Steroid-Responsive Encephalopathy Associated With Autoimmune Thyroiditis

Pablo Castillo, MD; Bryan Woodruff, MD; Richard Caselli, MD; Steven Vernino, MD, PhD; Claudia Lucchinetti, MD; Jerry Swanson, MD; John Noseworthy, MD; Allen Aksamit, MD; Jonathan Carter, MD; Joseph Sirven, MD; Gene Hunder, MD; Vahab Fatourechi, MD; Bahram Mokri, MD; Daniel Drubach, MD; Sean Pittock, MD; Vanda Lennon, MD, PhD; Brad Boeve, MD

Background: Steroid-responsive encephalopathy associated with autoimmune thyroiditis (SREAT), often termed Hashimoto encephalopathy, is a poorly understood and often misdiagnosed entity.

Objective: To characterize the clinical, laboratory, and radiologic findings in patients with SREAT to potentially improve recognition of this treatable entity.

Design: Retrospective analysis of clinical features and diagnostic test data.

Setting: Two affiliated tertiary care referral institutions.

Patients: Twenty consecutive (6 male) patients diagnosed as having SREAT from 1995 to 2003.

Main Outcome Measures: Clinical features and ancillary test findings associated with SREAT.

Results: The median age at disease onset was 56 years (range, 27-84 years). The most frequent clinical features were tremor in 16 (80%), transient aphasia in 16 (80%), myoclonus in 13 (65%), gait ataxia in 13 (65%), seizures in 12 (60%), and sleep abnormalities in 11 (55%). All patients were assigned an alternative misdiagnosis at presentation, most commonly viral encephalitis (n=5), Creutzfeldt-Jakob disease (n=3), or a degenerative dementia (n=4). The most frequent laboratory abnormalities were increased liver enzyme levels in 11, increased serum sensitive thyroid-stimulating hormone levels in 11, and increased erythrocyte sedimentation rate in 5. In only 5 patients (25%) did cerebrospinal fluid abnormalities suggest an inflammatory process. Magnetic resonance imaging abnormalities believed to be related to the encephalopathy were present in 5 patients (26%).

Conclusions: The clinical, laboratory, and radiologic findings associated with SREAT are more varied than previously reported. Misdiagnosis at presentation is common. This treatable syndrome should be considered even if the serum sensitive thyroid-stimulating hormone level and erythrocyte sedimentation rate are normal, the cerebrospinal fluid profile does not suggest an inflammatory process, and neuroimaging results are normal. Until the pathophysiologic mechanism of this and other autoimmune encephalopathies is better characterized, we believe that descriptive terms that reflect an association rather than causation are most appropriate for this syndrome.

Arch Neurol. 2006;63:197-202
ports, small series, and an excellent recent literature review have characterized this entity further. Nevertheless, many uncertainties regarding the condition persist, including the spectrum of clinical findings, the associated laboratory and radiologic findings, the clinical significance of the quantitative level of TPO antibody, the criteria required for diagnosis, the appropriate terms for the condition, and the typical outcome of steroid treatment. The literature thus far has not provided sufficient data on these challenging issues to aid the diagnosis of this disorder and guide its management. We sought to address some of these issues by analyzing data on a series of patients in whom the diagnosis of SREAT was made at Mayo Clinic Rochester (in Minnesota) and Mayo Clinic Scottsdale (in Arizona) during an 8-year period.

