Autoimmune Dementia: Clinical Course and Predictors of Immunotherapy Response

EOIN P. FLANAGAN, MBBCh; ANDREW McKEON, MBBCh; VANDA A. LENNON, MD, PhD;
BRADLEY F. BOEVE, MD; MAX R. TRENNERY, PhD; K. MENG TAN, MD; DANIEL A. DRUBACH, MD;
KEITH A. JOSEPHS, MD; JEFFREY W. BRITTON, MD; JAYAWANT N. MANDREKAR, PhD; VAL LOWE, MD;
JOSEPH E. PARISI, MD; AND SEAN J. PITTOCK, MD

OBJECTIVE: To define the diagnostic characteristics and predictors of treatment response in patients with suspected autoimmune dementia.

PATIENTS AND METHODS: Between January 1, 2002, and January 1, 2009, 72 consecutive patients received immunotherapy for suspected autoimmune dementia. Their baseline clinical, radiologic, and serologic characteristics were reviewed and compared between patients who were responsive to immunotherapy and those who were not. Patients were classified as responders if the treating physician had reported improvement after immunotherapy (documented in 80% by the Kokmen Short Test of Mental Status, neuropsychological testing, or both).

RESULTS: Initial immunotherapeutic regimens included methylprednisolone in 56 patients (78%), prednisone in 12 patients (17%), dexamethasone in 2 patients (3%), intravenous immune globulin in 1 patient (1%), and plasma exchange in 1 patient (1%). Forty-six patients (64%) improved, most in the first week of treatment. Thirty-five percent of these immunotherapy responders were initially diagnosed as having a neurodegenerative or prion disorder. Pretreatment and posttreatment neuropsychological score comparisons revealed improvement in almost all cognitive domains, most notably learning and memory. Radiologic or electroencephalographic improvements were reported in 22 (56%) of 39 patients. Immunotherapy responsiveness was predicted by a subacute onset ($P<.001$), fluctuating course ($P<.001$), tremor ($P=.007$), shorter delay to treatment ($P=.005$), seropositivity for a cation channel complex autoantibody ($P=.01$), neuronal voltage-gated potassium channel more than calcium channel or neuronal acetylcholine receptor), and elevated cerebrospinal fluid protein (>100 mg/dL) or pleocytosis ($P=.02$). Of 26 immunotherapy-responsive patients followed up for more than 1 year, 20 (77%) relapsed after discontinuing immunotherapy.

CONCLUSION: Identification of clinical and serologic clues to an autoimmune dementia allows early initiation of immunotherapy, and maintenance if needed, thus favoring an optimal outcome.

Mayo Clin Proc. 2010;85(10):881-897

AChR = acetylcholine receptor; CSF = cerebrospinal fluid; EEG = electroencephalographic; IV = intravenous; IVIG = IV immune globulin; MRI = magnetic resonance imaging; NMDA = N-methyl-D-aspartate; PET = positron emission tomographic; SPECT = single-photon emission computed tomographic; STMS = Short Test of Mental Status; TMT = Trail-Making Test; TPO = thyroid peroxidase; VGKC = voltage-gated potassium channel

When a patient presents with a primary symptom of cognitive decline, an important and challenging component of the diagnostic process is to determine whether the disorder is reversible. Misdiagnosis of a potentially reversible condition as a progressive neurodegenerative

disorder on the basis of the presumption of irreversibility has devastating consequences for the patient and family. Traditionally, neurologists have been reluctant to consider a diagnosis of autoimmune dementia in the absence of delirium. However, despite being poorly defined, some new-onset dementias are immunotherapy-responsive.¹ Recent reports support the concept of a broader spectrum of autoimmune cognitive impairment than “limbic encephalitis.”²⁻⁴ Case series reports and clinical-serologic observations have demonstrated that progressive dementia without delirium may represent an autoimmune neurologic disorder.^{3,4}

Reported clinical features suggesting an autoimmune basis for dementia include a subacute onset with a rapidly progressive, often fluctuating course; coexisting organ-specific autoimmunity; and inflammatory spinal fluid.²⁻⁸ The confusing nomenclature applied to autoimmune encephalopathies with cognitive impairment reflects the evolution of understanding of these disorders. Customary classification has been based on a syndromic presentation (eg, Morvan syndrome⁹ or progressive encephalomyelopathy with rigidity and myoclonus¹⁰), a specific serologic marker (eg, voltage-gated potassium channel [VGKC] complex antibody-associated encephalopathy⁶ or thyroid autoantibody-associated [Hashimoto] encephalopathy^{2,11}), or histopathologic findings (eg, nonvasculitic

**For editorial
comment,
see page 878**

From the Department of Neurology (E.P.F., A.M., V.A.L., B.F.B., K.M.T., D.A.D., K.A.J., J.W.B., J.E.P., S.J.P.), Department of Laboratory Medicine and Pathology (A.M., V.A.L., J.E.P., S.J.P.), Department of Immunology (V.A.L.), Department of Psychiatry and Psychology (M.R.T.), Division of Biomedical Statistics and Informatics (J.N.M.), and Department of Radiology (V.L.), Mayo Clinic, Rochester, MN.

Testing for antibody markers of neurological autoimmunity is offered on a service basis by Mayo Collaborative Service Inc, an agency of Mayo Foundation. However, neither the authors personally nor the laboratory benefits from this testing.

This article is freely available on publication, because the authors have chosen the immediate access option.

Individual reprints of this article are not available. Address correspondence to Sean J. Pittock, MD, Department of Neurology, Mayo Clinic, 200 First St SW, Rochester, MN, 55905 (pittock.sean@mayo.edu).

© 2010 Mayo Foundation for Medical Education and Research

autoimmune meningoencephalitis).¹² The potential for reversibility by immunotherapy unifies these disorders. The terms *encephalopathy*, *dementia*, *delirium*, and *cognitive impairment* all pertain to impaired cognition, but the definitions and implications for each term are slightly different. We will refer to these disorders henceforth as *autoimmune dementia* to emphasize that altered cognition is the principal clinical presentation and that autoimmunity is the underlying pathogenic mechanism.

With the goal of defining autoimmune dementias in terms of diagnostic characteristics and predictors of treatment response in patients presenting to Mayo Clinic in Rochester, MN, we established a multidisciplinary Autoimmune Dementia and Encephalopathy Study Group consisting of physicians from the Department of Neurology (Division of Multiple Sclerosis and Autoimmune Neurological Disorders and Division of Behavioral Neurology) and Department of Laboratory Medicine and Pathology (Neuroimmunology Laboratory). This article describes the clinical course and predictors of improvement in 72 consecutive patients presenting with dementia or encephalopathy who were evaluated between January 1, 2002, and January 1, 2009, and were selected for a trial of immunotherapy because an autoimmune basis for their condition was strongly suspected.

PATIENTS AND METHODS

The study used Mayo Clinic's computerized central diagnostic index and was approved by the Mayo Clinic Institutional Review Board. We reviewed 202 medical records of patients seen from January 1, 2002, to January 1, 2009, who fulfilled 3 criteria: (1) the recorded diagnosis included the search terms *cognitive*, *dementia*, and/or *encephalopathy* or *encephalitis*; (2) the Impression, Report, and Plan text of the physician's electronic medical consultation note contained the search terms *antibody*, *immune*, *channel*, *limbic*, *steroid*, *prednisone*, *methylprednisolone*, *Solu-Medrol* or *dexamethasone*, *intravenous immune globulin* (or *immunoglobulin* or *IVIg*), *mycophenolate mofetil* or *CellCept*, *azathioprine* or *Imuran*, *plasmapheresis*, *reversible*, or *resolving*; and (3) the clinical evaluation was performed by 1 or more members of the Autoimmune Dementia and Encephalopathy Study Group.

Seventy-two (36%) of the 202 identified patients met the following inclusion criteria: (1) a neurologic presentation that was predominantly cognitive, (2) an autoimmune basis suspected and a trial of immunotherapy initiated, and (3) pretreatment and posttreatment neurologic assessment at Mayo Clinic. We excluded the remaining 130 patients (64%) for the following reasons: lack of a cogni-

tive presentation, 28 patients; lack of surveillance for a therapeutic response, 18 patients; or no immunotherapy prescribed, 84 patients. Of the 84 patients who did not receive immunotherapy, 42 (50%) were assigned a different diagnosis after subsequent evaluation (eg, neurodegenerative dementia, central nervous system infection, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, depression, Rasmussen encephalitis, trauma, developmental disorder); 26 (31%) proved to have search terms unrelated to the cognitive disorder (eg, *resolving* leg pain and dementia); 12 (14%) had an incomplete evaluation due to a lack of follow-up; 3 (4%) had a complete evaluation but withdrew from the study before planned immunotherapy could be administered; and 1 (1%) had terminal cancer, which contraindicated immunotherapy.

EVALUATION OF COGNITION

Sixty-eight patients (94%) completed the Kokmen Short Test of Mental Status (STMS) during their evaluation; 56 patients were tested before treatment, and 41 were tested before and after an immunotherapy trial.^{13,14} The Kokmen STMS assesses and scores orientation (8 points), attention (7 points), learning (4 points), calculation (4 points), abstraction (3 points), construction (4 points), information (4 points), and recall (4 points). The maximum score is 38 points.

