Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.9707-22
Intern Med 62: 469-474, 2023
http://internmed.jp

【 CASE REPORT 】

# Autoimmune Encephalitis Associated with Anti-N-methyl-D-aspartate Receptor and Anti-Hu Antibodies Successfully Treated with Carboplatin and Etoposide for Small-cell Lung Cancer

Ryogo Shobatake[1], Aya Kumazawa[1], Noriko Koyama[2] and Nobuyuki Takahashi[1]

**Abstract:**
The coexistence of multiple autoantibodies associated with autoimmune encephalitis (AE) is rare. A 63-year-old woman developed psychosis and consciousness disorder. Her cerebrospinal fluid was positive for anti-N-methyl-D-aspartate receptor antibodies, and her serum was positive for anti-Hu antibodies. Enhanced computed tomography revealed a mass in the right pulmonary hilum. AE complicated with small-cell lung cancer was diagnosed. Immunotherapy (steroid therapy and intravenous immunoglobulin) and four courses of carboplatin-etoposide chemotherapy were required to improve her neurological symptoms. When the coexistence of multiple antibodies is detected, despite its rarity, aggressive detection and treatment of any underlying malignancy may be recommended.

**Key words:** autoimmune encephalitis, anti-NMDAR antibody, anti-Hu antibody, small-cell lung cancer, carboplatin, etoposide

**(Intern Med 62: 469-474, 2023)**
**(DOI: 10.2169/internalmedicine.9707-22)**

## Introduction

Autoimmune encephalitis (AE), which occurs when a host's immune system targets self-antigens expressed in the central nervous system, can be triggered by tumors. When autoantibodies react with proteins in the limbic areas of the brain, the patient presents with limbic symptoms characterized by subacute cognitive disorder with severe memory impairment, seizures, and psychiatric symptoms, including depression, anxiety, and hallucinations (limbic encephalitis) (1).

Several autoantibodies to neuronal cell-surface antigens and intracellular antigens are involved in the development of AE, including anti-N-methyl-D-aspartate receptor (NMDAR) antibody and anti-Hu antibody/antineuronal nuclear autoantibody (ANNA) type 1, respectively (2). Most patients with anti-NMDAR encephalitis initially present with subacute psychiatric symptoms, such as mania, social withdrawal, and psychosis, followed by neurological abnormalities, including short-term memory impairment, seizures, movement disorders, central hypoventilation, and altered levels of consciousness (3). Symptoms of most patients with anti-NMDAR antibodies can be improved with immunotherapy, and disturbances of consciousness during the first month independently predict poor outcomes (4).

In contrast, the anti-Hu antibody is associated with a wider spectrum of syndromes, such as paraneoplastic encephalomyelitis, paraneoplastic sensory neuronopathy, paraneoplastic cerebellar degeneration, and limbic encephalitis (5), and its treatment has not yet been supported by high-level evidence (6). Autoantibodies that target intracellular antigens rarely respond even to aggressive immunosuppression; therefore, stabilizing the neurologic deficit is frequently considered a good achievement (7).

Very few patients with AE positive for both anti-NMDAR and anti-Hu antibodies have been reported according to our extensive search of the literature (8, 9), and its clinical characteristics are not fully understood.

We herein report a case of both anti-NMDAR and anti-Hu

[1]Department of Neurology, Nara City Hospital, Japan and [2]Department of Respiratory Medicine, Nara City Hospital, Japan
Received: March 4, 2022; Accepted: May 25, 2022; Advance Publication by J-STAGE: June 28, 2022
Correspondence to Dr. Ryogo Shobatake, rshobatake@naramed-u.ac.jp

