Idiopathic transverse myelitis

Corticosteroids, plasma exchange, or cyclophosphamide

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ABSTRACT Transverse myelitis is a focal disorder of the spinal cord in which an immune-mediated process results in neural injury. In this large retrospective study, we compare patients who received one of four treatments to identify the most effective therapies. We identified subsets of patients who received clinical benefit from plasma exchange or cyclophosphamide being included in their treatment regimen. **NEUROLOGY 2007;68:1614–1617**

Transverse myelitis (TM) is a monofocal inflammatory disorder of the spinal cord in which an immune-mediated process results in neural injury. Fifty percent of patients experience loss of all movement in their legs, over 80% experience sensory changes, and almost all patients experience autonomic symptoms.[1]

Several small studies support the administration of corticosteroids in patients with TM, but other investigations have suggested they may not be effective.[2,3] The varied results are likely due to the fact that only a subset of patients with TM respond adequately from steroid therapy, whereas other patients require more aggressive therapies.[4] At the Johns Hopkins Transverse Myelitis Center, we routinely offer daily doses of IV methylprednisolone (MP; 1,000 mg) for 3 to 5 days unless there are compelling reasons to avoid this therapy.

Often, patients have TM with coexisting systemic rheumatologic disorders.[5] Although no controlled information currently exists regarding the use of other treatments, some clinicians consider pulse dose IV cyclophosphamide (CP) for these patients. In this article, we review the clinical and paraclinical features and outcome data of patients who met the recently established criteria for idiopathic TM (Transverse Myelitis Consortium Working Group).

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Table 1 Cohort characteristics

Characteristics	Treatment groups				Test of significant difference
	IV MP (n = 66)	PLEX (n = 32)	IV CP (n = 13)	PLEX + IV CP (n = 11)	
Mean ± SEM age at onset, y	43.9 ± 2.23	38.6 ± 3.4	41.62 ± 4.5	41 ± 5.5	NSS
Gender, % women	58	56.3	92.3	54.5	NSS
Recurrent TM, %	34.8*‡	46.9†§	84.6%*†	81.8‡§	$p = 0.001$
Mean ± SEM time to nadir at attack, d	9.96 ± 1.44	5.7 ± 1.09	4.9 ± 1.4	9.9 ± 2.6	NSS
Mean ± SEM time to follow-up, mo	20.4 ± 2.23	16.06 ± 2.57	20.92 ± 4.0	10.4 ± 2.8	NSS
% (n) with systemic autoimmune disease	20.0 (13/66)*	12.5 (4/32)†	69.2 (9/13)*‡	0 (0/11)‡	$p = 0.00$
% (n) with multifocal lesions	9.4 (6/64)*	9.7 (3/31)†	38.5 (5/13)*†	36.4 (4/11)‡	$p = 0.009$
% (n) with gadolinium enhancing lesions	85.5 (53/62)	71 (22/31)	76.9 (10/13)	100 (11/11)	NSS
Mean extent of lesion	5.4 ± 0.66	9.7 ± 1.17	8.5 ± 1.75	8.8 ± 1.88	$p = 0.006$
Level of signal abnormality (rostral border)	53% cervical 42% thoracic	69% cervical 31% thoracic	85% cervical 15% thoracic	64% cervical 36% thoracic	
% (n) patients with CSF pleocytosis	67.2 (41/61)	66.7 (20/30)	84.6 (11/13)	45.5 (5/11)	NSS
% (n) patients with elevated protein	66.7 (40/60)	60.7 (17/28)	100 (9/9)	80 (8/10)	NSS
% ASIA A at nadir	10.6*	34.3*	30.7	36.4	$p < 0.02$

†‡§Used to compare treatment groups within a category. Values with matching symbols are the ones that achieve significance. For example, when comparing treatment groups in terms of percent with recurrent TM, there was a greater percentage of patients with recurrent TM in the third and fourth treatment group vs the first (‡) and a greater percentage of patients with recurrent TM in the third and fourth group vs the second group (†‡), but there was no significant difference when comparing Groups 1 and 2.
MP = methylprednisolone; PLEX = plasma exchange; CP = cyclophosphamide; TM = transverse myelitis; ASIA = American Spinal Injury Association.