Neuropsychological test results were available for 51 patients (34 were retested after immunotherapy). A clinical neuropsychologist (M.R.T.) analyzed all baseline test results and compared results before and after immunotherapy. The following cognitive domains were evaluated: (1) intellectual function (Wechsler Adult Intelligence Scale¹⁵ or Wechsler Abbreviated Scale of Intelligence¹⁶); (2) premorbid intelligence (Wide Range Achievement Test–Revision 3 reading subtest¹⁷); (3) learning and memory (Auditory Verbal Learning Test [AVLT]¹⁸); (4) language (Controlled Oral Word Association Test [COWAT],¹⁹ Boston Naming Test,²⁰ and Category Fluency Test [CFT]²¹); (5) executive function (Trail-Making Test [TMT] A and B^{22,23}); and (6) overall cognition with the Dementia Rating Scale.²⁴ In TMT A, the time taken for a participant to connect the dots of 25 numbers scattered on a screen is assessed. In TMT B, the time taken for a participant to connect the dots of 25 numbers and 25 letters, alternating between the two, is assessed (for example: 1, A, 2, B...). Trail-Making Test B is considered more difficult and a better test of brain function than TMT A.²⁵ To facilitate comparison between different indices, the AVLT, COWAT, CFT, and TMT scores were converted to Mayo Older Americans Normative Studies scaled scores. A mean score of 10 points, with a standard deviation of 3 points, is normal.^{21,26,27}

Definitions. A subacute onset was defined as symptoms evolving over 1 to 6 weeks. A fluctuating course was defined as variability of symptoms over days to weeks.

Criteria for Responder Status. Patients were classified as responders if the treating physician had reported improvement after immunotherapy. Improvement was confirmed objectively by formal cognitive testing (Kokmen STMS or neuropsychological testing) in 37 (80%) of 46 responders.

Neuroimaging and Electroencephalographic Evaluations. Neuroimaging (positron emission tomographic [PET], magnetic resonance imaging [MRI], and single-photon emission computed tomographic [SPECT]) and electroencephalographic (EEG) results were reviewed, and findings before and after immunotherapy were compared.

AUTOIMMUNE SEROLOGIC EVALUATION

Results of neural autoantibody screening were recorded. We used a composite substrate of mouse tissues (kidney, stomach, cerebellum, and midbrain) in a standardized indirect immunofluorescence assay to detect neuronal and glial nuclear and cytoplasmic IgG autoantibodies (antineuronal nuclear autoantibodies, types 1 [anti-Hu], 2 [anti-Ri], and 3; Purkinje cell cytoplasmic autoantibodies, types 1 [anti-Yo], 2, and Tr; antiglial/antineuronal nuclear antibody-type 1; collapsin response mediator protein-5 IgG and amphiphysin IgG).²⁸⁻³⁰ For this study, we added sections of mouse cerebral cortex, hippocampus, and thalamus to allow detection of other central nervous system synapse-reactive IgG autoantibodies (*N*-methyl-D-aspartate [NMDA], α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and γ -aminobutyric type B receptor specificities). We performed radioimmunoprecipitation assays to detect antibodies reactive with cation channel complexes (neuronal voltage-gated calcium channels [P/Q-type and N-type], VGKCs, nicotinic acetylcholine receptors [AChRs, muscle-type and ganglionic-type]), and glutamic acid decarboxylase-65³¹⁻³⁴; an enzyme-linked immunosorbent assay and a Western blot (recombinant human protein) assay were used to detect skeletal muscle striational antibodies³⁴ and collapsin response mediator protein-5 IgG,²⁸ respectively.

STATISTICAL ANALYSES

Continuous variables were reported as mean $\pm$ SD. Categorical variables were reported as frequency and percentage. Clinical, laboratory, cerebrospinal fluid (CSF), and neuroimaging features in responders and nonresponders were compared using the Fisher exact test. The association of responder status with clinically relevant variables was assessed using univariate logistic regression analysis. The associations were reported as odds ratios with

95% confidence intervals. The time from symptom onset to immunotherapy was compared using the Wilcoxon rank sum test. The paired *t* test was used to compare Kokmen STMS scores and neuropsychological test results before and after immunotherapy. *P* < .05 was considered significant.

RESULTS

BASELINE CHARACTERISTICS SUGGESTING AN AUTOIMMUNE DEMENTIA

Seventy-two patients fulfilled inclusion criteria for the study. Their demographic, clinical, neuroimaging, and autoimmune serologic characteristics are outlined in Appendices 1 and 2 at the end of this article. The clinical characteristics of the patients are summarized and compared using the Fisher exact test in Tables 1 and 2. Exclusion of other treatable causes of dementia involved evaluations for endocrine, infectious, inflammatory, iatrogenic, metabolic, neoplastic, nutritional, psychiatric, toxic, and vascular disorders. Autoimmunity was suspected, and a trial of immunotherapy justified, on the basis of 1 or more of the following findings, among 72 patients unless otherwise specified: subacute onset (over 1-6 weeks), 52 (72%); fluctuating symptoms, 47 (65%); thyroid peroxidase (TPO) antibodies, 40 (59%) of 68; neural-specific autoantibodies, 31 (44%) of 70; signs of myoclonus or tremor, 26 (36%); neuroimaging abnormality considered atypical for a neurodegenerative disorder, 21 (29%) (MRI signal abnormalities, 16; increased uptake on PET or SPECT, 1; or both, 4); CSF protein elevation (>100 mg/dL) or pleocytosis, 19 (28%) of 67; and EEG evidence of epileptiform activity, 12 (18%) of 66. For the 56 patients who were tested using the Kokmen STMS score before treatment, the median score was 27 points (range, 1-37 points [maximum score, 38 points]). It is noteworthy that attention in most patients was not severely impaired (median attention score by digit span forward task, 6 points [maximum score, 7 points]).

TREATMENTS UNDERTAKEN

Initial immunotherapeutic regimens included intravenous (IV) methylprednisolone, 56 patients (78%) (most often 1 g/d for 3-10 days; 47 [84%] of the 56 patients were treated once daily for 5 days); oral prednisone, 12 (17%); IV dexamethasone, 2 (3%); IV immune globulin (IVIG), 1 (1%); and plasma exchange, 1 (1%).

IMMUNOTHERAPY RESPONDERS

Initial Diagnoses. Before consideration of an immunotherapy-responsive disorder, 16 (35%) of the 46 responders were assigned an initial diagnosis of a neurodegenerative or prion disorder (not otherwise specified, 6; Creutzfeldt-

TABLE 1. Clinical Characteristics^a

	Total (N=72)	Responders (n=46)	Nonresponders (n=26)	P value ^b
Male	30 (42)	20 (43)	10 (38)	.80
Age (y) at onset	58±11.9	59±12.1	57±11.8	.57
Time to treatment (mo)	16±17.9	11±12.1	25±22.6	<.001
White	64 (89)	41 (89)	23 (88)	
Subacute onset	52 (72)	43 (93)	9 (35)	<.001
Fluctuating course	47 (65)	42 (91)	5 (19)	<.001
Pure cognitive presentation	21 (29)	10 (22)	11 (42)	.1
Normal examination (excluding cognitive findings)	26 (36)	13 (28)	13 (50)	.13
Other neuropsychiatric symptoms or signs				
Psychiatric	38 (53)	25 (54)	13 (50)	.81
Depressed mood	25 (35)	15 (33)	10 (38)	
Psychosis/hallucinations	20 (28)	15 (33)	5 (19)	
Excess anxiety	3 (4)	1 (2)	2 (8)	
Hypersomnolence	27 (38)	20 (43)	7 (27)	.21
Seizures	18 (25)	14 (30)	4 (15)	.25
Headache	12 (17)	11 (24)	1 (4)	.04
Tremor	21 (29)	19 (41)	2 (8)	.003
Other parkinsonian	21 (29)	13 (28)	6 (23)	.78
Myoclonus	14 (19)	12 (26)	2 (8)	.07
Apraxia	10 (14)	5 (11)	5 (19)	.47
Aphasia	9 (13)	6 (13)	3 (12)	>.99
Peripheral neuropathy	16 (22)	10 (22)	6 (23)	>.99
Family history of dementia	26 (36)	10 (22)	16 (62)	<.001

^a Categorical data are provided as number (percentage) of patients and continuous data as mean ± SD.

^b P values are from the Fisher exact test.

TABLE 2. Evidence of Autoimmunity and Cancer in 72 Study Patients^a

	Total (N=72)	Responders (n=46)	Nonresponders (n=26)	P value ^b
Nonneural autoantibodies				
TPO antibody ^c	40/68 (59)	22/44 (50)	18/24 (75)	.11
Non-organ-specific (ANA, APL, ENA, dsDNA, ANCA, and RF)	29 (40)	18 (39)	11 (42)	.80
Neural autoantibodies ^c	31/70 (44)	24/45 (53)	7/25 (28)	.05
Cation channels	18/58 (31)	16/37 (43)	2/21 (10)	.01
VGKC (nmol/L), median (range)		0.87 (0.13-4.22)	0.05	.01
No. of patients	11	10	1	
AChR (ganglionic or muscle) (nmol/L), median (range)		0.11 (0.03-0.22)	0.28 (0.11-0.46)	>.99
No. of patients	6	4	2	
CaCh (N- or P/Q-type) (nmol/L), median (range)		0.11 (0.04-0.41)		.28
No. of patients	4	4	0	
Neuronal nuclear or cytoplasmic antibodies	13/61 (21)	9/40 (23)	4/21 (19)	>.99
ANNA-1 or amphiphysin, median		1:1920	1:30,720	>.99
No. of patients	2	1	1	
GAD65 (nmol/L), median (range)		0.15 (0.04-25.8)	113 (41.8-403)	.73
No. of patients	11	8	3	
Coexisting autoimmune disorder				
Thyroid autoimmunity	34 (47)	22 (48)	12 (46)	>.99
Diabetes	9 (13)	4 (9)	5 (19)	.26
Pernicious anemia	4 (6)	2 (4)	2 (8)	.62
Rheumatoid arthritis, systemic lupus erythematosus, or Sjögren syndrome	6 (8)	5 (11)	1 (4)	.41
Other (Wegener granulomatosis, vitiligo, pemphigus)	3 (4)	1 (2)	2 (8)	.29
CSF analysis				
High protein (>100 mg/dL) or pleocytosis	19/67 (28)	17/43 (40)	2/24 (8)	.01
Other ^d	9 (13)	4/43 (9)	5/22 (23)	.26
Neoplastic disease ^e	17 (24)	10 (22)	7 (27)	.77
Family history of autoimmunity	36 (50)	25 (54)	11 (42)	.46

^a Categorical data are provided as number (percentage) of patients, unless otherwise indicated. AChR = acetylcholine receptor; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibody; ANNA-1 = antineuronal nuclear autoantibody, type 1; APL = antiphospholipid antibody; CaCh = voltage-gated calcium channel; CSF = cerebrospinal fluid; dsDNA = double-stranded DNA; ENA = extractable nuclear antigen; GAD65 = glutamic acid decarboxylase-65; RF = rheumatoid factor; TPO = thyroid peroxidase; VGKC = voltage-gated potassium channel.

