

# Multiple sclerosis presented as clinically isolated syndrome: the need for early diagnosis and treatment

Sigliti-Henrietta Pelidou  
Sotirios Giannopoulos  
Sotiria Tzavidi  
Georgios Lagos  
Athanasios P Kyritsis

Department of Neurology, University  
of Ioannina School of Medicine,  
Greece

**Objective:** To aid in the timely diagnosis of patients who present with clinically isolated syndrome (CIS).

**Patients and methods:** We studied 25 patients (18 women, 7 men), originally presented in our clinic with a CIS suggestive of multiple sclerosis (MS). All patients underwent the full investigation procedure including routine tests, serology, cerebrospinal fluid (CSF) examinations, evoked potentials (EPs), and magnetic resonance imaging (MRI) of brain and cervical spinal cord. Patients were imaged at baseline, and every three months thereafter up to a year.

**Results:** The CIS was consisted of optic neuritis in 12 cases, incomplete transverse myelitis (ITM) in 7 cases, Lhermitte sign in 2 cases, internuclear ophthalmoplegia (INO) in 2 cases, mild brainstem syndrome in 1 case, and tonic clonic seizures in 1 case. Using the baseline and three month scans 18/25 (72%) patients developed definite MS in one year of follow up while 7 (28%) had no further findings during this observation period. Immunomodulatory treatments were applied to all definite MS patients.

**Conclusion:** In light of new treatments available, MRIs at 3 month intervals are helpful to obtain the definite diagnosis of MS as early as possible.

**Keywords:** multiple sclerosis, clinically isolated syndrome, optic neuritis, transverse myelitis

## Introduction

Multiple sclerosis (MS) is a clinical diagnosis based on the dissemination of lesions of the central nervous system (CNS) in time and space (Poser and Brinar 2001). Recent proposed diagnostic criteria for MS utilize MRI findings to document dissemination of CNS lesions in time and space (McDonald et al 2001; Polman et al 2005). Optic neuritis (ON) may be the heralding manifestation of MS (ONSG 1991; Hickman et al 2002). More than 50% of adult patients who present with isolated ON will eventually develop other signs of MS (ONSG 1997). The risk stratification for the future development of MS in patients presenting with ON can be assessed by the number of white matter lesions on the baseline cerebral MRI study (Bhatti et al 2005). The risk is increased in women and in those patients who have oligoclonal bands (OCB) in the cerebrospinal fluid (CSF) (Ghezzi et al 1999).

Incomplete transverse myelitis (ITM) can be the presenting feature of MS. Patients with ITM who develop MS are more likely to have asymmetric clinical findings, predominant sensory symptoms with relative sparing of motor systems, spinal cord lesions extending over less than two spinal segments, abnormal brain MRI, and OCB in the CSF (Miller et al 1989; TMC 2002). Measurement of spinal cord atrophy that reflects destructive, irreversible pathology in patients presenting with ITM has important implications for the early treatment of MS (Lin et al 2004).

Correspondence: Sotirios Giannopoulos  
Dept., of Neurology, University of Ioannina  
School of Medicine, University Campus  
Ioannina, 451 10, Greece  
Tel 30 26510 97514  
Fax 30 26510 97011  
Email [sgiannop@uoi.gr](mailto:sgiannop@uoi.gr)

Central nervous system involvement in MS may be difficult to differentiate from other autoimmune diseases such as systemic lupus erythematosus (SLE), antiphospholipid syndrome (APS), and Sjogren syndrome (SS). Thus, a large number of patients with APS or SLE may be misdiagnosed as MS, but the exact proportion is unknown and may receive inappropriate treatment (Ferreira et al 2005). A retrospective study in 82 patients with primary Sjogren syndrome reported that 40.2% had brain involvement, 15.8% optic neuropathy, and 35.4% spinal cord involvement (Delalande 2004). Thus, the differential diagnosis may require careful assessment of all clinical and MRI findings, serological results, and CSF analysis (Reske et al 2005).

Our objective was to aid in the timely diagnosis of MS in patients who presented with CIS and thus employ the proper treatment early during the course of the disease.

