anti-N-methyl-d-aspartate receptor encephalitis: review of clinical presentation, diagnosis and treatment. BJPsych Bull 2015; 39: 19-23.
[76] Iizuka T, Sakai F, Ide T, Monzen T, Yoshii S, Iigaya M, Suzuki K, Lynch D, Suzuki N, Hata T and Dalmau J. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008; 70: 504-511.
[77] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, Dessain SK, Rosenfeld MR, Balice-Gordon R and Lynch DR. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008; 7: 1091-1098.
[78] Barry H, Hardiman O, Healy DG, Keogan M, Moroney J, Molnar PP, Cotter DR and Murphy KC. Anti-NMDA receptor encephalitis: an important differential diagnosis in psychosis. Br J Psychiatry 2011; 199: 508-509.
[79] Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, Baehring JM, Shimazaki H, Koide R, King D, Mason W, Sansing LH, Dichter MA, Rosenfeld MR and Lynch DR. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007; 61: 25-36.
[80] Eng LF, Ghirnikar RS and Lee YL. Glial fibrillary acidic protein: GFAP-thirty-one years (1969-2000). Neurochem Res 2000; 25: 1439-1451.
[81] Flanagan EP, Hinson SR, Lennon VA, Fang B, Aksamit AJ, Morris PP, Basal E, Honorat JA, Alfugham NB and Linnoila JJ. Glial fibrillary acidic protein immunoglobulin G as biomarker of autoimmune astrocytopathy: analysis of 102 patients. Ann Neurol 2017; 81: 298-309.
[82] Dubey D, Hinson SR, Jolliffe EA, Zekeridou A, Flanagan EP, Pittock SJ, Basal E, Drubach DA, Lachance DH, Lennon VA and McKeon A. Autoimmune GFAP astrocytopathy: prospective evaluation of 90 patients in 1 year. Journal of neuroimmunology 2018; 321: 157-63.
[83] Klein CJ, Wijdicks EF and Earnest F 4th. Full recovery after acute hemorrhagic leukoencephalitis (Hurst's disease). J Neurol 2000; 247: 977-979.
[84] Hofer M, Weber A, Haffner K, Berlis A, Klingel K, Krüger M, Kandolf R and Volk B. Acute hemorrhagic leukoencephalitis (Hurst's disease) linked to Epstein-Barr virus infection. Acta Neuropathol 2005; 109: 226-230.
[85] Hart MN and Earle KM. Haemorrhagic and perivenous encephalitis: a clinical-pathological review of 38 cases. J Neurol Neurosurg Psychiatry 1975; 38: 585-591.
[86] Kuperan S, Ostrow P, Landi MK and Bakshi R. Acute hemorrhagic leukoencephalitis vs. ADEM: FLAIR MRI and neuropathology findings. Neurology 2003; 60: 721-722.
[87] Magaña SM, Keegan BM, Weinshenker BG, Erickson BJ, Pittock SJ, Lennon VA, Rodriguez M, Thomsen K, Weigand S, Mandrekar J, Linbo L and Lucchinetti CF. Beneficial plasma exchange response in central nervous system inflammatory demyelination. Arch Neurol 2011; 68: 870-878.
[88] Das G, Damotte V, Gelfand JM, Bevan C, Cree BA, Do L, Green AJ, Hauser SL and Bove R. Rituximab before and during pregnancy: a systematic review, and a case series in MS and NMOSD. Neurol Neuroimmunol Neuroinflamm 2018; 5: e453.
[89] Kim SH, Kim W, Li XF, Jung IJ and Kim HJ. Does interferon beta treatment exacerbate neuromyelitis optica spectrum disorder? Mult Scler 2012; 18: 1480-1483.
[90] Min JH, Kim BJ and Lee KH. Development of extensive brain lesions following fingolimod (FTY720) treatment in a patient with neuromyelitis optica spectrum disorder. Mult Scler 2012; 18: 113-115.
[91] Yoshii F, Moriya Y, Ohnuki T, Ryo M and Takahashi W. Fingolimod-induced leukoencephalopathy in a patient with neuromyelitis optica spectrum disorder. Mult Scler Relat Disord 2016; 7: 53-57.
[92] Hauser SL, Waubant E, Arnold DL, Vollmer T, Antel J, Fox RJ, Bar-Or A, Panzara M, Sarkar N, Agarwal S, Langer-Gould A and Smith CH; HERMES Trial Group. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med 2008; 358: 676-688.
