Multiple Sclerosis and Related Disorders 37 (2020) 101452

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Review article

Differential diagnosis of multiple sclerosis and other inflammatory CNS diseases

Paula Wildner, Mariusz Stasiołek*, Mariola Matysiak

Department of Neurology, Medical University of Lodz, Lodz, Poland

ARTICLE INFO

Keywords:
Multiple sclerosis
Rheumatic diseases
White matter lesions
CNS inflammatory disorder
Magnetic resonance imaging

ABSTRACT

Multiple sclerosis (MS) is the most common acquired demyelinating disorder of the central nervous system (CNS). Diagnosing MS can be very challenging owing to its variable clinical features and lack of specific tests. Magnetic resonance imaging (MRI) is a key measure in this process. Although white matter lesions on brain MRI are regarded as a hallmark of MS, they are a common radiological finding and their pattern may overlap in particular CNS inflammatory diseases. The increasing availability of therapies for MS and the knowledge of benefits associated with an early treatment underscore the importance of precise and quick diagnosis. Despite an extensive research, currently no fully specific diagnostic test is available to distinguish between CNS inflammatory disorders. In this review, we discuss characteristic findings and distinctive features of CNS inflammatory disorders, with particular focus on rheumatic diseases.

1. Introduction

White matter lesions (WML) on brain magnetic resonance imaging (MRI) are common findings and in high percentage of cases they imply further diagnosis of multiple sclerosis (MS) and related demyelinating disorders. The reported prevalence of MS is increasing (Browne et al., 2014), which is at least partially a consequence of growing consciousness of MS in the society and also a wider availability of diagnostic tools, especially MRI. This situation, together with an inappropriate use of the diagnostic criteria, results in a considerable proportion of misdiagnoses. Since early implementation of treatment is crucial for its efficacy, precise diagnosis seems to be essential. Recent studies have emphasized the issue of erroneous diagnosis of MS and potential pernicious consequences which it entails, including aggressive immunosuppressive therapy (Solomon et al., 2016; Siva, 2018 Feb; Solomon et al., 2012; Solomon and Weinshenker, 2013). Studies have revealed that the most frequent disorder misdiagnosed as MS is migraine alone or in combination with other diagnosis, and it accounts for 22% of incorrectly diagnosed patients. Other conditions commonly misdiagnosed as MS are fibromyalgia, nonspecific white matter lesions, psychiatric disorders and neuromyelitis optica spectrum disorders (NMOSD). White matter lesions due to vasculitis also should not be disregarded (Solomon et al., 2016). Additionally, acute disseminated encephalomyelitis (ADEM) has to be considered as a cause of the first demyelinating episode, especially in the pediatric population. Differential diagnosis of MS involves also a broad spectrum of disorders eg.

Abbreviations: AC-13, apolipoprotein A1 C-terminal fragment; aCL, anticardiolipin antibodies; ADEM, acute disseminated encephalomyelitis; ANA, antinuclear antibodies; ANCA, antineutrophil cytoplasmic antibodies; anti-dsDNA, anti-double stranded DNA; anti-P, anti-ribosomal P; anti-Sm, anti-Smith; anti-β_2GP1, anti-beta2glycopretein 1; aPL, antiphospholipid antibodies; AQP4, aquaporin-4; BBB, blood-brain barrier; BD, Behçet disease; BLyS, B-lymphocyte stimulator; CIS, clinically isolated syndrome; CNS, central nervous system; CRP, C-reactive protein; CSF, cerebrospinal fluid; DIS, dissemination in space; DIT, dissemination in time; EAN, European Academy of Neurology; ECTRIMS, European Committee of Treatment and Research in Multiple Sclerosis; EGPA, eosinophilic granulomatosis with polyangitis; ESR, erythrocyte sedimentation rate; GABAR, gamma-aminobutyric acid receptor; GFAP, glial fibrillary acid protein; GPA, granulomatosis with polyangitis; HLA, human leukocyte antigen; ICAM, Intercellular Adhesion Molecule; IgG, immunoglobulin G; IL, interleukin; INF, interferon; LAC, lupus anticoagulant; LETM, longitudinally extensive transverse myelitis; MAGNIMS, Magnetic Resonance Imaging in Multiple Sclerosis; MOG, myelin oligodendrocytes glycoprotein; MPA, microscopic polyangitis; MPO, myeloperoxidase; MRI, magnetic resonance imaging; MS, multiple sclerosis; NBD, Neuro-Behçet disease; NMDA, N-methyl-D-aspartate; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorders; NPSLE, neuropsychiatric systemic lupus erythematosus; NR2, anti-N-methyl-D-aspartate receptor subtype 2 receptors; OCBs, oligoclonal bands; OCT, optical coherence tomography; PCNSV, primary central nervous system vasculitis; PPMS, primary progressive multiple sclerosis; Q_{alb}, abumin quotient; RRMS, relapsing-remitting multiple sclerosis; SLE, systemic lupus erythematosus; SPMS, secondary progressive multiple sclerosis; STM, short transverse myelitis; TIA, transient ischemic attack; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor; WML, white matter lesions

* Corresponding author.
E-mail address: mariusz.stasiolek@umed.lodz.pl (M. Stasiołek).

https://doi.org/10.1016/j.msard.2019.101452
Received 16 August 2019; Received in revised form 11 October 2019; Accepted 14 October 2019

Table 1
MRI 'red flags' (Jog and James, 2017; Ungprasert and Matteson, 2017; Maggi et al., Feb; Chen et al., Sep; Ramanathan et al., 2016a; Charil et al., Oct).

MRI finding	typical for MS	'red flags'
shape and size of lesions	ovoid, perivenular, Dawson's fingers	massive, confluent
U-fibers involvement	yes	no
lesion morphology	regular, distinct border	fluffy, indistinct border
gadolinium enhancement	homogeneous; ring, open ring; pattern changing in successive MRIs	heterogeneous enhancement; cloud-like, pencil-thin; pattern persistent over months
location	periventricular, juxtacortical/ asymmetrical	peripheric, cortical/ symmetrical
mass effect	rare, eg. in tumefactive MS	prominent in granulomatous diseases
optic neuritis		more than half of the length of the optic nerve, comprising intracranial segment, typically extending to the chiasm and optic tract
corpus callosum	small ovoid lesions, atrophy in later phase	ependymal surface involvement; "arch bridge" appearance - NMOSD
posterior fossa-brainstem lesions	small	upward/downward extension of brainstem lesion - NBD
spinal cord lesions	short (less than 3 vertebral segments); <50% of the cross-sectional area; peripheral	longitudinally extensive (at least 3 vertebral segments); >50% of the cord area; central gray matter
meningeal involvement	no	yes, leptomeningeal and pachymeningeal
infarcts or hemorrhages	no	yes, especially multiple
calcifications	no	yes
typical sign	central vein sign	Bagel sign - NBD; punctuate enhancement and swelling of basal ganglia – NPSLE; diencephalon involvement – NMOSD; area postrema involvement - NMOSD; bright spotty lesions in the spinal cord - NMOSD; "string of pearls" (clusters of snowball-like callosal lesions) – Susac syndrome

genetic metabolic disorders, such as Alexander disease, X-linked adrenoleukodystrophy, metachromatic leukodystrophy, Canavan disease, infectious diseases, mostly opportunistic such as toxoplasmosis, progressive multifocal leukoencephalopathy, neuroborreliosis and lymphoproliferative diseases (Siva, 2018 Feb). On the other hand, delayed MS diagnosis in people who obtain treatment for another disorder even for years is an equally important issue. Although MRI is currently the most valuable tool in differential diagnosis of MS, excessive reliance on radiological features is often responsible for diagnostic errors. Because the issue of MS misdiagnosis is of such a paramount importance, further search for specific biomarkers seems mandatory. In this review, we shall discuss MS and other demyelinating autoimmune disorders of the central nervous system (CNS), with a particular focus on rheumatic diseases, and highlight the distinctive features which may facilitate the proper diagnosis.

2. Multiple sclerosis

MS is presumed to be the most common acquired demyelinating disorder of the central nervous system. MS is assumed to affect over 2.5 million people globally, and is regarded as one of the primary causes of disability, especially among young adults (Pelletier and Hafler, 2012). The prevalence of MS is highly heterogeneous. The incidence of MS differs between populations and reaches even 10 new cases per 100 000 (Kingwell et al., 2015; Grytten et al., 2016). Although a meta-analysis, including 59 countries, revealed a statistically significant latitudinal gradient for MS prevalence (Simpson et al., 2011), other studies have shown no remarkable latitudinal or longitudinal gradient in some regions (Poppe et al., 2008; Melcon et al., 2008). The risk of developing MS is determined by genetic as well as environmental factors. Current data on genetic, epigenetic, and transcriptome studies in monozygotic twins has proven discordance for MS (Mumford et al., 1994; Baranzini et al., 2010).

Even though demyelination is regarded as the pathologic hallmark of MS, studies indicate that axonal injury is playing a key role in the persistence of neurological deficits (van Waesberghe et al., 1999; Fisher et al., 2007). The exact etiology and pathomechanisms of MS remain not fully known. However, the leading role of autoimmune and neurodegenerative processes has long been postulated. The cascade of MS pathology comprises demyelination, oligodendrocyte loss, neuronal loss, axonal damage, astrogliosis, and progressive failure of remyelination (Zeydan and Kantarci, 2018; Lassmann et al., 2012). It is assumed that inflammatory reaction associated with different cell types including T cells, B cells, activated microglia, macrophages and their products results in demyelination (Lassmann, 2011), whereas various inflammation induced and/or mediated processes e.g. oxidative stress leading to mitochondrial injury perpetuate neurodegeneration (Lassmann, 2011). All the processes coincide at every stage of the disease, though their intensity varies in time and the progressive phase of MS becomes clinically apparent when the axonal damage threshold is surpassed (Confavreux et al., 2003). The present disease course classification comprises the relapsing-remitting MS (RRMS) and progressive MS, which is divided into primary progressive MS (PPMS) and secondary progressive MS (SPMS) (Lublin et al., 2014; Miller and Leary, 2007). Each phenotype is further defined by the status of disease activity and progression (Lublin et al., 2014).

