Autoimmune Encephalitis With Multiple Autoantibodies
A Diagnostic and Therapeutic Challenge

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Introduction: Indications for autoantibody testing in patients with rapid-onset cognitive impairment have expanded in step with the growing number of disease-associated autoantibodies and clinical syndromes. Although increased access to autoantibody testing has broadened our understanding of the spectrum of autoimmune encephalitis (AE), it has also produced new challenges associated with deciphering the contributions of disease-associated autoantibodies in patients with atypical clinical features and/or multiple autoantibodies. These challenges are illustrated through presentation of a patient with AE associated with autoantibodies against intracellular and cell-surface neuronal antigens. The implications of detection of multiple autoantibodies are considered in the context of relevant literature, and used to frame a diagnostic and therapeutic approach.

Case Report: A previously well 67-year-old man presented with encephalopathy and psychosis, impaired visual fixation, and ataxia, emerging over 3 months. Hu, CRMP-5, and NMDAR autoantibodies were identified in the cerebrospinal fluid. No malignancy was discovered despite extensive investigations. An aggressive course of immunotherapy temporarily stabilized his course; however, the patient succumbed to his illness 10 months after symptom onset. Lack of sustained response to immunotherapy and neuropathologic findings suggested that AE associated with Hu antibodies was primarily responsible for this patient's progressive decline.

Conclusions: Multiple autoantibodies may be detected in patients with AE. When antibodies targeting intracellular and cell-surface antigens are detected together, investigation and treatment of syndromes associated with intracellular antibodies should be prioritized, acknowledging the link between these antibodies and irreversible neuronal injury. In paraneoplastic cases, prognosis may be tied to early detection and treatment of the underlying malignancy.

Key Words: autoimmune encephalitis, Hu antibody, NMDA receptor antibody, rapidly progressive dementia

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Autoimmune encephalitis (AE) is an important cause of rapid cognitive and neurological decline, particularly in younger patients.[1] Although a possible diagnosis can be established on the basis of clinical criteria, the detection of antibodies against central nervous system antigens establishes definitive AE in patients with compatible clinical symptoms and signs, and may inform subsequent investigation, treatment, and prognosis.[2] The detection of autoantibodies directed against cell-surface neuronal antigens tends to predict a favorable response to treatment, while diseases associated with autoantibodies targeting intracellular antigens often present a greater treatment and rehabilitation challenge, owing to their frequent association with underlying malignancies, and T-cell–mediated neuronal degeneration.[3] Accordingly, the diagnosis and management of patients with AE has been greatly advanced by ongoing efforts to identify novel disease-associated syndromes and autoantibodies, and through improved access to reliable and affordable panels that allow rapid and sensitive screening of serum and cerebrospinal fluid (CSF) for AE-associated autoantibodies.

Although overall beneficial, increased access to antibody testing has presented new challenges for the practicing neurologist who must now determine the clinical relevance of autoantibodies when detected in patients with atypical presentations, or weigh the implications of multiple disease-associated autoantibodies when reported together. These challenges are likely to intensify as the number of disease-associated autoantibodies increases, and as indications for testing continue to expand. Recognizing this, we emphasize the need to develop and operationalize diagnostic and therapeutic approaches that can be applied to patients with AE associated with atypical autoantibody findings.

CASE REPORT

A previously healthy 67-year-old man presented with a 3-month history of cognitive impairment and gait instability, which rapidly progressed to psychosis, agrypnia excitata, and akinetic mutism. On examination, the patient was encephalopathic, with ocular flutter, ataxia, and spasticity (see Video, Supplemental Digital Content 1, http://links.lww.com/NRL/A35). The first clip depicts the patient 3 months after

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R.C.B. has also served on an advisory board for MT Pharma America. G.S.D. serves as the clinical director of the Anti-NMDA Receptor Encephalitis Foundation (Inc., Canada). The remaining authors declare no conflict of interest.

