NÖRO PSİKİYATRİ ARŞİVİ
ARCHIVES OF NEUROPSYCHIATRY

REVIEW

Arch Neuropsychiatry 2018;55: (Supplement 1): S1–S9
https://doi.org/10.29399/npa.23418

Multiple Sclerosis: Diagnosis and Differential Diagnosis

Sami ÖMERHOCA, Sinem YAZICI AKKAŞ, Nilüfer KALE İÇEN

Department of Neurology, İstanbul Bağcılar Research and Training Hospital, İstanbul, Turkey

ABSTRACT

The diagnostic criteria for multiple sclerosis (MS) have been continuously evolved since 1950's, and gained speed parallel to the development of detailed laboratory methods. The common aim for all the defined criteria up to now, is to establish the dissemination in space and time of the clinical picture caused by the lesions in the central nervous system (CNS), and to rule out other diseases which might mimic MS. There is no definite measure or laboratory marker for the diagnosis of MS, yet. Both the clinical features of the disease, and laboratory investigations such as magnetic resonance imaging (MRI), and cerebrospinal fluid (CSF) analyses are being used.

Clinical and imaging findings that may be seen in MS, can also be mimicked by some infectious, neoplastic, genetic, metabolic, vascular and other idiopathic inflammatory demyelinating disorders (IIDD). In the earlier stages of the disease, especially IIDD's such as neuromyelitis optica spectrum disorders (NMOs) and acute disseminated encephalomyelitis (ADEM) can cause diagnostic difficulty, however, these disorders which have both distinct pathogeneses and clinical courses than MS, should also be treated differently. Therefore, to identify MS-related attacks and determine the final diagnosis is vital for the correct treatment choice and longterm disability prevention. In this manuscript the principal approach for the diagnosis and differential diagnosis of MS has been reviewed regarding the recent guidelines.

Keywords: Multiple sclerosis, McDonald's criteria, diagnostic markers, MS differential diagnosis, inflammatory demyelinating disorders

Cite this article as: Ömerhoca S, Yazıcı Akkaş S, Kale İçen N. Multiple Sclerosis: Diagnosis and Differential Diagnosis. Arch Neuropsychiatry 2018;55: (Suppl 1):S1-S9. https://doi.org/10.29399/npa.23418

INTRODUCTION

Multiple sclerosis (MS) is an acquired idiopathic, inflammatory demyelinating disorder of the central nervous system (CNS) in which the myelin sheath is disrupted due to genetic and environmental factors (1, 2). The basic pathological data for MS have been unveiled by the histopathological studies started by Carswell in 1838, and Cruveilhier in 1941 (3, 4). Later, Charcot has noted the relationship between the clinical and histopathological aspects of MS in 1868, and named the disease as ***"la sclerose en plaques"***. In his studies, Charcot noted that MS lesions were characterized by ***"plaques"*** consisting of focal demyelination, inflammation, gliosis and various degrees of axonal loss. The distribution of these plaques in the CNS, and their histopathological components have also been described at that time. At the earlier stages of the plaques, inflammation and demyelination is abundant, whereas in the later stages axonal damage and neuronal loss are predominant (5). This description is still valid as a gold standard today.

Different clinical and pathological subtypes of MS have been identified. In about 80–85% of the patients there are attacks (relapses), and complete or partial remissions following them, whereas in 10–15%, there is a slow progressive course without any relapses (6). Inflammatory demyelinating MRI findings suggestive of MS in patients who has never experienced a relapse, but had an MRI for other reasons, named as radiological isolated syndrome (RIS) (7). Since there are no clinical signs or symptoms associated with MS, this group is not included to the subtypes of MS. On the other hand, patients presenting with isolated optic neuritis, spinal cord involvement, or brainstem syndrome, and/or hemispheric involvement, with findings resembling MS plaques on MRIs, are called to have clinical isolated syndrome (CIS) which is considered the first attack of MS (8). Lublin et al. grouped the clinical patterns in 1996 as relapsing remitting MS (RRMS), relapsing progressive MS (RPMS), secondary progressive MS (SPMS), and primary progressive MS (PPMS) (6). Moreover, in 2013, active and non-active forms were added (9):

1. Clinical isolated syndrome (CIS)
2. Relapsing remitting MS (RRMS): Active and non-active RRMS
3. Progressive MS (PMS): Active progressive, active non-progressive, non-active progressive, non-active non-progressive (stable) subtypes were described.

Correspondence Address: Nilüfer Kale İçen, İstanbul Bağcılar Eğitim ve Araştırma Hastanesi, Nöroloji Bölümü, İstanbul, Turkey • E-mail: sinemyazici@gmail.com
Received: 08.10.2018, **Accepted:** 01.11.2018
©Copyright 2018 by Turkish Association of Neuropsychiatry - Available online at www.noropskiyatriarsivi.com

The main aim in MS treatment is to reduce the inflammatory response, and resulting neuroaxonal damage in order to prevent sustained disability. One of the major factors that influence the treatment success is to establish the correct and early diagnosis, and to start the right treatment at the right time. In this manuscript, we reviewed the principal approach for the diagnosis and differential diagnosis of MS, and diagnostic algorithms based on recent updates of the MS diagnostic guidelines.

Approach to the Diagnosis of MS

There are no markers specific for MS diagnosis. Diagnosis mainly depends on the medical history and neurological examination. Therefore, it is crucial to define the attacks correctly. The attacks are defined as new neurological deficits lasting more than 24 hours, that can be associated with an anatomical localization, in the absence of fever or any infection. Usually the neurological deficit develops subacutely over 2 to 4 weeks, and it usually resolves completely or partially over 6 to 8 weeks, either spontaneously, or after treatment with corticosteroids. On the MRI, there could be an involvement of a single anatomical region as presented by monofocal attack, or the involvement may consist more than one anatomical CNS regions concurrently such seen by multifocal attacks (1, 2).

In a patient presenting with an attack, the most important paraclinical test to confirm the diagnosis is magnetic resonance imaging (MRI) with intravenous (iv) contrast agent containing gadolinium. This can both present the nature of the lesions (inflammatory and demyelinating characteristics) for differential diagnosis, and the distribution of the lesions within the CNS (evidence of dissemination in time [DIT] and space [DIS] for the latest diagnostic criteria).

Another important examination in the diagnosis of MS is lumbar puncture for cerebrospinal fluid (CSF) examination, and basic CSF biochemistry (glucose, protein, albumin, IgG, and lactate levels), microbiological tests (cell count, and, if needed, other microbial and ELISA tests), cytopathological evaluation (screening for malignant cells) and tests for intrathecal immunoglobulin G (IgG) synthesis, both quantitatively (IgG index) and qualitatively (oligoclonal band [OCB] analysis). Other than those, when needed, electrophysiological tests (visual evoked potentials [VEP] and somatosensory evoked potentials [SEP]) can be done. All the tests and investigations included to the diagnostic workup of a patient with suspected MS are listed on Table 1.

