Neurologic, MR Imaging, and MR Spectroscopic Findings in Eosinophilia Myalgia Syndrome


BACKGROUND AND PURPOSE: Eosinophilia myalgia syndrome (EMS), a multisystemic disease induced by exposure to L-tryptophan, may result in serious CNS abnormalities. The purpose of this study was to determine the pattern of neurologic characteristics, MR imaging abnormalities, and brain neurometabolites in EMS.

METHODS: Sixteen patients with EMS and CNS abnormalities (CNS-EMS) and 12 control subjects underwent evaluation, including medical and neurologic examination, proton MR spectroscopy, and MR imaging.

RESULTS: Neurologic findings that were increased in CNS-EMS included minor depression (100%), amnesia (88%), and intermittent confusion (38%), although fatigue (31%), motor disorders (31%), recurrent headache (19%), major depression (13%), and dementia (6%) also occurred, but at a lesser significance. Self-reported disability was markedly increased in CNS-EMS. MR imaging findings included subcortical focal lesions, focal lesions in deep white matter, cortical atrophy, ventricular dilatation, and diffuse and periventricular white matter abnormalities. MR spectroscopic findings established two distinct spectral patterns: 1) increased choline-containing compounds, decreased N-acetylaspartate, and increased lipid-macromolecules, consistent with inflammatory cerebrovascular disease; and 2) increased glutamine, decreased myo-inositol, and decreased choline, consistent with acute CNS injury or metabolic encephalopathy.

CONCLUSION: Neurologic abnormalities, self-reported disability, brain lesions, and MR spectroscopic abnormalities are common in CNS-EMS. The pattern of cerebral lesions and neurometabolites is consistent with widespread inflammatory cerebrovascular disease. However, a subgroup of patients with CNS-EMS have neurometabolic changes consistent with a metabolic encephalopathy identical or similar to hepatic encephalopathy. The neurologic abnormalities in EMS and related hypereosinophilic syndromes should be interpreted cautiously, with the recognition that both cerebrovascular injury and secondary metabolic encephalopathies may be involved.

Eosinophilia myalgia syndrome (EMS), a multisystemic disease induced by exposure to L-tryptophan and its derivatives, was first recognized in 1989 (1, 2). EMS is characterized by a peripheral eosinophilia greater than 1500 eosinophils/cm³, severe myalgia, and severe and sometime fatal systemic complications (3). Diagnosis of EMS includes exclusion of other causes of eosinophilia, including parasitic infection, drug reactions, autoimmune disease, and neoplasm. L-Tryptophan, an amino acid produced commercially as an over-the-counter supplement, was administered commonly to enhance sleep, but preparations of L-tryptophan distributed widely throughout the world were contaminated with toxic chemical by-products of the production process (4–8). These toxic compounds apparently induced the epidemic of EMS. However, although EMS is well recognized in the epidemic form (as in the 1989–1991 epidemic that was related to the administration of L-tryptophan), it may also occur sporadically with less obvious epidemiologic associations.

Patients affected by EMS suffer severe generalized symptoms and inflammation of multiple organs, including the CNS (4–8). Early symptoms of EMS...
include fatigue, fever, arthralgias, myalgias, headache, neuralgia, confusion, shortness of breath, chest pain, and other systemic symptoms. Peripheral signs of EMS include rash, vasculitis, arthritis, pulmonary infiltrates, pericarditis, myositis, peripheral neuropathy, and eosinophilic fasciitis. CNS manifestations of EMS (CNS-EMS), which may occur early but are more typical of late or established disease, include headache, encephalopathy, cognitive defects, ataxia, memory loss, motor dysfunction, dyslexia, anxiety, stroke, and depression (9–16). MR imaging findings in patients with CNS-EMS have revealed focal lesions in the white matter, similar to those of multiple sclerosis or diffuse cerebrovascular atherosclerosis (10, 17, 18). However, many patients have normal or minimally abnormal findings on MR images, suggesting that a significant metabolic or nonfocal component of disease is present that contributes to CNS symptoms. We applied MR imaging and proton MR spectroscopy to patients with EMS to determine whether CNS-EMS would be characterized primarily by anatomic and neurochemical evidence of focal or generalized brain injury or by neurochemical markers indicative of a metabolic encephalopathy.

