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Clinical and Neurophysiological Features in Patients Presenting Clinically Isolated Syndrome Suggestive on Multiple Sclerosis

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SUMMARY

Clinically isolated syndrome suggestive on multiple sclerosis is monophasic clinical presentation with suspected underlying inflammatory demyelinating disease. Clinically isolated syndrome supported with magnetic resonance evidence may present the earliest manifestation of multiple sclerosis. Clinical manifestations are still the basis of the first step in making the diagnosis of multiple sclerosis in patients presenting clinically isolated syndromes. The aim of the study was to find the most frequent clinical and neurophysiological features which characterize patients presenting clinically isolated syndromes suggestive on multiple sclerosis.

The examination included the patients investigated and treated at the Clinic of Neurology, Clinical Center Niš, during 2005-2008. The examination involved the patients which fulfilled criteria for clinically isolated syndrome suggestive on multiple sclerosis after detailed investigations. We were looking for clinical presentation and neurophysiological features of the disease.

In the examined patients we found clinically monofocal (43,18%) and multifocal presentations (52,27%). Patients with monofocal presentation most frequently showed hemispheric lesion signs (18,18%) and efferent clinical signs (36,36%). Patients with multifocal clinical presentation most frequently showed combined efferent-cerebellar clinical presentation (38,64%). Among single clinical manifestations, the majority of patients showed pyramidal lesion signs (72,72%) and cerebellar syndrome (45,45%). Neurophysiological procedures documented the normal findings in only 11,36% of the examined patients.

Patients with clinically isolated syndrome suggestive on multiple sclerosis most frequently present with hemispheric lesion signs, neurophysiologically efferent clinical signs and pyramid lesion signs. Multimodal evoked potentials in these patients found high degree of subclinical and clinical abnormalities, mostly in somatosensitive system.

Key words: **multiple sclerosis, clinically isolated syndrome, clinical features, evoked potentials**

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INTRODUCTION

Multiple sclerosis (MS) is clinical diagnosis based on the central nervous system (CNS) lesion dissemination in time and space (1). Dissemination in time means clinical evidence of a new demyelinating event timely separated from the initial one. A necessity for the evidence of a new neurological syndrome limits the possibility of an early diagnosis. That is the reason why new diagnostic criteria for MS were introduced. The new criteria use magnetic resonance (MR) evidence for the documentation of the CNS lesion dissemination in space and in time (2). McDonald criteria (3) enable the usage of the MR evidence for the dissemination in space and time in MS diagnostics in patients presenting the first atack of the disease - a clinically isolated syndrome.

Clinically isolated syndrome (CIS) stands for a monophasic clinical presentation with suspected underlying inflammatory demyelinating disease. Monophasic presentation means a single clinical episode on the first clinical presentation with a relatively rapid onset (4). As majority of the patients presenting CIS will develop another event within months or years after the initial event, diagnostic criteria for CIS are both prognostic (in term of developing a new neurological event) and diagnostic (the instrument for differentiation of early MS from other diseases) (4).

The international panel of the experts in multiple sclerosis defined five types of CIS (4):
Type 1 CIS: clinically monofocal, at least one asymptomatic MRI lesion
Type 2 CIS: clinically multifocal, at least one asymptomatic MRI lesion
Type 3 CIS: clinically monofocal, MRI may appear normal, no asymptomatic MRI lesions
Type 4 CIS: clinically multifocal, MRI may appear normal, no asymptomatic MRI lesions
Type 5 CIS: no clinical presentation to suggest demyelinating disease (without symptoms, headache, dizziness), but MRI is suggestive.

The same panel defined three CIS categories according to dominant clinical features:
a) with features typically seen in MS,
b) less common CIS features which may be seen in MS,
c) atypical CIS features not expected in MS.

CIS present monophasic clinical event which supported with magnetic resonance evidence may present the earliest manifestation of multiple sclerosis. CIS may be one or the initial manifestation of the other neurological or non-neurological disease which secondarily causes a damage in the CNS. Considering that CIS mostly do not fulfill Barkhof MR criteria needed for MS diagnosis (5), a possibillity for wrong interpretation of this finding remains great. On the other side, MS presents a chronic inflammatory disease with presumed long preclinical duration and usual clinical course in which neurological dissability after several months or years is less the consequence of reversibile inflammatory - demyelinating but ireversibile neurodegenerating process. That is why the early treatment with immunomodulating therapy presents imperative in an attempt to maintain the working and social functionallity in these patients (6).

