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Steroid-responsive Encephalopathy Subsequently Associated with Alzheimer Disease Pathology: A Case Series

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Abstract

Background—Steroid-responsive encephalopathies can be considered vasculitic or nonvasculitic. Clinicopathological studies of nonvasculitic steroid-responsive encephalopathy are unusual, but can explain the range of diagnoses consistent with a steroid responsive presentation in life.

Objective—To extend the range of clinical features and pathological findings consistent with steroid-responsive encephalopathy.

Design, Methods, and Patients—A clinicopathological case series of four patients (ages 54–71 years, 2 women) with steroid-responsive encephalopathy followed at this institution until the time of death.

Results—Clinical features were suggestive of Creutzfeldt-Jakob disease, dementia with Lewy Bodies, and parkinsonism, but pathological examination revealed only Alzheimer's Disease-related findings without evidence of Lewy bodies or prion disease in all cases. All patients demonstrated marked, sustained improvement following steroid treatment, based on clinical, magnetic resonance imaging, and/or electroencephalogram studies. Alzheimer's Disease was not diagnosed in life due to a lack of hippocampal atrophy on brain imaging and a dramatic symptomatic response to steroids.

Conclusions—Steroid-responsive encephalopathy is the clinical presentation of some patients with Alzheimer's Disease related pathology at autopsy, and can be consistent with the clinical diagnoses of parkinsonism, dementia with Lewy Bodies, or Creutzfeldt-Jakob Disease in life.

Keywords

Alzheimer's Disease; corticosteroids; dementia; encephalopathy; Hashimoto's encephalopathy; neuropathology

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Introduction

There is growing interest and awareness of the steroid-responsive encephalopathies and the potential treatment benefit that can occur in some patients with these disorders. The pathological findings among patients with steroid-responsive encephalopathies are often unknown to treating clinicians because the condition improves with available treatment. The underlying causes are multiple and can include both vasculitic and non-vasculitic etiologies. In the case of non-vasculitic causes, the additional lack of a pathogen-specific antibody may raise the possibility of nonvasculitic autoimmune meningoencephalopathy or NAIM (Table 1).

Clues to the diagnosis of NAIM include an acute or subacute onset, presence of headache, seizures, or status epilepticus, clinical and/or laboratory evidence of autoimmunity, evidence of inflammation on cerebrospinal fluid (CSF) examination, marked abnormalities on electroencephalography (EEG), or some combination of these.^{1,2} In many instances, however, the diagnosis of NAIM is considered only after structural, infectious, paraneoplastic, toxic, and metabolic etiologies have been excluded. High dose corticosteroid treatment often results in complete or near complete resolution of all neurologic signs, symptoms, and EEG abnormalities.³ Diagnosis of nonvasculitic steroid-responsive encephalopathies can be particularly challenging in individuals who have a rapidly progressive course accompanied by myoclonus, therefore suggesting Creutzfeldt-Jacob disease (CJD); in older individuals with fluctuations in alertness and cognition, accompanied by visual hallucinations and/or parkinsonism, therefore suggesting dementia with Lewy bodies (DLB); and in those with a relatively young age of onset and prominent behavioral changes and psychosis, therefore suggesting schizophrenia or frontotemporal dementia (FTD). If cerebral angiography reveals findings suggestive of primary central nervous system vasculitis (PCNSV) a trial of high doses corticosteroids, and in some patients, cyclophosphamide administration is warranted. Meningeal/brain biopsy is often considered, but is only rarely performed. In the absence of tissue confirmation, another way to potentially differentiate NAIM from a neurodegenerative, prion, or psychotic disorder is to empirically treat with high-dose corticosteroids, as dramatic clinical improvement would be expected with NAIM but not the other conditions.