**Methods**

**Study Population**

The patients of this CNS-EMS cohort were studied in 1991 and 1992 in the postacute phase of EMS, when eosinophilia, rash, fevers, and life-threatening organ involvement had resolved, but recurrent incapacitating myalgias, fatigue, and neurologic symptoms persisted. Twelve healthy control subjects and 16 patients with EMS were studied. This study was approved by the institutional review board. The patients with EMS were referred from out of state by their legal representatives specifically for MR imaging studies, with the travel expenses and the cost of MR imaging and MR spectroscopy paid by the legal firms. Copies of the MR images and other requested data were returned to the legal representatives as per agreement. The patients were asked to bring copies of their medical records for review to confirm the diagnosis of EMS. Because the patients were from out of state, follow-up studies were not possible. As part of the research design, the research data—comprising MR imaging, MR spectroscopy, and neurologic data—were collated and analyzed separately from the data used for legal proceedings and were not specifically analyzed or reported until the time of the present study to allow the legal claims associated with EMS to be resolved to minimize any perceived bias in this study. One of the investigators (R.R.S.) was a paid consultant and interpreted MR images for the legal firms in the EMS cases, whereas the other investigators (L.J.H., W.L.S., B.L.H.) were not paid consultants, but were independently responsible for analysis and interpretation of the research MR imaging, MR spectroscopy, and neurologic data that were not used in the legal proceedings. The separate analysis of research data by individuals not paid by the law firms was performed to minimize bias.

EMS was diagnosed according to the criteria established by the Centers for Disease Control (1, 2). The mean age of the control subjects was 46 ± 16 years (range, 35–68 years); the mean age of the patients with EMS was 51 ± 12 years (range, 44–71 years) (P > 0.2). All patients reported neurologic symptoms attributable to the CNS (CNS-EMS) (Table 1). Patients with symptoms suggestive of peripheral neuropathy but without CNS symptoms were not studied. Although the addition of other control groups, especially patients with EMS but without CNS symptoms, would have provided the best design to specifically exclude confounding variables associated with EMS, these patients were not available to us at the time of the study.

**Medical Evaluation**

Subjects underwent a social and medical interview, general medical examination, neurologic examination, review of all laboratory tests, and self-reported disability rating. Neurologic signs and symptoms and findings were specifically recorded for each individual. Self-reported disability measures were rated using the numerical handicap scales of the World Health Organization (WHO) International Classification of Impairments, Disabilities, and Handicaps (19). Six forms of handicap were rated from 0 to 9 in the WHO classification scheme: economic self-sufficiency, occupation handicap, orientation handicap, social integration handicap, physical independence handicap, and mobility handicap. A total disability score was then defined as the sum of the individual handicap scores. Although bias is intrinsic to any self-reported disability measure, particularly when the potential for financial gain associated with legal proceedings is ongoing, self-reported disability ratings are both necessary and fundamental to any disability determination. Thus, although the potential for bias is recognized, these self-reported disability measures are important, especially when objective disability measures specifically for EMS have not been scientifically formulated or validated.

**Proton MR Imaging and MR Spectroscopy**

Localized proton MR spectroscopy and MR imaging were performed on a 1.5-T system. MR images were obtained in the sagittal, axial, and coronal planes, using a head coil, multiecho classic spin-echo pulse sequences, and a field of view of 20 cm. Sagittal (600/20/2 [TR/TE/excitations]), axial (2800/20/80/1), and coronal (2800/20/80/1) series were obtained. The section thickness was 5 mm, with a 2.5-mm section gap and a 256 × 192 acquisition matrix. MR images were blindly analyzed for pathologic findings as follows: 0 = no abnormality, 1 = mild abnormality, 2 = moderate abnormality, 3 = severe abnormality. Using this scale, seven specific types of brain injury were rated: 1) cortical atrophy, 2) ventricular dilation, 3) diffuse white matter changes, 4) periventricular white matter changes, 5) small focal lesions in subcortical white matter, 6) small focal lesions in deep white matter, and 7) gross infarct. A composite measure of brain injury, the total brain injury score, was defined as the sum of all seven brain injury scores and was recorded for each subject.