^b P values are from the Fisher exact test.

^c Reference ranges: TPO antibody, <9 IU/mL; VGKC antibody, 0.00-0.02 nmol/L; muscle and ganglionic neuronal AChR antibody, 0.00-0.02 nmol/L; N-type CaCh antibody, 0.00-0.03 nmol/L; P/Q-type CaCh antibody, 0.00-0.02 nmol/L; ANNA-1, <240; amphiphysin antibody, <240; GAD65 antibody, 0.00-0.02 nmol/L.

^d Supernumerary oligoclonal bands (reference range, ≤5), elevated IgG index (reference range, ≤0.85), or elevated IgG synthesis rate (reference range, 600-1600 mg/dL).

^e Remote (diagnosed >3 y before symptom onset): breast carcinoma, 5; plasmacytoma, 1; thymic carcinoma, 1; melanoma, 1. Recent (diagnosed within 3 y of symptom onset): breast carcinoma, 1; prostate carcinoma, 1; small cell lung carcinoma, 1. Subsequent: colon carcinoma, 2; small cell lung carcinoma, 2; lung adenocarcinoma, 1; multiple myeloma, 1; astrocytoma, 1.

FIGURE 1. Improvements in Kokmen Short Test of Mental Status (STMS) score among responders after immunotherapy. Kokmen STMS scores improved in 32 of 46 patients responding to immunotherapy. Scores of nonresponders, by definition, did not improve.

*Mild postimmunotherapy improvements in Kokmen STMS score were accompanied by significant improvements on neuropsychological testing.

Jakob disease, 4; Lewy body disease, 3; mild cognitive impairment, 2; semantic dementia, 1).

Cognitive Assessments Before and After Treatment.

Posttherapy improvements in cognition were documented in 46 (64%) of 72 patients: by both Kokmen STMS score and neuropsychological testing, 17; Kokmen STMS score alone, 14; neuropsychological testing alone, 6; and physician-reported improvement by neurologic assessment alone, 9. Improvements were evident within 1 week in 36 (78%) of the responders and within 4 weeks in 46 (100%). By Kokmen STMS score, the mean improvement (Figure 1) was 9 points (SD, ± 7 points; $P < .001$; maximum score, 38 points); the mean $\pm$ SD pretherapy score was 23 ± 9 points; and the mean $\pm$ SD posttherapy score was 33 ± 4 points. Neuropsychological scores revealed that individual patients improved in almost all cognitive domains after immunotherapy ($P < .01$, paired t test; Table 3). Improvements were most notable in learning and memory and were more marked in patients who were seropositive for VGKC complex antibodies (6 of 10 seropositive patients; Figure 2).

Maintenance Immunotherapy and Relapse. Clinical relapse occurred after discontinuing or tapering initial immunotherapy in 20 (77%) of 26 patients who were followed up for 1 year or longer and had initially responded to immunotherapy. Long-term immunosuppression was instituted in 35 (76%) of 46 patients, usually IV corticosteroids or IVIG with or without a corticosteroid-sparing agent. Most patients were reevaluated every 3 to 6 months, and, depending on their

clinical response to treatment, attempts were made to reduce the frequency or dose of corticosteroids or IVIG infusions or to maintain remission with an alternative oral agent. Immunotherapy regimens included combinations of methylprednisolone infusions (1 g IV at 1- to 4-week intervals), 18 patients; oral prednisone, 17 patients; mycophenolate mofetil, 16 patients; IVIG infusions (6-8 doses at 1- to 4-week intervals), 13 patients; azathioprine, 8 patients; methotrexate, 4 patients; cyclophosphamide, 4 patients; plasma exchange, 2 patients; and rituximab, 1 patient. In 20 (57%) of 35 patients who received long-term immunosuppression therapy, symptoms relapsed in the course of reducing the dose or increasing the interval between IV infusions of immune globulin or methylprednisolone. Of 26 patients followed up for 1 year or longer, 21 (81%) were treated with long-term immunosuppression and 13 (62%) attained long-term remission (median, 26 months; range, 13-108 months).

Neuroimaging and EEG Findings Before and After Treatment. Nineteen responders (41%) had normal findings or nonspecific abnormalities (mild leukoaraiosis or mild generalized atrophy) on MRI of the brain. Signal abnormalities were noted in 16 patients (35%): 6 patients, mesiotemporal lobes only, and 10 patients, multiple regions (subcortical more than cortical: frontal, 7; parietal, 4; temporal, 4; occipital, 2; diffuse subcortical, 2; basal ganglia, 1; caudate and thalamus, 1 [compatible with Creutzfeldt-Jakob disease]; brainstem, 1). Eight patients with signal abnormalities (50%) had associated contrast enhancement:

TABLE 3. Neuropsychological Test Scores Before and After Treatment in 22 Immunotherapy Responders

Neuropsychological test	Patients with scores available before and after treatment	Area of cognition tested	Mean score before treatment	Mean score after treatment	P value
Dementia Rating Scale	10	Overall cognition	110	125	.03
AVLT trial 5 score	19	Learning and memory	7	10	<.001
AVLT delayed recall	19	Learning and memory	3	6	<.001
WAIS 3 verbal comprehension	10	Intelligence	100	106	.02
WAIS 3 perceptual organization	12	Intelligence	89	96	.03
TMT A (time in seconds taken to complete task)	19	Executive function	47	45	.65
TMT B (time in seconds taken to complete task)	14	Executive function	118	89	.03
COWAT	19	Language	28	32	.05
Category fluency	18	Language	31	39	.01
BNT long	13	Naming	49	52	.004
WRAT 3 SS	13	Reading	99	100	.32

Raw scores rather than Mayo Older Americans Normative Studies (MOANS) scaled scores were used because at the time of testing 8 of the 22 patients were younger than 56 years (the lower age limit in MOANS). AVLT = Auditory Verbal Learning Test; BNT long = Boston Naming Test long score; COWAT = Controlled Oral Word Association Test; TMT = Trail-Making Test; WAIS 3 = Wechsler Abbreviated Scale of Intelligence, Third Edition; WRAT 3 SS = Wide Range Achievement Test–Revision 3 reading subtest standardized score.

nonspecific, 4 patients; leptomenigeal, 3 patients; and periventricular, 1 patient. Six patients had moderate atrophy (diffuse, 4; focal, 2). Abnormalities were noted on PET in 13 of 17 patients tested (symmetric, 10; asymmetric, 3): hypometabolism in 11 patients (temporal, 8; parietal, 8; frontal, 7; posterior cingulate, 2; occipital, 1) and hypermetabolism in 2 patients (both mesiotemporal). Abnormalities were noted on SPECT in 11 (92%) of 12 patients tested (asymmetric, 6; symmetric, 5): hypoperfusion in 9 patients (temporal, 4; parietal, 4; frontal, 3; occipital, 2) and hypermetabolism in 2 patients (mesiotemporal, 1; frontal, 1).

Posttherapy improvement of abnormalities reported in brain imaging studies (Figure 3) included the following: MRI, 11 (73%) of 15 patients (mesiotemporal, 4; other regions, 7); PET, 4 (80%) of 5 patients (resolution of hypermetabolism, 2; resolution of hypometabolism, 2); and SPECT, 4 (57%) of 7 patients (resolution of hypometabolism, 3; resolution of hypermetabolism, 1). Electroencephalographic abnormalities were detected in 33 of 44 patients tested (symmetric in 22): slowing, 29 patients (diffuse, 18 [mild, 9; moderate, 8; severe, 1]; focal, 11 [moderate, 7; mild, 11; temporal, 8; frontal, 4]); and epileptiform activity, 8 patients (temporal, 5; frontal, 3; parietal, 1; diffuse, 1). Improvements in EEG abnormalities were seen in 8 (42%) of 19 patients treated by combinations of immunotherapy and antiepileptic medications: less slowing in 6 patients and resolution of epileptiform activity in 2 patients. Electroencephalographic findings for 2 patients are shown in Figure 4.

Brain or Nerve Biopsy Findings in 5 Immunotherapy Responders (Appendix 1). Patient 9 (right parietal lobe biopsy due to a radiologically suspected glioma) had

reactive gliosis and scant perivascular lymphocytes. Patient 43 (right frontal lobe and meningeal biopsy) had no abnormality. Patient 46 (temporal lobe biopsy) had marked gliosis and scant perivascular lymphocytic infiltrate. Patient 41 (right frontal lobe biopsy) had moderate chronic lymphocytic inflammation in white matter, both perivascular and parenchymal. Patient 4 (left sural nerve biopsy) had interstitial abnormalities and epineural mononuclear cellular infiltration consistent with an inflammatory process.

Autopsy Findings in 4 Immunotherapy Responders (Appendix 1). All had evidence of neurofibrillary tangles and neuritic plaques. The final diagnosis was Alzheimer disease with amyloid angiopathy in patients 12, 13, 15, and 43.

