Spontaneously Resolving Seronegative Autoimmune Limbic Encephalitis

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Objective: We describe a patient with seronegative autoimmune limbic encephalitis (SNALE) masquerading as glioma. Brain magnetic resonance imaging (MRI) abnormalities, distinctive pathological findings, and spontaneous remission are highlighted.

Background: There are 15 previously reported SNALE cases, 1 with pathology.

Materials and Methods: A 66-year-old man presented with prominent amnestic syndrome, progressive cognitive decline, and refractory complex partial seizures. Initial brain MRI suggested herpes limbic encephalitis. A 3-week course of intravenous acyclovir was ineffective. Cerebrospinal fluid analysis revealed no pleocytosis. Repeat brain MRI showed a left uncal-hippocampal, contrast-enhancing lesion, with full seizure control and significant cognitive improvement, occurred. Pathology revealed perivascular and parenchymal mixed lymphocytic inflammatory infiltrates, microglial activation, astrocytosis, and lymphocyte emperipolesis within neurons. Thorough searches for infectious pathogens and autoantibodies were negative. Six weeks later, a new enhancing right mesial temporal lesion appeared, with increased seizure activity and further cognitive impairment. Although immune therapy was declined, spontaneous resolution of the new enhancing lesion, with full seizure control and significant cognitive improvement, occurred.

Conclusions: SNALE may masquerade as glioma. Pathologic changes in our case of SNALE are distinctive. Spontaneous resolution of a focal SNALE lesion may potentially occur without immune therapy.

Key Words: limbic encephalitis, autoimmunity, emperipolesis, VGKC-complex, pathology

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MATERIALS AND METHODS

Case Report

A 66-year-old right-handed man presented with a few-week history of a prodromal viral-like illness that was characterized by intermittent mild low-grade fever, fatigue, nonspecific muscle aches, and mild diffuse headaches, which were followed by progressive short-term memory impairment and complex partial seizures averaging 1 seizure per day. The seizures began with “a dreamy state” followed by motionless staring and unresponsiveness for several minutes. The patient was started on phenytoin. Past medical and neurologic histories were unremarkable. There were no earlier symptoms of cognitive or affective disorders. The patient had completed 2 years of undergraduate schooling and subsequently ran his own business.

RESULTS

Initial brain magnetic resonance imaging (MRI) on T2-weighted image (T2-wi) and fluid-attenuated inversion recovery (FLAIR) sequence showed marked left mesial temporal lobe hyperintensity. Cerebrospinal fluid (CSF) was normal. Screening for infectious agents in the CSF and serum was negative. He was treated empirically with 3-week intravenous acyclovir, without improvement. Five weeks after the onset, he was admitted to our institution for refractory seizures. Medical examination was normal, without signs of infections or systemic autoimmune disorders. On neurologic examination, performed by an epileptologist, the patient was alert and oriented to person, place, and time and had a profound short-term memory deficit. The patient was able to recall 0 out of 3 items at 15 seconds (Fig. 4). Verbal fluency was normal with no paraphasic errors or obvious word-finding difficulty. He was able to follow 3 simple stage commands. Praxis was normal. There were no signs of meningismus or encephalopathy. Fundoscopic examination was benign. The segmental neurological examination was entirely normal. No signs of autonomic instability, spontaneous or action-induced myoclonus, or any other muscle twitches to suggest neuromyotonia were noted. Levetiracetam and valproate were added.

Repeat brain MRI, performed with and without gadolinium, showed a contrast-enhancing hyperintensity lesion on T2-wi/FLAIR in the left uncus and hippocampal formation (Fig. 1A–C), with minimal mass effect (Fig. 1A, B). These findings were initially thought to represent a glioma. A subtle right anterior mesial

FIGURE 1. A to C, Preoperative MRI. A, Axial T2-weighted image; B, Axial FLAIR; C, Postcontrast sagittal T1-weighted image. A to C show diffuse swelling with enhancement of the left temporal uncus and hippocampal formation. Arrows in A and B indicate subtle hyperintensity in the right uncus and hippocampal formation that was unrecognized preoperatively. D, Postcontrast axial T1-weighted image showing no residual enhancement after surgical resection. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.
temporal lobe hyperintensity on T2-wi/FLAIR went undetected at the time (Fig. 1A, B).

Electroencephalogram showed left temporal focal slowing and epileptiform sharp activity. Wada test demonstrated left hemispheric language dominance and right hemispheric memory dominance.