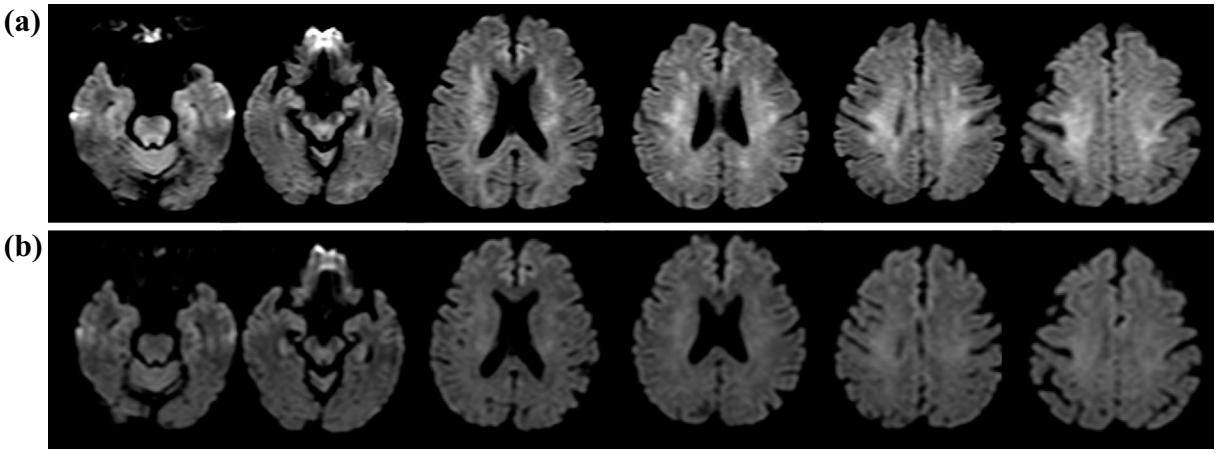


**Figure 1.** **Brain diffusion-weighted magnetic resonance imaging (a) on admission and (b) four days later. High-signal areas were observed in the bilateral cerebral white matter and disappeared four days later without specific treatment.**

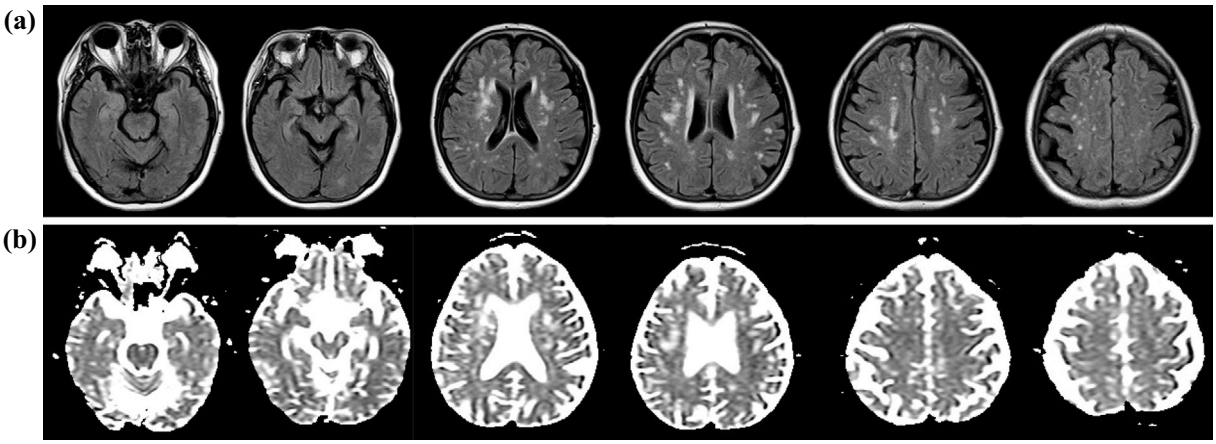


**Figure 2.** **(a) Fluid-attenuated inversion recovery and (b) apparent diffusion coefficient magnetic resonance imaging sequence showed high-signal areas in some of the high-signal regions shown on diffusion-weighted imaging.**

antibody-positive AE associated with possible small-cell lung cancer (SCLC) that was successfully treated with carboplatin and etoposide chemotherapy in addition to immunotherapy.

## Case Report

A 63-year-old Japanese woman with a medical history of hypertension and dyslipidemia developed cenesthopathy, an abnormal and strange abdominal sensation of something moving around in her stomach, as well as appetite loss. Subsequently, she developed abnormal behavior, hand tremors, and emotional incontinence. Approximately three weeks after the onset, she eventually stopped eating and talking, became almost bedridden, and was admitted to our hospital.