Since 1950's, there were many attempts to develop various criteria to increase the sensitivity and specificity in the diagnosis of MS. The main aim of these criteria was to show the dissemination in time and space of the lesions within the CNS that cause the clinical picture, and to discriminate other disorders that might mimic MS clinically and radiologically. In some cases, MS could be easily diagnosed by the clinical and the laboratory features. However, in early stages of the disease, or in patients with atypical clinical and radiological features, making the final diagnosis might be difficult.

The first comprehensive clinical criteria were proposed by Schumacher, et al, in 1965 (10). According to those criteria, after a neurologist eliminated other probable diagnoses, and defined the attack leading to a diagnosis of "probable MS", there should be two conditions that must be present. The first was two or more attacks, at least 1 month apart, lasting at least 24 hours (currently we call this DIT), and the second is the presence of two or more neurological findings showing the involvement of more than one region in the CNS (currently we call this DIS).

In 1983, Poser included paraclinical tests to these criteria, and defined the diagnosis as "clinically definite", or "laboratory supported definite" MS, which increased the reliability of the diagnosis (11). At this time evoked potentials and CSF analyses were added to the clinical criteria as paraclinical supportive findings. MRI criteria were developed later, and are still being used (Table 2).

Table 1. Investigations for the diagnosis of MS

Primary Tests

1. **Blood tests** (hemogram, renal and liver function tests, electrolyte levels, sedimentation, CRP, B12, folate and vitamin D, thyroid function tests, lipid panel, viral serology (anti HIV, anti HCV, HbsAg, anti-Hbs), VDRL-RPR, ANA (1/320 titer and patterns), if ANA positive ENA profile, antiphospholipid antibodies, anti-ds DNA
2. **MRI** (cranial, cervical and thoracal)
3. **CSF analyses** (CSF protein, CSF and concurrent blood glucose, CSF albumin and IgG, CSF lactate, serum albumin and IgG, CSF IgG index, CSF OCB analysis with IEF electrophoresis)
4. **In patients with optic neuritis: VEP and optic coherence tomography**

Secondary Tests

1. **Evoked potentials (VEP ve SEP)**
2. **Optic coherence tomography**
3. **Urodynamic testing**
4. **Cognitive testing**

Other tests for differential dagnosis

1. **Further biochemical tests** (if there is suspicion of vasculitis, wider autoantibody panel, 24-hour urine analysis, GFR evaluation, for rheumatological disorders anti CCP, serum complement levels, for lymphoma serum anti beta2 microglobulins, for sarcoidosis blood and CSF ACE levels, for adrenoleukodystrophy adrenal hormone levels, long/very long chain fatty acids, for mitochondrial diseases serum piruvate, lactate levels, for neuromyelitis optica anti-aquaporin 4 and anti-MOG tests)
2. **Specific tests for infectious etiologies** (antibodies for Lyme disease and Brucellosis, PPD and quantiferon tests for tuberculosis)
3. **Angiography (cerebral, fluorescein, MRA)**
4. **Biopsy** (skin, lymph node, brain and/or leptomeninx, peripheral nerve, other)
5. **Eye examination** (retina evaluation for metabolic disorders, uvea evaluation for sarcoidosis and Behçet's disease)
6. **Hearing tests** (for Susac)
7. **Electrophysiology (nerve conduction studies, EMG)**
8. **Chest X-ray** (for chronic latent/sequel infectious lung disorders, and hilar adenopathy)
9. **Cardiac examination** (echocardiography for SLE, and mitochondriopathies)
10. **Others** (Schirmer test for Sjögren's disease, and salivary gland syntigraphy, for malignancies and metabolic disorders SPECT and PET)

McDonald criteria were first developed in 2001, and were later revised in 2005, 2010, and lately in 2017 (12–15). Radiological criteria were first included in 2001, later the description of dissemination in time was changed, therefore without waiting for a new attack it became possible to diagnose "definite MS", if the criteria for dissemination in space were met. Besides VEP findings and CSF OCB positivity, elevated IgG index was also included to the criteria. Therefore, it became possible to diagnose definite MS at the first attack. In the 2001 criteria the MS diagnosis was classified as "definite MS", "suspected MS" and "non-MS" (12). In the 2005 revision, MRI and CSF criteria were modified to prevent misunderstanding, and for the first time criteria for PPMS were added (Tables 3 and 4). When 2001 and 2005 criteria were compared, the diagnostic sensitivity remained similar (91% versus 88%), while specificity increased from 50%

Table 2. MRI criteria for the MS diagnosis, used up to now

Paty, 1988	>4 T2 hyperintense lesions or >3 T2 hyperintense lesions, at least one periventricular (PV)
Fazekas et al., 1988	>3 T2 hyperintense lesions with the characteristics below; >1 infratentorial, >1 PV, >1 lesion larger than 6 mm
Barkhof et al., 1997	At least 3 of the following: (1) >1 lesion with gadolinium (Gd) enhancement (2) >1 juxtacortical lesion (3) >1 infratentorial lesion (4) >3 PV lesions
Barkhof & Tintore, 2000	Only item (1) of Barkhof 1997 criteria was changed: >1 lesion with Gd enhancement; or >9 T2 hyperintense lesions

to 60% (13). In 2010, OCB positivity and VEP test were taken out of the criteria and the criteria for dissemination in space were simplified (Table 3). However, these simplified new criteria were criticized for being too widely covering. Moreover, removal of CSF analysis from the criteria increased the difficulty of diagnosis in atypical cases (14).

In 2015, basic features of MRI scanning were defined by Magnetic Resonance Imaging in MS Study Group (MAGNIMS). Features such as the minimum slice thickness, technical characteristics of the sequences and contrast sections, such as the amount of the contrast agent (Gadolinium, Gd), and the timing of the rescanning after gadolinium administration were clearly defined. Additionally, the necessary timing for the follow-up MRIs at earlier stages (RIS, CIS) were also clarified (16). Among the paraclinical investigations, MRI is the most important diagnostic tool with its high sensitivity up to 95%. However, over time its negative predictive value increased up to 65% and these high false positive diagnostic inaccuracy consisted other disorders such as neuromyelitis optica (NMO), systemic connective tissue disorders, vasculitis, or even healthy asymptomatic persons, which would let to a a revision of the McDonald's criteria in 2017 (15).

The three major revisions in the Mc Donald's 2017 criteria are that (Table 5):

1. If the patients with typical CIS would have clinical or radiological evidence of dissemination in space, and CSF-specific OCB's were present, then the diagnosis of definite MS can be made without the need for the disseamination in time demonstrated by MRI or second new attack.

2. In the 2010 criteria spinal symptomatic lesions were not considered as an evidence for dissemination in space or time, however, since it was shown that these lesions decreased the diagnostic sensitivity when they were added, so spinal lesions were also included in 2017 criteria.