## Patients and methods

We studied 25 consecutive patients (18 women, 7 men), age 30.6 (range: 17–49) presented in our clinic with CIS suggestive of MS. The inclusion and exclusion criteria of the CIS patients are listed in Table 1. The clinical, laboratory, and imaging findings were studied in all patients. Laboratory investigations included complete blood count, serum values of liver enzymes, bilirubin, albumin, glucose, creatinine, and urine analysis. In addition, erythrocyte sedimentation rate, C-reactive protein, antinuclear antibodies (ANA), double-stranded DNA (ds-DNA), complement C3/C4, and anti-cardiolipin (ACL) antibodies were also performed.

All patients were evaluated for MS with CSF serology (cells, protein, glucose, IgG index), visual evoked potentials (VEPs), somatosensory evoked potentials (SEPs), and brain and cervical spinal cord MRI. Patients were imaged

at baseline, at three month intervals, and one year. CSF oligoclonal bands were not included in the evaluation since it is not an available test in our hospital laboratory. For MS diagnosis, the revised McDonald criteria were employed (Polman et al 2005). Dissemination in space was demonstrated by either MRI alone when three of the following conditions were met: a) at least one gadolinium-enhancing lesion or nine T2 hyperintense lesions if there was no gadolinium enhancing lesion; b) at least one infratentorial lesion; c) at least one juxtacortical lesion; and d) at least three periventricular lesions, or two or more MRI-detected lesions consistent with MS plus elevated CSF IgG index. Dissemination in time was demonstrated by either MRI (detection of gadolinium enhancing abnormality at least 3 months after the onset of the initial clinical event and if not at the site corresponding to the initial event detection of a new T2 lesion if it appeared at any time compared with the baseline scan performed at least 30 days after the onset of the initial clinical event), or by a second clinical attack.

None of the studied patients had history of head trauma, neuropsychiatric disorder, diabetes mellitus, hypertension, thalassemia, iron and B12 deficiency, cardiac, hepatic and renal failure (Table 1). Finally, the protocol was approved by the Institutional Review Board Committee.

## Results

The characteristics of all CIS patients are depicted in Table 2. There were 25 patients (18 women, 7 men), of 30.6 years mean age (range 17–49). The mean age of patients at onset of CIS varied from 26.9 years for ON to 29.2 years for the patient with seizures. The mean follow-up time was 18.9 months in patients with ON, 17.5 months in patients with ITM, 18 months in patients with brainstem syndrome. The mean disease severity on the expanded disability status scale (EDSS) performed at least one month after the CIS varied from 0.41 to 1. Only 12 woman had isolated ON, 7 had ITM, 3 had mild brainstem syndrome (2 with internuclear ophthalmoplegia (INO), 1 with dysarthria), and 1 had sudden onset of tonic-clonic seizures. The predominant neurological examination findings during the acute phase of the CIS were: reduced unilateral visual acuity in the patients with ON, paraparesis, Lhermitte sign, sensory symptoms, diplopia, dysarthria, and hemiparesis as shown in Table 3.

The paraclinical data of the patients are shown in Table 4. Twenty four patients had abnormal brain MRI consisted of periventricular MS-like white matter lesions and 9 (36%) patients had evidence of myelitis. Both brain and cervical cord MRI were positive in 7 cases (28%).

**Table 1** List of inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Optic neuritis	Head trauma
Diplopia	Neuropsychiatric disorder
Internuclear ophthalmoplegia	Diabetes mellitus
Myelitis	Hypertension
Hemiparesis-paraparesis	Cardiac failure
Dysarthria	Hepatic failure
Sensory symptoms	Renal failure
MRI criteria:	Thalassemia,
a. 1 GD enhancing lesion	Sickle cell disease,
b. 1 infratentorial lesion	Iron deficiency,
c. 1 juxtacortical lesion	B12 deficiency
d. 3 periventricular lesions	