Little histopathologic data exist on the steroid-responsive encephalopathies, and the findings have been variable. Most cases associated with TPO or antithyroglobulin antibodies (often termed “Hashimoto’s encephalopathy”) have had perivascular inflammation involving veins and venules,^{4,5} with only a few cases showing true vasculitis involving arteries and arterioles.^{6,7} In some instances, no distinctive abnormalities have been seen in the meninges or brain parenchyma.^{8–10} Brain biopsies in cases with NAIM associated with Sjögren’s syndrome have shown perivascular inflammation without true vasculitis,^{1,11,12} and one case of NAIM lacking autoantibodies had panencephalitis at autopsy.¹³ Neuropsychiatric lupus may also present with striking MRI findings without evidence of inflammation at autopsy.¹⁴

One of the case reports noted above involved a 77-year-old woman with hypokinesia and rigidity leading to a diagnosis of Parkinson’s disease (PD).⁴ At autopsy, leptomeningeal lymphocytic infiltrates were identified in venules with sparse senile plaques and neurofibrillary tangles. The density was too minimal to warrant the pathologic diagnosis of Alzheimer’s disease, and vascular amyloid, nigral degeneration, and Lewy bodies were all absent.⁴ This is the only published case, to our knowledge, with NAIM who clearly improved with corticosteroids, had other clinical features suggesting PD, and who subsequently had Alzheimer-type changes upon histological examination.

We have recently encountered four patients who experienced a steroid-responsive encephalopathy in which autopsy revealed Alzheimer's disease-related pathology and/or A β -related amyloid deposition in the walls of the small cerebral vessels. All were followed longitudinally with a clinically typical course for steroid-responsive encephalopathy and possibly NAIM, yet autopsy revealed Alzheimer's disease pathology. Inflammatory changes in the meninges, brain parenchyma, and intracranial vessels were absent, and three of these cases exhibited varying degrees of parkinsonism prior to death. Due to the uncertain relationship between a frank autoimmune inflammatory encephalopathy and Alzheimer's disease (in which inflammatory mechanisms are regarded as integral to the degenerative cascade), we present these cases in the context of the available pertinent literature.

Case Series

Case 1

A 70-year-old woman had a 5-month history of confusion, cognitive decline, hypersomnolence, new-onset bi-frontal headaches, word blocking, emotional lability, and intermittent dysnomia. She could no longer balance her checkbook or drive her car. Her family described her movements as "slow." She had treated hypothyroidism.

Examination revealed constructional apraxia and attentional difficulties (unable to repeat more than 5 numeric digits) with relatively preserved delayed recall. Her upgaze was diminished. There was subtle unilateral decreased arm swing and increased tone. The initial clinical impression was possible DLB. While she met criteria for clinically probable DLB,¹⁵ a non-neurodegenerative cause was suspected based on the short course and prominent headaches.

Investigations revealed a sedimentation rate of 39 mm/1hr, thyroid stimulating hormone (TSH) mildly elevated at 5.8 mIU/L, and thyroid peroxidase (TPO) antibodies elevated at 90 IU/mL (Table 2). Lyme serology, RPR, paraneoplastic panel, and other infectious studies were negative. MRI showed parenchymal changes in the right frontal and left occipital regions (Figure 1A,B) with diffuse pial enhancement with gadolinium. Cerebral angiogram was normal. No significant hippocampal atrophy was evident on subsequent MRI scans (Figure 1C); meningeal/brain biopsy was declined.

Although the abnormalities seen on neuroimaging were viewed as atypical for NAIM, a diagnosis of possible NAIM led to methylprednisolone (IVMP) treatment. One week after completion, she returned to her cognitive baseline, and the headaches and hypersomnolence resolved. One month later, the MRI showed resolution of the parenchymal and meningeal abnormalities (Figure 1D,E). She was followed annually with clinical examinations, neuropsychological assessments, and MRI scans of the brain (not shown), and was functionally independent for the next four years, never requiring additional corticosteroids. Throughout this time, her diagnosis was mild cognitive impairment plus mild parkinsonism, not significant enough to warrant cholinesterase inhibitor or dopaminergic therapy. Multiple microhemorrhagic foci and left frontal superficial siderosis were noted in the gradient recalled echo sequence. (Figure 1F).

