

# Neuropsychiatric Autoimmune Encephalitis without VGKC-Complex, NMDAR, and GAD Autoantibodies: Case Report and Literature Review

Souhel Najjar, MD,\*† Daniel Pearlman, BA,\*‡ Orrin Devinsky, MD,\*†§|| Amanda Najjar, ¶  
Siddhartha Nadkarni, MD,\*†|| Tracy Butler, MD,\*† and David Zagzag, MD, PhD¶

**Abstract:** We report a patient with a seronegative autoimmune panencephalitis, adding a subtype to the emerging spectrum of seronegative autoimmune encephalitis, and we review the sparse literature on isolated psychiatric presentations of autoimmune encephalitis. (A PubMed search for “seronegative autoimmune encephalitis,” “nonvasculitic autoimmune inflammatory meningoencephalitis,” and related terms revealed < 25 cases.) A 15-year-old girl developed an acute-onset isolated psychosis with prominent negative symptoms and intermittent encephalopathy. Despite clinical worsening, her brain magnetic resonance imaging (MRI) scans remained normal for 7 years. Serology was negative for voltage-gated potassium channel (VGKC)-complex, *N*-methyl-d-aspartate receptor (NMDAR), and glutamic acid decarboxylase (GAD) autoantibodies. We excluded genetic, metabolic, paraneoplastic, degenerative, and infectious etiologies. The patient’s symptoms remitted fully with immune therapy, but recurred in association with widespread bihemispheric brain lesions. Brain biopsy revealed mild nonvasculitic inflammation and prominent vascular hyalinization. Immune therapy with plasma exchanges cleared the MRI abnormalities but, 10 years after onset, the patient still suffers neuropsychiatric sequelae. We conclude that autoimmune panencephalitis seronegative for VGKC-complex, NMDAR, and GAD autoantibodies is a subtype of autoimmune encephalitis that can present with pure neuropsychiatric features and a normal brain MRI. Immunologic mechanisms may account for psychiatric symptoms in a subset of patients now diagnosed with classical psychotic disorders. Delay in starting immune therapy can lead to permanent neuropsychiatric sequelae. We propose a standardized classification system for the autoimmune encephalitides, integrating earlier pathology-oriented terms with more recently defined serologic and clinical phenotypes.

**Key Words:** neuroinflammation, autoimmune, psychosis, encephalitis, seronegative

(*Cogn Behav Neurol* 2013;26:36–49)

**A**utoimmune encephalitis is characterized by an acute or subacute onset of encephalopathy, seizures, cognitive impairment, and neuropsychiatric symptoms.<sup>1</sup> The clinical subtypes of autoimmune encephalitis—defined by the localization of seizures and abnormalities on magnetic resonance imaging (MRI)—are paraneoplastic and nonparaneoplastic (1) limbic encephalitis (LE), (2) extra-limbic encephalitis (ELE), and (3) panencephalitis.

The paraneoplastic subtype is associated with antibodies targeting intracellular onconeural antigens, such as anti-Hu, anti-CV2/CRMP5, and anti-Ma2 antibodies.<sup>1</sup> Antibodies targeting the GluR1 and GluR2 subunits of the amino-3-hydroxy-5-methyl-L-4-isoxazolepropionic acid receptor (AMPAR)<sup>2</sup> and the B1 subunit of the gamma aminobutyric acid-B (GABA<sub>B</sub>) receptor<sup>3</sup> are frequently associated with paraneoplastic LE, older age, and seizures.<sup>2</sup> Antibodies targeting glutamic acid decarboxylase (GAD)<sup>4</sup> are associated with an often-refractory nonparaneoplastic ELE,<sup>4</sup> LE,<sup>1</sup> and panencephalitis.<sup>5</sup> Anti-voltage-gated potassium channel (VGKC)-complex antibodies are often associated with a nonparaneoplastic LE,<sup>1</sup> while antibodies targeting the NR1/NR2B heteromers of the *N*-methyl-d-aspartate receptor (NMDAR) are associated with the typical paraneoplastic and nonparaneoplastic etiologies of panencephalitis.<sup>1,6,7</sup> Sometimes, autoimmune encephalitides are associated with an underlying systemic autoimmune disorder<sup>8</sup> or negative serology.<sup>9</sup>

*Seronegative autoimmune encephalitis* describes a nonparaneoplastic, noninfectious subgroup of autoimmune encephalitides with suspected immunologic mechanisms but no established pathogenic autoantibody or corresponding targeted neural autoantigens.<sup>9</sup> The absence of pathogenic serum autoantibodies may result from a spontaneous decline in previously elevated autoantibody titers,<sup>10</sup> or from an autoimmune process involving novel autoantibodies to specific neural antigens.<sup>9</sup> A third possibility—that the serum is truly negative—would suggest the pathogenic role of a not-yet-defined cellular autoimmune process.

Received for publication October 23, 2011; accepted October 9, 2012.  
From the \*New York University Comprehensive Epilepsy Center;

†Department of Neurology; ¶Division of Neuropathology, Department of Pathology; §Department of Neurosurgery; ||Department of Psychiatry, New York University School of Medicine, New York, NY; and ‡Geisel School of Medicine at Dartmouth College, The Dartmouth Institute for Health Policy and Clinical Practice, Lebanon, NH.

The authors declare no conflicts of interest.

Reprints: Souhel Najjar, MD, New York University Comprehensive Epilepsy Center, 223 E 34th St, New York, NY 10016 (e-mail: mna1024231@aol.com).

Copyright © 2013 by Lippincott Williams & Wilkins

We present the clinical and pathologic findings of a young woman with VGKC-complex, NMDAR, and GAD autoantibody-seronegative autoimmune panencephalitis (SNAPE). She presented with a cyclic neuropsychiatric disorder characterized by florid psychosis with prominent negative symptoms and intermittent encephalopathy, without seizures or focal neurologic deficits. Only 7 years later did she develop abnormalities visible on brain MRI. We show evidence for the neuroinflammatory and immunologic mechanisms associated with neuropsychiatric manifestations of seronegative autoimmune encephalitides. We also propose a system for classifying autoimmune encephalitides that aims to synthesize the pathology-oriented term *nonvasculitic autoimmune inflammatory meningoencephalitis* (NAIM) with more recently defined serologic and clinical phenotypes of these disorders.

## CASE REPORT

A 21-year-old right-handed woman was brought to our center at New York University for evaluation of intermittent psychosis and encephalopathy over the past 6 years and 2 months. She had been living at home with her family, and was neither enrolled in school nor employed.

Born at 33 weeks' gestation, the patient had reached normal developmental milestones and functioned above average academically into the 10th grade. During that grade, when she was 15 years old, she suddenly began having psychotic episodes that tracked with her menstrual cycle, which was notable for excessive menstrual bleeding (menorrhagia). Each psychotic episode started a few days before her monthly menstrual period and lasted for up to 15 days. Episodes consisted of odd behavior, emotional disconnection, mild disorientation, inappropriate and abnormal smiling and laughing, inability to perform activities of daily living, lack of hygiene, mild dyspraxia, mild dysphasia, and marked insomnia. The most consistent features were severe social isolation, severe emotional blunting, and very poor self-care and hygiene. Rare episodes brought agitation, but without violence. The neuropsychiatric symptoms persisted at a low level during the intervals between menstrual periods. The patient had no history of substance abuse.

She was treated in an inpatient psychiatric unit for 4 weeks and then was enrolled in a day-treatment program.

A brain MRI performed within the first year of her illness was reportedly normal. Neuropsychological evaluation at the time showed a full-scale intelligence quotient (IQ) of 77 (6th percentile), verbal IQ of 93 (32nd percentile), and performance IQ of 55 (<1st percentile). The patient had difficulties with language processing, memory, attention, and the organizational skills of mental flexibility and decision making. At school, she had significant problems with reading comprehension, mathematics, and expressive writing.

Repeat neuropsychological testing 2 years after disease onset revealed similar IQ scores, but worse scores for visuospatial and visuoperceptual processing, language

processing, auditory (5th percentile) and reading (36th percentile) comprehension, written expression (18th percentile), verbal fluency (50th percentile), auditory memory (immediate recall in the 9th percentile, short-term spontaneous and delayed recall in the <1st percentile), attention, and executive function, particularly organizational skills (1st percentile).

A repeat brain MRI 6 years after onset was normal (Figs. 1, 2). Follow-up neuropsychological evaluation at the time revealed mild worsening of her cognitive function, with superimposed symptoms of depression (Beck Depression Inventory score 52) and anxiety (Beck Anxiety Inventory score 39). The patient and her mother denied any history of hallucinations, delusions, manic symptoms, panic attacks, obsessions, compulsions, and motor and vocal tics.