This retrospective study was reviewed and approved by the Mayo Clinic institutional review board. The authors identified consecutive patients in whom a diagnosis of SREAT was made at Mayo Clinic Rochester or Mayo Clinic Scottsdale between November 1995 and July 2003. For the purpose of this study, the diagnosis of SREAT required fulfillment of the following criteria: (1) encephalopathy manifested by cognitive impairment and 1 or more of the following: neuropsychiatric features (eg, hallucinations, delusions, or paranoia), myoclonus, generalized tonic-clonic or partial seizures, or focal neurologic deficits; (2) presence of serum thyroid antibody (TPO or microsomal); (3) euthyroid status (serum sensitive thyroid-stimulating hormone [TSH], 0.3-5.0 mIU/L) or mild hypothyroidism (serum sensitive TSH, 5.1-20.0 mIU/L) that would not account for encephalopathy; (4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process; (5) no serologic evidence of the neuronal voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis; (6) no findings on neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy; and (7) complete or near-complete return to the patient’s neurologic baseline status following corticosteroid treatment. This last criterion was specifically required because our primary aim was to identify patients who responded to treatment and then characterize their clinical, laboratory, and radiologic features. These criteria are similar to those previously published, except that we required the absence of voltage-gated calcium and potassium channels and other paraneoplastic autoantibodies for inclusion in this analysis.

We retrospectively reviewed and analyzed all available clinical, laboratory, radiologic, and brain biopsy data to determine the spectrum of features and findings associated with SREAT. A review of patients evaluated at our institution before 1996 has been published, which includes 2 of the cases in this study.7 A review of the EEG findings in SREAT, which included 15 patients in this study, has also been published.12 The current article expands on the report in abstract form of 17 patients in our original data set.8

During this same approximately 8-year period, we treated additional patients who fulfilled the same criteria described in this article, except that no significant improvement occurred following high-dose corticosteroid treatment (ie, steroid-unresponsive encephalopathy associated with autoimmune encephalopathy). We present data on these patients and argue that they likely have a nonautoimmune or noninflammatory origin for their encephalopathy.

### RESULTS

#### DEMOGRAPHIC AND CLINICAL FINDINGS

Twenty patients met criteria for the diagnosis of SREAT as noted herein. The symptoms and findings for the 20 patients are given in Table 1. All but 1 patient required hospitalization during the acute phase of illness because of the severity of their deficits. The median age at onset was 56 years (range, 27-84 years). There was a preponderance of female patients (70%). The most common associated manifestations were behavioral-cognitive abnormalities (by definition) in 20 (100%), tremor in 16 (80%), transient aphasia in 16 (80%), myoclonus in 13 (65%), gait ataxia in 13 (65%), seizures in 12 (60%), and sleep abnormalities in 11 (55%). The initial clinical diagnoses are given in Table 2. Misdiagnoses were common. The most frequent misdiagnoses were viral encephalitis, Creutzfeldt-Jakob disease, and degenerative dementia.

Nine patients had a history of hypothyroidism that antedated the onset of neurologic symptoms, and 2 had euthyroid goiter. Five additional patients developed hypothyroidism after the resolution of encephalopathy. Other

### METHODS

This retrospective study was reviewed and approved by the Mayo Clinic institutional review board. The authors identified consecutive patients in whom a diagnosis of SREAT was made at Mayo Clinic Rochester or Mayo Clinic Scottsdale between November 1995 and July 2003. For the purpose of this study, the diagnosis of SREAT required fulfillment of the following criteria: (1) encephalopathy manifested by cognitive impairment and 1 or more of the following: neuropsychiatric features (eg, hallucinations, delusions, or paranoia), myoclonus, generalized tonic-clonic or partial seizures, or focal neurologic deficits; (2) presence of serum thyroid antibody (TPO or microsomal); (3) euthyroid status (serum sensitive thyroid-stimulating hormone [TSH], 0.3-5.0 mIU/L) or mild hypothyroidism (serum sensitive TSH, 5.1-20.0 mIU/L) that would not account for encephalopathy; (4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process; (5) no serologic evidence of the neuronal voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis; (6) no findings on neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy; and (7) complete or near-complete return to the patient’s neurologic baseline status following corticosteroid treatment. This last criterion was specifically required because our primary aim was to identify patients who responded to treatment and then characterize their clinical, laboratory, and radiologic features. These criteria are similar to those previously published, except that we required the absence of voltage-gated calcium and potassium channels and other paraneoplastic autoantibodies for inclusion in this analysis.

