Acute partial transverse myelitis: risk factors for conversion to multiple sclerosis

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Acute partial transverse myelitis (APTM) may be the first clinical manifestation of multiple sclerosis (MS), of relapsing myelitis, or remain a monophasic event. Identification of risk factors associated with relapse or conversion to MS is important, as prognostic information might help to guide management. The objective of this study was to define clinical, laboratory and neuroimaging factors in patients with first-ever APTM that predict relapses or conversion to MS. We identified 73 patients with a first-ever APTM admitted to our institution from January 1999 to June 2005. The follow-up time ranged from 12 to 90 months (mean follow-up 46 months). Patient demographics, clinical impairment at onset and after 3 months, ancillary tests including cerebrospinal fluid (CSF), magnetic resonance imaging (MRI), evoked potentials, recurrent and new symptoms and signs during follow-up were analysed. APTM remained a monophasic event in 35 patients (47.9%), conversion to MS occurred in 32 (43.8%) and recurred as relapsing myelitis in six patients (8.2%). According to univariate analysis, a family history of MS (P = 0.02), higher expanded disability status scale (EDSS) at onset (P = 0.03) and lesions on brain MRI (P = 0.03) were predictive factors for conversion to MS. CSF-specific oligoclonal bands (P = 0.04) or abnormal IgG-index (P = 0.04) were associated with increased risk for MS as well. In patients with a first-ever APTM, a family history of MS, high EDSS at presentation, lesions on brain MRI, CSF-specific oligoclonal bands or abnormal IgG-index may indicate an increased risk for conversion to MS.

Introduction

Multiple Sclerosis (MS) is the most common chronic disabling disease of the central nervous system (CNS) in young adults in Western countries [1]. Its overall course is characterized by great individual variability in initial presentation, evolution of symptoms and final outcome. The clinical spectrum of MS ranges from an asymptomatic course over decades to rapid progression and permanent disability within a few years.

The first symptoms of MS (clinically isolated syndrome, CIS) can be attributed to a single inflammatory CNS lesion in approximately 85%. Such lesions are often localized within the optic nerve (38.4%), the spinal cord (27.8%) or the brainstem (24.4%) [2]. Inflammatory lesions of the spinal cord usually manifest as acute partial transverse myelitis (APTM) with rapid onset and tend to show asymmetric neurological signs. APTM may be the first manifestation of MS, may remain the only neurological event during life or recur as relapsing myelitis. In a recent study, the risk of developing MS was shown to be higher after APTM than after optic neuritis [2]. Initial sensory symptoms in APTM, posterior-lateral spinal cord lesions, oligoclonal bands in cerebrospinal fluid (CSF) and lesions on brain magnetic resonance imaging (MRI) may also indicate an increased risk of MS [3,4]. On the contrary, peripheral nerve involvement detected by nerve conduction studies may be present in monophasic APTM only [5].

In APTM, as in any CIS, the question of prognosis arises. Prognostic information is crucial for the patient and to decide on long-term management. There is mounting evidence that an early start of immunomodulatory treatment is beneficial and may delay eventual disability in the long-term [6]. However, unnecessary treatments which impair quality of life, induce side effects and are costly should be avoided. In order to further define prognostic factors we analysed clinical, laboratory and neuroimaging findings of a large series of patients presenting with a clinical syndrome attributable to a first-ever inflammatory lesion of the spinal cord.
Patients and methods

Patient population and data collection

All patients with a clinical syndrome attributable to a first-ever inflammatory lesion of the spinal cord, who were admitted to our institution from January 1999 to June 2005, were included in this retrospective study. The study was approved by the Institutional Review Board.