MR spectroscopy was performed by selecting a 2 × 2 × 2-cm³ volume of interest (voxel) in the parietooccipital deep white matter from preliminary axial images (see Fig 1). Point-resolved spectroscopy (PRESS), a single-voxel, water-suppressed spin-echo sequence (2000/26–272/128), was used (20). In this sequence, all the contributions to the broad resonance at 1.3 ppm were in phase at TE’s (< 30). However, at a long TE (136), the signal from lactate that might be present would be inverted because of spin-spin coupling. In addition, contributions from molecules with short T2 (lipids and other macro-molecules) would be negligible because of rapid transverse relaxation. A total of 128 averages were summed, zero filled, and treated with an exponential filter corresponding to 1 Hz of line broadening before Fourier transformation. A baseline simulation method, similar to the spline-fitting baseline correction method (21), was used to remove underlying broad resonances based on points defined by the bases of the choline (Cho), creatinine (Cre), N-acetylaspartate (NAA), and absolute baseline point at 0 ppm as previously described (22, 23). Metabolic resonance peaks were integrated and metabolic ratios were calculated for myo-inositol (mI)/Cre, Cho/Cre, and NAA/Cre. Identical objective criteria were used for analyzing every spectrum, ensuring that the same assumptions regarding inclusion or exclusion of ambiguous line shapes were used across the
whole data set. Although curve-fitting of the resonance peaks could have been used, the integrative method has excellent reproducibility (23, 24), and simultaneous analysis of peaks using the integrative and curve-fitting methods has established no significant statistical difference (25). The resonances of glutamate and glutamine (Glx) were overlapping, contained multiple peaks, and were not independently resolvable, and thus all these peaks were integrated together for a composite Glx/Cre ratio. It has been established previously that Glx/Cre corresponds well to alterations in the true glutamine concentration (26).

In the spectroscopic sequence used, the contributions to the broad resonance at 1.3 ppm (lipid and macromolecules) are in phase at TE (30), but at a long TE (136, 272) signals from these molecules are minimal because of the rapid transverse relaxation. Moreover, at a long TE (136), lactate is inverted because of spin-spin coupling. Thus, this sequence with variable TEs (26, 68, 136, 272) permits qualitative editing that determines whether the resonance at 1.3 ppm is attributable to major contributions from lactate or lipid macromolecules. Absolute quantification was not performed, because these data were collected when the techniques for absolute quantification were not generally available or validated. Reproducibility of spectroscopic measures based on repeated image in individual subjects was excellent, with the coefficient of variation for individual metabolic ratios ranging from 3.8 to 4.8.

### Statistical Analysis

Statistical analyses were conducted with SPSS 6.1.1 for Macintosh (SPSS Inc, Chicago, IL). Means of groups were compared with the two-tailed t-test with Satterthwaite’s correction. For individual spectra, abnormal values were defined as those exceeding the mean metabolic ratio of the control group + 2 SD. Corrections for multiple comparisons were applied across the data set. Categorical data were analyzed using non-parametric methods.

### Results

Neurologic complaints and findings were common in patients with CNS-EMS compared with healthy control subjects (Table 2). Intermittent minor depression was the most common CNS complaint (100%). Amnesic disorders, principally intermittent difficulties in word finding, were the next most common neurologic complaint or finding (88%), followed by episodes of confusion (38%), fatigue (31%), motor disturbances (31%), recurrent headache (19%), major depression (13%), and dementia (6%). Motor disturbances or findings included weakness on ambulation, tremor, spasticity, asterixis, incontinence, or hyperreflexia. Patients with CNS-EMS also reported increased disability compared with control subjects on the WHO handicap scales (P < .00001) (Table 2). Functions that required effective cognitive function (economic self-sufficiency, occupation handicap, orientation handicap, social integration handicap) were most impaired in CNS-EMS, whereas those
functions that required motor skills (physical independence handicap and mobility handicap) were the least impaired.

Extensive brain lesions were present in CNS-EMS as revealed by MR imaging (15 of 16 images showed abnormal findings) (Table 1 and Fig 2). The imaging findings in patients with CNS-EMS are compared with the findings in control subjects in Table 3. As can be seen, statistical increases in cortical atrophy, ventricular dilatation, subcortical focal lesions, deep focal lesions, and periventricular and diffuse white matter abnormalities were present ($P < .00001$). Gross infarct and basilar plaquelike lesions were not present in either the CNS-EMS group or the control group.

