Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eAppendix. Case Description: Patients 1, 7, 9-15

Patient 1

A 21-year-old man was admitted to our hospital in February 1999 with acute encephalitis. The patient had been in his usual state of health until 4 weeks before admission, when he had flu-like prodromal symptoms. However, 14 days before admission paranoid psychosis and violent behaviors developed, and he became incoherent. Nine days before admission he was admitted to psychiatry department at another hospital. Five days later high fever, dysphagia and nocturnal apnea developed. On the next day convulsive seizure developed, and then he was brought to the emergency room at the other hospital, where he was intubated and sedated with intravenous infusion of midazolam. CSF examination revealed mild pleocytosis: white blood cell (WBC) was 41/μL (mono: 86%), with normal protein level. Two days later, he was transferred to our hospital with a possible diagnosis of encephalitis. His past medical history and family history were unremarkable. He had no habits of the use of illicit drugs.

On admission (day 1) the temperature was 37.9°C, the blood pressure 162/70 mmHg, the pulse 120 beats per minutes, and the oxygen saturation 98.8% while the patient was breathing though ventilatory support. The patient was being sedated but no brainstem sign or seizure was seen. The deep tendon reflexes were hyperactive but no Babinski sign was seen. The neck was supple. The blood test-results on admission were unremarkable, except mild inflammatory changes, and elevated CK level (1575 IU/L). Antibody testing for Hu and Yo antigens was negative. CSF examination on admission revealed mild pleocytosis (WBC 28/μL) and normal protein level (44 mg/dl) with oligoclonal bands (OCBs). HSV-1 PCR was negative. A brain MRI showed mild T2/FLAR high signal in bilateral medial temporal lobes. An EEG showed diffuse slow activity without paroxysmal discharges.

The patient was treated with intravenous high-dose methylprednisolone (IVMP: 1000 mg/day, 3 days) on day 1 with intravenous acyclovir and vidarabine, followed by short tapering of prednisone. He was also treated with various anti-epileptic agents, including phenytoin, carbamazepine, valproate, clonazepam, and zonisamide. During his hospitalization, orofacial-limb dyskinesias developed with fever and sinus tachycardia.

The patient required ventilatory support for 6 weeks, during which time intermittent infusion of midazolam was used to suppress involuntary movements. Although the patient was not treated with intravenous immunoglobulin (IVIg: 0.4g/kg/day, 5 days) plasma exchange, intravenous cyclophosphamide (IVCPA) or chronic immunosuppressant, these symptoms had gradually improved. A CT coincidentally showed asymptomatic deep vein thrombosis in bilateral common iliac veins but no other serious complication developed. Approximately 6 months later, he was discharged but subsequently admitted to Department of Psychiatry because of psychiatric symptoms and rehabilitation. After discharge he returned to the university. No tumor was found during the follow-up period. No brain atrophy was seen at the last 7-month follow-up MRI.

Ten years after symptom presentation, we examined antibody assay using archived serum/CSF samples obtained at presentation, which were positive for NMDAR antibodies. The long-term outcome was good (mRS 1) at the last follow-up (10 years and 5 months later), without recurrence of encephalitis.

Patient 7

A 27-year-old woman was transferred to our hospital in September 2009 with apallic state approximately 8 months after symptoms presentation. The patient had been well until 10 days before admission to another hospital when she had fever and headache. Fever and headache spontaneously subsided but 2 days before admission she became euphoric with incoherent speech and hallucination, and unable to eat. She was initially brought in by her family and admitted to psychiatry department at the hospital. After admission she fell into unresponsive state following intravenous infusion of haloperidol, and the temperature rose up 38°C. Three days later, she was transferred to the other hospital.