Inclusion criteria were [4]:
(i) acute or subacute motor or sensory symptoms with or without sphincter dysfunction,
(ii) duration of symptoms for 24 h or longer and
(iii) no history of previous neurological symptoms. Excluded were patients with myelopathy related to spinal cord compression, trauma, spinal or meningeal tumors, arteriovenous fistulas, previous irradiation of the spine as well as patients with CSF protein levels greater than 1 g/l and white blood cell (WBC) counts higher than 100 cells/mm³. In addition, patients fulfilling the diagnostic criteria of neuromyelitis optica (NMO) were excluded [7]. However, tests for NMO-antibodies were not available. Laboratory tests were performed to exclude patients with infectious myelopathy. Immune-related connective tissue disorders (CTD) were ruled out with serological tests including blood sedimentation rate, C-reactive protein, rheuma factor, and by testing for anti-nuclear antibody, antineutrophil cytoplasmic antibody and anti-cardiolipin antibody. The differential diagnosis of spinal cord ischaemia was considered but felt to be highly unlikely by the physicians managing the patients. In addition, none of our patients had vascular risk factors.

We identified 73 patients, 18 years or older, matching the inclusion criteria and followed them on average for 46 months (range 12–90 months). At follow-up, patients were classified into three subgroups:
(i) The ‘MS group’ for patients who converted to definite MS according to McDonald’s criteria [8],
(ii) ‘APTM’ for those who continued to meet criteria for a monophasic APTM or
(iii) Relapsing APTM for those with recurrent myelitis. A relapse was defined as new symptoms or exacerbation of pre-existing symptoms for at least 24 h and required an interval of at least 28 days between the first episode.

Clinical findings

Age, sex, family history and clinical findings (motor, sensory or sphincter dysfunction) were noted on admission. Initial neurological symptoms were classified according to sensory and motor levels (cervical, thoracic and lumbar) and distribution (segmental, hemi-, para- or tetracorporal). Disability status was defined by the expanded disability status scale (EDSS) score on admission [9]. EDSS ≤1.5 was considered as mild deficit, EDSS 2 as moderate and EDSS score ≥2.0 as severe. All patients were treated with intravenous steroids followed by an oral tapering regimen. The standard dose was 500 mg methylprednisolone daily for 5 days.

Recovery from APTM was evaluated within the first 3 months after the initial episode of symptoms. When follow-up examination was normal and when there were no residual complaints, recovery was classified as ‘complete’. If there were abnormalities or complaints, recovery was considered ‘incomplete’.

CSF findings

A spinal tap was performed in all 73 patients. CSF analysis included evaluation of cell count, cytology, protein content and intrathecal IgG synthesis. Complete data sets were available for 64 of 73 patients (88%). Information on the presence of CSF-specific oligoclonal bands (OCB) assessed by isoelectric focusing was available in 68 of 73 patients (93%).

Magnetic resonance imaging findings

At onset, 72 of 73 patients (99%) underwent MRI at the clinically appropriate spinal cord level. T1-weighted sequences with and without Gadolinium and T2-weighted sequences were performed. For all MR scans, the presence and number of spinal cord lesions, their localization and enhancement after gadolinium administration were noted. Sixty-nine of 73 patients (95%) had brain MRI scans. Brain lesions were classified as suggestive or atypical for MS [10].

Neurophysiological examinations

Visually evoked potentials (VEPs) were performed in 57 of 73 patients (78%), and median or tibial nerve somatosensory evoked potentials (SSEPs) in 52 of 73 patients (71%).

Both investigations were performed according to standard procedures.

Statistical analysis

For statistical analysis, patients were categorized into two groups based on conversion to definite MS by June 2006. All statistical analyses were performed using spss version 13.0 software. Categorical variables were compared using Fisher’s exact test or chi-square test. 
Non-categorical variables were compared using the Mann–Whitney U-test. Univariate and multivariate analyses were performed. However, only results of the univariate analysis are reported because of the small sample size in the respective groups. Differences with a $P$-value $< 0.05$ were considered significant.

**Results**

**Demographic findings**

Demographic findings and characteristics at onset are shown in Table 1. There were 47 women and 26 men (ratio 1.8:1) with a mean age (SD) of 40.1 (10.5) years (range 21–65) at onset of symptoms.

Thirty-two patients (43.8%) converted to MS after a mean time (SD) of 3.1 (1.9) years. In two patients (2.7%), the diagnosis of MS was based on a second cranial MRI which showed new peri-ventricular white-matter lesions. There was no difference of age, sex and follow-up time of patients who converted to MS and those who did not.