3. Cortical lesions were also included in dissemination in space besides juxtacortical, periventricular, and infratentorial lesions.

The Role of CSF Analysis in MS Diagnosis

CSF evaluation is the most reliable investigation in differentiation of infectious and non-infectious inflammatory disorders of the CNS. The

Table 4. Change of the criteria for primary progressive MS over time

McDonald 2005	>1 year of progressive clinical course (dissemination in time) and at least 2 of the following: (1) >9 cranial T2 hyperintense lesions (2) >4 cranial T2 hyperintense lesions and positive VEP (3) >2 focal spinal cord T2 hyperintense lesions (4) Positive CSF*
McDonald 2010	>1 year of progressive clinical course (dissemination in time) and at least 2 of the following: (1) >1 T2 hyperintense lesion in cranial** area (2) >2 T2 hyperintense lesions in spinal*** area (3) Positive CSF*
McDonald 2017	>1 year of progressive clinical course (PR or PP) (dissemination in time) and at least 2 of the following: (1) >1 T2 hyperintense lesion in cranial area (cortical area added to others) (2) >2 T2 hyperintense lesions in spinal area (with brainstem and spinal cord symptomatic lesions) (3) CSF OCB positivity

* Increased IgG index or OCB positivity.
** At least one of juxtacortical, periventricular or infratentorial areas.
*** Symptomatic lesions in brainstem or spinal cord are not counted.

Table 3. McDonald 2010 criteria; and according to McDonald 2010 criteria, MRI criteria for dissemination in time and space

McDonald 2010 criteria		
Clinical finding	**Criteria met**	**Required condition**
>2 attacks >2 lesions' objective clinical finding	Dissemination in time Dissemination in space	-
>2 attacks 1 lesion's objective clinical finding	Dissemination in time	Dissemination in space
1 attack >2 lesions' objective clinical finding	Dissemination in space	Dissemination in time
1 attack 1 lesion's objective clinical finding	-	Dissemination in space and time

MRI criteria for dissemination in time and space	
Dissemination in space	**Dissemination in time**
Presence of at least 3: (1) 1 Gd (+) lesion, or 9 T2 hyperintense lesions (2) 1 infratentorial* lesion (3) 1 juxtacortical lesion (4) 3 periventricular lesions	(1) New Gd (+) lesion >3 months after the first attack or (2) newT2 lesion >30 days after the first MRI

* Spinal cord lesions are equivalent of an infratentorial lesion.

Table 5. Revised 2017 Mc Donald criteria for MS diagnosis

Clinical attack	Number of lesions with objective clinical finding	Requirements for MS diagnosis
>2	>2	None
>2	1 (a lesion from a different CNS area which clearly indicates the previous attack)	None
>2	1	Dissemination in space (I): A new attack on a different CNS region or dissemination in space shown on MRI
1	>2	Dissemination in time (II): A new attack on a different CNS region or OCB (+) in CSF
1	1	Dissemination in space (I) and time (II) (I) A new attack on a different CNS region or dissemination in space shown on MRI (II) A new attack on a different CNS region or dissemination in time shown on MRI or OCB (+) in CSF

pathological changes reflected by CSF can extremely beneficial in the diagnosis of patients with atypical MRI findings. Besides its role in the differential diagnosis, CSF analysis is especially an important and useful diagnostic tool in earlier stages of MS such as RIS and CIS.

Measuring albumin and immunoglobulin levels in CSF and serum helps us to discriminate whether the increased protein content is resulting from the disrupted blood brain barrier (BBB), or an isolated intrathecal synthesis is in question. CSF/serum albumin concentration gradient (Qalb) is an important parameter which reflects the BBB permeability (17). In patients with MS, CSF protein and Qalb levels were found usually normal or slightly elevated, in about 20% of the patients a mild increase in the BBB permeability might be seen. Isolated intrathecal IgG synthesis has been formulated mathematically by Reiber as quantitative intrathecal IgG analysis (18). Whereas the commonly used IgG index equals QIgG/Qalb (CSF IgG/serum IgG)/(CSF albumin/serum albumin) with a normal value below 0.7. On the other hand, oligoclonal IgG detection is a qualitative method which performed by parallel electrophoresis of serum and CSF samples with isoelectric focusing (19). In about 80–90% of the patients with definite MS OCBs were found positive, however, the presence of OCBs in CSF is not pathognomonic for MS. The CSF in MS is typically clear with normal pressure and glucose levels, in about 1/3 there may be elevated protein, but if it is above 100 mg/dl a diagnosis of MS should be highly unlikely. There might be a lymphocytic mild pleocytosis; however, if the cell count is over 50/mm^3, again other diseases in the differential diagnosis should be considered (18, 19).

DIFFERENTIAL DIAGNOSIS OF MS

1. Other Idiopathic Inflammatory Demyelinating Disorders (IIDD)

Acute Disseminated Encephalomyelitis (ADEM)

ADEM is an immune mediated inflammatory demyelinating CNS disease which is classically monophasic, but might occasionally be recurrent. The exact mechanism of ADEM is not completely understood, but it has been associated with environmental triggers such as some infectious organisms and immunizations in genetically susceptible individuals. In about 70–77% of the cases there is a preceding infection or vaccination before attacks. In the clinical picture encephalopathy is predominant, and on MRI there are characteristically multiple, widespread, asymmetric T2 hyperintense lesions bilaterally throughout the brain with variable contrast enhancement sign (20). It is more common in pediatric age and affects preferably males than females. The clinical picture is typically an acute or subacute onset encephalopathy that may range from lethargy to coma, accompanied with other focal or multifocal signs according to the affected CNS site. The encephalitis-like prodromal symptoms such as fever, fatigue, headache, or nausea were not seldom (20, 21). Cranial nerve involvements, meningismus, epileptic seizures or cortical impairment, which are quite atypical for MS were also seen often in ADEM. It might be difficult to discriminate the disease from infectious, granulomatous, or malignant pathologies. There is no specific biomarker or laboratory test to establish the diagnosis of ADEM. CSF findings may reveal abnormalities in 50%-80% of the patients. CSF analyses may include lymphocytic pleocytosis (usually <100 cells/mm3, but occasionally higher), and mildly elevated protein levels (usually <100 mg/ml). CSF pressure might also slightly elevated, and glucose levels are typically normal. In about 1/3 there might be a transient OCB positivity and IgG index elevation (21, 22). The most sever form of ADEM is acute hemorrhagic encephalopathy (Weston Hurst hemorrhagic encephalopathy) which course is usually fatal. In recent studies, some of the patients with ADEM were shown to have anti-MOG antibodies (44%), which is much higher than CIS (8%) or RRMS (2%) patients (23).

Schilder's Disease

Schilder's myelinoclastic diffuse sclerosis has been described as a single or multiple large supratentorial lesions, and seen more commonly in children than adults. In the early stages it can be misdiagnosed as MS due to white matter lesions, however, impaired consciousness and rapid radiological progression might be discriminative. It may show similar characteristics to tumefactive MS due to the lesion morphology on MRI ie large lesions accompanied with edema and peripheral contrast enhancement (24).