MATERIAL AND METHODS

The examination was performed on the patients investigated and treated at the Clinic of Neurology, Clinical Center Niš, in the period 2005-2008. The examination included patients which fulfilled criteria for clinically isolated syndrome suggestive on multiple sclerosis and who do not fulfill criteria for diseminating the demyelinating disease at the moment of investigation.

Diagnostic examination included: anamnesis and physical examination, neurophysiological procedures (multimodal evoked potentials), MR examination of the cranial structures, biochemical-hematological laboratory testing, electrocardiography and cerebrospinal fluid investigation including the oligoclonal bands testing. The including criteria for clinical examination were finding the clinical features tipically seen in MS according to the recommendations from the panel of experts for MS, and the evidence of more than one asymptomatic, suggestive demyelinating MR lesion. We also included the patients who did not present clinical features suggestive on demyelinating disease but with MRI.

Excluding criteria imply patients presenting: head trauma, psychiatric disease, diabetes mellitus, hypertensive disease, cardiac failure, renal failure, hepatic failure, hematological disturbances (anaemia, low serum feritine). We also excluded patients with abnormalities on coagulation screening tests or positive immunologic-rheumatologic test findings: antinuclear antibodies (ANA), antibodies against duble - strained DNK (anti ds DNK antibodies), anticardiolipin antibodies (ACl), anti neutrophilic cytoplasmatic antibodies (ANCA), anti thyreoglobulin and anti thyreoperoxidasa antibodies, and disturbances in C3 and C4 components of the complement and/or immunal complexes.

Forty-four patients were examined (14 men and 30 women). The investigated patients were 19-51 years old, mean age 28,95 years.

Clinical features were divided into categories:

1. clinically monophocal (lesion in one neurologycal system) or multifocal presentation (more than one neurologycal system) or without clinical presentation suggestive on demyelinating disease but with MR suggestive;

2. according to topographic presentation: optical neuritis, brain stem syndrome, medullary syndrome, hemispheric syndrome;

3. clinical presentation in form of neurophysiologycally afferent, efferent and/or cerebellar features;

4. according to single clinical feature.

Neurophysiologycal examination was performed using the multimodal evoked potentials (MMEP). We examined evoked responses on visual (visual evoked potentials-VEP), somatosensitive (somatosensitive evoked potentials-SSEP) and auditive system (acustic evoked potentials-AEP). We considered abnormal findings of extension of the wave form latencies and/or changes of the amplitudes who were out of the normative criteria limits in performing neurophysiologycal laboratory.

RESULTS

Clinically monofocal presentation of CIS was evidenced in 19 patients (43,18%), clinically multifocal in 23 (52,27%), and in two patients (4,55%) we did not find clinical presentation suggestive on demyelinating disease; however, MR evidence was suggestive.

Patients with monofocal presentations most frequently showed hemispheric lesion signs (eight patients - 18,18% of all), medullar lesion signs (six patients - 13, 63%), optical neuritis (three patients - 6,81%) and brain stem syndrome (two patients - 4,54%). The majority of patients with monofocal clinical presentations (16 patients - 36,36% of all) showed efferent clinical signs, while afferent presentation were evidented in three patients (6,82%). We did not register isolated cerebellar presentations in these patients.

In patients with multifocal clinical presentations, the most frequent combination were efferent-cerebellar ones - in 17 patients (38,64% of all), afferent, efferent and cerebellar signs in combination in five patients (11,36%), and afferent - efferent combination in one patient (2,27%) (Table 1).

Among single clinical features in majority of patients were evidenced pyramidal lesion signs (hemiparesis, paraparesis)- 32 cases (72,72%), and cerebellar syndrome (ataxia, nystagmus) in 20 patients (45,45%). The other clinical features were evidenced unfrequently: VI cranial nerve lesion, sensitive defficit (six patients), sphincterial disturbances (five patients), optical neuritis, peripheric origin VII cranial nerve lesion, internuclear ophtalmoplegia (three patients), Lhermitte's sign, tonical spasm (two patients) and without clinical presentation suggestive on demyelinating event two patients.

