J Neurol (2008) 255:89–93
DOI 10.1007/s00415-007-0686-5

ORIGINAL COMMUNICATION

Jai Perumal
Rana Zabad
Christina Caon
Megan MacKenzie
Alexandros Tselis
Fen Bao
Zahid Latif
Imad Zak
Robert Lisak
Omar Khan

Acute transverse myelitis with normal brain MRI

Long-term risk of MS

Received: 27 December 2006
Received in revised form: 17 June 2007
Accepted: 21 June 2007
Published online: 20 December 2007

J. Perumal, MD · R. Zabad, MD · C. Caon, MSN, NPC · M. MacKenzie, MS · A. Tselis MD, PhD · F. Bao, MS · R. Lisak, MD · O. Khan, MD
Multiple Sclerosis Center
Dept. of Neurology
Wayne State University School of Medicine
Detroit, MI, USA

F. Bao, MS · Z. Latif, BSc · I. Zak MD
MR Research Center
Dept. of Radiology
Wayne State University School of Medicine
Detroit, MI, USA

Current address:
R. Zabad, MD
Dept. of Clinical Neurosciences
University of Calgary

O. Khan, MD (✉)
4201 St Antoine
8D-UHC
Detroit, MI 48201, USA
Tel.: +1-313/745-4280
Fax: +1-313/966-9271
E-Mail: okhan@med.wayne.edu

Abstract *Objective* To investigate the long-term risk of developing MS in patients presenting with acute transverse myelitis (ATM) and normal brain MRI scans at onset. *Methods* We studied 58 ATM patients with normal brain MRI at presentation for up to 5 years with serial neurologic and imaging studies. All patients underwent CSF analysis at onset which was defined positive if two or more IgG oligoclonal bands and/or elevated IgG index were present. Brain and spinal cord MRI scans were obtained every 6 months for the first 2 years, and annually thereafter unless the patient experienced a second neurologic attack different from the initial episode to confirm CDMS or there was demonstration of MRI lesions confirming dissemination in time and space to fulfill McDonald imaging criteria to diagnose MS. *Results* Seventeen of 58 (29 %) patients developed MS of which 7 (41 %) patients developed CDMS and 10 (59 %) developed MS using McDonald Imaging Criteria. Mean time to CDMS by a second clinical attack was 11.1 months compared to 19.2 months by MRI lesions ($P = 0.03$). None of the patients developed MS after 24 months of onset. All 17 patients who developed MS had positive CSF although 15 patients who had positive CSF did not develop MS during the 5 years of follow-up. *Conclusions* The majority of patients with ATM and normal brain MRI do not develop MS after 5 years of follow-up confirming the relatively low risk compared to patients with abnormal brain MRI scans. CSF is helpful in distinguishing patients more likely to develop MS. Compared to clinical attacks, serial imaging may not lead to an earlier diagnosis in ATM patients with normal brain MRI.

Key words multiple sclerosis · clinically isolated syndrome · transverse myelitis · brain MRI

Introduction

Acute transverse myelitis (ATM) may be a clinically isolated syndrome (CIS) presenting as the initial manifestation of multiple sclerosis (MS). The utility of an abnormal brain MRI scan in predicting the long-term outcome in the context of CIS including ATM has been extensively studied placing these patients at high risk of developing [4, 10, 18, 23]. However, few studies have examined the long-term outcome in a relatively large number of CIS patients presenting with ATM and a normal brain MRI scan at onset [5, 22]. This is not an infrequent observation in clinical practice and often raises diagnostic and prognostic issues. Furthermore, the incorporation of the MRI-based evidence of dissemina-

JON 2686

tion in time and space for diagnosing MS has not been examined in ATM with normal brain MRI scan at presentation.

We report the long-term outcome in 58 ATM patients with normal brain MRI scans at onset followed longitudinally for five years with serial neurologic examination and imaging studies.