**Abbreviation:** MRI, magnetic resonance imaging.

**Table 2** Characteristics of CIS patients

	ON	ITM	Brainstem syndrome
Sex ratio (female/male)	12/0	3/4	2/1
Age at diagnosis mean / SD (range)	29.5 16 (17–46)	28.9 8.7 (20–42)	29.6 12 (24–49)
Age at onset of CIS mean / SD (range)	26.9 10.3 (17–43)	28.7 9.1 (19–37)	29.1 9.6 (21–48)
Follow up time mean months (range)	18.9 (9–60)	17.5 (3–26)	18 (17–29)
Duration of disease mean months, (range)	20.7 (9–61)	19.3 (4–26)	19.5 (17–29)
Disease severity on EDSS <sup>a</sup> mean (range)	0.41 (0–1)	0.6 (0–2.5)	1 (1–1)

**Abbreviations:** CIS, clinically isolated syndrome; ON, optic neuritis; ITM, incomplete transverse myelitis; EDSS, expanded disability status scale.

**Note:** <sup>a</sup>EDSS was assessed at least one month after the CIS.

VEP's were abnormal in 16 (64%) and SEP's in 6 (24%) patients. Nineteen patients (76%) had increased IgG index, while in 6 patients it was normal.

Serological features of the patients are demonstrated in Table 5. ANA were positive in 5 (20%) and anti-ds-DNA in 2 (8%) of patients, but no patient had low complement (C3 or C4). ACL-ab was positive in only 3 (12%) patients.

Using the baseline and three-month MRI scans and the clinical and paraclinical data, 72% of patients with CIS developed definite MS according to the revised McDonald's criteria within one year, while 28% had no further neurological and MRI findings during this observation period.

## Discussion

Patients with CIS may develop MS (Miller et al 2005). Clinically the identification of patients with a CIS at high risk to develop clinically definite MS remains difficult (Kieseier et al 2005). Monthly brain MRI scans in patients with CIS showed that the majority of patients with an abnormal baseline scan were diagnosed with MS after three months (Pestalozza et al 2005). Application of the new McDonald criteria to patients with CIS suggestive of MS doubled the rate of diagnosis of MS within one year of presentation (Dalton et al 2002). It has been suggested that monthly triple-dose Gd-enhanced

MRIs accurately detected inflammation which is an important factor in the pathogenesis of brain tissue loss in CIS patients (Paolillo et al 2004).

Although a CIS could be indicative of MS, it might occasionally be the first manifestation of systemic autoimmune diseases such as SLE, APS, and SS. In these cases not only the clinical presentation but the MRI findings may be similar (Theodoridou and Settas 2006). Thus, serology tests, eg, ANA, C3, C4, and antiphospholipid antibodies, could help in the differential diagnosis of MS from the various connective tissue diseases. In the present study 20% of CIS patients had positive ANA and a few patients had other autoantibodies but there were no other findings to indicate evidence of SLE, primary SS, and APS according to the currently used criteria (Tan et al 1982; Wilson et al 1999; Vital et al 2002). Presence of various autoantibodies such as ANA in the serum of patients with MS is a frequent finding (Speciale et al 2000). Brain MRI can be inconclusive in patients with CIS but intrathecal synthesis of OCB are helpful in establishing the diagnosis of MS (Sastre-Garriga et al 2003; Rot and Mesec 2006), thus the lack of OCB measurements is a limitation of our study. A new OCB test may also improve the conversion of a CIS to MS (Masjuan et al 2006). Prediction of conversion from CIS to MS can be improved if CSF

**Table 3** Clinical data of CIS patients

Neurological symptoms and signs	No. of patients (%)
Optic neuritis	12 (48%)
Myelitis	7 (28%)
Internuclear ophthalmoplegia	2 (8%)
Seizures	1 (4%)
Paraparesis	5 (25%)
Lhermitte sign	2 (8%)
Sensory symptoms	9 (36%)
Diplopia	3 (12%)
Dysarthria	1 (4%)
Hemiparesis	1 (4%)

