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CROATIAN SOCIETY OF NEUROLOGY OF CROATIAN MEDICAL ASSOCIATION

REFERRAL CENTER FOR DEMYELINATING DISEASES OF THE CNS

RECOMMENDATIONS FOR DIAGNOSIS AND MANAGEMENT OF MULTIPLE SCLEROSIS

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SUMMARY – Multiple sclerosis (MS) is a chronic demyelinating neurologic disorder that mainly affects young individuals (aged 20 to 50 years). Approximately 85% of patients experience an initial course with relapses and remissions (relapsing-remitting multiple sclerosis). Guidelines for the management of MS should be focused on three main areas: (a) the diagnosis of MS; (b) treatment of relapses; and (c) long-term preventive treatment including clinical follow up, dose adjustment, drug switch, control of therapeutic efficacy, and disease progression. Diagnosis should be established according to clinical and paraclinical criteria. Discussion on therapeutic recommendations is focused on the disease-modifying agents in acute phases and drugs for long-term treatment and symptomatic treatment. Differential diagnoses must be taken into account on making the diagnosis of MS. Therefore, diagnosis of MS should be established on clinical and radiological diagnostic criteria, cerebrospinal fluid analysis and evoked potentials.

Key words: *Multiple sclerosis – clinical evaluation, diagnostic criteria, treatment*

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Clinical Evaluation

The signs and symptoms of multiple sclerosis (MS) may resemble those of other conditions; therefore diagnosis continues to be largely clinical, which determines the need to apply diagnostic criteria. Clinical diagnosis requires complete medical history and neurological examination. Patients with MS, particularly on the first visit, should be examined carefully with special dedication. Neurologists treating these patients must have extensive experience in the management of MS. The Kurtzke Expanded Disability Status Scale (EDSS) is a method of quantifying disability in MS. The EDSS quantifies disability in eight Functional Systems (FS) and allows neurologists to assign a Functional System Score (FSS) in each of these. The Functional Systems are: pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual, cerebral, and others (Table 1).

Table 1. EDSS steps 1.0 to 4.5 refer to people with multiple sclerosis (MS) who are fully ambulatory. EDSS steps 5.0 to 9.5 are defined by impairment to ambulation (FS, Functional Systems)

	Kurtzke Expanded Disability Status Scale
0.0	Normal neurological examination
1.0	No disability, minimal signs in one FS
1.5	No disability, minimal signs in more than one FS
2.0	Minimal disability in one FS
2.5	Mild disability in one FS or minimal disability in two FS
3.0	Moderate disability in one FS, or mild disability in three or four FS; fully ambulatory
3.5	Fully ambulatory but with moderate disability in one FS and more than minimal disability in several others
4.0	Fully ambulatory without aid, self-sufficient, up and about some 12 hours a day despite relatively severe disability; able to walk without aid or rest some 500 meters
4.5	Fully ambulatory without aid, up and about much of the day, able to work a full day, may otherwise have some limitation of full activity or require minimal assistance; characterized by relatively severe disability; able to walk without aid or rest some 300 meters
5.0	Ambulatory without aid or rest for about 200 meters; disability severe enough to impair full daily activities (work a full day without special provisions)
5.5	Ambulatory without aid or rest for about 100 meters; disability severe enough to preclude full daily activities
6.0	Intermittent or unilateral constant assistance (cane, crutch, brace) required to walk about 100 meters with or without resting
6.5	Constant bilateral assistance (canes, crutches, braces) required to walk about 20 meters without resting
7.0	Unable to walk beyond approximately five meters even with aid, essentially restricted to wheelchair; wheels self in standard wheelchair and transfers alone; up and about in wheelchair some 12 hours a day
7.5	Unable to take more than a few steps; restricted to wheelchair; may need aid in transfer; wheels self but cannot carry on in standard wheelchair a full day; may require motorized wheelchair
8.0	Essentially restricted to bed or chair or perambulated in wheelchair, but may be out of bed itself much of the day; retains many self-care functions; generally has effective use of arms
8.5	Essentially restricted to bed much of the day; has some effective use of arms; retains some self care functions
9.0	Confined to bed; can still communicate and eat
9.5	Totally helpless bed patient; unable to communicate effectively or eat/swallow
10.0	Death due to MS

EDSS is gold standard in evaluating disability in MS patients, but it is criticized for placing too much emphasis on the use of legs and being insensitive to clinical change. Still, it has an important role in the evaluation of disease progression because many of magnetic resonance imaging (MRI) lesions are clinically silent (without symptoms)[1]. However, in centers with trained staff, it is recommended to apply MS Functional Composite scale (MSFC) as accurate measurement of three dimensions at the same time, i.e. leg function/ambulation, arm/hand function and cognitive functions in MS patients. Standard MSFC includes three testing categories: Timed 25 foot walk Test, 9 Hole Peg Test, and Paced Auditory Serial Addition Test (PASAT 3"). One of the difficulties that neurologists most frequently have in clinical application of this scale is the administration of the Paced Auditory Serial Addition Test (PASAT) that requires a series of complex calculations. Some of the experts suggest replacing the PASAT with the Symbol Digit Modalities Test in such patients. The quality of life in MS patients should be evaluated by means of SF-36 scale, at adequate intervals, as determined by the treating neurologist. Beck depression scale should be administered in order to evaluate mood disorders and Visual Analog Scale (VAS) in order to evaluate pain in MS patients (if it is present)[2].

Cerebrospinal Fluid Analysis

Analysis of CSF should be included in the work-up of MS suspected patient. The presence of oligoclonal bands through isoelectric focusing should be obtained. This technique is specific and sensitive; on the contrary, the use polyacrylamide gel may yield up to 50% of false-negative results. Another useful cerebrospinal fluid (CSF) test to diagnose MS is the immunoglobulin G index.

CSF analysis was one of the main paraclinical diagnostic criteria for MS (it is mandatory in the 2010 revision of McDonald criteria for MS); nowadays, it is of great importance in differential diagnosis of MS (Table 2)[3,4].

Evoked Potentials

Visual evoked potentials (EPs) are useful in confirming the involvement of the optic nerve in case of diagnostic uncertainty, and to identify subclinical abnormalities at the onset of the disease. In patients with established optic neuritis, visual EPs add no information. The technique of choice is checkerboard stimulation; EPs to flash provide little information and are not useful, except for patients with severe visual field restriction. As abnormal findings are permanent, visual EPs are not useful for patient follow up. EPs are not included in the 2010 revised McDonald criteria for MS as paraclinical criteria (Table 2).