We retrospectively reviewed and analyzed all available clinical, laboratory, radiologic, and brain biopsy data to determine the spectrum of features and findings associated with SREAT. A review of patients evaluated at our institution before 1996 has been published, which includes 2 of the cases in this study.7 A review of the EEG findings in SREAT, which included 15 patients in this study, has also been published.12 The current article expands on the report in abstract form of 17 patients in our original data set.8

During this same approximately 8-year period, we treated additional patients who fulfilled the same criteria described in this article, except that no significant improvement occurred following high-dose corticosteroid treatment (ie, steroid-unresponsive encephalopathy associated with autoimmune encephalopathy). We present data on these patients and argue that they likely have a nonautoimmune or noninflammatory origin for their encephalopathy.

### METHODS

This retrospective study was reviewed and approved by the Mayo Clinic institutional review board. The authors identified consecutive patients in whom a diagnosis of SREAT was made at Mayo Clinic Rochester or Mayo Clinic Scottsdale between November 1995 and July 2003. For the purpose of this study, the diagnosis of SREAT required fulfillment of the following criteria: (1) encephalopathy manifested by cognitive impairment and 1 or more of the following: neuropsychiatric features (eg, hallucinations, delusions, or paranoia), myoclonus, generalized tonic-clonic or partial seizures, or focal neurologic deficits; (2) presence of serum thyroid antibody (TPO or microsomal); (3) euthyroid status (serum sensitive thyroid-stimulating hormone [TSH], 0.3-5.0 mIU/L) or mild hypothyroidism (serum sensitive TSH, 5.1-20.0 mIU/L) that would not account for encephalopathy; (4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process; (5) no serologic evidence of the neuronal voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis; (6) no findings on neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy; and (7) complete or near-complete return to the patient’s neurologic baseline status following corticosteroid treatment. This last criterion was specifically required because our primary aim was to identify patients who responded to treatment and then characterize their clinical, laboratory, and radiologic features. These criteria are similar to those previously published, except that we required the absence of voltage-gated calcium and potassium channels and other paraneoplastic autoantibodies for inclusion in this analysis.

We retrospectively reviewed and analyzed all available clinical, laboratory, radiologic, and brain biopsy data to determine the spectrum of features and findings associated with SREAT. A review of patients evaluated at our institution before 1996 has been published, which includes 2 of the cases in this study.7 A review of the EEG findings in SREAT, which included 15 patients in this study, has also been published.12 The current article expands on the report in abstract form of 17 patients in our original data set.8

During this same approximately 8-year period, we treated additional patients who fulfilled the same criteria described in this article, except that no significant improvement occurred following high-dose corticosteroid treatment (ie, steroid-unresponsive encephalopathy associated with autoimmune encephalopathy). We present data on these patients and argue that they likely have a nonautoimmune or noninflammatory origin for their encephalopathy.

### METHODS

This retrospective study was reviewed and approved by the Mayo Clinic institutional review board. The authors identified consecutive patients in whom a diagnosis of SREAT was made at Mayo Clinic Rochester or Mayo Clinic Scottsdale between November 1995 and July 2003. For the purpose of this study, the diagnosis of SREAT required fulfillment of the following criteria: (1) encephalopathy manifested by cognitive impairment and 1 or more of the following: neuropsychiatric features (eg, hallucinations, delusions, or paranoia), myoclonus, generalized tonic-clonic or partial seizures, or focal neurologic deficits; (2) presence of serum thyroid antibody (TPO or microsomal); (3) euthyroid status (serum sensitive thyroid-stimulating hormone [TSH], 0.3-5.0 mIU/L) or mild hypothyroidism (serum sensitive TSH, 5.1-20.0 mIU/L) that would not account for encephalopathy; (4) no evidence in blood, urine, or CSF analyses of an infectious, toxic, metabolic, or neoplastic process; (5) no serologic evidence of the neuronal voltage-gated calcium channel, voltage-gated potassium channel, or other currently recognized paraneoplastic autoantibodies to indicate another diagnosis; (6) no findings on neuroimaging studies indicating vascular, neoplastic, or other structural lesions to explain the encephalopathy; and (7) complete or near-complete return to the patient’s neurologic baseline status following corticosteroid treatment. This last criterion was specifically required because our primary aim was to identify patients who responded to treatment and then characterize their clinical, laboratory, and radiologic features. These criteria are similar to those previously published, except that we required the absence of voltage-gated calcium and potassium channels and other paraneoplastic autoantibodies for inclusion in this analysis.