Patients with monofocal clinical presentation mostly showed pyramidal system lesion (14 patients - 31,81%), then optical neuritis (three patients - 6,81%) and one patient with internuclear ophtalmoplegia and VI cranial nerve lesion. Patients with multifocal clinical presentations showed pyramidal lesions (23 patients - 52,27% of all), cerebellar signs (22 patients - 50%), while other features appeared less frequently: sensitive defficit (six patients), VI cranial nerve lesion, sphincterial disturbances (five patients), peripheral origin VII cranial nerve lesion (three patients) internuclear ophtalmoplegia, Lhermitte sign, tonic spasms (two patients) (Table 2).

MMEP showed high degree of abnormalities among the examined patients. Normal finding after all three neurophysiological investigations were evidenced in only five patients (11,36%), while others showed abnormalities in one (seven patients), two (ten patients) or all three modalities (22 patients - 50%).

Among single-evoked potential modalities, the most frequent findings were abnormalities in somatosensitive system; SSEP showed pathology in 36 patients (81,81%) of which in 11 (25% of all) cases they were the only patological neurophysiological indicators. Abnormal VEP was reported in 26 patients (59,09%), and as a single patologic evidence in two patients. Acoustic - evoked potentials showed pathologic evidence in 21 patients (47,73%), but never as a single patologic evidence. Among patients who fulfilled criteria for Type 5 CIS, we found abnormal VEP in one, while the other had normal MMEP evidence (Table 3).

Table 1. *Frequency of afferent, efferent and cerebellar signs in patients presenting clinically isolated syndromes suggestive on multiple sclerosis*

	Efferent	Afferent	Cerebellar	Efferent-cerebellar	Efferent-afferent-cerebellar	Efferent-afferent
Mono-focal	16 (36,36%)	3 (6,82%)	0			
Multi-focal				17 (38,64%)	5 (11,36%)	1 (2,27%)

Table 2. *Frequency of a single clinical feature in patients presenting clinically isolated syndromes suggestive on multiple sclerosis*

	Pyramidal syndrome	Cerebellar syndrome	Sensitive defficit	Optical neuritis	INO	CN lesions	Other
Mono-focal	14 (31,82%)	0	0	3 (6,81%)	1 (2,27%)	1 (2,27%)	0
Multi-focal	23 (52,27%)	22 (50%)	6 (13,64%)	0	2 (4,55%)	8 (18,18%)	9 (20,45%)

INO - internuclear ophtalmoplegia; CN - cranial nerves

Table 3. *Frequency of pathologic findings of multimodal evoked potentials in patients presenting clinically isolated syndromes suggestive on multiple sclerosis*

	VEP	SSEP	AEP	Normal MMEP	MMEP one modality	MMEP two modalities	MMEP three modalities
CIS	26 (59,09%)	36 (81,81%)	21 (47,73%)	5 (11,36%)	7 (15,91%)	10 (22,73%)	22 (50%)

CIS - clinically isolated syndrome; MMEP - multimodal evoked potentials; VEP - visual evoked potentials; SSEP - somatosensitive evoked potentials; AEP - acoustic evoked potentials.

DISCUSSION

No matter how heterogeneous they are, clinical features are still the basis of the first step towards making the diagnosis of multiple sclerosis presented through clinically isolated syndromes. Miller et al. (7) reported that in 85% of young adult patients, the initial clinical features were optical neuritis, brain stem syndrome or medullar syndrome. These lesion - localised presentation of clinical features was frequent among our patients, but the most frequent findings were hemispheric lesion signs.

In our patients, the most frequent clinical features were efferent signs in both monofocal and multifocal clinical presentation groups. Rot et al. (8) and Pelidou et al. (9) found afferent signs more frequently than efferent or cerebellar in the group of patients presenting CIS, and also by comparing CIS and patients with clinically definite multiple sclerosis. We belive that the explanation for this difference may be a more complex recognition of the somatosensitive afferent manifestations by patients and general practicioners. That is why patients do not start detailed neurological investigations until the onset of "restlessness" efferent neurologic features, but at that time they do not fulfill criteria for the CIS. There is also evidence for more frequent afferent expression in our patients (mostly on subclinical level) in high percentage of multimodal evoked potentials pathology because they ivestigate only afferent neurological systems.