Methods

Patients with ATM [26] were followed longitudinally with serial neurologic and imaging studies to monitor conversion to MS. The protocol was approved by the local Human Investigations Committee and all participants gave written informed consent. All patients met the following criteria for inclusion: (i) Presentation of ATM between the ages of 18 and 60 years without prior history of symptoms suggestive of a CNS demyelinating event, (ii) evolution of symptoms over no more than 4 weeks and sustained for at least 48 hours, (iii) Varying degrees of motor, sensory and sphincter dysfunction, but without complete paraplegia, (iv) no evidence of symptoms or neurologic signs suggestive of cranial involvement at onset, (v) normal brain MRI scan at presentation, (vi) presence of one or two intramedullary lesions seen on spinal cord MR imaging with each lesion ≤2 vertebral segments in length, (vii) no evidence of spinal cord compression, (viii) CSF obtained in all patients at initial presentation and negative for infections, with cell count < 50/mm^3 and total protein < 100 mg/dl. All CSF samples were examined for oligoclonal IgG bands (OCB), mostly by isoelectric focusing on agarose gels as well as CSF IgG index measurements. However, technical details were not available in many instances, (ix) negative serology for infections or connective tissue disorders, and (x), normal visual evoked potentials at onset.

Patients were examined every six months and unscheduled visits were conducted whenever clinically warranted. All patients underwent brain and spinal cord MRI scans every 6 months for the first two years and annually thereafter for up to approximately five years unless the patient developed MS confirmed by the occurrence of a second clinical attack consistent with a CNS demyelinating episode that was neurologically different from the initial episode (CDMS according to Poser et al. criteria) [21] or the development of new MRI lesions that fulfilled the definition for dissemination in time and space according to the McDonald MRI criteria [17]. An attack was defined as new neurologic symptom(s) persisting for at least 48 hours and accompanied by objective change on neurologic examination in the absence of fever or infection. Relapses were typically treated with a five day course of intravenous methylprednisolone at one gram a day for 5 days. All brain MRI scans included pre and post contrast images. Spinal cord MRI scans were performed in a sagittal plane with T1-weighted pre and post contrast, and T2-weighted images. If a lesion was identified on these images, additional images in the axial plane were obtained for confirmation.

Statistical analysis

Statistical analysis was performed using Fisher's exact test, student's t test, chi square, and the Mann-Whitney *U*-test as appropriate with a 95% level of significance. All p values < 0.05 were regarded as statistically significant.

Results

Demographics and clinical characteristics of 58 consecutive patients who met the study criteria are shown in Table 1. After a mean follow-up of 61.8 months, 17 of 58 (29%) of the patients developed MS after an average of 15.9 months. No patient developed MS after 24 months of initial presentation. Thirty-two of 58 (55%) had abnormal CSF defined by the presence of two or more CSF OCB not noted in the serum or elevated CSF IgG Index or both. All 17 patients who developed MS had abnormal CSF. However, 15 of 41 (37%) patients who did not develop MS also had abnormal CSF. Abnormal CSF predicted a 53% conversion rate to MS within 2 years of onset ($r = 0.6$, $P < 0.0001$). Patients who developed MS had a younger onset of disease but not significantly different from those who did not develop MS.

Table 1 Clinical characteristics of the cohort

Total number of patients	58
Mean age at onset, years (± SD)	32.7 (8.5)
Gender (F/M)	41/17
Ethnicity, CA/AA	38/20
Mean Duration of follow-up, months (± SD)*	61.8 (± 2.6)
CSF +, n (%)	32 (55.2%)
No of Patients who developed MS by Poser et al. criteria (CDMS) or McDonald MRI Criteria (%)	17 (29.3%)

+ *CSF* Two or more OCB and/or elevated IgG Index
* Range of follow-up for all patients was between 58 and 68 months

Subgroup analysis (Table 2) showed mean time to develop CDMS by Poser criteria (n = 7) was 11.1 months versus 19.2 months in patients who developed MS according to McDonald MRI criteria (n = 10) (11.1 vs 19.2 months, $P = 0.01$). Mean time to initiation of DMT from the initial presentation in patients developing CDMS by Poser criteria was 17.7 months in contrast to 26.6 months in patients who developed MS according to McDonald MRI criteria (17.7 vs 26.6 months, $P = 0.01$).

We see a large population of African-American (AA) patients at our clinic with an unusually high representation in this cohort. Clinical characteristics of the AA-ATM patients and comparison with Caucasian ATM patients are shown in Table 3. Twenty of 58 (34%) were AA and 7 of 20 (35%) developed MS in contrast to 10 of 38 (26%) Caucasian ATM patients who developed MS. Mean time to MS in AA-ATM patients was significantly less than Caucasian ATM patients (9.6 vs 20.3 months, $P = 0.001$) and mean EDSS at last observation was higher in AA than Caucasians (5.20 vs 3.45, $P = 0.003$) despite significantly less time to initiation of DMT in AA than Caucasians (16.6 vs 27.4 months, $P = 0.001$) despite longer duration of exposure to DMT in AA than Caucasians (45.1 vs 35.6 months, $P = 0.0004$).