Of the remaining 41 patients (56.1%), six patients (8.2% of all and 14.2% of the patients not converted to MS) acquired relapsing myelitis because of a second neurological event consistent of a second episode of spinal cord inflammation. All of these patients experienced a recurrence of previous spinal cord symptoms. The mean time for recurrence of myelitis leading to this second episode was 2.4 (1.4) years (range 1–43 months). No differences were found between the transition time to MS and occurrence of a second myelitis leading to recurrent APTM (Table 3). None of the patients had a third APTM during the observation period. None of the patients developed NMO during the follow-up period.

In 35 patients (47.9%), the initial APTM remained the only neurological event during the study period. In addition, the patient with the shortest follow-up time of 12 months did not convert to MS.

**Clinical findings**

In 8 (13.6%) of 59 cases, a positive family history of MS was reported (Table 1). Seven of these patients converted to MS; hence, a positive family history of MS was found to be a significant risk factor for conversion to MS in the observed period [$P = 0.02$; odds ratio (OR) 8.86, CI 1.36–3.32].

The clinical symptoms on admission ($n = 73$) were compared with regard to the presence of sensory, motor and sphincter dysfunction and the number of functional systems affected (Table 1). Occurrence of sensory (97.3%) and motor deficits (47.9%) were most common and sphincter dysfunction was present in a quarter of the patients. Most frequently, only one functional system was affected (47.9%). Presence of symptoms in two (34.2%) or three functional systems (27.4%; sensory, motor and sphincter) was also found. The number of functional systems affected did not differ between the MS group and monophasic/recurrent APTM. However, patients who did not convert to MS showed a trend towards more functional systems being affected ($P = 0.05$).

The sensory level was most often within the thoracic and cervical cord regions (43.8% and 42.4%, respectively). Only a small number of patients had a lumbar sensory level (13.8%). The pattern of impairment was present in a single quadrant (5.4%), more often as ‘hemicorporal’ (27.5%) and most commonly as ‘paracorporal’ (52%). Neither sensory levels nor patterns of impairment were predictive for conversion to MS.

| Table 1 | Demographic data and presenting characteristics of 73 patients with APTM, and comparison of patients who converted to MS ($n = 32$) and the remainder (monophasic and relapsing APTM; $n = 41$) |
|---------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| All ($n = 73$) | Monophasic and relapsing APTM | $P$-value |
| Mean age (SD) | 40.1 (10.5) | 41.4 (10.3) | 39.0 (10.6) | 0.35 |
| Sex (f/m) | 47/26 | 21/11 | 26/15 | 0.5 |
| Family history with MS | 8/59 | 7/28 | 1/31 | 0.02 |
| Presenting symptoms | | | | |
| Sensory deficit | 71 | 31 | 40 | 0.68 |
| Motor deficit | 35 | 16 | 19 | 0.47 |
| Sphincter dysfunction | 18 | 7 | 11 | 0.42 |
| Localization of lesion level | | | | |
| Cervical | 31 | 14 | 17 | 0.88 |
| Thoracic | 34 | 14 | 20 | |
| Lumbar | 8 | 4 | 4 | |
| Clinical impairment | | | | |
| Mild (EDSS $\leq 1.5$) | 22 | 7 | 15 | 0.03 |
| Moderate (EDSS 2) | 31 | 12 | 19 | |
| Severe (EDSS $\geq 2.5$) | 20 | 13 | 7 | |
The mean EDSS score on admission was 2.1 (SD 0.8; range 1–5), and 30.1% patients had mild, 42.5% moderate and 27.4% severe impairment. We found that patients who converted to MS had significantly higher EDSS values ($P = 0.03$), as shown in Table 1.

**CSF findings**

A CSF pleocytosis (threshold > 4 cells) was present in 51.6% and albumin content was above the upper limit of normal (> 7.4) in 15.6% of patients. Cytological analysis revealed a predominantly lymphocytic pleocytosis in all patients with increased cell counts. Cell count and albumin content did not differ between the groups (Table 2). The median IgG-index (SD) was 0.78 (0.49) and an IgG-index above the upper limit of normal (> 0.57) was detected in 73.4% of patients. Patients who converted to MS were more probably to have a higher IgG-index ($P = 0.04$) and an abnormal IgG-index ($P = 0.04$; OR 4.67, CI 0.98–8.22). We found OCB in CSF in 75% of the patients and the detection of these bands was more probably to be associated with later conversion to MS ($P = 0.03$; OR 4.73, CI 1.09–6.76).