Neuroimaging

The McDonald criteria as revised by Polman and colleagues have introduced changes in the demonstration of dissemination in time and space through MRI, with subsequent key revisions with respect to the use and interpretation of imaging criteria. This has made conventional MRI (cMRI) the most important paraclinical tool in diagnosing MS and establishing prognosis at the clinical onset of the disease. These are the main reasons why cMRI findings have a major role in the revised diagnostic criteria for MS. The Consortium of Multiple Sclerosis Centers issued guidelines on the most appropriate MRI technique. These include obtaining weighted images at T1 and T2 with gadolinium contrast, sagittal section at T2, coronal section to examine the optic nerve, sagittal section to view the spinal cord, and sagittal section to compare it with the lesions observed elsewhere. If any of the lesions are dubious, 0.5-mm slices must be obtained. Although it is recommended to use 1.5 tesla scanners, where such equipment is not available, the experts consider that MRI scans with lower resolution are equally useful for diagnosis. In centers with magnetization transfer (MT) capabilities, these images may aid diagnosis, although there are no standards and longitudinal follow up with MT MRI is difficult in daily clinical practice. Despite the sensitivity of cMRI for detecting MS lesions, the correlation between cMRI metrics (i.e. hyperintense lesions on T2- and post-contrast T1-weighted images, hypointense lesions on T1-weighted images, and atrophy measurements) and clinical findings of MS is still limited. Amongst the likely reasons for this clinical/MRI discrepancy, a major one is the low pathological specificity of the abnormalities seen on cMRI scans and the inability of cMRI metrics to detect and quantify the extent of

Table 2. Polman's revision of McDonald multiple sclerosis criteria 2010

Clinical presentation	Additional data needed for MS diagnosis
≥2 attacks[a]; objective clinical evidence of ≥2 lesions or objective clinical evidence of 1 lesion with reasonable historical evidence of a prior attack[b]	None[c]
≥2 attacks[a]; objective clinical evidence of 1 lesion	Dissemination in space, demonstrated by: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or await a further clinical attack[a] implicating a different CNS site
1 attack[a]; objective clinical evidence of ≥2 lesions	Dissemination in time, demonstrated by: simultaneous presence of asymptomatic gadolinium-enhancing and non enhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesions(s) on follow up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
1 attack[a]; objective clinical evidence of 1 lesion (clinically isolated syndrome)	Dissemination in space and time, demonstrated by: for DIS: ≥1 T2 lesion in at least 2 of 4 MS-typical regions of the CNS (periventricular, juxtacortical, infratentorial, or spinal cord)[d]; or await a second clinical attack[a] implicating a different CNS site; and for DIT: simultaneous presence of asymptomatic gadolinium-enhancing and non enhancing lesions at any time; or a new T2 and/or gadolinium-enhancing lesions(s) on follow up MRI, irrespective of its timing with reference to a baseline scan; or await a second clinical attack[a]
Insidious neurological progression suggestive of MS (PPMS)	1 year of disease progression (retrospectively or prospectively determined) plus 2 or 3 following criteria[d]: 1. evidence for DIS in the brain based on ≥1 T2 lesions in the MS-characteristic (periventricular, juxtacortical or infratentorial) regions 2. evidence for DIS in the spinal cord based on ≥2 T2 lesions in the cord 3. positive CSF (isoelectric focusing evidence of oligoclonal bands and/or elevated IgG index)

[a] An attack (relapse, exacerbation) is defined as patient-reported or objectively observed events typical of an inflammatory demyelinating event in the CNS, current or historical, with duration of at least 24 hours, in the absence of fever or infection. It should be documented by contemporaneous neurological examination, but some historical events with symptoms and evolution characteristic of MS, but for which no objective neurological findings are documented, can provide reasonable evidence of a prior demyelinating event. Reports of paroxysmal symptoms (historical or current) should, however, consist of multiple episodes occurring over not less than 24 hours. Before a definitive diagnosis of MS can be made, at least 1 attack must be corroborated by finding on neurological examination, visual evoked potential response in patients reporting prior visual disturbance, or MR consistent with demyelination in the area of the CNS implicated in the historical report of neurological symptoms.

[b] Clinical diagnosis based on objective clinical findings for 2 attacks is most secure. Reasonable historical evidence for 1 past attack, in the absence of documented objective neurological findings, can include historical events with symptoms and evolution characteristic of a prior inflammatory demyelination event; at least 1 attack, however, must be supported by objective findings.

[c] No additional tests are required. However, it is desirable that any diagnosis of MS be made with access to imaging based on these Criteria. If imaging or other tests (for instance, CSF), are undertaken and are negative, extreme caution needs to be taken before making a diagnosis of MS, and alternative diagnoses must be considered. There must be no better explanation for the clinical presentation, and objective evidence must be present to support the diagnosis of MS.

[d] Gadolinium-enhancing lesions are not required; symptomatic lesions are excluded from consideration in subjects with brainstem or spinal cord syndromes.

MS = multiple sclerosis; CNS = central nervous system; MRI = magnetic resonance imaging; DIS = dissemination in space; DIT = dissemination in time; PPMS = primary progressive multiple sclerosis; CSF = cerebrospinal fluid; IgG = immunoglobulin G.

Table 3. Differential diagnosis[12]

Underlying pathology	Clinical diagnosis	Main recommended work-up
Vascular	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) Lacunar infarcts Leukoencephalopathies Vasculitis Fabry disease	Family history of neurologic disorders CSF analysis Brain MRI scan Carotid Doppler ultrasound Echocardiogram Blood and urine testing Genetic tests
Infectious (CNS involvement)	Brucellosis	*Brucella* culture in CSF Antibody detection (microagglutination, Coombs or Bengali rose) CSF analysis Brucellosis confirmed at another body site
	Cysticercosis Echinococcosis	ELISA in blood and CSF Western blot (immunoelectrotransfer) in blood and CSF
	Neurotrophic viruses	ELISA Western blot Immunofluorescence Particle agglutination Virus detection (polymerase chain reaction (PCR) testing)
	Borrelia burgdorferi Syphilis *Listeria*	ELISA Western blot Immunofluorescence
Immune	Systemic lupus erythematosus Sarcoidosis Histiocytosis	Serology with antinuclear antibody and anti-dsDNA serum and urine ACE, CD4/CD8, whole body gallium imaging, bronchoalveolar lavage analysis
	Isolated CNS vasculitis	Autoantibodies (immunology) Angiography
Metabolic	Vitamin B12 deficiency	Abnormal blood test results: low serum B12, methylmalonic acid and homocysteine concentrations, antiparietal cells (APS) Malnutrition General clinical examination
	Toxic agents	Abnormal blood test results General clinical examination Toxicology for metals
Hematologic	Thrombophilia	Inherited: C and S proteins, gene mutations for coagulation factor II,V and PAI I (PCR testing) Acquired: according to presumptive diagnosis
Tumors	Primary and secondary expansive processes of the CNS	History General clinical examination Brain MRI scan Tumor markers

CSF = cerebrospinal fluid; ELISA = enzyme-linked immunosorbent assay; MRI = magnetic resonance imaging.

damage in normal-appearing brain tissues (NABTs). These inherent limitations of cMRI have prompted the development and application of modern quantitative MR techniques [MR spectroscopy (1H-MRS), MT MRI, diffusion-weighted (DW) MRI and functional MRI (fMRI)] to the study of MS. Although these techniques have provided important insight into the pathobiology of MS, their practical value in the assessment of MS patients in clinical practice has yet to be realized[5-7].

