Successful Treatment of Acute Autoimmune Limbic Encephalitis With Negative VGKC and NMDAR Antibodies

Anna Modoni, MD, PhD, Marcella Masciullo, MD,* Pietro Spinelli, MD,* Camillo Marra, MD, PhD,* Tommaso Tartaglione, MD,† Francesca Andreetta, PhD,‡ Pietro Tonali, MD,*§ and Gabriella Silvestri, MD, PhD*§*

Objective: To describe a case of acute nonherpetic limbic encephalitis (LE) with negative testing for antibodies directed against onconeuronal and cell membrane antigens, including voltage-gated potassium channels and *N*-methyl-D-aspartate receptor, that showed a dramatic response to immune therapy.

Materials and Methods: A 30-year-old woman manifested generalized seizures, altered consciousness, and memory impairment shortly after a prodromal viral illness. Few days later the patient developed a drug-resistant epileptic status.

Results: Electroencephalograph showed bitemporal slowing and paroxysmal slow wave bursts. Brain magnetic resonance imaging showed bilateral swelling in the medial temporal lobes. Cerebrospinal fluid analysis ruled out viral etiologies. A diagnostic search for cancer, including serum testing for known onconeuronal antibodies proved negative. Screening for cell membrane antigen antibodies, including voltage-gated potassium channels and *N*-methyl-D-aspartate receptor, was also negative. Suspecting an autoimmune etiology, we started an immunomodulatory treatment with intravenous immunoglobulin followed by a short course of oral prednisone, obtaining a full clinical recovery.

Conclusions: Our report confirms previous observations of "seronegative" autoimmune LE, suggesting the presence of other, still unknown central nervous system antigens representing a target of a postinfectious, autoimmune response in these patients. Moreover, it emphasizes the importance of early recognition and treatment of acute autoimmune LE, to reduce the risk of intensive care unit-related complications and the occurrence of permanent cognitive or behavioral defects.

Key Words: autoimmune limbic encephalitis, VGKC, NMDAR

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From the Departments of *Neuroscience; †Radiodiagnostic, Catholic University of Sacred Heart; §Fondazione Don C. Gnocchi, Rome; and ‡Department of Clinical Neurosciences, Neurological Institute C. Besta, Milan, Italy.
The authors disclose no financial interest regarding this work.
Reprints: Dr Gabriella Silvestri, MD, PhD, Department of Neuroscience, Catholic University of Sacred Heart, L.go F. Vito, Rome 1 00168, Italy (e-mail: gsilvestri@rm.unicatt.it).

Limbic encephalitis (LE) is an autoimmune disorder manifesting with seizures, confusion, and psychiatric and memory disturbances.[1,2] Brain magnetic resonance imaging (MRI) typically shows abnormal, bilateral T2, and fluid attenuated inversion recovery hyperintensities in medial temporal lobes.[3]

The autoimmune etiology can be either related to antibodies against various onconeural antigens or to antibodies directed against cell membrane antigens.[1,2]

The first group of autoimmune LE are usually associated with cancer, show brain infiltrates of cytotoxic T cells and limited response to treatment.[1,2]

The second group of autoimmune LE are more frequently nonparaneoplastic: in such forms, the main cell membrane antigens include voltage-gated potassium channels (VGKC),[4,5] NR1/NR2B heteromers of the *N*-methyl-D-aspartate receptor (NMDAR),[6,7] and unknown antigens predominantly expressed on the neuropil of the hippocampus or cerebellum.[8,9] LE with antibodies to cell membrane antigens have less frequent brain inflammatory infiltrates and respond significantly better to immunotherapy.[1]

So far, few cases of acute LE with negative antibodies testing have been reported: an autoimmune etiology was also suspected in these cases, due to their positive response to immune therapies.[9,10]

Supporting this issue, here we describe the case of a young woman affected by an acute nonherpetic LE who underwent a full clinical recovery after therapy with intravenous immunoglobulin (IVIg) and steroids. Serum testing for onconeural and antibodies to cell membrane antigens, including VGKC and NMDAR antibodies, were both negative.

CASE REPORT

A 30-year-old woman, who had complained of "flu-like" symptoms during the previous 3 days, was admitted to our hospital because of the occurrence of 3 generalized tonic-clonic seizures during sleep.

On admission she appeared lethargic, without evidence of focal neurologic deficits. Routine blood tests and brain computed tomography scan were normal and electroencephalograph (EEG) showed diffuse slowing. Seizures were treated with IV diazepam.