On admission, her body temperature was 38.3°C. On a neurological examination, her consciousness level was fluctuating [at worst, E2V1M5 on the Glasgow Coma Scale (GCS)], and fine tremors of her lower extremities and rigidity of the extremities and the neck were observed. The cranial nerves, cerebellar function, sensory functions, and deep tendon reflexes were normal. Her white blood cell count was 11,590/μL, and a cerebrospinal fluid (CSF) analysis showed no pleocytosis or elevated protein levels. The intracranial pressure was 120 mm$H_2O$, and real-time polymerase chain reaction of the CSF was negative for both the herpes simplex virus and varicella-zoster virus.

Brain diffusion-weighted imaging-magnetic resonance imaging (DWI-MRI) on admission showed bilateral hyperintensities in the white matter, which disappeared four days later without specific treatment (Fig. 1). Fluid-attenuated inversion recovery (FLAIR) and apparent diffusion coefficient (ADC) MRI sequence showed high-signal areas in some of the high-signal regions shown on DWI (Fig. 2). Contrast-enhanced MRI of the brain was not performed.

After five days of hospitalization, the patient's level of consciousness improved slightly, and she became responsive without specific treatment, but severe fluctuations in body temperature and pulse rate were further observed. Electroencephalography (EEG) showed generalized flattening, no

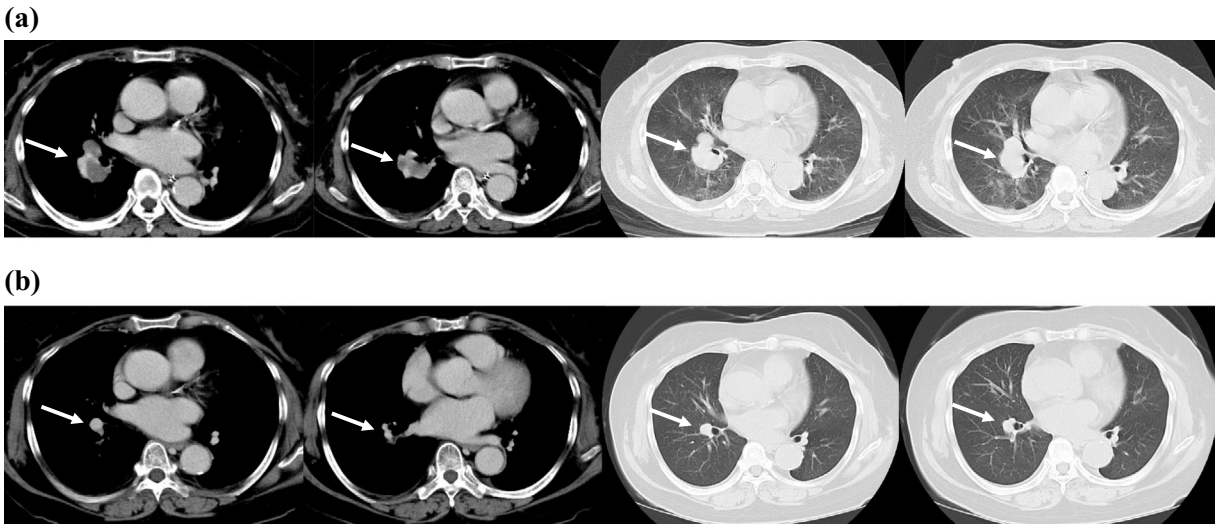


**Figure 3. Enhanced computed tomography of the chest. A tumor was detected in the right pulmonary hilum before (a, arrowhead) and after (b, arrowhead) four courses of chemotherapy using carboplatin and etoposide.**

derivation of alpha waves, and no epileptic waveforms. A EUROPattern (EUROIMMUN, Luebeck, Germany) immunofluorescence cell-based assay with HEK293A cells showed positive results for anti-NMDAR antibodies in the CSF with a 20-fold antibody titer. Immunoblotting of serum by EUROLineScan (EUROIMMUN, Luebeck, Germany) also demonstrated positive anti-Hu antibody as + (EUROLineScan Flatbed scanner signal intensity 0: 0-5; (+): 6-10; +: 11-25; ++: 26-50, +++: >50), while other AE-related autoantibodies, such as anti-amphiphysin, anti-collapsin response-mediator protein-5 (CRMP5)/CV2, anti-paraneoplastic antigen Ma2, ANNA type 2/Ri, anti-Purkinje cell cytoplasmic antibody type 1/Yo, anti-recoverin, anti-SRY-box transcription factor 1, anti-titin, anti-zic4, anti-glutamic acid decarboxylase 65 (GAD65), and anti-Delta/Notch-like epidermal growth factor-related receptor/Tr antibodies, were negative. The results of nerve conduction studies were normal. Thus, the patient was diagnosed with AE with coexistent anti-NMDAR and anti-Hu antibodies, and a course of steroid pulse therapy with 1 g of methylprednisolone for 3 days was administered.