Diagnosis of Multiple Sclerosis

Over time, different sets of criteria have been developed to support the diagnosis of MS in clinical practice. Historically, most relevant have been those proposed by Schumacher and colleagues, Poser and colleagues, and McDonald and colleagues. The revisions to the McDonald criteria made by Polman and colleagues are the currently used criteria for the diagnosis of MS (Table 2)[8-11].

If the Criteria are fulfilled and there is no better explanation for the clinical presentation, the diagnosis is „MS"; if suspected, but the Criteria are not completely met, the diagnosis is „possible MS"; if another diagnosis arises during the evaluation that better explains the clinical presentation, then the diagnosis ins „not MS".

Clinically Isolated Syndrome

The concept of clinically isolated syndrome (CIS) was developed following Polman and colleagues' revision of the McDonald criteria. The term is used to describe the first acute neurological episode lasting for more than 24 h, caused by inflammation or demyelination at one or more central nervous system (CNS) sites, i.e. monofocal or multifocal CIS. There are different MRI diagnostic criteria for CIS. These criteria have changed over time and must be correlated with clinical manifestations. Recently, the European multicenter network for the study of MS through MRI scans (MAGNIMS) has proposed new criteria for dissemination in time and space, as well as a diagnostic algorithm to predict the conversion of CIS into clinically defined MS[13,14].

CIS can be divided into 5 subtypes:

type 1: clinically monofocal, at least one asymptomatic lesion on brain MRI
type 2: clinically multifocal, at least one asymptomatic lesion on brain MRI
type 3: clinically monofocal, brain MRI normal, without any lesion
type 4: clinically multifocal, brain MRI normal, without any lesion
type 5: without clinical manifestation suggestive of demyelinating disease, brain MRI suggestive of demyelinating disease (radiologically isolated syndrome, RIS)[12].

Radiological Isolated Syndrome (RIS)

The widespread availability of MRI as an imaging diagnostic test has led to the incidental finding of white matter lesions at the CNS that are suggestive of MS and not attributable to any other disease in asymptomatic patients. These lesions are known as 'radiological isolated syndrome'. The natural history of these lesions and the evolution of these patients regarding their risk of developing MS are unclear, and further evidence is required to establish this risk[15].

Neuromyelitis Optica

It is of great importance to distinguish neuromyelitis optica (NMO) from MS because of its different course and prognosis and putative differences in response to immunomodulatory therapy. NMO is the most commonly seen non-MS idiopathic inflammatory demyelinating disease (IIDD). It has been distinguished in the past from MS by the restricted manifestations such as optic neuritis and myelitis, and for having a monophasic, not relapsing course. However, recent studies suggest that NMO is usually a relapsing IIDD, overlapping in clinical course with MS. Normal brain imaging and longitudinally extensive cord lesions in the context of acute myelitis have helped distinguish NMO from MS. A recently discovered, highly specific and moderately sensitive serum biomarker NMO-IgG is useful for the diagnosis of NMO. The following should be taken into account on distinguishing NMO from MS:

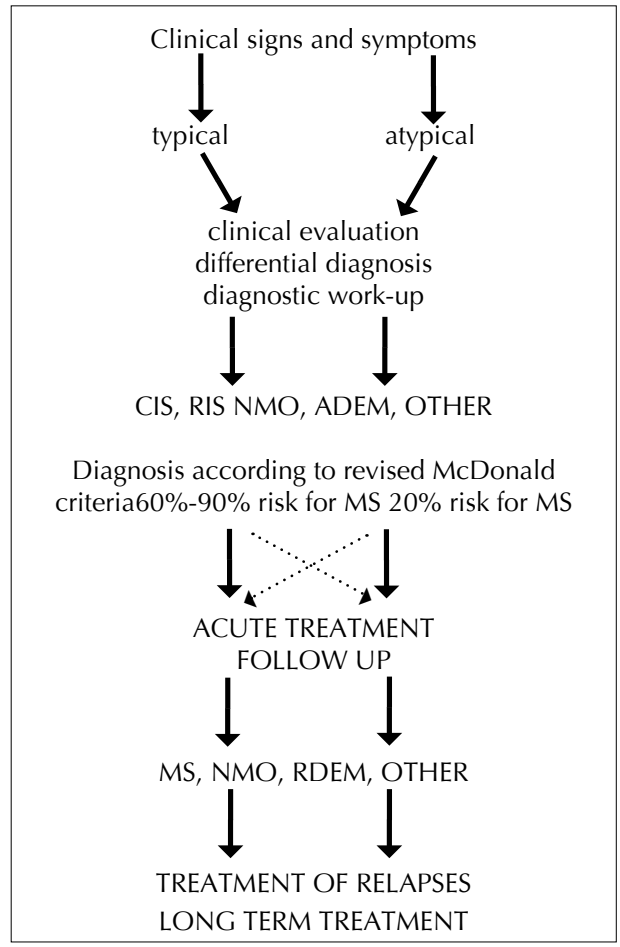
– NMO is most commonly a relapsing disorder, and hence that characteristic is not useful to distinguish it from MS;

- the key clinical difference is NMO predilection for severe episodes of myelitis that often but not always manifest as a complete transverse myelitis, and for severe episodes of optic neuritis, often but not always with incomplete recovery;
- the myelitis, unlike that which occurs in MS, is usually accompanied in the acute phase by a T2-weighted spinal cord lesion extending over three or more spinal segments (longitudinally extensive transverse myelitis, LETM), which may be hypointense on T1-weighted MRI and also associated with varying degrees of gadolinium enhancement;
- usually, there is no brain involvement in NMO, and brain MRI is often normal, particularly in the early stages of the disease;
- if present, brain lesions generally do not fulfill typical criteria for dissemination in space (usually presented in regions with high expression of aquaporin 4, including the hypothalamus, medulla, and other brainstem areas);
- oligoclonal bands or elevated IgG index in CSF are detected in 10%-20% of patients with NMO compared with 70%-90% of patients with MS; and
- limited syndromes of NMO can be presented with recurrent transverse myelitis alone accompanied by long spinal cord lesions or recurrent optic neuritis alone, and are seropositive for NMO-IgG. Such spatially limited syndromes should not be qualified as NMO, even in the presence of a positive NMO-IgG serum assay. The subsequent development of optic neuritis in a patient with myelitis or *vice versa* may permit a later diagnosis of NMO[12].