Stereotactic resection of the left mesioanterior temporal lobe was performed 6 weeks after the onset. Pathologic findings in the mesial temporal structures, cortex, and white matter included focally intense perivascular and parenchymal inflammatory infiltrates of T lymphocyte and slightly predominate B lymphocyte subtypes (Fig. 2A, B, Fig. 2F, G), prominent microglial nodules (Fig. 2B, C), and neuronophagia (Fig. 2D). There were rare lymphocytes within neurons (emperipolesis) (Fig. 2E). Immunostains for viruses (including HSV and cytomegalovirus), bacteria, fungi, and spirochetes were all negative. Repeat CSF analysis revealed no pleocytosis, normal glucose level, and elevated protein concentration (170 mg/dL). Negative CSF and serologic tests included Cryptococcus neoformans, Borrelia burgdorferi, syphilis, and a comprehensive antiviral antibody panel for HSV-1, HSV-2, HHV-6, varicella zoster, cytomegalovirus, Cox sackie, Echo, Epstein-Barr, influenza, measles, mumps, Rubella, HIV-1, and HIV-2. Polymerase chain reaction testing for HSV-1, HSV-2, and varicella zoster was negative. Negative serologic screening for systemic autoimmune disorders included ANA, anti-dsDNA, antineutrophilic cytoplasmic antibodies, Sjogren’s antibodies, antithyroglobulin, thyroid peroxidase antibody, C3, C4, CH50, and antiphospholipid. Tests for autoantibodies targeting VGKC-complex, GAD, and onconeural antigens (eg, Hu Abs, Ma2 Abs, CV2/CRMP5 Abs) were negative. Whole-body computed tomography scan revealed no occult malignancy.

Postoperatively, the patient was seizure-free for only 6 weeks, after which point seizures recurred. The frequency of complex partial seizures progressed to 4 to 6 per day, with an associated prominent amnestic syndrome. The patient’s seizures were refractory to more than 5 antiepileptic drugs. Repeat brain MRI, with and without gadolinium enhancement, revealed a new enhancing lesion in the right mesial temporal structures (Fig. 3A, B). Repeat serological screening for autoimmune antibodies remained negative. Formal neuropsychological evaluation (Fig. 4) showed profound impairment of verbal and visual memory. Immediate and delayed recall of a word list was at the first percentile or below. Immediate recall of contextual verbal information was at the 37th percentile, whereas delayed recall of the same
material was at the second percentile, suggesting decay over time. Verbal functioning was reduced. Reading rate was adequate, but reading comprehension was severely impaired (4.1 grade level) and was characterized by both inefficiency and inaccuracy. Although auditory attention was adequate, performance on simple and complex tests

FIGURE 3. A to D, 6-week postoperative MRI. A, Axial FLAIR; B, Postcontrast axial T1-weighted image. A and B show progressive hyperintensity and new enhancement in the right uncus and anterior hippocampal formation. C, Diffusion-weighted image. D, Apparent diffusion coefficient. C and D show no diffusion restriction abnormality. E and F, 14-week postoperative MRI. E, Axial FLAIR; F, Postcontrast axial T1-weighted image. E and F show dramatic interval improvement of FLAIR hyperintensity and enhancement abnormalities. G and H, 3-year postoperative MRI. G, Axial FLAIR; H, Postcontrast axial T1-weighted image. G and H show a residual subtle FLAIR signal abnormality and complete resolution of enhancement of the right mesial temporal lobe. FLAIR indicates fluid-attenuated inversion recovery; MRI, magnetic resonance imaging.

FIGURE 4. Timeline of clinical course and diagnostic testing.
of visual attention was problematic. Visual perceptual abilities were impaired. Nonverbal abstract reasoning ability and symbol reproduction were both at the 16th percentile. Performance on a block design task was at the second percentile, and his ability to copy a complex figure was below the first percentile. Cognitive flexibility was intact. He was able to maintain a problem-solving strategy and able to shift his strategy when the task demanded change. Superimposed depression was noted.

A diagnosis of SNALE was entertained. The family declined steroids or intravenous immunoglobulin. Repeat brain MRI 14 weeks postoperatively demonstrated dramatic improvement of the enhancing lesion (Fig. 3E, F), accompanied by full seizure control. In addition, there was significant improvement of cognitive function with only mildly improved memory functions (the patient was able to recall 1 out of 3 items at 15 and 30 s and 0 out of 3 items at 3 min) demonstrated by neurological/cognitive examination that was completed by the same epileptologists who performed the initial evaluation (Fig. 4). A 3-year postoperative brain MRI showed a subtle residual FLAIR signal abnormality and complete resolution of enhancement of the right mesial temporal lobe (Fig. 3G, H). Without immune therapy, during the follow-up of 8 years, he continued to report slow but steady improvement of his general cognitive function, whereas improvement of short-term/long-term memory deficits was less evident. The patient declined repeat formal neuropsychological testing. However, on his most recent neurological examination, he was able to recall 2 out of 3 items at 30 seconds and 1 out of 3 items at 3 and 15 minutes (Fig. 4). He had fluent speech with no paraphasic errors, but with mild word-finding difficulty. Processing speed and abstract reasoning were improved. He showed high levels of anxiety, frustration, and mild depression. The segmental neurologic examination remained unremarkable. His seizures are controlled on a low dose of lamotrigine. A chronological timeline of the aforementioned clinical course and diagnostic tests is summarized in Figure 4.