METHODS We collected information on the acute clinical and paraclinical features of patients who presented with idiopathic TM to the Johns Hopkins Transverse Myelitis Center between 2001 and 2005. Information was collected on demography, antecedent factors, description of the acute illness, serology, and functional status during acute attack. MRI and lumbar puncture results were also collected. All patients were followed for a minimum of 6 months.

We obtained institutional review board approval to examine the clinical records of these patients. Complete data for was available for 122 patients, and they are included in this analysis.

Outcome measures. Outcome was measured on an Expanded Disability Status Scale (EDSS). ΔEDSS scores were calculated as the difference between the acute and follow-up functional status. We also utilized the American Spinal Injury Association (ASIA) classification of myelopathy, which rates patients on an A, B, C, D, or E scale. In this rating scale, a normal patient is rated as ASIA E and a patient with complete loss of motor and sensory functions from a spinal cord injury is rated as ASIA A.

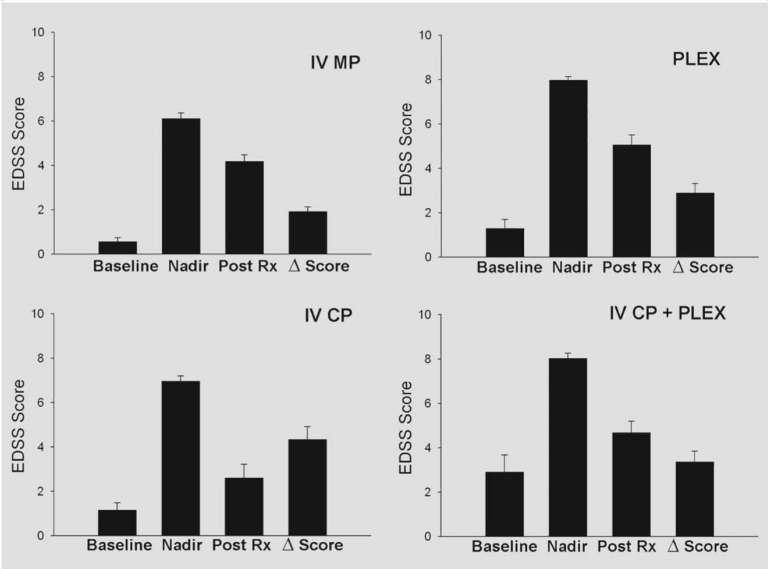
Statistical analysis. SPSS 12.0 was used for the statistical analyses. χ^2 tests were used to analyze the differences between groups for nominal variables. Group differences were analyzed using the Kruskal–Wallis test for continuous variables. Differences between two independent samples were analyzed using the Mann–Whitney *U* test. Significance was assessed at the 0.05 level.

RESULTS All 122 patients met the recently established criteria for the diagnosis of idiopathic TM and received 3 to 5 days of IV MP. Sixty-six patients received no other therapy, 32 patients additionally received five exchanges of 1.1 plasma volumes every other day (PLEX), 13 patients additionally received IV CP (750 to 1,000 mg/m^2), and 11 patients additionally received IV CP and PLEX.

The four treatment groups were similar in terms of various demographic and clinical features (table 1). In the IV CP group, there were more women, more patients with systemic autoimmune disease (systemic lupus erythematosus, Sjogren syndrome, type I diabetes, Hashimoto thyroiditis, Grave disease, mixed connective tissue disorders, etc.), more patients with recurrent TM, and more patients with multifocal lesions. There were no significant differences in average CSF white blood cell count or average protein levels among treatment groups (table 1).

Patients in the IV MP group had a nadir EDSS of

Figure Measure of treatment effects



Disability measured as EDSS at baseline, nadir, post-treatment, and change in EDSS score for patients treated with IV steroids alone, PLEX, IV CP, and PLEX + IV CP. EDSS = Expanded Disability Status Scale; MP = methylprednisolone; PLEX = plasma exchange; CP = cyclophosphamide.