However, despite the initiation of treatment, repeated seizures occurred, so anti-epileptic treatment was also administered. Steroid pulse therapy was initiated again, followed by oral prednisolone (30 mg, rapidly tapered to 10 mg/day) and intravenous immunoglobulin (IVIG). Despite a series of immunotherapy, the impaired consciousness (GCS E3V4M6) did not improve sufficiently.

Screening for malignancy by enhanced computed tomography (CT) revealed a 3.2-cm diameter mass in the right pulmonary hilum, and additional blood tests showed an elevated pro-gastrin-releasing peptide (proGRP) level (224 pg/mL). Because it was difficult to obtain a bronchoscopic biopsy of the lung tumor, the patient was started on carboplatin-etoposide chemotherapy, based on the presumed diagnosis of SCLC by an expert respiratory physician, while taking 10 mg of prednisolone daily. Shortly after the initiation of chemotherapy, the patient's level of consciousness improved gradually, and she was able to have simple conversations and walk with little assistance.

Five months later, after receiving four courses of carboplatin-etoposide chemotherapy, her lung tumor had shrunk remarkably (Fig. 3), and she had become almost independent in her daily activities. At that time, the serum proGRP level had remarkably decreased to 22.9 pg/mL; however, anti-Hu antibodies were still detected at the same positivities in the serum. Notably, follow-up lumbar puncture was not performed for anti-NMDAR antibodies. The scattered high-signal areas in the cerebral white matter on MRI-FLAIR seen on admission remained unchanged. Three years after the onset of her neurological symptoms, she is living well despite mild cognitive impairment and is being followed up by a respiratory physician.

## Discussion

The identified autoantibodies associated with AE include antibodies to NMDAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR), leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein-like 2 (CASPR2), gamma-aminobutyric acid receptors B ($GABA_BR$), myelin oligodendrocyte glycoprotein, GAD65, glial fibrillary acidic protein, Hu, Ri, ANNA type 3, Yo, Purkinje cell cytoplasmic antibody types 2, Tr, amphiphysin, dipeptidyl peptidase-like protein 6, metabotropic glutamate receptor 1, and CRMP5/CV2, most of which are often associated with tumors (10). Although the coexistence of multiple autoantibodies is rarely observed in AE, much attention has been paid to the clinical significance of multiple autoantibodies. In a recent retrospective study of 814 adults who

were positive for autoimmune or paraneoplastic autoantibodies, multiple antibodies were identified in the serum of 28 (3.4% of seropositive adults) and in the CSF of 42 (5.2% of seropositive adults) patients, and the coexistence of anti-NMDAR and anti-Hu antibodies was detected in the serum and CSF of 1 and 2 patients, respectively (10). According to a PubMed search, there have been only a few published cases of coexistent anti-NMDAR antibody and anti-Hu antibody, none of which were complicated with lung cancer. There is one case of encephalopathy associated with anti-Hu, CRMP5/CV2, and NMDAR autoantibodies but not complicated with malignancy (8). Another report described a case of neurological deficits associated with anti-NMDAR and anti-Hu antibodies complicated with a primary mediastinal seminoma (9). We encountered a rare case of AE positive for both anti-NMDAR antibody in the CSF and anti-Hu antibody in the serum complicated by SCLC that was successfully treated with carboplatin and etoposide in addition to immunotherapy.