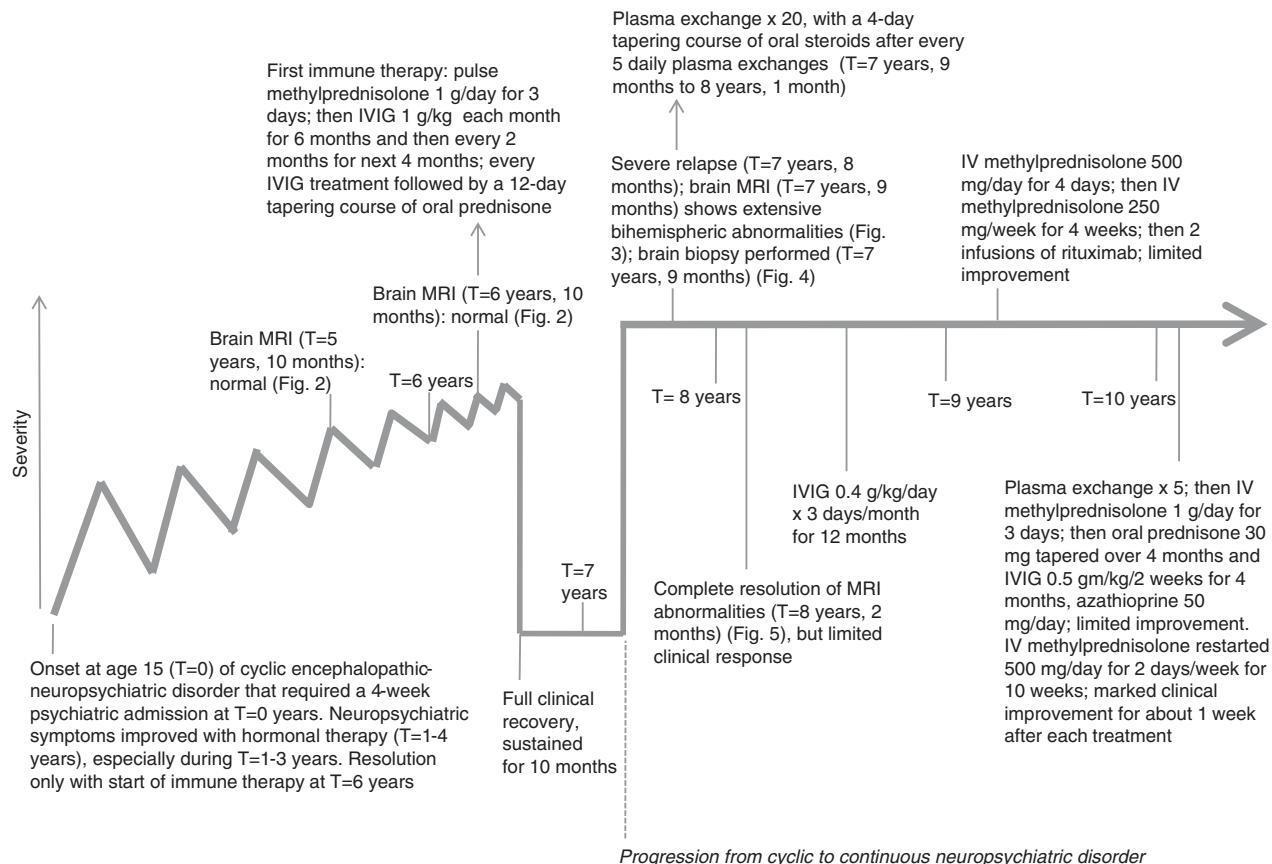
The patient's clinical features painted a picture of a cyclic encephalopathic-psychotic disorder with the prominent negative symptoms of loss of social connection, affect, and self-care, but without positive symptoms such as delusions and hallucinations.

The various classes of psychotropic agents tried during the first 6 years of her illness were ineffective. She was not helped by the antidepressants citalopram, escitalopram, paroxetine, fluoxetine, sertraline, venlafaxine, and bupropion; the antipsychotics olanzapine, risperidone, and quetiapine; or the benzodiazepines clonazepam and lorazepam.

Because the patient's menses correlated with her psychotic episodes, she was started on hormonal therapy a year after disease onset. Although she was not responding to the psychotropic agent that she was then taking, her psychosis improved substantially with ethinyl estradiol and norgestrel. The benefit continued for 2 years, but then her symptoms recurred. She was tried on alternative hormonal therapies: transdermal estradiol, progesterone lozenges, and leuprolide therapy with oral estrogen and progesterone cream. These treatments brought only limited and transient responses.

Despite her academic problems with reading comprehension, math, and expressive writing, the patient was able to graduate from high school with the help of such accommodations as professional tutoring and extra time to finish tests. About 3 years later, she began to attend a college that provided a highly structured environment geared to the needs of learning-disabled students. After struggling academically over the next year, she sought an outpatient neurologic examination at our institution. This was 6 years and 2 months after the onset of her illness.

When we first evaluated the patient, she was a well-groomed young woman who appeared younger than her stated age and who exhibited odd-eccentric behavior. She cooperated to the best of her ability and made eye contact fairly well. She exhibited psychomotor slowing. Her speech was slow and soft. Her mood was "sad." Her affect was incongruent and largely unreactive, dysphoric, distant, and constricted. Intermittently, she smiled or cried without reason and without associated feelings of sadness or happiness. Her thought content was sparse and truncated,



**FIGURE 1.** Timeline of this patient's clinical course, diagnostic testing, and hormonal and immune therapies. T indicates time from disease onset; MRI, magnetic resonance imaging; IVIG, intravenous immunoglobulin.

without suicidal or homicidal ideation, obsessions, compulsions, hallucinations, or delusions. She appeared to be internally preoccupied. She displayed difficulties with generating speech, short-term memory (recall 1/3 at 10 seconds, and 0/3 at 1 minute), attention and concentration, and integrating simple ideas. She was perseverative in her clock drawing, disoriented to day/month/year, and unable to follow motor commands such as "close your eyes" or "make a fist." She had congenital exotropia in her right eye. No other eye abnormalities were noted, specifically, no cherry red macula or retinitis pigmentosa. Muscle strength, coordination, sensation, and reflexes were all normal. Gait was steady, with a flexed posture.

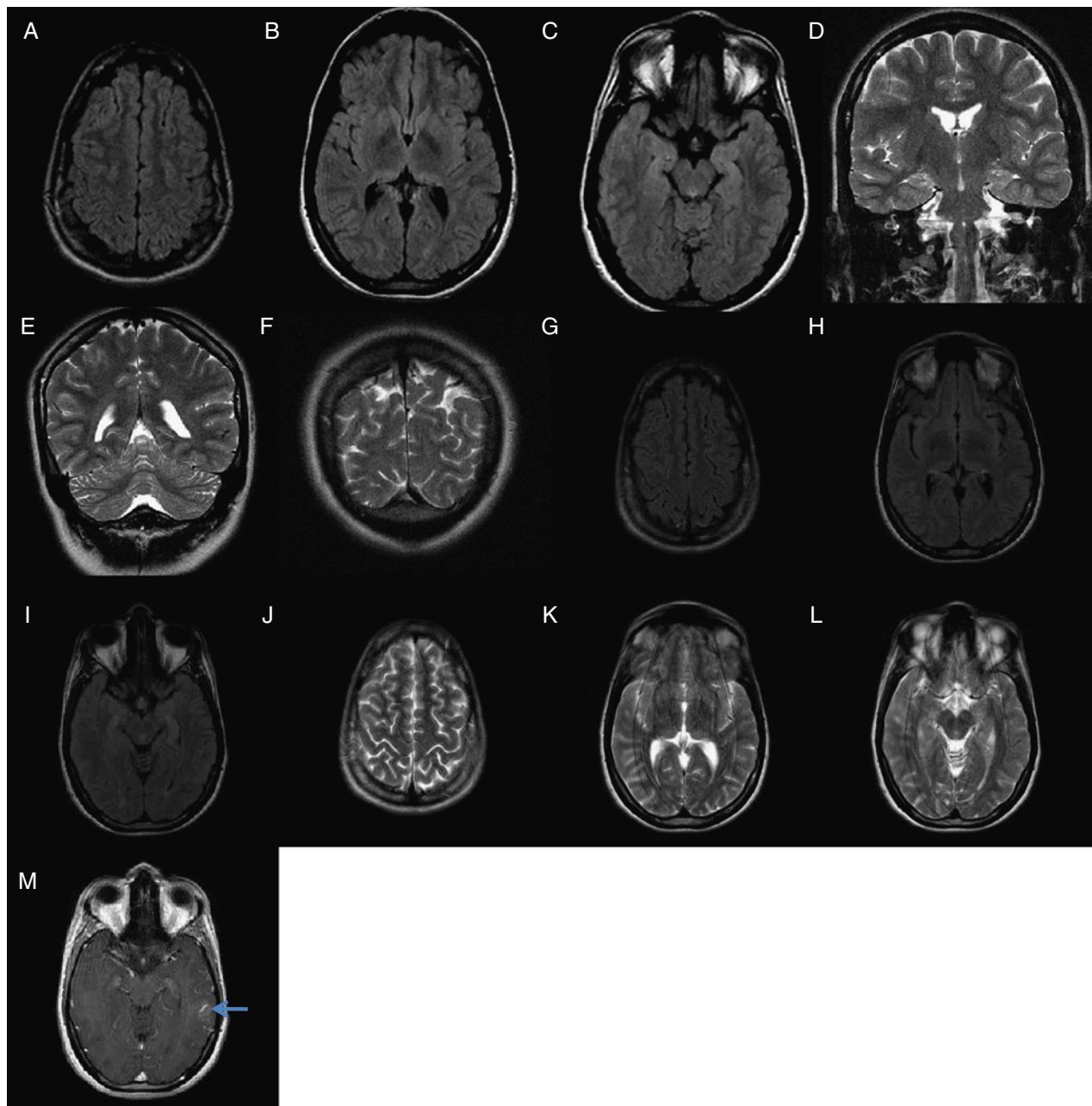
General examination showed no organomegaly or dysmorphic features. She had no signs of meningismus, autonomic instability, spontaneous or action-induced myoclonus, or any other muscle twitches to suggest neuromyotonia.

Her medications were clonazepam 0.5 mg in the morning, 0.5 mg in the afternoon, and 1 mg at night, and methylphenidate 5 mg in the morning.

Brain MRI revealed a small contrast-enhancing lesion in the left posterior temporal region (Figs. 2, 3). Cerebral angiography confirmed this small lesion to be an arteriovenous malformation. Cerebrospinal fluid (CSF) analysis revealed no cells, a normal glucose, and normal

protein concentrations. There were no oligoclonal bands, and the CSF immunoglobulin G index was normal. Screening for pathogens in the CSF and serum was negative for *Cryptococcus neoformans*, *Borrelia burgdorferi*, syphilis, *Rickettsia*, and a comprehensive antiviral antibody panel for herpes simplex virus (HSV)-1, HSV-2, human herpesvirus (HHV)-6, cytomegalovirus, varicella zoster, *Coxsackie*, enteric cytopathic human orphan (ECHO), Epstein-Barr, mumps, measles, rubella, human immunodeficiency virus (HIV)-1, and HIV-2. Polymerase chain reaction testing was negative for HSV-1, HSV-2, varicella zoster, and *Tropheryma whipplei*.