Brain neurometabolites in CNS-EMS were characterized by mean increases in Glx/Cre and 1.3 ppm/Cre (lipid macromolecules at 1.3 ppm) relative to healthy control subjects ($P < .005$) (Table 4 and Fig 3). Lactate was not observed in any patients or control subjects on the basis of spectra obtained at TE = 26, 136, and 270. Individual differences were established in NAA/Cre, Cho/Cre, and mI/Cre in patients with EMS (Table 4), but mean values did not reach significance ($P > .05$). However, it was noted that the EMS group had considerably increased variance in all metabolic ratios relative to control subjects, suggesting that the EMS cohort might be extremely heterogeneous in terms of neurometabolic disturbance. Indeed, analysis of the spectra of individual patients determined several distinct spectral patterns that were responsible for the increased variance in the EMS groups, including increased Glx/Cre in five patients (one with reduced mI/Cre and one with both reduced mI/Cre and reduced Cho/Cre), increased Cho/Cre in five patients, reduced NAA/Cre in four patients, and increased lipid macromolecules/Cre in six patients (Tables 1 and 4). Figure 3A shows a normal control spectrum. Figure 3B shows increased Glx, decreased Cho, and decreased mI in a patient with EMS.

### Discussion

EMS has generated considerable interest in the scientific community because of the similarity of this syndrome to previously reported toxin-induced epidemics as well as to classic autoimmune diseases (27). The most recent epidemic of EMS has been attributed to an autoimmune or toxic reaction to contaminants in preparations of L-tryptophan (28). EMS is characterized by a profound inflammatory reaction, resulting in eosinophilia, cytokine release, vasculitis, thrombosis, connective tissue proliferation, and, in some cases, death (29, 30). Neurologic involvement, particularly peripheral neuropathy, was recognized as an early and severe manifestation of EMS (4, 5, 31). However, as further longitudinal data from patients with EMS were obtained, the increased prevalence of cerebral involvement became evident, including focal motor deficits, encephalopathy, dementia, cognitive defects, and affective disorders (10–12, 15, 16).

EMS has many similarities to classic autoimmune diseases, especially systemic lupus erythematosus (SLE) and systemic sclerosis (9, 14, 27, 32). The MR imaging findings of CNS-EMS closely resemble those cerebral lesions found in autoimmune disease, with atrophy, focal white matter lesions, and basilar plaquelike lesions predominating (10, 15, 17, 18, 33). However, these lesions are both nonspecific and non-diagnostic and are commonly observed in many other CNS diseases, including atherosclerotic cerebrovascular disease (34). The present study confirms the presence of extensive brain abnormalities in CNS-EMS. The most frequent lesions in CNS-EMS were subcor-
tical white matter focal lesions, followed in frequency by deep white matter focal lesions, cortical atrophy, and ventricular dilatation. Periventricular and diffuse white matter abnormalities also occurred, but less frequently. Unlike previous reports, stroke and basilar plaquelike lesions did not occur in this EMS cohort.

The pathogenesis of the CNS lesions in EMS is unknown, but is probably related to the same processes that induce inflammatory lesions in other areas of the body (6). The MR imaging abnormalities seen in CNS-EMS predominately affected the subcortical and deep white matter but generally spared the basal regions, suggesting that the brain lesions visible on MR images were attributable to small-vessel disease, resulting in occlusive and thrombotic microfocal infarct, rather than the classic demyelinating lesions of multiple sclerosis (34). Indeed, histopathologic changes of EMS include endothelial cell injury, endothelial hyperplasia, perivascular mononuclear cell infiltrates, and occlusive microangiopathy, which are consistent with the MR imaging findings (9, 28). These cerebral changes mimic those of both neuropsychiatric SLE and animal models of inflammatory brain disease and are probably responsible for the SLE-like MR imaging and clinical findings (35, 36).