Current 2017 McDonald diagnostic criteria for multiple sclerosis include clinical, imaging and laboratory findings (Thompson et al., 2018). MRI is of utmost importance in the diagnosis of MS. Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) network and the Consortium of Multiple Sclerosis Centers have given recommendations on the use of MRI in MS diagnosis (Wattjes et al., 2015; Traboulsee et al., 2016). Brain and spinal cord MRI may replace clinical features to meet the dissemination in space (DIS) or dissemination in time (DIT) criteria. Typical MS MRI findings are T2-hyperintense lesions in four areas of the CNS: periventricular, cortical or juxtacortical, infratentorial and spinal cord (Thompson et al., 2018). Besides the diagnostic criteria of MS, MRI is highly advantageous in detecting findings suggestive of disorders other than MS. Awareness of such features seems to be essential for understanding the concept of 'no better explanation' (Charil et al., Oct). Table 1 shows common MS MRI findings and "red flags"- suggestive of other inflammatory CNS diseases. Fig. 1 (a-f) demonstrates different types of white matter lesions. Although cerebrospinal fluid (CSF) examination is not obligatory to set the diagnosis of MS, 2017 revisions of McDonald criteria has emphasized the significance of the presence of CSF-specific oligoclonal bands (OCBs), which may substitute MRI criterion for DIT in patients with clinically isolated syndrome (CIS) (Thompson et al., 2018). Moreover, the presence of CSF oligoclonal bands was shown to represent an independent predictor of a second attack in patients with CIS (Andreadou et al., 2013; Dobson et al., 2013). On the other hand, such CSF findings as elevated protein concentration above 100 mg/dL, pleocytosis over 50 cells/mm^3 or presence of neutrophils, eosinophils or atypical cells are uncommon in MS, and should imply consideration of other diagnosis

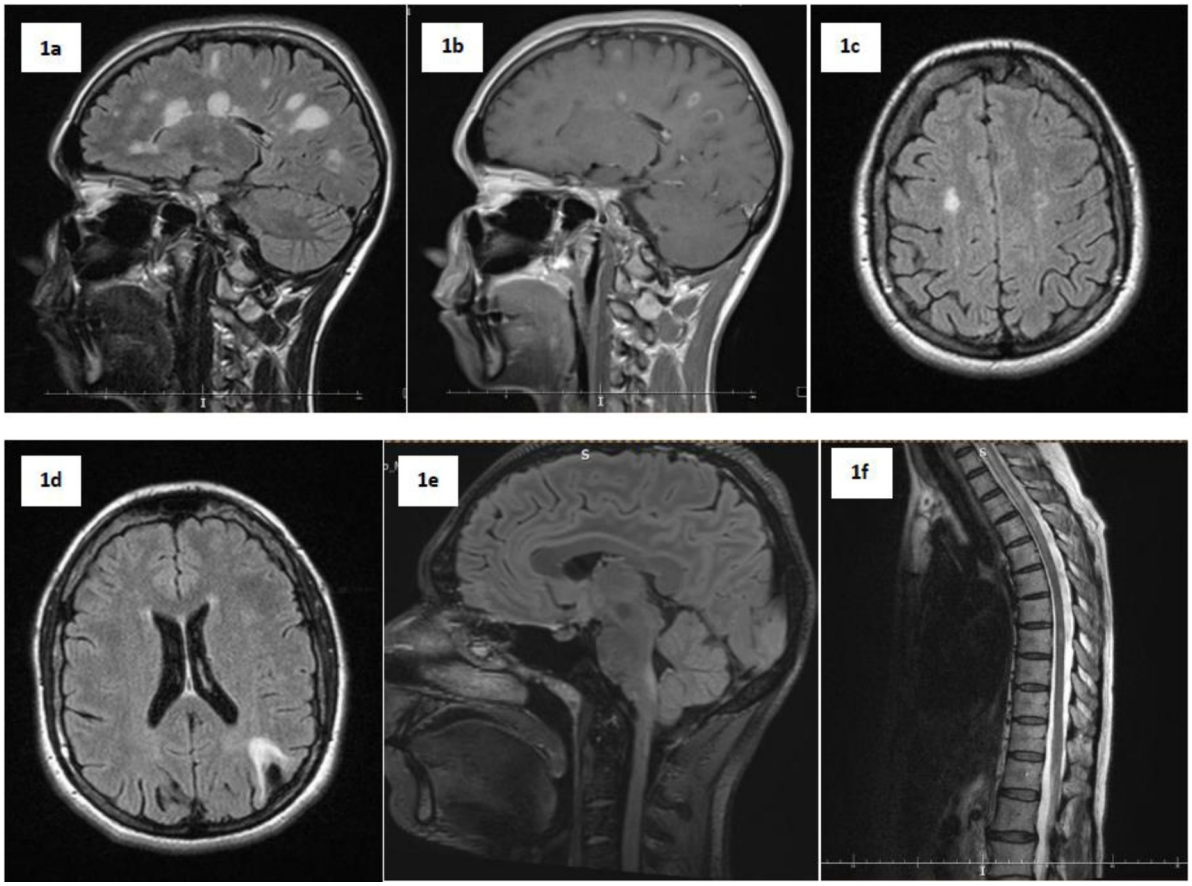

Fig. 1. Different types of white matter lesions in CNS inflammatory diseases. (a). Typical MRI findings in MS: T2-hyperintense periventricular and juxtacortical lesions. (b). T1 scan showing ring and open ring gadolinium enhancement pattern of lesions present in Fig.1a. (c). Subcortical FLAIR-hyperintense white matter lesions in a patient with APS secondary to SLE. (d). Cortical-subcortical malacia after an ischaemic stroke in the same patient with APS secondary to SLE presented in fig. 1c. (e). T2 dark fluid-hyperintense lesion in area postrema in a patient with SLE which needs to be differentiated from NMOSD. (f). Diffuse T2-hyperintense lesion at the level Th1 to Th4 affecting white as well as gray matter of spinal cord in NMO patient. Small T2-hyperintense lesions visible also at the level of Th8 and Th10.

(Stangel et al., 2013a). Until now, no fully specific biomarker of MS is available, which makes careful exclusion of other possible causes of observed clinical symptoms mandatory (Miller et al., 2008). It is worth to mention, that neurofilament light chain (NfL) levels in serum of MS patients are associated with clinical and MRI-related measures of disease activity and neuroaxonal damage and have prognostic, but not diagnostic value (Kuhle et al., 2019). The European Committee of Treatment and Research in Multiple Sclerosis (ECTRIMS) and the European Academy of Neurology (EAN) have issued practical guidelines on the pharmacological MS treatment (Montalban et al., 2018). Despite the knowledge of a few prognostic factors (Tintore et al., 2015; Jokubaitis et al., 2016), there is still an unmet need for biomarkers, which would facilitate the stratification of patients into groups suited for particular treatment approach.

3. Neuromyelitis optica spectrum disorders

NMOSD, including neuromyelitis optica (NMO) or Devic's syndrome, comprise a group of the central nervous system (CNS) inflammatory conditions, affecting preferentially optic nerves and spinal cord (Bruscolini et al., 2018). NMO is a relatively uncommon disease, with the incidence and prevalence ranging from 0.05–0.4 and 0.52–4.4 per 100,000, respectively. NMO primarily affects young adults, with a mean age 32.6–45.7 years. A significant predominance in women is observed, who constitute from 68% to 88% of the affected population (Pandit et al., 2015). The core clinical characteristics of NMOSD are optic neuritis, acute myelitis, area postrema syndrome, acute brainstem syndrome, symptomatic narcolepsy or acute diencephalic clinical syndrome with NMOSD-typical diencephalic MRI lesions and symptomatic cerebral syndrome with NMOSD-typical brain lesions (Wingerchuk et al., 2015). Acute optic neuritis, in particular bilateral or rapidly sequential, and longitudinally extensive transverse myelitis (LETM), are the most usual manifestations of NMO (Wingerchuk et al., 1999). Thus, the most common symptoms involve ocular pain with a severe visual acuity loss, symmetric paraplegia, sensory loss and bladder dysfunction (Wingerchuk et al., 2007). Other alarm signs are nausea/vomiting, intractable hiccups, diplopia and nystagmus, hearing and balance disorder, narcolepsy, obesity or even acute respiratory failure (Bruscolini et al., 2018; Sahraian et al., 2013).

Current criteria divide NMOSD into two subtypes according to the seropositivity of aquaporin-4 immunoglobulin G (AQP4-IgG): NMOSD with AQP4-IgG (NMOSD- AQP4-IgG) and NMOSD without AQP4-IgG or with unknown AQP4-IgG status (Wingerchuk et al., 2015). The diagnosis of NMOSD is based on clinical manifestations, serological testing and MRI. In the presence of AQP4-IgG, only one of the core clinical characteristics is sufficient to make the diagnosis, provided that alternative diagnoses have been excluded. In patients with a negative AQP4-IgG test or when the test is unavailable, at least two core characteristics of NMOSD have to be present (one of them obligatory being optic neuritis, acute myelitis with LETM or area postrema syndrome) alongside with supportive MRI features and an exclusion of alternative diagnoses (Wingerchuk et al., 2015). AQP4 is the key target in NMO pathogenesis. AQP4 is an astrocyte water channel protein which promotes the movement of water across cell membranes in response to osmotic gradients (Papadopoulos and Verkman, 2012). AQP4 is primarily expressed in astrocyte foot processes, in particular within the

optic nerves, spinal cord, periventricular areas, hypothalamus, subpial regions in cerebellar hemispheres, brainstem and area postrema (Zekeridou and Lennon, 2015). The clinical course of NMOSD seems to vary between AQP4-IgG-seropositive and seronegative patients. In the AQP4-IgG-seropositive group, more severe and frequent relapses, higher female to male ratio, more unfavorable outcomes and more often coexisting autoimmune disorders should be expected (Jarius et al., 2012). In addition to AQP4, a few other immune pathogenic targets have been revealed in the context of NMOSD, mainly myelin oligodendrocytes glycoprotein (MOG), but also glial fibrillary acid protein (GFAP), S100 protein, metalloprotease-9, VEGF A, ICAM-1, VCAM-1 (Lennon et al., 2004; Jarius et al., 2014). The available information regarding the MOG-IgG-positive patients with NMOSD indicate that the disease usually starts at a younger age, the female to male ratio is lower, is more often monophasic and with a less severe outcome than in AQP4-IgG-positive NMOSD (Sato et al., 2014; van Pelt et al., 2016; Jurynczyk et al., 2017). The recently described concept of MOG antibody disease comprises a group of autoimmune disorders with a predilection for optic nerve and spinal cord involvement (Denève et al., 2019; Lana-Peixoto and Talim, 2019).

