

DIFFERENTIAL DIAGNOSIS AND DIAGNOSTIC ALGORITHM OF DEMYELINATING DISEASES

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SUMMARY – Demyelinating diseases of the central nervous system include a wide spectrum of different disorders that may resemble multiple sclerosis (MS). The diagnosis of MS is based on typical clinical and paraclinical criteria. The simplified McDonald's criteria, which combine clinical picture, NMR findings, CSF analysis and visual evoked potentials, are appropriate for daily neurologic routine. If some of these criteria are atypical, diagnostic algorithm should be extended to some other procedures to exclude other diseases that can mimic MS not only in symptoms, signs or course of the disease but also in laboratory findings. In such a case, an alternative, better explanation for the clinical manifestations should be considered and performing specific tests is helpful to exclude alternative diagnoses.

Key words: *Neurology – standards; Diagnosis, differential; Nervous system diseases – diagnosis; Algorithms; Demyelinating diseases – diagnosis*

Introduction

Demyelinating diseases of the central nervous system are divided into inflammatory and non-inflammatory diseases. Inflammatory diseases can be idiopathic and include clinical isolated syndrome, multiple sclerosis (MS), acute disseminated encephalomyelitis (ADEM) and optic neuromyelitis, and specific demyelinating diseases that include neurosarcoidosis, neuroborreliosis, and demyelinating diseases in connecting tissue disorders. Non-inflammatory demyelinating diseases are vascular, metabolic, toxic and different genetic disorders. All of these demyelinating diseases can mimic MS as the most common demyelinating disease in clinical features, course of the disease and paraclinical criteria. Therefore, a wide spectrum of diagnostic procedures is by no means in-

frequently needed to make the diagnosis and to start the treatment.

Fifty years ago, the diagnosis of MS was exclusively based on 'dissemination in time and space', i.e. occurrence of two different symptoms at different time point, as the result of involvement of different parts of the central nervous system. Today, a variety of diagnostic methods (nuclear magnetic resonance (NMR) of the brain and spinal cord, specific finding in cerebrospinal fluid (CSF) and visual evoked potentials (VEP)) are available upon which the paraclinical criteria are based^{1,2}. However, despite their high sensitivity, these methods are not specific enough to make an accurate diagnosis due to different clinical presentation, especially in the early course of the disease, which can pose a major problem.

Differential Diagnosis of Demyelinating Diseases

The most common presentations in a clinical isolated syndrome are optic neuritis and transverse myelitis. Fifty percent of patients presenting with optic

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neuritis develop MS within the next 15 years³. Bilateral or rapidly sequential optic neuritis could be caused by the toxic effect of methanol or tobacco, or by vitamin B12 deficiency, and can be part of a specific inflammatory disease such as sarcoidosis, vasculitis or systemic lupus erythematosus (SLE), or may be due to infection, ischemia, tumor growth or Leber's hereditary optic neuropathy.

Transverse myelitis mostly affects thoracic spinal cord. Idiopathic form affects the whole transverse course of the cord causing progressive motor weakness, sensory loss and incontinence⁴. Partial cord lesion is a more specific manifestation of transverse myelitis in MS. The primary causes to be considered include post-infection (varicella, Epstein-Barr virus, mycoplasma, herpes zoster), post-vaccination (influenza), systemic inflammatory disorders (sarcoidosis, SLE, Sjögren's syndrome, antiphospholipid syndrome, giant cell arteritis). Typical CSF findings are pleocytosis, proteinorachia, and rarely oligoclonal bands (OCB).

A combination of optic neuritis and severe form of transverse myelitis is typical for Devic's disease or neuromyelitis optica. Brain NMR is normal in more than 50% of cases, and OCB are positive in a small percent. A specific finding are serum anti-aquaporin-4 IgG antibodies⁵.

Disseminated demyelinating diseases include ADEM and variants of MS (Marburg disease, Schilder's diffuse sclerosis and Baloo's concentric sclerosis).

ADEM occurs predominantly in children and young adults as a consequence of prior virus infection or vaccination, or it can be idiopathic⁶. Typical is the syndrome of meningoencephalomyelitis. CSF and NMR findings are very similar in MS, although demyelinating lesions are more symmetric and usually larger. OCB are transiently positive and disappear in 6 months. ADEM can be multiphasic or recurrent, which is hardly distinguishable from MS.

Marburg disease and Schilder's diffuse sclerosis have an aggressive course leading to death in weeks to months. Schilder's diffuse sclerosis is characterized by cortical dysfunction (dementia, hemiplegia, cortical blindness and deafness). Baloo's concentric sclerosis is characterized by specific demyelinated plaques in which concentric rings of demyelination alternate with normal myelin⁷.

Inherited disorders of adrenoleukodystrophy and metachromatic leukodystrophy can resemble progressive MS. These disorders are specific for positive family history, disturbed intellectual development, adrenal gland insufficiency and abdominal symptoms. OCB are absent.

In the group of infectious diseases, neuroborreliosis, neuroAIDS and neurosyphilis can present as demyelinating diseases. Neuroborreliosis is characterized by myelitis, cerebellar ataxia and recurrent cranial neuropathies⁸. NMR and CSF findings can be very similar to those in MS, so that definitive diagnosis depends on ELISA and Western blot serologic analysis of serum and CSF. Demyelinating changes seen in neuroAIDS are mostly caused by progressive multifocal leukoencephalopathy as a consequence of JC virus. Neurosyphilis is increasing in frequency, but due to NMR rarely causes a picture confused with MS.