Balo's Concentric Sclerosis

Typical MRI feature of Balo's concentric sclerosis differs from other IIDDs with a helix of intertwined T2 hyper-and hypointense ribbons. Histopathology shows an onion ring appearance of demyelinated and normal myelinated layers. It has a monophasic course with a rapid progression, and could be confused in clinical practice with fatal Marburg's disease. Headache, cognitive impairment, encephalopathy, and epileptic seizures which are not usual in MS clinic, may be helpful in the differential diagnosis (25).

Marburg Variant of MS

Marburg's disease is a fulminant and potentially fatal IIDD. It presents with a rapidly progressive impaired consciousness leading to coma, and usually ending within weeks with decerebration and death. On MRI supratentorial, infratentorial and spinal cord lesions also progress rapidly, and corticosteroids are not beneficial in the disease management unlike to MS (26).

Neuromyelitis Optica (NMO) and NMO Spectrum Disorders (NMOSD)

Neuromyelitis optica (NMO), also called as Devic's syndrome, is a rare idiopathic IIDD which typically involves optic nerves and spinal cord with recurrent severe attacks causing permanent disability. Its patophysiology has been shown to be a channelopathy due to antibodies against

aquaporin-4, a protein localized in foot processes of astrocytes, which is specific for NMO. On MRI there may be unilateral or bilateral optic nerve and/or chiasma involvement, whereas transverse myelitis attacks involve typically more than 3 vertebral segments, representing longitudinal expanded lesions with edema and contrast enhancement (27). Brain MRI may be uninteresting or show unexplained clinically silent and nonspecific white matter abnormalities. In 50-85% of patients brain white matter lesions were demonstrated. Periependymal lesions surrounding the ventricular system both in diencephalic area surrounding the third ventricles and cerebral aqueduct, and most spesifically in the dorsal brainstem adjacent to the fourth ventricle near the periaqueductal area. Optic neuritis and transverse myelitis attacks may occur concurrently or at different times. Monophasic and relapsing forms of NMO may be mistakenly considered as CIS related to MS, RR or RPMS, however, it can be discriminated by clinical course presenting rapid progression of the neurological deficits, and less responsiveness to the corticosteroid treatment. MS relapses may show spontaneous remissions, however, NMOs attacks usually require more aggressive treatments like plasma exchange (28). Besides clinical and MRI characteristics, anti-aquaporin-4 antibodies (NMO-IgG) has high specificity, and relatively high sensitivity, however, it should kept in mind that it may be negative in about 30–40% of the patients. Recently, antibodies against myelin-oligodendrocyte glycoprotein (MOG) have been found in some patients with clinical features of NMOSD. Patients who were suggestive for NMOSD but lacking on NMO IgG, should be tested for anti-MOG antibodies. Since NMO and MS have immunopathological differences, their long term treatment are also different. Therefore, it is crucial to discriminate them early to prevent disability accumulation (29).

2. Idiopathic Inflammatory Non-Demyelinating Diseases

Neuro-Behçet's Disease

Behçet's disease is a chronic recurrent multisystemic idiopathic vasculitic disease affecting all sizes of veins, and to a lesser extent, arteries. Its diagnosis depends on patients history and clinical findings, consisting of oral aphthae recurring at least 3 times a year, plus any two findings out of genital ulcers, or scars, skin lesions such as erythema nodosum, pseudofolliculitis or papulopustular lesions, uveitis, and positive pathergy test are required for the diagnosis. Although the ethiopatogenesis is not clear yet, it is presumed to be caused by the effects of environmental factors such as stress and infections in patients with genetic susceptibility (30). Neurological involvement may be seen in 3–9% of patients with Behçet's disease. The neurological symptoms and signs may present either during the disease course or occure as the first clinical manifestation. In the absence of any other causes, as well as existing typical MRI and abnormal CSF findings compatible with the neurologic involvement of Behçet, have been described as neuro-Behçet's disease (NBD). NBD has characteristic clinical presentation patterns which were grouped in two main syndromes as parenchymal and nonparanchymal. Paranchymal syndromes are consisted from brainstem involvement (including ophthalmoparesis, cranial neuropathy, cerebellar or pyramidal dysfunction), multifocal presentations, myelopathy, optic neuropathy and cerebral hemispheric involvement (including encephalopathy, hemiparesis, hemisensory loss, seizures and dysphasia, and mental changes including cognitive dysfunction and psychosis). Venous thrombosis, pseudotumour cerebri, intracranial aneurysm/dissection and acute meningeal syndrome were referred as nonparanchymal syndromes. Besides CNS involvement peripherial nervous system could also be affected in form of peripheral neuropathy, mononeuritis multiplex and myopathy/myositis. Most common neurologic manifestation among all these various clinical pictures is brainstem-diencephalic involvement (30, 31). When NBD was presented with parenchymal focal or multifocal T2/FLAIR hyperintense CNS lesions during an ongoing course with attacks and remissions, and with a good response to steroid treatment, it may mimic MS clinically. However, MRI findings are usually pathognomonic for NBD. The lesions are most commonly located in mesencephalo-diencephalic region, reaching up to the basal ganglia, and could be unilateral or bilateral T2 hyperintense lesions presenting with edema and contrast enhancement. Pontobulbar lesions may also be found. Infrequently, periventricular or subcortical white matter lesions, or transverse myelitis may be seen (31).

Although the age of disease onset is similar to MS, NBD is seen most commonly in males. Frequent symptoms of MS such as optic neuritis, internuclear ophthalmoplegia and sensory symptoms are infrequent in NBD. When clinical characteristics are difficult to discriminate, MRI characteristics may be helpful, the large mesodiencephalic lesions are quite typicall for NBD. On the other hand, periventricular and callosal ovoid plaques which are typical for MS, are not seen in NBD. However, it should be kept in mind that both disorders could be seen together at the same time. CSF findings could be used to discriminate NBD from MS, as in NBD there may be a marked disruption of the BBB (increased Qalb), prominent pleocytosis which might be neutrophillic in early, and lymphocytic in later stages, and a mild protein elevation could exist, while OCBs are rarely positive in NBD (<% 20) (31, 32).