CSF examination on admission revealed pleocytosis (while blood cells: 97/μL; mono: 100%), normal protein level (31 mg/dL), and normal glucose level (88 mg/dL); PCR for HSV-1 was negative. A brain MRI showed bilateral T2/FLAIR high signal in bilateral mesial temporal lobes (Figure 3). She was initially treated with acyclovir, but 4 days later she developed multiple types of seizures and dyskinesias requiring ventilatory assistance. In addition to continuous infusion of midazolam (15 weeks), thiopental (8 weeks), and propofol (3 weeks), the patient was treated with various anti-epileptics drugs, including valproate (1200-300 mg), phenytoin (300-500 mg), zonisamide (400 mg), carbamazepine (200-1200mg), lamotrigine (25 mg), and diazepam (15-21 mg). The clinical course was complicated by systemic complications such as recurrent infection, hepatic enzyme elevation, pulmonary embolism, and deep vein thrombosis involving the inferior vena cava. During her 8-month hospitalization she was not treated with immunotherapy. Eight months later she was transferred to our hospital. Her past medical history and family history were unremarkable. On transfer the patient was being put on phenytoin (300 mg), clobazam (30 mg), zonisamide (400 mg), valproate (3000 mg), and diazepam (15 mg).

On admission, the temperature was 38.2°C, the blood pressure 84/59mmHg, the pulse 92 beats per minute, and oxygen saturation 100% on mechanical ventilatory support ($FI0_2$ 0.35). The patient was unresponsive to external noxious stimuli, without withdrawal response, and the muscle tone was flaccid in all extremities but the patient had mild orofacial dyskinesias. The eyes were opened, but she did not close her eyes in response to visual threat stimuli or bright light. She required mechanical ventilatory support because no spontaneous breathing was seen. A lumbar puncture on admission revealed a cellular fluid with normal protein level (38 mg/dl) and normal glucose level. OCBs were negative. A brain MRI obtained 8 months after presentation showed marked diffuse cerebral atrophy without cerebellar atrophy (Figure 3). A pelvic MRI revealed teratoma of 2 cm in size in the right ovary.

The patient was first treated with IVMP and IVIg with prednisone tapering-off, and one month later (9 months after symptoms presentation) the tumor of the right ovary was removed (pathologically confirmed as mature teratoma), followed by plasma exchange, IVMP and IVIg. Two weeks after tumor removal, the patient began to follow simple commands, afterwards she rapidly improved, and she was weaned off from mechanical ventilation 5 weeks after tumor removal. Three months after admission to our hospital she was transferred to the rehabilitation facility (a total stay in hospital was 11.1 months).

Serum/CSF obtained at symptoms presentation was not available for antibody assay; thus antibody assay was performed with serum/CSF obtained at transfer to our hospital (8 months after presentation). NMDAR antibodies were negative in serum but positive in CSF. During her hospitalization at our hospital she was also treated with continuous infusion of midazolam (5 weeks), propofol (10 days), and anti-epileptic drugs, including valproate (300 mg), zonisamide (300 mg), clobazam (30 mg), phenytoin (150 mg), diazepam (24 mg), clonazepam (6 mg), topiramate (600 mg), or gabapentin (2400 mg), but on discharge 3 months later she took only clonazepam 0.5 mg daily.

On discharge (11 months after symptoms presentation) the revised Hasegawa Dementia Scale (HDS-R), which is established as a screening test for dementia in Japan and psychometrically equivalent to the mini-mental state examination (MMSE), was19/30, but afterwards, she continued improving over years; HDS-R 27/30 was at 18 months after symptom presentation. Follow-up MRI showed that diffuse cerebral atrophy reversed 2 years after symptoms presentation (Figure 3); a reversal process of brain atrophy was accelerated by immunotherapeutic intervention in this patients, compared with very slow recovery of brain atrophy in *Patients 4,5,* who did not receive intensive immunotherapy during the active stage of the disease (see Figure 1, 2). After that the patient continued improving; she was back to work 5 years after disease onset, and continues working 7 years after onset she still has short-term memory loss (29/30 on MMSE), but otherwise neurologically intact (mRS 2).

Patient 9

A 14-year-old girl was initially admitted to another hospital though several hospitals with altered level of consciousness in late November 2010, and approximately one year later she was transferred to our hospital for re-evaluation.

This patient had been well until a few weeks before admission when low-grade fever, fatigue, and headache developed. Two weeks before admission her family noticed her unusual psycho-behavioral changes. Ten days before admission generalized tonic clonic seizure developed, and then she was admitted to a local hospital and started on carbamazepine, but a dissociative disorder was suspected. After discharge she lost appetite and began to suffer from insomnia, anxiety, delusion, obsession and auditory hallucination, and fell into unresponsive state. Two days before admission she was brought to psychiatric hospital where she had fever and seizures, and then she was transferred to another hospital. She had no past history of febrile convulsion or psychiatric illness, and family history was unremarkable.