MMEP are important additional procedures in clinical investigating in patients presenting CIS. Pelayo et al. (10) found high frequency of pathologic MMEP in their group of patients. This study reported normal findings in only 29% of the patients. Our results show even higher sensitivity for MMEP for subclinical and clinical lesions in neurophysiological systems. Among the patients with abnormal MMEP, in the study by Pelayo et al., in about one half of the examinees pathology in only one neurophysiological system was reported. Our finding of higher percentage of abnormal findings in all three modalities may be explaned by more frequent clinically multifocal presentation among our patients.

VEP abnormalities were not dominant in our patients similar to the examination of Rot et al. (8), although clinical presentation of optical neuritis was the second single clinical feature in the CIS patients examined by Pelidou et al (9).

According to the recommendation of the expert panel (4) that CIS presentation may involve the patients without clinical presentation suggestive on MS but with MR suggestive, Lebrun et al. (11) examined 70 patients who fulfilled this criteria.

They reported less frequently abnormal VEP findings in these patients by comparing them with the patients with clinically definite multiple sclerosis. In two of our patients who fulfilled type 5 CIS criteria (4), VEP finding was abnormal in one.

CONCLUSIONS

1. Patients presenting CIS suggestive on MS with monofocal clinical presentation the most frequently present efferent neurological signs, hemispheric lesion signs and pyramidal lesion signs.

2. Patients with CIS suggestive on MS with multifocal clinical presentation most frequently present combined efferent - cerebellar signs and pyramidal lesion signs.

3. MMEP show subclinical and clinical abnormalities in majority of patients presenting CIS suggestive on MS, mostly somatosensitive modalities' pathology.

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KLINIČKE I NEUROFIZIOLOŠKE KARAKTERISTIKE BOLESNIKA SA KLINIČKI IZOLOVANIM SINDROMOM KOJI UKAZUJE NA MULTIPLU SKLEROZU

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Sažetak

Klinički izolovani sindrom koji ukazuje na multiplu sklerozu predstavlja monofaznu kliničku prezentaciju sa suspektnom osnovom inflamatorne demijelinizacione epizode. Klinički izolovani sindrom potkrepljen nalazom magnetne rezonance može ukazivati na najraniju manifestaciju multiple skleroze. I pored velike heterogenosti, kliničke manifestacije ostaju okosnica prvog koraka u dijagnostici multiple skleroze kod bolesnika koji pokazuju klinički izolovane sindrome. Cilj ispitivanja bio je da utvrdi koje su najčešće

kliničke i neurofiziološke manifestacije karakteristične za bolesnike koji imaju klinički izolovane sindrome koji ukazuju na multiplu sklerozu.

Ispitivanje je izvršeno na bolesnicima koji su ispitivani i lečeni na Klinici za neurologiju Kliničkog centra u Nišu tokom 2005-2008. godine. Ispitivanje je obuhvatalo bolesnike koji su nakon detaljnog dijagnostičkog sagledavanja ispunili kriterijume za klinički izolovani sindrom koji ukazuje na multiplu sklerozu. Razmatrane su klinička prezentacija bolesti i neurofiziološke karakteristike.

Ispitivani bolesnici pokazivali su klinički monofokalnu (43,18%) i multifokalnu prezentaciju (52,27%). Bolesnici sa monofokalnom kliničkom prezentacijom najčešće su pokazivali znake hemisfernog oštećenja (18,18%) i eferentne kliničke znake (36,36%). Bolesnici sa multifokalnom kliničkom prezentacijom najčešće su prezentovali kombinaciju eferentno-cerebelarne kliničke prezentacije (38,64%). Od pojedinačnih kliničkih manifestacija kod najvećeg broja bolesnika evidentirani su znaci piramidnog oštećenja (72,72%) i elementi cerebelarnog sindroma (45,45%). Neurofiziološke procedure evidentirale su uredan nalaz samo kod 11,36% ispitivanih bolesnika.

Bolesnici sa klinički izolovanim sindromom koji ukazuje na multiplu sklerozu najčešće ispoljavaju znake hemisfernog oštećenja, neurofiziološki eferentne kliničke karakteristike i manifestacije piramidnog oštećenja. Multimodalni evocirani potencijali kod ovih bolesnika pokazuju visok stepen subkliničkih i kliničkih abnormalnosti, najčešće u domenu somatosenzitivnog sistema.

Ključne reči: **multipla skleroza, klinički izolovani sindrom, kliničke karakteristike, evocirani potencijali**