ORIGINAL CONTRIBUTION

Long-term Follow-up of Acute Partial Transverse Myelitis

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Background: Acute partial transverse myelitis (APTM) may be the first clinical symptom of multiple sclerosis (MS) or may remain a monophasic event.

Objectives: To evaluate the risk of conversion to MS and long-term disability, and to determine prognosis factors for disability.

Design: We identified patients with no previous history of neurological disease who experienced APTM between January 1998 and December 2005 and were followed up at 3 university hospitals in France. Data on the patients' demographics and clinical states during follow-up, as well as data on cerebrospinal fluid (CSF) analysis, brain and spinal cord magnetic resonance imaging (MRI), and visual evoked potentials, were analyzed.

Setting: Neurology departments of 3 university hospitals in Lille, Strasbourg, and Rouen, France, respectively.

Patients: A total of 85 patients with no previous history of neurological disease who experienced APTM.

Results: The mean (SD) follow-up period was 104.8 (29.8) months. There were 57 women (67%) and 28 men (33%), with a mean (SD) age at onset of 36.7 (11.7) years. At the end of follow-up, 53 patients (62%) were classified as having MS with a mean (SD) Expanded Disability Status Scale score of 2.6 (1.8), 1 patient (1%) was classified as having postinfectious myelitis, 1 (1%) as having neuromyelitis optica, 1 (1%) as having Sjögren syndrome, and 29 (34%) still had APTM of undetermined etiology. Oligoclonal bands in CSF were more frequent in patients with MS (92%) than in patients with APTM of undetermined etiology (38%). Brain MRI results were abnormal in 87% of patients with MS and 27% of patients with APTM of undetermined etiology; visual evoked potentials were abnormal in 43% of patients with MS and 4% of patients with APTM of undetermined etiology. Oligoclonal bands in CSF (odds ratio, 15.76 [95% CI, 2.95-84.24]) and at least 1 MRI-detected brain lesion (odds ratio, 7.74 [95% CI, 2.42-24.74]) were independent predictive factors for conversion to MS.

Conclusion: Our study confirms that abnormal brain MRI results and the presence of oligoclonal bands in CSF are 2 independent predictive factors for conversion to MS. No clinical, biological, or MRI factor at onset was predictive of long-term disability.

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MULTIPLE SCLEROSIS (MS) is the most common inflammatory disease of the central nervous system affecting young adults in Western countries. It is characterized by a huge interindividual variability of clinical symptoms and an unpredictable course ranging from asymptomatic sequelae to severe disability. Early initiation of treatment has proved effective in delaying the second neurological episode and reducing long-term disability.[1] It is therefore mandatory to identify as early as possible patients who may develop the disease. First attacks of MS, also called clinically isolated syndrome (CIS), usually consist of optic neuritis, brainstem involvement, or partial myelitis. Conversion rates of CIS to MS have previously been studied in 3 populations of patients presenting with CIS: a patient population in London, England, over periods of 7, 14 and 20 years[2,3]; in Barcelona, Spain, over 7 years[4]; and in North America, electively concerning optic neuritis, over 15 years.[5] In these 3 studies, the probability of developing MS ranged from 42% to 63%, but the authors of these studies did not analyze each initial symptom, especially acute partial transverse myelitis (APTM). This specific manifestation was only referred to in small and retrospective studies: the conversion rate to MS was evaluated at between 11% and 57.7%.[6-10] Some predictive factors for conversion from CIS to MS have been identified: sensory symptoms,[7] presence of oligoclonal bands (OCBs) in the cerebrospinal fluid (CSF), and presence of brain

lesions detected on magnetic resonance imaging (MRI) scans.[7,10]

The aim of our study was to evaluate the long-term risk for conversion from APTM to MS. The second objective was to determine prognosis factors for disability.