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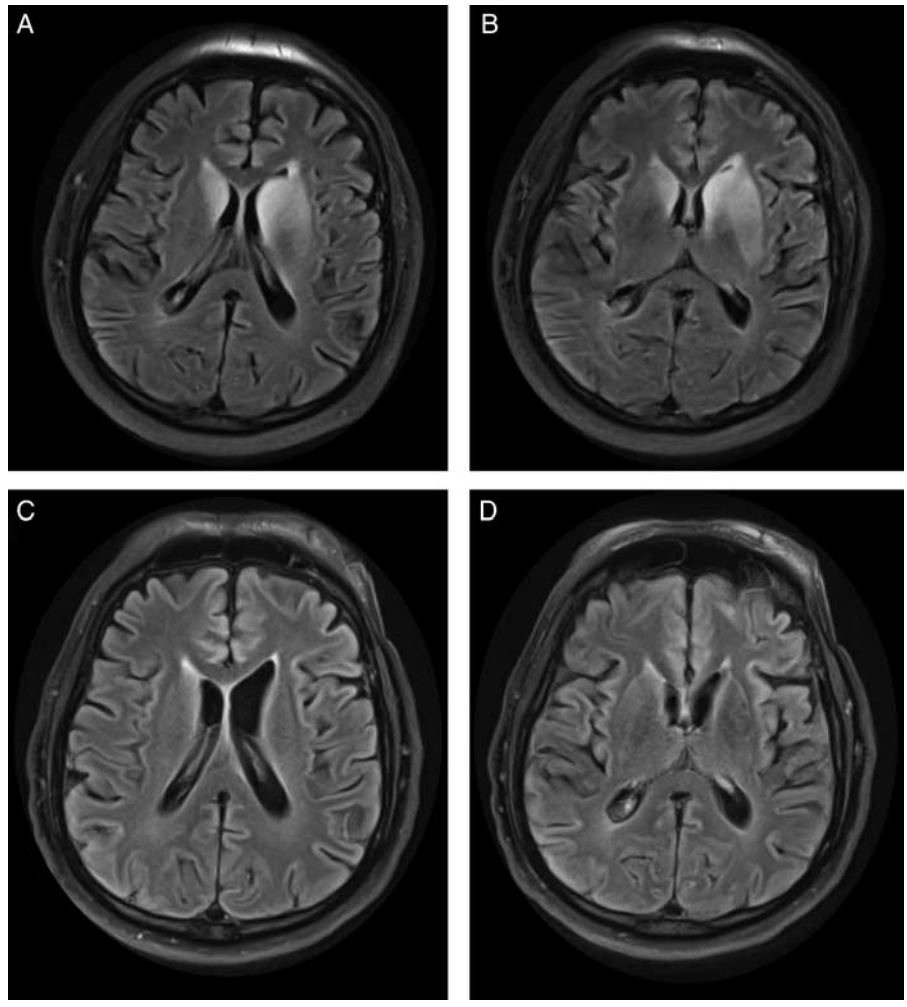

FIGURE 1. Brain magnetic resonance imaging at presentation (A, B), and after treatment with intensive immunotherapy (C, D). A, B, T2-FLAIR hyperintensities were evident in the left caudate, putamen and globus pallidus, and right caudate. There were no areas of contrast enhancement or diffusion restriction (not shown). C, D, T2-FLAIR hyperintensities markedly improved after treatment. Repeat imaging 3 months following presentation showed global atrophy and subtly increased T2-FLAIR intensities within the temporal lobes (not shown). Images are displayed in radiologic convention. FLAIR indicates fluid-attenuated inversion recovery.

onset of symptoms and before immunotherapy. Encephalopathy, ocular flutter, and breath-holding spells are highlighted. The next clip depicts the patient after monthly cyclophosphamide treatments (6 mo after symptom onset). Here, he is appropriately following commands and conversing with the clinical team]. Brain magnetic resonance imaging showed T2-fluid-attenuated inversion recovery (FLAIR) hyperintensities involving the bilateral basal ganglia without contrast enhancement (Figs. 1A, B). CSF analyses revealed 71 nucleated cells/mm^3 (84% lymphocytes), 178 mg/dL of protein, and 11 CSF-specific oligoclonal bands. Infectious etiologies were excluded with extensive testing. Hu (anti-neuronal nuclear antibody, type 1) and CRMP-5 antibodies were identified at high titers in the serum (1:7680 and 1:15360, respectively) and CSF (1:256 and 1:1024, respectively). IgG autoantibodies against N-methyl-D-aspartate receptors (NMDAR) were identified in the CSF only (Mayo Clinic Laboratories, Rochester, MN). No malignancy was detected in the antemortem period despite an exhaustive search that included CSF flow cytometry and cytology, whole-body fluorodeoxyglucose-positron emission tomography (FDG-PET), testicular ultrasound, and bone marrow biopsy.