We retrospectively reviewed and analyzed all available clinical, laboratory, radiologic, and brain biopsy data to determine the spectrum of features and findings associated with SREAT. A review of patients evaluated at our institution before 1996 has been published, which includes 2 of the cases in this study.7 A review of the EEG findings in SREAT, which included 15 patients in this study, has also been published.12 The current article expands on the report in abstract form of 17 patients in our original data set.8

During this same approximately 8-year period, we treated additional patients who fulfilled the same criteria described in this article, except that no significant improvement occurred following high-dose corticosteroid treatment (ie, steroid-unresponsive encephalopathy associated with autoimmune encephalopathy). We present data on these patients and argue that they likely have a nonautoimmune or noninflammatory origin for their encephalopathy.
autoimmune disorders were present in 6 patients and included diabetes mellitus type 1 in 2 (10%), systemic lupus erythematosus in 1 (5%), and Crohn disease in 1 (5%). Two patients had symptoms of sicca syndrome (10%). Other autoimmune disorders were diagnosed subsequently in 2 patients, primary Sjögren syndrome in one (5%) and pernicious anemia in the other (5%). Subacute combined degeneration developed in the latter case before the diagnosis of pernicious anemia was made. Five patients (25%) had a family history of non–organ-specific (rheumatologic) or organ-specific autoimmune disease.

**BLOOD AND SEROLOGIC ABNORMALITIES**

Pertinent laboratory findings are given in Table 3. The serum sensitive TSH level was mildly elevated in 11 (55%). By definition, all patients had thyroid antibodies. The microsomal antibody titer was elevated in 7 of 7 tested (median, 1,6400; range, 1,400 to 1,102 400; reference range, <1:100), and the TPO antibody titer was elevated in 13 of 13 tested (median, 250 IU/mL; range, 65-4830 IU/mL; reference range, <20 IU/mL). All patients experienced a marked degree of encephalopathy, and the levels of thyroid antibodies did not correlate with the severity of neurologic deficits. Eleven patients had mild thyroid failure (serum sensitive TSH, 5.1-15.6 mIU/L). Erythrocyte sedimentation rate was mildly to moderately elevated (median, 38 mm/h; range, 30-75 mm/h) in 5 (26%) of 19 tested. The C-reactive protein level was elevated in 3 of 9 patients tested. Eleven patients (55%) had a mild elevation of serum aminotransferase levels.

**CSF FINDINGS**

The CSF was analyzed in all patients. No infectious origins were identified (Table 4). The protein level was elevated in 17 patients (85%) (range, 55-680 mg/dL [0.055-0.68 g/dL]; reference range, <45 mg/dL [<0.045 g/dL]). Neuron-specific enolase and 14-3-3 protein levels were normal in 6 patients tested. Five had mild lymphocytic pleocytosis (white blood cell count, 5-30 cells/µL). The CSF IgG index was normal in all of 14 tested, and the CSF IgG synthesis rate was elevated in 2.

**EEG FINDINGS**

All patients underwent EEG studies, of which 19 results were abnormal. Generalized slowing was seen in 19 patients. Other findings included focal slowing, triphasic waves, epileptiform abnormalities, and photomyogenic response. One patient had a normal routine EEG result. Steroid therapy was associated with improvement or resolution of EEG abnormalities in all 17 patients who had EEG follow-up.