In the following 24 hours, she was febrile and appeared confused and agitated; EEG showed bitemporal burst of spikes

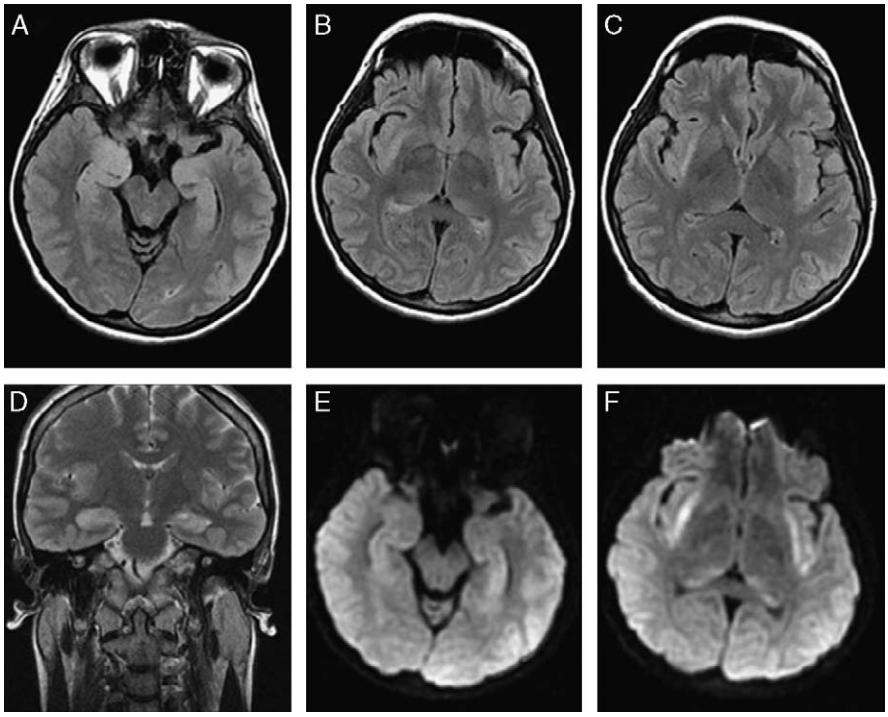

FIGURE 1. A to C, Axial T2 images; D, coronal T2w turbo spin-echo image; E and F, axial diffusion weighted images (DWI). Fluid attenuated inversion recovery and T2w images show diffuse and bilateral swelling of temporal uncus, hippocampal formation, subcortical insular white matter, and pulvinar, characterized by hyperintensity on T2wi. The highly hyperintense signal observed on DWI is related to hyperacute cellular swelling.

and multispikes. Cerebrospinal fluid (CSF) examination documented normal glucose and protein content, and no pleocytosis. Suspecting a herpes simplex virus (HSV) encephalitis, IV acyclovir (10 mg/kg × 3/d) was started and seizures were treated with carbamazepine.

On the following day, the patient was alert but disoriented, manifesting short-term memory deficits; ceftriaxone (2 g/d IV) was added because of evidence of pneumonia by chest x-ray.

Brain MRI showed diffuse and bilateral swelling of temporal uncus, hippocampal formation, subcortical insular white matter, and pulvinar, characterized by hyperintensity on T2-weighted imaging. A highly hyperintense signal was also evident on diffusion weighted images, possibly related to hyperacute cellular swelling (Fig. 1).

During the subsequent 72 hours, the patient manifested frequent complex partial seizures and on the fifth day from admission she eventually developed a drug-resistant epileptic status that could be only resolved by general anesthesia (propofol 2 mg/kg bolus over 5 min, then 2-4 mg/kg/h).

During the following 4 days, attempts to decrease propofol dosage failed, despite starting a combined antiepileptic treatment (phenobarbital, valproic acid, and levetiracetam).

An extensive search for antiviral and antibacterial antibodies in CSF and serum (HSV1 and HSV2, HHV6, Echo, Coxsackie, mumps, measles, Rubella, Epstein-Barr, Varicella-Zoster, human immunodeficiency virus type 1 and 2, Cytomegalovirus, *Borrelia burgdoferi*, syphilis, Parvovirus B19, *Leptospira*, *Coxiella burnetii* 1 and 2, *Legionella*, influenza and parainfluenza virus, Cryptococcus, respiratory virus, and enterovirus) and PCR for HSV, repeated at a time interval of 1 week, were always

TABLE 1. Neuropsychologic Profile Before and After Treatment

	Cutoff	I Evaluation	II Evaluation
Mini-Mental State Examination	23.0	**14**	**26**
Rey's Auditory Learning test			
Immediate evoking	28.53	**14.3**	**33.8**
Recency effect	< 19; > 61	100	100
Learning curve		Flat	Increment
Deferred evoking	4.69	**1**	**7.4**
Ideomotor apraxia test	18	20	20
Buccofacial apraxia test	18	20	20
Copy of a geometrical simple figure			
Free	3	4	4
Reference point help	16	21	21
Double barrage			
Accuracy (%)	90	**88**	**97**
False recognitions	0/67	1	7
Time (s)	> 133	**122**	**72.65**