Discussion

To the best of our knowledge, this is the largest cohort of ATM patients with normal brain MRI scans at onset and

Table 2 Clinical characteristics of patients who converted to CDMS

	CDMS (Poser et al.) n = 7	MS (according to McDonald MRI Criteria) n = 10	Patients who did not develop MS n = 41
Mean age at onset, years (± SD)	27.6 (5.2)	28.7 (4.6)	32.1 (8.9)
Gender (F/M)	5/2	10/0	26/15
Ethnicity (AA/CA)	4/3	3/7	13/28
Mean duration of follow-up, months (± SD)	61.7 (2.7)	63.0 (2.5)	60.9 (2.6)
Mean time to second event, months (± SD)*	11.1 (4.5)	19.2 (8.4)	na
Mean time to initiation of therapy from onset, months (± SD)**	17.7 (3.9)	26.6 (8.1)	na
Mean EDSS (± SD)	4.6 (1.0)	3.9 (1.2)	1.06 (0.8)
CSF +, n (%)	7 (100 %)	10 (100 %)	15 (37 %)

+ *CSF* Two or more OCB and/or elevated IgG Index; *AA* African-Americans; *CA* Caucasians
* 11.1 vs 19.2 months (p = 0.01); ** 17.7 vs 26.6 months (p = 0.01)

Table 3 Effect of ethnicity: ATM and the development of MS in Caucasians and African-Americans

	Caucasians n = 38	African-Americans n = 20
Mean age at onset, years (± SD)	32.7 (9.6)	32.7 (6.1)
Gender, F/M	24/14	17/3
Mean duration of follow-up, months (± SD)	61.8 (2.6)	61.7 (2.6)
Mean time to second event, months (± SD)*	20.3 (7.5)	9.6 (2.4)
Mean time to initiation of therapy from onset, months (± SD)**	27.4 (7.2)	16.6 (3.0)
Mean EDSS (± SD)***	3.45 (0.7)	5.2 (0.9)
CDMS by Poser et al. criteria (%)	3 (42.9 %)	4 (57.1 %)
MS using McDonald MRI criteria (%)	7 (70 %)	3 (30 %)
CSF +, n (%)§	19 (50 %)	13 (65 %)

+ *CSF* Two or more OCB and/or elevated IgG Index
* 20.3 vs 9.6 months; p = 0.001; ** 27.4 vs 16.6 months; p = 0.001; *** 3.45 vs 5.20; p = 0.003

followed for at least five years with serial MRI scans. Our study showed that 29 % of ATM patients presenting with normal brain MRI scan at onset developed MS according to clinical or imaging criteria. The development of MS in other studies of ATM with normal brain MRI scans at onset has varied between 10 to 33 % [2, 3, 5, 9, 15, 16, 19, 22]. Several factors including but not limited to study design, number of patients, duration of follow-up, and image analysis may account for the wide range of conversion to MS in previous reports. Interestingly, we found only one study reporting a zero rate of conversion in ATM patients with normal brain MRI scans followed clinically for 44 months from onset [24]. No details of this sub-cohort were described precluding further comment on their contrasting findings.

The presence of OCB in the CSF has been associated with a higher risk of developing MS [13, 20]. The importance of OCB in the context of ATM in determining future risk of MS has been highlighted with a strong predictive value in several studies [2, 16, 19]. We reported abnormal CSF (defined in this study by the presence of two or more OCB or elevated CSF IgG Index or both) in 55 % (32 of 58) of patients of which 53 % (17 of 32) went on to develop MS ($r = 0.6, P < 0.0001$). This highlights the significance of obtaining CSF when evaluating the patients with ATM and assessing the risk of future conversion to MS. Cerebrospinal fluid analysis has been recommended by the Transverse Myelitis Consortium Working Group in the work-up and evaluation of ATM, particularly, for distinguishing inflammatory from non-inflammatory etiologies [26]. No other tests in the CSF have been reported to predict a higher risk of conversion to MS in ATM patients with normal brain MRI scans. However, increased CSF glucose levels and CSF IL-6 levels have been associated with a poor outcome [3, 15].