Serologic screening for systemic autoimmune disorders was negative for antinuclear antibodies (ANA), anti-dsDNA antibodies, Sjögren antibodies, antineutrophilic cytoplasmic antibodies, thyroglobulin antibodies, thyroid peroxidase antibodies, antigliadin antibodies, antiphospholipid antibodies, C3, C4, CH50, and B2-glycoprotein. Tests performed before the patient was started on immune therapy were negative for CSF anti-NMDAR antibodies; serum antibodies targeting VGKC-complex, GAD, NMDAR, and onconeural antigens such as anti-Hu and anti-Ma2; and anti-CV2/CRMP5 antibodies. Serum levels of ammonia, pyruvate, lactate, and ceruloplasmin were normal. Liver function was normal.

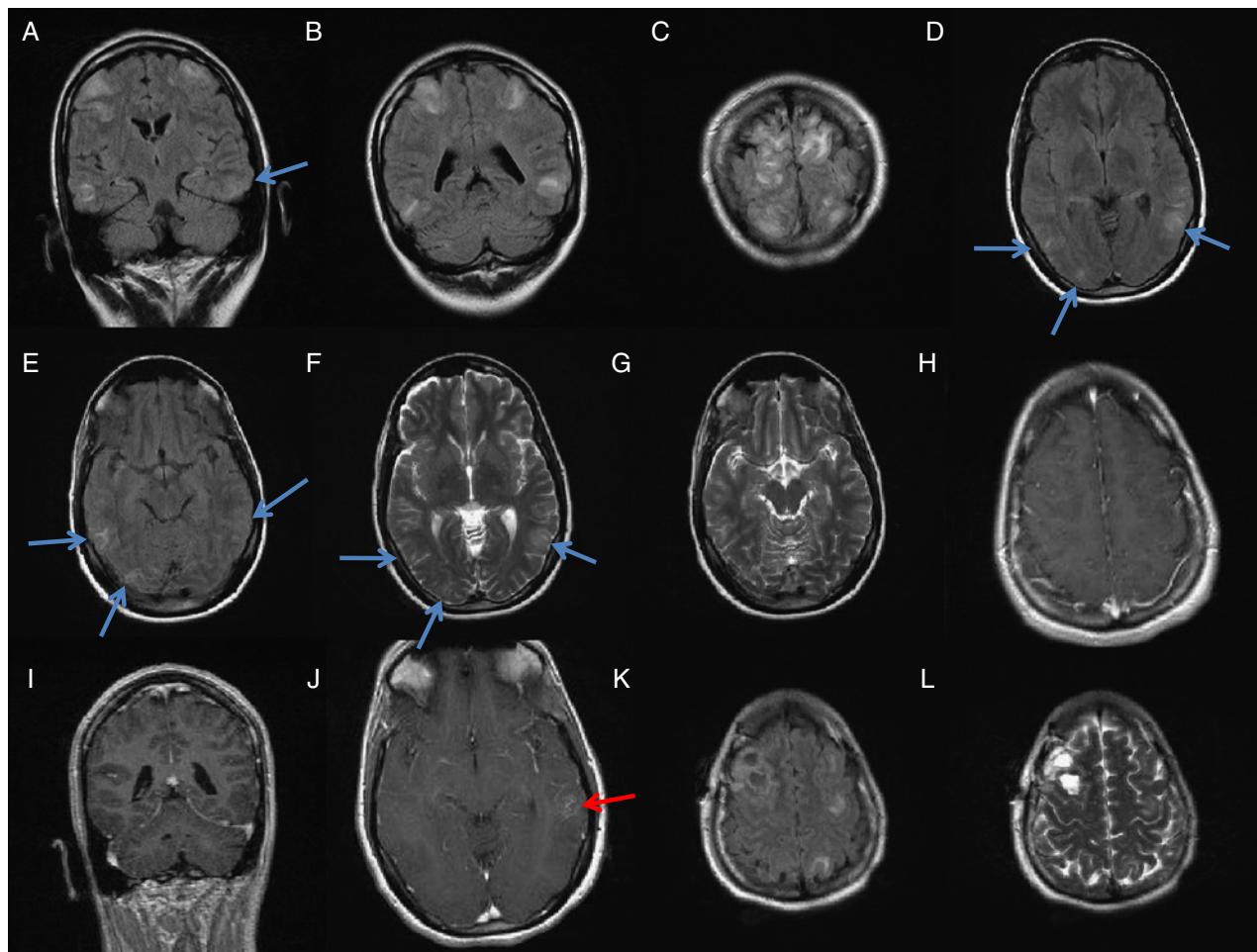


**FIGURE 2.** Panels A–F (A–C, axial FLAIR; D–F, coronal T2-weighted images) were taken from this patient's MRI scan 5 years and 10 months after diagnosis, when her cyclic neuropsychiatric disorder was worsening. The images show normal FLAIR/T2 intensities within the hippocampi and cortex. Panels G–M (G–I, axial FLAIR; J–L, axial T2-weighted images; M, post-contrast axial T1-weighted image) were taken from the patient's MRI scan 6 years after diagnosis, shortly before she sought help at our center because of her difficulty keeping up at college. Panels G–L again show normal FLAIR/T2 intensities within the hippocampi and cortex. Panel M shows serpentine enhancement within the left posterior temporal region (arrow), later proved by conventional cerebral angiogram to be a small arteriovenous malformation. FLAIR indicates fluid-attenuated inversion recovery.

Hormonal studies were normal for follicle-stimulating hormone (FSH), luteinizing hormone (LH), prolactin, thyroid-stimulating hormone (TSH), dehydroepiandrosterone (DHEA), adrenostenedione, insulin, gastrin, thyroid functions, beta human chorionic gonadotropin ( $\beta$ -hCG), and total testosterone level. Metabolic studies were negative for inborn errors of metabolism such as lysosomal

storage, peroxisomal and mitochondrial disorders, and porphyria.

Skin and bone marrow biopsies excluded such lysosomal storage diseases as Niemann-Pick type C and GM2 gangliosidosis. Tests were normal for quantitative plasma amino acids as well as for urine organic acids and amino acids such as orotic acid, uracil, xanthine, and



**FIGURE 3.** Panels A–J (A–C, coronal FLAIR; D and E, axial FLAIR; F and G, axial T2-weighted images; H and J, post-contrast axial T1-weighted images; I, post-contrast coronal T1-weighted image) were taken from this patient's MRI scan 7 years and 9 months after diagnosis, when her neuropsychiatric disorder had progressed from cyclic to continuous. Panels A–G show bilateral cortical and subcortical FLAIR/T2 hyperintensities involving frontal, parietal, parieto-occipital, and temporal regions. Panel A also shows mild FLAIR hyperintensity and atrophy of the hippocampi. Blue arrows mark some of the more subtle lesions. Panels H–J show no post-contrast enhancement of the FLAIR/T2 hyperintense lesions. Panel J shows persistent left posterior temporal enhancement related to the incidental arteriovenous malformation (red arrow). Panels K and L (K, axial FLAIR; L, axial T2-weighted image) were taken from an MRI scan 2 weeks later, performed 4 days after the patient underwent a right frontal lobe biopsy. These images show postoperative changes and prior FLAIR/T2 hyperintense lesions. FLAIR indicates fluid-attenuated inversion recovery.

hypoxanthine. Methyltetrahydrofolate was not measured in the CSF, but neither the patient's clinical presentation nor her brain MRI abnormalities were typical of cerebral folate deficiency. Muscle biopsy was negative for mitochondrial disorders. Chromosomal studies were normal. Testing for transthyretin gene mutations was negative.

Abdominal and pelvic computed tomography (CT) scans did not reveal occult malignancy. Video-electroencephalogram (V-EEG) studies showed intermittent mild diffuse slowing, most prominently in the temporal regions, and no epileptiform discharges.

We increased the patient's clonazepam dose to 1 mg 3 times a day and titrated her methylphenidate up to 20 mg a day, but her symptoms did not improve. Given the acute onset of her disorder, its cyclic pattern, associated global cognitive deficits, partial response to hormonal

therapy, lack of significant response to conventional psychiatric treatments, and diffuse EEG slowing, we suspected an immunologic cause.

We started her on trials of oral pulse methylprednisolone and infusions of intravenous immunoglobulin (IVIG). Within a few weeks of beginning treatment, she responded dramatically and completely (Fig. 1). She was able to return to college, with highly structured support for her learning disabilities. She maintained a "B" average with a course load of biology, English, sociology, art, and history. Ten months later, however, despite continuing immune therapy, her psychosis recurred, now with catatonia and global cognitive impairment (Fig. 1).

A repeat brain MRI performed at 7 years and 9 months showed widespread bihemispheric cortical and subcortical nonenhancing lesions (Fig. 3). As before,

repeat serum and CSF screening for autoimmune antibodies, infectious agents, and CSF oligoclonal bands was negative. A prolonged V-EEG study again showed mild diffuse slowing, but captured no clinical or subclinical seizures. A whole-body positron emission tomography/computed tomography scan did not reveal any evidence of a neoplasm.

