

[ CASE REPORT ]

## Cryptococcus Meningitis Can Co-occur with Anti-NMDA Receptor Encephalitis

Yusuke Sakiyama<sup>1</sup>, Eiji Matsuura<sup>1</sup>, Ayano Shigehisa<sup>1</sup>, Yuki Hamada<sup>1</sup>, Mika Dozono<sup>1</sup>,  
Satoshi Nozuma<sup>1</sup>, Tomonori Nakamura<sup>1</sup>, Keiko Higashi<sup>1</sup>, Akihiro Hashiguchi<sup>1</sup>,  
Yukitoshi Takahashi<sup>2</sup> and Hiroshi Takashima<sup>1</sup>

### Abstract:

We herein report a 50-year-old man with alcoholic cirrhosis who developed loss of consciousness and tremor of the upper limbs. Magnetic resonance imaging findings were suggestive of limbic encephalitis with bilateral hippocampal damage, and a cerebrospinal fluid (CSF) examination confirmed anti-N-methyl-D-aspartate (NMDA) and anti-glutamate receptor antibodies. Despite initial corticosteroid therapy, meningeal irritation symptoms appeared, owing to the development of cryptococcal meningitis (CM), diagnosed by the detection of cryptococcal capsular polysaccharide antigen in the follow-up CSF analysis. Cerebral infarction with reversible stenosis of major cerebral arteries during the clinical course was also observed. Following administration of antifungals and corticosteroids, the number of cells in the CSF gradually declined, and NMDA receptor antibodies disappeared. Our study demonstrates the unique coexistence of CM with anti-NMDA receptor encephalitis in adults.

**Key words:** cryptococcal meningitis, NMDA receptor, glutamate receptor (GluR), limbic encephalitis, cerebral infarction

(Intern Med 59: 2301-2306, 2020)

(DOI: 10.2169/internalmedicine.4629-20)

### Introduction

Cryptococcal meningitis (CM) is the most frequent fungal infection of the central nervous system (CNS). Most patients with CM are immunocompromised, including those with human immunodeficiency virus, cancer, sarcoidosis, hepatic failure, or a history of solid organ transplantation or glucocorticoid therapy (1). The balance of Th1-Th2 cytokines has been reported as the immunologic mechanism underlying cryptococcal infection (2). Recently, a case of concomitant CM and anti-N-methyl-D-aspartate (NMDA) receptor encephalitis was reported (3); however, whether or not cryptococcal infection is related to brain auto-immunity is unclear.

We herein report an immunocompromised adult patient with concurrent CM and anti-NMDA receptor encephalitis

during the same hospitalization period.