**MRI FINDINGS**

Cranial MRI was performed in 19 patients (1 patient had a permanent pacemaker). Fourteen patients (74%) had normal imaging results or nonspecific white matter abnormalities consistent with age. Four patients had a diffuse increased signal on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images in the cerebral white matter, and 1 MRI showed extensive dural enhancement. Following corticosteroid therapy, the MRI findings normalized in the 4 cases with white matter signal changes (as exemplified in the study by Bohnen et al12); meningeal enhancement has persisted for throughout 5 years in the other patient.

**CEREBRAL ANGIOGRAPHY**

Cerebral angiography was performed in 5 patients to look for evidence of vasculitis. Findings were normal in each case except for 1, which showed a nonspecific slow transit time in the distribution of the anterior cerebral artery.

**MENINGEAL OR BRAIN BIOPSY**

Meningeal or brain biopsy was performed in 2 cases. Histologic findings were entirely normal in the 1 patient with striking meningeal thickening and dural enhancement on MRI. In another patient with diffuse white matter signal changes on imaging, histologic findings included patchy myelin pallor, scant perivascular chronic inflammation, mild gliosis, and microglial activation.

**THERAPY**

By definition, marked clinical improvement was seen in all patients following high-dose corticosteroid therapy, in which 15 returned to their normal neurologic baseline status and 5 had mild residual symptoms, which included tremor in 1, gait impairment in 1, mild forgetfulness in 1, mild forget-
fulness and tremor in 1, and mild forgetfulness and gait impairment in 1. Intravenous methylprednisolone, 1 g/d for 5 days, was used in 17 patients followed by a course of oral steroids in 6 patients. Oral prednisone, 60-100 mg/d for 10 to 30 days, was used in 3 patients. Eight patients (40%) were able to discontinue the use of steroids after initial treatment and had no relapses. Three required treatment of relapses with additional short courses of intravenous methylprednisolone, and 9 patients required continuous treatment with oral steroids or with other immunomodulatory therapy to maintain remission. These other therapies included azathioprine (n = 3), methotrexate (n = 2), cyclophosphamide (n = 1), and intravenous immunoglobulin (n = 1). Thyroid hormone therapy was initiated in patients with laboratory evidence of hypothyroidism, but neurologic improvement did not correlate with thyroid hormone therapy.

**STEROID NONRESPONDERS**

Data on 12 patients with a subacute encephalopathy associated with autoimmune thyroiditis who failed to improve with high-dose corticosteroids are given in Table 5. All of these patients fulfilled criteria 1 through 6 as stated in the "Methods" section. The 2 patients with autopsy-proven Creutzfeldt-Jakob disease (cases 1 and 2) and case 5 had an increased signal in the cerebral cortical ribbon on FLAIR-positive and FLAIR-negative diffusion-weighted images and increased neuron-specific enolase or 14-3-3 protein levels; thus, these patients were suspected to have Creutzfeldt-Jakob disease ante mortem. However, because of our experience with another patient with an increased signal in the cortical ribbon on FLAIR images who responded to corticosteroids (B.B., unpublished data, 1997) and the report of increased 14-3-3 protein levels in other patients diagnosed as having Hashimoto encephalopathy who responded to steroids, we treated these 3 patients with steroids in the unlikely but possible event that an autoimmune or inflammatory mechanism was the cause of their illness. The patient with autopsy-proven Lewy body disease had a history of dream enactment behavior that was highly suggestive of rapid eye movement (REM) sleep behavior disorder and thus of underlying Lewy body disease, but the markedly elevated thyroid microsomal antibody titer led the physicians involved in his care to diagnose him as having probable Hashimoto encephalopathy and to treat him with steroids. The patient with neurofilament inclusion body disease had clinical and radiologic features typical of frontotemporal dementia, but the markedly elevated thyroid microsomal antibody titer led the physicians involved in his care to diagnose him as having probable Hashimoto encephalopathy and to treat him with steroids. The patient with neurofilament inclusion body disease had clinical and radiologic features typical of frontotemporal dementia, but the markedly elevated thyroid microsomal antibody titer led the physicians involved in his care to diagnose him as having probable Hashimoto encephalopathy and to treat him with steroids. The patient with neurofilament inclusion body disease had clinical and radiologic features typical of frontotemporal dementia, but the markedly elevated thyroid microsomal antibody titer led the physicians involved in his care to diagnose him as having probable Hashimoto encephalopathy and to treat him with steroids.