There is consensus that the risk of developing MS is significantly high with an abnormal brain MRI scan at onset [11, 12]. Furthermore, the use of the McDonald MRI criteria demonstrating dissemination in time and space has been shown to establish the diagnosis of MS in a shorter period of time compared to CDMS by Poser et al. criteria [8, 25]. However, there is no information on the utility of the McDonald MRI criteria in ATM with a normal brain MRI at onset. We compared the time to develop MS by the two sets of criteria, i.e., Poser et al. versus McDonald MRI criteria. This comparison was done

retrospectively since our study began before the publication of the McDonald criteria, and we did not obtain a brain scan 3 months after onset. Interestingly, we noted the development of CDMS defined by the occurrence of a second clinical attack fulfilling the requirement of dissemination in time and space in a significantly shorter period of time compared to the development of MS based on MRI evidence of dissemination in time and space (11.1 vs 19.2 months, $P = 0.01$). Thus, it appears that serial MRI studies in ATM patients with normal brain scans do not shorten the time to diagnose MS which is in contrast to their well-known utility in CIS patients with abnormal brain MRI scans [4, 10]. Nevertheless, more patients were diagnosed with MS according to the McDonald MRI criteria than the Poser criteria indicating the sensitivity of imaging in this type of cohort. This also adds to the overall validity of the McDonald diagnostic criteria scheme that includes both clinical as well as imaging criteria for the diagnosis of CDMS. Since all 17 of the patients who developed MS in our study did so within 24 months of onset, we suggest that the routine use of serial MRI scans in ATM patients with normal brain MRI scans may not be cost-effective after 24 months from onset. Furthermore, it also appears that the risk of developing MS in our cohort was significantly reduced after the first 24 months. We can not extend our observations to CIS patients with optic neuritis or brainstem syndromes because it is unclear if localization within the CNS may affect risk of developing MS.

Lately, there is increasing recognition that CNS demyelinating disease including MS may be clinically more aggressive and less responsive to therapy in AA with MS than Caucasians [6, 7, 14, 27]. Thirty four percent of our patients were AA and 35% of them developed MS. At last observation, AA patients had greater disability than Caucasians despite earlier diagnosis and longer exposure to therapy. These observations expand our knowledge about the spectrum of CNS demyelinating diseases in AA concurring with several previous reports suggesting a more aggressive disease course in AA than Caucasians. Factors contributing to a more aggressive disease course in AA than Caucasians remain unclear although, possible association with APOE *E*4 (40% heterozygote carriers in AA), greater spinal cord involvement and more tissue destruction quantified by non-conventional imaging have been implicated [1, 14].

In summary, majority of the patients who present with ATM and a normal brain MRI scan do not develop MS after five years of follow-up. Those who do develop MS (29%), do so within 24 months of onset and have OCB or elevated CSF IgG Index in the CSF. Serial MRI scans are not helpful in establishing an earlier diagnosis in this cohort. Finally, once again, we observe that AA with ATM develop MS in a shorter period of time than Caucasians and also appear to respond less favorably to therapy. Further long-term studies with larger number of patients including biomarkers are needed to confirm our findings and establish markers for risk of developing MS as well as predicting clinical outcomes.

Acknowledgement Dr Perumal is a recipient of the Sylvia Lawry Fellowship by the National Multiple Sclerosis Society (USA). The study was supported in part by the Mary Parker Neuroscience Fund, the Parker-Webber Endowment, and the Wayne State University Neuroscience Program.