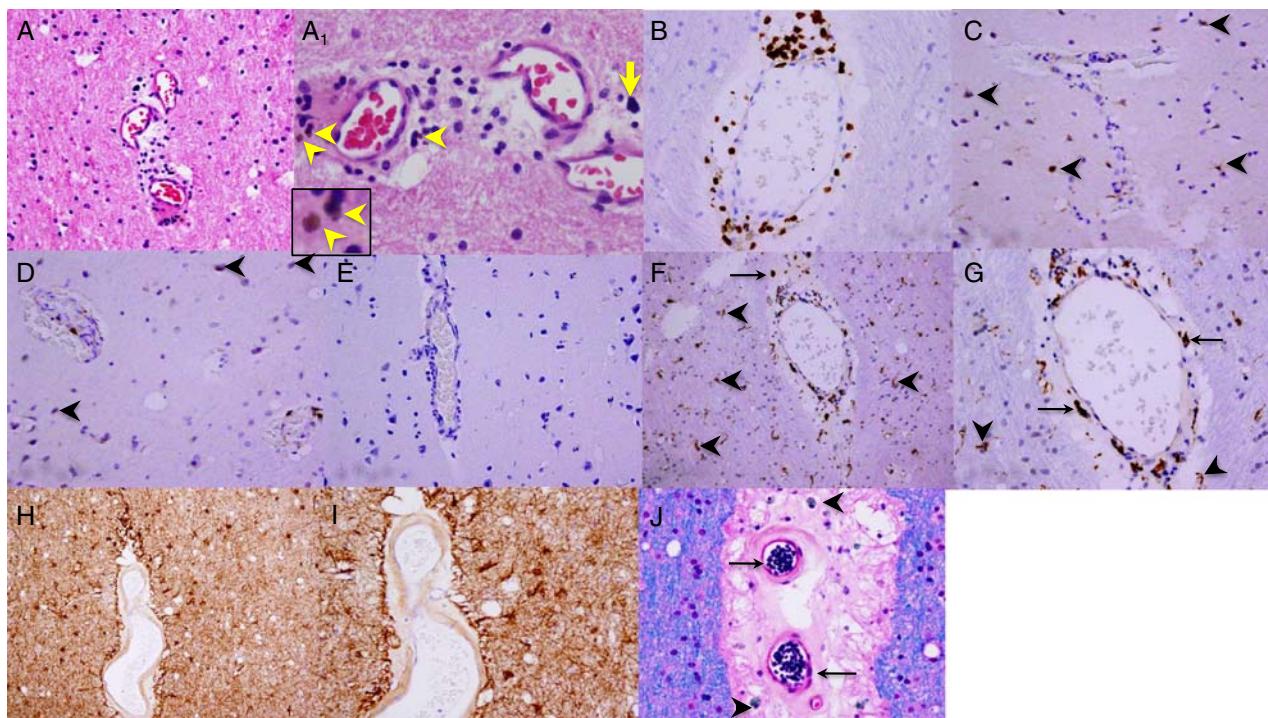
A diagnostic brain biopsy, performed 2 weeks later, showed a mild perivascular mixed inflammatory infiltrate (Figs. 4A–D, F, G), mild to moderate microglia activation (Figs. 4F, G), mild to moderate astrogliosis (Figs. 4H, I), prominent vascular hyalinization, and well-preserved myelin (Fig. 4J). The inflammatory infiltrate consisted of T lymphocytes (Figs. 4B–D) and scattered macrophages and histiocytes (Figs. 4A, A<sub>1</sub>, F, G), some of which contained hemosiderin deposits (Fig. 4A<sub>1</sub>). There was no evidence of microglial nodules, viral inclusions, vasculitis, granulomas, demyelinating disease, or a neoplastic process. Immunostains were negative for viruses (HSV, cytomegalovirus, etc), bacteria, fungi, and spirochetes. The brain pathology was consistent with mild nonvasculitic inflammation, and did not suggest a metabolic, degenerative, paraneoplastic, or infectious process.

Based on the biopsy findings, we changed the patient's immune therapy to plasma exchanges. She underwent 20 daily exchanges, given in 4 cycles. After every 5 exchanges, she took a 4-day tapering course of oral steroids (Figs. 1, 5). After she completed this treatment, at 8 years and 2 months, we obtained another brain MRI. Apart from her arteriovenous malformation, all of the lesions that we had observed on the previous MRI (Fig. 3) were fully resolved (Fig. 5).

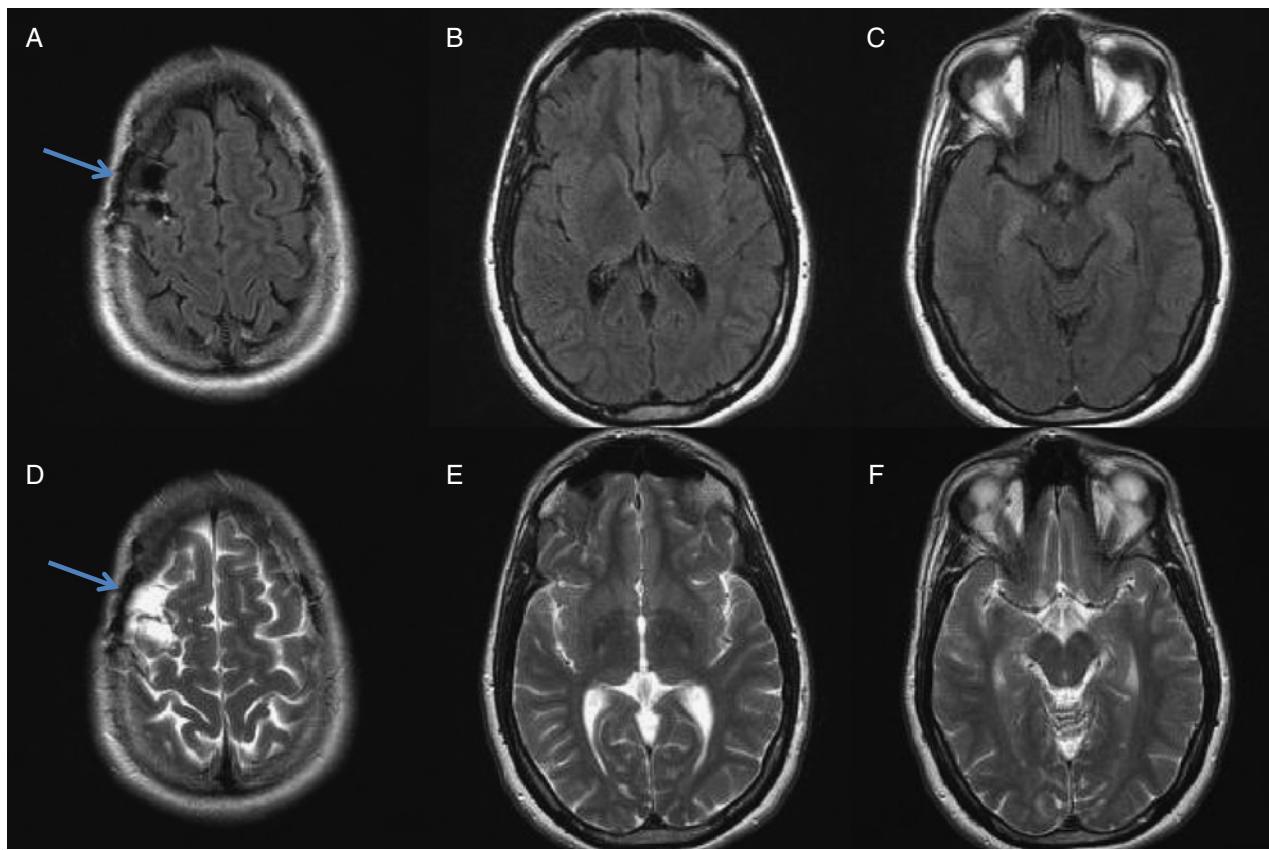
Despite the normalization of her brain MRI, the patient's neuropsychiatric symptoms progressed, transitioning from moderate, cyclic episodes to a severe, continuous state that has continued ever since (Fig. 1). Her segmental neurologic exam findings remain nonfocal.

Over time, we tried several more immune therapies. Repeat plasma exchanges azathioprine and rituximab (Fig. 1) produced only limited and transient responses. Most effective was repeat intravenous pulse methylprednisolone 500 mg/day for 2 days/week for 10 weeks; this produced moderate improvement that lasted for 1 week after each treatment.

The most recent CSF analysis was normal, as before. The patient's current medications are oral prednisone



**FIGURE 4.** Findings from this patient's brain biopsy. Panels A and A<sub>1</sub>: Mild perivascular mixed inflammatory infiltrate: lymphocytes and macrophages with histiocytes. Panel A<sub>1</sub> shows scattered perivascular macrophages and histiocytes (yellow arrow and arrowheads), some of which contain brown hemosiderin deposits (yellow arrowheads; highlighted by magnified inset). Hematoxylin and eosin stain, magnification  $\times 400$ . Panel B: Perivascular T lymphocytic infiltration. CD3,  $\times 400$ . Panels C and D: Scattered parenchymal (arrowheads) and rare perivascular T lymphocytic infiltration. (Panel C: CD4,  $\times 400$ . Panel D: CD8,  $\times 400$ .) Panel E: Negative B-cell immunostaining. CD20,  $\times 400$ . Panels F and G: Mildly to moderately activated microglia (arrowheads) and scattered macrophages and histiocytes (long arrows) clustered around the blood vessels and infiltrating parenchyma. (Panel F: CD68,  $\times 200$ . Panel G: CD68,  $\times 400$ .) Panels H and I: Mild to moderate astrogliosis, predominantly perivascular. (Panel H: GFAP,  $\times 200$ . Panel I: GFAP,  $\times 400$ .) Panel J: Fully preserved myelin (blue stain), prominent hyalinization of vessel wall (ie, vascular injury, long arrows) without inflammatory cells within the vessel wall, and perivascular macrophages and histiocytes (purple stain, arrowheads). Luxol-fast blue,  $\times 400$ .



**FIGURE 5.** Panels A–F (A–C, axial FLAIR; D–F, axial T2-weighted images) were taken from this patient's MRI scan performed 8 years and 2 months after diagnosis and 5 months after her brain biopsy. She had completed 20 sessions of plasma exchange. The scan shows stable postoperative changes (arrows in A and D) and complete resolution of the diffuse bilateral FLAIR/T2 hyperintense abnormalities seen at 7 years and 9 months (Fig. 3). FLAIR indicates fluid-attenuated inversion recovery.

10 mg/day, azathioprine 50 mg/day, clonazepam 0.5 mg twice a day, trimethoprim-sulfamethoxazole double strength 3 tabs/week, and, when needed, intravenous pulse methylprednisolone for severe symptom exacerbations.