### Table 5. Data From 12 Patients With Subacute Encephalopathy Associated With Autoimmune Thyroiditis Who Experienced No Significant Clinical Improvement Following High-Dose Corticosteroid Treatment

<table>
<thead>
<tr>
<th>Patient No./Sex/ Age, y</th>
<th>Antibody*</th>
<th>Treatment</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/M/67</td>
<td>TM, 1:400</td>
<td>Methylprednisolone, 1 g intravenously for 3 d, then prednisone, 60 mg orally with gradual taper</td>
<td>No improvement, progressive encephalopathy with death 1 y later; autopsy showed CJD</td>
</tr>
<tr>
<td>2/F/72</td>
<td>TPO, 170</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, progressive encephalopathy with death 8 mo later; autopsy showed CJD</td>
</tr>
<tr>
<td>3/M/75</td>
<td>TM, 1:102 400</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, progressive encephalopathy with death 1 y later; autopsy showed nLBD</td>
</tr>
<tr>
<td>4/F/53</td>
<td>TM, 1:25 600</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, progressive encephalopathy with death 2 y later; autopsy showed nLBD</td>
</tr>
<tr>
<td>5/F/56</td>
<td>TPO, 723</td>
<td>Methylprednisolone, 1 g intravenously for 3 d</td>
<td>No improvement during 3 d of therapy, transferred to local hospice care with death 5 d later; no autopsy performed</td>
</tr>
<tr>
<td>6/M/72</td>
<td>TM, 1:400; TG+</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, progressive encephalopathy with death 5 y later; no autopsy performed</td>
</tr>
<tr>
<td>7/F/85</td>
<td>TPO, 184</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, progressive encephalopathy during following 4 y</td>
</tr>
<tr>
<td>8/F/28</td>
<td>TPO, 25; TG+</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, fluctuating encephalopathy during the following 1 y</td>
</tr>
<tr>
<td>9/F/66</td>
<td>TPO, 1150</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement, static encephalopathy during the following 2 y</td>
</tr>
<tr>
<td>10/M/71</td>
<td>TG+</td>
<td>Prednisone, 60 mg for 30 d, with taper</td>
<td>No improvement, progressive encephalopathy during the following 2 y</td>
</tr>
<tr>
<td>11/F/73</td>
<td>TPO, 1031</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement during subsequent 3 mo, lost to follow-up</td>
</tr>
<tr>
<td>12/F/78</td>
<td>TPO, 114</td>
<td>Methylprednisolone, 1 g intravenously for 5 d</td>
<td>No improvement; progressive encephalopathy during the following 1 y</td>
</tr>
</tbody>
</table>

Abbreviations: CJD, Creutzfeldt-Jakob disease; NIBD, neurofilament inclusion body disease; nLBD, neocortical-predominant Lewy body disease; TG+, thyroglobulin antibody positive, TM, thyroid microsomal antibody titer; TPO, thyroperoxidase antibody level.

*The reference ranges in Mayo Medical Laboratories (Rochester, Minn, and Scottsdale, Ariz) at the time the samples were analyzed were as follows: TM, less than 1:100; TPO, less than 20 IU/mL; and TG, negative.
This large series of patients provides an additional characterization of SREAT and should aid in improving recognition of patients in whom to consider instituting therapy. The clinical findings are varied but consistent with those reported previously.11 Cognitive impairment and behavioral changes are the defining characteristics of any encephalopathy. Other features that characterize SREAT include fluctuating symptoms, tremor, myoclonus, transient aphasia, sleep abnormalities, seizures, and gait difficulties. Headache, neuropsychiatric features, and lateralized motor or sensory deficits were present in a few cases. Given the nonspecific nature of the neurologic and laboratory findings, and the age at onset spanning several decades, it is not surprising that alternative initial diagnoses were considered in all of our patients. Notably, disorders such as Creutzfeldt-Jakob disease, Alzheimer disease, and dementia with Lewy bodies were suspected in many cases, underscoring the need to consider autoimmune encephalopathy even in those with features that suggest irreversible prion and degenerative disorders.

