ADENDDUM

(SUPPLEMENTARY INFORMATION)

PATIENTS

Patient 1

A 60-year old computer programmer was admitted in June 2004 for a 4-week history of short-term memory loss, confusion, akathisia, and multifocal muscle twitching preceded by a week of diarrhea. He described spells of odd smell, piloerection, diaphoresis and palinopsia, and the family noted occasional staring. Physical examination demonstrated severe short-term memory loss and fasciculations, without undulating myokymia or neuromyotonia. EEG showed diffuse slowing. Sensory and motor conduction velocities were normal; EMG showed small excess of normal-long duration polyphasic units in 3/11 muscles tested, without myotonia, neuromyotonia or signs of abnormal muscle membrane depolarization. All blood tests were normal except for hyponatremia (129 mEq/L). Brain MRI showed bilateral medial temporal lobe FLAIR abnormalities with FDG uptake in the PET scan (Figure 1). CSF results are shown in Table 1. Serum and CSF were positive for VGKC antibodies (Figure 4). Body CT and FDG-PET, and ultrasound of the testis were normal. After 5 days of IVIg and corticosteroids, the patient was discharged home on oral prednisone, and he started to improve two weeks after discharge. A repeat brain MRI obtained 4 months after symptom presentation showed significant improvement of the medial temporal lobe FLAIR hyperintensities without atrophy (Figure 1). The patient is back to his job with normal performance. He drives but

has mild difficulty with directions. The hyponatremia normalized, and the muscle twitching, akathisia, anosmia and decreased libido have resolved. His current treatment includes prednisone (70 mg every other day) and azathioprine (100 mg daily).

Patient 2

A 65-year old retired factory worker with a history of smoking was noted to have short-term memory loss, confusion, agitation and a behavioral change associated with drinking large amounts of fluid. She was admitted to an outside hospital where she was found to have hyponatremia attributed to antidepressants and high fluid intake. Ten days after discharge she was re-admitted for worsening confusion, memory deficits, and being verbally abusive with family members. EEG and brain MRI were normal. CSF showed 26 WBC/ l (75% lymphocytes), total protein concentration of 66 mg/dL, and normal glucose. Her symptoms improved after IV methylprednisolone, and she was discharged on a prednisone taper. At the time the prednisone was discontinued her family noted recurrence of symptoms. On admission to our facility, she had severe short-term memory deficits and downbeating nystagmus. Her serum sodium was 130 mEq/L; all blood tests listed in methods were normal except for ANA (1:160). Brain MRI showed mild FLAIR hyperintensity in the medial aspects of the temporal lobes with diffuse FDG hypoactivity in the PET scan (Figure 1). The CSF results are shown in Table 1. Immunohistochemical analysis of serum and CSF demonstrated predominant reactivity with the neuropil of hippocampus (Figure 4) and to a lesser degree the cerebellum; in addition serum and CSF contained an antibody that reacted with a subset of neurons lining the internal aspect of the granular layer of the hippocampus (Figure 6) and neurons scattered in the cerebral

cortex and cerebellum. Body CT and FDG-PET, and EEG were unremarkable. The serum sodium normalized with fluid restriction. She was treated with plasma exchange and methylprednisolone, and was discharged with a slow prednisone taper. Dramatic improvement was noted by the family 3 weeks later and by 5 weeks the patient was back to her normal daily activities. Attempts to decrease the dose of prednisone resulted in symptom recurrence without change in the brain MRI. Symptoms improved again with methylprednisolone and IVIg. Currently, she has returned to some activities at home, but has residual behavioral changes and still improving short-term memory deficits; treatment includes prednisone (40 mg every other day) and azathioprine (100 mg daily).