6.1 ± 0.5, and only 10.6% of the patients were classified as ASIA A. At follow-up, the mean EDSS of this group was 4.2 ± 0.3 (ΔEDSS 1.9 ± 2.1). Patients in the PLEX group were more likely to be ASIA A at nadir and had a higher nadir EDSS (7.9 ± 0.3). ΔEDSS was 2.9 ± 0.4 in the PLEX therapy group. Patients in the IV CP group had nadir disability similar to the IV MP patients, but recovered more function as reflected in their lower posttreatment EDSS (2.6 ± 0.61; $p < 0.05$) and higher ΔEDSS (4.4 ± 0.6; $p < 0.05$). Patients in the combination IV MP, PLEX, and IV CP group had the highest baseline EDSS (2.9 ± 1.7), the highest nadir EDSS (8.0 ± 0.5; $p < 0.05$ vs the IV MP group), and the highest percentage of patients who were ASIA A (36.4%; $p < 0.05$ vs the IV MP group). Despite this, these patients recovered to an EDSS of 4.7 ± 0.5, which was virtually identical to the outcome of the less severe IV MP patients (figure).

We found little evidence of recovery in the ASIA A patients treated with either IV MP (ΔEDSS 0.3 ± 0.2) or PLEX (ΔEDSS 0.5 ± 0.2) (table 2). However, there was significant improvement in the ASIA A patients treated with IV CP (ΔEDSS 3.0 ± 1.3) or IV CP/PLEX (ΔEDSS 4.4 ± 0.7). Of the non-ASIA A patients, there was a benefit from PLEX compared to IV MP (ΔEDSS 4.1 ± 0.4 vs 2.1 ± 0.2; $p < 0.001$). In this cohort of non-ASIA A patients, the addition of IV CP to PLEX therapy did not have an additive benefit. The ΔEDSS for the patients receiving IV MP, PLEX, and IV CP was 2.8 ± 0.03 vs 4.1 ± 0.4 in the patients receiving IV MP combined only with PLEX (table 2).

Table 2 Outcomes based on ASIA scores at nadir

	ΔEDSS	
Treatment groups	ASIA A (acute)	Non ASIA A (acute)
IV MP (n =66)	0.3 ± 0.2	2.1 ± 0.2*
PLEX (n = 32)	0.5 ± 0.2	4.1 ± 0.4*
IV CP (n = 13)	3.0 ± 1.3	4.9 ± 0.5
PLEX + IV CP (n = 11)	4.4 ± 0.7	2.8 ± 0.6

*Achieves significance ($p < 0.001$) when comparing ASIA A and non-ASIA A patients.
ASIA = American Spinal Injury Association; EDSS = Expanded Disability Status Scale; MP = methylprednisolone; PLEX = plasma exchange; CP = cyclophosphamide.

Of the 13 patients who transitioned from IV steroids to IV CP, 70% had evidence of an autoimmune condition. This subset of the IV CP group had a significant response to this regimen with a ΔEDSS of 4.4 ± 0.5.

DISCUSSION Our retrospective review has generated the following conclusions: 1) In our patients with TM who do not have an ASIA A level of disability at nadir or a history of autoimmune disease, PLEX provided benefit beyond steroids, but IV CP did not; 2) in patients who are ASIA A at presentation, PLEX alone is not helpful, whereas a combination of IV CP with PLEX showed benefit.

We recognize, however, that these should be viewed as only provisional conclusions because the data reflect uncontrolled, retrospective analysis. The distinct differences among the treatment groups (percentage with recurrent disease and percentage with autoimmune conditions) highlight the inherent biases that were a part of treatment strategies in this cohort. Nonetheless, this review suggests that ASIA A patients receive significant benefit from medical regimens that include CP. If a patient's disability did not reach a level of ASIA A, the addition of IV CP to their regimen was not of significant benefit, whereas the group of patients receiving combination PLEX and IV MP did better than the group receiving IV MP alone.

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