The levels of thyroid antibodies were variable. All patients were encephalopathic, but antibody levels did not correspond to the severity of the clinical deficits. The presence of thyroid antibodies in serum, not the level, was the clinically relevant issue, indicating that SREAT should be considered in patients with encephalopathy even if thyroid antibody levels are only mildly elevated. Furthermore, SREAT should be considered in patients with encephalopathy regardless of whether they are euthyroid or mildly hypothyroid.

As has long been recognized for patients with autoimmune thyroid disease, multiple other autoimmune disorders commonly coexist.4,5,18-21 One third of our patients had evidence of multiple autoimmune disorders. The finding of elevated serum levels of liver aminotransferases in 60% of our cases was not anticipated. Whether the elevated liver enzyme levels represent a forme fruste of autoimmune hepatitis or some other process is not clear, but this finding warrants further investigation.

The finding of elevated CSF protein levels in most of our patients is consistent with prior reports.8,11,22 However, it is important to recognize that normal CSF protein levels, absence of lymphocytic pleocytosis, normal IgG synthesis rate, and absence of oligoclonal bands do not exclude the diagnosis of SREAT.

The MRI abnormalities found in some of our patients were consistent with an active encephalopathic process, including diffuse white matter signal abnormalities and meningeal enhancement. In several patients these abnormalities resolved following steroid therapy, a phenomenon that has been reported previously.13 Most patients with the diagnosis of SREAT had normal neuroimaging results, including normal cerebral angiography findings. These imaging characteristics are different from the striking mesial temporal lobe abnormalities encountered in subacute inflammatory autoimmune or paraneoplastic limbic encephalitis.12,14

Although the data in this study may improve the recognition of potential patients with SREAT, the underlying pathogenesis remains unclear. The putative role of thyroid autoimmunity in the pathogenesis of Hashimoto encephalopathy is complicated by the fact that serum TPO levels are elevated in approximately 10% of healthy adults, and the prevalence of individuals with elevated TPO levels increases with increasing age.23 Thyroid autoantibodies are also commonly found in patients with other autoimmune neurologic disorders, including paraneoplastic and nonparaneoplastic limbic encephalitis.7 It therefore seems unlikely that thyroid antibodies are the direct cause of the encephalopathy. We consider TPO antibody 1 of several related thyroid and gastric autoantibody markers of neurologic autoimmunity.

Several other etiologies have been proposed, including hypothryoidism itself, humoral factors, antigen-antibody complexes, overt vasculitis, intrathecal thyroid antibodies, and global cerebral hypoperfusion.11,24-27 It is certainly possible that more than 1 etiologic mechanism could lead to an autoimmune or inflammatory encephalopathy that responds to corticosteroids. Systematic studies of patients with encephalopathy, which could include a battery of serum and CSF autoimmune markers or other radiologic studies, may offer insights into the pathogenetic mechanisms.

The nomenclature in the autoimmune encephalopathies remains confusing. Encephalopathy, steroid responsiveness, and evidence of autoimmunity in the serum and CSF are common to most forms of autoimmune meningoencephalopathy, including Sjögren syndrome,29 systemic lupus erythematosus,29 and cerebellitis associated with glutamic acid decarboxylase autoantibody.23 The term nonvasculitic autoimmune inflammatory meningoencephalitis has been suggested to facilitate the recognition and treatment of the autoimmune encephalopathies with similar clinical features.30 In our view, the term Hashimoto encephalopathy implies that the encephalopathy is caused by Hashimoto thyroiditis, but as noted in this article, no conclusive evidence of this exists. We therefore propose the term nonvasculitic autoimmune inflammatory meningoencephalitis as the most appropriate term for encompassing all subtypes of steroid-responsive encephalopathies of nonvasculitic origin and favor the terms steroid-responsive encephalopathy associated with autoimmune thyroiditis5 or steroid-responsive encephalopathy associated with Hashimoto thyroiditis41 for the subtype of nonvasculitic autoimmune inflammatory meningoencephalitis described in this report. Debate over the nomenclature will likely continue until the precise autoimmune or inflammatory processes are identified and proved to be pathogenic.