In the month following admission, the patient was treated sequentially with corticosteroids (methylprednisolone 1 g IV QD×5 d), plasmapheresis (full-volume exchange Q2 d×5), rituximab (375 mg/m^2 Q7 d×2), and IV immunoglobulin (2 g/kg, divided over 5 d; Fig. 2). One week after treatment, he exhibited waxing and waning lucidity, with stabilization of psychosis. At the peak of his recovery, he was intermittently conversant, and was able to follow commands and interact with the clinical team. Repeat CSF analysis showed 0 nucleated cells/mm^3, 56 mg/dL of protein, and 7 CSF-specific oligoclonal bands. There was dramatic interval improvement of T2-FLAIR hyperintensities (Figs. 1C, D).

Maintenance treatments with monthly pulse IV cyclophosphamide were provided (1 gm/m^2×6 mo). However, at the conclusion of this treatment course, the patient exhibited increasing levels of agitation. Peripheral blood tests suggested adequate immunosuppression (CD19 B-cell count 0, CD4 T-cell count 594, CD8 cell count 200). At the family's request, supportive care was instituted, and the patient was transitioned to hospice care. He died 10 months from symptom onset of complications of AE. A complete postmortem examination failed to identify a disease-associated visceral malignancy. Neuropathologic evaluation showed characteristic findings of Hu-mediated encephalitis (Fig. 3).

DISCUSSION

We report a case of AE in a 67-year-old gentleman with multiple autoantibodies against cell-surface (NMDAR) and