[93] Hawker K, O'Connor P, Freedman MS, Calabresi PA, Antel J, Simon J, Hauser S, Waubant E, Vollmer T, Panitch H, Zhang J, Chin P and Smith CH; OLYMPUS trial group. Rituximab in patients with primary progressive multiple sclero-

sis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol 2009; 66: 460-471.
[94] Martin Mdel P, Cravens PD, Winger R, Kieseier BC, Cepok S, Eagar TN, Zamvil SS, Weber MS, Frohman EM, Kleinschmidt-Demasters BK, Montine TJ, Hemmer B, Marra CM and Stüve O. Depletion of B lymphocytes from cerebral perivascular spaces by rituximab. Arch Neurol 2009; 66: 1016-1020.
[95] Naismith RT, Piccio L, Lyons JA, Lauber J, Tutlam NT, Parks BJ, Trinkaus K, Song SK and Cross AH. Rituximab add-on therapy for breakthrough relapsing multiple sclerosis A 52-week phase II trial. Neurology 2010; 74: 1860-1867.
[96] Stiebel-Kalish H, Hammel N, Van Everdingen J, Huna-Baron R and Lee AG. Intravenous immunoglobulin in recurrent-relapsing inflammatory optic neuropathy. Can J Ophthalmol 2010; 45: 71-75.
[97] Thorne JE, Wittenberg S, Kedhar SR, Dunn JP and Jabs DA. Optic neuropathy complicating multifocal choroiditis and panuveitis. Am J Ophthalmol 2007; 143: 721-723.
[98] Goodkin D, Kinkel R, Weinstock-Guttman B, Medendorp SV, Secic M, Gogol D, Perryman J, Uccelli M and Neilley L. A phase II study of iv methylprednisolone in secondary-progressive multiple sclerosis. Neurology 1998; 51: 239-245.
[99] Morrow SA, Stoian CA, Dmitrovic J, Chan SC and Metz LM. The bioavailability of IV methylprednisolone and oral prednisone in multiple sclerosis. Neurology 2004; 63: 1079-1080.
[100] Keegan M, Pineda AA, McClelland RL, Darby CH, Rodriguez M and Weinshenker BG. Plasma exchange for severe attacks of CNS demyelination: predictors of response. Neurology 2002; 58: 143-146.
[101] Interferon beta-1b is effective in relapsing-remitting multiple sclerosis I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. Neurology 1993; 43: 655-661.
[102] Barbero P, Verdun E, Bergui M, Pipieri A, Clerico M, Cucci A, Ricci A, Bergamasco B and Durelli L. High-dose, frequently administered interferon beta therapy for relapsing-remitting multiple sclerosis must be maintained over the long term: the interferon beta dose-reduction study. J Neurol Sci 2004; 222: 13-19.
[103] Kappos L, Li D, Calabresi PA, O'Connor P, Bar-Or A, Barkhof F, Yin M, Leppert D, Glanzman R, Tinbergen J and Hauser SL. Ocrelizumab in relapsing-remitting multiple sclerosis: a phase 2, randomised, placebo-controlled, multicentre trial. Lancet 2011; 378: 1779-1787.
[104] Johnson KP, Brooks BR, Cohen JA, Ford CC, Goldstein J, Lisak RP, Myers LW, Panitch HS, Rose JW, Schiffer RB, Vollmer T, Weiner LP and Wolinsky JS. Extended use of glatiramer acetate (copaxone) is well tolerated and maintains its clinical effect on multiple sclerosis relapse rate and degree of disability. Neurology 1998; 50: 701-708.
[105] Kappos L, Radue EW, O'Connor P, Polman C, Hohlfeld R, Calabresi P, Selmaj K, Agoropoulou C, Leyk M, Zhang-Auberson L and Burtin P; FREEDOMS Study Group. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med 2010; 362: 387-401.
[106] Polman CH, O'Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, Phillips JT, Lublin FD, Giovannoni G, Wajgt A, Toal M, Lynn F, Panzara MA and Sandrock AW; AFFIRM Investigators. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med 2006; 354: 899-910.
[107] CAMMS223 Trial Investigators, Coles AJ, Compston DA, Selmaj KW, Lake SL, Moran S, Margolin DH, Norris K and Tandon PK. Alemtuzumab vs. interferon beta-1a in early multiple sclerosis. N Engl J Med 2008; 359: 1786-1801.