IMMUNOTHERAPY NONRESPONDERS

Final Diagnosis and Pathologic Findings. The final diagnoses documented for the 26 nonresponders (Appendix 2) were neurodegenerative dementia, 19 patients (not otherwise specified, 5; frontotemporal dementia, 4; Alzheimer disease, 2; Creutzfeldt-Jakob disease, 2 [confirmed by autopsy in patient 61]; dementia with Lewy bodies, 1; primary progressive aphasia, 1; semantic dementia, 1; mixed Alzheimer disease and Lewy body disease, 1 [confirmed by autopsy in patient 56]; mixed Alzheimer disease and multi-infarct dementia, 1; and mixed Alzheimer disease and autoimmune dementia, 1); nonresponsive autoimmune dementia, 4 patients; complex partial epilepsy, 1 patient; obstructive sleep apnea, 1 patient; and grade 3 astrocytoma, 1 patient.

Neuroimaging and EEG Findings Before and After Treatment. Of the 25 patients who underwent MRI, findings were normal in 16 (64%) and showed nonspecific

FIGURE 2. Neuropsychological evaluations before and after treatment in 6 patients positive for voltage-gated potassium channel (VGKC) complex antibody. Mayo Older Americans Normative Studies (MOANS) scaled scores in 6 patients with VGKC complex antibodies illustrate the initial severity of neuropsychological impairment and posttreatment improvement. Patient 1 (patient 42 in Appendix 1, which appears at the end of this article) presented with severely impaired verbal memory and lexical fluency, intact verbal learning, and mild-to-moderate impairment of other indices; treatment was followed by substantial improvement in verbal memory and less impressive improvement in other scores. Patient 2 (patient 5 in Appendix 1) had severe impairment of verbal learning, verbal memory, and semantic fluency and showed a stepwise, protracted, but nevertheless complete recovery over 8 months. Patient 3 (patient 45 in Appendix 1) had impaired verbal learning and memory, semantic fluency, and executive function; all deficits except that in semantic fluency resolved after treatment. Patient 4 (patient 46 in Appendix 1) presented with impairment in all cognitive domains. After initial treatment with intravenous methylprednisolone, followed by intravenous immune globulin, the patient had mild initial improvement but marked cognitive fluctuation during the next 9 months; follow-up tests showed improvement in some areas and deterioration in others. Patients 5 (patient 33 in Appendix 1) and 6 (patient 35 in Appendix 1) both had dramatic clinical improvement after receiving intravenous corticosteroids but relapsed within 1 month. Cognitive testing during relapse showed impaired perceptual organization (PO) and verbal learning and memory, which resolved after resumption of treatment (completely in patient 5, incompletely in patient 6). Median VGKC complex autoantibody values for these 6 patients decreased significantly from 1.04 nmol/L (range, 0.13-4.22 nmol/L; reference range, 0.00-0.02 nmol/L) to 0.14 nmol/L (range, 0.00-1.87 nmol/L) after immunotherapy. CFT = Category Fluency Test; COWAT = Controlled Oral Word Association Test; DR = delayed recall; LOT = learning over trials; TMT = Trail-Making Test; VC = verbal comprehension.

abnormalities (mild leukoaraiosis or mild generalized atrophy) in 9 (36%). Abnormalities included moderate atrophy, 8 patients (diffuse, 5; parietal, 1; frontotemporal, 1; parietal and hippocampal, 1); mesiotemporal T2 signal changes, 4 patients (2 enhancing); and Creutzfeldt-Jakob disease-like restricted diffusion in the cortical ribbon and basal ganglia, 1 patient. No improvements were not-

ed in patients for whom pretreatment and posttreatment images were available. All 12 patients who underwent PET had abnormalities: hypometabolism in 11 patients (temporoparietal, 4; bifrontal or bilateral frontotemporal, 3; focal frontal, 1; temporo-occipital, 1; temporal and posterior cingulate, 1; diffuse, 1) and hypermetabolism in 1 patient (bitemporal). Findings on SPECT were abnormal

FIGURE 3. Neuroimaging in patients with an immunotherapy-responsive cognitive disorder.

Magnetic resonance imaging: yellow arrows indicate areas of abnormality on fluid-attenuated inversion recovery (FLAIR). A, 36-year-old woman (patient 10 in Appendix 1) had fluctuating memory problems and was seropositive for glutamic acid decarboxylase-65 autoantibody. Bilateral hippocampal axial FLAIR abnormality, shown in A1, almost completely resolved after treatment with intravenous (IV) methylprednisolone (A2). B, 51-year-old woman (patient 20 in Appendix 1) had subacute fluctuating memory problems, multifocal neurologic examination findings, and evidence of autoimmunity (IgM antiphospholipid antibody). Symmetric confluent T2 signal abnormality in the white matter of both hemispheres (B1) decreased after treatment with IV methylprednisolone (B2). C, 60-year-old man (patient 41 in Appendix 1) had memory, language, and gait problems and was seropositive for both striational and glutamic acid decarboxylase-65 antibodies. Axial T1 magnetic resonance imaging with contrast demonstrated periventricular vessel enhancement (C1) and resolution after treatment (C2). D, 53-year-old woman (patient 29 in Appendix 1) had memory loss, hallucinations, and subsequent seizure; cerebrospinal fluid protein was elevated (>100 mg/dL), and she was seropositive for thyroid peroxidase antibodies and neuronal and muscle acetylcholine receptor antibodies. Axial FLAIR images show diffusely increased T2 signal in the midbrain (D1), which improved after treatment with IV methylprednisolone (D2). Multiple myeloma was diagnosed 18 months after neurologic presentation.

Positron emission tomographic imaging: Brain reconstructions (brighter color represents regions of hypometabolism) in a 58-year-old man (patient 21 in Appendix 1) who presented with personality change and memory problems and had elevated cerebrospinal fluid protein (>100 mg/dL). Hypometabolism, predominantly frontal and temporal (E1), improved after treatment with IV methylprednisolone (E2).

Single-photon emission computed tomographic brain imaging: Brain neuroimaging in a 35-year-old man (patient 22 in Appendix 1) who presented with vertigo and memory problems, had multiple coexisting autoimmune conditions, and was seropositive for muscle acetylcholine receptor and striational antibodies. Diffuse decrease in uptake in frontotemporoparietal regions (F1) was markedly improved globally after treatment with IV methylprednisolone (F2).

in 4 (67%) of 6 patients (diffuse frontotemporoparietal hypoperfusion, 2; asymmetric hemispheric hypoperfusion, 2). Posttreatment improvements in functional (PET) imaging were seen in 1 of 3 patients (resolution of hypermetabolism) despite lack of clinical improvement. Elec-

troencephalographic abnormalities were detected in 18 (82%) of 22 patients tested: slowing, 13 patients (diffuse, 8 [moderate, 5; mild, 3]; focal temporal lobe, 5 patients [moderate, 3; mild, 2]); epileptiform activity, 4 patients (temporal, 3; frontal, 1); and triphasic waves, 1 patient.

FIGURE 4. Electroencephalogram (EEG) before and after immunotherapy in patients with immunotherapy-responsive cognitive disorders. A, EEG in a 60-year-old man (patient 31 in Appendix 1) who presented with memory difficulty and inattention and had elevated cerebrospinal fluid protein (>100 mg/dL) and voltage-gated potassium channel complex autoantibody. Before treatment, the EEG showed a left anterior temporal lobe seizure (A1) and left temporal intermittent rhythmic delta and sharp wave activity (A2). This resolved after treatment with both a loading dose of phenytoin and intravenous methylprednisolone (A3). Of note, this patient had corresponding improvements in mesiotemporal signal abnormality on magnetic resonance imaging and resolution of left temporal hypermetabolism on positron emission tomography. B, EEG in a 71-year-old man (patient 13 in Appendix 1) who presented with subacute, rapidly progressing memory problems mimicking Creutzfeldt-Jakob disease. He was seropositive for thyroid peroxidase antibody and had inflammatory cerebrospinal fluid. Note severe, diffuse theta and delta wave slowing maximal over the left hemisphere (B1), and improvement with mild background slowing (7-8 Hz posterior alpha) after treatment with intravenous methylprednisolone (B2).

Resolution of epileptiform activity was seen in 1 (14%) of 7 patients after treatment with combinations of immunotherapy and antiepileptic medications.

Neuropathology and Autopsy Findings. In 1 patient, right temporal lobe biopsy demonstrated a grade 3 astrocytoma. In another patient, autopsy revealed widespread spongiform change, mild gliosis, and proteinase-resistant scrapie prion protein consistent with Creutzfeldt-Jakob disease. In a third patient, autopsy revealed neurofibrillary tangles, neuritic plaques, and amyloid angiopathy plus widespread brainstem, limbic, and cortical Lewy bodies, pale bodies, and Lewy neurites, as is consistent with mixed Alzheimer and Lewy body disease.

FACTORS ASSOCIATED WITH IMMUNOTHERAPY RESPONSIVENESS

The mean interval from symptom onset to first immunotherapy treatment was 11 months in responders and 25 months in nonresponders ($P<.001$). Predictors of response to immunotherapy were identified by univariate logistic regression analysis and are summarized in Table 4 (with odds ratios and 95% confidence intervals): subacute onset ($P<.001$); fluctuating course ($P<.001$); tremor ($P=.007$); headache ($P=.06$); inflammatory CSF ($P=.02$); any neural autoantibody ($P=.03$); cation channel neural autoantibody ($P=.01$); and VGKC complex antibodies alone ($P=.05$).