**DISCUSSION**

Our case documents spontaneous remission of clinical and neuroimaging abnormalities in SNALE, without immune therapy. The diagnosis of SNALE is supported by (1) pathology documenting inflammation without virus or other pathogens, (2) no relapse or evidence of an occult tumor over 8 years excluding paraneoplastic LE, (3) negative CSF and serological viral studies, (4) negative tests for serum autoantibodies, including VGKC-complex Abs and GADAbs, and (5) MRI abnormalities confined to the mesial temporal structures.

Our case is unusual because of (i) the MRI abnormalities mimicking glioma, (ii) the spontaneous remission without immune therapy, and (iii) the distinctive pathological findings.

In 15 previous reports of SNALE (Table 1), the clinical presentations were similar to other cases of autoimmune LE. In addition, brain MRI reports consistently revealed hyperintense signal changes in the hippocampus, often bilaterally, without enhancement (Table 1). The sequential bilateral enhancement observed in our case (Fig. 1C, Fig. 3B), however, has not been described in previous published cases of SNALE (Table 1).

The response to immune therapy in SNALE cases varies from full recovery (Table 1) to limited improvement of cognitive and behavioral functions and seizures (Table 1). Although in our patient, clinical remission and spontaneous resolution of the right mesial temporal encephalitis may raise doubt regarding the efficacy of immune therapy in SNALE, this single observation is insufficient evidence to refute its therapeutic role. Moreover, early initiation of immune therapy may have halted the immunological process, thereby preventing the sequential involvement of the right mesial temporal lobe.

Some of the previously reported cases of SNALE may have resulted from autoantibodies targeting newly defined autoantigens, such as GluR1/GluR2 subunits of the AMPAR and GABA\textsubscript{B}R. In our case, testing for autoantibodies targeting NMDAR, AMPAR, or GABA\textsubscript{B}R was not performed, as these were not available in 2002. However, the pathological changes in our case are distinct from the limited available pathologic data describing cases of known cell membrane autoimmunity, such as those with antibodies targeting VGKC complex or NMDAR.

Pathology reports of VGKC-complex-Abs-related LE document focal neuronal loss of the CA4 region and scattered parenchymal and focal perivascular infiltrates with neither neuronophagia nor microglia nodules. The pathologic finding of lymphocyte emperipolesis (Fig. 2A, B, Fig. 2F, G), with both prominent microglial nodules (Fig. 2B, C) and neuronophagia (Fig. 2D). In the sole previous case of SNALE with neuro-pathological data, the disorder was fatal owing to limbic and extralimbic brain inflammatory changes. The severity was attributed to the patient's comorbidities: myasthenia gravis and relapsing polychondritis. The pathologic finding of lymphocyte emperipolesis within neurons (Fig. 2E) in our case is a rare phenomenon that we could not find previously described in any autoimmune encephalitis, including LE subtypes. Emperipolesis in human brains can involve oligodendrocytes within astrocytes (eg, demyelinating disease), lymphocytes within histiciocytes (eg, Rosai-Dorfman disease), lymphocytes within astrocytes (eg, multiple sclerosis and brain tumors), and lymphocytes within oligodendrocytes (eg, experimental autoimmune encephalomyelitis). One animal study reported lymphocyte emperipolesis within neurons, induced by intraneural injection of ricin. The significance of lymphocyte emperipolesis in our case is uncertain. It may represent a form of neuronal toxicity by overstimulated lymphocytes.
In summary, an acute or subacute presentation of a prodromal viral-like illness followed by cognitive dysfunction with behavioral or psychiatric manifestations, and/or seizures, should raise the clinical suspicion of autoimmune LE, notwithstanding the absence of serum autoantibodies. Diagnostic tests, such as brain MRI or single photon emission computed tomography scan, both of which may reveal bilateral hippocampal involvement, electroencephalogram, and CSF analysis, can be helpful in corroborating the diagnosis of SNALE. If the diagnosis remains uncertain, then the demonstration of a significant response to immune therapy trials (e.g., corticosteroids, intravenous immunoglobulin) may be confirmatory.