MRI is of great importance in the process of NMOSD diagnosis, especially among the AQP4-negative patients. Optic neuritis in NMOSD is commonly bilateral and longitudinally extensive, involving over one half of the optic nerve, most typically in the posterior segment prolonging to the chiasm and optic tract (Ramanathan et al., 2016a). On the contrary, optic neuritis associated with MOG antibody localizes typically in the anterior part of the nerve, is stretched, oedematous, with more prominent inflammation than in AQP-4-IgG positive patients (Carra-Dalliere et al., 2018). Characteristic MRI feature of MOG antibody disease is enhancement of the peri-optic nerve sheath, partly extending into the surrounding orbital fat (Ramanathan et al., 2016b). LETM, as the manifestation of NMOSD, extends for at least three adjacent vertebral segments and involves primarily the central gray matter of the spinal cord and over 50% of the cord area, constituting transversally extensive lesions (Pekcevik et al., 2016a; Dumrikarnlert et al., 2017). Lesions within the cervical spine, typically spread to the area postrema (Kim et al., 2015). Bright spotty lesions with a strong hyperintensity on axial T2-weighted images, with higher signal intensity than the surrounding cerebrospinal fluid, without flow void effects are suggested as one of the most characteristic CNS MRI features in NMOSD (Yonezu et al., 2014). Cord swelling and irregular enhancement on T1-weighted images can be observed in acute phase. The ring enhancement pattern in NMOSD LETM has a lens-shaped appearance on sagittal scans (Zalewski et al., 2017). Besides LETM, the most typical NMOSD lesion, short transverse myelitis (STM), previously considered contradictory to NMOSD, is the first sign of 14,5% of all NMO myelitis (Flanagan et al., 2015). However, STM in NMO is generally located in the central gray matter and is often longer than the spinal lesion in MS (Huh et al., 2017). Interestingly, conus involvement is highly specific for MOG antibody disease (Jarius et al., 2018). Accurate diagnosis of myelopathy is crucial as irreversible neurological deterioration may develop promptly without adequate treatment. Moreover, results of a recently published retrospective analysis suggest that the majority of patients diagnosed with idiopathic transverse myelitis have other specific myelopathy (Zalewski et al., 2018). Brain lesions are not an uncommon phenomenon in NMOSD, as they can be detected in 25–59% of patients (Wang et al., 2011; Chan et al., 2011). Most importantly, 16% of these lesions are found to meet the Barkhof MRI criteria for MS (Wingerchuk et al., 2015). The prevailing brain NMO lesions are confluent hyperintensities on FLAIR/T2-weighted images scattered asymmetrically in periependymal areas. The ependymal surface of corpus callosum, diencephalon and brainstem, involving the area postrema, are the key sites of NMO brain lesions (Wingerchuk et al., 2015). Cortical lesions are incompatible with NMO, and thus they are considered a ‘red flag’ implying the need for other diagnosis. Nevertheless, cortical involvement, particularly in the subpial layer associated with leptomeningeal enhancement, has been reported (Pekcevik et al., 2016b). The most frequent patterns of enhancement are cloud-like enhancement and the periependymal linear pattern, or pencil-thin enhancement, along the ventricular surface system. When existing together, these two patterns might present a flame-like impression. Ring and ‘open ring’ enhancement indicate rather the diagnosis of MS (Pekcevik et al., 2016b). However, MRI of patients with acute optic neuritis may be normal. In these cases, visual evoked potentials and optical coherence tomography (OCT) are substantial. OCT is a valuable tool in the assessment of optic nerve fibers damage, and it was suggested that this parameter may potentially serve as a marker of disease progression and treatment response (Bennett et al., 2015). Importantly, OCT in NMOSD shows a more apparent than in MS retinal nerve fiber layer and ganglion cells layer thinning (Bennett et al., 2015). Unlike in MS, CSF tests in NMOSD more often show elevated pleocytosis (in 35%), especially with predominant neutrophils or eosinophils (Wingerchuk et al., 2015). Another differentiating factor between NMOSD and MS is an increased CSF level of IL-6 in the former disease (Uzawa et al., 2014). Although CSF oligoclonal bands might be transiently detectable during exacerbations, their absence is considered as supportive evidence for NMOSD (Wingerchuk et al., 2015). The proper differentiation between MS and NMOSD is crucial for therapy planning. Several maintenance therapies approved for MS have been found ineffective or even aggravating the severity of clinical symptoms in NMOSD (Uzawa et al., 2014). Furthermore, recently published results of clinical trials have proved effectiveness of therapeutic approaches based on the pathomechanism of NMOSD such as intervention in the cascade of complement (Pittock et al., 2019)

4. Neuropsychiatric systemic lupus erythematosus

Systemic lupus erythematosus (SLE) is a chronic systemic autoimmune disease displaying a wide variety of clinical manifestations (Jafri et al., 2017). Central nervous system involvement in SLE is associated with a more severe course of the disease and a worse prognosis (Cervera et al., 1999). The reported prevalence of neuropsychiatric SLE (NPSLE) differs considerably, ranging from 14% to 75% of all SLE cases, most probably due to the vast variety of symptoms and changing rules of assignment to the primary disease (Unterman et al., 2011). The American College of Rheumatology defined 19 manifestations of NPSLE, which affect central, peripheral or autonomic nervous system. Among the CNS manifestations of SLE, cerebrovascular disease and epilepsy are considered the most clinically important. Demyelinating syndrome, aseptic meningitis and psychiatric disorders also need to be mentioned as significant medical challenges (Hanly, 2004; Hanly, 2014a). NPSLE manifestations can be categorized as diffuse or focal, depending on the prevailing pathomechanism. Diffuse manifestations include headaches, affective disorders, psychosis, cognitive dysfunction and acute confusional state (Jafri et al., 2017). Crucial focal manifestations of NPSLE are cerebrovascular disease and epilepsy. Cerebrovascular events are reported in 5% to 18% of SLE patients. The increased risk of stroke is contributed to procoagulant factors such as antiphospholipid antibodies (aPL), endothelial activation and vasculitis, as well as accelerated atherosclerosis (Hanly et al., Oct). Seizures affect 8% to 18% of SLE patients (Muscal and Brey, 2010) and are associated with the presence to anti-Smith antibodies (Mikdashi et al., 2005) and aPL antibodies in serum (Herranz et al., 1994). Another focal NPSLE manifestation is transverse myelitis, which mimics NMOSD. There is a strong association between transverse myelitis and the presence of aPL antibodies in patients with SLE (Kovacs et al., 2000a). Histopathological studies have shown that the predominant process in NPSLE is a noninflammatory microangiopathy with concomitant brain microinfarction. Other reported pathological findings have been glial hyperplasia and diffuse neuronal and axonal loss (Sibbitt et al., 2010). It is also assumed that NPSLE may be a result of the blood-brain barrier

(BBB) disruption, resulting from complex immune disturbances (Hanly, 2014b). Among them, antibody production and immune complex formation are of primary importance in the pathogenesis of SLE. Until now, as many as 180 different autoantibodies have been detected in SLE patients (Yaniv et al., 2015). In routine clinical practice, usually only anti-double stranded DNA (anti-dsDNA) and aPL are evaluated. Other important antibodies associated with NPSLE are anti-ribosomal P (anti-P), anti-$GABAR_{B1b}$ and anti-$GABAR_{B2}$, anti-neuronal and anti-endothelial antibodies (Clark et al., 2017). Anti-dsDNA antibodies are highly specific (92% to 96%) and of moderate sensitivity (57% to 67%) for SLE (Cozzani et al., 2014). High levels of anti-dsDNA antibodies are found in 70% of patients presenting NPSLE symptoms (Joseph et al., 2007). A subset of anti-dsDNA antibodies cross-react with anti-N-methyl-D-aspartate receptor subtype 2 receptors (NR2). Anti-NR2 antibodies in the CSF can be identified in one third of all SLE patients, which is a higher prevalence than in any other autoimmune disease (Gono et al., 2011). Bound to active NMDA receptors, the anti-NR2 antibodies induce excess calcium influx leading to neuronal dysfunction and cell death (Faust et al., 2010). Antiphospholipid antibodies comprise anticardiolipin antibodies (aCL), lupus anticoagulant (LAC) and anti-beta2glycoprotein 1 (anti-β_2GP1) antibodies. Among focal NPSLE manifestations, aPL are highly prevalent in patients with transverse myelitis, which involves especially the thoracic cord (Kovacs et al., 2000b). aCL antibodies are the most sensitive and the least specific finding. Importantly, aCL antibodies can be temporarily induced by many drugs and infections. LAC has a strong correlation with cerebrovascular disease, particularly sinus thrombosis (Hanly et al., 2011). Anti-β_2GP1 antibodies are more specific for thrombotic events than aCL (Bertolaccini and Khamashta, 2006). Anti-P antibodies are detected in 15% to 20% of SLE patients (Zandman-Goddard et al., 2007) and are considered to have a strong association with psychosis and depression (Hirohata et al., 2007). Besides the abovementioned antibodies, serum analysis may reveal an elevated erythrocyte sedimentation rate (ESR) with normal C-reactive protein levels (Joseph et al., 2007) and decreased concentrations of complement – finding typical of active disease (Magro-Checa et al., 2016). Cerebrospinal fluid analysis should be performed in each case of suspected NPSLE. The usual mild non-specific abnormalities observed in NPSLE are: slightly raised white cell count (typically lymphocytosis), elevated protein and IgG index with a decreased or normal glucose level (Joseph et al., 2007). It might be useful to assess BBB integrity. Since albumin is not generated intrathecally, the relatively high leakage across the BBB may be demonstrated by the assessment of albumin concentration gradient between CSF and plasma - albumin quotient (Q_{alb}) (Abbott et al., 2003). CSF oligoclonal bands can be found in 15% to 85% of NPSLE cases (Clark et al., 2017), which may indicate considerable heterogeneity of investigated SLE patient populations. CNS MRI is the key measure in diagnosis of NPSLE. The primary MRI manifestations of SLE are large infarcts and multifocal white matter T2-hyperintense lesions. White matter T2-hyperintense lesions are the most common radiological finding in NPSLE and it seems crucial to differentiate them from MS lesions. In contrary to MS, SLE white matter lesions more often exhibit a vascular distribution (Jennekens and Kater, 2002). Another distinction from MS is the bilateral involvement of basal ganglia, with swelling and punctuate enhancement. Calcifications in the basal ganglia, dentate nucleus, centrum ovale and corticosubcortical junctions can also be observed (Raymond et al., 1996). Leptomeningeal enhancement may be also present in CNS MRI of SLE patients. Spinal cord lesions are often longitudinally extensive (Jog and James, 2017). Importantly, MRI findings in NPSLE may in some cases fulfill the radiologic diagnostic criteria for MS, which underlines the need for development of specific biomarkers. Given the abundant psychiatric manifestations of SLE, neuropsychological assessment should be performed. Treatment strategies of NPSLE depend on the prevailing manifestations and severity of the disease. Interestingly, it is suggested that the optimal treatment window in NPSLE occurs much earlier than the average time of diagnosis. Thus, the therapy should be introduced without delay, in patients with unspecific clinical syndrome and multifocal brain and spinal cord lesions. Unfortunately, no specific test allows early and definite diagnosis of NPSLE. Thus, further research is required to facilitate the diagnostic strategy.

5. Antiphospholipid syndrome

As mentioned above, aPL antibodies are of paramount importance in the context of the pathogenesis of neuropsychiatric lupus manifestations. Antiphospholipid syndrome (APS) is an acquired systemic disorder related to the circulating aPL antibodies. Current classification criteria for APS include fulfillment of at least one of clinical criteria such as vascular thrombosis or particular pregnancy related conditions and at least one of the laboratory criteria which is a positive test for aPL antibodies: LAC, aCL or anti-β_2GP1, present on 2 or more occasions not less than 12 weeks apart (Miyakis et al., 2006). APS might be primary or secondary to other autoimmune disease, with SLE being the most common cause of secondary APS (Graf, 2013). Besides vascular thrombosis and pregnancy morbidity, APS comprises a wide spectrum of symptoms, including hematological, cutaneous, renal, cardiac and pulmonary involvement (Negrini et al., 2017). Hematological manifestations of APS are aPL-associated idiopathic thrombocytopenic purpura and autoimmune hemolytic anemia (Cervera et al., 2002). Livedo reticularis is the hallmark of APS (Cervera et al., 2002) and has been proposed as an independent risk factor of arterial thrombosis (Frances et al., 2005). APS nephropathy can be acute or chronic and in secondary APS may coexist with immune-complex-mediated lupus nephritis (Pons-Estel and Cervera, 2014; Alchi et al., 2010). Other systemic manifestations of APS involve Libman-Sacks endocarditis, intraalveolar hemorrhage, acute respiratory distress syndrome and fibrosing alveolitis (Hojnik et al., 1996; Kanakis et al., 2013; Barnini et al., 2012). The most frequently affected arterial system in APS is the cerebral circulation and consequently the most prevalent neurological complication of APS is a cerebrovascular event (Rodrigues et al., 2010). Ischemic stroke may be related to vessels of any size and located in any area of the brain, without typical predilection (Tanne and Hassin-Baer, 2001). It is estimated that at least 20% of stroke cases under the age of 45 can be attributed to APS (Hughes, 2003). In particular, in patients with secondary APS, LAC is a remarkably stronger predictor of CNS ischemic events than the aCL antibodies (de Amorim et al., 2017; Petri et al., 1987). Cognitive symptoms are another important manifestation of APS. It has been demonstrated that between 42% and 80% of APS patients exhibit global cognitive impairment (Yelnik et al., 2016; Brey et al., 2011). Studies have shown a positive correlation between cognitive dysfunction and aCL antibodies (Jacobson et al., 1999; Menon et al., 1999; Hanly et al., 1999). Epilepsy is considered as one of the main CNS manifestations of APS. It is more frequent in secondary APS, in which it affects 13,7% of patients (Shoenfeld et al., 2004). Although epileptogenic foci secondary to ischemic events are considered as the most important cause of seizures in APS, autoimmune process is presumed to be also substantially involved. It needs to be indicated that clinical features of APS might resemble MS. Possible MS-like manifestations of APS encompass e.g. optic neuritis or transverse myelitis with CNS MRI revealing MS-type white matter lesions. It may be particularly misleading, as scattered hyperintensive subcortical white matter lesions are the most common MRI finding in APS (Zhu et al., 2014). Taking into consideration the lack of fully specific diagnostic tests, differential diagnosis in such cases may prove to be complex and difficult (Rodrigues et al., 2010). Similarly to NPSLE, treatment approach in APS needs to be adjusted to the prevailing manifestations and severity of symptoms.