Regarding anti-NMDAR encephalitis, the frequency of an underlying tumor varies with age and sex, ranging from 0-5% in children (both sexes) <12 years old to 58% in women >18 years old (usually an ovarian teratoma), whereas only 6.4% of men of any age develop tumors (11). Adults >45 years old have a lower frequency of tumors (23%) than younger adults (18-44 years), which are usually carcinomas instead of teratomas (12). In the present case, our patient did not have an ovarian teratoma but was clinically diagnosed with SCLC, which is reported to be strongly associated with anti-Hu antibodies (13). However, no strong association between anti-NMDAR encephalitis and SCLC has been established, as anti-NMDAR encephalitis has rarely been reported in patients with SCLC (14-16). From this perspective, our case of SCLC with coexistent anti-NMDAR antibody and anti-Hu antibody is even rarer.

As onconeural antibodies, including anti-Hu, anti-amphiphysin, and anti-Yo antibodies, target intracellular proteins and are predominantly associated with neuronal death and brain infiltration by cytotoxic T cells, patients with AE expressing such antibodies are rarely sensitive to immunomodulatory treatment (17). Furthermore, anti-Hu antibody-negative patients who develop both SCLC and limbic encephalitis are more likely to recover with treatment than anti-Hu antibody-positive patients (13). In contrast, patients with AE with antibodies against membrane antigens or synaptic receptors, such as anti-NMDAR antibodies, recover more effectively after the removal of autoantibodies by prompt immunosuppressive treatment than patients with AE with antibodies against intracellular antigens. Anti-NMDAR antibody recognizes an extracellular epitope in the GluN1 subunit of the NMDAR, crosslinks the NMDARs, and promotes internalization of the receptors, thereby decreasing receptor density on the neuronal surface and resulting in neuronal dysfunction (18).

Although 67% of patients with anti-NMDAR encephalitis might have normal brain MRI findings, 90% of patients show EEG abnormalities (11). Despite no obvious abnormality in the MRI signal being determined, EEG abnormalities were observed in our case. According to the diagnostic criteria for anti-NMDAR encephalitis by Dalmau et al., the present case met the criteria of the six major groups of symptoms, including abnormal (psychiatric) behavior or cognitive dysfunction; speech dysfunction (pressured speech, verbal reduction, or mutism); seizures; movement disorder, dyskinesia, rigidity, or abnormal postures; decreased consciousness; and autonomic dysfunction or central hypoventilation, as well as IgG GluN1 antibodies in the CSF, allowing a definite diagnosis (19). It can thus be inferred that anti-NMDAR antibodies are involved in the pathogenesis to some extent.

In addition, immunotherapy, including high-dose intravenous methylprednisolone pulses and IVIG, alone was insufficient to achieve adequate neurological recovery, and the addition of carboplatin-etoposide chemotherapy was required to improve neurological symptoms proportionate to lung tumor shrinkage. The clinical features of the paraneoplastic syndrome of anti-Hu encephalitis are extremely heterogeneous (20). In a previous study of 71 patients with anti-Hu-associated paraneoplastic neurological syndrome, among 32 patients whose MRI findings were obtained, only 4 had areas of high intensity in the temporal lobe on T2-weighted imaging, and all of them had limbic symptoms. However, the number of patients with abnormal MRI findings was not reported among 14 patients with limbic symptoms (21). In our case, the anti-Hu antibody titer on admission was not strongly positive, and DWI-MRI findings were reversible without the typical T2 high-signal area in the bilateral temporal lobes, which partly suggests that the contribution of anti-Hu antibodies to the pathology may not have been substantial because the pathogenesis of anti-Hu antibody encephalitis is due to T-cell damage and often considered irreversible (17). The presence of anti-Hu antibodies even after the improvement of neurological symptoms also supports this speculation. In addition, previous reports have also noted that a low titer of anti-Hu antibodies might be observed in SCLC cases without neurologic symptoms, which may predict successful tumor treatment (22, 23).