Cerebral vasculitis presents as primary vasculitis of the brain and spinal cord, or more commonly as part of systemic diseases (Wegener granulomatosis, SLE, Sjögren's syndrome, rheumatoid arthritis), or it can be seen in drug addicts (cocaine, heroin)⁹. Neurologic complications are the second cause of morbidity in SLE, next to nephrologic ones¹⁰. It can present with headache, epilepsy, ischemic attacks, encephalopathy, myelopathy, or optic neuropathy. OCB are found in about 50% of patients and disappear with immunosuppressant therapy. Sjögren's syndrome can present as optic neuropathy, cerebellar ataxia or internuclear ophthalmoplegia, resembling MS. Characteristic signs are xerostomia, xerophthalmia, involvement of peripheral nervous system, and epileptic and ischemic attacks.

Neurosarcoidosis presents with cranial nerve involvement, involvement of peripheral nervous system and cognitive impairment. OCB can be found in CSF. NMR of the brain is specific due to white matter lesions and leptomeningeal enhancement¹¹.

Behcet's disease is a multisystemic inflammatory disease that affects CNS in about 5% of cases. OCB are uncommon, and NMR abnormalities are nonspecific, so brain biopsy may be required.

Vascular diseases of the CNS, especially arteriovenous malformations, embolization of endocarditic vegetations or atrial myxoma can mimic the symptoms of MS.

Malignant diseases such as lymphoma, foramen magnum tumors or multifocal gliomas can resemble MS.

Diagnostic Algorithm of Demyelinating Diseases

According to all these possible differential diagnoses, a broad spectrum of diagnostic procedures may occasionally be required. We usually start with thorough history and physical examination, then the following studies are performed¹²: 1) NMR of the brain and spinal cord using T1, T2 and FLAIR sequence and gadolinium as a paramagnetic contrast medium, to assess the activity of demyelinating disorder; 2) lumbar puncture with analysis of IgG index and OCB in serum and CSF, MRZ reaction; 3) neurophysiologic studies: visual, auditory and somatosensory evoked potentials; 4) hematologic and biochemical analysis of peripheral blood (complete blood count, erythrocyte sedimentation rate (ESR), coagulogram, C-reactive protein (CRP), protein S, antithrombin III, serum immunoelectrophoresis); 5) molecular analysis of prothrombotic factors (FII, factor V Leiden, MTHFR, PAI-1); 6) immunologic analysis (ANCA, ANA, ENA, antiDNA, aCL, C3, C4, CIC); 7) thyroid gland hormones; 8) vitamin B12 and folic acid; 9) serologic analysis for neurotropic viruses and *Borrelia burgdorferi*, and serologic analysis for HIV, hepatitis B and C; 10) VLDR, TPHA; 11) cardiac studies; and 12) brain biopsy.

Conclusion

Due to the very broad spectrum of differential diagnosis of demyelinating diseases, we have to strictly follow the eligible diagnostic algorithm for MS. Most of these procedures are not obligatory if the main clinical and paraclinical criteria are present. Atypical systemic features such as fever, night sweats, weight loss, arthropathy, rash, ulcers, dry mouth and eyes, ocular disease; atypical neurologic features such as persistent headache, fits, encephalopathy, meningitis, movement disorders, stroke-like events, peripheral neuropathy; and atypical laboratory findings such as raised ESR and/or CRP, absent OCB, persistent pleocytosis, normal NMR or pronounced meningeal enhancement, should prompt a doubt in the diagnosis of MS, although it is possible that MS coexists with

some other demyelinating disease. After all the above mentioned diseases have been ruled out, a finding of demyelinating lesions in the brain or spinal cord points to two options: MS or possible MS. Then, we are exactly where we were 50 years ago: waiting for 'dissemination in time and space'.

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Sažetak

DIFERENCIJALNA DIJAGNOSTIKA I DIJAGNOSTIČKI ALGORITAM ZA DEMIJELINIZACIJSKE BOLESTI

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Demijelinizacijske bolesti središnjega živčanog sustava čine širok spektar različitih poremećaja koji mogu nalikovati multiploj sklerozi. Dijagnoza multiple skleroze temeljena je na tipičnim kliničkim i parakliničkim kriterijima. Pojednostavljeni McDonaldovi kriteriji u kojima se klinička slika kombinira s nalazom magnetske rezonancije, nalazom cerebrospinalne tekućine i vidnim evociranim potencijalima korisni su u svakodnevnoj neurološkoj praksi. Ako je neki od tih kriterija atipičan, treba proširiti dijagnostički postupak kako bi se isključile druge bolesti koje mogu oponašati multiplu sklerozu ne samo u simptomima, znacima ili tijeku bolesti, nego i u nalazima laboratorijskih pretraga. U svakom slučaju, treba razmišljati o drugom, boljem objašnjenju kliničkih manifestacija te je izvedba specifičnih testova korisna u isključenju alternativne dijagnoze.

Key words: *Neurologija – standardi; Dijagnostika, diferencijalna; Bolesti živčanog sustava – dijagnostika; Algoritmi; Demijelinizacijske bolesti – dijagnostika*