6. Primary central nervous system vasculitis

Primary central nervous system vasculitis (PCNSV), also known as

primary angitis of the CNS, is an insufficiently investigated inflammatory condition which affects vessels of brain, spinal cord and meninges (Mandal and Chung, 2017). Due to an ample spectrum of clinical manifestations and absence of any specific diagnostic test, PCNSV remains a commonly overlooked disorder. Although rare, PCNSV should be taken into consideration in each case of suspected CNS vasculitis when secondary causes e.g. infectious, connective tissue diseases, or systemic vasculitis, cannot be confirmed. Unlike in secondary vasculitis, men are more susceptible to PCNSV than women, with the male to female ratio estimated at 2:1, and a mean age of onset being 50 years (Salvarani et al., 2007). Patients with PCNSV may exhibit multiple symptoms. The disease usually starts with a protracted prodromal period, lasting weeks or months, during which headaches and mild cognitive disturbances often appear (Salvarani et al., 2015). After prodromal phase, diverse neurological manifestations can emerge, such as visual disturbances, cranial neuropathies, stroke with focal deficits, cerebellar syndrome, epilepsy (Boysson et al., 2014). Constitutional symptoms, such as fever and weight loss, are usually absent, and they imply rather the diagnosis of secondary vasculitis (Salvarani et al., 2015). PCNSV is a highly heterogeneous disease, which may affect vessels of various size, mainly medium and small. Also the pathological findings differ considerably. Several PCNSV subtypes have been characterized, with granulomatous angitis of the CNS being the most common (Salvarani et al., 2007). The clinical course of granulomatous angitis is indolent. The prodromal period with headaches and cognitive impairment lasts from 3 to 6 months, and is typically followed by focal deficits or epilepsy (Suri et al., 2014). As granulomatous angitis typically involves small vessels, angiography usually shows no abnormalities (Suri et al., 2014). Currently, there is no specific laboratory test available for PCNSV. Immunological tests, ESR and CRP should be assessed to exclude secondary vasculitis. CSF examination should be performed in each case of suspected PCNSV, mainly to differentiate with infections and neoplastic causes. In majority of patients with PCNSV some nonspecific CSF abnormality is found, usually mild lymphocytic pleocytosis or elevated protein level, with normal glucose (Salvarani et al., 2015). Brain MRI is an obligatory step in the diagnosis of PCNSV and it typically shows multifocal, often bilateral, infarcts in numerous vascular territories, with parenchymal enhancement (Boulouis et al., 2017; Goertz et al., 2010). Conventional cerebral angiography remains the basic tool to evaluate cases of highly probable PCNSV. Characteristic picture of “beading”, which is formed by alternating segments of stenotic and dilated vessels, is a cornerstone of diagnosis (Edgell et al., 2016). Other possible findings include focal occlusion, collateral circulation, microaneurysms. Magnetic resonance angiography, in particular high resolution multicontrast wall and lumen imaging, with the use of the 3T scanner or stronger, can also prove beneficial (Cosottini et al., 2013). Gold standard test for PCNSV diagnosis is brain and leptomeningeal biopsy. The biopsied sample needs to contain leptomeninges, cortex and subcortical white matter from radiologically altered location (Hajj-Ali et al., 2011; Miller et al., 2009).

7. ANCA-vasculitis

The antineutrophil cytoplasmic antibodies (ANCA)-associated CNS vasculitis is a group of primary systemic vasculitic diseases comprising granulomatosis with polyangitis (GPA), microscopic polyangitis (MPA) and eosinophilic granulomatosis with polyangitis (EGPA) (Graf, 2017 Nov). GPA is an idiopathic necrotizing small-vessel disease related to ANCA specific for proteinase 3 (PR3) (Graf, 2017 Nov). The most common neurological manifestation of GPA, observed in 60% of cases, is peripheral neuropathy. CNS is affected in 4% to 11% of GPA patients (Dutra et al., Feb). Three different types of manifestations can be distinguished including: cerebral vasculitis and two predominantly granulomatous phenotypes - chronic hypertrophic pachymeningitis and pituitary disease (Graf, 2017 Nov). The vascular phenotype can lead to ischemic as well as hemorrhagic complications. The imaging results of GPA ischemic lesions are nonspecific. Brain MRI might reveal both extensive cerebral infarctions and diffuse white matter lesions as seen in small-vessel vasculopathy (De Luna et al., 2015). The size of involved vessels is often below the level of resolution of MRI or conventional angiography (Ghinoi et al., 2010). GPA affects more frequently pachymeninges than leptomeninges and intracranial dura matter is more often involved than spinal (Holle and Gross, 2011). Chronic hypertrophic pachymeningitis can manifest clinically with variety of symptoms such as headache, cranial neuropathy, ataxia, myelopathy, epilepsy and thickening of the dura on MRI scans (Shimojima et al., 2017). MPA is associated with ANCA directed against myeloperoxidase (MPO) and affects small- to medium-sized vessels (Graf, 2017 Nov). Although MPA mostly exhibits as glomerulonephritis and diffuse alveolar hemorrhage, CNS may be involved as well (Duvuru and Stone, 2013). CNS vasculitis in the course of EGPA is a rare phenomenon and usually constitutes the final phase of the disease. The primary EGPA manifestations are asthma and nasal polyps or rhinosinusitis, followed by an eosinophilic phase characterized by peripheral eosinophilia and organ involvement (Greco et al., 2015). EGPA affects the CNS in 6% to 10% cases and causes encephalopathy, ischemic infarcts and hemorrhages (Murthy et al., 2013).

8. Neuro-Behçet disease

Behçet disease (BD) is a chronic relapsing inflammatory vascular disease of not fully known etiopathogenesis. CNS presentation is described in 5% to 10% of BD cases (Siva and Saip, 2009). Several genetic, environmental and microbiological factors have been postulated as risk factors for BD (Onder and Gürer, 2001). Among genetic factors, a significant relationship has been found between human leukocyte antigen (HLA)-B51 and BD (Demirseren et al., 2014). HLA-B51 gene is presumed to be the strongest risk factor for BD (Kirino et al., 2013). It has been also shown that HLA-B51 is associated with a lower frequency of neurological involvement (Hamzaoui et al., Jun). However, this correlation may be more complicated and HLA-B51 subtype specific, since in one study an increased frequency of HLA-B5103 has been observed in BD patients with CNS involvement (Demirseren et al., 2014). As there is no pathognomonic test for BD, the diagnosis is based on clinical criteria. To meet current International Criteria for Behçet Disease (ICBD), a patient needs to score at least 4 points, 2 points being ascribed for any of ocular lesions, oral aphthosis, genital aphthosis and 1 point for any of skin lesions, neurological manifestations, and vascular manifestations. An extra point may be assigned for positive pathergy test (International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD) 2014). There are two major forms of Neuro-Behçet disease (NBD). A vascular-inflammatory disease, also called parenchymal NBD, often mimics MS clinical picture. The other major NBD presentation - non-parenchymal NBD encompasses an isolated cerebral venous sinus thrombosis and intracranial hypertension (Siva and Saip, 2009; Al-Araji and Kidd, 2009). Parenchymal NBD is usually more severe than non-parenchymal NBD, and it comprises such manifestations as meningoencephalitis involving brainstem, cranial nerve palsies and epilepsy (Al-Araji and Kidd, 2009). In contrary to MS, NBD affects men more often than women. Optic neuritis, spinal cord involvement and sensory symptoms are rare in NBD and thus should always warrant careful differential diagnostics with other possible causes e.g. MS (Kocer et al., 1999). MRI is the gold-standard in NBD diagnosis. Typical CNS MRI finding in NBD is a large lesion in brainstem, without apparent border, with a tendency to spread to diencephalon and basal ganglia, less frequently caudally (Kocer et al., 1999). Heterogeneous contrast enhancement may be observed in acute phase, resolving usually incompletely in subsequent imaging. Typically, brainstem lesions on MRI are much smaller in MS. As mentioned above, spinal cord involvement is uncommon in NBD, but when it occurs, the lesions are longitudinally extensive, resembling lesions characteristic of

NMOSD (Uygunoglu et al., 2016). The most specific spinal MRI feature of NBD, described till now, is the "bagel sign" pattern, visible in axial T2WIs, and defined as a central spinal cord lesion with hypointense core and hyperintense rim, with or without contrast enhancement (Uygunoglu et al., 2017). CSF OCBs positivity in NBD patients is significantly less common than in MS, observed in only up to 15% of cases (Siva, 2018 Feb).

9. Neurosarcoidosis

Another inflammatory disease exhibiting multiple brain lesions on MRI is neurosarcoidosis, a chronic granulomatous disorder of unknown origin. Nervous system involvement is reported in 3% to 10% of patients with sarcoidosis, but such prevalence is presumed to be underestimated (Ungprasert and Matteson, 2017). Although isolated neurosarcoidosis is a rare condition, in about 70% to 80% of patients neurological symptoms are one of the earliest disease manifestations (Ferriby et al., 2001). The most prevalent neurological complication of sarcoidosis is cranial neuropathy, with a particular predilection for cranial nerves VII, II and III. Facial nerve palsy may be bilateral and is probably a result of epi- and perineural inflammation and external compression by granuloma (Carlson et al., 2014). Optic neuritis, often bilateral, has been observed as an initial disease presentation in even 35% of neurosarcoidosis cases (Pawate et al., 2009a). Vestibulocochlear nerve injury is considered to result from granulomatous meningitis (Kane, 1976). Brain parenchymal disease constitutes another significant issue and is presumed to be a result of chronic inflammation and consecutive atherosclerosis (Pawate et al., 2009b). It can manifest as headache, cognitive impairment, affective disorders and epilepsy (Ungprasert et al., 2017). Sarcoidal granulomas may infiltrate the pituitary gland and hypothalamus, causing endocrinological disturbances (Stern et al., 1985), or spinal cord with a predilection for thoracic and cervical segments (Cohen-Aubert et al., 2010). The most prevalent MRI findings in neurosarcoidosis are multiple nonenhancing periventricular white matter lesions, which imitate MS or vasculitis (Smith et al., 2004). CSF findings are similar to those seen in SLE, including hypoglycorrhachia (Terushkin et al., 2010). Increased level of CSF angiotensin-converting enzyme is insensitive and not sufficiently specific, as it may be observed in other pathologic conditions i.e. MS (Nozaki and Judson, 2012).