Patient 3

A 44-year old day care worker was admitted to the psychiatric unit for acute personality change, agitation, and visual hallucinations. She was tachypneic and developed respiratory failure requiring intubation one day after admission. A chest CT demonstrated a pulmonary embolism and an anterior mediastinal mass. She progressively deteriorated and became stuporous. Multiple EEGs showed a low voltage pattern in the theta range; in one EEG epileptic activity was recorded in the left temporal lobe. Brain MRI was normal except for bilateral small foci of FLAIR and T2 abnormalities of unclear significance (not shown in Figure 1). Brain FDG-PET obtained during the time there was no EEG evidence of epileptic activity, showed hyperactivity in the left frontal temporal region (Figure 1). CSF results are shown in Table 1. All blood tests indicated in methods were normal as was a cerebral angiogram. Three weeks after admission, resection of the anterior mediastinal mass demonstrated a mature cystic teratoma. Subsequent analysis of

serum demonstrated immunoreactivity with the neuropil of hippocampus, sparing the cerebellum, and mild reactivity with cortical neuronal processes (data not shown). After surgery the patient slowly improved but had persistent word finding difficulties and mild right-sided weakness. She did not receive steroids, IVIg, or plasma exchange. Her symptoms gradually improved and she returned to work with minimal word-finding difficulties. The last follow-up, 22 months after symptom development, showed a normal neurological examination and MRI except for the indicated small foci of FLAIR and T2 abnormalities in the frontal lobes.

Patient 4

A 26-year old preschool teacher was admitted to the psychiatry unit for inappropriate laughing and crying associated with headache. Two days after admission she developed hyperthermia, generalized tonic-clonic seizures, worsening mental status, and central hypoventilation that required intubation. Brain MRI showed FLAIR and T2 hyperintensities over the left cerebral cortex and cerebellum, with mild cerebellar contrast enhancement (data not shown). Results of the initial CSF analysis are described in Table 1. Immunohistochemical analysis of CSF and serum demonstrated a novel antibody with predominant reactivity with the neuropil of hippocampus (Figure 5). A repeat brain MRI performed one week later showed new hyperintensities over the left cerebral cortex and a hypointensity in the left cerebellum. Multiple EEGs showed generalized theta and delta slowing with no epileptic discharges. FDG-PET demonstrated increased FDG activity in the right temporal lobe and brainstem, and hypoactivity in the occipital lobes. CT of abdomen and pelvis demonstrated an ovary with fat and calcification and bilateral

obturator muscle lesions consistent with a dermoid cyst. The lesions were not removed and the patient was treated with IV corticosteroids. Five months after symptom presentation she had a normal examination and MRI. A repeat FDG-PET showed minimal decreased activity in the left temporoparietal region. Her serum no longer reacted with the neuropil of hippocampus.

Patient 5

A 44-year old right-handed secretary presented with three weeks of progressive short-term memory loss and inability to perform her job. She was admitted to an outside psychiatric institution due to confusion and combativeness. By the time of transfer to our institution, she was only oriented to person and could not remember any events of the previous day. In addition to predominant anterograde memory deficits the neurologic examination only showed right beating nystagmus. EEG was normal. The initial brain MRI was normal, but another obtained 5 days later showed mild FLAIR hyperintensity involving the right temporal lobe more than the left, with small foci of FDG-PET hyperactivity in the right temporal lobe and left cerebellum (Figure 1). The CSF results are shown in Table 1. All other laboratory values were normal except for ANA (1:1280), double stranded DNA antibodies (409 IU/ml), and rheumatoid factor (154 IU/ml). Her serum and CSF demonstrated intense reactivity with the neuropil of hippocampus (Figure 6) and to a lesser degree the cerebellum. A chest CT demonstrated an invasive mediastinal tumor that was removed; the pathology demonstrated thymic carcinoma. Because of repetitive movements of the right hand another EEG was obtained, showing delta slowing of the posterior dominant rhythm and occasional epileptic activity in the

left temporal lobe. The patient was partially treated with IVIg and corticosteroids due to gastrointestinal bleeding and sepsis. Two months after neurologic symptom development she started to improve and was discharged home. At the last follow-up 27 months later, the neurological examination and brain MRI were normal. She is back to work, and has not developed symptoms of systemic lupus erythematosus or other autoimmune disorders. The titers of ANA, ds DNA antibodies, and rheumatoid factor remain elevated, but the neuropil antibodies are no longer detectable.