Acute Disseminated Encephalomyelitis

Historically, acute disseminated encephalomyelitis (ADEM) was distinguished from MS by its monophasic course and encephalopathy or coma in combination with multifocal symptoms (e.g., cerebellar signs, cerebral motor or sensory features, optic neuritis or myelitis) characteristic of an IIDD, often following an infectious illness. MRI typically shows usually symmetric multifocal or diffuse brain lesions. Some patients experience recurrence of their initial ADEM symptoms with reactivation of the same MRI lesions as were present at the time of the initial illness appearance (recurrent ADEM-RDEM). Although characteristics such as encephalopathy with multifocal symptoms may be more likely for ADEM than for MS, no clinical, paraclinical or imaging criteria reliably distinguish fulminant initial episodes of MS from ADEM, therefore follow up of such patients and differential work-up is of great importance. Diagnosis of ADEM should be made in patients with a first event compatible with demyelinating disease that is acute or subacute in onset (over days to weeks), with a stable or stuttering course, but only when additional characteristics are present, e.g., encephalopathy manifested either as altered level of consciousness, behav-

Table 4. Diagnostic algorithm when MS is suspected



MS = multiple sclerosis; NMO = neuromyelitis optica;
ADEM = acute disseminated encephalomyelitis;
CIS = clinically isolated syndrome;
RIS = radiologically isolated syndrome;
RDEM = recurrent disseminated encephalomyelitis

ioral change, or altered cognitive functioning. New symptoms may emerge over intervals up to 3 months from onset without intervening remission (but not beyond 3 months; RDEM). If remission of the initial symptoms occurs, followed by new symptoms after an interval of 1 month, the diagnosis of MS is more likely than ADEM.

The presence of multiple supra- or infratentorial lesions in combination with lesions of deep grey nuclei and at least one lesion greater than 1-2 cm in diameter is characteristic of brain MRI in ADEM patients. Spinal cord lesions may or may not be present, but when present, they tend to be longitudinally extensive[12].

Treatment

Treatment of relapses as well as long term treatment should be planned according to the results of clinical trials and evidence based medicine (Table 5). The main goals in the treatment of MS patients should be:

1) improving the speed of recovery from attacks (acute treatment, mostly with steroid drugs),
2) reducing the number of attacks or the number of MRI lesions, and
3) attempting to slow progression of the disease (2 and 3 treatment with disease modifying drugs, DMDs).

Treatment of Relapses

An attack should last for at least 24 h and, according to the McDonald criteria there should be expert opinion that the event is not a pseudoattack as might be caused by an increase in body temperature or infection. Multiple episodes of paroxysmal symptoms, e.g., tonic spasms or trigeminal neuralgia occurring over not less than 24 h, may also constitute a relapse. Although the majority of relapses improve to some ex-

Table 5. Levels of evidence and classes of recommendations

Clinical level I: high level of evidence	Source a: primary endpoint from randomized, double-blind study with sufficient sample size	CLASS A Consistent level I studies or a systematic review (SR) or meta analysis (MA)
	Source b: properly performed meta-analysis of qualitatively outstanding randomized trials	
Clinical level II: intermediate level of evidence	Source a: randomized, non-blind studies	CLASS B Consistent level II studies or single level I study
	Source b: small randomized trials	
	Source c: predefined secondary endpoints of large randomized trails	
Clinical level III: low level of evidence	Source a: prospective case series with concurrent or historical control	CLASS B Consistent level III study
	Source b: post hoc analyses of randomized trials	
Clinical level IV: undetermined level of evidence	Source a: small case series without control, case reports	CLASS C Consistent level III study or extrapolations from level II or III
	Source b: general agreement despite the lack of scientific evidence from controlled trials	
Clinical level V	Expert opinion	CLASS D Level V of evidence or inconsistent studies of levels I-IV

tent, incomplete recovery is an important determinant of irreversible neurological impairment in MS at least in the earlier stages of MS[16-18].

Corticosteroids

There is evidence from several class I studies and meta-analyses for a beneficial effect of glucocorticoid treatment in MS relapses. Treatment with intravenous or oral methylprednisolone in a dose of at least 500 mg daily for 5 days should be considered for treatment of relapses (level A recommendation). Treatment with i.v. methylprednisolone (1 g once daily for 3 days) should be considered as an alternative treatment. Treatment with i.v. methylprednisolone (1 g once daily for 3 days with an oral tapering dose) may be considered for treatment of acute optic neuritis (level B recommendation). There is no evidence for major differences in the efficacy of methylprednisolone treatment given i.v. or orally in terms of clinical efficacy or side effects, but prolonged oral treatment may possibly be associated with a higher prevalence of side effects. Due to a small number of patients included in clinical trials, efficacy differences between the i.v. and oral route of administration cannot be excluded. The optimal dosage, the specific glucocorticoid to be used, and whether to use a taper after initial pulse therapy, have not been adequately evaluated in randomized, controlled trials. These issues should be evaluated in new, randomized studies in order to assess the risk/benefit ratios and adverse effects of specific glucocorticoids, dose, and route of administration for the treatment of MS relapses.

Due to the lack of clinical proofs, there is still the need to define patient subgroups that are more likely to respond to methylprednisolone treatment. It looks like that treatment may be more efficacious in patients with clinical, MRI, or CSF evidence (increased myelin basic protein concentration in CSF) indicating higher disease activity (level C recommendation).

Therapy administration in inpatient or outpatient setting has not been addressed in clinical trials, but consideration could be given to administering the first course of methylprednisolone in inpatient setting due to the possible side effects and complications of this therapy (good clinical practice).

In patients who fail to respond to therapy with methylprednisolone in the previously recommended doses, treatment with higher doses (up to 2 g daily for 5 days) should be considered (level C recommendation).

Interdisciplinary rehabilitation program should be considered after treatment with i.v. methylprednisolone, as evidence from a single trial suggests that it probably further improves recovery (level B recommendation)[16-19].