10. Sjogren syndrome

Primary Sjogren syndrome belongs to autoimmune diseases, which may affect CNS. The pathological process in primary Sjogren syndrome is associated with the presence of antinuclear antibodies, especially anty-Ro/SSA and anty-La/SSB. Although the main affected organs are salivary and lacrimal glands, neurologic symptoms may also appear (Delalande et al., 2004; Massara et al., 2010). Peripheral neuropathies, mainly distal sensory and sensorimotor, are the most common neurological manifestations in primary Sjogren syndrome (Pavlakis et al., 2012; Brito-Zeron et al., 2013). However, CNS involvement might be the first presentation of primary Sjogren syndrome and comprises diverse neurological syndromes such as multiple sclerosis-like disease, encephalopathy, psychiatric disorders, NMOSD – like disease, cerebellar syndromes and movement disorders (Margaretten, 2017). The underlying pathology is mainly mononuclear inflammatory vasculopathy (Alexander, 1993). However, small vessel vasculitis can be observed in a remarkable percentage of primary Sjogren syndrome patients with the use of cerebral angiography. It has been found that such angiographic findings are associated with anti-Ro/SSA antibodies seropositivity (Alexander et al., 1994). CSF analysis might reveal increased lymphocytosis, elevated IgG index and protein concentration as well as oligoclonal bands (Delalande et al., 2004).

MRI abnormalities in primary Sjogren syndrome are nonspecific. In majority of patients with focal CNS involvement, diffuse hyperintense T2-weighted lesions are observed (Manthorpe et al., 1992). Lesions are often located in areas typically observed in MS (Massara et al., 2010). In contrary to other autoimmune diseases, primary Sjogren syndrome itself is not related to an elevated risk of ischemic stroke. However, aPL antibodies and LAC, associated with increased risk of thrombotic events, are commonly detected in this condition (Pasoto et al., 2012).

11. Practical considerations

Differential diagnosis of disseminated white matter lesions is very complex and apart from MS, primarily systemic diseases including connective tissue disorders, diverse vasculopathies e.g. genetic and infectious diseases have to be taken into account. Symptoms such as impaired consciousness, rapidly progressive cognitive deficits, aphasia and epilepsy should make us consider diagnoses other than MS. A fulminant course of the disease is also rare in MS. Extrapyramidal symptoms should imply rather a suspicion of a hereditary or metabolic disorder. Apparent symmetricity of symptoms and lack of involvement of the optic nerves also raise the probability of disease other than MS. In clinical practice, an absolute lack of response to intravenous methylprednisolone treatment is not typical of MS (Siva, 2018 Feb). Despite extensive search for biomarkers, until now no laboratory test has proven 100% specific of MS. Nonetheless, such findings as an elevated ESR and lymphopenia indicate the need for search for a systemic disease. On the other hand, positive ANA tests have been observed in 22.5% to 30.4% of MS patients without any systemic autoimmune disease. However, in most cases of such nonspecific autoantibodies presence, ANA titers are usually not higher than 1:320 (Barned et al., 1995). One study in MS population has shown ANA positivity in as much as 51.0% and a positivity for either aCL or anti-β_2GP1 antibodies was observed in 32.6% of participants (Roussel et al., 2000). Although such nonspecific prevalence of these autoantibodies is considerably high, the possibility of coexisting autoimmune disease should not be neglected, especially in NMOSD (Siva, 2018 Feb). Taking into consideration the dynamic development of the idea of NMO spectrum and most recently MOG spectrum disorders, other antibodies may prove to be useful in the diagnosis of atypical cases, including AQP4-IgG, anti-MOG, anti-NMDAr antibodies and panels for rheumatologic, infectious and paraneoplastic disorders (Siva, 2018 Feb). According to the latest revisions of McDonald criteria for MS, CSF examination and especially OCBs detection should be a standard diagnostic step. Although OCBs are not specific and are often present in other disorders e.g. connective tissue diseases, their presence is reported in approximately 90% of MS patients. Consequently, lack of CSF OCBs should raise the suspicion of disorder other than MS (Stangel et al., 2013b). The pattern of OCBs is also a valuable information (Gastaldi et al., 2016). Vast majority of MS patients show type 2 pattern, that is CSF OCBs positivity with no corresponding abnormality in serum. In some cases of MS type 3 OCBs can be detected, which means the IgG bands are present both in the CSF and serum with additional bands detected in the CSF. Identical CSF and serum OCBs constitute type 4 positivity and are usually detected in systemic inflammatory diseases or infections (Deisenhammer et al., 2006). Moreover, CSF pleocytosis higher than 20–30 cells/μL and protein level increased over 60 mg/dL should raise clinician's vigilance (Stangel et al., 2013b; Zettl and Tumani, 2005). Table 2 presents serological/CSF findings characteristic of all abovementioned CNS inflammatory disorders.

12. Conclusion

Despite the growing availability of tools, diagnosis of CNS inflammatory disorders remains complex and often extends over time. Although MRI is the cornerstone of this process, in some cases it may be a source of confusion, as radiological findings in certain conditions can overlap. Taking into consideration the abovementioned data, the need for specific biomarkers seems to be of primary importance. It appears

Table 2
Serum/CSF typical findings in CNS inflammatory disorders (Jog and James, 2017; Clark et al., 2017; Bruscolini et al., 2018; Graf, 2013; Mandal and Chung, 2017; Siva, 2018 Feb; Dutra et al., Feb; Stangel et al., 2013b; Gastaldi et al., 2016; Nozaki and Judson, 2012; Massara et al., 2010).

Disease	Typical serological/CSF finding	Comment
MS	CSF IgG OCBs	OCBs positivity in 90% of MS usually type 2, in some cases type 3
	CSF pleocytosis < 30 cells/μL	
	CSF protein < 60 mg/Dl	
NMOSD	AQP4-IgGs	sensitivity 73%, specificity 91%, present in 68% − 91%
	MOG-IgGs	present in 10% − 25%
NPSLE	ANA, eg.	titer 1:80
	- anti-dsDNA	high specificity
	- anti-Sm	high specificity
	- anti-P	associated with psychosis and depression
	-anti-NR2	associated with cognitive dysfunction
	- antineuronal	typical of NPSLE and not SLE
	- anti-Ro/SSA	Sjogren syndrome, vasculitis
	Anti-$GABAR_{B1b}$ IgGs	exclusive to SLE, present in 15%
	Anti-$GABAR_{B2}$ IgGs	exclusive to SLE, present in 15%
	Nitrated nucleosome levels	serum titers twice as high in NPSLE flares
	Increased erythrocyte C4d levels	
	Increased B-cell C4d levels	
	Decreased C3 and C4 levels	
	Increased INF-γ, IL-5, IL-6	
	Increased BLyS (B-lymphocyte stimulator)	
APS	Anticardiolipin antibody	Antiphospholipid antibodies should be tested on at least 2 occasions more than 12 weeks and less than 5 years apart
	Anti-β − 2-glycoprotein I antibody	
	Lupus anticoagulant	
PCNSV	none	Extremely elevated erythrocyte sedimentation rate argues against PCNSV
EGPA	ANCA, mainly MPO-ANCA	active EGPA
	Eosinophilia > 1500 cells/μl	active EGPA
	Increased eotaxin-3 (CCL26)	
	Increased CCL17	
MPA	MPO-ANCA	non-specific
	AC-13 (apolipoprotein A1 C-terminal fragment)	activity marker
GPA	ANCA, mainly PR3-ANCA	
	Increased High-mobility group box 1 protein	activity marker
	Increased serum S100A8/A9 levels	
Behçet's disease	less than 15% positivity for CSF OCBs, prominent pleocytosis and protein level	non-specific
Neurosarcoidosis	increased level of CSF angiotensin-converting enzyme	insensitive, not fully specific
Sjögren's syndrome	ANA, particularly to Ro/SSA and La/SSB	

that serological markers deserve particular attention. Unlike CSF, peripheral blood samples are easily obtainable in routine ambulatory care on numerous time points, and thus they would not only facilitate proper diagnosis, but also enable non-invasive monitoring of treatment response. Nevertheless, a thorough combination of clinical examination, radiological assessment, laboratory tests and often an interdisciplinary approach remains currently mandatory to provide a proper diagnosis.

Declaration of Competing Interest

None of the authors has any potential financial conflict of interest related to this manuscript.

Our manuscript has not, in whole or in part, been published previously and is not under consideration for publication elsewhere.

Acknowledgments

This work has not been supported by any funding sources.

References

Abbott, N.J., Mendonca, L.L., Dolman, D.E., 2003. The blood-brain barrier in systemic lupus erythematosus. Lupus 12, 908–915.
Al-Araji, A., Kidd, D.P., 2009. Neuro-Behçet's disease: epidemiology, clinical characteristics, and management. Lancet Neurol. 8, 192–204.
Alchi, B., Griffiths, M., Jayne, D., 2010. What nephrologists need to know about antiphospholipid syndrome. Nephrol. Dial. Transplant. 25 (10), 3147–3154.
Alexander, E.L., 1993. Neurologic disease in Sjogren's syndrome: mononuclear inflammatory vasculopathy affecting central/peripheral nervous system and muscle. A clinical review and update of immunopathogenesis. Rheum. Dis. Clin. North Am. 19 (4), 869–908.
Alexander, E.L., Ranzenbach, M.R., Kumar, A.J., et al., 1994. Anti-Ro (SS-A) autoantibodies in central nervous system disease associated with Sjogren's syndrome (CNS-SS): clinical, neuroimaging, and angiographic correlates. Neurology 44 (5), 899–908.
Andreadou, E., Chatzipanagiotou, S., Constantinides, V.C., Rombos, A., Stamboulis, E., Nicolaou, C., 2013. Prevalence of cerebrospinal fluid oligoclonal IgG bands in Greek patients with clinically isolated syndrome and multiple sclerosis. Clin. Neurol. Neurosurg. 115, 2094–2098.
Baranzini, S.E., Mudge, J., van Velkinburgh, J.C., et al., 2010. Genome, epigenome and RNA sequences of monozygotic twins discordant for multiple sclerosis. Nature 464, 1351–1356.
Barned, S., Goodman, A.D., Mattson, D.H., 1995. Frequency of antinuclear antibodies in multiple sclerosis. Neurology 45, 384–389.
Barnini, T., Silvestri, E., Emmi, G., et al., 2012. Pulmonary fibrosis and lymphocytic alveolitis associated with triple antiphospholipid antibody positivity: a diagnostic puzzle. Clin, Exp, Rheumatol, 30 (5), 806.
Bennett, J.L., de Seze, J., Lana-Peixoto, M., et al., 2015. Neuromyelitis optica and multiple sclerosis: seeing differences through optical coherence tomography. Mult. Scler. 21, 678–688.
Bertolaccini, M.L., Khamashta, M.A., 2006. Laboratory diagnosis and management challenges in the antiphospholipid syndrome. Lupus 15 (3), 172–178.
Boulouis, G., de Boysson, H., Zuber, M., et al., 2017. Primary angiitis of the central nervous system: magnetic resonance imaging spectrum of parenchymal, meningeal, and vascular lesions at baseline. Stroke 48 (5), 1248–1255.
Boysson, H., Zuber, M., Naggara, O., et al., 2014. Primary angiitis of the central nervous system: description of the first fifty-two adults enrolled in the French cohort of patients with primary vasculitis of the central nervous system. Arthritis Rheumatol. 66 (5), 1315–1326.
Brey, R., Muscal, E., Chapman, J., 2011. Antiphospholipid antibodies and the brain: a consensus report. Lupus 20 (2), 153–157.
Brito-Zeron, P., Akasbi, M., Bosch, X., et al., 2013. Classification and characterisation of peripheral neuropathies in 102 patients with primary Sjogren's syndrome. Clin. Exp. Rheumatol. 31 (1), 103–110.
Browne, P., Chandraratna, D., Angood, C., et al., 2014. Atlas of multiple sclerosis 2013: a growing global problem with widespread inequity. Neurology 83, 1022–1024.