**Evoked potentials**

Visually evoked potentials examination was abnormal in 15.8% and SSEP in 44.2% of the patients. Abnormal evoked potential examinations were not identified as a risk factor for conversion to MS.

**Magnetic resonance imaging findings**

Spinal MRI lesions were visible in 63 patients (87.5%); 63.5% of the lesions were enhanced after gadolinium administration (Table 2). Except for one lesion in the lumbar spinal cord, lesions were located in the cervical and thoracic spinal cord (both 42.9%). Multiple lesions were found in seven patients, and lesions extended over ≥2 vertebral levels in six patients. Neither presence, number, localization, extension nor Gadolinium enhancement were indicative for later development of MS. Amongst the six patients with lesion size ≥2 vertebral segments, a VEP examination was performed in three patients and was normal in all of them. Three of these six patients developed MS. None of the lesions showed aspects of spinal cord ischaemia.

Brain MRI lesions were detected in 50.7% and Gadolinium enhancement was present in 10.1% of the examined scans. The T2-lesions were classified as MS-typical in 83.3% and MS-atypical in 16.7% of the patients. The presence of MS-typical brain lesions was significantly higher in patients who converted to MS ($P = 0.03$; OR 2.85, CI 1.01–3.37). After a mean interval of 46 months 55% of those with MS-typical brain lesions had developed MS, but only 26.4% of those with normal brain MRI.

**Recovery within 3 months**

Data on clinical examination 3 months after APTM were available in 62 patients (84.9%), as shown in
Table 3 Three-month outcome of APTM and mean time [years (SD)] for conversion to MS or occurrence of a second myelitis episode leading to the diagnosis of relapsing APTM

<table>
<thead>
<tr>
<th>Outcome (monophasic/relapsing)</th>
<th>MS</th>
<th>APTM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete recovery (n = 33)</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Incomplete recovery (n = 29)</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Second event (only relapsing)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean time (SD)</td>
<td>3.1 (1.9)</td>
<td>2.4 (1.4)</td>
</tr>
<tr>
<td>n</td>
<td>32/73</td>
<td>6/73</td>
</tr>
</tbody>
</table>

Table 3. Complete recovery from symptoms occurred in 53.2% of patients whilst 46.8% experienced an incomplete recovery. Amongst the patients with incomplete recovery, one patient showed no improvement.

Presence of incomplete or complete recovery after 3 months was not a predictor for the later development of MS.

Discussion

In this retrospective study 73 patients with a first-ever inflammatory lesion of the spinal cord were followed for an average of almost 4 years. We looked for clinical findings and results from ancillary tests that were associated with conversion to MS. These turned out to be:

i) a family history of relatives with MS (OR 8.9),
ii) severe impairment at onset,
iii) MS-typical lesions on brain MRI (OR 2.85),
iv) abnormal IgG-index (OR 4.67) and
v) the presence of CSF-specific oligoclonal bands (OR 4.73).

Table 4 summarizes the studies to date which aimed to identify risk factors for conversion to MS after a CIS of the spinal cord. Only one study was prospective [4]; all other studies including ours have been retrospective. In these studies, the mean age of patients ranges from 20.9 to 65.1 years and the rate of conversion to MS from 11% to 58%. In our cohort the mean age of patients was 40.1 years, and 43.8% of our patients were diagnosed with MS during follow-up.

Familial occurrence of MS is well known. The risk of MS for first-, second- and third-degree relative of MS patients may be as high as 20% [11]. In our APTM cohort, patients with one or several relatives suffering from MS were also at an increased risk of conversion to MS. A survey of MS in our catchment area in 1986 showed a family history of MS in 8.6% of all patients [12]. The large number of patients in our series and a high rate of familial MS in our area may explain why it was possible to identify an increased risk of conversion to MS after APTM in patients with a positive family history.