On admission (day 1), the temperature was 37.7°C, the blood pressure 118/51 ㎜ Hg, the pulse 76 beats per minute, the respiratory rate 18 breaths per minute, and the oxygen saturation 100% while the patient was breathing through nasal cannula (1 L/min). On examination the patient was post-ictal drowsy, with orofacial dyskinesias during interictal state. A brain MRI was unremarkable. CSF examination revealed only mild pleocytosis (WBC 6/μL; mono 67%), normal protein level (31 mg/dl), and normal glucose level (60 mg/dl). The patient was empirically treated with acyclovir and IVMP (1000 mg/day, 5 days) from day 7, but on day 14 the oxygen saturation decreased, and her trachea was intubated, and she was transferred to ICU. On the next day, sinus arrest developed for several ten seconds, during which time cardiopulmonary resuscitation were carried out by pressing the breastbone, and then sinus rhythm recovered soon. However, a few days later she developed septic shock, and cardiac arrest suddenly occurred at 2 am on day 21, for which cardiopulmonary resuscitation was performed without significant hypoxia. Nine minutes later sinus rhythm restored, without insertion of a pacemaker. She required a mechanical ventilatory support for only 2 weeks, but afterwards her breathing did not require ventilatory support.

During her hospitalization at the hospital she received continuous infusion of midazolam (13 weeks) and thiamylal (7.6 weeks) to suppress hyperkinetic movements. The clinical course was complicated by serious complications, including deep vein thrombosis (requiring a transient insertion of inferior vena cava filter), recurrent infections, and transient cardiac arrest. She underwent a percutaneous endoscopic gastrostomy. NMDAR antibodies were detected in serum/CSF obtained at presentation; the antibody titers were subsequently determined as positive in CSF (1:80 dilution) and serum (1:400 dilution). Ovarian teratoma was not seen. Based on the positive result for NMDAR antibodies, during her approximately 9-month hospitalization, she was treated with 2 courses of IVMP, 1 course of plasma exchange, and 3 courses of IVIg, with taper of oral prednisone. Anti-epileptic drugs used included valproate (800-1200 mg), carbamazepine (100 mg), gabapentine (200-400 mg), and zonisamide (300 mg). However, she remained in an unresponsive and bed-ridden state.

Follow-up brain MRI on day 56 showed bilateral thalamic lesions but diffuse cerebral and cerebellar atrophy were seen (eFigure 1D, Figure 4). Nine months after admission, she was once transferred to a rehabilitation hospital, but due to a request from the patient's family, she was transferred to our hospital approximately one year after presentation (December 2011). At the time of transfer, she was put on zonisamide 300 mg, carbamazepine 100 mg, and prednisone 5 mg.

On admission (day 1) physical examination was unremarkable, and a gastrostomy tube was being inserted; her eyes were opened; she was able to close her eyes in response to visual threat stimuli or bright light, and follow the objects presented in her visual field. Although she could cry or make a loud voice but only incomprehensible sound; she was almost mute and unresponsive to verbal commands (global aphasia). She could raise the left upper extremity spontaneously or passively and keep the posture, but the left wrist showed "dropped hand posture" mimicking radial nerve palsy. She did not show withdrawal response of the extremities to noxious stimuli and barely showed grimacing to noxious stimuli on the face. Muscle tone was markedly increased in both lower extremities mimicking spastic paraparesis. She could only move her let upper extremity purposelessly and remained in a bed-ridden.