**Abbreviations:** CIS, clinically isolated syndrome.

**Table 4** Paraclinical data of CIS patients: Initial 2/25

Parameters	(+)	( )
Initial brain MRI	23/25 (92%)	2/25 (8%)
Brain MRI <sup>a</sup>	24/25 (96%)	1/25 (4%)
Cervical SC MRI <sup>a</sup>	9 (36%)	16 (64%)
VEP's	16/25 (64%)	9/25 (36%)
SEP's	6/25 (24%)	19/25 (76%)
CSF <sup>b</sup> /WBC	1/25 (4%)	24/25 (96%)
CSF <sup>b</sup> /IgG INDEX	19/25 (76%)	6/24 (24%)

**Abbreviations:** CIS, clinically isolated syndrome; SC, spinal cord; VEP, visual evoked potentials; SEP, somatosensory evoked potentials; CSF, cerebrospinal fluid.

**Notes:** <sup>a</sup>Brain and cervical SC MRIs were considered ( ) when findings were observed at any time during the 3 month intervals up to a year; <sup>b</sup>CSF serology was performed during the baseline evaluation.

**Table 5** Serological features of the patients

Parameters	(+)	(-)	Not done
ANA	5 (20%)	17 (68%)	3 (12%)
Anti-ds-DNA	2 (8%)	17 (68%)	6 (24%)
ACL-ab	3 (12%)	22 (88%)	0
C3/C4	0	25 (100%)	0

**Abbreviations:** CIS, clinically isolated syndrome; ANA, antinuclear antibodies; ds-DNA, double-stranded DNA; ACL-ab, anticardiolipin antibodies; C3/C4, complement fractions C3 and C4.

markers (either elevated tau or neurofilaments [NfHSMI35] are combined with MRI findings (Brettschneider et al 2006). On the contrary, serum antimyelin antibodies did not seem to permit earlier diagnosis of MS (Lim et al 2005). Intrathecal B-cell clonal expansion in the CSF of patients with CIS, often precedes both OCB and multiple MRI lesions and is associated with a high rate of conversion to definite MS (Qin et al 2003).

## Conclusion

Patients with MS deserve an accurate diagnosis, because new effective immunomodulatory treatments could modify the disease progression. It is obvious that definite diagnosis of MS must be obtained as early as possible in order to initiate early immunomodulatory treatment. We believe that frequent MRI scans during the first year after the CIS facilitate the early and accurate diagnosis of definite MS.

## References

- Bhatt MT, Schmitt NJ, Beatty RL 2005 Acute inflammatory demyelinating optic neuritis: current concepts in diagnosis and management *Optometry*, 76:526-35
- Brettschneider J, Petzold A, Junker A, et al 2006 Axonal damage markers in the cerebrospinal fluid of patients with clinically isolated syndrome improve predicting conversion to definite multiple sclerosis *Mult Scler*, 2: 43-8
- Daton CM, Brex PA, Mszek KA, et al 2002 Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis *Ann Neurol*, 52:47-53
- De Andrade S, de Seze S, Fauchas AL, et al 2004 Neurologic manifestations in primary Sjogren syndrome: a study of 82 patients *Medicine*, 83:280-9
- Ferreira S, D'Cruz DP, Hughes GR 2005 Multiple sclerosis, neuropsychiatric lupus and antiphospholipid syndrome: where do we stand? *Rheumatology*, 44:434-42
- Ghezzi A, Martini V, Torr V, et al 1999 Long-term follow-up of isolated optic neuritis: the risk of developing multiple sclerosis, its outcome, and the prognostic role of paraneoplastic tests *J Neurol*, 246:770-75
- Hickman SJ, Daton CM, Meri DH, et al 2002 Management of acute optic neuritis *Lancet*, 360: 953-62
- Keseer BC, Hemmer B, Hattung HP 2005 Multiple sclerosis novelties and new therapeutic strategies *Curr Opin Neurol*, 8:2-20
- Lim ET, Berger T, Rend M, et al 2005 Antimyelinated bodies do not allow earlier diagnosis of multiple sclerosis *Mult Scler*, 1:492-4
- Linn X, Tench CR, Evangeou N, et al 2004 Measurement of spinal cord atrophy in multiple sclerosis *J Neuroimaging*, 4(Suppl 3):20S-26S