METHODS

PATIENTS

We included 87 patients referred to the neurology departments of 3 university hospitals (in Lille, Strasbourg, and Rouen, France, respectively) for myelitis between January 1998 and October 2005. Data were collected prospectively in Lille (43 patients) and retrospectively in Strasbourg and Rouen (44 patients), and patients were followed up until May 2010. For the latter patients, we performed a review of the medical records of those who received a diagnosis of myelitis, encephalomyelitis, and MS in the hospital databases. We used the inclusion criteria for APTM proposed by Ford et al[11]: acute or subacute motor or sensory symptoms with or without sphincter dysfunction, occurrence of symptoms lasting a minimum of 48 hours and a maximum of 3 weeks, neither clinical nor radiological evidence of spinal compression, and no previous history of neurological symptoms. The exclusion criterion was a diagnosis of transverse myelitis (patients with a severe sensorimotor feature and an extended hypersignal on a spinal cord MRI scan). An exhaustive laboratory investigation was also performed to exclude medullary infarct, infectious myelitis, or vasculitis, as detailed in a previous study.[12]

Demographic data (age and sex of patients) and clinical features (motor or sensory deficits, sphincter dysfunction, and acute or subacute onset) were noted on admission. Initial symptoms were classified as acute if they developed in less than 3 days. At the end of follow-up, patients were classified into 3 groups: the "MS group," comprising patients who fulfilled the revised criteria of McDonald et al[13]; the "undetermined group," comprising patients who did not experience any new neurological symptoms; and the "other diseases group," comprising patients with Sjögren syndrome, postinfectious myelitis, or neuromyelitis optica. For patients in the MS group, disability status at end point was defined as the 6-month sustained Expanded Disability Status Scale score.[14]

On admission, patients underwent 1.5-T MRI of the spinal cord. T1, T2, and gadolinium-enhanced sequences of the cervical, thoracic, and lumbar spine were performed in the sagittal plane. If a lesion was detected, complementary sequences in the axial plane were acquired. We evaluated the number of lesions, their localization in the sagittal and axial planes (anterior, central, posterior, and lateral), and their extent (number of vertebral levels).

Patients also underwent 1.5-T MRI of the brain, with T1, T2, and T1 gadolinium infusion sequences. We used the criteria of Barkhof et al[15] to evaluate these brain MRI scans, and we applied the revised criteria of McDonald et al[13] for a diagnosis of MS. Patients also underwent evaluation of visual evoked potentials (VEPs).

A lumbar puncture was performed for all patients. Analysis of the CSF included evaluation of cell count, cytology, protein content, and intrathecal IgG synthesis. For 72 patients, OCBs were searched for by using the isoelectrofocusing method.

The patients were followed up with a clinical evaluation at 3, 6, and 9 months after the occurrence of APTM and every year during the remainder of our study. Patients also consulted with us when a relapse occurred. A relapse was defined as an exacerbation of preexisting symptoms or the occurrence of new symptoms sustained for at least 48 hours. At the end of our study, we noted the Expanded Disability Status Scale score assessed by the patient's neurologist. During the follow-up period, 71 of 85 patients (84%) had a second spinal cord MRI scan after a mean (SD) of 13.7 (16.4) months, and 75 of 85 patients (88%) had a second brain MRI scan.

Statistical analysis was based on the χ^2 test, and we also performed a binary logistic regression based on Spearman coefficients. $P < .05$ was assumed to be statistically significant. Results are presented as mean (SD) values. We used Matlab16 software (MathWorks) for Windows (Microsoft).

RESULTS

PATIENTS

Six of the 87 patients initially identified as having APTM were lost to follow-up: 2 during the first year and 4 after a mean of 76.7 months, all of whom had been included prospectively. The first 2 patients received a diagnosis of MS, as did 2 of the other 4 patients. We estimated the follow-up period to be long enough for the latter 4 patients to be included in the statistical analysis.

Of the 85 remaining patients, 53 (62%) had APTM that converted to MS, 29 (34%) still had APTM of undetermined etiology, 1 (1%) had postinfectious myelitis, 1 (1%) had Sjögren syndrome, and 1 (1%) had neuromyelitis optica. The mean (SD) follow-up period was 104.8 (29.8) months (range, 43.8-172.5 months).

Some differences were found between prospectively included patients (in Lille) and retrospectively included patients (in Rouen and Strasbourg). The ratio of patients with MS to patients without was higher in patients from Lille (31 of 40 patients [77%] vs 22 of 42 patients [52%]; $P = .03$). Seven of the 31 patients with MS from Lille (23%) had sphincter dysfunction compared with none of the 22 patients with MS from Rouen and Strasbourg ($P = .048$). The MRI-detected lesions were more frequently located in the dorsal (61% vs 29%; $P = .04$) or dorsolateral part (100% vs 78%; $P = .049$) of the spinal cord in patients with MS from Lille.