Some may argue with our use of the term steroid-responsive in describing this entity, in which the response to a treatment defines the entity of interest. Although we recognize the inherent circularity of defining a syndrome based on response to treatment (as could also be argued regarding the utility of levodopa responsiveness in diagnosing Parkinson disease), we conceded to the considerable practical utility of emphasizing steroid responsiveness that we hope will improve the diagnosis and therapy of encephalopathic patients. We hypothesize that patients with an encephalopathy associated with thyroid antibodies who do not markedly improve with corticosteroids represent those with a nonautoimmune or noninflammatory disorder, and our 4 patients who underwent autopsy and who did not respond to high-dose corticosteroids support this contention. We suspect that most of the other nonresponders in Table 5, and most others who do not respond
to corticosteroids, have an underlying neurodegenerative or prion disorder. The issue for physicians who evaluate patients with a subacute encephalopathy associated with autoimmune thyroiditis is whether corticosteroid therapy is justified. Given the fact that the alternative diagnoses, such as Creutzfeldt-Jakob disease or a neurodegenerative disorder, can be incurable, a corticosteroid trial may be warranted in appropriate patients. Perhaps certain features or findings may predict which patients will and will not respond to corticosteroids, and this important issue is certainly worthy of further study.

We acknowledge several limitations of this study. Because of the retrospective nature of this clinical series, not all patients underwent the same tests and evaluations. Our data should not be viewed as inclusive of all patients with SREAT at our institution during an 8-year period. In addition, the data should not be viewed as showing the entire spectrum of neurologic and laboratory findings associated with SREAT. In this period of study, numerous patients seen at our institution with a steroid-responsive encephalopathy were not tested for thyroid autoimmunity and therefore would not have been identified for inclusion in our analysis. However, we hope that our findings improve the recognition of patients who may have an autoimmune or inflammatory mechanism underlying their encephalopathy, as well as stimulate further research into SREAT and other forms of nonvascular autoimmune inflammatory meningoencephalitis.

Accepted for Publication: May 24, 2005.

Correspondence: Brad Boeve, MD, Mayo Clinic, 200 First St SW, Rochester, MN 55905.

Author Contributions: Study concept and design: Castillo, Mokri, and Boeve. Acquisition of data: Castillo, Vernino, Lucchinetti, Aksamit, Carter, Sirven, Hunder, Mokri, Drubach, Lennon, and Boeve. Analysis and interpretation of data: Woodruff, Caselli, Vernino, Swanson, Noseworthy, Carter, Fatourechi, Drubach, Pittocck, Lennon, and Boeve. Drafting of the manuscript: Castillo, Woodruff, Vernino, Noseworthy, Lennon, and Boeve. Critical revision of the manuscript for important intellectual content: Caselli, Vernino, Lucchinetti, Swanson, Aksamit, Carter, Sirven, Hunder, Fatourechi, Mokri, Drubach, Pittocck, Lennon, and Boeve. Obtained funding: Boeve. Administrative, technical, and material support: Sirven, Fatourechi, Mokri, Drubach, Pittocck, and Lennon. Study supervision: Vernino, Noseworthy, Aksamit, Fatourechi, Lennon, and Boeve.

Funding/Support: This study was supported in part by the Robert H. and Clarice Smith and Abigail Van Buren Alzheimer’s Disease Research Program of the Mayo Foundation, Rochester, Minn, and grant P50 AG16574 from the National Institute on Aging, Bethesda, Md.

References