Systemic lupus erythematosus (SLE)

SLE is an autoimmune disorder with unclear etiology, where genetic, hormonal, immune and environmental factors are thought to play an important role. Pathogenic autoantibodies, immunecomplexes, and complement system are involved in the disease ethiopathogenesis. SLE is a multisystemic disorder with various manifestations such as arthritis, malar rash, photosensitivity, serositis, renal disorders, hematologic disorders, oral/nasal ulcers, discoid rash, presence of antinuclear antibodies (ANA), neurologic and immunologic disorders (anti-dsDNA, anti-Sm, antiphospholipid antibodies, anti-SSA, anticardiolipins, anti-nRNP, anti-beta2GPI, lupus anticoagulant, and anti-SSB). Various degrees of neurological involvement may be seen in about 10% to 50% of the patients. Rarely, neurological involvement might be the first manifestation, and could present with headache, psychotic changes, dementia, aseptic meningitis, and epileptic seizures (33). Similar to MS, SLE is affecting mostly young adults, and females. There may be diagnostic challenge when the disease onset is occurred with nonspecific symptoms such as depressive findings and mild cognitive decline. Attacks with scotoma or focal neurologic deficits could be suggestive for MS diagnosis, and cause a diagnostic inaccuracy. On MRI detected periventricular and subcortical white matter lesions, specially in patients with pure neurologic manifestations, could also mimic MS. Moreover, OCBs may be present in CSF of SLE patients. Systemic symptoms of SLE must be questioned in suspected patients, autoantibody tests will also helpful in the diagnosis. Vasculitic involvement of cerebral vessels might be shown with neuroradiological investigations such as angiography. There are some cases in the literature where MS and SLE can occur together (33, 34).

Sjögren Syndrome

Sjögren syndrome is a chronic, inflammatory, autoimmune, systemic disease characterized by dysfunction of exocrine glands that results in symptoms of dry eyes (keratokonjunktivitis sicca; xeroftalmia), dry mouth (xerostomia), and with a range of other systemic manifestations such as arthritis, Raynaud phenomenon, lung, kidney, liver, gastrointestinal, endocrine, vascular, and CNS involvements. It is associated with anti-SS-A (anti-Ro) and anti-SS-B (anti-La) autoantibodies. Secondary Sjogren syndrome is associated with other autoimmune (such as MS and antiphospholipid syndrome) or connective tissue disorders (mostly with SLE), and the course is than more severe. Neurological involvement in primary Sjögren syndrome may be seen in about 20–25% of the patients. In both types of the disease different forms of peripheral and central neuropathies were common (87%), whereas the CNS involvement is

thought to be rare. Focal or diffuse CNS involvement may mimic MS clinically or radiologically. Myelitis or optic neuropathy attacks may be also confused as MS (35). In 80% of patients presenting with focal neurological deficits, MRI shows hyperintense lesions compatible with demyelinating disease similar to MS. In the differential diagnosis, CSF analysis might be helpful, since in Sjögren syndrome instead of oligoclonal pattern seen in MS, only one or two bands could be detected. The investigation of the exocrine gland dysfunction by Schirmer test for dry eye and/or Rose Bengal test (one of the most commonly used tests for evaluation of ocular surface epithelial damage), screening for autoantibodies (anti-SS-A, anti-SS-B), and salivary gland biopsy will be helpful in the diagnosis. In patients presenting with the first TM attack, increased sedimentation rate, and positive autoantibodies (ANA, anti-SSA, anti-SSB) may be suggestive for a systemic autoimmune diasese other than MS, and in case of CNS involvement with periventricular lesions CSF analyses and detailed systemic clinical evaluation may be helpful (36).

Paraneoplastic Neurological Syndromes

Paraneoplastic neurological syndromes (PNS) were described relatively recently, and include immune mediated disorders associated with cancer, however without an effect of direct invasion, metastasis, or treatment complications or opportunistic infections. Although their etiology is not clear, it is proposed that immune response driven against the cancer cells might be effecting the CNS through the molecular mimicry. They are most commonly associated with small cell lung cancer (35–50%), thymoma (30–50%), and monoclonal gammapathies (5–15%). Two major groups are defined, first is those associated with intracellular anti-neuronal antibodies (anti-Hu, anti-Yo, anti-CV/CRMP5, anti-Ri, anti-Ma1/Ma2, anti-Amfifizin, etc.), and the second includes two subgroups, one with little or no response to immunotherapy, those associated with cell surface antibodies, mostly voltage gated ion channels (VGKC, NMDAR, VGCC, AMPAR, etc.) and the other with complete or partial response to immunotherapy (37). Classical neurological presentations include paraneoplastic encephalomyelitis, limbic encephalitis, opsoclonus-myoclonus-ataxia, with subacutely developing cognitive and behavioural changes and saccadic eye movement abnormalities. These do not cause a differential diagnostic issue with MS. However, paraneoplastic cerebellar degeneration, paraneoplastic myelitis, and retinopathies (cancer-associated retinopathy [CAR], and melanoma-associated retinopathy [MAR]), can mimic MS optic involvement clinically, although their MRI findings do not resemble MS (38).

Sarcoidosis

Sarcoidosis is a multisystemic disease with noncaseating granulomatous lesions, with an unknown Ietiology, and pathogenesis. It involves primarily the lungs, lymph nodes, and eye, however any organ system can be damaged. Sarcoidosis could form a widespread neurological involvement, affecting both the central and peripheral nervous system. CNS involvement has been reported in about 5–15% of the patients, probably due to a leptomeningeal or vascular involvement. The most common findings are cranial neuropathies (50–75% in general, and mostly facial paralysis 25–50%), and intracranial mass lesions due to granulomas. Various symptoms could be presented according to the localization of the lesions such as encephalopathy, seizures, hydrocephalus, optic chiasm involvement, cognitive and psychiatric findings. Autopsy studies imply that asymptomatic CNS involvement occurs in about 25%. Clinical course is slowly progressive, wheras acute attacks are seen very rare. Isolated neurological involvement which may be misdiagnosed as MS has been reported very rare (1%). The most likely mimics of MS due to sarcoidosis are cranial neuropathies, and uveitis. For differentiation from MS, the diagnostic work-up including pulmonary radiology, serum angiotensin converting enzyme levels (ACE), serum C-reactive protein (CRP) levels, serum and 24-hour urinary calcium levels, as well as CSF examination are mandatory. If needed transbronchial hilus biopsy or skin biopsy should be done for the histopathological diagnosis (39).

Wegener Granulomatosus (Granulomatous Poliangiitis)

Wegener granulomatosis is a multisystemic necrotizing angiitis affecting midsize and small arteries with unknown etiology. Characteristically it affects upper and lower respiratory system and kidneys (glomerulonephritis) by causing necrotizing granulomas. A seropositivity for antineutrophil cytoplasmic antibodies (c-ANCA) could be fould. The most common neurological complication is polineuropathy presenting with mononeuritis multiplex. Other involvement types are cranial neuropathies (mostly II., VI., and VII. nerves), pachymeningitis, cerebrovascular events, and epileptic seizures. Focal neurological findings and cranial neuropathies can rarely be misdiagnosed as MS, usually presence of systemic findings, elevated sedimentation rate, and c-ANCA positivity are suggestive for Wegener (40).