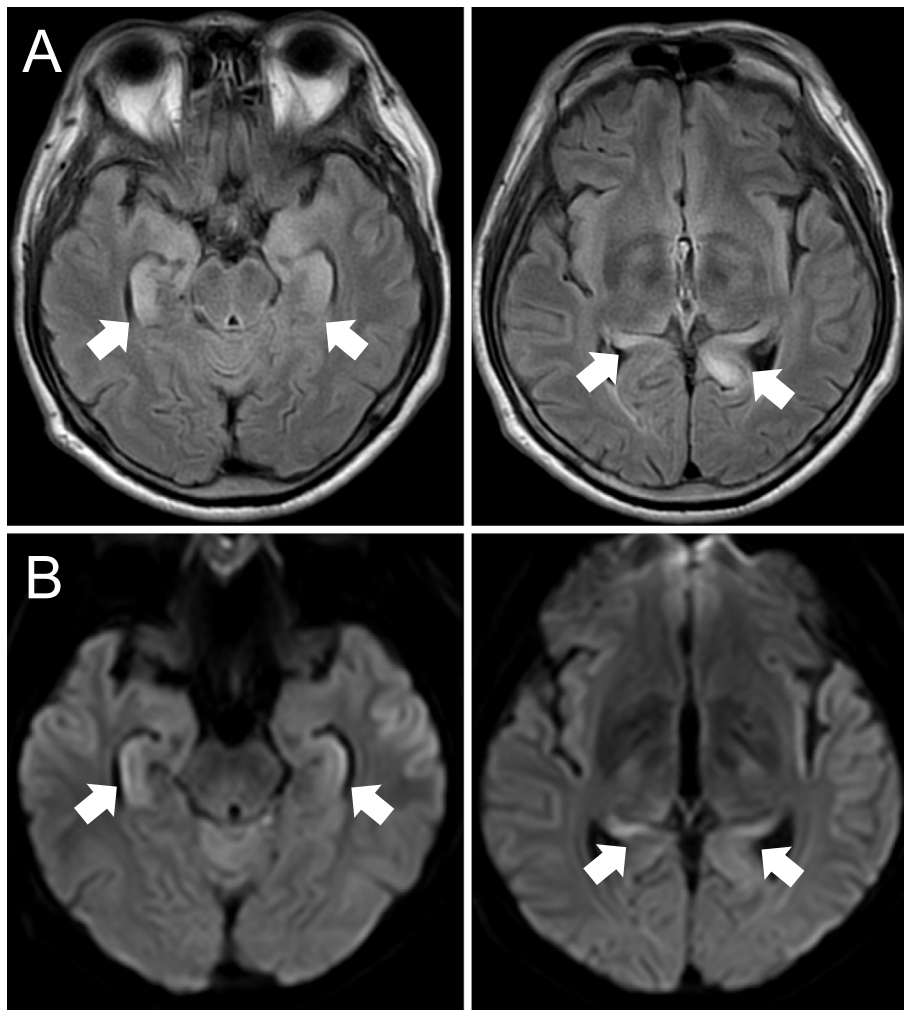
### Case Report

A 50-year-old man with a history of alcoholic cirrhosis had a seizure and transient loss of consciousness in September 2016. The symptoms disappeared the same day. The patient developed drowsiness one morning in December 2016, followed by dysarthria later during the day. The next morning, the patient suffered a fall and was diagnosed with hepatic encephalopathy with metabolic/respiratory acidosis at a hospital (ammonia concentration: 585 µg/dL). That same day, the patient was admitted to our university hospital. Despite a low-grade fever (37.7°C), the white blood cell (WBC) count and C-reactive protein (CRP) levels were normal. Despite treatment with lactulose, vitamin B1, and bi-

<sup>1</sup>Department of Neurology and Geriatrics, Kagoshima University Graduate School of Medical and Dental Sciences, Japan and <sup>2</sup>Department of Pediatrics, National Epilepsy Center, NHO Shizuoka Institute of Epilepsy and Neurological Disorders, Japan

Received: February 7, 2020; Accepted: March 27, 2020; Advance Publication by J-STAGE: June 9, 2020

Correspondence to Dr. Eiji Matsuura, pine@m.kufm.kagoshima-u.ac.jp



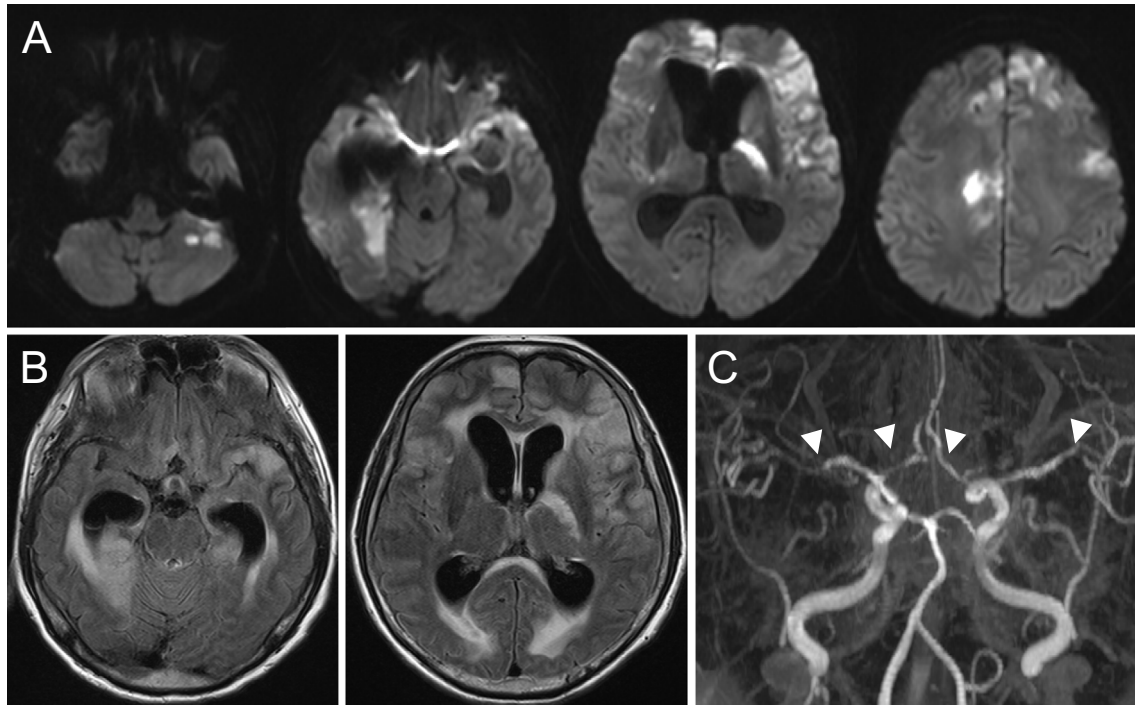
**Figure 1.** Brain MRI findings on day 7 after admission in our patient. **A:** FLAIR sequence shows hyperintensity in the bilateral limbic and temporal areas (arrows) in the axial view. **B:** Diffusion-weighted imaging (DWI) also shows hyperintensity in the same areas (arrows).