### TABLE 1. Clinical and MRI Findings in 15 Cases of SNALE

<table>
<thead>
<tr>
<th>Study</th>
<th>Sex</th>
<th>Age (Median)</th>
<th>Immunotherapy</th>
<th>Seizures</th>
<th>MRI</th>
<th>CSF</th>
<th>Tumor</th>
<th>Outcome</th>
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<tbody>
<tr>
<td>Graus et al&lt;sup&gt;6&lt;/sup&gt; (n = 5) of 45 cases</td>
<td>Male (n = 3), female (n = 2)</td>
<td>40-67 (64)</td>
<td>NS (n = 5)</td>
<td>No (n = 5)</td>
<td>NS (n = 5)</td>
<td>WBC: pleocytosis, type NS (n = 3)</td>
<td>NS (n = 5)</td>
<td>Ruled out (n = 5)</td>
</tr>
<tr>
<td>storey et al&lt;sup&gt;7&lt;/sup&gt; (n = 1) of 1 case</td>
<td>Male (n = 1)</td>
<td>73 (73)</td>
<td>Corticosteroid, IVIG, plasma exchange, (n = 1)</td>
<td>Yes (n = 1)</td>
<td>T2/FLAIR: bilateral hippocampal hyperintensities, vascular white matter lesions, moderate cerebral atrophy. ES NS. (n = 1)</td>
<td>WBC: 89 Mononuclear cells/µL</td>
<td>Protein: 66 mg/dL</td>
<td>Glucose:NS</td>
</tr>
<tr>
<td>Bataller et al&lt;sup&gt;8&lt;/sup&gt; (n = 3) of 39 cases</td>
<td>Male (n = 1), female (n = 2)</td>
<td>28-60 (40)</td>
<td>Corticosteroids (n = 3), Azathioprine (n = 1)</td>
<td>NS (n = 3)</td>
<td>T2/FLAIR: bilateral mesial temporal hyperintensities (n = 2), NS (n = 1). ES NS (n = 3)</td>
<td>WBC: 2-119/µL (type NS)</td>
<td>Protein: 32-132 mg/dl</td>
<td>Glucose:NS</td>
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<tr>
<td>Modoni et al&lt;sup&gt;9&lt;/sup&gt; (n = 1) of 1 case</td>
<td>Female (n = 1)</td>
<td>30</td>
<td>Corticosteroids, IVIG (n = 1)</td>
<td>Yes (n = 1)</td>
<td>T2/FLAIR: bilateral diffuse swelling of temporal unci, hippocampi, subcortical insular white matter, and pulvinaria. DWI: positive (n = 1). ES NS. (n = 1)</td>
<td>WBC: NS</td>
<td>Protein: normal</td>
<td>Glucose: normal</td>
</tr>
<tr>
<td>Samarasekera SR, et al,&lt;sup&gt;10&lt;/sup&gt; (n = 4) of 4 cases</td>
<td>Male (n = 1), female (n = 3)</td>
<td>21-36 (24)</td>
<td>Corticosteroids (n = 2), NS (n = 2)</td>
<td>Yes (n = 4)</td>
<td>FLAIR: bilateral hyperintensity in hippocampi (n = 4) and amygdalae (n = 4). ES NS (n = 4)</td>
<td>WBC: 0 (n = 3), 5 lymphocytes (n = 1). Protein: normal (n = 2), 67 mg/dL (n = 1), 70 mg/dL (n = 1). Glucose: normal (n = 4)</td>
<td>OB: negative</td>
<td>Ruled out (n = 1)</td>
</tr>
<tr>
<td>Rinaldi et al&lt;sup&gt;11&lt;/sup&gt; (n = 1) of 1 case</td>
<td>Male (n = 1)</td>
<td>56</td>
<td>Corticosteroids, IVIG, plasma exchange (n = 1)</td>
<td>“Unremarkable,” (n = 1). ES NS. (n = 1)</td>
<td>WBC: NS</td>
<td>Protein: NS</td>
<td>Glucose: NS</td>
<td>OB: NS</td>
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CSF indicates cerebrospinal fluid; DWI, diffusion weighted image; ES, enhancement study; IVIG, intravenous immunoglobulin; MRI, magnetic resonance imaging; NA, not applicable; NS, not specified; OB, oligoclonal bands; SNALE, seronegative autoimmune limbic encephalitis; WBC, white blood cells.
Given the absence of data describing the incidence of spontaneous remission of SNALE and that other researchers have emphasized the importance of immunotherapy in SNALE and NMDA encephalitis, future studies of SNALE clarifying both its natural course and the role of immunotherapy are needed. Therefore, in the absence of such studies, notwithstanding the spontaneous resolution of the right mesial temporal encephalitis in our patient, we advocate initiating immune therapy early, to optimize neurological, neuropsychiatric, and cognitive outcomes. In planning future clinical trials aimed at assessing the efficacy of immune therapy in SNALE, researchers should consider the possibility that spontaneous resolution without treatment may occur. Clinically, this case highlights that (1) SNALE may be under-diagnosed; (2) the absence of positive autoantibody tests should not exclude SNALE; (3) the need to recognize that SNALE may masquerade as gliomas, to avoid unwarranted resective surgery; and (4) SNALE can spontaneously resolve without therapy.

REFERENCES