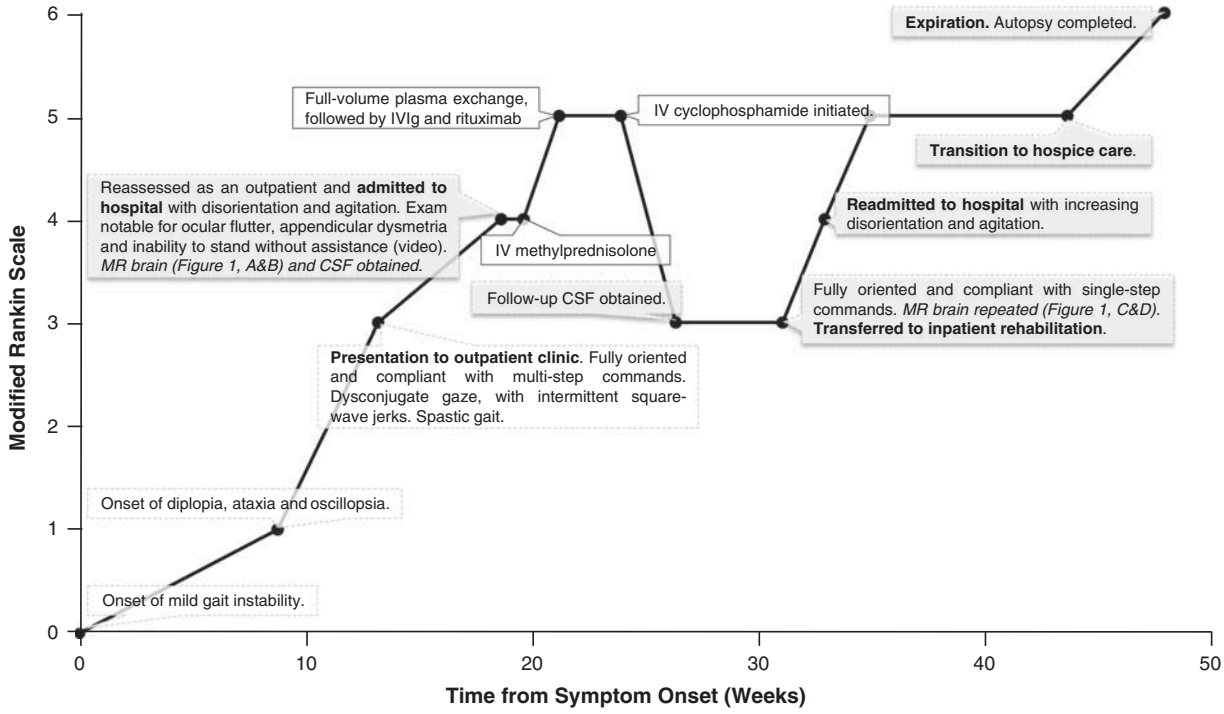

FIGURE 2. Clinical course and details of treatment. Clinical details (gray dashed boxes) and treatment course (black solid boxes) are depicted from time from symptom onset. Severity of impairment is measured via the modified Rankin Scale.[4] CSF indicates cerebrospinal fluid; IV, intravenous; MRI, magnetic resonance imaging.

intracellular (Hu, CRMP-5) neuronal antigens, who presented with symptoms and signs known to associate with Hu (cerebellar and limbic dysfunction),[5] CRMP-5 (dementia, ataxia, and myelopathy)[6] and NMDAR (adventitious movements, acute psychoses, and mutism) autoantibodies.[7] Although it was initially difficult to determine which antibody (or combination thereof) best accounted for the clinical presentation, the emergence of progressive neurological deficits without a sustained response to tiered immunotherapy was compelling for AE associated with Hu autoantibodies. Neuropathologic assessment confirmed this clinical diagnosis.

Identifying the pathogenic autoantibody(ies) is critical when evaluating patients with AE, recognizing the prognostic and therapeutic implications associated with detection of cell-surface versus intracellular neuronal autoantibodies (Table 1).[8] When present in isolation, the discovery of autoantibodies against cell-surface neuronal antigens confers a favorable prognosis, with good outcomes reported in $>80\%$ of patients with NMDAR encephalitis after treatment with first-line and second-line immunotherapies.[7] By contrast, the detection of autoantibodies against intracellular neuronal antigens portends poorer responses to therapy and outcomes.[9] For this reason, thorough screening of serum and CSF is recommended in all patients with suspected AE, preferring diagnostic panels that test for intracellular and cell-surface autoantibodies over testing for individual autoantibodies. Had testing been limited to investigation for NMDAR autoantibodies in this case, a vastly different therapeutic course would have been pursued, and inaccurate prognostic information would have been provided to the family.

Little is known concerning outcomes in patients in whom autoantibodies against cell-surface and intracellular neuronal antigens are reported together. The few reported cases of AE associated with both cell-surface and intracellular neuronal autoantibodies occurred in the setting of visceral malignancy, implicating cross-reactivity of tumor-directed antibodies in the pathogenesis of central nervous system autoimmune disease.[5,6] A recent analysis of serum from nearly 80,000 patients with suspected autoimmune neurological disorders concluded that the frequency of cancer was higher when Hu and CRMP-5 autoantibodies were detected together, with thymoma and small cell lung carcinoma most commonly identified.[10] These findings reinforce the conclusions of an earlier case series, which uncovered neoplasms in $>90\%$ of patients presenting with coexisting Hu and CRMP-5 autoantibodies.[11] These findings also emphasize the importance of thoroughly screening for tumors in patients with multiple disease-associated autoantibodies through the use of structural imaging of the chest, abdomen, and pelvis. Other modalities may be incorporated when indicated and available (eg, FDG-PET).

The detection of disease-associated tumors has important implications for treatment in patients with AE, as tumor-specific therapies—such as resection, chemotherapy, and radiation—may stabilize neurological disease.[6,12] As this case illustrates, however, multiple autoantibodies may be identified in the absence of a detectable tumor. In such cases, it may be reasonable to consider staged provision of immunomodulatory therapies targeting B lymphocytes and T lymphocytes,[5,10] accepting that the likelihood of sustained benefit may be lower compared with patients with disease-associated malignancies amenable to treatment.