In our case, on admission, the DWI-MRI of the patient showed high-signal areas in the cerebral white matter that spontaneously disappeared with mild improvement in the level of consciousness. This abnormal signal on DWI might have reflected the impaired consciousness but was not specific for limbic encephalitis, which typically shows a hyperintense signal in the medial temporal lobe on T2-weighted or FLAIR MRI (24). In the abnormally high-signal area on DWI, there was no signal reduction in ADC, and the abnormality was also reversible, suggesting that it was due to some form of angioedema with an unknown etiology. It is difficult to determine whether or not this atypical, transient, and abnormal DWI-MRI signal in the bilateral white matter observed on admission has obvious pathological significance. However, the high-signal area in the cerebral white

matter on FLAIR-MRI on admission remained unchanged after treatment, suggesting that it may have been nonspecific and due to ischemic changes. Solnes et al. reported that all five cases of anti-NMDAR encephalitis and two cases of anti-Hu encephalitis without abnormal MRI findings showed hypometabolism on fluorodeoxyglucose-positron emission tomography ($^{18}$F-FDG PET)/CT, suggesting that brain $^{18}$F-FDG PET/CT may serve as an important and early biomarker of AE (25). Although an FDG PET was not available at our hospital, it might have been effective in localizing the area of brain damage caused by AE.

This study is limited by its retrospective nature and single-case-report format. Although cases of AE positive for both anti-NMDAR antibody and anti-Hu antibody complicated by SCLC are rare, it should be noted that not all patients with AE in previous reports were extensively tested for the AE-related autoantibodies. Indeed, no autoantibodies against neuronal surface antigens, such as AMPAR, LGI1, CASPR2, and $GABA_BR$, which are often associated with SCLC (24), other than NMDAR, were examined. In addition, although not possible in the present study, immunostaining of lung cancer biopsy tissue to confirm GluN1 expression on the cell surface may have helped elucidate the pathogenesis (26). If GluN1 expression in lung cancer tissue were confirmed and anti-NMDAR antibodies were the primary etiology, it could have been established that the neurological symptoms improved with lung cancer treatment. Furthermore, the involvement of anti-NMDAR antibodies in the pathogenesis could have been verified if negative results of anti-NMDAR antibodies in the CSF had been confirmed when the neurological symptoms improved after chemotherapy.

Our patient did not completely recover with immunotherapy alone, although the proportion of the anti-NMDAR and anti-Hu antibodies involved in the pathogenesis could not be determined. Malignancy was thus investigated and identified, and chemotherapy led to an almost complete recovery. If limbic symptoms are strongly suspected to be due to anti-NMDAR encephalitis but are not improved with immunotherapy alone, other autoantibodies, either targeting intracellular antigens or cell-surface antigens, may be involved; therefore, tumors and accessible autoantibodies related to AE should be identified, although multiple autoantibodies are rarely identified in patients with AE. It is important for clinicians to search for a wide range of AE-associated autoantibodies in order to establish a diagnostic and therapeutic approach and understand the characteristics of an overlapping syndrome of multiple autoantibodies. It is necessary to accumulate more cases of AE positive for these two antibodies in order to clarify the pathogenesis of AE positive for both anti-NMDAR and anti-Hu antibodies.

In conclusion, even in the absence of typical abnormal brain imaging findings, when multiple antibodies, whether they target intracellular antigens or cell-surface antigens, are detected and immunotherapy is only partially effective, aggressive detection and treatment of any underlying malignancy should be recommended.