carbonate Ringer's solution, the patient still exhibited disturbed consciousness and also developed upper limb tremor.

On an examination by a neurologist on day seven of hospitalization, the patient showed fluctuating consciousness and meningeal irritation symptoms, such as neck stiffness, jolt accentuation, and Kernig's sign. Other neurological findings were almost normal, including those of his cranial nerves, muscle strength, tendon reflex, muscle tonus, coordination movement, tactile sensation, deep sensation, and bladder rectal function. The body temperature was 37.8°C. The results of a blood test revealed a mild inflammatory reaction (WBC: 10,280/μL and CRP: 0.38 mg/dL). Anemia and moderate thrombocytopenia were observed, and liver function test revealed mildly elevated transaminases, while total bilirubin was normal. The ammonia concentration was elevated (84 μg/dL), while the renal function and HbA1c were normal. A cerebrospinal fluid (CSF) examination revealed pleocytosis (229 cells/μL; predominantly mononuclear cells) and elevated protein (149 mg/dL; normal <40). The CSF-to-blood glucose ratio was reduced (0.18; normal >0.5). The T-SPOT and QuantiFERON-TB tests were also

negative. Cryptococcus pathogens were undetectable in the initial CSF specimen using either an antigen test or microscopic examination with Burri's staining method. The initial CSF specimen was also negative for Herpes simplex virus type 1. Brain magnetic resonance imaging (MRI) revealed abnormal lesions in the medial bilateral temporal lobes, including the hippocampus (Fig. 1). An electroencephalogram showed no evidence of triphasic wave, spike-wave, or extreme delta brush.

Treatment was initiated at day seven with acyclovir, meropenem, and dexamethasone for a tentative diagnosis of limbic encephalitis and infectious meningitis. The symptoms improved over six days of treatment; however, disturbed consciousness and neck stiffness reappeared. On day 21, cryptococcal capsular polysaccharide antigen was detected in the follow-up CSF analysis. Antimicrobial treatment was changed to liposomal amphotericin B (L-AMB; 300 mg/day) and 5-fluorocytosine (5-FC; 10 g/day). Dexamethasone was used in combination with the antimicrobial treatment to prevent cerebral edema. On the same day, acute hydrocephalus developed with signs of impending herniation, such as



**Figure 2.** Brain MRI findings on day 25. **A:** DWI sequence showing restricted diffusion in right temporal lobe, both frontal lobes and left internal capsule, and left cerebellar hemisphere. **B:** FLAIR sequence showing dilated ventriculus and hyperintensity of paraventricular regions. **C:** Multiple cerebral arterial stenosis was observed on an MRA (arrows). These findings indicate hydrocephalus and an ischemic event of various territories, including both middle cerebral arteries, both anterior communicating arteries, and the left posterior inferior cerebellar artery.