Bruscolini, A., Sacchetti, M., La Cava, M., Gharbiya, M., Ralli, M., Lambiase, A., De Virgilio, A., Greco, A., 2018. Diagnosis and management of neuromyelitis optica spectrum disorders - An update. Autoimmun Rev. 17 (3), 195–200 Mar.
Carlson, M.L., White, J.R., Espahbodi, M., et al., 2014. Cranial base manifestation of neurosarcoidosis: a review of 305 patients. Otol. Neurotol. 36, 156–166.
Carra-Dalliere, C., Menjot de Champfleur, N., Ayrignac, X., Labauge, P., 2018. Optic chiasmand oculomotor nerves involvement in active multiple sclerosis. J. Neuroradiol.
Cervera, R., Khamashta, M.A., Font, J., et al., 1999. Morbidity and mortality in systemic lupus erythematosus during a 5-year period. A multicenter prospective study of 1,000 patients. European working party on systemic lupus erythematosus. Medicine (Baltimore) 78, 167–175.
Cervera, R., Piette, J.C., Font, J., et al., 2002. Antiphospholipid syndrome: clinical and immunologic manifestations and patterns of disease expression in a cohort of 1,000 patients. Arthritis Rheum. 46 (4), 1019–1027.
Chan, K.H., Tse, C.T., Chung, C.P., et al., 2011. Brain involvement in neuromyelitis optica spectrum disorders. Arch. Neurol. 68 (11), 1432–1439.
Charil, A., Yousry, T.A., Rovaris, M., et al., 2006 Oct Oct. MRI and the diagnosis of multiple sclerosis: expanding the concept of "no better explanation". Lancet Neurol. 5 (10), 841–852.
Chen, J.J., Carletti, F., Young, V., Mckean, D., Quaghebeur, G., 2016 Sep Sep. MRI differential diagnosis of suspected multiple sclerosis. Clin. Radiol. 71 (9), 815–827.
Clark, K.E., Clark, C.N., Rahman, A., 2017. A critical analysis of the tools to evaluate neuropsychiatric lupus. Lupus 26 (5), 504–509 Apr.
Cohen-Aubert, F., Galanaud, D., Grabli, D., et al., 2010. Spinal cord sarcoidosis. Clinical and laboratory profile and outcome of 31 patients in a case-control study. Medicine 89, 133–140.
Confavreux, C., Vukusic, S., Adeleine, P., 2003. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. Brain 126, 770–782.
Cosottini, M., Canovetti, S., Pesaresi, I., et al., 2013. 3-T magnetic resonance angiography in primary angiitis of the central nervous system. J. Comput. Assist. Tomogr. 37 (4), 493–498.
Cozzani, E., Drosera, M., Gasparini, G., Parodi, A., 2014. Serology of lupus erythematosus: correlation between immunopathological features and clinical aspects. Autoimmune Dis. 2014, 321359.
de Amorim, L.C.D., Maia, F.M., Rodrigues, C.E.M., 2017. Stroke in systemic lupus erythematosus and antiphospholipid syndrome: risk factors, clinical manifestations, neuroimaging, and treatment. Lupus 26 (5), 529–536.
De Luna, G., Terrier, B., Kaminsky, P., et al., 2015. Central nervous system involvement of granulomatosis with polyangiitis: clinical-radiological presentation distinguishes different outcomes. Rheumatology (Oxford) 54 (3), 424–432.
Deisenhammer, F., Bartos, A., Egg, R., et al., 2006. Guidelines on routine cerebrospinal fluid analysis. Report from an EFNS task force. Eur. J. Neurol. 13, 913–922.
Delalande, S., de Seze, J., Fauchais, A.L., et al., 2004. Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients. Medicine (Baltimore) 83 (5), 280–291.
Demirseren, D.D., Ceylan, G.G., Akoglu, G., et al., 2014. HLA-B51 subtypes in Turkish patients with Behçet's disease and their correlation with clinical manifestations. Genet. Mol. Res. 13 (3), 4788–4796 Jul 2.
Denève, M., Biotti, D., Patsoura, S., Ferrier, M., Meluchova, Z., Mahieu, L., Heran, F., Vignal, C., Deschamps, R., Gout, O., Champfleur, N.M., Ayrignac, X., Dallière, C.C., Labauge, P., Dulau, C., Tourdias, T., Dumas, H., Cognard, C., Brassat, D., Bonneville, F., 2019. MRI features of demyelinating disease associated with anti-MOG antibodies in adults. J. Neuroradiol. 46 (5), 312–318 Sep.
Dobson, R., Ramagopalan, S., Davis, A., Giovannoni, G., 2013. Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. J. Neurol. Neurosurg. Psychiatry 84, 909–914.
Dumrikarnlert, C., Siritho, S., Chulapimphan, P., Ngamsombat, C., Satukijchai, C., Prayoonwiwat, N., 2017. The characteristics of spinal imaging in different types of demyelinating diseases. J. Neurol. Sci. 372 (January 15), 138–143.
Dutra, L.A., de Souza, A.W., Grinberg-Dias, G., et al., 2017 Feb Feb. Central nervous system vasculitis in adults: an update. Autoimmun. Rev. 16 (2), 123–131.
Chapter 33Duvuru, G., Stone, J.H., 2013. Microscopic polyangiitis. In: Imboden, J.B., Hellmann, D.B., Stone, J.H. (Eds.), Current Diagnosis & treatment: Rheumatology. The McGraw-Hill Companies, New York.
Edgell, R.C., Sarhan, A.E., Soomro, J., et al., 2016. The role of catheter angiography in the diagnosis of central nervous system vasculitis. Interv. Neurol. 5 (3–4), 194–208.
Faust, T.W., Chang, E.H., Kowal, C., et al., 2010. Neurotoxic lupus autoantibodies alter brain function through two distinct mechanisms. Proc. Natl. Acad. Sci. U S A 107, 18569–18574.
Ferriby, D., de Seze, J., Stojkovic, T., et al., 2001. Long-term follow-up of neurosarcoidosis. Neurology 57, 927–929.
Fisher, E., Chang, A., Fox, R.J., et al., 2007. Imaging correlates of axonal swelling in chronic multiple sclerosis brains. Ann. Neurol. 62 (3), 219–228.
Flanagan, E.P., Weinshenker, B.G., Krecke, K.N., et al., 2015. Short myelitis lesions in aquaporin-4-IgG-positive neuromyelitis optica spectrum disorders. JAMA Neurol. 72 (1), 81–87.
Frances, C., Niang, S., Laffitte, E., Pelletier, F., Costedoat, N., Piette, J.C., 2005. Dermatologic manifestations of the antiphospholipid syndrome: two hundred consecutive cases. Arthritis Rheum. 52 (6), 1785–1793.
Gastaldi, M., Zardini, E., Franciotta, D., 2016. An update on the use of cerebrospinal fluid analysis as a diagnostic tool in multiple sclerosis. Expert Rev. Mol. Diagn. 17 (1), 31–46.
Ghinoi, A., Zuccoli, G., Pipitone, N., et al., 2010. Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis involving the central nervous system: case report and review of the literature. Clin. Exp. Rheumatol. 28 (5), 759–766.
Goertz, C., Wegner, C., Bru¨ck, W., et al., 2010. Primary angiitis of the CNS with pure spinal cord involvement: a case report. J. Neurol. 257 (10), 1762–1764.
Gono, T., Kawaguchi, Y., Kaneko, H., Nishimura, K., Hanaoka, M., Kataoka, S., et al., 2011. Anti-NR2A antibody as a predictor for neuropsychiatric systemic lupus erythematosus. Rheumatology (Oxford, UK) 50, 1578–1585.
Graf, J., 2013. Chapter 23. Antiphospholipid antibody syndrome. In: Imboden, J.B., Hellmann, D.B., Stone, J.H. (Eds.), Current Diagnosis & treatment: Rheumatology. The McGraw-Hill Companies, New York.
Graf, J., 2017 Nov Nov. Central nervous system disease in antineutrophil cytoplasmic antibodies-associated vasculitis. Rheum. Dis. Clin. North Am. 43 (4), 573–578.
Greco, A., Rizzo, M.I., De Virgilio, A., et al., 2015. Churg–Strauss syndrome. Autoimmun. Rev. 14, 341–348.
Grytten, N., Aarseth, J.H., Lunde, H.M., Myhr, K.M., 2016. A 60- year follow-up of the incidence and prevalence of multiple sclerosis in Hordaland county, Western Norway. J. Neurol. Neurosurg. Psychiatry 87, 100–105.
Hajj-Ali, R.A., Singhal, A.B., Benseler, S., et al., 2011. Primary angiitis of the CNS. Lancet Neurol. 10 (6), 561–572.
Hamzaoui, A., Houman, M.H., Massouadia, M., et al., 2012 Jun. Contribution of Hla-B51 in the susceptibility and specific clinical features of Behcet's disease in Tunisian patients. Eur. J. Intern. Med. 23 (4 June), 347–349.
Hanly, J.G., 2004. ACR classification criteria for systemic lupus erythematosus: limitations and revisions to neuropsychiatric variables. Lupus 13, 861–864.
Hanly, J.G., 2014b. Diagnosis and management of neuropsychiatric SLE. Nat. Rev. Rheumatol. 10, 338–347.
Hanly, J.G., 2014a. Diagnosis and management of neuropsychiatric SLE. Nat. Rev. Rheumatol. 10, 338–347.
Hanly, J.G., Hong, C., Smith, S., et al., 1999. A prospective analysis of cognitive function and anticardiolipin antibodies in systemic lupus erythematosus. Arthritis. Rheum. 42 (4), 728–734.
Hanly, J.G., Li, Q., Su, L., et al., 2018 Oct. Cerebrovascular events in systemic lupus erythematosus: results from an international inception cohort study. Arthritis Care Res. (Hoboken) 70 (10 October), 1478–1487.
Hanly, J.G., Urowitz, M.B., Su, L., Bae, S.C., Gordon, C., Clarke, A., et al., 2011. Autoantibodies as biomarkers for the prediction of neuropsychiatric events in systemic lupus erythematosus. Ann. Rheum. Dis. 70, 1726–1732.
Herranz, M.T., Rivier, G., Khamashta, M.A., et al., 1994. Association between antiphospholipid antibodies and epilepsy in patients with systemic lupus erythematosus. Arthritis Rheum. 37, 568–571.
Hirohata, S., Arinuma, Y., Takayama, M., Yoshio, T., 2007. Association of cerebrospinal fluid anti-ribosomal p protein antibodies with diffuse psychiatric/neuropsychological syndromes in systemic lupus erythematosus. Arthritis Res. Ther. 9, R44.
Hojnik, M., George, J., Ziporen, L., Shoenfeld, Y., 1996. Heart valve involvement (Libman–Sacks endocarditis) in the antiphospholipid syndrome. Circulation 93 (8), 1579–1587.
Holle, J.U., Gross, W.L., 2011. Neurological involvement in Wegener's granulomatosis. Curr. Opin. Rheumatol. 23 (1), 7–11.
Hughes, G.R.V., 2003. Migraine, memory loss, and "multiple sclerosis." neurological features of the antiphospholipid (Hughes') syndrome. Postgrad. Med. J. 79 (928), 81–83.
Huh, S.Y., Kim, S.H., Hyun, J.W., et al., 2017. Short segment myelitis as a first manifestation of neuromyelitis optica spectrum disorders. Mult. Scler. 23 (3), 413–419.
International Team for the Revision of the International Criteria for Behçet's Disease (ITR-ICBD), 2014. The International Criteria for Behçet's Disease (ICBD): a collaborative study of 27 countries on the sensitivity and specificity of the new criteria. J. Eur. Acad. Dermatol. Venereol. 28 (3), 338–347 Mar.
Jacobson, M.W., Rapport, L.J., Keenan, P.A., et al., 1999. Neuropsychological deficits associated with antiphospholipid antibodies. J. Clin. Exp. Neuropsychol. 21 (2), 251–264.
Jafri, K., Patterson, S.L., Lanata, C., 2017. Central nervous system manifestations of systemic lupus erythematosus. Rheum. Dis. Clin. North Am. 43 (4), 531–545 Nov.
Jarius, S., Paul, F., Aktas, O., et al., 2018. MOG encephalomyelitis: international recommendations on diagnosis and antibody testing. J. Neuroinflammation 15, 134.
Jarius, S., Ruprecht, K., Wildemann, B., et al., 2012. Contrasting disease patterns in seropositive and seronegative neuromyelitis optica: a multicentre study of 175 patients. J. Neuroinflammation 9, 14.
Jarius, S., Wildemann, B., Paul, F., 2014. Neuromyelitis optica: clinical features, immunopathogenesis and treatment. Clin. Exp. Immunol. 176, 149–164.
Jennekens, K.G.I., Kater, L., 2002. The central nervous system in systemic lupus erythematous. Part 2. Pathogenetic mechanisms of clinical syndromes: a literature investigation. Rheumatology 41, 619–630.
Jog, N.R., James, J.A., 2017. Biomarkers in connective tissue diseases. J. Allergy Clin. Immunol. 140 (6), 1473–1483 Dec.
Jokubaitis, V.G., Spelman, T., Kalincik, T., et al., 2016. Predictors of long-term disability accrual in relapse-onset multiple sclerosis. Ann. Neurol. 80, 89–100.
Joseph, F.G., Lammie, G.A., Scolding, N.J., 2007. CNS lupus: a study of 41 patients. Neurology 69, 644–654.
Jurynczyk, M., Geraldes, R., Probert, F., et al., 2017. Distinct brain imaging characteristics of autoantibody-mediated CNS conditions and multiple sclerosis. Brain 140 (3), 617–627.
Kanakis, M.A., Kapsimali, V., Vaiopoulos, A.G., Vaiopoulos, G.A., Samarkos, M., 2013. The lung in the spectrum of antiphospholipid syndrome. Clin. Exp. Rheumatol. 31 (3), 452–457.
Kane, K., 1976. Deafness in sarcoidosis. J. Laryngol. Otol. 90, 531–537.
Kim, H.J., Paul, F., Lana-Peixoto, M.A., et al., 2015. MRI characteristics of neuromyelitis