CLINICAL FINDINGS

The clinical features of the MS group and the undetermined groups are presented in **Table 1**. There was no statistical difference in terms of age, sex ratio, or presenting signs. Most of the patients had sensory signs (96% in the MS group and 100% in the undetermined group). Acute partial transverse myelitis was preferentially acute for patients in the undetermined group (35% of patients in the undetermined group vs 15% of patients in the MS group; $P = .03$) and was subacute for patients whose APTM subsequently converted to MS (85% of patients in the MS group vs 66% of patients in the undetermined group; $P = .03$).

MRI FINDINGS

Spinal cord MRI results are summarized in **Table 2**. Of the 85 analyzed patients, 65 (76%) had an axial plane MRI analysis, and 75 (88%) a gadolinium injection. We noted a mean (SD) of 1.23 (0.78) lesions in the MS group and

Table 1. Clinical Data on Presentation of Patients With Multiple Sclerosis and Patients With Undetermined Etiology

Group	Age, Mean, (Range), y	Sex, No.		Patients, No. (%)				
		Male	Female	Motor Symptoms	Sensory Symptoms	Sphincter Symptoms	Acute Onset	Subacute Onset
MS (n = 53)	34.8 (17-54)	14	39	21 (40)	51 (96)	7 (13)	8 (15)[a]	45 (85)[a]
Undetermined (n = 29)	38.6 (16-76)	13	16	10 (34)	29 (100)	3 (10)	10 (34)	19 (66)
Combined (n = 82)	36.7 (16-76)	27	55	31 (38)	80 (98)	20 (24)	18 (22)	64 (78)

Abbreviation: MS, multiple sclerosis.
[a] $P = .03$ (comparison between the MS and undetermined groups determined by use of the χ^2 test).

Table 2. Data of Spinal Cord Magnetic Resonance Imaging on Presentation

Group	Lesions, Mean (Range), No.	Mean Vertebral Level, No.	Patients,[a] No./Total No. (%)									
			Sagittal Plane			Axial Plane						
			Cervical	Dorsal	Lumbar	Anterior	Lateral	Posterior	Central	Postero-lateral	Centro-lateral	Gadolinium Enhancement
MS (n = 53)	1.23 (0-6)	1.51	27/52 (52)	25/52 (48)	5/52 (10)	1/39 (3)	19/39 (49)[b]	19/39 (49)	7/39 (18)[c]	38/39 (97)[d]	26/39 (67)	26/47 (55)[c]
Undetermined (n = 29)	1.21 (0-5)	1.33	14/29 (48)	14/29 (48)	2/29 (7)	0/26 (0)	5/26 (19)	14/26 (54)	11/26 (42)	19/26 (73)	16/26 (62)	9/26 (35)
Combined (n = 82)	1.22 (0-6)	1.42	41/81 (51)	39/81 (48)	7/81 (9)	1/65 (2)	24/65 (37)	33/65 (51)	18/65 (28)	57/65 (88)	42/65 (65)	35/73 (48)

Abbreviation: MS, multiple sclerosis.
[a] Comparisons between the MS and undetermined groups determined by use of the χ^2 test.
[b] $P = .03$.
[c] $P = .02$.
[d] $P = .011$.

1.21 (0.94) lesions in the undetermined group ($P = .91$), extending over a mean (SD) of 1.51 (1.16) and 1.33 (1.00) vertebral levels, respectively ($P = .50$). The location of lesions in the sagittal plane was similar: more than half were in either the cervical region (52% in the MS group and 48% in the undetermined group) or the dorsal region (48% in both groups). Lesions were seldom in the anterior part of the spinal cord (2% in the MS group and 0% in the undetermined group) but were preferentially in the posterolateral (97%) or lateral (49%) part in the MS group. Centrally located lesions were more frequent in the undetermined group than in the MS group (42% vs 18%; $P = .02$). Gadolinium enhancement was more frequent in the MS group (55%) than in the undetermined group (55% vs 35%; $P = .02$).