Immunoglobulins

There are insufficient data to support the use of intravenous immunoglobulin (IVIG) therapy as monotherapy for relapses of MS. IVIG has not fulfilled the promise indicated by the results of many well-designed studies. Four randomized double-blind studies have all shown a beneficial effect on disease activity in relapsing-remitting multiple sclerosis (RRMS). IVIG 0.15-0.2 g/kg every 4 weeks during 2 years showed pronounced reduction in the relapse rate in two placebo-controlled trials. A meta-analysis of four studies showed significant reduction in the annual relapse rate and disease progression (class I evidence). The prevention of relapses with IVIG trial (PRIVIG) re-evaluating the effects of IVIG given 0.2 and 0.4 g/kg monthly failed to show effect on the proportion of relapse-free patients and MRI activity in a placebo-controlled study in 127 patients with RRMS. Thus, this trial failed to support earlier observations on a beneficial effect of IVIG in RRMS. In secondary progressive MS, a large placebo-controlled trial of IVIG 1 g/kg monthly in 318 patients failed to show any beneficial effect on the relapse rate, deterioration in EDSS, and change in lesion volume of T2 weighted images (class I evidence). The only beneficial effect was reduction in brain atrophy[45]. Small studies with historical controls suggested that IVIG might reduce relapse rate after childbirth (class IV evidence).

IVIG could still be considered as a second- or third-line therapy in RRMS if conventional immunomodulatory therapies are not tolerated because of side effects or concomitant diseases (level B), and in particular in pregnancy where other therapies may not be used (good clinical practice point). IVIG cannot be recommended for treatment in secondary progressive MS (level A). IVIG does not seem to have any valuable effect as add-on therapy to methylprednisolone for acute exacerbations (level B) and cannot be rec-

ommended as treatment for chronic symptoms in MS (level A). In clinically isolated syndromes and in primary progressive MS, there is not sufficient evidence to make any recommendations[16-18].

Plasma Exchange

A single class I crossover study of 22 patients with severe relapses of inflammatory demyelination (including 12 with MS) who were refractory to treatment with high-dose methylprednisolone suggested a beneficial effect of treatment with plasma exchange. A Cochrane review and studies of treatment with intravenous immunoglobulin (IVIG) have shown that prophylactic treatment may result in a decrease in the number of relapses in patients with RRMS. A single class IV study of IVIG treatment in relapses of MS suggested that as many as 68% of patients improved within 24 h of treatment. Two recent studies have investigated if IVIG treatment as add-on therapy to high-dose i.v. methylprednisolone is superior to add-on placebo treatment (class I study). Both studies were negative on primary and secondary end-point.

This treatment option should be restricted to a subgroup of patients with severe relapses (level B recommendation) or those that have not responded to treatment with corticosteroids. We should have in mind the fact that only about one-third of treated patients are likely to respond[16-18].

Long Term Treatments

First line therapies

Treatment of RRMS must be started with a drug with the best risk-benefit ratio. Presently, the first line drugs regularly used for the treatment of MS include glatiramer acetate (Copaxone) 20 mg/day s.c.; IFN beta-1a, 30 mg (6 MIU)/week i.m. (Avonex), IFN beta-1a, 22 mg three times a week s.c. or 44 mg three times a week s.c. (Rebif), IFN beta-1b, 250 mg (9.6 MIU) every other day s.c. (Betaferon).

Glatiramer acetate

Glatiramer acetate (GA) is a random polymer composed of four amino acids that are found in myelin basic protein. It shifts the population of T cells from proinflammatory Th1 cells to regulatory Th2 cells that suppress the inflammatory response. These Th2 cells can enter the CNS and inhibit inflammatory activity through so called bystander effect as well as release of neurotrophins that may exert neuroprotective effect. There is no evidence for glatiramer acetate to have immunosuppressive effects and therefore there are no opportunistic infections recorded or neoplastic diseases associated with its use. This treatment is considered safe and there is no need for routine laboratory work-up. Side effects of glatiramer acetate usage are immediate injection site reactions and post-injection syndrome in some patients, as well as lipoatrophy, particularly in young women[20,21].

Interferon beta

All three interferon beta preparations influence inhibition of T cell activation and proliferation in the periphery and reduction of T cell passage across the blood-brain barrier. There is no evidence for adverse immunosuppressive effects of interferon beta. Side effects mostly present as flu-like symptoms. Monitoring of hepatic enzymes and complete blood count should be regularly performed (due to possible liver failure and leukopenia). There is also some evidence that interferon beta can trigger depression.

Several comparative studies have shown that glatiramer acetate and high-dose IFNs are similarly effective (BEYOND, REGARD study; evidence level 1, recommendation grade A)[20,21]. High IFN doses are more effective than low doses (recommendation grade B). Glatiramer acetate and IFN are useful at the doses mentioned above; final therapeutic decision must be made on the basis of available evidence and together with the patient, taking into account factors such as expected treatment adherence and the potential side effects of the drug. A follow-up visit should be scheduled at 3-6 months to control the course of the disease. No treatment change is necessary if patients are stable. In some cases, it is necessary to switch medications or to adjust the dose, either due to treatment failure or to the development of severe and/or serious adverse events[22-27]. Patients who initially respond to IFN but later present with treatment failure must be switched from IFN to glatiramer acetate. In patients who initially respond to glatiramer acetate and become refractory to treatment, IFN should be administered.

Neutralizing antibodies (NAbs) are another factor associated with treatment failure. The role of NAbs on the progression of MS is controversial, and, in fact, their determination does not alter therapeutic approach. In patients treated with IFN and with persistently high NAbs titers, their determination upon treatment failure might play a role[28].

The treating neurologist must establish a control method to ensure strict compliance with treatment (100% adherence), although at present there are no studies to determine the best choice. Nurses specialized in MS should be included in the treatment team.

Second line therapies

If there is a first line treatment failure, the patient must be switched to a drug with a higher strength (escalation therapy), usually with higher toxicity. Treating physician must find treatment option at which therapeutic effectiveness and side effects have an 'acceptable' ratio[29].

Fingolimod

Fingolimod (sphingosine-1-phosphate) is a receptor antagonist that prevents egress of activated T cells from the lymph nodes (shown in clinical trials compared to placebo and interferon beta 1a). Oral therapy with fingolimod is an attractive option in correlation with natalizumab according to the way of administration as well as low risk of complications such as progressive multifocal leukoencephalopathy (PML). The drug is registered as first line therapy in the United States and as second line therapy in Europe.