**The authors state that they have no Conflict of Interest (COI).**

## References


1. Bakheit AM, Kennedy PG, Behan PO. Paraneoplastic limbic encephalitis: clinico-pathological correlations. J Neurol Neurosurg Psychiatry **53**: 1084-1088, 1990.
2. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology **77**: 179-189, 2011.
3. Nosadini M, Eyre M, Molteni E, et al. Use and safety of immunotherapeutic management of N-methyl-D-aspartate receptor antibody encephalitis: a meta-analysis. JAMA Neurol **78**: 1333-1344, 2021.
4. Gong X, Chen C, Liu X, et al. Long-term functional outcomes and relapse of anti-NMDA receptor encephalitis: a cohort study in Western China. Neurol Neuroimmunol Neuroinflamm **8**: e958, 2021.
5. Grativvol RS, Cavalcante WCP, Castro LHM, Nitrini R, Simabukuro MM. Updates in the diagnosis and treatment of paraneoplastic neurologic syndromes. Curr Oncol Rep **20**: 92, 2018.
6. Darnell RB, Posner JB. Paraneoplastic syndromes involving the nervous system. N Engl J Med **349**: 1543-1554, 2003.
7. Sechi E, Flanagan EP. Antibody-mediated autoimmune diseases of the CNS: challenges and approaches to diagnosis and management. Front Neurol **12**: 673339, 2021.
8. Kim AE, Kang P, Bucelli RC, et al. Autoimmune encephalitis with multiple autoantibodies: a diagnostic and therapeutic challenge. Neurologist **23**: 55-59, 2018.
9. Pohley I, Roesler K, Wittstock M, Bitsch A, Benecke R, Wolters A. NMDA-receptor antibody and anti-Hu antibody positive paraneoplastic syndrome associated with a primary mediastinal seminoma. Acta Neurol Belg **115**: 81-83, 2015.
10. Kunchok A, McKeon A, Zekeridou A, et al. Autoimmune/paraneoplastic encephalitis antibody biomarkers: frequency, age, and sex associations. Mayo Clin Proc **97**: 547-559, 2022.
11. Titulaer MJ, McCracken L, Gabilondo I, et al. Treatment and prognostic factors for long-term outcome in patients with anti-NMDA receptor encephalitis: an observational cohort study. Lancet Neurol **12**: 157-165, 2013.
12. Titulaer MJ, McCracken L, Gabilondo I, et al. Late-onset anti-NMDA receptor encephalitis. Neurology **81**: 1058-1063, 2013.
13. Alamowitch S, Graus F, Uchuya M, Reñé R, Bescansa E, Delattre JY. Limbic encephalitis and small cell lung cancer. Clinical and immunological features. Brain **120**: 923-928, 1997.
14. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol **10**: 63-74, 2011.
15. Jeraiby M, Depincé-Berger A, Bossy V, Antoine JC, Paul S. A case of anti-NMDA receptor encephalitis in a woman with a NMDA-R(+) small cell lung carcinoma (SCLC). Clin Immunol **166-167**: 96-99, 2016.
16. Boangher S, Mespouille P, Filip CM, Goffette S. Small-cell lung cancer with positive anti-NMDAR and anti-AMPAR antibodies paraneoplastic limbic encephalitis. Case Rep Neurol Med **2016**: 3263718, 2016.
17. Shen K, Xu Y, Guan H, et al. Paraneoplastic limbic encephalitis associated with lung cancer. Sci Rep **8**: 6792, 2018.
18. Kumar R. Understanding and managing acute encephalitis. F1000 Res **9**: F1000 Faculty Rev-60, 2020.
19. Dalmau J, Armangue T, Planagumà J, et al. An update on anti-NMDA receptor encephalitis for neurologists and psychiatrists:

mechanisms and models. Lancet Neurol **18**: 1045-1057, 2019.

**20.** Ding JB, Dongas J, Hu K, Ding M. Autoimmune limbic encephalitis: a review of clinicoradiological features and the challenges of diagnosis. Cureus **13**: e17529, 2021.

**21.** Dalmau J, Graus F, Rosenblum MK, Posner JB. Anti-Hu-associated paraneoplastic encephalomyelitis/sensory neuronopathy. A clinical study of 71 patients. Medicine (Baltimore) **71**: 59-72, 1992.

**22.** Graus F, Dalmou J, Reñé R, et al. Anti-Hu antibodies in patients with small-cell lung cancer: association with complete response to therapy and improved survival. J Clin Oncol **15**: 2866-2872, 1997.

**23.** Dalmau J, Furneaux HM, Gralla RJ, Kris MG, Posner JB. Detection of the anti-Hu antibody in the serum of patients with small cell lung cancer - A quantitative western blot analysis. Ann Neurol **27**: 544-552, 1990.

**24.** Zhang H, Zhou C, Wu L, Ni F, Zhu J, Jin T. Are onconeural antibodies a clinical phenomenology in paraneoplastic limbic encephalitis? Mediators Inflamm **2013**: 172986, 2013.

**25.** Solnes LB, Jones KM, Rowe SP, et al. Diagnostic value of $^{18}$F-FDG PET/CT versus MRI in the setting of antibody-specific autoimmune encephalitis. J Nucl Med **58**: 1307-1313, 2017.

**26.** Kobayashi Y, Sato M, Kinoshita M, et al. An elderly case of paraneoplastic anti-NMDA receptor encephalitis associated with small-cell lung cancer expressing NR1 subunits. Intern Med **59**: 2307-2309, 2020.