Four years after initial presentation, she experienced a subtle decline in cognition over five months, then several TIA-like spells over three days, and died suddenly due to a massive cerebral hemorrhage. Autopsy revealed diffuse amyloid angiopathy in the leptomeningeal and parenchymal arterioles, moderate neocortical neuritic plaques, and moderate neurofibrillary tangles in the temporal limbic and neocortical structures (Braak stage V), satisfying NIA-Reagan criteria for high likelihood AD. No evidence of vasculitis or inflammation was present. There were no Lewy bodies or Lewy neurites.

Case 2

A 54-year-old former business executive presented with 4 years of progressive hypersomnolence, reclusiveness, and cognitive deficits, marked by prominent memory loss. Her family first noted this change following cosmetic face-lift surgery, when she became unable to recall names and lists. She was easily disoriented, forgot conversations, misplaced objects, and wrote checks for incorrect amounts. Eventually, she was unable to turn on her computer or recognize previously familiar people. A three-month course of donepezil did not lead to improvement.

She had flat affect, hypoproductive speech, mild left upper extremity cogwheeling, and difficulty with every basic task of mental status testing (9/38 on the Kokmen Test of Mental Status (KTMS),¹⁶ 5/30 on the Mini-Mental State Examination (MMSE)).

Autoantibodies were elevated (Table 2). Brain MRI showed moderate atrophy primarily involving the left frontal and posterior temporoparietal cortices without significant hippocampal atrophy (Figure 2). There was severely reduced uptake in the left frontal, temporal, and parietal cortices on single photon emission computed tomography (SPECT).

Given her persistent symptoms, combined with a high suspicion of an autoimmune encephalopathy, she received a trial of dexamethasone. On day 5, her speech was clearer, with less word searching (MMSE 20/30). Her husband remarked on her improved memory and volition, reduced abulia, and lack of word-finding difficulties. She returned home, independent in many but not all activities of daily living (ADLs). Her neuropsychiatric features were almost nonexistent.

Three months later, she had insidious cognitive decline, with need for repeat inpatient psychiatric hospitalization by six months. She was nearly dependent for all ADLs due to profound memory loss and disorganization. She became seclusive, tearful, agitated, depressed, and expressed suicidal plans. Clonazepam and escitalopram were tried without noticeable benefit. ANA, ENA, and U1RNP remained elevated. Cerebral angiogram and CSF analysis was normal. Dexamethasone for five days and then oral prednisone was given. She became more calm and cooperative, but required quetiapine thrice daily and lorazepam, each evening, for agitation. She was dismissed on oral prednisone 60mg daily.

Three months later, she rapidly declined, experiencing medication-refractory seizures, and died despite treatment. Autopsy revealed frequent neocortical neuritic plaques and diffuse neocortical neurofibrillary tangles (Braak stage VI) characteristic of high-likelihood AD. There was no evidence of vasculitis or inflammation and no Lewy bodies or Lewy neurites.

Case 3

A 67-year-old male farmer presented with recurrent episodes of encephalopathy associated with subjective fever, frontal headaches, neck stiffness, anorexia, nausea, incontinence, lethargy, and visual hallucinations. He was unable to care for himself. His first two episodes were similar and each lasted less than one week. Symptoms spontaneously resolved. The third episode was more severe with subjective left-sided weakness and hemineglect. He was obtunded upon presentation, with eye opening to speech or sternal rub only. He had inappropriate speech and was completely disoriented. (More detailed mental status testing was not possible due to his disorientation and obtundation). Bizarre, choreoathetotic movements were observed in his left upper extremity with left plantar drift. There was diffuse hyporeflexia with bilateral plantar flexor responses.

Extensive work up was unrevealing, including autoimmune panel with TPO antibody titre, HSV-PCR, and two cerebral angiograms. MRI showed increased T2 signal on fluid-

attenuated inversion recovery (FLAIR) along the right frontoparietal cortical ribbon suggestive of Creutzfeldt-Jakob disease, as well as hazy increased T2 signal in much of the supratentorial white matter (Figure 3A).