Although no tumor was detected in this case, we acknowledge that a disease-associated malignancy may have contributed to AE pathogenesis, but either remained undetectable (despite thorough antemortem and postmortem investigations), or was eliminated by a robust host immune response or immunotherapies provided as treatment for AE. Regardless of the drivers of disease

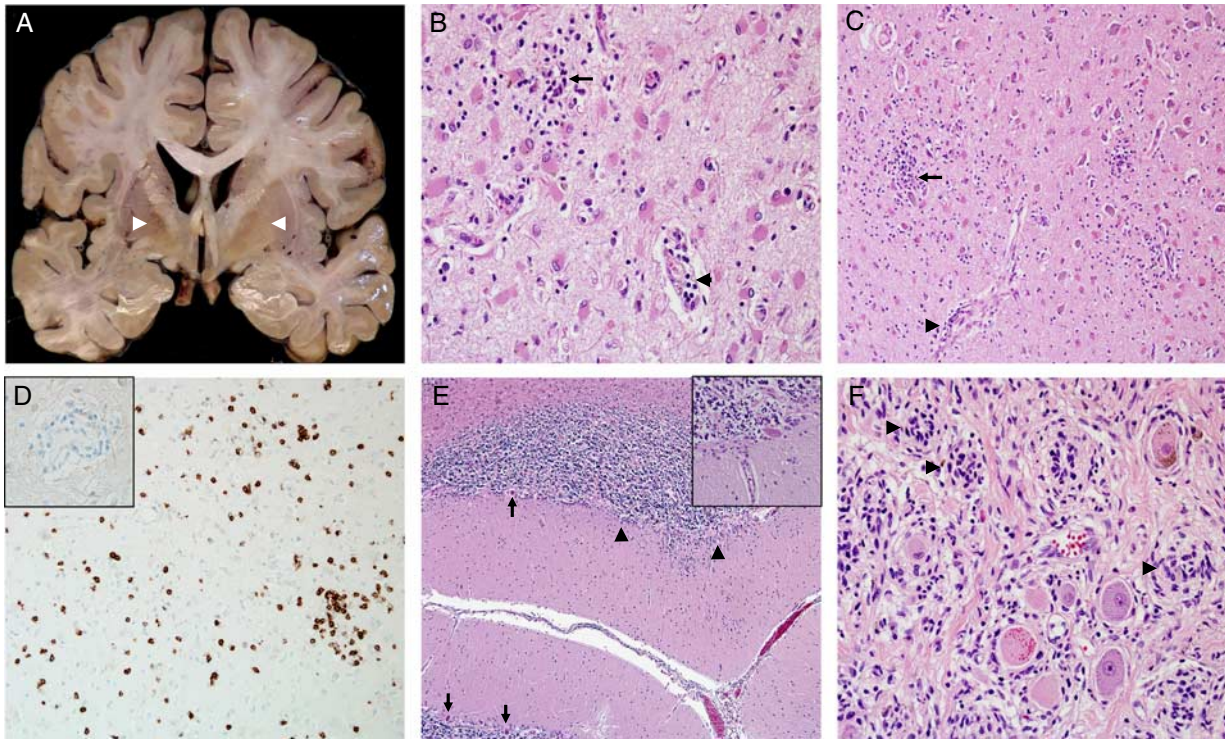

FIGURE 3. Neuropathology. A, Coronal brain section. There is yellow discoloration of the right and left globus pallidus (arrowheads). The gross appearance belies the extensive histopathologic changes. B, The putamen (H&E stain, ×400) displays perivascular lymphocytic cuffing (arrowhead), microglial nodules (arrow), and marked neuronal loss with astrogliosis. C, The amygdala (H&E, ×200) demonstrates similar pathologic changes, with additional note of scattered parenchymal lymphocytes (arrowhead and arrow depicting features as in B). D, The inflammatory infiltrate within the putamen is rich in cytotoxic T lymphocytes (CD8 immunostain, ×200), but contains very few B cells (inset: CD20 immunostain, ×600). E, The cerebellar cortex shows marked loss of Purkinje neurons (arrows mark residual cells) accompanied by Bergman gliosis (arrowheads; H&E, ×100; inset: H&E, ×400). F, Lumbar dorsal root ganglia are overrun by inflammatory cells. Numerous nodules of Nageotte are visible (arrowheads), reflecting neuronal death and capsular cell collapse (H&E, ×400). H&E indicates hematoxylin and eosin.