ataxic respiration and anisocoria. External ventricular drainage was performed; the state of consciousness gradually recovered, and the number of spinal fluid cells also decreased; however, motor aphasia and right hemiparesis appeared on day 28. Multiple cerebral infarctions with stenosis of the major cerebral arteries, meningitis within the interpeduncular cistern, and hydrocephalus were detected on brain MRI and a magnetic resonance angiogram (MRA) (Fig. 2). On day 39, thrombocytopenia secondary to L-AMB was observed, and the antimicrobial treatment was changed to voriconazole (VRCZ: 200 mg/day).

With improving consciousness and a decline in the number of spinal fluid cells, the patient was transferred for rehabilitation on the day 76. At the time of transfer, the level of consciousness was I-3 on the Japan Coma Scale, and right upper limb paralysis remained. The patient avoided relapse under treatment with fluconazole (FLCZ) alone. CSF cells renormalized (4/ $\mu$ L), and an MRA showed the disappearance of cerebrovascular stenosis in May 2018 (Fig. 3). The patient's clinical presentation and course are shown in Fig. 4.

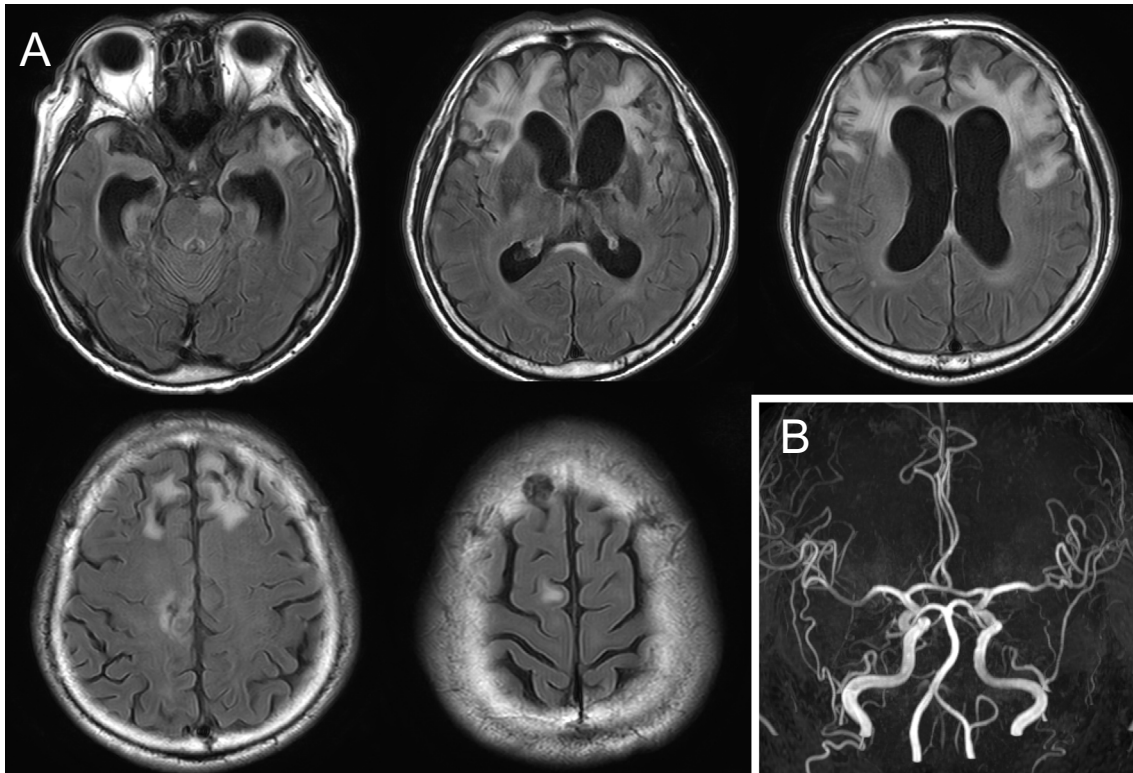
Anti-NMDA receptor-IgG was positive in the initial CSF specimen using cell-based assays. In addition, anti-glutamate receptor (GluR)  $\epsilon$ 2,  $\zeta$ 1, and  $\delta$ 2 (GluN2B, GluN1, and GluD2) antibodies were strongly positive in the initial CSF at 2.618 [average: 0.235, standard deviation (SD): 0.093], 3.006 (average: 0.364, SD: 0.115), and 3.203 (average: 0.358, SD: 0.165), respectively. No malignancy was detected

on whole-body computed tomography (CT) or upper endoscopy during acute hospitalization. Anti-voltage-gated potassium channel (VGKC)-complex antibodies in the initial serum were negative.