Right frontal meningeal and brain biopsy was normal. IVMP was given with markedly improved alertness and orientation to month and year, by day 1. He was able to make jokes with his relatives, and continued to slowly improve after 5 days, with resolved hallucinations, choreoathetoid movements, and incontinence. MRI performed two weeks after completion of the methylprednisolone trial showed resolution in the T2 signal abnormality, although the hazy white matter signal changes persisted (Figure 3B). He was fully independent by hospital dismissal, and returned to managing his finances again and performing occupational tasks. The MRI changes resolved completely (KTMS 31/28 at nine months).

Over the following five years, he experienced less dramatic periods of encephalopathy, reasonably well-managed with oral prednisone. After experiencing a lacunar caudate infarct, with a negative work-up for cardioembolism, he was treated with cyclophosphamide with excellent symptomatic control.

Five years after initial presentation, he experienced cognitive decline, visual hallucinations, delusions, and parkinsonism, and was diagnosed with probable dementia with Lewy bodies. MRI of the brain again showed the hazy increased signal in the cerebral white matter (not shown), and only mild hippocampal atrophy (Figure 3C). He did not benefit from donepezil. His progression continued until death, one year later, whereupon neuropathologic examination showed moderate neocortical neuritic plaques and sparse neocortical neurofibrillary tangles (Braak stage IV) characteristic of intermediate likelihood AD, and moderate diffuse amyloid angiopathy. No histopathologic evidence of vasculitis or inflammation was present. There were no Lewy bodies or Lewy neurites.

Case 4

A 71-year-old man with a two-year history of angioinflammatory myeloid metaplasia had a six-month course of rapidly progressive forgetfulness, behavioral change, agitation, and low-grade headaches following laparoscopic cholecystectomy. He had experienced post-operative delirium, but this had resolved in hospital. After returning home, he slept up to 18 hours daily and had episodes of erratic driving, incoherent babbling, and emotional lability. There was new episodic bowel and bladder incontinence and unstable gait. He was brought to medical attention after he was unable to bathe himself.

He was oriented to time and person. He could not remember where he lived, and recalled zero of four objects after one and five minutes. There was mild dysmetria. Negative studies included protein 14-3-3, neuron specific enolase, paraneoplastic panel, and brain MRI.

Atypical CJD was suspected, but considering an elevation in TPO antibodies (Table 2), he was started on IVMP. There was no change by day 5. He was dismissed to a nursing home on 100mg daily oral prednisone.

Over the following week, he experienced marked cognitive and functional improvements. He was able to feed and bathe himself and the incontinence ceased. He returned home and performed household and farm chores with little difficulty. He began using the microwave, shower, and television remote control properly. Although he reported persistent forgetfulness by 3 weeks post-hospitalization (29/38 KTMS), his overt confusion and headaches resolved. At 9-months, he performed all ADLs, maintained his own finances, and drove a car.

Months afterwards, he developed asymmetric parkinsonism, and then increased encephalopathy thought to be associated with progression of his myeloid metaplasia. He died at 30 months after his initial neurologic presentation. Neuropathologic examination showed moderate patchy amyloid angiopathy, frequent neocortical neuritic plaques and diffuse neocortical neurofibrillary tangles (Braak stage VI), all consistent with high likelihood AD, but no evidence of vasculitis, inflammation, or Lewy body pathology.