The most frequent symptoms of APTM in our cohort and other patient series were sensory and motor deficits (Table 4). APTM patients who later convert to MS had significantly more severe clinical impairment, i.e. more frequent EDSS scores ≥2.5. This has been noted by other authors as well. Jeffrey et al. reported that patients with MS-associated APTM have more severe weakness compared with parainfectious myelitis [13]. However, NMO was shown to be associated with even more severe impairment of spinal cord function than MS-related myelitis [14].

Unlike other authors, we did not find any association between type of symptoms and conversion risk to MS [4,13], and localization of sensory levels or patterns of spinal cord dysfunction were not a prognostic factor.

The frequency of sphincter dysfunction in APTM ranges from 6% to 25% (current study, [15,16]). Sphincter dysfunction was not a prognostic marker of MS in our series.

Cordonnier et al. have reported that elevated cell count and OCB are associated with risk for developing MS [4]. In our study, the presence of OCB and an abnormal IgG-index were associated with increased risk for MS as well. These findings underline the importance of CSF analysis. CSF findings are important to rule out other aetiologies of spinal cord syndromes and, if not present, help to assess the risk of MS.

In a recent study, monophasic APTM was shown to be associated with involvement of the peripheral nervous system (PNS) [5]. Hence, normal SSEP results may be of prognostic value. However, in our patient series SSEP results were not associated with prognosis. Furthermore, we could not confirm that pathological VEPs are associated with increased risk for MS [4,17].

Spinal cord lesions on MRI were detected in 60–96% of patients with APTM [3–5] and in 87.5% in our series. They were primarily located in the cervical and thoracic cord, and more than half of the lesions were as in previous series in the cervical cord [5,18]. Contrast enhancement was found in 63.5% of the scans and in 8% multiple lesions were detected. The longitudinal extension of spinal lesions did not differentiate patients with MS-associated APTM and patients with monophasic APTM. However, Bakshi et al. reported that monophasic APTM is characterized by more longitudinal expansion of the lesions [19]. Our findings may be influenced by the strict inclusion criteria and advances in neuroimaging for exclusion myelopathies of other origin. On the contrary, our study confirms a different observation by the same authors. In our patients with brain lesions (n = 35) the conversion rate to MS was 54.3%. When brain MRI was normal (n = 34) this rate
<table>
<thead>
<tr>
<th>Source</th>
<th>Study type</th>
<th>Patients n (f/m)</th>
<th>Mean age (±SD or range)</th>
<th>Mean follow-up (±SD or range)</th>
<th>Conversion rate to MS (%)</th>
<th>Predictive factors for conversion to MS</th>
<th>Positive OCB (%)</th>
<th>MRI spinal lesions (%)</th>
<th>MRI brain lesions (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cordonnier et al. (2003) [4]</td>
<td>Prosp.</td>
<td>52 (37/15)</td>
<td>35 years (19–68)</td>
<td>35 ± 15.9 months</td>
<td>57.7%</td>
<td>Positive OCB (P = 0.003); high cell count (P = 0.01); presence of brain MRI lesions (P = 0.015); posterior-lateral localization (P = 0.01); sensory symptoms (P = 0.009)</td>
<td>62.5% (MS 76.7%)</td>
<td>T2-MRI, 96%; Gadolinium uptake, 20%</td>
<td></td>
</tr>
<tr>
<td>Bruna et al. (2006) [3]</td>
<td>Retros.</td>
<td>45 (24/21)</td>
<td>39.1 years (±15.3)</td>
<td>41.7 ± 51.3 months</td>
<td>11%</td>
<td>Younger age (P &lt; 0.05); female sex (P &lt; 0.01)</td>
<td>57.8%</td>
<td>T2-MRI, 64%; Gadolinium uptake, 56%; ≥2 levels 60%</td>
<td>Exclusion of patients with brain MRI abnormalities</td>
</tr>
<tr>
<td>Scott et al. (2005) [26]</td>
<td>Retros.</td>
<td>30 (23/7)</td>
<td>not reported</td>
<td>61 months (24–132 months)</td>
<td>10%; 43.3% relapsing APTM</td>
<td>Trend for relapsing course: multiple lesions (P = 0.1)</td>
<td>62%</td>
<td>90%; 29.6% ≥2 levels</td>
<td>Exclusion of patients with brain MRI abnormalities</td>
</tr>
<tr>
<td>Harzheim et al. (2004) [5]</td>
<td>Retros.</td>
<td>45 (35/10)</td>
<td>38 years (21–71)</td>
<td>No data</td>
<td>22%</td>
<td>Mono-segmental involvement of the spinal cord; no PNS involvement in MS (but in 27% APTM)</td>
<td>61.4% (MS 90%)</td>
<td>96% (44.4% single lesions); 33.3% ≥1 segment</td>
<td>50%; 58.8% MS-typical</td>
</tr>
<tr>
<td>Present study (2007)</td>
<td>Retros.</td>
<td>73 (47/26)</td>
<td>40.1 years (21–65)</td>
<td>46 months (12–90 months)</td>
<td>42.5%</td>
<td>Positive family history (P = 0.02); positive OCB (P = 0.03); abnormal IgG-index (P = 0.04); MS-typical brain lesions (P = 0.03); higher EDSS at onset (P = 0.03)</td>
<td>51.8% (MS 83.9%)</td>
<td>87.5%; Gadolinium uptake, 63.5%; 11.3% (≥2 levels)</td>
<td>50.7%; Gadolinium uptake, 10.1%; MS: MS-typical 78.9%; APTM: MS-typical 18.8%</td>
</tr>
</tbody>
</table>
was 26.4% only. This means that patients with lesions on brain MRI compatible with MS are at an increased risk for developing MS, but the absence of such lesions at the onset of APTM does not exclude later transition to MS. Nevertheless, brain MRI is helpful to assess the MS risk of patients with APTM.