optica spectrum disorder: an international update. Neurology 84 (11), 1165–1173.
Kingwell, E., Zhu, F., Marrie, R.A., et al., 2015. High incidence and increasing prevalence of multiple sclerosis in British Columbia, Canada: findings from over two decades (19912010). J. Neurol. 262, 2352–2363.
Kirino, Y., Bertsias, G., Ishigatsubo, Y., et al., 2013. Genome-wide association analysis identifies new susceptibility loci for Behçet's disease and epistasis between HLA-B*51 and ERAP1. Nat. Genet. 45 (2), 202–207 Feb.
Kocer, N., Islak, C., Siva, A., et al., 1999. CNS involvement in neuro-Behcet's syndrome: an MR study. AJNR Am. J. Neuroradiol. 20, 1015–1024.
Kovacs, B., Lafferty, T.L., Brent, L.H., et al., 2000b. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann. Rheum. Dis. 59, 120–124.
Kovacs, B., Lafferty, T.L., Brent, L.H., et al., 2000a. Transverse myelopathy in systemic lupus erythematosus: an analysis of 14 cases and review of the literature. Ann. Rheum. Dis. 59 (2), 120–124.
Kuhle, J., Kropshofer, H., Haering, D.A., Kundu, U., Meinert, R., Barro, C., Dahlke, F., Tomic, D., Leppert, D., Kappos, L., 2019. Blood neurofilament light chain as a biomarker of MS disease activity and treatment response. Neurology 92 (10 March), e1007–e1015.
Lana-Peixoto, M.A., Talim, N., 2019. Neuromyelitis optica spectrum disorder and Anti-MOG syndromes. Biomedicines 7 (2 June).
Lassmann, H., 2011. Review: the architecture of inflammatory demyelinating lesions: implications for studies on pathogenesis. Neuropathol. Appl. Neurobiol. 37, 698–710.
Lassmann, H., van Horssen, J., Mahad, D., 2012. Progressive multiple sclerosis: pathology and pathogenesis. Nat. Rev. Neurol. 8, 647–656.
Lennon, V.A., Wingerchuk, D.M., Kryzer, T.J., et al., 2004. A serum autoantibody marker of neuromyelitis optica: distinction from multiple sclerosis. Lancet 364, 2106–2112.
Lublin, F.D., Reingold, S.C., Cohen, J.A., et al., 2014. Defining the clinical course of multiple sclerosis: the 2013 revisions. Neurology 83, 278–286.
Maggi, P., Absinta, M., Grammatico, M., et al., 2018 Feb Feb. Central vein sign differentiates multiple sclerosis from central nervous system inflammatory vasculopathies. Ann. Neurol. 83 (2), 283–294.
Magro-Checa, C., Schaarenburg, R.A., Beaart, H.J., Huizinga, T.W., Steup-Beekman, G.M., Trouw, L.A., 2016. Complement levels and anti-C1q autoantibodies in patients with neuropsychiatric systemic lupus erythematosus. Lupus 25, 878–888.
Mandal, J., Chung, S.A., 2017. Primary angiitis of the central nervous system. Rheum. Dis. Clin. North Am. 43 (4 November), 503–518.
Manthorpe, R., Manthorpe, T., Sjoberg, S., 1992. Magnetic resonance imaging of the brain in patients with primary Sjogren's syndrome. Scand. J. Rheumatol. 21 (3), 148–149.
Margaretten, M., 2017. Neurologic manifestations of primary sjögren syndrome. Rheum. Dis. Clin. North Am. 43 (4), 519–529 Nov.
Massara, A., Bonazza, S., Castellino, G., et al., 2010. Central nervous system involvement in Sjogren's syndrome: unusual, but not unremarkable–clinical, serological characteristics and outcomes in a large cohort of Italian patients. Rheumatology (Oxford) 49 (8), 1540–1549.
Melcon, M., Gold, L., Carra, A., et al., 2008. Argentine patagonia: prevalence and clinical features of multiple sclerosis. Mult. Scler. 14, 656–662.
Menon, S., Jameson-Shortall, E., Newman, S.P., et al., 1999. A longitudinal study of anticardiolipin antibody levels and cognitive functioning in systemic lupus erythematosus. Arthritis. Rheum. 42 (4), 735–741.
Mikdashi, J., Krumholz, A., Handwerger, B., 2005. Factors at diagnosis predict subsequent occurrence of seizures in systemic lupus erythematosus. Neurology 64, 2102–2107.
Miller, D.H., Leary, S.M., 2007. Primary-progressive multiple sclerosis. Lancet Neurol. 6, 903–912.
Miller, D.H., Weinshenker, B.G., Filippi, M., et al., 2008. Differential diagnosis of suspected multiple sclerosis: a consensus approach. Mult. Scler. 14, 1157–1174.
Miller, D.V., Salvarani, C., Hunder, G.G., et al., 2009. Biopsy findings in primary angiitis of the central nervous system. Am. J. Surg. Pathol. 33 (1), 35–43.
Miyakis, S., Lockshin, M.D., Atsumi, T., et al., 2006. International consensus statement on an update of the classification criteria for definite antiphospholipid syndrome (APS). J. Thromb. Haemost. 4 (2), 295–306.
Montalban, X., Gold, R., Thompson, A.J., et al., 2018. ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. Mult. Scler. 24 (2 February), 96–120.
Mumford, C.J., Wood, N.W., Kellar-Wood, H., et al., 1994. The British Isles survey of multiple sclerosis in twins. Neurology 44, 11–15.
Murthy, S.B., Khalaf, N., Shah, S., et al., 2013. Churg-Strauss syndrome. JAMA Neurol. 70, 1580–1581.
Muscal, E., Brey, R.L., 2010. Neurologic manifestations of systemic lupus erythematosus in children and adults. Neurol. Clin. 28, 61–73.
Negrini, S., Pappalardo, F., Murdaca, G., et al., 2017. The antiphospholipid syndrome: from pathophysiology to treatment. Clin. Exp. Med. 17 (3 August), 257–267.
Nozaki, K., Judson, M.A., 2012. Neurosarcoidosis: clinical manifestations, diagnosis and treatment. Presse. Med. 41, e331–e348.
Onder, M., Gürer, M.A., 2001. The multiple faces of Behçet's disease and its aetiological factors. J. Eur. Acad. Dermatol. Venereol. 15 (2 March), 126–136.
Pandit, L., Asgari, N., Apiwattanakul, M., et al., 2015. Biorepository for neuromyelitis, demographic and clinical features of neuromyelitis optica: a review. Mult. Scler. 21, 845–853.
Papadopoulos, M.C., Verkman, A.S., 2012. Aquaporin 4 and neuromyelitis optica. Lancet Neurol. 11 (6), 535–544.
Pasoto, S.G., Chakkour, H.P., Natalino, R.R., et al., 2012. Lupus anticoagulant: a marker for stroke and venous thrombosis in primary Sjogren's syndrome. Clin. Rheumatol. 31 (9), 1331–1338.
Pavlakis, P.P., Alexopoulos, H., Kosmidis, M.L., et al., 2012. Peripheral neuropathies in Sjogren's syndrome: a critical update on clinical features and pathogenetic mechanisms. J. Autoimmun. 39 (1–2), 27–33.
Pawate, S., Moses, H., Sriram, S., 2009b. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM 102, 449–460.
Pawate, S., Moses, H., Sriram, S., 2009a. Presentations and outcomes of neurosarcoidosis: a study of 54 cases. QJM 102 (7 July), 449–460.
Pekcevik, Y., Mitchell, C.H., Mealy, M.A., et al., 2016a. Differentiating neuromyelitis optica from other causes of longitudinally extensive transverse myelitis on spinal magnetic resonance imaging. Mult. Scler. 22 (3), 302–311.
Pekcevik, Y., Orman, G., Lee, I.H., Mealy, M.A., Levy, M., Izbudak, I., 2016b. What do we know about brain contrast enhancement patterns in neuromyelitis optica? Clin. Imaging 40 (3), 573–580.
Pelletier, D., Hafler, D.A., 2012. Fingolimod for multiple sclerosis. N. Engl. J. Med. 366 (4), 339–347.
Petri, M., Rheinschmidt, M., Whiting-O'Keefe, Q., et al., 1987. The frequency of lupus anticoagulant in systemic lupus erythematosus. A study of sixty consecutive patients by activated partial thromboplastin time, Russell viper venom time, and anticardiolipin antibody level. Ann. Intern. Med. 106 (4), 524–531.
Pittock, S.J., Berthele, A., Fujihara, K., et al., 2019. Eculizumab in aquaporin-4-positive neuromyelitis optica spectrum disorder. N. Engl. J. Med. 381 (7 August), 614–625.
Pons-Estel, G.J., Cervera, R., 2014. Renal involvement in antiphospholipid syndrome. Curr. Rheumatol. Rep. 16 (2), 397.
Poppe, A., Wolfson, C., Zhu, B., 2008. Prevalence of multiple sclerosis in Canada: a systematic review. Can. J. Neurol. Sci. 35, 593–601.
Ramanathan, S., Prelog, K., Barnes, E.H., et al., 2016a. Radiological differentiation of optic neuritis with myelin oligodendrocyte glycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. Mult. Scler. 22 (4), 470–482.
Ramanathan, S., Prelog, K., Barnes, E.H., Tantsis, E.M., Reddel, S.W., Henderson, A.P., et al., 2016b. Radiological differentiation of optic neuritis with myelin oligodendrocyteglycoprotein antibodies, aquaporin-4 antibodies, and multiple sclerosis. MultScler. J. 22, 470–482.
Raymond, A.A., Zariah, A.A., Samad, S.A., et al., 1996. Brain calcification in patients with cerebral lupus. Lupus 5, 123–128.
Rodrigues, C.E.M., Carvalho, J.F., Shoenfeld, Y., 2010. Neurological manifestations of antiphospholipid syndrome. Eur. J. Clin. Invest. 40 (4), 350–359.
Roussel, V., Yi, F., Jauberteau, M.O., et al., 2000. Prevalence and clinical significance of anti-phospholipid antibodies in multiple sclerosis: a study of 89 patients. J. Autoimmun. 14, 259–265.
Sahraian, M.A., Radue, E.W., Minagar, A., 2013. Neuromyelitis optica: clinical manifestations and neuroimaging features. Neurol. Clin. 31, 139–152.
Salvarani, C., Brown, R.D., Calamia, K.T., et al., 2007. Primary central nervous system vasculitis: analysis of 101 patients. Ann. Neurol. 62 (5), 442–451.
Salvarani, C., Brown Jr, R.D., Christianson, T., et al., 2015. An update of the mayo clinic cohort of patients with adult primary central nervous system vasculitis: description of 163 patients. Medicine 94 (21), e738.
Sato, D.K., Callegaro, D., Lana-Peixoto, M.A., et al., 2014. Distinction between MOG antibody-positive and AQP4 antibody-positive NMO spectrum disorders. Neurology 82 (6), 474–481.
Shimojima, Y., Kishida, D., Hineno, A., et al., 2017. Hypertrophic pachymeningitis is a characteristic manifestation of granulomatosis with polyangiitis: a retrospective study of anti-neutrophil cytoplasmic antibody-associated vasculitis. Int. J. Rheum, Dis, 20 (4), 489–496.
Shoenfeld, Y., Lev, S., Blatt, I., et al., 2004. Features associated with epilepsy in the antiphospholipid syndrome. J. Rheumatol. 31 (7), 1344–1348.
Sibbitt Jr, W.L., Brooks., W.M., Kornfeld, M., et al., 2010. Magnetic resonance imaging and brain histopathology in neuropsychiatric systemic lupus erythematosus. Semin. Arthritis Rheum. 40, 32–52.
Simpson, S.J., Blizzard, L., Otahal, P., et al., 2011. Latitude is significantly associated with the prevalence of multiple sclerosis: a meta-analysis. J. Neurol. Neurosurg. Psychiatry 82, 1132–1141.
Siva, A., 2018 Feb. Common clinical and imaging conditions misdiagnosed as multiple sclerosis: a current approach to the differential diagnosis of multiple sclerosis. Neurol. Clin. 36 (1 February), 69–117.
Siva, A., Saip, S., 2009. The spectrum of nervous system involvement in Behcet's syndrome and its differential diagnosis. J. Neurol. 256 (4), 513–529.
Smith, J.K., Matheus, M.G., Castillo, M., 2004. Imaging manifestations of neurosarcoidosis. AJR Am. J. Roentgenol. 182, 289–295.
Solomon, A.J., Bourdette, D.N., Cross, A.H., et al., 2016. The contemporary spectrum of multiple sclerosis misdiagnosis: a multicenter study. Neurology 87, 1393–1399.
Solomon, A.J., Klein, E.P., Bourdette, D., 2012. "Undiagnosing" multiple sclerosis: the challenge of misdiagnosis in MS. Neurology 78, 1986–1991.
Solomon, A.J., Weinshenker, B.G., 2013. Misdiagnosis of multiple sclerosis: frequency, causes, effects, and prevention. Curr. Neurol. Neurosci. Rep. 13, 403.
Stangel, M., Fredrikson, S., Meinl, E., et al., 2013b. The utility of cerebrospinal fluid analysis in patients with multiple sclerosis. Nat. Rev. Neurol. 9 (5), 267–276.
Stangel, M., Fredrikson, S., Meinl, E., Petzold, A., Stuve, O., Tumani, H., 2013a. The utility of cerebrospinal fluid analysis in patients with multiple sclerosis. Nat. Rev. Neurol. 9, 267–276.
Stern, B.J., Krumholz, A., Johns, C., et al., 1985. Sarcoidosis and its neurological manifestations. Arch. Neurol. 42, 909–917.
Suri, V., Kakkar, A., Sharma, M.C., et al., 2014. Primary angiitis of the central nervous system: a study of histopathological patterns and review of the literature. Folia Neuropathol. 52 (2), 187–196.
Tanne, D., Hassin-Baer, S., 2001. Neurologic manifestations of the antiphospholipid syndrome. Curr. Rheumatol. Rep, 3 (4), 286–292.
Terushkin, V., Stern, B.J., Judson, M.A., et al., 2010. Neurosarcoidosis. Presentations and