Discussion

Herein, we present four cases with the following shared key features: (1) steroid-responsive encephalopathy, (2) unrevealing investigation for rheumatological and paraneoplastic disorders, (3) Alzheimer's Disease related pathology on brain tissue examination, (4) prominent behavioral change as a key feature in symptomatic improvement and decline, and (5) absence of typical symptoms and imaging features of Alzheimer's Disease. Encephalopathy with steroid responsivity subsequently associated with AD pathology has not been reported to our knowledge. In 1966, Brain *et al* described a case of encephalopathy that "waxed and waned for over a year" in a 48-year-old man who also had Hashimoto's disease of the thyroid.¹⁷ Brain tissue was never examined in the originally described patient and his condition did not respond to steroids. Nonetheless, more than 100 subsequent cases of presumed "Hashimoto's encephalopathy" have been reported in which steroid-responsivity has been considered a defining feature. This has included less than 10 autopsy-based cases. Isolated pathological reports reveal perivascular lymphocytic infiltration, particularly in the walls of small vessels^{2,4,7,18} without vasculitis, but not in all cases.⁸ Other nonspecific markers than thyroid antibodies occur in a minority of patients including elevated sedimentation rate,^{2,18} C-reactive protein, and ANA.¹⁸

In 1999, the terms "steroid-responsive encephalopathy associated with autoimmune thyroiditis" (SREAT) and "nonvasculitic autoimmune inflammatory meningoencephalitis" (NAIM) were coined to describe five encephalopathic patients with clinical steroid responsivity.¹ The intent of the new terminology was to encompass a wider group of diseases that were ultimately steroid-responsive but could be related a variety of possible diseases including systemic lupus erythematosus, Sjögren's syndrome, and eosinophilic syndrome, as well as Hashimoto's encephalopathy. Other diseases within this categorization could include vasculitis without vasculitic changes on brain biopsy (potentially due to mild or early disease) or autoimmune encephalopathies due to recognized autoantibodies such as voltage-gated potassium-channel antibodies.

Response in the five patients initially reported as "NAIM" ranged from modest improvement and gradual resolution over months to complete remittance of symptoms. Four had elevated concentrations of serum autoantibodies, and all had histological evidence of inflammation on biopsy (brain, leptomeningeal, or salivary gland). Later, autopsy of a single case of NAIM revealed panencephalitis without vasculitis.¹³ A subsequent case of probable NAIM (without autopsy) was reported to mimic CJD¹⁸ with steroid-responsive parkinsonian features of rest tremor, shuffling gait, and cogwheel rigidity. However, a pathological case series of NAIM included a majority of steroid-"nonresponders" making steroid-responsivity an uncertain defining criterion for NAIM; rather, NAIM is best considered a clinicopathological diagnosis marked quite literally by nonvasculitic meningoencephalitis on tissue examination and/or imaging preceded by a presumed autoimmune encephalopathy in life. It has been proposed that Hashimoto's encephalopathy represents just one form of NAIM.¹ In fact, multiple disease entities show a tendency towards steroid responsivity, but the core features, age predilection, test results, and/or autopsy features have important differences (Table 3).

In this series, although all cases would fall under the broad categorization of steroid-responsive encephalopathy, cases 1 and 4 could be considered examples of “Hashimoto’s encephalopathy.” These cases revealed a combination of clouded consciousness, cognitive dysfunction, headaches, and high serum concentrations of TPO antibodies.¹⁸ These same patients (1,4) were once thought to have CJD. Three cases (1,3,4) had clinical features suggesting Lewy body disease, but Lewy bodies were absent. None had sufficient hippocampal atrophy to strongly suspect evolving Alzheimer’s disease, and two had MRI abnormalities that resolved following steroid treatment. There was no evidence of vasculitis or inflammation of any kind on brain biopsy (n=1), cerebral angiography (n=2), or autopsy (all 4).

The present cases are unique in the existing literature because they document a coincidence of Alzheimer’s disease related pathology with a clinical condition that is steroid responsive. The number of people with Alzheimer’s Disease and amnestic mild cognitive impairment who experience benefit from steroids is unknown to the authors, but we postulate that β -amyloid deposition in the brain can rarely be responsible for an inflammatory encephalopathic condition. Alternatively, an inflammatory condition in the brain may prompt the deposition of A β . Both theories remain somewhat speculative. Therefore, steroid responsiveness of the symptoms in these patients may be either coincidental or related to the inflammation-neurodegeneration cascade that has been postulated to exist for β -amyloid deposition in the brain.^{20–24}

In 2005, Scolding et al. introduced the term “A β -related angiopathy” (ABRA) for the rare condition in which (A β) is deposited in the small cerebral vessels.²⁵ Nine histology-positive cases of ABRA were reported (median age 72 years) and 3 showed improvement following immunosuppression. The pathological findings in our cases fit most closely with ABRA in 3 of the presented cases. ABRA is consistent with a normal cerebral angiogram²⁶ as occurred in two of our cases and does not imply the presence of a larger vessel vasculitis.