## DISCUSSION

Historically, the term *seronegative autoimmune encephalitis* has been used to describe a subgroup of autoimmune encephalitis cases with negative serologic tests for autoantibodies. However, with the constant discovery of new neuronal autoantibodies, some of the cases that were previously classified as seronegative autoimmune encephalitis are now known to be associated with newer autoantibodies.<sup>1,11</sup> For example, anti-GABA<sub>B</sub> antibodies have been detected in the serum of patients with small cell carcinoma-related paraneoplastic LE who were previously thought to have seronegative LE.<sup>12</sup> Hence, although our patient had negative serologic screening for conventional VGKC-complex, NMDAR, and GAD autoantibodies, it is possible that research laboratories will someday detect new autoantibodies targeting novel neuronal surface antigens of the neuropil of her hippocampus and cerebellum.<sup>11</sup>

Our patient is the first reported to have pathologically confirmed autoimmune encephalitis—without VGKC, NMDAR, or GAD autoantibodies—presenting with isolated neuropsychiatric features of a florid psychosis with prominent negative symptoms, affective symptoms, and cognitive impairment. Our patient's history differs from the most similar reported other cases in that she did not have seizures, sensorimotor deficits, or other autoimmune disorders (contrast Storey et al<sup>13</sup>), and she had documented negative serology for all commercially available and relevant autoantibodies (contrast Caselli et al<sup>8</sup> and Josephs et al<sup>14</sup>).

Given that patients with autoimmune encephalitis associated with AMPAR autoantibody can present with isolated psychosis (Table 1) and that our patient was not tested for AMPAR autoantibody in a research laboratory, we cannot exclude entirely the possibility that she had AMPAR antibody encephalitis. However, we suspect that this diagnosis is unlikely, as our patient's clinical presentation did not match the clinical profile typical for this subtype of autoimmune encephalitis, reported in a recent cohort<sup>2</sup> (Table 1): isolated limbic rather than extralimbic involvement; frequent association with lung, breast, and thymus tumors; seizures; and a median age of 60 years, with a range of 38 to 87.

TABLE 1. Case Reports of Autoimmune Encephalitis Presenting with Isolated Acute or Subacute Psychosis

Case Report	Antibodies	Age/ Sex	MRI	Cerebrospinal Fluid	Positive Symptoms of Psychosis	Negative Symptoms of Psychosis	Treatment	Recovery
Graus et al, 2010 <sup>15</sup>	AMPAR	60/F	Normal	Normal	Aggressive behavior, agitation, confusion	Not specified	Antipsychotics, corticosteroids	Refractory to antipsychotics; complete recovery after corticosteroids
Graus et al, 2010 <sup>15</sup>	AMPAR	58/F	Normal	Normal	Confusion, episodes of aggressive behavior	Personality changes with apathy	Antipsychotics, corticosteroids	Refractory to antipsychotics; complete recovery after corticosteroids
Zandi et al, 2011 <sup>16*</sup>	NMDAR	21/M	Normal	Not specified	Grandiose and paranoid delusions, delusions of control	Anergia, poor motivation	Antipsychotics	Complete recovery
Zandi et al, 2011 <sup>16*</sup>	NMDAR	28/M	Normal	Not specified	Auditory and visual hallucinations, paranoid delusions, delusions of control	None	Antipsychotics	Partial recovery (patient partly compliant)
Zandi et al, 2011 <sup>16*</sup>	NMDAR	19/M	Normal	Not specified	Auditory and visual hallucinations, thought disorder, paranoid grandiose delusions	Poor motivation, social withdrawal, incongruent affect	Plasma exchange, corticosteroids	Partial recovery
Zandi et al, 2011 <sup>16*</sup>	VGKC-complex	22/F	Normal	Not specified	Paranoid delusions, thought disorder	Poor self-care and motivation, anergia	Antipsychotics	Relapsing and remitting symptoms over 12 months; lost to follow-up
De Nayer et al, 2009 <sup>17</sup>	NMDAR	17/F	Normal	3 mononuclear cells; normal glucose and protein; 2 IgG bands; free kappa chains	Excitability, euphoria, agitation, aggressiveness	Social withdrawal, poor personal care	Antipsychotics (resection of ovarian teratoma)	Complete recovery
Najjar et al, 2012 <sup>18*</sup>	GAD	19/F	Normal	Normal	Auditory and visual hallucinations, delusions	Dissociative behavior, tangential thinking, catatonia, staring, affective flattening, avolition	Plasma exchange, corticosteroids, IVIG	Relapsing and remitting, partial recovery
Najjar et al, patient reported in this article	Seronegative for VGKC-complex, NMDAR, and GAD autoantibodies	25/F	Normal for 7 years after diagnosis; then multibed bilateral lesions	Normal	None	Social isolation, affective blunting, impaired self-care and hygiene	Antidepressants, antipsychotics, hormonal therapy, pulse steroids, IVIG, plasma exchange, rituximab	Relapsing and remitting, partial recovery; MRI lesions fully resolved after plasma exchange and pulse steroids

\*Cases that met the criteria for schizophrenia in American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th edition, Text Revision (DSM-IV-TR). Washington, DC: American Psychiatric Association; 2000.

MRI indicates magnetic resonance imaging; AMPAR, amino-3-hydroxy-5-methyl-1,4-isoaxazolepropionic acid receptor; NMDAR, N-methyl-D-aspartate receptor; VGKC, voltage-gated potassium channel; GAD, glutamic acid decarboxylase; IgG, immunoglobulin G; F, female; M, male; IVIG, intravenous immunoglobulin.

An autoimmune etiology for our patient's illness is supported by her biopsy-proven neuroinflammation without evidence of infectious, metabolic, or genetic causes; her clinical improvement after immune therapies (Fig. 1); and the full resolution of her brain MRI abnormalities after 20 plasma exchanges, with a 4-day tapering course of oral steroids after every 5 exchanges (Figs. 1, 5). Her lack of CSF pleocytosis is consistent with prior reports of autoimmune encephalitis.<sup>1</sup> Her lack of CSF oligoclonal bands suggests no intrathecal synthesis of immunoglobulin G autoantibodies,<sup>1</sup> and is consistent with the absence of B lymphocytes and plasma cells in her brain biopsy.

Our patient's autoimmune encephalitis has 4 clinically important features. First, her psychosis with prominent negative symptoms progressed over 7 years, from mild-to-moderate and cyclic, to severe and continuous. Few reports to date have included histologic descriptions<sup>8</sup> or long-term follow-up documenting the natural course of the seronegative autoimmune encephalitides. Our evidence for the natural history of our patient's illness included repeated MRI scans, the early ones looking normal, a later one showing prominent multi-lobed bihemispheric lesions (Figs. 1, 2).

Second, the patient had immunologically mediated psychosis with prominent negative symptoms but without serologic abnormalities and, for many years, without brain MRI abnormalities (Fig. 3). This presentation led to an incorrect diagnosis of a primary psychiatric disorder and delayed the start of potentially curative early immune therapy. This clinical scenario highlights the fact that normal-looking MRI, serum, and CSF in a patient with psychosis do not rule out the possibility of an underlying organic illness.

Third, conventional psychiatric treatments have limited ability to improve the symptoms of autoimmune encephalitis. This limitation is a good reason to include SNAPE without VGKC-complex, NMDAR, and GAD autoantibodies in the differential diagnosis of unexplained psychosis.

Fourth, hormonal therapy helped to ease our patient's neuropsychiatric manifestations of SNAPE (Fig. 1). Even for correctly diagnosed SNAPE, ours is the first description of treatment with hormones.

Emerging evidence supports the theory that neuroinflammation plays a direct pathogenic role in a subgroup of patients with such classical psychiatric disorders as schizophrenia,<sup>19</sup> major depression,<sup>19–21</sup> obsessive-compulsive disorder,<sup>22,23</sup> and bipolar disorder.<sup>24</sup> Our patient, along with the earlier patients with seronegative autoimmune encephalitis who presented with psychiatric symptoms (Table 2), adds support to this theory, particularly in patients with atypical psychoses.

Primary psychotic disorders have been associated with serum autoantibodies.<sup>25</sup> Conversely, some patients with seropositive<sup>26</sup> and seronegative<sup>9,27</sup> autoimmune encephalitides present with isolated psychiatric symptoms—including psychosis—that can dominate the clinical picture and even precede cognitive and neurologic abnormalities<sup>18</sup> (Table 1). Taken together, these observations

strongly suggest that a subgroup of patients manifesting isolated psychiatric symptoms may have underlying autoimmune encephalitis. Well-informed physicians may find it relatively easy to diagnose autoimmune encephalitis in seropositive patients; seronegative patients pose a greater diagnostic challenge. This challenge points to the need for future research to characterize more autoantibodies that may contribute to the disorders, and to refine novel imaging modalities that can detect neuroinflammation without the need for a brain biopsy.

As early as 1937, serum autoantibodies were being identified in patients with a primary psychotic illness.<sup>25</sup> Such studies documented serum<sup>28</sup> and CSF<sup>25</sup> autoantibodies in 48% to 70% of patients with schizophrenia. However, these antibodies were specific to such neuroanatomic regions as the amygdala, frontal cortex, cingulate, and septal area, rather than being specific to particular neural autoantigens. A 2011 study screening for well-characterized specific pathogenic autoantibodies in 46 patients with schizophrenia found 3 patients whose serum tested positive for anti-NMDAR antibodies, and 1 who tested positive for anti–VGKC-complex antibodies<sup>16</sup> (Table 1).

Seropositive autoimmune encephalitis presenting with isolated psychosis has been reported in association with autoantibodies targeting AMPAR, NMDAR, VGKC-complex, and GAD autoantigens (Table 1).<sup>16–18</sup> All of the patients from these reports presented with a normal brain MRI, and 6 of 8 exhibited negative psychotic symptoms,<sup>16–18</sup> suggesting that these features represent a clinical pattern rather than being peculiar to our patient.

Isolated psychiatric features are less common in seronegative<sup>9</sup> than in seropositive autoimmune encephalitides. Similar to our patient, the 2 previous reports of “seronegative” NAIM (Table 2) described patients with neuropsychiatric manifestations.<sup>8,14</sup> However, neither of these patients with “seronegative” NAIM was screened for antineuronal (VGKC-complex, NMDAR, and GAD) autoantibodies, and, therefore, neither would meet the current criteria for seronegative autoimmune encephalitis.