3. Infectious Diseases

Lyme Disease

Lyme disease is a chronic infection, which is most common vector conveyed infectious diseases, because it is transmitted by tick bite caused by Borrelia burgdorferii, a gram-negative bacterium, and is endemic in North America and Northern Europe. There are 3 stages of the disease: 1st stage (first few weeks), local infection and fever, 2nd stage (until the sixth month) heart and nervous system involvements (meningitis, meningoencephalitis, meningoradiculoneuritis [Bannwarth syndrome]); and 3rd stage (after the 6th month) chronic hematological, cardiac and cerebral vasculitic stage with spastic paraparesis (41). If untreated at the first stage, CNS involvement is almost certain. Commonly there is a lymphocytic meningitis and multifocal peripheral nerve involvement, and rarely a clinical picture resembling demyelinating disease may occur. On cranial MRI lesions of vasculitic involvement and/or diffuse CNS demyelination can be found. If suspected, the history about tick bite have to be questioned, and antibodies against B.burgdorfei (IgM and IgG) should be screened. CSF analysis could show a lymphocytic pleocytosis and elevated protein levels, however CSF OCB are rarely positive. Detection of bacterial antibodies in CSF is diagnostic for Lyme (42).

HTLV-1 (Human T-Lymphotropic Virus-1) Associated Myelitis

HTLV-I associated infections are endemic in India and Far East. They can be transmitted sexually, or with blood products, iv substance use, although the transmission rate is very high, it rarely causes clinical manifestations. A slowly progressive paraparesis with brisk tendon reflexes, muscle pain, and sphincteric dysfunction is the common neurological presentations. Radiologically there could be seen areas with supratentorial demyelination, and/or spinal cord atrophy. Rare cases of HTLV-1 associated myelitis and concurrent NMO have been reported in endemic areas. With the increasing immigration all over the world, its importance in the differential diagnosis of MS is increasing. Especially in patients with myelitis it could be difficult to discriminate the slowly progressive course from PPMS, however, lack of OCB positivity and detection of HTLV-1 antibodies in CSF and serum would be helpful (43).

HIV (Human Immunodeficiency Virus) Associated CNS Involvement

HIV-associated neurological disorders are being more commonly encountered due to the management of highly active antiretroviral treatments. However, far before the diagnosis, about 10–20% of the patients were presenting first with neurological symptoms. Neurological involvement could occur by a direct affect of the pathogen (meningitis, encephalopathy, myelopathy, peripheral neuropathy, and cranial neuropathy), or indirectly to opportunistic infections (toxoplasma,

Table 6. Differential diagnosis in CIS and RRMS patients

Monophasic and Monofocal involvement
Optic Neuropathy - Idiopathic inflammatory demyelinating diseases: Neuromyelitis Optica - Viral: Herpes Viruses, hepatitis A, enteroviruses, exhantema - Bacterial: Streptococci, meningococci, brucellosis, salmonella, borrelia, micobacteria - Systemic Vasculitides - Sarcoidosis - Metabolic disorders: Leber's hereditary optic neuropathy (LHON) - Chronic recurrent inflammatory optic neuropathy (CRION) **Transverse Myelitis** - Idiopathic (30%) - Acute necrotizing myelitis: after rabies vaccination, acute lymphoblastic leukemia, lymphoma, carcinomas, tuberculosis, HIV, HTLV-1
Multifocal involvement and relapsing course
Idiopathic inflammatory disorders - Acute disseminated encephalomyelitis (rarely recurrent) - Systemic Lupus Eritematosus - Antiphospholipid Syndrome - Behçet's disease - Sjogren's Syndrome - Isolated CNS Vasculitis - Susac's Syndrome - Neurosarcoidosis

CMV, PML, etc), neoplasias, vascular diseases, nutritional/metabolic impairments, and drug toxicity. Both the CNS, and the peripheral nervous system can be affected (44). It may be easier to diagnose secondary neurological involvements in patients who already have HIV diagnosis. However, in those without a diagnosis yet, who are presenting with a myelopathy at the first time, MS could be misdiagnosed since radiological findings may also confusing. A slowly progressive spastic paraparesis may mimic the clinical course of PPMS. There may be white matter lesions in the brain MRI, as well. It can be diagnosed with anti-HIV positivity (45).

Progressive Multifocal Leukoencephalopathy (PML)

It is a rare CNS disease caused by JC virus (John Cunningham virus). Healthy individuals may be seropositive for JCV without having the disease, however, in case of acquired or medical immunosuppressions the disease would result to an opportunistic infection. Motor or cognitive symptoms would arise according to the involved site of the CNS. The characteristic radiological manfestations are bilateral, mostly large, diffuse, asymmetric, supratentorial T2 and FLAIR hyperintense lesions (46, 47). Any hematological disease, malignancy, history of chemotherapy, or other immunosuppression, or HIV seropositivity should be questioned. Both radiologically the presence of bilateral widespread large white matter lesions with poor or no contrast enhancement, and clinically the findings of encephalopathy, seizures, aphasia with rapid progression could be the clues for atypical MS features (47).

Neurosyphilis

Neurosyphilis is one of the chronic complications of an untreated spirochetal infection caused by Treponema pallidum. It may occur months or years after the first transmission. Practically, it can involve any site of the CNS or the peripheral nervous system roots. Widespread involvement patterns may cause diagnostic difficulties. Cranial nerve involvement, ataxia, walking difficulty, sphinctery disturbance could be seen in neurosyphilis which might mimic MS. On cranial MRI supratentorial white matter lesions might be seen (48). In CSF analyses, a lymphocytic pleocytosis and elevated protein leves are prominent, but OCB positivity is very rare. For the diagnosis the antibodies (VDRL, RPR, TPHA, FTA-ABS) should be screened in serum and CSF.

4. Metabolic Disorders

Adrenoleukodystrophy (X-linked adrenoleukodystrophy, Addison-Schilder disease)

Adrenoleukodystrophy (ALD) is an X-linked recessive peroxisomal neurodegenerative disorder which is caused by disrupted very long chain fatty acid metabolism due to defect in ABCD1 gene on Xq28. It results a slow progressing myelopathy and demyelination in the CNS. Typical MRI findings may be discriminative for the diagnosis, and it is important to detect the carriers, and asymptomatic individuals to prevent the disease development because of newly developing treatment options. Typical cases have an onset at pediatric age, which is quite earlier than typical MS. Besides typical radiological features, no elevation of plasma cortisol levels in response to ACTH test, and increased amounts of very long chain fatty acids (over 90%) on metabolic screening are useful for the current diagnosis (49).

Leber's Hereditary Optic Neuropathy (LHON)

LHON, is a genetic disorder transmitted by mitochondrial DNA, which leads to attacks of vision loss in young adults. Unlike MS, it is seen more frequently in males, and visual loss tends to be bilateral. For definite diagnosis mitochondrial genetic testing is required. Usually there is a progressive impairment of vision, but in some cases there may be an relapsing course which might mimic MS in early stages. The cranial MRI findings are usually limited to optic chiasma, and it is uncommon to see parenchymal demyelinating lesions (50). The vasculitic appearance of the optic disks on fluorescein angiography, without any leakage is typical for LHON involvement.