In vitro A β is known to induce an inflammatory response in endothelial cells^{27,28} and can induce an interferon-gamma dependent meningoencephalitis in a mouse model of AD. Therefore, A β may induce an innate inflammatory response once it is deposited in the vasculature of the small vessels with consequent activation of astrocytes, microglia and complement, cytokine release, and free radical formation.²⁷ Conversely, an inflammatory reaction may be responsible for the deposition of A β , and antiinflammatory treatment may hypothetically quell such deposition.^{19, 27}

Identification of the subset of patients with AD who harbour a vigorous inflammatory response to A β may soon prove crucial. Approximately 6% of participants developed meningoencephalitis in the clinical trial of AN-1792 -parenteral A β synthetic peptide ‘vaccination’ for AD,²⁸ necessitating discontinuation of the phase II trial. Attempts to link the presence or titer of A β antibodies were unhelpful in identifying the few patients who developed a self-limited inflammatory reaction.²⁵ Thus, an indeterminate factor(s) might be responsible in some individuals who would presumably *not* be well-suited for A β -vaccination. Gathering characteristics of these patients could be a first step in identifying this important subgroup.

Finally, it is possible that there is an altogether different cause of the encephalopathies reported above. We cannot rule out that the AD-pathology is coincidental given its high prevalence in the aging population. Our cases differ from previously reported ABRA in that all of the patients in the present series had evidence of elevated autoantibodies. It was precisely these antibodies, of otherwise dubious significance, that led to steroid therapy and

eventual improvement of symptoms. Why three of our four cases subsequently developed clinical features suggesting underlying Lewy body disease is still not clear.

Yet these four cases underscore an important new observation – some patients may have elements of both an autoimmune/inflammatory and a neurodegenerative condition. Corticosteroid treatment can offer months or years of improved neurologic functioning and quality of life in these presumably exceptional cases.

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Case 1

Figure 1.
Magnetic resonance imaging of the brain of case 1.

Case 2

Figure 2.
Magnetic resonance imaging of the brain of case 2.

Case 3

Figure 3.
Magnetic resonance imaging of the brain of case 3.

Table 1**Proposed Classification of Autoimmune Encephalopathies**

I. NON-VASCULITIC	
a.	pathogenic antibody specific (e.g., voltage-gated potassium channel antibodies)
	i. paraneoplastic
	ii. non-paraneoplastic
b.	No known pathogenic antibody known (but association with seropositivity of some general autoimmune condition exists) (e.g. non-vasculitic autoimmune meningoencephalopathy (NAIM))
	i. thyroid autoimmunity
	ii. other autoimmune disorders
II. VASCULITIC	
a.	Primary
	i. autoimmune
b.	Secondary
	i. autoimmune
	ii. infectious
III. AMYLOID ANGIOPATHY-ASSOCIATED INFLAMMATORY	