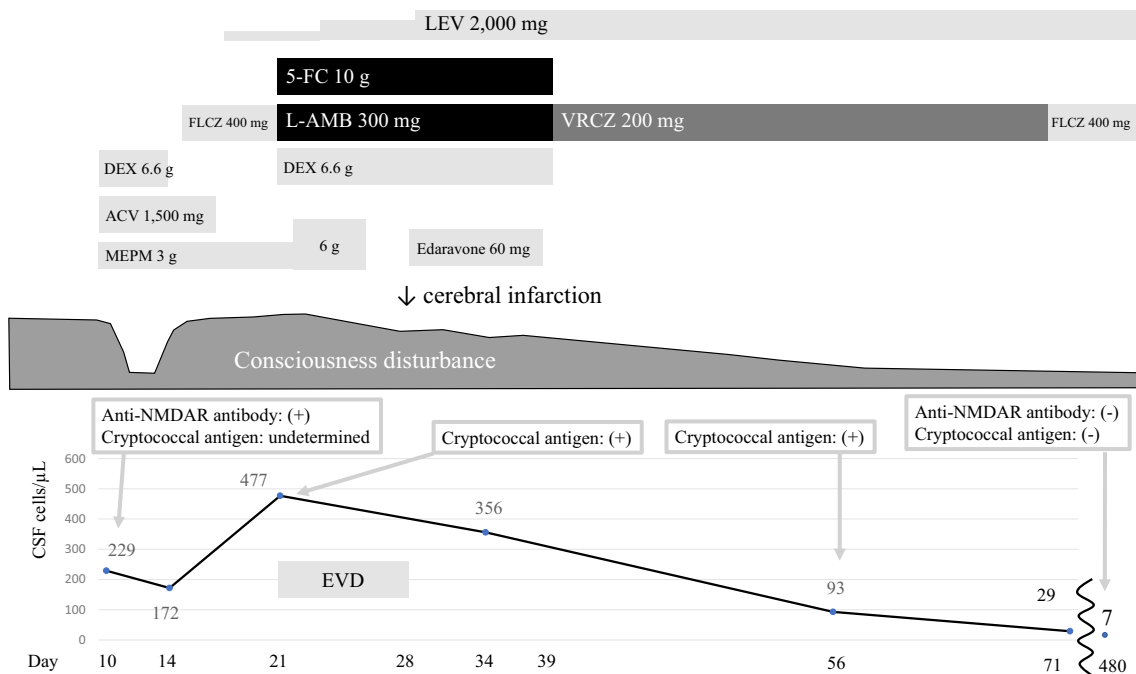
## Discussion

We present two key findings of an adult patient with CM: i) initial MRI findings of bilateral hippocampal damage, and ii) the detection of NMDA receptor antibody in the initial CSF. The diagnosis of CM was based on the detection of cryptococcal capsular polysaccharide antigen in the CSF [reported sensitivity and specificity of the antigen test is > 93% (4)] and response to antifungal treatments (L-AMB, 5-FC, VRCZ, and FLCZ). A history of cirrhosis and glucocorticoid therapy are risk factors for CM (1).