References

1. Abdelrahman N, Weinstock-Guttman B, Garg N, et al. (2006) MRI characteristics of Africans-Americans vs Caucasian/Hispanic Americans with Relapsing-remitting and secondary progressive multiple sclerosis. Neurology 66(Suppl 6):A96-A97
2. Bashir K, Whitaker JN (2000) Importance of paraclinical and CSF studies in the diagnosis of MS in patients presenting with partial cervical transverse myelopathy and negative cranial MRI. Mult Scler 6:312–316
3. Bruna J, Martinez-Yelamos S, Martinez-Yelamos A, Rubio F, Arbizu T (2006) Idiopathic acute transverse myelitis: a clinical study and prognostic markers in 45 cases. Mult Scler 12: 169–173
4. Brex PA, Cicarelli O, Jonathon I, et al. (2002) A longitudinal study of abnormalities on MRI and disability from multiple sclerosis. N Eng J Med 346: 158–164
5. Cordonnier C, de Seze J, Breteau G, et al. (2003) Prospective study of patients presenting with acute partial transverse myelopathy. J Neurol 250: 1447–1452
6. Cree BA, Al-Sabbagh A, Bennett R, Goodin DS (2005) Response to interferon beta-1a treatment in African-American multiple sclerosis patients. Arch Neurol 63:627–628
7. Cree BA, Khan O, Bourdette D, Goodin DS, Cohen JA, Marrie RA, et al. (2004) Clinical characteristics of African Americans vs Caucasian Americans with multiple sclerosis. Neurology 63: 2039–2045
8. Dalton CM, Brex PA, Miszkiel KA, Hickman SJ, MacManus DG, Plant GT, et al. (2002) Application of the new McDonald criteria to patients with clinically isolated syndromes suggestive of multiple sclerosis. Ann Neurol 52(1): 47–53
9. de Seze J, Stojkovic T, Breteau G, et al. (2001) Acute myelopathies: clinical, laboratory and outcome profiles in 79 cases. Brain 124:1509–1521
10. Filippi M, Horsfield MA, Morissey SP, et al. (1994) Quantitative brain MRI lesion load predicts the course of clinically isolated syndromes suggestive of multiple sclerosis. Neurology 44: 635–641
11. Filippi M, Rocca MA, Arnold DL, et al. (2006) EFS guidelines on the use of neuroimaging in the management of multiple sclerosis. Eur J Neurol 13: 313–325
12. Frohman EM, Goodin DS, Calabresi PA, et al. (2003) The utility of MRI in suspected MS. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Neurology 61:602–611

13. Jacobs LD, Kaba SE, Miller CM, Priore RL, Brownscheidle CM (1997) Correlation of clinical, magnetic resonance imaging, and cerebrospinal fluid findings in optic neuritis. Ann Neurol 41: 392–398
14. Khan O, Ching W, Ozust C, et al. (2004) APOE E4 frequency in African-American MS patients and association with disease severity. Neurology 62 (Suppl 5):A387
15. Krishnan C, Kaplin AI, Calabresi PA, Kerr DA (2004) Clinical characteristics and prognostic factors in 170 patients and idiopathic transverse myelitis. Neurology 62(Suppl 5):A231
16. Martinelli V, Comi G, Rovaris M, et al. (1995) Acute myelopathy of unknown etiology: a clinical, neurophysiological and MRI study of short and long-term prognostic factors. J Neurol 242: 497–503
17. 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 50:121–127
18. Morrissey SP, Miller DH, Kendall BE, et al. (1993) The significance of brain-magnetic resonance imaging abnormalities at presentation with clinically isolated syndromes suggestive of multiple sclerosis. A 5 year follow up study. Brain 116:135–146
19. O'Riordan JI, Thompson AJ, Kingsley DP, et al. (1998) The prognostic value of brain MRI in clinically isolated syndromes of the CNSA 10-year follow up. Brain 121:495–503
20. Paolino E, Fainardi E, Ruppi P, et al. (1996) A prospective study on the predictive value of CSF oligoclonal bands and MRI in acute isolated neurological syndromes for subsequent progression to multiple sclerosis. J Neurol Neurosurg Psychiatry 60:572–575
21. Poser CM, Paty DW, Scheinberg L, et al. (1983) New diagnostic criteria for multiple sclerosis: guidelines for research proposals. Ann Neurol 13:227–231
22. Scott TF, Kassab SL, Singh S (2005) Acute partial transverse myelitis with normal cerebral magnetic resonance imaging: transition rate to clinically definite multiple sclerosis. Mult Scler 11:373–377
23. Tintore M, Rovira A, Rio J, et al. (1999) Optic neuritis, brainstem syndromes and myelitis: early conversion to multiple sclerosis. Med Clin (Barc) 112: 693–694
24. Tintore M, Rovira A, Rio J, et al. (2005) Is optic neuritis more benign than other first attacks in multiple sclerosis? Ann Neurol 57:210–215
25. Tintore M, Rovira A, Rio J, et al. (2003) New diagnostic criteria for multiple sclerosis: application in first demyelinating episode. Neurology 60:27–30
26. Transverse Myelitis Consortium Working Group (2002) Proposed diagnostic criteria and nosology of acute transverse myelitis. Neurology 59:499–505
27. Weinstock-Guttman B, Jacobs LD, Brownscheidle CM (2003) Multiple sclerosis characteristics in African-Americans in the New York State Multiple Sclerosis Consortium. Mult Scler 3:293–298