Clinical trials were evaluating the impact of fingolimod on MS relapses. The first trial demonstrated a decrease in the number of relapses, a slowdown of disability progression time, reduction in T2 and T1 lesion volume and gadolinium enhancing lesion count, and a decrease in volume loss. The second trial found a lower relapse rate, a decreased number of new lesions or decreased size of T2 lesions, less atrophy, and no significant differences in terms of progression of disability among different treatment groups. In the placebo controlled phase III trial of fingolimod (FREEDOMS), tolerability of fingolimod and placebo were closely comparable, with a similar proportion of serious adverse events and adverse events leading to treatment discontinuation. Certain adverse events were more common in fingolimod group compared to placebo, i.e. back pain, hypertension and bradycardia (the latter two attributable to the mechanism of drug action).

In a trial comparing fingolimod and interferon beta 1a, some serious adverse events were recorded. Two deaths due to herpetic infections occurred in fingolimod group (possibly due to immunosuppressive effect, which can facilitate development of opportunistic infections). Skin cancers, both malignant melanomas and malignant basal cell carcinomas, were also reported in this trial, therefore special monitoring of the skin status should be performed in patients on fingolimod therapy.

Experience with this drug is limited and there are no long term side effect data available, therefore closer and thorough follow up of patients is required than with the currently employed drugs. The standard fingolimod dosage for treating MS is 0.5 mg taken once daily orally (capsules). Studies have shown that doses higher than 0.5 mg once daily increase the risk of side effects, without improving effectiveness[30,31].

Monoclonal antibodies

There are several monoclonal antibodies currently used in the treatment of MS that have been approved for other indications. All of them have been subject to phase II trials and have phase III trials underway or planned. Their availability on the market allows for off-label uses in patients with especially severe or rapidly evolving MS[32-34].

The current treatment of choice for escalation therapy would be natalizumab, a monoclonal antibody directed against the VLA-4 adhesion molecule that prevents access of circulating cells to the CNS. Two large phase III randomized clinical trials have proven natalizumab to be extremely effective in preventing relapses and radiological indices of disease activity in patients with RRMS[35,36]. During the treatment with natalizumab, the potential adverse events can be present, particularly PML caused by reactivation of quiescent JC virus infections in the CNS. Before administering the drug, the physician must order laboratory tests including CD4 and CD8 counts, chest x-ray, and MRI scan, as well as evaluation of JC virus serology status in order to prevent PML as a neurologic condition of na-

talizumab therapy. A two-step ELISA immunoassay for anti JC virus has been developed, as reported from the STRATIFY-1 and STRATIFY-2 studies[37].

Patients above 60 years of age, those previously treated with immunosuppressive agents (a wash-out period of at least 6 months must be allowed before administering natalizumab), and patients living with HIV are at a higher risk of adverse events. Furthermore, experts underscore that both the physician who administers the drug and the infusion center must be broadly experienced in the management of the drug and must be certified for its administration. In the event that previous treatments are not effective and MRI scans continue to reveal inflammatory activity, or if the patient continues to relapse, the neurologist may consider escalation to a third level of treatment, including the use of drugs not approved for the treatment of MS (off-label indications), such as rituximab or alemtuzumab (phase III trials underway), or bone marrow transplant.

Azathioprine

Azathioprine is an immunosuppressant; it suppresses proliferation of T and B lymphocytes. This drug reduced the number of patients having relapses and disability progression during the first year of treatment, and at two- and three-year follow up as well. Adverse effects such as gastrointestinal disturbances, bone marrow suppression and hepatic toxicity occurred frequently; but they were known and anticipated and therefore well managed; with drawals due to adverse events were few, and mainly due to gastrointestinal intolerance. Two studies had deaths reported, including four persons in the control group and eight in the azathioprine group. These small numbers do not allow for statistical analysis. Conflicting conclusions on the potential risk of cancer in MS patients on long term azathioprine treatment have been reported in eight published papers, not considered in the present review because they came from sources other than clinical trials. The presence of patients who developed cancer (3 in azathioprine group and 1 in placebo group) was reported in two of five studies. The usual dose for treatment of MS patients is 1-3 mg/kg *per* day orally (50 mg tablets)[29].

Cyclophosphamide

Cyclophosphamide has been widely studied for the treatment of MS and effective stabilization of selected patients on this therapy has been suggested in several studies. This drug has selective effects on the immune response, such as suppression of helper Th1 activity and enhancement of helper Th2 responses; both of these processes are thought to be involved in the beneficial effect of cyclophosphamide in MS. Over years, especially with the advent of MRI, there has been an improved understanding of the profound anti-inflammatory effect of cyclophosphamide, evidenced by its effect on clinical relapses and contrast-enhancing lesions on MRI. Toxic effects on urinary bladder and the risk of malignancy prevent the widespread use of cyclophosphamide in early MS; however, it can be dosed safely and is usually well tolerated in actively progressing RRMS or early secondary progressive MS cases that are unresponsive to beta interferon and glatiramer acetate. Patients with aggressive MS should receive 50 mg/kg/day for four consecutive days.

There are some alternative protocols with pulse doses of cyclophosphamide applied monthly or every 3 months. Due to toxic effects on urinary bladder during therapy with cyclophosphamide, patients should receive uromitexan (disodium 2-mercapto ethane sulfonate, MESNA), which has been developed as a prophylactic agent to prevent urothelial toxicity (hemorrhagic cystitis) induced by oxazaphosphorine alkylating agents viz. ifosfamide or cyclophosphamide. Uromitexan should be administered by intravenous injection, usually at doses of 20% of the respective cyclophosphamide dose, at times 0 (administration of the cytostatic agent), 4 h and 8 h[38].

Mitoxantrone

This drug was for a long time considered as the best choice for second line therapy, but it is not safe as it was previously thought, as it is associated with a high incidence of leukemia (1:135) and cardiomyopathy in treated patients.

A French-British collaboration reported in 1997 included 42 people with RRMS or secondary progressive MS randomized to receive either a combination of mitoxantrone (20 mg i.v. monthly) and the steroid methylprednisolone (1 g i.v. monthly), or methylpred-

nisolone only for six months. In the mitoxantrone group, there was a significant reduction in the number of relapses and improvement on the EDSS. In a larger phase III study known as the MIMS study (Mitoxantrone in MS) reported in 2002, 194 people with worsening RRMS or secondary progressive MS received placebo, or 5 mg/m^2 of mitoxantrone, or 12 mg/m^2 of mitoxantrone administered i.v. every three months for 24 months. The higher dose of mitoxantrone was shown to be effective and generally well tolerated, reducing the progression of disability and the number of relapses compared to placebo. The benefits for those assigned to 5 mg/m^2 dose were less convincing. Cumulative dose of mitoxantrone should not exceed 120-140 mg/m^2. Different treatment regimens are used in different countries according to different regulatory demands, but the two regimens most commonly used are 12 mg/m^2 mitoxantrone i.v. every three months for two years (based on the MIMS study) or 20 mg mitoxantrone i.v. and 1 g methylprednisolone every four weeks for six months (based on the French-British study)[39,40].