pathogenesis, it is likely that the same processes responsible for neuronal destruction and formation of antibodies against intracellular neuronal antigens (namely Hu) contributed to the formation of cell-surface autoantibodies in this patient. Indeed, the secondary formation of NMDAR autoantibodies has been described in other neuroinflammatory diseases (eg, primary demyelinating diseases,[13] herpes simplex encephalitis[14]). The alternative possibility—that AE driven by cell-surface antibodies precedes formation of antibodies against intracellular antigens—is less likely, as neuronal integrity (and hence exposure of intracellular antigens to immune cells) is

TABLE 1. Clinical Features Associated With Autoantibodies Against Cell-surface and Intracellular Neuronal Autoantibodies

	Cell-surface Autoantibodies	Intracellular Autoantibodies
Common clinical phenotype	Limbic dysfunction (NMDAR, AMPAR, $GABA_BR$), encephalitis (NMDAR, AMPAR, LGI1, DPPX), seizures ($GABA_AR$, $GABA_BR$), faciobrachial dystonic seizures (LGI1), neuromyotonia (CASPR2), CNS hyperexcitability (DPPX, GlyR), stiff-person syndrome (GlyR)	Limbic dysfunction (Hu, Ma-1, Ma-2), cerebellar degeneration (Hu, Ri, Yo, Ma-1, Ma-2, GAD-65), sensory neuropathy/ganglionopathy (Hu, Yo, Ma-2, CRMP-5), myelopathy (Yo, CRMP-5), stiff-person syndrome (GAD-65, ampiphysin)
Associated tumor	Ovarian teratoma (NMDAR), small cell lung (AMPAR, $GABA_BR$), breast (AMPAR), thymoma (CASPR2), Hodgkin lymphoma (mGLUR5)	Small cell lung (Hu, Ri, Yo, Ma-1, CRMP-5), breast (Ro, Ma-1, Yo, ampiphysin), germ cell (Ma-1, Ma-2), ovarian (Yo, amphiphysin)
Therapeutic modalities	Tumor treatment (if present), IV methylprednisolone, IV immunoglobulin, plasmapheresis, B-cell immunotherapy (eg, rituximab)	Tumor treatment (if present), IV methylprednisolone, T-cell immunotherapy (eg, cyclophosphamide)
Prognosis	Outcome varies with autoantibody; however, most patients improve considerably. Earlier diagnoses and treatment associates with better outcomes	Outcome varies with associated tumor, although is overall poor. Stabilization of neurological deficits is often the best case scenario

AMPAR indicates amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR, contactin-associated protein-like receptor; CRMP, collapsing response-mediated protein; DPPX, dipeptidyl-peptidase-like protein; $GABA_{A/B}R$, γ-aminobutyric acid receptor, A/B subtypes; GAD, glutamic-acid decarboxylase; Hu, anti-neuronal nuclear antibody, type 1; IV, intravenous; LGI, leucine-rich glioma-inactivated; Ma, paraneoplastic Ma antigen; mGLUR, metabotropic glutamate receptor; NMDAR, N-methyl-D-aspartate receptor; Ri, anti-neuronal nuclear antibody, type 2; Yo, anti-neuronal nuclear antibody, type 3.

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thought to be preserved in patients with syndromes driven by antibodies against cell-surface neuronal antigens.[15] With this in mind, we suggest that management of patients with AE associated with antibodies against both intracellular and cell-surface neuronal antigens should include immunotherapies that modulate both T cells (eg, cyclophosphamide) and B cells (eg, rituximab).

As access to and indications for autoantibody testing continue to expand, it is likely that patients with AE associated with multiple autoantibodies will be encountered with increasing frequency. Accordingly, an organized approach to diagnosis, and treatment will become essential. Case series considering treatment responses and mitigating factors in larger numbers of patients with AE and multiple autoantibodies will be critical to optimizing therapeutic approaches and outcomes in this underinvestigated patient cohort.

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