Initial brain MRI revealed bilateral hippocampal damage. A previous report concerning the CT and MRI findings in 29 HIV patients with CM revealed cryptococcoma (mass lesions), dilated Virchow-Robin spaces (VRS), miliary enhancing nodules in the parenchyma and leptomeningeal-cisternal spaces, along with a mixed pattern (5). Another study in 114 non-HIV CM patients showed that initial MRI was most commonly characterized by radiological meningitis, followed by VRS dilation, hydrocephalus, masses, and pseudocysts/cryptococcomas (6). Bilateral hippocampal damage is uncommon in patients with CM. In our patient, responsive-



**Figure 3.** Brain MRI findings on day 473. A: FLAIR sequence showing alleviation of the hyperintensity in the frontal lobes, temporal lobes, and paraventricular regions of both frontal lobes. FLAIR hyperintensity lesions around the inferior horn/posterior horn of the bilateral lateral ventricles disappeared between day 25 and 473, possibly due to improvement of the inflammation. B: An MRA indicating the disappearance of cerebrovascular stenosis.



**Figure 4.** Clinical course and CSF findings during therapy. Consciousness disturbance, number of cells in CSF, findings of anti-NMDA receptor antibody and cryptococcal antigen tests, and various drug therapies instituted are shown. LEV: levetiracetam, 5-FC: 5-fluorocytosine, L-AMB: liposomal amphotericin B, FLCZ: fluconazole, DEX: dexamethasone, ACV: acyclovir, MEPM: meropenem, EVD: external ventricular drainage, VRCZ: voriconazole

ness to initial therapy lacking anti-fungal drugs precluded the diagnosis of cryptococcal infection while suggesting the presence of anti-NMDA receptor antibodies as the likely etiology of the observed hippocampal lesions. Although CM-related MRI findings were absent at the initial stage; meningitis and hydrocephalus were found at follow-up MRI in the advanced disease stage in our patient. These sequential MRI findings suggest two different pathologies affecting the brain.

A previous study of paraneoplastic anti-NMDA receptor encephalitis affecting young women with ovarian teratoma showed that NMDA receptor antibodies react with the nervous tissue contained in the tumor and are predominantly expressed in the hippocampus and forebrain (7). Recently, several studies have reported the occurrence of anti-NMDA receptor encephalitis following herpes simplex virus-1 encephalitis (HSVE) (8, 9). In a previous study on a post-HSVE adult patient with relapsing symptoms caused by anti-NMDA receptor encephalitis (8), NMDA receptor antibodies were absent in the serum and CSF during the acute phase of HSVE and appeared at relapse. In addition, the patient showed steroid-responsiveness, and the MRI findings at relapse were consistent with HSVE-related changes, suggesting that HSVE can trigger the expression of NMDA receptor antibodies (8, 9). Neurologists have reported detecting an abnormal intensity on brain MRI scans in the hippocampus and/or temporal lobe in patients with neurosyphilis (10, 11). Recently, Beiruti et al. reported a neurosyphilis case mimicking limbic encephalitis with anti-NMDA receptor antibody, without MRI abnormalities (10). Tsukita et al. reported a case of neurosyphilis with limbic encephalitis and anti-GluR antibody (11). Elevated anti-GluR antibodies in the CSF supported the autoimmune mechanisms of concomitant CM and limbic encephalitis in our patient.

The mechanism by which CM and anti-NMDA receptor encephalitis occurred concomitantly is unknown. Previous studies have suggested that some infectious diseases induce the production of NMDA receptor antibody by causing tissue damage and possibly by exposing NMDA receptor epitopes in neural cells (8, 9). The first episode of seizure occurred three months prior to the onset of disturbance of consciousness in our patient. Subacute meningitis is sometimes challenging to detect due to its few symptoms. Progressive brain injury may have led to NMDA receptor antibody production in our patient. However, it was also possible that NMDAR encephalitis preceded the occurrence of CM. This is because the NMDA receptor antibody was present in the initial CSF specimen but did not contain cryptococcal antigen. Further studies on the relationship between CM and autoimmune encephalitis are needed.

Remarkably, extensive cerebral infarction was observed in our patient. Cerebral infarction, typically lacunar infarction at the basal ganglia, develops in 4-32% of patients with CM (12). Cryptococci invade the parenchyma through the blood-brain-barrier at the micro vessels surrounded by the VRS. Dilated VRS filled with cryptococcus is commonly

seen in the basal ganglia (13) and is associated with an enhanced frequency of CM-related brain lesions, including ischemic events, in the same territory (14). However, a brain MRA in our patient showed varying degrees of major cerebrovascular stenosis at the circle of Willis, resulting in multiple and extensive cerebral infarctions. In addition, the cerebrovascular stenosis disappeared after treatment with anti-fungal drugs and steroids, suggesting that vasospasm due to inflammation was the cause of the ischemic events. Thus, severe vascular injury and brain tissue infarction might explain the involvement of immunological mechanisms in our patient.