Mean neurometabolic changes in the CNS-EMS cohort included increased Glx/Cre and lipid macromolecules (1.3 ppm/Cre) ($P$, .05) (Table 4). However, increased variance was noted in the EMS cohort for all neurometabolites, suggesting marked neurometabolic heterogeneity with the EMS population relative to control subjects. Analysis of spectra from individual patients revealed that the EMS cohort was indeed neurometabolically heterogeneous and that this was the reason for the increased variance in mean neurometabolites. Analysis of individual spectra revealed the following abnormal neurometabolic patterns: increased Glx/Cre (5/16), with certain of these spectra also showing reduced mI/Cre and Cho/Cre; increased Cho/Cre (Cho-containing compounds) (5/16); decreased NAA/Cre (4/16); and increased lipid-macromolecules (1.3 ppm/Cre) (6/16). These results are consistent with evolving brain injury in different phases of neurometabolic resolution and, possibly, to the presence of a superimposed metabolic encephalopathy similar to hepatic encephalopathy. Thus, neurologic symptoms in patients with EMS may have a complex or multietiologic origin. This is not unexpected in a disease with multisystem involvement, variable MR imaging appearance, and extensive alterations in amino acid metabolism (11, 27, 28, 32).

While Glx/Cre was markedly increased in the patients with CNS-EMS compared with control subjects ($P < .005$) (Table 2), these abnormalities were particularly pronounced in five patients (Tables 1 and 4).
and Fig 3). Elevated levels of Glx/Cre have been reported primarily in hepatic cirrhosis, liver failure, and other hepatic diseases (26, 37), and the findings of increased Glx/Cre in CNS-EMS suggest hepatic encephalopathy or a similar metabolic encephalopathy. Increased Glx/Cre is not by itself diagnostic of metabolic encephalopathy but can also be seen in other disorders, including acute ischemia, postictal states, and certain brain tumors. However, the presence of hepatic encephalopathy in CNS-EMS was further supported by the finding of reduced mI/Cre and Cho/Cre in individual patients and by the presence of asterixis, consistent with and perhaps diagnostic of hepatic encephalopathy. EMS can induce hepatic abnormalities (9 –13), and these neurochemical findings are consistent with significant hepatic disease (26, 37). Although hepatic encephalopathy had not been recognized by the clinicians who had referred these patients with EMS for this study, a post hoc review of the medical records revealed that a substantial minority of the patients (4/16) had elevated transaminase and bilirubin. However, serum ammonia levels were not obtained at the time of the MR spectroscopic study, making definitive clinical confirmation of hepatic encephalopathy difficult. Because the EMS cohort was referred from out of state specifically for this one-time study, follow-up examinations at our center were not possible, making a definite association between these neurometabolic findings and proved end-stage hepatic disease impossible. Nevertheless, these results are important because they establish that neurologic dysfunction in EMS may not always be attributable to established brain disease, but may represent evolving acute injury or a secondary metabolic encephalopathy, in this case, hepatic encephalopathy or a closely related disease.

Elevated Cho/Cre and reduced NAA/Cre levels occurred in a number of patients (Tables 1 and 4). Almost identical brain metabolic changes have been reported in neuropsychiatric SLE, which has certain clinical similarities to EMS (22, 24, 33). Elevated Cho, which is an important constituent of membranes, is frequently observed with cerebral infarct, demyelination, and inflammation (36, 38). NAA is a neurochemical marker for mature neurons and axons, and reduced NAA is generally interpreted as indicating neuronal death or injury (39, 40). These results suggest that extensive neuronal injury and demyelination, either inflammatory or ischemic, are important aspects of CNS-EMS. The obvious explanation for these findings would be the presence of inflammatory cerebrovascular disease; however, some evidence also exists that the abnormal tryptophan metabolites in

<table>
<thead>
<tr>
<th>Neurometabolite</th>
<th>Control Subjects (n = 12)</th>
<th>EMS (n = 16)</th>
<th>Significance (P Value)</th>
<th>Individual Abnormal Metabolites (&gt;2 SD from Mean Normal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NAA/Cre</td>
<td>2.21 ± 0.17</td>
<td>2.17 ± 0.30</td>
<td>.74</td>
<td>Reduced 4/16</td>
</tr>
<tr>
<td>Cho/Cre</td>
<td>0.87 ± 0.14</td>
<td>0.99 ± 0.24</td>
<td>.09</td>
<td>Increased 5/16</td>
</tr>
<tr>
<td>mI/Cre</td>
<td>1.05 ± 0.19</td>
<td>1.07 ± 0.37</td>
<td>.85</td>
<td>Reduced 2/16</td>
</tr>
<tr>
<td>Glx/Cre</td>
<td>2.30 ± 0.13</td>
<td>3.21 ± 1.10</td>
<td>&lt;.005*</td>
<td>Increased 4/16</td>
</tr>
<tr>
<td>1.3 ppm/Cre</td>
<td>0.27 ± 0.03</td>
<td>1.35 ± 0.90</td>
<td>&lt;.0005*</td>
<td>Increased 6/16</td>
</tr>
<tr>
<td>Lactate</td>
<td>Not present</td>
<td>Not present</td>
<td></td>
<td>0/16</td>
</tr>
</tbody>
</table>