Predictors of immunotherapy nonresponsiveness on the univariate logistic regression analysis included a family his-

TABLE 4. Summary of Predictors of Immunotherapy Response by Univariate Logistic Regression^a

	Total (N=72)	Responders (n=46)	Nonresponders (n=26)	P value ^b	OR (95% CI)
Clinical					
Subacute onset	52 (72)	43 (93)	9 (35)	<.001	27.1 (6.5-112.2)
Fluctuating course	47 (65)	42 (91)	5 (19)	<.001	44.1 (10.7-181.6)
Headache	12 (17)	11 (24)	1 (4)	.06	7.9 (0.9-64.8)
Tremor	21 (29)	19 (41)	2 (8)	.007	8.4 (1.8-40.1)
Family history of dementia	26 (36)	10 (22)	16 (62)	<.001	0.1 (0.04-0.4)
Neural autoantibodies	31/70 (44)	24/45 (53)	7/25 (28)	.03	3.1 (1.1-8.8)
Cation channels	18/58 (31)	16/37 (43)	2/21 (10)	.01	8.0 (1.6-39.2)
VGKC (nmol/L), median (range) ^c	11/58 (19)	10/37 (27)	1/21 (5)	.05	8.1 (1.0-68.6)
TPO antibody	40/68 (59)	22/44 (50)	18/24 (75)	.05	0.3 (0.1-1.0)
CSF analysis					
High protein (>100 mg/dL) or pleocytosis	19/67 (28)	17/43 (40)	2/24 (8)	.02	6.9 (1.4-33.1)
Time to treatment (mo), mean ± SD	16±17.9	11±12.1	25±22.6	.005	0.95 (0.91-0.98)

^a Data are provided as number (percentage) of patients unless otherwise indicated. CI = confidence interval; CSF = cerebrospinal fluid; OR = odds ratio; TPO = thyroid peroxidase; VGKC = voltage-gated potassium channel complex.

^b P values from univariate logistic regression analysis.

^c Reference range: 0.00-0.02 nmol/L.

tory of dementia ($P<.001$); a higher Kokmen score before treatment ($P=.03$); TPO antibody ($P=.05$); and delayed initial treatment ($P=.005$). Posttherapy improvements in neuroimaging studies were more frequent in responders than in nonresponders (17 [68%] of 25 vs 1 [17%] of 6; $P=.02$).

EXTENDED SCREENING FOR NEURAL-SPECIFIC IgGs

IgG immunostaining patterns consistent with VGKC complex autoimmunity were identified in 11 patients (Figure 5, D and E; Appendix 1: patients 31 and 33). The specificity of this antibody was confirmed by radioimmunoprecipitation

FIGURE 5. IgGs binding selectively to central nervous system tissues. Immunohistochemical staining by glutamic acid decarboxylase-65 (A-C; patient 29 in Appendix 1 and patients 53 and 70 in Appendix 2) and voltage-gated potassium channel complex (D, E; patients 31 and 33 in Appendix 1) antibodies on a composite of mouse tissues: kidney (Kid), cerebellum (CbL, both granular layers [GL] and molecular layers [ML]), midbrain (MB), entorhinal cortex (Cortex), hippocampus (Hip), and thalamus (Thal). F, Unclassified IgG restricted to central nervous system tissues in a patient with immunotherapy-responsive dementia (patient 14 in Appendix 1). No patient had an IgG targeting *N*-methyl-D-aspartate, α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, or γ -aminobutyric type B receptors.

tation assay: range of values, 0.13 to 4.22 nmol/L (reference ranges provided parenthetically) (0.00-0.02 nmol/L). All seropositive patients were immunotherapy responders. Glutamic acid decarboxylase-65 IgG, detected by immunostaining in 11 patients (Figure 5, A-C; Appendix 1 and 2: patients 29, 53, and 70), was also confirmed by a radioimmunoprecipitation assay (range of values, 0.04-403 nmol/L (0.00-0.02 nmol/L). No patient's serum yielded an immunostaining pattern consistent with NMDA,⁸ α -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid,³⁵ or γ -aminobutyric type B receptor reactivity.³⁶ One patient's serum contained a novel IgG that bound selectively to the hippocampus and cerebral cortex (Figure 5, F; Appendix 1: patient 14).

DISCUSSION

All patients for whom we describe clinical, serologic, and imaging findings had a predominantly cognitive clinical presentation that the treating physician suspected to have an autoimmune basis. The high frequency and striking extent of objective improvements in cognition after immunotherapy warrant emphasis. The assignment of an initial diagnosis of a neurodegenerative or prion disease to 35% of patients who subsequently improved after immunotherapy suggests that autoimmune dementia may be underrecognized and the potential benefit of immunotherapy missed in many patients. Although population-based studies are lacking for the incidence and prevalence of autoimmune dementia, 20% of dementia cases occurring in patients younger than 45 years presenting to an academic medical center were reported to have an autoimmune or inflammatory cause.³⁷

Documentation of cognitive deficits by mental status testing and standard neuropsychological testing was particularly helpful in objective measurement of improvements after immunotherapy. The data we present refute reliance on impaired attention as the primary domain of cognitive impairment on mental status testing. All areas of cognition were impaired, but in comparison with other cognitive deficits, deficits in recall were more frequent and severe and showed greater improvements after immunotherapy. This observation is consistent with MRI abnormalities often being located in mesiotemporal lobes.

The design of our study allowed the identification of clues that might predict immunotherapy responsiveness. Important clinical predictors of response to immunotherapy included a subacute onset, fluctuating course, and the physical finding of tremor. The detection of myoclonus on examination approached but did not reach statistical significance. In an autoimmune context, small-amplitude generalized myoclonus sometimes is mistaken clinically

for tremor.³⁸ Patients who benefited from immunotherapy were 8 times more likely to have headache than those who did not respond. Although not statistically significant ($P=.06$), headache may be a clue to an immune-mediated etiology for dementia. This finding warrants further investigation in larger studies. In evaluating a patient with cognitive symptoms, any of these clinical features heightens the suspicion for an immune-mediated dementia and warrants consideration of an immunotherapy trial.

The significant correlation of CSF protein elevation (>100 mg/dL) or pleocytosis with response to immunotherapy justifies analysis of CSF in evaluating a suspected autoimmune dementia. Other CSF markers of inflammation (raised IgG index or synthesis rate or excess oligoclonal bands) favor an autoimmune rather than neurodegenerative dementia, but their frequency in responders and nonresponders did not differ significantly in this study. Supernumerary CSF oligoclonal bands have been reported in 7% of pathologically proven neurodegenerative conditions.³⁹

In patients who responded to immunotherapy, brain biopsy revealed gliosis and perivascular lymphocytic infiltration similar to findings described in patients with nonvasculitic autoimmune inflammatory meningoencephalitis.⁴⁰ Brain biopsy should be considered in patients with an atypical dementia syndrome that is suspected to have a nondegenerative etiology but lacks objective evidence of autoimmunity. The 4 immunotherapy-responsive patients who had pathologic findings consistent with Alzheimer disease with amyloid angiopathy were especially informative. It is conceivable that 2 etiologic processes contributed to their cognitive impairment or, alternatively, that immunotherapy suppressed the amyloid angiopathy or an inflammatory component early in the course of an evolving neurodegenerative disorder.

Detection of neural antibodies, especially neuron-specific cation channel complex autoantibodies, was another laboratory-based clue predicting a favorable response to immunotherapy. We identified autoantibodies targeting the VGKC complex, voltage-gated calcium channels, or a neuronal AChR in 43% of responders and 10% of nonresponders. These findings justify a comprehensive serologic evaluation for neural autoantibodies in investigating a patient with suspected neurodegenerative dementia who has any atypical features. Cognitive impairment is a recognized association of several neuron-specific autoantibodies: the VGKC complex,^{6,41} the NMDA receptor,⁸ and neuronal AChR antibodies.⁷ Because neoplasia is found in 33% to 80% of seropositive patients,^{6,42} detection of these autoantibodies justifies a search for cancer. In the current study, cancer was identified in 3 seropositive patients: 1 with multiple myeloma, 1 with colonic adenocarcinoma,

and 1 with small cell lung carcinoma. Thus, the detection of a neuron-specific autoantibody in a patient with autoimmune dementia may lead to the diagnosis of an unsuspected neoplasm.

Despite the reported association of TPO antibodies and autoimmune encephalopathies, detection of thyroid antibodies was not predictive of immunotherapy responsiveness in patients in this study. This likely reflects the high prevalence of TPO antibodies in the general population (2%-10% in younger adults and 5%-20% in healthy older adults).⁴³⁻⁴⁵ We regard as obsolete the continued use of the term *Hashimoto encephalopathy* in patients with autoimmune dementia or autoimmune encephalopathy. Detection of TPO antibodies reflects a predisposition to an autoimmune neurologic disorder but does not imply a pathogenic role for those autoantibodies. We anticipate that continuing advances in autoimmune neurology will identify new neuron-specific autoantibodies as the cause of reversible cognitive decline in these patients.

A shorter delay from symptom onset to initiation of therapy for autoimmune dementia increased the likelihood of response to immunotherapy. This emphasizes the importance of early and correct diagnosis and prompt treatment. Evidence-based outcomes for treatment of autoimmune dementia are limited and confined to case reports and small case series.^{3,39,46} The improvements we observed after acute treatments were often not sustained. Most patients in our cohort had a clinical relapse on cessation or reduction of immunotherapy. Careful selection of patients for long-term immunotherapy is important, given the risk of serious adverse effects, especially when immunotherapy agents are combined.