Patient 6

A 38-year old right-handed man was admitted for seizures and altered mental status. His past medical history was relevant for a similar episode of confusion, with MRI abnormalities in the medial temporal lobes that resolved spontaneously 5 years earlier. At current admission he was noted to be extremely confused and agitated and required multiple anti-epileptic medications. He was unable to follow commands and had paraphasic errors with perseveration; memory could not be adequately assessed. The rest of the neurological examination was unremarkable. Two brain MRIs obtained one month apart showed multiple discrete limbic and cerebral cortical FLAIR abnormalities without contrast enhancement (Figure 3). Biopsy of the right frontal lesion showed perivascular lymphocytic infiltrates. An extensive laboratory work-up was negative except for the demonstration of insulin-dependent diabetes mellitus (IDDM). CSF results are shown in Table 1. The patient's serum and CSF contained antibodies reacting with the neuropil of the hippocampus (Figure 4) and GAD (not shown). A chest CT demonstrated an anterior mediastinal mass that was removed revealing a malignant thymoma. He received focal

radiation therapy and was subsequently treated with IV methylprednisolone for 3 days, followed by a slow prednisone taper. He experienced a dramatic improvement, becoming alert, oriented and independent over the next three weeks; the IDDM resolved as well. He married a month after recovery. Repeat MRI five months after symptom development showed marked improvement, with minimal residual abnormalities (Figure 3). When the prednisone dose was decreased to 5 mg/day he developed painful spasms and rigidity that did not improve with plasma exchange or IVIg, but responded to prednisone (20 mg per day). An EMG obtained after improvement showed no evidence of spontaneous activity. Attempts to lower the dose of prednisone were associated with recurrent muscle spasms. At last follow up, 3 years later, the patient has mild short-term memory deficits and gait difficulty, but he does not need a cane. He is being treated with prednisone (10 mg every other day).

Patient 7

A 56-year old engineer presented with a two-month history of progressive forgetfulness and confusion. He had lost his job and was diagnosed with depression. At admission he had severe short-term memory deficits but otherwise the neurologic examination was normal. EEG was normal. The initial CSF studies are shown in Table 1. All tests indicated in methods, and body CT and FDG-PET were normal. The brain MRI showed bilateral abnormalities in the medial temporal lobes that enhanced with contrast; FDG-PET showed hyperactivity in the same areas and a clinically asymptomatic area of activity in the cerebellar vermis (Figure 2). Ultrasound of the testes demonstrated a mass in the left testis, and a left orchiectomy showed replacement of tissue by fibrous scar,

without cancer. Treatment with IV methylprednisolone and IVIg resulted in no improvement, but his deficits in verbal learning and visual memory seemed to stabilize. Four months after symptom presentation, he developed progressive ataxia. A body FDG-PET demonstrated hyperactivity in the thyroid gland and biopsy revealed a papillary carcinoma. No metastases were identified and he underwent thyroidectomy. The serum and CSF contained a novel antibody that reacted with intracellular antigens expressed by all CNS neurons (Figure 6) and the tumor (not shown). The cerebellar ataxia and brainstem dysfunction progressed despite treatment with plasma exchange, mycophenolate mofetil, and rituximab. Transient stabilization was observed with oral cyclophosphamide (75 mg daily), and prednisone (70 mg every other day), but progressed again with the development of dysphagia, dysarthria, diplopia, and partial complex seizures. The family decided to proceed to best supportive care, and after discontinuation of cyclophosphamide and prednisone he had rapid deterioration and died in two weeks. No autopsy was obtained. Overall, he was followed for 22 months with periodic CSF studies, brain MRI and FDG-PET scans (Figure 2).