Mycophenolate mofetil

This drug has several proposed mechanisms of actions. Animal studies show that it causes a Th1 to Th2 shift with an anti-inflammatory profile. It also down-regulates MHC class II, chemokines and adhesion related molecules important to inflammation. It crosses the blood-brain barrier and may also play a neuroprotective role by increasing BDNF.

The first clinical study, ALLEGRO, was a two-year multi-national, multicenter randomized, double blind, placebo-controlled study designed to evaluate the efficacy, safety and tolerability of mycophenolate mofetil in MS patients (1106 MS patients). The second clinical study, BRAVO, is a two-year, multinational, multicenter, randomized, double blind, parallel-group, placebo-controlled study designed to compare the safety, efficacy and tolerability of a once-daily oral dose of 0.6 mg mycophenolate mofetil *versus* placebo and to perform a comparative risk-benefit assessment between mycophenolate mofetil and interferon beta-1a. Although comparison of efficacy across studies is difficult, the data generally show the relapse rate efficacy to be inferior to the injectable interferons and glatiramer, but reduction in disability progression may be more similar or superior. During the treatment with this drug, side effects such as gastrointestinal symptoms (bleeding, abdominal pain), urinary infections, skin rashes, unusual or persistent tiredness or weakness, unusual skin lumps or growths, unusual weight loss; unusually pale skin, white patches in the mouth or throat, yellowing of the skin or eyes (liver dysfunction) may occur[29].

Treatment of Clinically Isolated Syndrome

At the beginning of the disease course, MS is characterized by inflammatory demyelination, which may be clinically silent (RIS), therefore patients often present multiple old inactive lesions on brain and spinal cord MRI at the time of the onset of clinical symptoms. At the time of first clinical manifestation (CIS), neurodegenerative changes are already taking place in many patients. The disease then generally enters the relapsing-remitting course leading to conversion to secondary progressive course. Therapeutic window for current anti-inflammatory treatments is when the inflammatory component is most active.

CIS episode should be treated with high methylprednisolone doses to reduce the risk of second attack. The dose ranges from 500 mg/day for 5 days to 1 g/day for 3-5 days (evidence level 1, recommendation grade A). The administration of 2 g/day for 5 days (evidence grade U) has also been described. The total dose is administered i.v. during 2-4 hours, and blood pressure and heart rate must be monitored to identify the potential side effects caused by corticosteroids such as hypotension at an early stage. In case of severe relapses that do not respond to steroid therapy, or in case of adverse events, treatment with plasmapheresis (recommendation grade B) may be considered. In all other cases, there is no evidence to support the use of plasmapheresis in the treatment of MS. There is no strong evidence in support of the use of natalizumab, i.v. immunoglobulin, or a second course of corticosteroids during relapses.

All studies have shown that the administration of immunomodulating agents during CIS reduces the risk of a second demyelinating episode, without significant differences among the different types of immunomodulating agents. The criteria for treating CIS

Table 6. Drugs used in MS relapses and as preventive treatment: first line and second line therapies

	Drug name	Dosage	Level of evidence
Treatment of relapses	Methylprednisolone	0.5-1 g *per* day i.v. (3-7 days)	I
	Prednisone	0.5-1 mg/kg body weight in tapering doses; after 3-6 weeks, 5-10 mg maintenance dose	IV
	IVIG	2.0-0.4 g/kg body weight 2-5 days	III
	Plasma exchange	1-7 times every other day	IV
First line therapies	Glatiramer acetate	20 mcg *per* day	I
	Interferon beta 1a and interferon beta 1b	Avonex 6 MIU once *per* week, Betaferon 9.6 MIU every other day, Rebif 22 mcg or 44 mcg twice weekly	I
Second line therapies	Fingolimod	0.5 mg *per os per* day	I
	Natalizumab	300 mg i.v. every 4 weeks	I
	Azathioprine	2.5-3 mg/kg body weight *per* day; 1.5-2.5 maintenance dose	II
	Cyclophosphamide	1-5 mg/kg twice *per* day 1 g i.v. every month for 6-12 months, then every 5 weeks during 2nd year and every 6 weeks during 3rd year of application	IV II
	Mitoxantrone	20 mg +1 g methylprednisolone once monthly or once in 3 months or 2-3x20 mg *per* month followed by 10 mg once in 3 months till cumulative dose	I
	Mycophenolate mofetil	1 g twice daily	IV

with disease-modifying agents are based on the identification of those patients at a high risk of developing MS. Relapses must be treated with the administration of high i.v. doses of methylprednisolone. There is no strong evidence that the use of oral corticosteroids instead of i.v. methylprednisolone in these cases, as well as additional administration of prednisone orally after i.v. administration for maintenance purposes and dose tapering does not improve the course of relapses.

It has been proven that the introduction of interferon beta at the time of CIS relatively reduces disease activity by 40%-60% (CHAMPS study). Early treatment with glatiramer acetate is also efficacious in delaying conversion to clinically definitive MS in patients presenting with CIS and brain lesions detected by MRI (PreCISe study)[41-44].

Follow up

In order to evaluate treatment efficacy, once the diagnosis is confirmed and treatment has been established, first visit must be scheduled in 4-6 weeks and, in stable patients, follow up must be made every 3-6 months. If there are relapses, it is important to note duration of relapses, their frequency, severity, and subsequent recovery. Brain and spinal cord MRI during relapses is not mandatory (it does not alter the treatment course during acute episodes and is too costly for healthcare systems). It is absolutely necessary to obtain an MRI scan in cases of an attack in patients during treatment with natalizumab (Tysabri), if there are new signs or symptoms suggestive of potential side effects associated with this drug, particularly PML.