The use of long-term immunosuppressive treatment is advocated only for patients with objectively documented improvements in an initial trial of immunotherapy.¹ In patients who regain normal cognition after immunotherapy or continue to improve after acute treatment, we recommend close continued observation without continued immunosuppression. However, long-term immunotherapy should be considered in patients who respond suboptimally, plateau clinically, or relapse. The substantial improvements reported in our study justify offering the option of long-term immunotherapy for informed patients of this type. It is important to include a corticosteroid-sparing agent (such as azathioprine or mycophenolate mofetil) to minimize or possibly discontinue the use of corticosteroids. Maintenance immunotherapy is guided by symptoms reported by the patient or family members, periodic objective cognitive assessments, and medication adverse effects.

Prophylactic treatments to avert osteoporosis and *Pneumocystis jiroveci* infection are advised for patients requir-

ing long-term corticosteroid therapy. Use of mycophenolate mofetil or azathioprine as a corticosteroid-sparing agent requires careful monitoring of hematologic, hepatic, and renal function indices. We generally reserve the use of cyclophosphamide, rituximab, and plasma exchange for patients refractory to or intolerant of other therapies.

As a retrospective analysis, our study introduces the risk of observer bias, and the lack of a placebo-treated group makes it difficult to determine the natural course of an immune-mediated dementia. The limited sample size precluded a multivariate logistic regression analysis, and the width of the confidence intervals for odds ratio was higher than anticipated. Another potential shortcoming of our study is the heterogeneous cohort, which encompassed patients with neuron-specific, other organ-specific, and non-organ-specific autoantibodies, as well as patients without detectable autoantibodies. We recognize that some patients may have responded to immunotherapy through suppression of a nonautoimmune inflammatory process. Nevertheless, patient heterogeneity reflects the reality of the spectrum of immunotherapy-responsive cognitive impairment encountered in a clinical setting. Although clinical, radiologic, and serologic findings are diverse, they are unified diagnostically by the response to immunotherapy. This report provides a framework for future larger studies and represents current knowledge in the field.

The diagnosis and treatment of an autoimmune dementia is often delayed, reflecting a lack of recognition of this disorder. We have outlined in a diagnostic algorithm (Figure 6) a suggested stepwise approach to evaluating patients with suspected autoimmune dementia. We hope that this will assist neurologists and other physicians in identifying and managing patients with autoimmune dementia.

CONCLUSION

Autoimmune dementias are underrecognized and frequently misdiagnosed as neurodegenerative or prion disorders. Cognitive assessments by mental status examination or neuropsychological testing are helpful for documenting objective improvements after immunotherapy. This article reports objective improvements (often substantial) after an initial trial of immunotherapy in patients considered to have an irreversible neurologic disorder and maintenance of long-term remission with extended immunotherapy. Functional neuroimaging, EEG, and MRI improvements frequently correlated with clinical response to immunotherapy. Recognition of clinical and serologic clues to an autoimmune dementia allows early and sustained treatment, thus optimizing favorable neurologic outcomes.

FIGURE 6. Diagnostic algorithm for suspected autoimmune dementia or encephalopathy. CSF = cerebrospinal fluid; IVIG = intravenous immune globulin; IVMP = intravenous methylprednisolone.

* If no other cause for dementia is identified, consider a trial of immunotherapy.

† If findings on neural antibody testing are positive, consider screening for underlying malignancy with computed tomography or positron emission tomography.

‡ CSF protein level >100 mg/dL or pleocytosis (white blood cell count >5).

§ Reference 1.

// Repeat objective cognitive assessments to aid in evaluating response to immunotherapy.

We thank our colleagues Richard J. Caselli, MD, and the late Emre Kokmen, MD, for their contributions to the characterization and management of patients with autoimmune encephalopathies.

REFERENCES

1. McKeon A, Lennon VA, Pittock SJ. Immunotherapy-responsive dementias and encephalopathies. *Continuum Lifelong Learning Neurol.* 2010;16(2):80-101.
2. Castillo P, Woodruff B, Caselli R, et al. Steroid-responsive encephalopathy associated with autoimmune thyroiditis. *Arch Neurol.* 2006;63(2):197-202.
3. Geschwind MD, Tan KM, Lennon VA, et al. Voltage-gated potassium channel autoimmunity mimicking Creutzfeldt-Jakob disease. *Arch Neurol.* 2008;65(10):1341-1346.
4. McKeon A, Marnane M, O'Connell M, Stack JP, Kelly PJ, Lynch T. Potassium channel antibody associated encephalopathy presenting with a fronto-temporal dementia like syndrome. *Arch Neurol.* 2007;64(10):1528-1530.
5. Brain L, Jellinek EH, Ball K. Hashimoto's disease and encephalopathy. *Lancet.* 1966;2(7462):512-514.
6. Tan KM, Lennon VA, Klein CJ, Boeve BF, Pittock SJ. Clinical spectrum of voltage-gated potassium channel autoimmunity. *Neurology.* 2008;70(20):1883-1890.
7. McKeon A, Lennon VA, Lachance DH, Fealey RD, Pittock SJ. Ganglionic acetylcholine receptor autoantibody: oncological, neurological, and serological accompaniments. *Arch Neurol.* 2009;66(6):735-741.
8. Dalmau J, Gleichman AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol.* 2008;7(12):1091-1098.
9. Maselli RA, Agius M, Lee EK, Bakshi N, Mandler RN, Ellis W. Morvan's fibrillary chorea: electrodiagnostic and in vitro microelectrode findings. *Ann N Y Acad Sci.* 1998;841(May):497-500.
10. Spitz M, Ferraz HB, Barsottini OG, Gabbai AA. Progressive encephalomyelitis with rigidity: a paraneoplastic presentation of oat cell carcinoma of the lung: case report. *Arq Neuropsiquiatr.* 2004;62(2B):547-549.
11. Shaw PJ, Walls TJ, Newman PK, Cleland PG, Cartledge NE. Hashimoto's encephalopathy: a steroid-responsive disorder associated with high anti-thyroid antibody titers—report of 5 cases. *Neurology.* 1991;41(2, pt 1):228-233.
12. Caselli RJ, Boeve BF, Scheithauer BW, O'Duffy JD, Hunder GG. Non-vasculitic autoimmune inflammatory meningoencephalitis (NAIM): a reversible form of encephalopathy. *Neurology.* 1999;53(7):1579-1581.
13. Kokmen E, Smith GE, Petersen RC, Tangalos E, Ivnik RC. The short test of mental status: correlations with standardized psychometric testing. *Arch Neurol.* 1991;48(7):725-728.
14. Tang-Wai DF, Knopman DS, Geda YE, et al. Comparison of the short test of mental status and the mini-mental state examination in mild cognitive impairment. *Arch Neurol.* 2003;60(12):1777-1781.
15. Wechsler D. *Wechsler Memory Scale*. Revised ed. San Antonio, TX: Psychological Corp; 1987.
16. Wechsler D. *Wechsler Abbreviated Scale of Intelligence (WASI)*. San Antonio, TX: Harcourt Assessment; 1999.
17. Wilkinson GS. *Wide Range Achievement Test—Revision 3 (WRAT-3)*. Wilmington, DE: Jastak Association; 1993.
18. Rey A. *L'examen clinique en psychologie*. Paris, France: Presses Universitaires de France; 1970.
19. Benton AL, Hamsher K, Sivan AB. *Multilingual Aphasia Examination*. 3rd ed. San Antonio, TX: Psychological Corporation; 1994.
20. Kaplan E, Goodglass H, Weintraub S. *The Boston Naming Test*. Philadelphia, PA: Lea & Febiger; 1978.
21. Lucas JA, Ivnik RJ, Smith GE, et al. Mayo's older Americans normative studies: category fluency norms. *J Clin Exp Neuropsychol.* 1998;20(2):194-200.
22. Reitan R. Validity of the Trail-Making Test as an indication of organic brain damage. *Percept Mot Skills.* 1958;8:271-276.
23. Reitan RM. *Trail Making Test: Manual for Administration and Scoring*. Tucson, AZ: Reitan Neuropsychology Laboratory; 1992.
24. Hughes CP, Berg L, Danziger WL, Coben LA, Martin RL. A new clinical scale for the staging of dementia. *Br J Psychiatry.* 1982;140(6):566-572.