- Masjuan J, Alvarez-Cermeno JC, Garcia-Barragan N, et al 2006 Clinically isolated syndromes: a new oligoclonal band test accurately predicts conversion to MS *Neurology*, 66:576-8
- McDonald WI, Compston A, Edan G, et al 2001 Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis *Ann Neurol*, 50: 2-7
- Meri D, Barkhoff F, Montalban X, et al 2005 Clinically isolated syndromes suggestive of multiple sclerosis, part 2: non-conventional MRI, recovery processes, and management *Lancet Neurol*, 4:34-8
- Meri DH, Ormerod IE, Rudge P, et al 1989 The early risk of multiple sclerosis following isolated acute syndromes of the brain stem and spinal cord *Ann Neurol*, 26:635-9
- [ONSG] Optic Neuritis Study Group 1999 The clinical profile of optic neuritis: experience of the optic neuritis treatment trial *Arch Ophthalmol*, 117: 673-78
- [ONSG] Optic Neuritis Study Group 1997 The 5-year risk of MS after optic neuritis: experience of the optic neuritis treatment trial *Neurology*, 49: 404-3
- Paoletti A, Pantano P, et al 2004 The relationship between inflammation and atrophy in clinically isolated syndromes suggestive of multiple sclerosis: a monthly MRI study after triptorelin treatment *J Neurol*, 251:432-9
- Pesta-ozza IF, Pozzilli C, Legge S, et al 2005 Monthly brain magnetic resonance imaging scans in patients with clinically isolated syndrome *Mult Scler*, 11:390-4
- Poorman CH, Ringold SC, Edan G, et al 2005 Diagnostic criteria for multiple sclerosis: 2005 revisions to the "McDonald Criteria" *Ann Neurol*, 58:840-6
- Poser CM, Brnar VV 2007 Diagnostic criteria for multiple sclerosis *Clin Neurol Neurosurg*, 103: 1-10
- Qin Y, Duquette P, Zhang Y, et al 2003 Intrathecal B-cell clonal expansion, an early sign of humoral immunity, in the cerebrospinal fluid of patients with clinically isolated syndrome suggestive of multiple sclerosis *Lab Invest*, 83: 08-8
- Reske D, Petereit HF, Heiss WD 2005 Differences in the differential diagnosis of chronic inflammatory diseases of the central nervous system via use of cerebrospinal fluid analysis and immunologic abnormalities in the diagnosis *Acta Neurol Scand*, 115:207-3
- Rot U, Mesec A 2006 Clinically isolated syndrome, MRI, CSF and electrophysiological findings in different stages of multiple sclerosis *Clin Neurol Neurosurg*, 104:27-4
- Sastre-Garriga J, Tintore M, Rovira A, et al 2003 Conversion to multiple sclerosis after a clinically isolated syndrome of the brainstem: cranial magnetic resonance imaging, cerebrospinal fluid and neurophysiological findings *Mult Scler*, 9:39-43
- Speciale L, Saresa M, Caputo D, et al 2000 Serum autoantibodies presence in multiple sclerosis patients treated with beta-2-interferon *J Neurovirol*, 6(Suppl 2):S57-6
- Tan EM, Cohen AS, Fresco JF, et al 1982 The 1982 revised criteria for the classification of systemic lupus erythematosus *Arthritis Rheum*, 25: 27-7
- Theodoridou A, Settas L 2006 Demyelination in rheumatoid disease *J Neurol Neurosurg Psychiatry*, 77:290-5
- [TMC] Transverse Myelitis Consortium Working Group 2002 Proposed diagnostic criteria and nosology of acute transverse myelitis *Neurology*, 59:499-505
- Vatakencherry C, Bombardieri S, Jonsson R, et al 2002 European Study Group on Classification Criteria for Sjogren's Syndrome Classification criteria for Sjogren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group *Ann Rheum Dis*, 61:554-8
- Wason WA, Gharav AE, Koike T, et al 1999 International consensus statement on primary classification criteria for definite antiphospholipid syndrome: report of an international workshop *Arthritis Rheum*, 42: 309