Scores obtained by our patient before starting (I evaluation) and after 1 month of oral prednisone treatment (II evaluation). Raw scores obtained for each test were computed after the appropriate corrections for the age and educational level. The "cut-off" scores are reported for each test in the corresponding column. At the first evaluation a cognitive dysfunction involving in particular memory, learning, and attention abilities was evident (the pathologic performances are highlighted in bold). At the second evaluation, we documented a complete recovery of cognitive functions: in particular, at Mini-Mental State Examination, the patient showed unambiguous better scores (14/30 vs. 26/30) with a significant performance improvement (85.71%). Nevertheless, the most remarkable improvement was documented in short and long-term memory, as well as attentive and learning abilities.

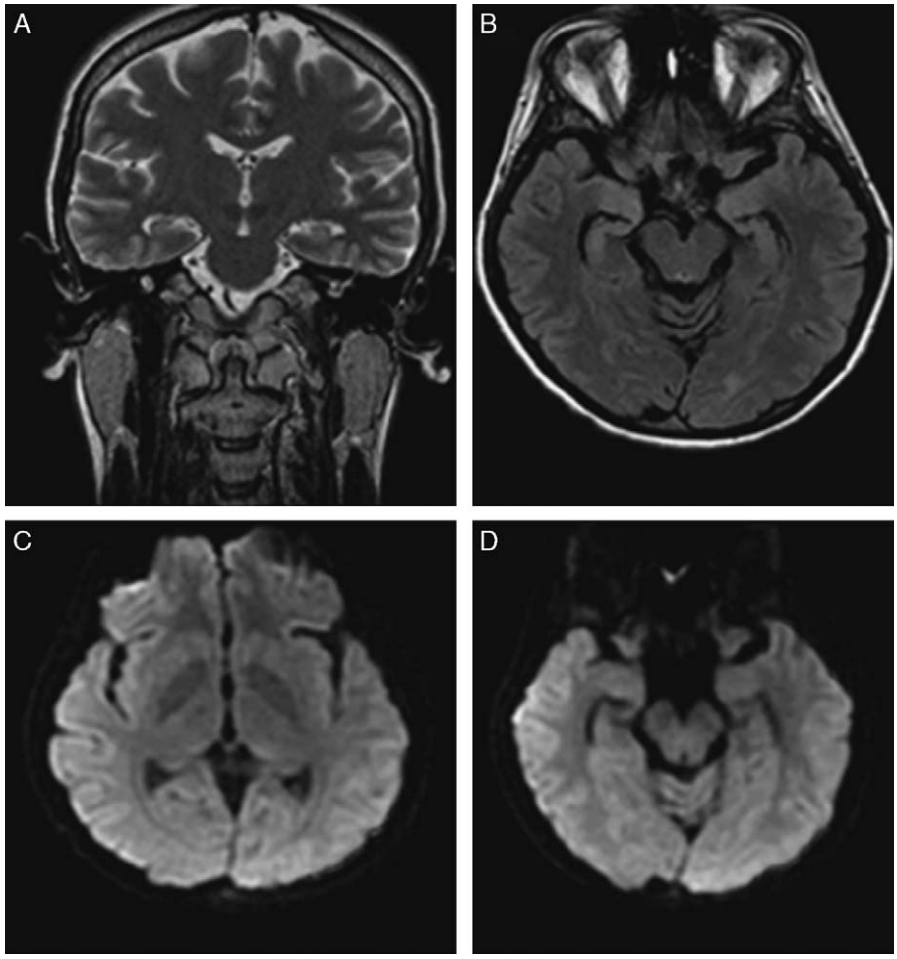

FIGURE 2. A and B, Axial fluid attenuated inversion recovery (FLAIR) images; C and D, axial diffusion weighted images (DWI). FLAIR and T2w images show atrophic and gliotic changes of temporal uncus, hippocampal formation, insular subcortical white matter, and pulvinar, characterized by faint hyperintensity on T2wi. On DWI all signal intensity alterations disappeared.

negative. CSF immunologic examination showed a blood-brain barrier damage, without oligoclonal bands.