25. Gaudino EA, Geisler MW, Squires NK. Construct validity in the Trail Making Test: what makes Part B harder? *J Clin Exp Neuropsychol.* 1995;17(4):529-535.
26. Ivnik RJ, Malec JF, Smith GE, Tangalos EG, Petersen RC. Neuropsychological testing norms above age 55: COWAT, BNT, MAE TOKEN, WRAT-R Reading, AMNART, Stroop, TMT, and JLO. *Clin Neuropsychol.* 1996;10(3):262-278.
27. Ivnik RJ, Malec JF, Smith GE, et al. Mayo's older Americans normative studies: updated AVLT norms for ages 56 to 97. *Clin Neuropsychol.* 1992;6(suppl 1):83-104.
28. Yu Z, Kryzer TJ, Griesmann GE, Kim K, Benarroch EE, Lennon VA. CRMP-5 neuronal autoantibody: marker of lung cancer and thymoma-related autoimmunity. *Ann Neurol.* 2001;49(2):146-154.
29. Pittock SJ, Kryzer TJ, Lennon VA. Paraneoplastic antibodies coexist and predict cancer, not neurological syndrome. *Ann Neurol.* 2004;56(5):715-719.
30. Pittock SJ, Yoshikawa H, Ahlskog JE, et al. Glutamic acid decarboxylase autoimmunity with brainstem, extrapyramidal, and spinal cord dysfunction. *Mayo Clin Proc.* 2006;81(9):1207-1214.
31. Dhamija R, Tan KM, Pittock SJ, Foxx-Orenstein A, Benarroch E, Lennon VA. Serological profiles aiding the diagnosis of autoimmune gastrointestinal dysmotility. *Clin Gastroenterol Hepatol.* 2008;6(9):988-992.
32. Pasha SF, Lunsford TN, Lennon VA. Autoimmune gastrointestinal dysmotility treated successfully with pyridostigmine. *Gastroenterology.* 2006;131(5):1592-1596.
33. Vernino S, Low PA, Fealey RD, Stewart JD, Farrugia G, Lennon VA. Autoantibodies to ganglionic acetylcholine receptors in autoimmune autonomic neuropathies. *N Engl J Med.* 2000;343(12):847-855.
34. Griesmann GE, Kryzer TJ, Lennon VA. Autoantibody profiles of myasthenia gravis and Lambert-Eaton myasthenic syndrome. In: Rose NR, Hamilton RG, Detrick B, eds. *Manual of Clinical and Laboratory Immunology*. 6th ed. Washington, DC: ASM Press; 2002:1005-1012.
35. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol.* 2009;65(4):424-434.
36. Lancaster E, Lai M, Peng X, et al. Antibodies to the GABA(B) receptor in limbic encephalitis with seizures: case series and characterisation of the antigen. *Lancet Neurol.* 2010;9(1):67-76.
37. Kelley BJ, Boeve BF, Josephs KA. Young-onset dementia: demographic and etiologic characteristics of 235 patients. *Arch Neurol.* 2008;65(11):1502-1508.
38. McKeon A, Pittock SJ, Glass GA, et al. Whole-body tremulousness: isolated generalized polymyoclonus. *Arch Neurol.* 2007;64(9):1318-1322.
39. Janssen JC, Godbolt AK, Ioannidis P, Thompson EJ, Rossor MN. The prevalence of oligoclonal bands in the CSF of patients with primary neurodegenerative dementia. *J Neurol.* 2004;251(2):184-188.
40. Lyons MK, Caselli RJ, Parisi JE. Nonvasculitic autoimmune inflammatory meningoencephalitis as a cause of potentially reversible dementia: report of 4 cases. *J Neurosurg.* 2008;108(5):1024-1027.
41. Vincent A, Buckley C, Schott JM, et al. Potassium channel antibody-associated encephalopathy: a potentially immunotherapy-responsive form of limbic encephalitis. *Brain.* 2004;127(pt 3):701-712.
42. Lucchinetti CF, Kimmell DW, Lennon VA. Paraneoplastic and oncologic profiles of patients seropositive for type 1 antineuronal nuclear autoantibodies. *Neurology.* 1998;50(3):652-657.
43. Sawin CT, Castelli WP, Herschman JM, McNamara P, Bacharach P. The aging thyroid: thyroid deficiency in the Framingham Study. *Arch Intern Med.* 1985;145(8):1386-1388.
44. Baker BA, Gharib H, Markowitz H. Correlation of thyroid antibodies and cytologic features in suspected autoimmune thyroid disease. *Am J Med.* 1983;74(6):941-944.
45. Vanderpump MP, Tunbridge WM, French JM, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. *Clin Endocrinol (Oxf).* 1995;43(1):55-68.
46. Vernino S, Geschwind M, Boeve B. Autoimmune encephalopathies. *Neurologist.* 2007;13(3):140-147.

APPENDIX 1 and APPENDIX 2 appear on the following pages.

APPENDIX 1. Clinical, Serologic, Oncologic, and Outcome Data for 46 Immunotherapy Responders^a

Patient No./ age (y)/ race/sex	Mem- ory loss	Sub- acute onset	Fluctu- ations	Other cognitive symptoms	Other neuro- logic manifes- tations	Initial Kokmen score (max score, 38)	Inflamma- tory CSF ^b	MRI signal abnormal- ities	TPO titer ^c (IU/mL)	Neural autoanti- body ^{c,d} (nmol/L)	Cancer	Time to immuno- therapy (mo)	Initial immuno- therapy type	Objective cognitive improvement Kokmen NP	Relapse during immuno- therapy taper	Follow- up dura- tion (mo)
1/53/W/M	+	+	+	ED, LM, VSD	-	37	-	-	361	-	-	5	IVMP	+	+	19
2/59/W/F	+	+	-	ED, LD	Pk	NT	NT	-	75	-	Breast	3	IVMP	NT	-	7
3/66/W/M	+	+	+	ED, LM, P	Sz	NT	-	+	-	VGKC 0.98	-	9	IVMP	NT	-	24
4/73/W/M	+	+	+	-	Sz, T	NT	-	-	-	-	-	1	IVMP	NT	-	68
5/65/W/M	+	+	+	LD	HA, My, Pk, T	21	-	+	455	GAD65 0.04 StrAb 480	-	1	IVMP	+	+	77
6/75/W/F	+	+	+	VH	Psv	6	+	-	-	-	WCC 19	2	IVMP	+	-	2
7/70/W/M	+	+	+	LM	HA, Sz	27	NT	+	115	-	-	5	IVMP	+	+	38
8/84/W/F	+	+	+	LM, P	Ataxia	23	-	-	-	gAChR 0.07	-	2	IVMP	+	+	28
9/72/W/F ^e	+	+	+	ED	PR	13	-	+	-	-	Breast	2	IVMP	+	-	8
10/36/W/F	+	+	+	-	Sz	27	-	+	-	GAD65 25.8	-	1	IVMP	+	-	99
11/49/U/F	+	+	+	ED, LD, VH	HA, muscle spasms, T	33	-	-	52	GAD65 0.15	-	3	IVMP	+	+	41
12/69/W/F ^f	+	+	+	LD, VSD	Apraxia, HA, Pk, T	32	-	+	90	-	Breast	10	IVMP	+	-	49
13/71/U/M ^f	+	+	+	VH, LM	T	NT	+	-	48	-	-	7	IVMP	NT	-	26
14/68/W/M	+	+	+	ED, LM	T	28	Pr 112 WCC 26	-	734	Novel synaptic ^g N-type CaCh 0.06	-	25	Dexa- methasone IVMP	+	-	10
15/50/W/F ^f	+	+	+	ED, LM	Pk, Sz	9	-	-	-	-	-	51	IVMP	+	-	10
16/44/W/F	+	+	+	ED, LD, LM	HA, Pk, Psv, PR, T	12	-	-	-	-	-	3	Dexa- methasone IVMP	+	-	54
17/48/W/M	+	+	+	ED, LD	-	NT	-	-	418	-	-	12	Prednisone IVMP	NT	+	13
18/47/W/F	+	+	+	ED	Ataxia, apraxia, Da, My (s), T	NT	-	+	46	GAD65 0.16	-	36	Prednisone IVMP	NT	+	37
19/50/W/F	+	+	+	ED, LD, VSD	Apraxia, ES, Pk, My, Sz, T	26	-	-	996	StrAb 30,720	-	9	IVMP	+	+	34
20/51/U/F	+	+	+	ED, LD, abulia	HA, Pk	11	-	+	-	-	-	2	IVMP	+	-	8
21/58/W/M	+	+	+	AH, ED, LD, LM	Aphasia, apraxia, PK, PR, T	16	+	-	-	-	-	45	IVMP	+	-	33
22/35/W/M	+	+	+	LD	Aphasia, vertigo	31	-	-	444	mAChR 0.19 StrAb 240	-	13	IVMP	+	-	37
23/40/W/F	+	+	+	AH, VH, LD	HA, My, T	34	-	-	20	-	-	24	Prednisone IVMP	+	+	18
24/58/U/F	+	+	+	ED, LD, P	Apraxia, My, PK, Sz	16	+	-	-	N-type CaCh 0.11	Breast	25	IVMP	+	-	29
25/75/W/F	+	+	+	H, LD, P	Aphasia	NT	Pr 112 WCC 6	-	99	-	-	0	IVMP	NT	-	3
26/57/W/M	+	+	+	ED, LD, LM	Pk	NT	-	-	-	-	-	6	IVMP	NT	-	2
27/42/W/F	+	+	+	ED, LD	HA	36	-	-	255	VGKC 0.13	-	13	IVMP	+	+	26

(Continued on page 896)

APPENDIX 1. Continued^a

Patient No./ age (y)/ race/sex	Mem- ory loss	Sub- acute onset	Fluctu- ations	Other cognitive symptoms	Other neuro- logic manifes- tations	Initial Kokmen score (max score, 38)	Inflamma- tory CSF ^b	MRI signal abnormal- ities	TPO titer ^c (IU/mL)	Neural autoanti- body ^{c,d} (nmol/L)	Cancer	Time to immuno- therapy (mo)	Initial immuno- therapy type	Objective cognitive improvement Kokmen NP	Relapse during immuno- therapy taper	Follow- up dura- tion (mo)
28/65/W/M	+	+	+	-	PK, My (p), My (s), T	26	-	-	-	N-type CaCh 0.2 P/Q-type CaCh 0.04 GAD65 0.76 Amp 1920	SCLC ^b	22	Prednisone	+	NT	21
29/53/W/F	+	+	+	ED, LD, H, LM, P	Apraxia, My (p), Sz	25	+	+	456	GAD65 0.14 mACHR 0.22 gACHR 0.11	Multiple myeloma ^h	3	IVMP	+	+	19
30/69/W/F	+	+	+	ED, LD	-	17	+	-	54	NT	-	9	Prednisone	NT	+	10
31/60/W/M	+	+	-	LM, P, VH	Sz	19	+	+	-	VGKC 2.68	-	1	IVMP	NT	-	9
32/67/W/M	+	-	-	ED	PR	NT	-	-	-	-	Melanoma	10	Prednisone	NT	+	2
33/62/W/F	+	+	+	LD	Sz, T	30	+	+	85	VGKC 0.13	-	6	IVMP	+	+	4
34/32/W/F	+	+	+	ED, TH	Ataxia, HA, T	31	+	+	-	-	-	12	IVMP	+	+	6
35/70/W/M	+	+	+	ED, VH	Ataxia, My, Sz	1	+	+	-	VGKC 1.87 gACHR 0.03	Colon ^h	2	IVMP	+	-	4
36/59/W/F	+	+	+	VH	My, PK, T	26	NT	-	NT	-	-	8	IVMP	+	+	2
37/53/W/M	+	+	+	AX, ED	T	36	-	-	-	-	-	21	IVMP	+	+	4
38/72/W/F	+	+	+	-	Ataxia, T, My	22	-	-	-	StrAb 1920	-	21	IVMP	+	-	3
39/74/W/M	+	+	+	ED, LD	My	35	-	+	39	VGKC 0.75	-	8	IVMP	NT	-	6
40/52/W/F	+	-	-	ED, LD	Apraxia, aphasia	16	-	-	116	GAD65 4.88	-	36	IVMP	+	+	2
41/60/W/M ^e	+	+	+	ED, LD	Ataxia, T	27	+	+	-	GAD65 0.05	-	4	IVMP	+	+	24
42/50/W/F	+	+	+	LM	HA	20	-	-	NT	StrAb 61,440 VGKC 2.09 N-type CaCh 0.41	Plasma- cytoma	0	Prednisone	NT	+	108
43/66/U/M ^{e,f}	+	-	+	ED, H	HA, PK, T	NT	+	+	-	-	Lung adenocarcinoma ^h	0	IVMP	NT	+	80
44/44/W/F	+	+	+	-	Ataxia, My, Sz	27	+	-	950	-	-	4	PLEX	+	NT	7
45/56/W/F	+	+	+	LD, LM, VSD	Sz	33	+	-	61	VGKC 4.22	-	6	IVMP	-	+	26
46/63/W/M ^e	+	+	+	LM	Sz, aphasia	27	+	-	-	VGKC 0.15	-	14	IVMP	+	+	22