In the previously reported series of 16 cases of SNALE<sup>9</sup> (Table 2), patients presented with acute confusion and memory deficits without seizures<sup>29</sup>; emotional lability, visual hallucinations, autonomic dysfunction, and muscle twitches without seizures<sup>29</sup>; seizures with memory impairment<sup>9,29,30</sup>; global encephalopathy with focal neurologic impairment and seizures<sup>13</sup>; and unspecified features.<sup>27</sup> In the sole prior report of SNAPE (Table 2), the patient presented with prominent focal neurologic deficits: cerebellar signs and aphasia, severe encephalopathy, the concomitant autoimmune diseases myasthenia gravis and relapsing polychondritis, and only late-onset hallucinations.<sup>13</sup>

The pathogenesis of neuropsychiatric impairment in seropositive autoimmune encephalitis is often attributed to an altering of neuronal functions by antineuronal autoantibodies<sup>26</sup> (Table 1); the impairment in seronegative autoimmune encephalitis is often attributed to cytotoxic

**TABLE 2.** Literature Review of Patients with Pathologically Confirmed SNALE, SNAPE, and NAIM

Source	Seronegativity	Neurologic and Psychiatric Features	Pathology
Najjar et al, 2011 <sup>9</sup> Review of the 16 known cases of seronegative autoimmune limbic encephalitis (SNALE)	Negative serologic screening for systemic autoimmune disorders	Acute confusion, emotional lability, visual hallucinations, memory deficits, global encephalopathy, focal neurologic impairment, autonomic dysfunction, seizures	Results available for only 1 patient. All findings confined to hippocampi: intense perivascular and parenchymal infiltrates, predominantly CD3+ T cells; prominent overt astrogliosis and microglial activation; microglial nodules; neuronophagia
Storey et al, 2011 <sup>13</sup> The sole report of seronegative autoimmune panencephalitis (SNAPE) before the patient described in this paper	Slightly elevated erythrocyte sedimentation rate and C-reactive protein; negative serologic screening for systemic autoimmune disorders, except for slightly raised antistriatal muscle antibodies. Negative tests for serum and CSF antibodies to VGK-complex, GAD, and NMDAR, and for serum antibodies to onconeural antigens	Prominent focal neurologic deficits (cerebellar signs and aphasia); severe encephalopathy; late-onset visual hallucinations associated with myasthenia gravis and treated with thymectomy; relapsing polychondritis; fatal outcome	Diffuse involvement of temporal lobes, visual cortex, thalamus, basal ganglia, and brainstem. Perivascular and diffuse parenchymal lymphocytic infiltration of unspecified type. Astrogliosis, microglial nodules, neuronal atrophy
Caselli et al, 1999 <sup>8</sup> Josephs et al, 2004 <sup>14</sup> Each paper reported 1 case of seronegative nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM)	Negative serologic screening for systemic autoimmune disorders. <sup>8,14</sup> No screening for antineuronal antibodies <sup>8,14</sup>	Patient 1: hallucinations, cognitive impairment without focal neurologic deficits <sup>8</sup> Patient 2: acute memory impairment, truncal and gait ataxia, late-onset post-steroid hallucinations <sup>14</sup> Because neither patient was screened for antineuronal antibodies, neither would meet the current criteria for seronegative autoimmune encephalitis	Diffuse brain involvement in both patients <sup>8,14</sup> : mild, diffuse leptomeningeal and parenchymal, perivascular lymphocytic infiltrate (cell type not specified in Patient 1 <sup>8</sup> , mixed B and T cells in Patient 2 <sup>14</sup> ). Moderate to profound astrogliosis and microglia activation in both patients <sup>8,14</sup>

VGK indicates voltage-gated potassium channel; GAD, glutamic acid decarboxylase; NMDAR, *N*-methyl-D-aspartate receptor; CSF, cerebrospinal fluid.

T-cell autoimmunity in paraneoplastic syndromes.<sup>31,32</sup> Still, the mechanisms of the neuropsychiatric features remain elusive. Without identifiable antineuronal auto-antibodies, we hypothesize a role by a currently undefined pathogenic antibody-related process, a cellular autoimmune-mediated process, or both.

Our patient's course supports an autoimmune etiology. First, her cyclic encephalopathic-psychiatric symptoms responded poorly to psychotropic agents, but remitted completely for 10 months while she was receiving immune therapy with pulse steroids and IVIG (Fig. 1). Second, her relapse was associated with extensive bihemispheric non-enhancing brain lesions (Fig. 3) that resolved fully after she received further immune therapy with plasma exchanges and steroids. Third, her neuropsychiatric symptoms eventually became persistent, with intermittent fluctuations that were only transiently improved by steroids. We hypothesize that the diminished efficacy of immune therapy nearly a decade into her illness might have resulted from permanently impaired neuronal functions and metabolism. Impairments like these could result from chronic inflammation-induced diffuse neocortical neuronal injury, which can persist even after inflammatory lesions have disappeared from conventional MRI scans.<sup>33</sup> The need to prevent permanent neuroinflammation-related neuropsychiatric

sequelae reinforces the importance of early diagnosis and aggressive immune therapy.

During the first 7 years of her illness, our patient's psychosis worsened cyclically a few days before each of her menses, and responded favorably to hormonal therapy for several years before she received any immune therapy. Cyclic psychosis associated with menses has been described in at least 80 reports.<sup>34</sup> Typically, menstrual psychosis involves abnormal menses, as with our patient. The therapeutic benefit of female hormones on our patient's encephalitic-neuropsychiatric condition is consistent with reports of the antiinflammatory effects of estrogen and progesterone receptor agonists.<sup>35-37</sup>

Estrogen receptor agonists inhibit reactive astrogliosis and microgliosis, and reduce the levels of inflammatory mediators such as astrocytic tumor necrosis factor alpha (TNF- $\alpha$ ), nuclear factor kappa B (NF- $\kappa$ B), CCL-2 cascades,<sup>35</sup> interleukin-6 (IL-6), interferon gamma (IFN- $\gamma$ ), protein-10, and NF- $\kappa$ B p65 transactivation.<sup>36</sup> Progesterone down-regulates reactive neuroinflammation by inhibiting IL-1, IL-6, TNF- $\alpha$ , C3 complement protein, NF- $\kappa$ B p65, IL-1 $\beta$ , cyclooxygenase-2 (COX-2), and nitric oxide synthase.<sup>37</sup> Progesterone limits neuronal loss by (1) down-regulating the pro-apoptotic enzymes caspase-3, B-cell lymphoma 2-associated X protein (bax), B-cell

lymphoma 2-associated death promoter (bad), and protein kinase B (PKB); (2) up-regulating the anti-apoptotic enzymes B-cell lymphoma 2 (bcl-2) and extracellular signal-regulated kinases (ERK); and (3) up-regulating GABAergic neurotransmission to prevent neuronal loss caused by excitotoxicity.<sup>37</sup> Future clinical studies are needed to investigate the role of hormonal therapy in treating seronegative autoimmune encephalitis in women.

Pathology reports documenting evidence of neuroinflammation in patients with psychiatric manifestations of seronegative autoimmune encephalitides (Table 2) are limited to 2 reports of NAIM,<sup>8,14</sup> 1 report of SNALE,<sup>9</sup> and 1 prior report of SNAPE.<sup>13</sup>

In 1999, Caselli et al<sup>8</sup> coined the term *nonvasculitic autoimmune inflammatiory meningoencephalitis* (NAIM). As used by these authors and by Josephs et al,<sup>14</sup> NAIM described the pathology, rather than the clinical phenotype, of a syndrome of often steroid-responsive, nonvasculitic, diffuse autoimmune-mediated inflammatory changes in the brain. These changes often, but not always, accompanied serologic abnormalities indicating either systemic autoimmune disease or Hashimoto thyroiditis.<sup>8,14</sup>

Because of advances in the understanding of autoimmune encephalitides, the term NAIM has become outdated, as it does not distinguish between now-distinctive serologic and clinical phenotypes. These distinctions are clinically relevant given the discovery, 12 years after the introduction of the term NAIM, of anti-neuronal antibodies with variable affinities and specificities for the neural targets of particular neuroanatomic regions. For example, seizures and acute amnestic syndrome are associated with LE, while anti-VGKC-complex antibody autoimmune encephalitis typically causes LE but not ELE, and anti-AMPA and anti-GABA<sub>A</sub> receptor antibodies tend to cause LE.

We would like to propose a classification system for seronegative autoimmune encephalitis. We have already discussed the limitations of this term. We suggest combining serologic autoantibody status (seropositive [eg, VGKC-complex, NMDAR] or seronegative) with clinical subtype of encephalitis (limbic, extralimbic, or panencephalitis). In addition to standardizing serologic and clinical phenotypes, we aim to encourage physicians to give early diagnostic consideration to autoimmune processes, particularly seronegative psychotic disorders with extralimbic involvement. Extralimbic autoimmune encephalitis is likely significantly under-recognized. By contrast, LE can be readily identified by mesial temporal lobe seizures, acute memory impairments, and a classical "limbic MRI."<sup>30</sup>

Of the 2 prior pathology reports of NAIM<sup>8,14</sup> (Table 2), the first patient had a mild, mostly leptomeningeal and minimally parenchymal, perivascular lymphocytic infiltration (the subtype of lymphocytes was not specified), with profound gliosis of the superficial cortical layer.<sup>8</sup> The second patient had mixed B- and T-cell perivascular lymphocytic infiltration, with activated astrocytes and microglia.<sup>14</sup>

Our patient's pathology evaluation showed mild perivascular—but not intramural (ie, nonvasculitic)—T

lymphocytic encephalitis (Figs. 4A–D, F, G) with scattered macrophages and histiocytes (Figs. 4A, A<sub>1</sub>, F, G), microglia activation (Figs. 4F, G), astrogliosis (Figs. 4H, I), and prominent vascular hyalinization (Fig. 4J). We hypothesize that the pathogenic cascade of the patient's immunologic events was started by the activation of peripheral T lymphocytes. We base this hypothesis on the finding of exclusively T lymphocytic infiltration around the blood vessels (Figs. 4B–D), the absence of both known relevant autoantibodies in the serum and of lymphocytic infiltration in the brain biopsy (as in Fig. 4E), and the total lack of therapeutic response to rituximab (ie, anti-CD20 antibody).