Table 2

Summary of clinical and pathological data

	Case 1	Case 2	Case 3	Case 4
Age of Onset/Sex	70F	54F	67M	71M
Presenting Signs & Symptoms	Cognitive impairment, hypersomnolence, bifrontal headache	Cognitive impairment, seclusiveness, seizures	Cognitive impairment, left hemineglect, left arm and leg choreoathetotic movements, hallucinations	Cognitive impairment, behavioral change with anger and emotional lability, somnolence, bowel & bladder incontinence
Cognitive Status	STMS 32/38	STMS 9/38 MMSE 5/30	Semi-comatose (mental status testing impossible)	Oriented to person and time, not place. Poor delayed recall
Abnormal Serum Laboratory Findings	TPO Ab 90 (N<40), TSH 5.8 (N 0.30–5.0 mIU/l)	ANA 4.1 (N <1.0) RF (25 IU/mL) Ab to ENA 137.3 (N <25 units) U1RNP 152.2 units (N < 25.0) ceruloplasmin 52.7 (N 22.9–43.1 mg/dL)	IgM phospholipid Ab 37.9 (no normal range, usually negative)	TPO Ab 48 (N<40) Thyroxin binding globulin 11 (N 12–26 ug/mL)
Abnormal CSF Findings	Protein 55 mg/dL (N<45 mg/dL)	Normal except Neuron Specific Enolase 29.1 ng/mL (14–3–3 normal)	Protein 65 mg/dL; 7 total nucleated cells (N≤5)	Protein 112 mg/dL
EEG Findings	Dysrhythmia grade 1 generalized, maximal bitemporal	Dysrhythmia grade 3 with right temporal sharp waves, bilateral TIRDA	Dysrhythmia grade 1, asymmetric and maximal over the left temporal area	Dysrhythmia grade 3 with moderately severe diffuse irregularities with excess slow wave activity in the background
MRI Findings	Multiple cortical and subcortical enhancing lesions in the occipital, parietal, and posterior temporal lobes bilaterally, multiple micro hemorrhages and left frontal superficial siderosis	Moderate generalized neocortical atrophy, leukoariosis	Increased cortical T2 signal in right frontal region	Mild generalized neocortical atrophy
ApoE Genotype	2, 3	NP	3, 4	NP
Treatment	1 gram IVMP x 5 days	187.5 mg IV DXMS x 5 days, given twice 6 months apart	1 gram IVMP x 5 days	1 gram IVMP x 5 days
Outcome	Complete return to neurologic baseline, mild and intermittent headache	Increased verbalization, improved memory and word finding, reduced abulia	Near complete return to neurologic baseline	Near complete return to neurologic baseline
Cognitive Status Post-Treatment	STMS 34–37/38	MMSE 20/30	STMS 31/38	STMS 29/38
Relapse	No	Yes	Yes	Yes
Age at Death	75	55	73	75
Pathologic Findings	Severe diffuse amyloid angiopathy, No evidence of inflammation or vasculitis	Severe patchy amyloid angiopathy, No evidence of inflammation or	Moderate diffuse amyloid angiopathy, No evidence of	Mild patchy amyloid angiopathy, No evidence of inflammation or

	Case 1	Case 2	Case 3	Case 4
	No Lewy body/ Lewy neurite pathology	vasculitis No Lewy body/ Lewy neurite pathology	inflammation or vasculitis No Lewy body/ Lewy neurite pathology	vasculitis No Lewy body/ Lewy neurite pathology
Braak NFT Stage/ NIA-Reagan	V / high likelihood	VI / high likelihood	IV / intermediate likelihood	VI / high likelihood

Abbreviations: Ab=antibody, ANA=antinuclear antigen, DXMS=dexamethazone, ENA=extractable nuclear antigens, IVMP=intravenous methylprednisolone, MMSE=Mini-Mental State Examination score, NIA-Reagan=National Institute on Aging-Reagan Institute Criteria, NFT=neurofibrillary tangle, NP=not performed, RF=Rheumatoid Factor, STMS=Short Test of Mental Status score, TIRDA=temporal intermittent rhythmic delta activity, TPO=thyroperoxidase.