Neuromyelitis optica is an important differential diagnosis of APTM. Characteristic findings of NMO include extensive longitudinal transverse myelitis (T2-abnormalities extending > 3 segments) and severe optic neuritis [20]. Lesions > 2 segments were found in six of our APTM patients but none fulfilled the revised criteria for the diagnosis of NMO at inclusion and none of our patients converted to NMO during follow-up [7]. The frequency of NMO presenting as a CIS is estimated at below 1% [21]. There is mounting evidence that NMO is distinct from MS and also from APTM. Scott and coworkers detected NMO-IgG, which shows high specificity for NMO, only in 1 of 22 patients with APTM at presentation [22]. Patients with acute necrotizing myelitis were not observed in our series either. Necrotizing myelitis is distinct from APTM, tends to relapse, and as there is no effective treatment, is associated with a bleak prognosis [23].

Patients with CTD, which is a frequent cause of relapsing myelitis, were not included in our series. Nevertheless, we still observed 8.2% patients with recurrent APTM. A search for anti-Ro antibodies, which may be present in recurrent APTM, was not performed [24]. The time to a second spinal manifestation indicating recurrent APTM ranges from 4 months to 1 year [13] and for NMO relapses a median of 166 days was reported [14]. In the present study, the mean interval to a second manifestation of APTM (relapsing APTM) was 2.4 years and shorter than the 3.1 years of patients converting to MS (Table 3). No clinical parameter or ancillary test distinguished relapsing myelitis from monophasic APTM or MS-related APTM. However, whether our patients with recurrent APTM had relapsing APTM or MS with spinal manifestations only, remains open. The outcome of our patients with recurrent myelitis within 3 months was fair. More than half recovered completely and only one patient had no improvement.

The main shortcoming of our study is its retrospective nature. Furthermore, infectious agents known to cause monophasic or recurrent APTM were excluded but not by means of a standardized protocol. In addition, the differential diagnosis of spinal cord ischaemia is highly unlikely but cannot be excluded.

With the availability of treatments to reduce frequency of relapses in MS, slow progression of brain atrophy and improve long-term prognosis, there is a need to identify patients with a high likelihood of developing MS and to treat such patients early [25]. On the contrary, because of potential side effects and of the high costs, such treatments should not be given to patients with a minimal chance of recurrent symptoms. In our study we found several clinical and paraclinical factors that indicate high or low likelihood of ongoing inflammation and later conversion to MS. Such factors might be helpful to identify patients who may need treatment against ongoing dissemination of inflammation after a first APTM. However, further studies are required to validate if they are useful for deciding on immunomodulatory therapy at such an early stage of the disease.

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References