Subacute Combined Degeneration

The CNS requires vitamin B12 in order to function optimally. Chronic deficiency of vitamin B12 causes neurological picture called subacute combined degeneration (SCD), with or without classical megaloblastic anemia. Posterior and lateral columns of the spinal cord are mainly affected, an intracranial demyelination could present in frontal white matter. Clinically there are sensorial ataxia due to the involvement of posterior columns, spastic paraparesis, sexual dysfunction, and Lhermitte's sign may be observed. On spinal MRI contrast enhancing posterior column lesions may be seen. For the diagnosis, the blood test abnormalities such as serum low vitamin B12 levels, megaloblastic anemia, increased serum homocysteine level, presence of methylmalonic asiduria are important to done. On the other hand, a peripheral neuropathy may accompany SCD, which is highly unlikely for MS (51).

Besides above mentioned disorders which can frequently mimic MS, other disorders such as primary CNS vasculitis, craniovertebral abnormalities, attacks of migraine with aura, CADASIL/CARASIL, Fabry's disease, Susac's syndrome, metastatic tumors, multifocal gliomas, primary CNS lymphoma, tuberculosis, toxoplasmosis and cysticercosis, and many others should be kept in mind in the differential diagnosis of MS (Table 6).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - NKİ; Design - NKİ, SÖ, SYA; Supervision - NKİ, SYA; Resource - SÖ, SYA; Analysis and/or Interpretation - SYA; Literature Search - SYA; Writing - SÖ, SYA; Critical Reviews - NKİ.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study has received no financial support.