Note.—EMS, eosinophilia myalgia syndrome; NAA, N-acetylaspartic acid; Cre, creatine; Cho, choline; mI, myo-inositol; Glx, glutamate glutamine. * Significance differences by the t-test. These ratios represent results obtained at TE = 26.

Fig 3. A, Normal control proton MR spectrum (PRESS [2000/26/128]) shows the characteristic resonances of mI (mIns), Cho, Cre, NAA, Glx, and lipid macromolecules (Lipid-Macro).
B, Proton MR spectrum in EMS (PRESS [2000/26/128]) shows a significant increase in Glx (upward-pointing arrows) and marked decreases in Cho and mI (mIns) (downward-pointing arrows), suggestive of hepatic encephalopathy.
EMS may be directly neurotoxic, which may contribute to the observed abnormalities (28, 41).

The peaks at 1.3 ppm (which could be lactate, lipid, or macromolecules) were increased in six of 16 patients with CNS-EMS ($P < .02$) (Tables 1 and 4). If ischemia were an important mechanism of neuronal injury, then increased lactate would be expected in brain tissues of patients with CNS-EMS (42, 43). Long-TE (136 milliseconds) MR spectroscopy showed minimal signal at 1.3 ppm, with no observable signal inversion (which would be indicative of the lactate doublet), indicating insignificant concentrations of lactate. These results suggest that anaerobic metabolism is not a fundamental characteristic of subacute EMS. It is likely, however, that the postulated ischemic episodes of acute EMS had already resolved, resulting in the absence of lactate, but leaving residual lipid and macromolecules in the region of injury. The absence of lactate in obvious cerebrovascular disease has been reported in other forms of inflammatory brain disease and has been attributed to the following: well-established end-stage lesions without lactate; placement of the spectroscopic voxel in relatively normal-appearing white matter, and not specifically in active focal lesions; the presence of only small foci of ischemia, resulting in a marked reduction of the lactate signal by volume-averaging with adjacent normal tissues; sampling error caused by the use of single voxels when active ischemia and lactate would have been revealed by multiple voxels in other areas of the brain; or rapid diffusion of the lactate out of relatively normal ischemic, but not infarcted tissues (23, 24). Similar peaks at 1.3 ppm consistent with membrane activation, degradation, or demyelination have been observed in multiple sclerosis and neuropsychiatric SLE (23, 44, 45), and it is likely that the pathogenesis is similar in CNS-EMS.

**Conclusion**

Patients with CNS-EMS have frequent neurologic disorders as well as MR imaging and spectroscopic abnormalities consistent with inflammatory cerebrovascular disease. A neurometabolic pattern characterized by increased Glx/Cr changes also occurs in a subset of patients with CNS-EMS, which could represent an active phase of injury to brain tissues or a superimposed metabolic encephalopathy. These data indicate that CNS disorders in patients with EMS may be of complex origin associated with established and active injury attributable to inflammatory cerebrovascular disease or to the presence of a secondary metabolic encephalopathy. More detailed studies of new cases of EMS may permit the determination of whether the observed Glx/Cr changes are attributable to active brain injury or to superimposed hepatic encephalopathy. However, because of the strongly epidemic nature of EMS, it is difficult to predict when further MR imaging and spectroscopic studies can be obtained during the acute and subacute phases of CNS-EMS. Thus, the present studies may be a unique data set of great importance in understanding the neurologic complications of EMS.

**Acknowledgments**

We gratefully acknowledge the assistance of Mela Chavez in preparation of the manuscript, and Helen Petropoulous and William Brooks for preparation of the figures and editorial comments.

**References**

22. Sibbitt WL Jr, Haseler LH, Griffey RH, Hart BL, Sibbitt RR,