Because we excluded hypertension, hyperlipidemia, diabetes mellitus, and other causes of vascular hyalinization, we believe that the vascular hyalinization in our patient was likely the consequence of repeated inflammatory cascades damaging blood vessels. Vascular injury may lead to blood-brain barrier dysfunction<sup>38–42</sup>; such dysfunction has been hypothesized to contribute to psychiatric disturbances,<sup>43,44</sup> including psychosis with prominent negative symptoms,<sup>45</sup> as in our patient. Perivascular astrocytic and microglial activation (Fig. 4F–I) is thought to be related to increased permeability of hyalinized cerebral vessels (Fig. 4J) to local or systemic inflammatory mediators (eg, cytokines) and to peripheral immune cells (eg, T lymphocytes, macrophages, and histiocytes [Figs. 4A, A<sub>1</sub>, B, F, G, J]).<sup>43</sup>

Astrocytic activation, but not proliferation,<sup>46–49</sup> and microglial activation and proliferation (Figs. 4F, G)<sup>50–52</sup> have been found in a subset of patients with schizophrenia, and are thought to facilitate hypoglutamatergic neurotransmission leading to psychosis.<sup>19</sup> The greater expression of astrocytic excitatory amino acid transporters 1 and 2 in patients with schizophrenia than in healthy controls suggests a mechanism, as these transporters account for >90% of synaptic glutamate reuptake.<sup>53–56</sup> Also, several meta-analyses and other studies have found that patients with schizophrenia have elevated serum, CSF, and postmortem tissue levels of S100B protein, a marker of astrocytic activation.<sup>48,49,57,58</sup> Elevated S100B is associated with increased astrocytic glutamate reuptake.<sup>59</sup> In such studies, S100B levels correlate particularly with psychosis with prominent negative symptoms,<sup>60</sup> as well as cognitive dysfunction<sup>48</sup> and neuronal apoptosis,<sup>61</sup> and levels decline with antipsychotic medications.<sup>48</sup> In schizophrenia, excessive microglial proinflammatory cytokines are associated with acute psychotic episodes,<sup>48</sup> impaired cognition,<sup>62</sup> astrocytic apoptosis,<sup>63</sup> and blood-brain barrier dysfunction.<sup>43</sup>

In the only 2 pathology reports of seronegative autoimmune encephalitis that documented negative serology for antineuronal antibodies, neither patient presented with isolated neuropsychiatric features. One patient had purely limbic involvement (SNALE)<sup>9</sup> and the other had SNAPE.<sup>13</sup> The man with SNALE<sup>9</sup> (Table 2) is clinically distinct from our young woman with SNAPE, in having presented with frequent complex partial seizures and an amnestic syndrome. The pathology evaluation in

this man with SNALE showed intense perivascular and diffuse parenchymal inflammatory infiltrates of CD3+ T lymphocytes and slightly predominant CD20+ B lymphocytes, as well as prominent microglial activation and microglial nodules, neuronophagia, and overt astrogliosis.<sup>9</sup> Our young woman had no evidence of microglial nodules or neuronophagia, and her infiltration was exclusively of T lymphocytes.

Our patient had isolated psychosis with prominent negative symptoms and she had diffuse cognitive deficits, without focal neurologic findings or autoimmunity. By contrast, the prior patient with SNAPE<sup>13</sup> (Table 2) exhibited prominent focal neurologic manifestations (cerebellar signs, aphasia) and severe encephalopathy, with concomitant autoimmunity in the form of myasthenia gravis and relapsing polychondritis. Late in his course, this patient developed psychotic hallucinations. His illness was fatal. Postmortem exam showed diffuse perivascular lymphocytic infiltrates (cell types were not specified), microglial nodules with neuronal atrophy, and astrogliosis, none of which we have found in our young woman.

Finally, in further contrast to our patient, the pathology from the 2 previous patients with seronegative autoimmune encephalitis<sup>8,14</sup> did not reveal vascular hyalinization.

## CONCLUSIONS

This case report and literature review lead us to several novel conclusions. First, the fact that autoimmune encephalitis without VGKC-complex, NMDAR, and GAD autoantibodies can present with prominent and isolated neuropsychiatric features underscores the need to add this entity to the differential diagnosis of psychosis with prominent negative symptoms, even in the absence of seizures or serologic, CSF, or MRI abnormalities. Second, immunologic alterations likely contribute to the psychiatric manifestations of autoimmune encephalitides, independent of serology, brain MRI findings, and direct limbic involvement. Third, brain biopsy plays an important role in confirming seronegative autoimmune encephalitis, particularly in patients (1) who present with neuropsychiatric disorders that are refractory to conventional psychotropic agents, (2) in whom immunologic mechanisms are strongly suspected, and (3) in whom serology, CSF, and brain MRI are nondiagnostic. Finally, patients in whom the diagnosis and start of rational immune therapies are delayed can suffer refractory psychiatric disturbances and permanent neuropsychiatric sequelae.

Evidence for the use of immune therapies in patients with seronegative autoimmune LE is derived largely from case series. The authors of 1 report discussed their preference for immediate treatment with intravenous methylprednisolone, followed by high-dose oral glucocorticoids.<sup>11</sup> For patients who do not respond well to glucocorticoids, the physician can consider plasma exchange or IVIG infusions.<sup>11</sup> Even in retrospect, it may be useful for research laboratories to study patients' blood and CSF to seek autoantibodies targeting novel neuronal membrane antigens. A finding of new antibodies would

justify prompt, aggressive immune therapies such as rituximab, which can exceed conventional therapies in limiting neurotoxicity of autoantibodies that have already bound to their neuronal receptors.

We suspect that SNAPE without VGKC-complex, NMDAR, and GAD autoantibodies is an under-recognized entity that should be considered in the differential diagnosis for patients with atypical psychiatric symptoms that do not respond to conventional treatment. SNAPE may be found even in patients who have an isolated psychiatric presentation,<sup>18</sup> normal CSF,<sup>18,64</sup> and no visible lesions on brain MRI.<sup>15,18,65</sup> With the future refinement of its signal-to-noise ratio, (11)C-(R)-PK11195 positron emission tomography may prove important to diagnosis because of its ability to label the peripheral benzodiazepine receptors<sup>66,67</sup> located on the outer mitochondrial membrane of microglia cells. Prospective studies are needed to determine the true prevalence of seronegative autoimmune encephalitides and the efficacy of various immune therapies.<sup>68,69</sup> Further research to characterize novel pathogenic autoantibodies holds promise to permit their detection in the serum of patients who are now classified as having seronegative autoimmune encephalitides.

## REFERENCES

1. Graus F, Saiz A, Dalmau J. Antibodies and neuronal autoimmune disorders of the CNS. *J Neurol*. 2010;257:509–517.
2. Lai M, Hughes EG, Peng X, et al. AMPA receptor antibodies in limbic encephalitis alter synaptic receptor location. *Ann Neurol*. 2009;65:424–434.
3. 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;9:67–76.
4. Najjar S, Pearlman D, Najjar A, et al. Extralimbic autoimmune encephalitis associated with glutamic acid decarboxylase antibodies: an underdiagnosed entity? *Epilepsy Behav*. 2011;21:306–313.
5. Cianci V, Labate A, Lanza P, et al. Non-paraneoplastic limbic encephalitis characterized by mesio-temporal seizures and extra-temporal lesions: a case report. *Seizure*. 2010;19:446–449.
6. Irani SR, Vincent A. NMDA receptor antibody encephalitis. *Curr Neurol Neurosci Rep*. 2011;11:298–304.
7. Dalmau J, Gleichen AJ, Hughes EG, et al. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol*. 2008;7:1091–1098.
8. Caselli RJ, Boeve BF, Scheithauer BW, et al. Nonvasculitic autoimmune inflammatory meningoencephalitis (NAIM): a reversible form of encephalopathy. *Neurology*. 1999;53:1579–1581.
9. Najjar S, Pearlman D, Zagzag D, et al. Spontaneously resolving seronegative autoimmune limbic encephalitis. *Cogn Behav Neurol*. 2011;24:99–105.
10. Buckley C, Oger J, Clover L, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. *Ann Neurol*. 2001;50:73–78.
11. Ahmad SA, Archer HA, Rice CM, et al. Seronegative limbic encephalitis: case report, literature review and proposed treatment algorithm. *Pract Neurol*. 2011;11:355–361.
12. Boronat A, Sabater L, Saiz A, et al. GABA(B) receptor antibodies in limbic encephalitis and anti-GAD-associated neurologic disorders. *Neurology*. 2011;76:795–800.
13. Storey K, Matěj R, Rusina R. Unusual association of seronegative, nonparaneoplastic limbic encephalitis and relapsing polychondritis in a patient with history of thymectomy for myasthenia: a case study. *J Neurol*. 2011;258:159–161.
14. Josephs KA, Rubino FA, Dickson DW. Nonvasculitic autoimmune inflammatory meningoencephalitis. *Neuropathology*. 2004;24:149–152.