Tumor search, including total body computed tomography scan, abdominal and thyroid echography, serum tumoral markers (CEA, TPA, CA15-3, 19-9, enolase, α-feto protein, and CYFRA) and antionconeuronal paraneoplastic antibodies testing by immunoblot assays (anti-Hu, Ri, Yo, CRMP5/CV2, and amphiphysin) were negative. An extensive autoimmune screening including antinuclear, antidouble-strand DNA, Smith/Rnp, Sjogren's (SSA, SSB), antineutrophilic cytoplasmic antibodies, anticardiolipin, antithyroglobulin, antimicrosomal antibodies determination were also negative. Thyroid hormones were normal.

Hence, suspecting an autoimmune etiology, we started IVIg administration (0.4 g/kg/d for 5 consecutive days): commencing 3 days after the first infusion, propofol could be suspended without recurrence of significant epileptic activity. Two days later, the patient was discharged from the intensive care unit (ICU) and during the following days antiepileptic drugs dosage was further reduced without recurrence of seizures.

However, the patient still appeared agitated, confused, and manifested an impairment of short-term memory. At that time, an extensive neuropsychologic evaluation, including Mini-Mental State Examination and the Mental Deterioration Battery,[11] documented a cognitive dysfunction involving in particular memory, learning, and attention abilities, whereas general visual deductive competence and praxis abilities were spared (Table 1).

We started a course of oral prednisone (50 mg/d); 1 month later, at clinical examination, the patient appeared awake and oriented. EEG showed mild bitemporal slowing, whereas brain MRI documented atrophic and gliotic changes of temporal uncus, hippocampal formation, insular subcortical white matter, and pulvinar, characterized by faint hyperintensity on T2wi, whereas all signal alterations on diffusion weighted images had disappeared (Fig. 2). The neuropsychologic follow-up documented a complete recovery of cognitive functions: indeed, at Mini-Mental State Examination the patient showed better scores (4/30 vs. 26/30) with a performance improvement (85.71%). Nevertheless, the most remarkable improvement was documented in short and long-term memory, as well as attentive and learning abilities (Table 1).

In 6 months, prednisone was tapered until suspension: at the end of this period, no malignancies were detected at a further clinical diagnostic re-evaluation.

Finally, a 1-year follow-up confirmed stable neuropsychologic and EEG findings; at this time a whole-body

fluorodeoxyglucose-positron emission tomography was also performed, resulting negative.

To further characterize the autoimmune etiology of LE in our patient, serum samples (drawn at ICU before commencing immune therapy) were sent for VGKC (performed at Prof A. Vincent's Oxford Laboratory)[4,5] and anti-NMDAR antibodies (performed at Prof J. Dalmau's Pennsylvania Laboratory)[6,7] determination, and both tests resulted negative.

DISCUSSION

LE is an autoimmune disorder manifesting with seizures, confusion, and memory disturbances.[1,2] The acute variant of LE often follows flu-like symptoms, resembling herpes simplex (HSV) encephalitis. Acute LE is usually nonparaneoplastic, being frequently associated with antibodies to cell membrane antigens, including VGKC, NMDAR, and others that remain to be characterized.[1,2] These forms usually respond to immune therapies.[1–3,5–10]

Our patient showed clinical and neuroradiologic features suggestive for an acute autoimmune LE, yet an extensive screening for known immune etiologies, such as onconeural paraneoplastic antibodies and antibodies to cell membrane antigens, including VGKC and NMDAR, was negative.

In our opinion, the negativity of these tests does not exclude a diagnosis of autoimmune LE in our patient, which seems indeed supported by the following issues: (1) our patient developed an acute onset of neurologic symptoms shortly after a prodromal viral-like illness. Such presentation can be frequently observed in many immune-mediated neurologic diseases, including acute LE with positive cell membrane antigen antibodies[7]; (2) immune therapy with IVIg and steroids produced a full clinical recovery: in particular, our patient showed a dramatic positive response at the start of IVIg administration, similarly to what is observed in other antibodies-mediated immune neurologic disorders[12]; (3) the neuroradiologic follow-up showed the regressive course of the temporomedial MRI abnormalities in our patient, as previously reported in patients affected by autoimmune LE[3]; (4) acute LE negative both to known onconeural and cell membrane antigen antibodies have already been described in the literature[9,10]: as in the case of our patient, an autoimmune etiology was postulated owing to the positive response to immune therapies in a few treated cases.[9,10]

Therefore, this report emphasizes the importance of an early recognition and treatment of "seronegative" autoimmune LE, demonstrating that immune therapy can be highly efficient in the treatment of autoimmune LE, even in the absence of typical serum markers. In fact, a prompt immune therapy reduced the risk of prolonged ICU stay complications and led to a full clinical recovery in our patient, as assessed by the results of the neuropsychologic follow-up (Table 1). This last issue seems important, considering that other studies[10] have emphasized the evidence of permanent cognitive and behavioral changes in patients with autoimmune LE not treated by immunosuppressive drugs.

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