REFERENCES

1. Sobel RA, Moore GRW. Demyelinating diseases. S Love, DN Louis, DW Ellison, editors. Greenfield's Neuropathology. New York: Oxford Univ. Press; 2008. p.1513–1608.
2. Lucchinetti CF, Brück W, Parisi J, Scheithauer B, Rodriguez M, Lassmann H. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. Ann Neurol 2000;47:707–717.
3. Carswell, R. Pathological Anatomy: Illustrations on Elementary Forms of Disease. London: Longman; 1838.
4. Cruveilhier J. Anatomie pathologique du corps humain; ou description, avec figures lithographiees et coloriees, des diverses alterations morbides dont le corps humain est susceptible. Vol. II. Paris: Bailliere 1829–1842; 1981.
5. Charcot JM. Histologie de la sclérose en plaques. Gaz Hop (Paris) 1868;41:554–555.
6. Lublin FD, Reingold SC; National Multiple Sclerosis Society (USA) Advisory Committee on Clinical Trials of New Agents in Multiple Sclerosis. Defining the clinical course of multiple sclerosis: results of an international survey. J Neurol 1996;46:907–911. [CrossRef]
7. Siva A, Saip S, Altintas A, Jacob A, Keegan BM, Kantarci OH. Multiple sclerosis risk in radiologically uncovered asymptomatic possible inflammatory-demyelinating disease. Mult Scler 2009;15:918–927. [CrossRef]
8. Miller DH, Barkhoff F, Montalban X, Thomson A, Filippi M. Clinically isolated syndromes suggestive of multiple sclerosis Part I. Natural history, pathogenesis, diagnosis and prognosis. Lancet Neurol 2005;4:281–288. [CrossRef]
9. Lublin FD, Reingold SC, Cohen JA, Cutter GR, Sørensen PS, Thompson AJ, Wolinsky JS, Balcer LJ, Banwell B, Barkhof F, Bebo B Jr, Calabresi PA, Clanet M, Comi G, Fox RJ, Freedman MS, Goodman AD, Inglese M, Kappos L, Kieseier BC, Lincoln JA, Lubetzki C, Miller AE, Montalban X, O'Connor PW, Petkau J, Pozzilli C, Rudick RA, Sormani MP, Stüve O, Waubant E, Polman CH. Defining the clinical course of multiple sclerosis: the 2013 revisions. J Neurol 2014;83:278–286. [CrossRef]
10. Schumacher GA. Multiple sclerosis. Arch Neurol 1966;14:571–573. [CrossRef]
11. Poser CM, Paty DW, Scheinberg L, McDonald WI, Davis FA, Ebers GC, Johnson KP, Sibley WA, Silberberg DH, Tourtellotte WW. New diagnostic criteria for multiple sclerosis: guidelines for research protocols. Ann Neurol 1983;13:227–231. [CrossRef]
12. 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, 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. [CrossRef]
13. Polman CH, Reingold SC, Edan G, Filippi M, Hartung HP, Kappos L, Lublin FD, Metz LM, McFarland HF, O'Connor PW, Sandberg-Wollheim M, Thompson AJ, Weinshenker BG, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria". Ann Neurol 2005;58:840–846. [CrossRef]
14. Polman CH, Reingold SC, Banwell B, Clanet M, Cohen JA, Filippi M, Fujihara K, Havrdova E, Hutchinson M, Kappos L, Lublin FD, Montalban X, O'Connor P, Sandberg-Wollheim M, Thompson AJ, Waubant E, Weinshenker B, Wolinsky JS. Diagnostic criteria for multiple sclerosis: 2010 revisions to the McDonald criteria. Ann Neurol 2011;69:292–302. [CrossRef]
15. Alan J Thompson, Brenda L Banwell, Frederik Barkhof, William M Carroll, Timothy Coetzee, Giancarlo Comi, Jorge Correale, Franz Fazekas, Massimo Filippi, Mark S Freedman, Kazuo Fujihara, Steven L Galetta, Hans Peter Hartung, Ludwig Kappos, Fred D Lublin, Ruth Ann Marrie, Aaron E Miller, David H Miller, Xavier Montalban, Ellen M Mowry, Per Soelberg Sorensen, Mar Tintoré, Anthony L Traboulsee, Maria Trojano, Bernard M J Uitdehaag, Sandra Vukusic, Emmanuelle Waubant, Brian G Weinshenker, Stephen C Reingold, Jeffrey A Cohen. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol 2018;17:162–173. [CrossRef]
16. Rovira À, Wattjes MP, Tintoré M, Tur C, Yousry TA, Sormani MP, De Stefano N, Filippi M, Auger C, Rocca MA, Barkhof F, Fazekas F, Kappos L, Polman C, Miller D, Montalban X; MAGNIMS study group. Evidence-based guidelines: MAGNIMS consensus guidelines on the use of MRI in multiple sclerosis-clinical implementation in the diagnostic process. Nat Rev Neurol 2015;11:471–482. [CrossRef]
17. Lowenthal A, Karcher D. Cerebrospinal fluid in multiple sclerosis. Clin Neurosci 1994;2:211–214.
18. Reiber H, Felgenhauer K. Protein transfer at the blood-cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. Clin Chim Acta 1987;163:319–328. [CrossRef]
19. Kabat EA, Freedman DA, Murray JP, Knaub V. A study of the crystalline albumin, gamma globulin and total protein in the cerebrospinal fluid of one hundred cases of multiple sclerosis and in other diseases. Am J Med Sci 1950;219:55–64. [CrossRef]
20. Tenembaum S, Chitnis T, Ness J, Hahn JS; International Pediatric MS Study Group. Acute disseminated encephalomyelitis. J Neurol 2007;68(S2):S23–S36. [CrossRef]
21. Koelman DL, Mateen FJ. Acute Disseminated Encephalomyelitis: current controversies in diagnosis and outcome. J Neurol 2015;262:2013–2024. [CrossRef]
22. Wingerchuk DM. Postinfectious encephalomyelitis. Curr Neurol Neurosci Rep 2003;3:256–264. [CrossRef]
23. Di Pauli F, Mader S, Rostasy K, Schanda K, Bajer-Kornek B, Ehling R, Deisenhammer F, Reindl M, Berger T. Temporal dynamics of anti-MOG antibodies in CNS demyelinating diseases. Clin Immunol 2011;138:247–254. [CrossRef]
24. Bacigaluppi S, Polonara G, Zavanone ML, Campanella R, Branca V, Gaini SM, Tredici G, Costa A. Schilder's disease: non-invasive diagnosis?: A case report and review. Neurol Sci 2009;30:421–430. [CrossRef]
25. Hardy TA, Tobin WO, Lucchinetti CF. Exploring the overlap between multiple sclerosis, tumefactive demyelination and Baló's concentric sclerosis. Mult Scler 2016;22:986–992. [CrossRef]
26. Kuhlmann T, Lassmann H, Brück W. Diagnosis of inflammatory demyelination in biopsy specimens: a practical approach. Act Neuropathol 2008;115:275–287. [CrossRef]
27. Jarius S, Wildemann B. Aquaporin-4 antibodies (NMO-IgG) as a serological marker of neuromyelitis optica: a critical review of the literature. Brain Pathol 2013;23:661–683. [CrossRef]
28. de Seze J, Kremer L, Collongues N. Neuromyelitis optica spectrum disorder (NMOSD): A new concept. Rev Neurol 2016;172:256–262. [CrossRef]
29. Akman-Demir G, Tüzün E, Waters P, İçöz S, Kürtüncü M, Jarius S, Yapıcı Z, Yeşilot N, Vincent A, Eraksoy M. Prognostic implications of aquaporin-4 antibody status in neuromiyelitis optica patients. J Neurol 2011;258:464–470. [CrossRef]
30. Akman-Demir G, Serdaroglu P, Tasci B. Clinical patterns of neurological involvment in Behçet's disease: evaluation of 200 patients. Brain 1999;122:2171–2182. [CrossRef]
31. Kocer N, Islak C, Siva A, Saip S, Akman C, Kantarci O, Hamuryudan V. CNS involvement in neuro-Behçet's syndrome: an MRI study. AJNR Am J Neuroradiol 1999;20:1015–1024.
32. Siva A, Kantarci O, Saip S, Altintas A, Hamuryudan V, Islak C, Kocer N, Yazici H. Behçet's disease: diagnostic and prognostic aspects of neurological involvement. J Neurol 2001;248:95–103. [CrossRef]
33. Tani C, Palagini L, Moraes-Fontes MF, Carli L, Mauri M, Bombardieri S, Mosca M. Neuropsychiatric questionnaires in systemic lupus erythematosus. Clin Exp Rheumatol 2014;32:59–64.
34. Cannerfelt B, Nystedt J, Jönsen A, Lätt J, van Westen D, Lilja A, Bengtsson A, Nilsson P, Mårtensson J, Sundgren PC. White matter lesions and brain atrophy in systemic lupus erythematosus patients: correlation to cognitive dysfunction in a cohort of systemic lupus erythematosus patients using different definition models for neuropsychiatric systemic lupus erythematosus. Lupus 2018;27:1140–1149. [CrossRef]
35. Berkowitz AL, Samuels MA. The neurology of Sjogren's syndrome and the rheumatology of peripheral neuropathy and myelitis. Pract Neurol 2014;14:14–22. [CrossRef]
36. Moreira I, Teixeira F, Martins Silva A, Vasconcelos C, Farinha F, Santos E. Frequent involvement of central nervous system in primary Sjögren syndrome. Rheumatol Int 2015;35:289–294. [CrossRef]
37. Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 2007;13:261–271. [CrossRef]
38. McKeon A, Pittock SJ. Paraneoplastic encephalomyelopathies: pathology and mechanisms. Acta Neuropathol 2011;122:381–400. [CrossRef]
39. Hebel R, Dubaniewicz-Wybieralska M, Dubaniewicz A. Overview of neurosarcoidosis: recent advances. J Neurol 2015;262:258–262. [CrossRef]
40. Asakura K, Muto T. Neurological involvement in Wegener's granulomatosis. Brain Nerve 2013;65:1311–1317.
41. Younger DS. Epidemiology of Lyme Neuroborreliosis. Neurol Clin 2016;34:875–886. [CrossRef]
42. Halperin JJ. Neuroborreliosis. J Neurol 2017;264:1292–1297. [CrossRef]
43. Bangham CR, Araujo A, Yamano Y, Taylor GP. HTLV-1-associated myelopathy/tropical spastic paraparesis. Nat Rev Dis Primers 2015. [CrossRef]
44. Smail RC, Brew BJ. HIV-associated neurocognitive disorder. Handb Clin Neurol 2018;152:75–97. [CrossRef]

45. Letendre S. Central nervous system complications in HIV disease: HIV associated neurocognitive disorder. Top Antivir Med 2011;19:137–142.
46. Tan CS, Koralnik IJ. Progressive multifocal leukoencephalopathy and other disorders caused by JC virus: clinical features and pathogenesis. Lancet Neurol 2010;9:425–437. [CrossRef]
47. Augusto L, Neves N, Reis C, Abreu C, Sarmento A. Clinical and Radiological Characterization of Progressive Multifocal Leukoencephalopathy in HIV-Infected Patients: A Retrospective Analysis and Review of the Literature. Acta Med Port 2015;28:286–296. [CrossRef]
48. Berger JR, Dean D. Neurosyphilis. Handb Clin Neurol 2014;121:1461–1472. [CrossRef]
49. Berger J, Forss-Petter S, Eichler FS. Pathophysiology of X-linked adrenoleukodystrophy. Biochimie 2014;98:135–142. [CrossRef] https://doi.org/10.1016/j.biochi.2013.11.023
50. Riordan-Eva P, Harding MD. Leber's hereditary optic neuropathy: the clinical revelance of different mitochondrial DNA mutations. J Med Genet 1995;32:81–87. [CrossRef]
51. Kumar N. Neurologic aspects of cobalamin (B12) deficiency. Handb Clin Neurol 2014;120:915–926. [CrossRef]