Brain MRI results are shown in **Table 3**. The frequency of patients with lesions fulfilling 3 or more of the criteria in Barkhof et al[15] was higher in the MS group (54%) than in the undetermined group (54% vs 0%; $P = 9 \times 10^{-6}$). Conversely, brain MRI results were normal in 73% of the patients in the undetermined group compared with 13% of the patients in the MS group.

CSF ANALYSIS

The CSF results are presented in Table 3. There were no statistical differences between the MS group and the undetermined group in terms of mean (SD) cell counts (13.5 [17.3] vs 9.5 [24.3] cells/mm^3, respectively) or mean (SD) protein levels (4.5 [1.8] vs 5.2 [2.9] g/dL, respectively [to convert to grams per liter, multiply by 10.0]). However, OCBs in the CSF were more frequently observed in patients in the MS group than in patients in the undetermined group (92% vs 38%; $P = 4 \times 10^{-6}$).

VISUAL EVOKED POTENTIALS

The results of VEP studies are presented in Table 3. Of the 73 patients examined (47 patients from the MS group and 26 patients from the undetermined group), 20 patients from the MS group (43%) and 1 patient from the undetermined group (4%) had abnormal results ($P = 5 \times 10^{-7}$).

RISK OF CONVERSION TO MS

Using the χ^2 test for single variable analysis, we found 6 factors predictive of conversion to MS: subacute onset of APTM ($P = .03$), presence of lateral ($P = .03$) and posterolateral ($P = .011$) spinal cord lesions, gadolinium enhancement of these lesions ($P = .02$), MRI-detected brain abnormalities fulfilling 3 or 4 of the criteria in Barkhof et al[15] ($P = 9 \times 10^{-6}$), OCBs in the CSF ($P = 4 \times 10^{-6}$), and abnormal VEPs ($P = 5 \times 10^{-7}$).

Using binary logistic regression, we identified 2 variables as risk factors: brain abnormalities, with an odds ratio (OR) of 7.74 (95% CI, 2.42-24.74), and OCBs, with an OR of 15.76 (95% CI, 2.95-84.24). According to these 2 variables, it is possible to classify patients as shown in our **Figure**. We can also estimate the sensitivity (91.3%), the specificity (62.5%), the positive predictive value (82.4%), and the negative predictive value (78.9%) of OCBs.

Table 3. Results of Paraclinical Examination at Presentation

	Patients, No./Total No.						
	Brain MRI Results			CSF Analysis			
Group	No Lesions	≥1 Lesions	Fulfilling Barkhof et al[15] criteria	Protein Level, Mean (Range), g/dL	Cell Count, Mean (Range), cells/mm^3	Presence of OCBs	Abnormal VEPs
MS	7/52 (13)[a]	45/52 (87)[b]	28/52 (54)[c]	4.5 (1.6-9.2)	13.5 (0-87)	43/47 (91)[d]	20/46 (43)[e]
Undetermined	19/26 (73)	7/26 (27)	0/26 (0)	5.2 (1.9-14.3)	9.38 (0-133)	10/26 (38)	1/26 (4)
Combined	26/78 (33)	52/78 (67)	28/78 (36)	4.8 (1.6-14.3)	11.42 (0-133)	53/73 (73)	21/72 (29)

Abbreviations: CSF, cerebrospinal fluid; MRI, magnetic resonance imaging; MS, multiple sclerosis; OCBs, oligoclonal bands; VEPs, visual evoked potentials.
SI conversion factor: To convert protein to grams per liter, multiply by 10.0.
[a] $P = 5 \times 10^{-7}$.
[b] $P = 5.43 \times 10^{-7}$.
[c] $P = 9 \times 10^{-6}$.
[d] $P = 4 \times 10^{-6}$.
[e] $P = .001$.