In other patients, the treating physician must evaluate the convenience of administering an MRI during relapses based on its severity, the patient's response to corticosteroid treatment, and other special circumstances of the patient. Disease progression may be evaluated based on clinical or paraclinical parameters,

Table 7. Drugs used in symptomatic treatment of multiple sclerosis patients

Symptom	**Treatment**		
	Pharmacological		**Non pharmacological**
	Drug	**Dosage**	
Spasticity	Baclofen Tizanidine Diazepam Gabapentin Sativex spray (tetrahydrocannabinol 9-THC/Canabidiol CBD ratio 2.7/2.5)* Botulinum toxin Intrathecal injection of corticosteroids (triamcinolone acetonide) Intrathecal baclofen *via* implantable pump	10-120 mg/day 2-24 mg/day 5-30 mg/day 300-3600 mg/day max 12 sprays/day 40 mg every 3rd day up to 6 times	Physiotherapy Treat concurrent infections
Fatigue	Amantadine Modafinil Pemoline	200-400 mg/day 200-400 mg/day 37.5-112.5 mg/day	Exclude depression and hypothyroidism Physical training and multimodal rehabilitation Lowering body temperature
Pain **(MS related)** **Paroxysmal symptoms** **Epileptic seizures**	Amitriptyline Carbamazepine Gabapentin Lamotrigine Pregabalin	25-150 mg/day 200-1600 mg/day 300-2400 mg/day 200-400 mg/day 150-600 mg/day	Physiotherapy Kinesitherapy Speech therapy
Bladder symptoms increased detrusor activity, urinary incontinence, hyperactive bladder	Anticholinergic drugs Oxybutynin Tolterodine Trospium chloride Propiverine	5-20 mg/day divided into 2 doses 2-4 mg twice/day 40-60 mg/day 45/day	Acute urinary infection treatment Prophylaxis of recurrent urinary infections Intermittent or continuous urinary catheterization
Spastic or dyssynergic sphincter **Nocturnal micturition** **Involuntary detrusor contractions** **Spastic bladder sphincter**	Alpha blockers Alfuzosin Tamsulosin Baclofen Desmopressin Oxybutin Trospium chloride Capsaicin Botulinum toxin	0.4 mg/day 0.8 mg/day 10-120 mg/day 20 μg/day intranasally Intravesical application	

Symptom	Treatment		
	Pharmacological		Non pharmacological
	Drug	Dosage	
Bowel dysfunction	Laxatives		Physioterapy
Sexual dysfunction **Erectile dysfunction** **Dyspareunia**	Sildenafil Alprostadil Tibolone (estrogen unguent)	25-100 mg 1 h before intercourse Injection into the cavernous body of penis Locally	
Tremor **Intention** **Tremor** **Cerebellar**	Propranolol Gabapentin Carbamazepine Topiramate Clonazepam	40-120 mg/day 300-2400 mg/day 200-1600 mg/day 25-150 mg/day 3-6 mg/day	Occupational therapy Physiotherapy VIM thalamotomy VIM deep brain stimulation
Cognitive dysfunction	Cholinesterase inhibitors 1) physostigmine 2) donepezil Amantadine	 10 mg/day 100 mg twice daily	Attention training Memory training Relaxation techniques Compensational strategies
Dysarthria **Dysphonia** **Adductor spasmodic dysphonia** **Constriction of glottis and/or vocal paresis**	 Botulinum toxin A Teflon or collagen fluids	 Injections locally Injections locally	Multidisciplinary approach: neurologist, otorhinolaryngologist, speech therapist Velum prosthesis Electronic voice amplifiers Velopharyngeal surgery
Dysphagia			Functional therapy (muscular function, swallowing techniques, adaptation of food consistency) Nasogastric tubes Percutaneous endoscopic gastrostomy (PEG)

* **not registered in Croatia**

and represents another indicator of treatment failure. Progression of disease should also be evaluated by means of EDSS, MSFC, SF 36, VAS and Beck depression scale; therefore it is advisable to perform them at the onset of the disease in order to have a baseline value for comparison with relapses.

Symptomatic Treatment

Besides immunomodulation and immunosuppression, specific treatment of symptoms is an essential component of the overall management of MS patient. The aim of symptomatic treatment is to reduce symptoms that cause impairment of functional abilities and quality of life[45].

There is a wide range of different symptoms that can appear in MS patient:

- motor function and coordination: spasticity, pareses, ataxia and tremor
- cranial neuralgias, diplopia, nystagmus, dysarthria, dysphagia
- autonomic nervous system involvement: bladder and bowel dysfunction, sexual dysfunction
- psychiatric and psychological problems: depression, fatigue, cognitive dysfunctions
- pain and paroxysmal symptoms including epileptic seizures

Centers for Demyelinating Diseases

In order to improve the management of patients with demyelinating diseases of the CNS, specialized centers should be established. Such centers should include educated teams who will recognize the symptoms of demyelinating diseases at their early stages, hospitalize such individuals in order to perform differential diagnostic work up and to establish appropriate diagnosis. Furthermore, individuals with demyelinating diseases should be followed up, with possibilities of acute treatment application at the time of relapse as well as introducing preventive treatment. Teams should include neurologists, physiotherapists and technicians, speech therapists, nurses who will educate patients about therapy applications and lifestyle modifications, and neuroradiologists, along with modern neuroimaging equipment, biochemical laboratory with the possibility of evaluating different genetic testing and biomarkers. As part of such centers, there should be the possibility of reproduction counseling as well as counseling on different aspects of the disease (symptomatic treatment). Of great importance is cooperation with specialized physiotherapy centers in order to minimize neurologic sequels of the disease and to improve the quality of life of these patients.

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Sažetak

PREPORUKE ZA DIJAGNOSTIKU I LIJEČENJE MULTIPLE SKLEROZE

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Multipla skleroza (MS) je kronična demijelinizirajuća neurološka bolest koja najčešće pogađa mlade bolesnike (u dobi 20-50 godina). Oko 85% bolesnika boluje od oblika bolesti obilježenog relapsima i fazama remisije (relapsno remitentni oblik bolesti, RRMS). Smjernice za zbrinjavanje bolesnika oboljelih od MS moraju biti usredotočene na tri glavna područja: a) postavljanje ispravne dijagnoze, b) liječenje relapsa, c) dugotrajno preventivno liječenje uključujući praćenje bolesnika, prilagodbu doze lijeka, po potrebi promjenu lijeka, kontrolu učinka liječenja na progresiju bolesti. Dijagnoza bolesti postavlja se na temelju kliničkih i parakliničkih kriterija. Posebna je pozornost posvećena lijekovima za liječenje relapsa bolesti, lijekovima za preventivno dugoročno liječenje te simptomatskoj terapiji. Kod postavljanja dijagnoze MS treba uzeti u obzir diferencijalne dijagnoze. Stoga bi se dijagnoza MS trebala temeljiti na kliničkim i radiološkim dijagnostičkim kriterijima, analizi cerebrospinalne tekućine i evociranim potencijalima.

Ključne riječi: *Multipla skleroza – klinička slika, dijagnostički kriteriji, liječenje*