15. Graus F, Boronat A, Xifró X, et al. The expanding clinical profile of anti-AMPA receptor encephalitis. *Neurology*. 2010;74:857–859.
16. Zandi MS, Irani SR, Lang B, et al. Disease-relevant autoantibodies in first episode schizophrenia. *J Neurol*. 2011;258:686–688.
17. De Nayer AR, Myant N, Sindic CJ. A subacute behavioral disorder in a female adolescent. Autoimmune anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Biol Psychiatry*. 2009;66:e13–e14.
18. Najjar S, Pearlman D, Zagzag D, et al. Glutamic acid decarboxylase autoantibody syndrome presenting as schizophrenia. *Neurologist*. 2012;18:88–91.
19. Steiner J, Bogerts B, Sarnyai Z, et al. Bridging the gap between the immune and glutamate hypotheses of schizophrenia and major depression: potential role of glial NMDA receptor modulators and impaired blood-brain barrier integrity. *World J Biol Psychiatry*. 2012;13:482–492.
20. Haroon E, Raison CL, Miller AH. Psychoneuroimmunology meets neuropsychopharmacology: translational implications of the impact of inflammation on behavior. *Neuropsychopharmacology*. 2012;37:137–162.
21. McNally L, Bhagwagar Z, Hannestad J. Inflammation, glutamate, and glia in depression: a literature review. *CNS Spectr*. 2008;13:501–510.
22. Rotge JY, Aouizerate B, Tignol J, et al. The glutamate-based genetic immune hypothesis in obsessive-compulsive disorder. An integrative approach from genes to symptoms. *Neuroscience*. 2010;165:408–417.
23. Bhattacharyya S, Khanna S, Chakrabarty K, et al. Anti-brain autoantibodies and altered excitatory neurotransmitters in obsessive-compulsive disorder. *Neuropsychopharmacology*. 2009;34:2489–2496.
24. Brietzke E, Stabellini R, Grassi-Oliveira R, et al. Cytokines in bipolar disorder: recent findings, deleterious effects but promise for future therapeutics. *CNS Spectr*. 2011;16:157–168.
25. Pandey RS, Gupta AK, Chaturvedi UC. Autoimmune model of schizophrenia with special reference to antibrain antibodies. *Biol Psychiatry*. 1981;16:1123–1136.
26. Kayser MS, Dalmau J. Psychiatric presentations of autoimmune encephalopathies an autoimmune basis for behavioral abnormalities. *Psychiatric Times*. 2010;27:1–8.
27. Bataller L, Kleopa KA, Wu GF, et al. Autoimmune limbic encephalitis in 39 patients: immunophenotypes and outcomes. *J Neurol Neurosurg Psychiatry*. 2007;78:381–385.
28. Henneberg AE, Horter S, Ruffert S. Increased prevalence of antibrain antibodies in the sera from schizophrenic patients. *Schizophr Res*. 1994;14:15–22.
29. Samarasekera SR, Vincent A, Welch JL, et al. Course and outcome of acute limbic encephalitis with negative voltage-gated potassium channel antibodies. *J Neurol Neurosurg Psychiatry*. 2007;78:391–394.
30. Modoni A, Masciullo M, Spinelli P, et al. Successful treatment of acute autoimmune limbic encephalitis with negative VGKC and NMDAR antibodies. *Cogn Behav Neurol*. 2009;22:63–66.
31. Bernal F, Graus F, Pifarré A, et al. Immunohistochemical analysis of anti-Hu-associated paraneoplastic encephalomyelitis. *Acta Neuropathol*. 2002;103:509–515.
32. Voltz R, Dalmau J, Posner JB, et al. T-cell receptor analysis in anti-Hu associated paraneoplastic encephalomyelitis. *Neurology*. 1998;51:1146–1150.
33. Butler T, Ichise M, Teich AF, et al. Imaging inflammation in a patient with epilepsy due to focal cortical dysplasia. *J Neuroimaging*. 2011;23:129–131.
34. Brockington IF. Menstrual psychosis: a bipolar disorder with a link to the hypothalamus. *Curr Psychiatry Rep*. 2011;13:193–197.
35. Giraud SN, Caron CM, Pham-Dinh D, et al. Estradiol inhibits ongoing autoimmune neuroinflammation and NFκB-dependent CCL2 expression in reactive astrocytes. *Proc Natl Acad Sci USA*. 2010;107:8416–8421.
36. Arevalo MA, Diz-Chaves Y, Santos-Galindo M, et al. Selective oestrogen receptor modulators decrease the inflammatory response of glial cells. *J Neuroendocrinol*. 2012;24:183–190.
37. Feeser VR, Loria RM. Modulation of traumatic brain injury using progesterone and the role of glial cells on its neuroprotective actions. *J Neuroimmunol*. 2011;237:4–12.
38. Cao C, Matsumura K, Yamagata K, et al. Induction by lipopolysaccharide of cyclooxygenase-2 mRNA in rat brain; its possible role in the febrile response. *Brain Res*. 1995;697:187–196.
39. Schiltz JC, Sawchenko PE. Distinct brain vascular cell types manifest inducible cyclooxygenase expression as a function of the strength and nature of immune insults. *J Neurosci*. 2002;22:5606–5618.
40. Serrats J, Schiltz JC, García-Bueno B, et al. Dual roles for perivascular macrophages in immune-to-brain signaling. *Neuron*. 2010;65:94–106.
41. Matsumura K, Cao C, Ozaki M, et al. Brain endothelial cells express cyclooxygenase-2 during lipopolysaccharide-induced fever: light and electron microscopic immunocytochemical studies. *J Neurosci*. 1998;18:6279–6289.
42. Temel SG, Kahveci Z. Cyclooxygenase-2 expression in astrocytes and microglia in human oligodendrogloma and astrocytoma. *J Mol Histol*. 2009;40:369–377.
43. Shalev H, Serlin Y, Friedman A. Breaching the blood-brain barrier as a gate to psychiatric disorder. *Cardiovasc Psychiatry Neurol*. 2009;2009:278531.
44. Friedman A, Kaufer D. Blood-brain barrier breakdown and blood-brain communication in neurological and psychiatric diseases. *Cardiovasc Psychiatry Neurol*. 2011;2011:431470.
45. Müller N, Ackenheil M. Immunoglobulin and albumin content of cerebrospinal fluid in schizophrenic patients: relationship to negative symptomatology. *Schizophr Res*. 1995;14:223–228.
46. Webster MJ, O’Grady J, Kleinman JE, et al. Glial fibrillary acidic protein mRNA levels in the cingulate cortex of individuals with depression, bipolar disorder and schizophrenia. *Neuroscience*. 2005;13:453–461.
47. Sugai T, Kawamura M, Iritani S, et al. Prefrontal abnormality of schizophrenia revealed by DNA microarray: impact on glial and neurotrophic gene expression. *Ann N Y Acad Sci*. 2004;1025:84–91.
48. Rothermundt M, Ahn JN, Jörgens S. S100B in schizophrenia: an update. *Gen Physiol Biophys*. 2009;28 Spec No Focus:F76–F81.
49. Rothermundt M, Ohrmann P, Abel S, et al. Glial cell activation in a subgroup of patients with schizophrenia indicated by increased S100B serum concentrations and elevated myoinositol. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31:361–364.
50. Bayer TA, Buslei R, Havas L, et al. Evidence for activation of microglia in patients with psychiatric illnesses. *Neurosci Lett*. 1999;271:126–128.
51. Radewicz K, Garey LJ, Gentleman SM, et al. Increase in HLA-DR immunoreactive microglia in frontal and temporal cortex of chronic schizophrenics. *J Neuropathol Exp Neurol*. 2000;59:137–150.
52. Steiner J, Bielau H, Brisch R, et al. Immunological aspects in the neurobiology of suicide: elevated microglial density in schizophrenia and depression is associated with suicide. *J Psychiatr Res*. 2008;42:151–157.
53. Bauer D, Gupta D, Haroutunian V, et al. Abnormal expression of glutamate transporter and transporter interacting molecules in prefrontal cortex in elderly patients with schizophrenia. *Schizophr Res*. 2008;104:108–120.
54. Rao JS, Kellom M, Reese EA, et al. Dysregulated glutamate and dopamine transporters in postmortem frontal cortex from bipolar and schizophrenic patients. *J Affect Disord*. 2012;136:63–71.
55. Matute C, Melone M, Vallejo-Illarramendi A, et al. Increased expression of the astrocytic glutamate transporter GLT-1 in the prefrontal cortex of schizophrenics. *Glia*. 2005;49:451–455.
56. Smith RE, Haroutunian V, Davis KL, et al. Expression of excitatory amino acid transporter transcripts in the thalamus of subjects with schizophrenia. *Am J Psychiatry*. 2001;158:1393–1399.
57. Schroeter ML, Abdul-Khalil H, Krebs M, et al. Neuron-specific enolase is unaltered whereas S100B is elevated in serum of patients with schizophrenia—original research and meta-analysis. *Psychiatry Res*. 2009;167:66–72.
58. Steiner J, Bernstein HG, Bielau H, et al. S100B-immunopositive glia is elevated in paranoid as compared to residual schizophrenia: a morphometric study. *J Psychiatr Res*. 2008;42:868–876.
59. Steiner J, Bogerts B, Schroeter ML, et al. S100B protein in neurodegenerative disorders. *Clin Chem Lab Med*. 2011;49:409–424.

60. Rothermundt M, Ponath G, Glaser T, et al. S100B serum levels and long-term improvement of negative symptoms in patients with schizophrenia. *Neuropsychopharmacology*. 2004;29:1004–1011.
61. Huttunen HJ, Kuja-Panula J, Sorci G, et al. Coregulation of neurite outgrowth and cell survival by amphotericin and S100 proteins through receptor for advanced glycation end products (RAGE) activation. *J Biol Chem*. 2000;275:40096–40105.
62. Layé S. Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins Leukot Essent Fatty Acids*. 2010;82:295–303.
63. Leonard BE. The concept of depression as a dysfunction of the immune system. *Curr Immunol Rev*. 2010;6:205–212.
64. Kayser MS, Dalmau J. The emerging link between autoimmune disorders and neuropsychiatric disease. *J Neuropsychiatry Clin Neurosci*. 2011;23:90–97.
65. Marchiori GC, Vaglia A, Vianello M, et al. Encephalitis associated with glutamic acid decarboxylase autoantibodies. *Neurology*. 2001;56:814.
66. Doorduin J, de Vries EF, Willemsen AT, et al. Neuroinflammation in schizophrenia-related psychosis: a PET study. *J Nucl Med*. 2009;50:1801–1807.
67. van Berckel BN, Bossong MG, Boellaard R, et al. Microglia activation in recent-onset schizophrenia: a quantitative (R)-[11C]PK11195 positron emission tomography study. *Biol Psychiatry*. 2008;64:820–822.
68. Müller N. COX-2 inhibitors as antidepressants and antipsychotics: clinical evidence. *Curr Opin Investig Drugs*. 2010;11:31–42.
69. Steiner J, Walter M, Gos T, et al. Severe depression is associated with increased microglial quinolinic acid in subregions of the anterior cingulate gyrus: evidence for an immune-modulated glutamatergic neurotransmission? *J Neuroinflammation*. 2011;8:94.