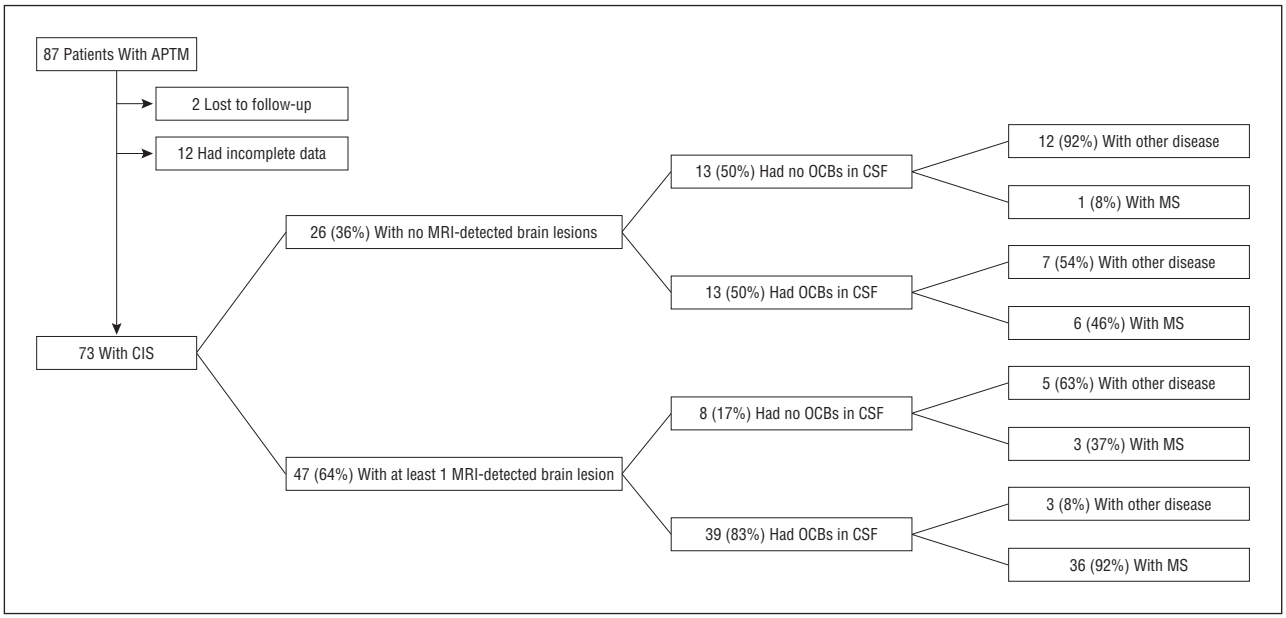

Figure. Flow diagram of patients with acute partial transverse myelitis (APTM), according to the results of brain magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis. CIS indicates clinically isolated syndrome; MS, multiple sclerosis; and OCBs, oligoclonal bands.

PREDICTIVE FACTORS OF LONG-TERM DISABILITY

None of the clinical variables (type of symptom and type of onset), biological variables (cell count, protein level, and presence of OCBs), or radiological variables (brain and spinal cord MRI results and VEPs) were predictive of disability at the end of follow-up in the MS group.

COMMENT

To our knowledge, this study is one of the largest studies of APTM (85 patients) and, after a long follow-up period (8.7 years), confirms that there are 2 risk factors for conversion to MS: white matter lesions on initial brain MRI scan and the presence of OCBs in CSF. These 2 risk factors are associated with ORs of 7.7 (95% CI 2.42-24.74) and 15.8 (95% CI, 2.95-84.24), respectively, for conversion to MS. None of the studied clinical, biological, or radiological variables was predictive of long-term disability in patients with MS.

Studies on APTM as a CIS are relatively rare. Only 2 of the 8 published studies[7-11] were prospective: one[11] with 15 patients followed up for 38 months and the other[7] with 52 patients followed up for 35 months. In our study, we included 85 patients (data collected prospectively for 41 patients [48%] and retrospectively for 44 patients [52%]) who were followed up for a mean period of 104.8 months, constituting, to our knowledge, the longest reported follow-up period. This collaborative work between 3 medical centers allowed us to smooth confounding factors and geographical specificities, but it may also have introduced a bias due to differences in complementary examinations. Despite our efforts to standardize patient inclusion criteria, there may well have been discrepancies in the collection of data on patients, as demonstrated by

the greater proportion of patients with MS in Lille (77%, included prospectively) than in Rouen or Strasbourg (52%, included retrospectively). This proportion of conversion to MS in prospectively included patients is greater than in retrospective studies,[6,8-10] illustrating the importance of standardizing the recruitment method.