management. Neurologist 16, 2–15.
Thompson, A.J., Banwell, B.L., Barkhof, F., et al., 2018. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. Lancet Neurol. 17, 162–173.
Tintore, M., Rovira, A., Rio, J., et al., 2015. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. Brain 138, 1863–1874.
Traboulsee, A., Simon, J.H., Stone, L., et al., 2016. Revised recommendations of the consortium of MS centers task force for a standardized MRI protocol and clinical guidelines for the diagnosis and follow-up of multiple sclerosis. AJNR Am. J. Neuroradiology 37, 394–401.
Ungprasert, P., Crowson, C.S., Matteson, E.L., 2017. Risk of cardiovascular disease among patients with sarcoidosis: a population-based retrospective cohort study, 1976-2013. Eur. Respir. J. 49, 1601290.
Ungprasert, P., Matteson, E.L., 2017. Neurosarcoidosis. Rheum. Dis. Clin. North Am. 43 (4), 593–606 Nov.
Unterman, A., Nolte, J.E.S., Boaz, M., et al., 2011. Neuropsychiatric syndromes in systemic lupus erythematosus: a meta-analysis. Semin. Arthritis Rheum. 41, 1–11.
Uygunoglu, U., Saip, S., Siva, A., et al., 2016. Behcet's syndrome and nervous system involvement. In: Lisak, R.P., Truong, D.D., Carroll, W.M. (Eds.), International Neurology, 2nd edition. John Wiley & Sons, Ltd, Chichester, West Sussex, Hoboken, NJ, pp. 88–93 Chapter 28.
Uygunoglu, U., Zeydan, B., Ozguler, Y., et al., 2017. Myelopathy in Behc¸et's disease: the bagel sign. Ann. Neurol.
Uzawa, A., Mori, M., Kuwabara, S., 2014. Neuromyelitis optica: concept, immunology and treatment. J. Clin. Neurosci. 21 (1), 12–21.
van Pelt, E.D., Wong, Y.Y., Ketelslegers, I.A., Hamann, D., Hintzen, R.Q., 2016. Neuromyelitis optica spectrum disorders: comparison of clinical and magnetic resonance imaging characteristics of AQP4-IgG versus MOG-IgG seropositive cases in the Netherlands. Eur. J. Neurol. 23 (3), 580–587.
van Waesberghe, J.H., Kamphorst, W., De Groot, C.J., et al., 1999. Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. Ann. Neurol. 46 (5), 747–754.
Wang, F., Liu, Y., Duan, Y., Li, K., 2011. Brain MRI abnormalities in neuromyelitis optica. Eur. J. Radiol. 80 (2), 445–449.
Wattjes, M.P., Rovira, A., Miller, D., et al., 2015. Evidence-based guidelines: magnims consensus guidelines on the use of MRI in multiple sclerosis-establishing disease prognosis and monitoring patients. Nat. Rev. Neurol. 11, 597–606.
Wingerchuk, D.M., Banwell, B., Bennett, J.L., et al., 2015. International consensus diagnostic criteria for neuromyelitis optica spectrum disorders. Neurology 85 (2), 177–189.
Wingerchuk, D.M., Hogancamp, W.F., O'Brien, P.C., Weinshenker, B.G., 1999. The clinical course of neuromyelitis optica (Devic's syndrome). Neurology 53, 1107–1114.
Wingerchuk, D.M., Lennon, V.A., Lucchinetti, C.F., et al., 2007. The spectrum of neuromyelitis optica. Lancet Neurol 6, 805–815.
Yaniv, G., Twig, G., Shor, D.B.-A., et al., 2015. A volcanic explosion of autoantibodies in systemic lupus erythematosus: a diversity of 180 different antibodies found in SLE patients. Autoimmun. Rev. 14, 75–79.
Yelnik, C.M., Kozora, E., Appenzeller, S., 2016. Non-stroke central neurologic manifestations in antiphospholipid syndrome. Curr. Rheumatol. Rep. 18 (2), 11.
Yonezu, T., Ito, S., Mori, M., et al., 2014. “Bright spotty lesions” on spinal magnetic resonance imaging differentiate neuromyelitis optica from multiple sclerosis. Mult. Scler. 20 (3), 331–337.
Zalewski, N.L., Flanagan, E.P., Keegan, B.M., 2018. Evaluation of idiopathic transverse myelitis revealing specific myelopathy diagnoses. Neurology 90 (2), e96–e102 Jan 9.
Zalewski, N.L., Morris, P.P., Weinshenker, B.G., et al., 2017. Ring-enhancing spinal cord lesions in neuromyelitis optica spectrum disorders. J. Neurol. Neurosurg. Psychiatry 88 (3), 218–225.
Zandman-Goddard, G., Chapman, J., Shoenfeld, Y., 2007. Autoantibodies involved in neuropsychiatric SLE and antiphospholipid syndrome. Sem. Arthritis Rheum. 36, 297–315.
Zekeridou, A., Lennon, V.A., 2015. Aquaporin-4 autoimmunity. Neurol. Neuroimmunol. Neuroinflamm. 2 (4), e110.
Zettl, U.K., Tumani, H., 2005. Multiple Sclerosis & Cerebrospinal Fluid. Blackwell Publishing Ltd, NavarraSpain, pp. 1–116.
Zeydan, B., Kantarci, O.H., 2018. Progressive Forms of Multiple Sclerosis: Distinct Entity Or Age-Dependent Phenomena 36. Neurol Clin, pp. 163–171 Feb.
Zhu, D.-S., Fu, J., Zhang, Y., et al., 2014. Neurological antiphospholipid syndrome: clinical, neuroimaging, and pathological characteristics. J. Neurol. Sci. 346 (1–2), 138–144.