In summary, this case illustrates the possibility of the co-existence of CM with autoimmune encephalitis in adults. When abnormal MRI signals in the hippocampus are observed in patients with CNS infections, it is necessary to consider whether or not the brain damage might be due to NMDA receptor antibody.

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

#### Financial Support

This work was supported by grants from the Nervous and Mental Disorders and Research Labour, Japan. Some laboratory tests, including anti-N-methyl-D-aspartate receptor (NMDA) receptor antibodies and anti-glutamate receptor (GluR)  $\epsilon 2$ ,  $\zeta 1$ , and  $\delta 2$  (GluN2B, GluN1, and GluD2) antibodies, that are not covered by public health insurance were performed by commercial laboratories using these funds.

#### References

- Bennett JE, Dismukes WE, Duma RJ, et al. A comparison of amphotericin B alone and combined with flucytosine in the treatment of cryptococcal meningitis. *N Engl J Med* **301**: 126-131, 1979.
- Koguchi Y, Kawakami K. Cryptococcal infection and Th1-Th2 cytokine balance. *Int Rev Immunol* **21**: 423-438, 2002.
- Valdoleiros SR, Calejo M, Marinho A, et al. First report of concomitant cryptococcal meningitis and anti-NMDAR encephalitis. *Brain Behav Immun* **2**: 100036, 2020.
- Tanner DC, Weinstein MP, Fedorciw B, et al. Comparison of commercial kits for detection of cryptococcal antigen. *J Clin Microbiol* **32**: 1680-1684, 1994.
- Tien RD, Chu PK, Hesselink JR, et al. Intracranial cryptococcosis in immunocompromised patients: CT and MR findings in 29 cases. *AJNR Am J Neuroradiol* **12**: 283-289, 1991.
- Zhong Y, Zhou Z, Fang X, et al. Magnetic resonance imaging study of cryptococcal neuroradiological lesions in HIV-negative cryptococcal meningitis. *Eur J Clin Microbiol Infect Dis* **36**: 1367-1372, 2017.
- Dalmau J, Tuzun E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. *Ann Neurol* **61**: 25-36, 2007.
- Leyboldt F, Titulaer MJ, Aguilar E, et al. Herpes simplex virus-1 encephalitis can trigger anti-NMDA receptor encephalitis: case report. *Neurology* **81**: 1637-1639, 2013.
- Armangue T, Leyboldt F, Malaga I, et al. Herpes simplex virus encephalitis is a trigger of brain autoimmunity. *Ann Neurol* **75**: 317-323, 2014.
- Beiruti K, Abu Awad A, Keigler G, et al. Atypical development of

- neurosyphilis mimicking limbic encephalitis. *Int J STD AIDS* **30**: 194-197, 2019.
11. Tsukita K, Shimotake A, Nakatani M, et al. A case of neurosyphilis presenting with limbic encephalitis. *Rinsho Shinkeigaku* **57**: 37-40, 2017 (in Japanese, Abstract in English).
  12. Shimoda Y, Ohtomo S, Arai H, et al. Subarachnoid small vein occlusion due to inflammatory fibrosis-a possible mechanism for cerebellar infarction in cryptococcal meningoencephalitis: a case report. *BMC Neurol* **17**: 157, 2017.
  13. Xia S, Li X, Li H. Imaging characterization of cryptococcal meningoencephalitis. *Radiol Infect Dis* **3**: 187-191, 2016.
  14. Chen SF, Lu CH, Lui CC, et al. Acute/subacute cerebral infarction (ASCI) in HIV-negative adults with cryptococcal meningoencephalitis (CM): a MRI-based follow-up study and a clinical comparison to HIV-negative CM adults without ASCI. *BMC Neurol* **11**: 12, 2011.

The Internal Medicine is an Open Access journal distributed under the Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 International License. To view the details of this license, please visit (<https://creativecommons.org/licenses/by-nc-nd/4.0/>).