Of the 85 patients who experienced APTM, 53 (62%) had APTM that converted to MS, and 29 (34%) did not develop any further disease. This conversion rate is similar to the rate previously described in the prospective study by Cordonnier et al[7] (57.7%) but is higher than the rates described in Sellner et al[10] (42.5%) and Scott et al[9] (43.3%). This difference may be due to the shorter mean follow-up in these studies (46 and 61 months, respectively) compared with our mean follow-up (104.8 months). Considering that there are all types of CISs (optic neuritis, cerebral, or brainstem involvement), their combined conversion rate to MS is lower: 49% after 7 years.[4] The follow-up duration may be, in part, responsible: this rate increases from 50% after 15 years[5] to 63% after 20 years.[3] Because differential diagnoses of APTM are fewer than in other CISs, the conversion rate may be increased: APTM seems to be a CIS with a high risk of conversion to MS.

Univariate analysis of clinical data at onset showed that subacute onset of symptoms was more frequent in patients who went on to develop MS than in other patients (85% vs 66%; $P=.03$). This factor was not detected by the binary logistic regression, in part because of its weakness. Only 1 of the 8 studies dealing with the APTM conversion risk to MS found a predictive clinical variable: sensory symptoms ($P=.009$).[7]

The characteristics of the spinal cord MRI scan at onset are interesting. Univariate analysis identified that lateral ($P=.03$), posterolateral ($P=.011$), or gadolinium-enhanced lesions ($P=.02$) were associated with MS. Conversely, centro-medullary lesions were more frequent in APTM in the undetermined group than in the MS group ($P=.02$). Unfortunately, these factors were not significant in binary logistic regression. This may in part be due to the fact that only 78% of patients underwent axial sections, thereby reducing the statistical power of our results. Cordonnier et al[7] also identified the posterolateral location of spinal cord lesions as a predictive factor for conversion to MS ($P=.01$), but none of the other studies[8-11] confirmed this result. Nevertheless, spinal cord lesions in CIS have never been independently assessed as a factor for conversion to MS.

Brain MRI data can discriminate among patients. In the MS group, 54% of patients had lesions fulfilling the criteria in Barkhof et al,[15] compared with none in the undetermined group ($P=9\times10^{-7}$); conversely, patients with no brain lesions were more frequent in the latter group (73%, compared with 13% in the MS group; $P=5\times10^{-7}$). The presence of brain lesions, also significant in binary logistic regression (OR, 7.74 [95% CI, 2.42-24.75]), has already been identified in patients with APTM[7,10] and in patients with CIS[3,5,16] as a predictive factor for conversion to MS. We failed to show any correlation between this and long-term disability, whereas several studies[2-4] have reported a correlation. However, these studies[2-4] included more patients (100-175 patients) and followed them between 7 and 20 years.[3,4]

Abnormal VEPs and the presence of OCBs are also predictive of conversion to MS. Visual evoked potentials were abnormal in 1 patient (3%) in the undetermined group compared with 20 patients (36%) in the MS group. However, the presence of OCBs in CSF was the only factor identified by binary logistic regression (OR, 15.76 [95% CI, 2.95-84.24]). This factor was identified by Sellner et al,[10] but the OR was 4.73 (95% CI, 1.09-6.76). The longer follow-up in our study (104.8 months compared with 45 months in Sellner et al[10]) may partly explain this difference. Negative brain MRI results and the absence of OCBs have a high clinical interest: patients developed MS only in 8% of cases compared with 46% or 54% of cases if OCBs were present (Figure). This result highlights the importance of analyzing CSF when the initial brain MRI result is normal.

Neither VEPs nor OCBs were predictive of the long-term disability in our patients. This result is in line with that of Schneider et al[17] but not with those of other studies.[18,19] The data of Mandrioli et al[18] must be analyzed with caution because their study was retrospective and focused on patients with clinically definite MS rather than on patients with CIS.

During this long-term (8.7 years) follow-up of 85 patients with APTM, 53 (62%) had APTM that converted to MS. Brain MRI scans that detected at least 1 lesion (OR, 7.74 [95% CI, 2.42-24.74]) and the presence of OCBs in CSF (OR, 15.76 [95% CI, 2.95-84.24]) were 2 independent factors highly predictive of conversion to MS. None of the clinical, biological, or radiological factors were predictive of long-term disability.

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