^a AH = auditory hallucinations; Amp = amphotericin; Ax = anxiety; CaCh = voltage-gated calcium channel; CSF = cerebrospinal fluid; Da = dysarthria; ED = executive dysfunction; ES = exaggerated startle; F = female; gACHR = ganglionic acetylcholine receptor; GAD65 = glutamic acid decarboxylase-65; H = hallucinations; HA = headache; IVMP = intravenous methylprednisolone; LD = language difficulties; LM = low mood; M = male; mACHR = muscle acetylcholine receptor; MRI = magnetic resonance imaging; My = myoclonus; My (p) = polymyoclonus; My (s) = startle myoclonus; NP = neuropsychological testing; NT = not tested; P = psychosis; PK = parkinsonism; PLEX = plasma exchange; PR = primitive reflexes; Pr = protein; Psv = perseveration; SCLC = small cell lung carcinoma; StrAb = striational antibody; Sz = seizures; T = tremor; TH = tactile hallucinations; TPO = thyroid peroxidase antibody; U = unknown; VGKC = voltage-gated potassium channel; VH = visual hallucinations; VSD = visuospatial difficulties; W = white; WCC = white blood cell count.

^b Pleocytosis, or protein >100 mg/dL. Unit of measure for protein values is mg/dL.

^c Reference ranges: TPO antibody, <9 IU/mL; VGKC antibody, 0.00-0.02 nmol/L; mACHR and gACHR antibody, 0.00-0.03 nmol/L; P/Q-type CaCh antibody, 0.00-0.02 nmol/L.

^d ANNA-1, <240; Amp antibody, <240; GAD65 antibody, 0.00-0.02 nmol/L; StrAb, <60. Values are provided in nmol/L, with the exception of StrAb and amphiphysin antibody.

^e Brain biopsy performed (see text).

^f Autopsy performed (see text).

^g See Figure 5, F.

^h Cancer detected after onset of neurologic symptoms.

APPENDIX 2. Clinical, Serologic, Oncologic, and Outcome Data for 26 Immunotherapy Nonresponders^a

Patient No./ age (y)/ race/sex	Memory loss	Sub- acute onset	Fluctua- tions	Other cognitive symptoms	Other neurologic manifesta- tions	Initial Kokmen score (max score, 38)	Inflamma- tory CSF ^b	MRI signal abnormal- ities	TPO titer ^c (IU/mL)	Neural autoanti- body ^{d,e} (nmol/L)	Cancer	Time to immuno- therapy (mo)	Initial immuno- therapy type	Follow- up duration (mo)	Final diagnosis to explain episode
47/71W/M	+	+	-	LD	My, Pk	27	-	-	-	-	Colon ^e	3	IVMP	9	Mixed Alzheimer and autoimmune dementia
48/72W/F	+	+	-	ED, LM	Apraxia, Pk	32	-	-	2337	StrAb 491,520	Breast	10	IVMP	2	Neurodegenerative dementia
49/67W/M	+	+	+	-	-	26	-	-	295	-	Thymic	25	IVMP	4	Nonresponsive autoimmune dementia
50/56W/M	+	+	-	LM, VH, VSD	Sz	32	-	+	NT	ANNA-1 30,720	Prostate	12	IVMP	47	Nonresponsive autoimmune dementia
51/46W/M	+	-	-	AH	-	34	-	-	408	GAD65 11.3	-	16	Prednisone	6	Nonresponsive autoimmune dementia
52/53W/F	+	-	-	ED	T	26	-	-	461	-	-	48	IVMP	0	Alzheimer disease
53/81W/M	+	+	-	LM	Pk	24	-	-	-	GAD65 41.8	-	82	IVMP	2	Neurodegenerative dementia
54/77W/F	+	-	-	ED, LD	Aphasia, PR, Pa	NT	NT	-	675	-	-	27	Prednisone	4	Semantic dementia
55/59W/F	+	-	-	LD	Aphasia, apraxia	NT	-	-	1848	-	Breast	17	IVMP	22	Frontotemporal dementia
56/62W/M ^f	+	-	+	LM, VH, VSD	Pk	24	NT	-	605	-	-	63	IVMP	77	Mixed Alzheimer and Lewy body dementia
57/66W/F	+	-	-	ED	-	NT	-	-	929	-	-	36	IVMP	30	Mixed Alzheimer and multi-infarct dementia
58/65W/F	+	-	-	LD, LM	Pk	32	-	-	1150	-	-	15	IVMP	64	Frontotemporal dementia
59/48W/M	+	-	-	LM, Ax	-	32	-	-	4000	-	-	37	IVMP	39	Neurodegenerative dementia
60/47W/M	+	+	+	-	Sz	27	-	+	-	-	SCLC ^e	13	IVMP	7	Nonresponsive autoimmune dementia
61/39W/F ^f	+	-	-	ED, LD	Ataxia, HA, My	31	-	-	263	-	-	2	IVMP	1	CJD
62/50W/F	+	-	-	ED, LM	Apraxia	31	-	-	998	-	-	25	IVMP	37	Alzheimer disease
63/62W/F	+	-	-	ED, LM, P	-	NT	-	-	NT	mAChR 0.11	-	11	Prednisone	10	Frontotemporal dementia
64/31W/M	+	-	-	-	-	NT	-	-	3230	-	-	4	Prednisone	0	Not specified
65/51W/F	+	-	-	LD	Aphasia, apraxia	29	-	-	>950	-	-	87	IVMP	8	Primary progressive aphasia
66/56W/F	+	-	-	Ax, LD	-	25	-	-	204.6	-	-	36	IVMP	12	Frontotemporal dementia
67/51U/F	+	-	-	ED	Apraxia	NT	+	-	-	-	-	11	Prednisone	5	Neurodegenerative dementia or CNS lupus
68/40W/F	+	+	-	LD, LM	Pa	25	-	+	-	-	-	7	IVMP	5	CJD
69/56U/F ^g	+	-	-	-	Sz	28	-	+	25.1	-	Astrocytoma ^e	10	IVMP	6	Fibrillary astrocytoma grade 3
70/56W/F	+	+	+	-	Sz	34	-	-	>950	GAD65 403	-	18	IVIG	13	Primary seizure disorder
71/63U/F	+	-	-	LM	-	22	+	-	183.3	StrAb 7680	-	25	IVMP	6	Neurodegenerative dementia
72/61W/M	+	+	+	AH, VH	Pk, T	33	-	-	-	gAChR 0.45 VGKC 0.05	-	16	IVMP	3	Lewy body dementia

^a AH = auditory hallucinations; ANNA-1 = antineuronal nuclear antibodies, type 1; Ax = anxiety; CJD = Creutzfeldt-Jakob disease; CNS = central nervous system; CSF = cerebrospinal fluid; ED = executive dysfunction; F = female; gAChR = ganglionic acetylcholine receptor; GAD65 = glutamic acid decarboxylase-65; IVIG = intravenous immune globulin; IVMP = intravenous methylprednisolone; LD = language difficulties; LM = low mood; M = male; mAChR = muscarinic acetylcholine receptor; MRI = magnetic resonance imaging; My = myoclonus; NT = not tested; P = psychosis; Pa = prosopagnosia; Pk = parkinsonism; PR = primitive reflexes; SCLC = small cell lung carcinoma; StrAb = striational antibody; Sz = seizures; T = tremor; TPO = thyroid peroxidase; U = unknown; VGKC = voltage-gated potassium channel; VH = visual hallucinations; W = white; WCC = white blood cell count.

^b Pleocytosis, or protein >100 mg/dL.

^c Reference ranges: TPO antibody, <9 IU/mL; VGKC antibody, 0.00-0.02 nmol/L; mAChR and gAChR antibody, 0.00-0.02 nmol/L; ANNA-1, <240; GAD65 antibody, 0.00-0.02 nmol/L; StrAb, <60.

^d Values are provided in nmol/L, with the exception of StrAb and ANNA-1.

^e Cancer diagnosed after neurologic presentation.

^f Autopsy performed (see text).

^g Brain biopsy performed (see text).