Table 3
Comparisons between steroid-responsive encephalopathies and the four cases in this report

	SREAT 7, 17, 29	PACNS 25,26,30,31	Mixed Amyloid Angiopathy with Angitis 22-25	Neuropsychiatric Lupus 32-35	Acute Demyelinating Encephalomyelitis 36-39	Our Cases
Age	Varies –mostly in middle- aged to elderly adults	Varies–Mostly in middle- aged adults but can occur in children	Mostly in middle- aged to elderly adults	Varies–Both adults and children	Most common in children & adolescents, F>M	54-71 years
Core Features	Encephalopathy often accompanied by stroke-like episodes, psychosis, myoclonus, seizures PLUS Elevated thyroid antibodies (see below)	Encephalopathy often accompanied by multifocal neurologic signs and symptoms, and headache PLUS Patchy inflammation of the small and medium-sized cerebral and leptomeningeal arteries	Encephalopathy often accompanied by multifocal neurologic signs and symptoms +/- headache PLUS Amyloid angiopathy PLUS inflammation of the small and medium-sized cerebral and leptomeningeal arteries	Encephalopathy often accompanied by stroke-like episodes, psychosis, movement disorder, headache PLUS Elevated ANA May have frank vasculitis, microangiopathy, arterial thrombosis and infarcts	Encephalopathy accompanied by varying degrees of behavioral changes, somnolence, headache, movement disorder	
Antibody Associations	Antithyroid microsomal, Antithyroid peroxidase Antithyroglobulin	None	None	Anti-neuronal Anti-phospholipid Antiribosomal-P	None	No consistent profile
CSF Findings	Usually normal, or only mildly elevated protein	Usually abnormal, with elevated protein and lymphocytic pleocytosis	Variably abnormal, with elevated protein and Lymphocytic pleocytosis	Often but not always abnormal, with elevated protein and lymphocytic pleocytosis	Usually abnormal with elevated protein, lymphocytic pleocytosis, and increased oligoclonal bands	Normal to mildly elevated protein
MRI Findings	Usually normal, or only non-specific age-related changes Diffuse increased signal in white matter is seen rarely	Confluent and multifocal white matter lesions, sometimes with space occupying lesions mimicking tumor	Variable, but usually abnormal with confluent and multifocal white matter lesions, sometimes with space occupying lesions mimicking tumor	Patchy gray matter hyperintensities not localized to a major cerebrovascular territory. Punctate, T2-high signal, transient periventricular and subcortical white matter changes May show accompanying venous sinus thrombosis, brain atrophy, infarction, myelopathy. May be normal.	Variable lesions, small or large, multifocal and asymmetric distribution, predominantly affecting white matter, many variations exist including periventricular lesions (in 60%)	Focal parenchymal changes (n=2), Resolving white matter changes on T2 FLAIR (n=1). Pial enhancement (n=1) Atrophy.

		SREAT 7, 17, 29	PACNS 25,26,30,31	Mixed Amyloid Angiopathy with Angitis 22-25	Neuropsychiatric Lupus³²⁻³⁵	Acute Demyelinating Encephalomyelitis 36-39 and initially N scans	Our Cases
EEG		Almost always abnormal, with slowing +/- epileptiform activity	Often abnormal, with slowing	Often abnormal, with slowing	Almost always abnormal, with slowing + epileptiform activity	No specific findings reported	Moderate slowing
Steroid Responsivity?		Yes (by definition) IVIG or PLEX sometimes needed	Usually Cyclophosphamide often needed	Usually Cyclophosphamide often needed	Usually Cyclophosphamide sometimes needed	Usually	Yes—in all 4 cases Cyclophosphamide needed in 1 case
Biopsy/ Autopsy Findings		Often normal Lymphocytic infiltration of small vessels, perivascular cuffs of lymphocytic cells rarely reported Very few case reports	Mixed inflammatory cell infiltrate in the small and medium sized vessels with fibrinoid necrosis in the leptomeninges and/or cerebral cortex.	Amyloid angiopathy PLUS Mixed inflammatory cell infiltrate in the small and medium sized vessels with fibrinoid necrosis in the leptomeninges and/or cerebral cortex.	Variable—normal to lymphocytic infiltration or perivascular cuffing to frank vasculitis and necrosis	Sleeve-like demyelination in hypercellular areas of lymphocytic perivenous inflammation	Amyloid angiopathy PLUS Neuritic plaques and neurofibrillary tangles characteristic of Alzheimer's disease NO evidence of inflammation or vasculitis