CSF examination revealed unremarkable; WBC was 2/μL, the protein 31 mg/dl and glucose 58 mg/dl, but OCBs were detected. A brain MRI showed diffuse cerebral atrophy and prominent cerebellar atrophy (Figure 4, eFigure 3). Nerve conduction study did not show peripheral nerve involvement. A cervical and thoracic MRI did not show intramedullary lesion in the cord; no intramedullary bleeding or compressive lesion was seen. A pelvic MRI did not show evidence of ovarian tumor. An EEG did not show paroxysmal discharge. The patient was treated with IVMP (1000 mg/day, 5 days) and IVIg from day 9 with taper of prednisone for persistent unresponsive state with catatonic features, which could not be explained by non-convulsive status epilepticus or peripheral neuropathy. After confirming sustained intrathecal production of anti-NMDAR antibodies; the antibody titers were determined as positive in CSF (1:160 dilution) but negative in serum, she began to receive IVCPA (500 mg/m^2) on day 21, and followed by chronic immunosuppression with tacrolimus 3 mg daily. Twenty-three days after IVCPA she began to follow simple verbal commands, afterwards, she became able to communicate with gesture although she was almost mute. She retuned back to the first hospital 3 months later; on discharge she began to eat with assistance and became able to walk with assistance and walker. Tacrolimus was subsequently changed to azathioprine. After this, she had gradually improved over 2 years and became able to talk slowly but she had marked limb ataxia, truncal ataxia and paraplegia without sensory level or bladder dysfunction. She remains confined to a wheel chair.

In April 2014, 3 years and 5 months after presentation, she was referred to our hospital again. The patient was alert, well oriented and able to speak and communicate by speech but prosody was severely impaired; her spoken words were broken up into separate syllables as seen in scanning speech; her writing skill was also impaired due to limb ataxia. The MMSE was 22/30. She also had horizontal gaze-evoked nystagmus, saccadic pursuit eye movement, bilateral limb ataxias, hyperreflexia with up-going toe signs, and marked spasticity in the lower extremities without sensory level, bladder dysfunction, or hyperekplexia. She could stand with assistance but not able to walk due to truncal ataxia and leg spasticity. CSF examination was unremarkable; WBC was 2/μL with normal protein and normal glucose level. An EEG was normal. Follow-up brain MRI showed

prominent cerebellar atrophy but some improvement of the cerebral atrophy (Figure 4, eFigure 3). NMDAR antibodies remained detected in CSF. Three years and 10 months after symptom presentation she was treated with the second course of IVCPA but no improvement was seen. At the last follow-up, 4 year and 7 months after presentation, she became able to walk with a walker but marked cerebellar ataxia and spastic paraparesis remained unchanged (mRS 4).

Patient 10

A17-year-old girl was admitted to our hospital on July 2011 with progressive right hemiplegia. She had been well until 3 weeks before admission when she noticed dysesthesia in the right hand, after that progressive weakness in the right upper and lower extremities gradually developed. Eight days before admission the weakness rapidly developed, and she was admitted to our hospital. She had no past medical history except Kawasaki disease in her childhood or no history of the use of illicit drugs. She did not have a preceding illness before the onset of weakness.

On admission (day 1), the physical examination was normal. On neurologic examination the patient had moderate weakness in the right upper and lower extremities, with a grip power of 2.5 kg on the right side and 16 kg on the left. She had mild sensory loss in the right side of the body. The blood tests results, including anti-AQP4 antibodies, were negative or normal. CSF examination obtained on day 2 revealed a few cells (WBC 2/μL) and slightly elevated protein level (58 mg/dl) without OCBs. The IgG index was normal (0.48), but the myelin basic protein level was 355 pg/mL (normal < 102). A brain MRI showed multifocal white matter changes (eFigure 1E) with subtle gadolinium enhancement (not shown). CSF JC virus DNA was not detected.

The patient was treated with IVMP (1000 mg/day, 5 days) from day 2, followed by gradual tapering of prednisone. Despite the treatment with IVMP, she developed complete right hemiplegia on day 3. Then she was treated with IVIg (0.4g/kg/day, 5 days) from day 3, and plasma exchanges from day 9. Following the immunotherapy, the motor weakness began to improve since day 16. After that, the weakness gradually improved and she was discharged on day 61 with mild weakness in the right side. She was also treated with azathiopurine. On day 68, NMDAR antibodies were confirmed in serum/CSF obtained on admission. The motor function gradually recovered over years. Three years after discharge, azathiopurine was discontinued. The follow-up MRI showed gradual improvement of initial demyelinating lesions, without brain atrophy. At the last visit, she had hyperreflexia on the right side but had no disability; she is a college student, without cognitive deficit (mRS 1).

Patient 11

A 21-year-old man was admitted to our hospital in October 2012 with generalized seizure. Two weeks before admission he began to have dysesthesia in the lateral surface of the left leg and difficulty in moving the left lower extremity, which was gradually accompanied by pain. He also complained of some memory loss. Six days before admission he was seen at our hospital. On examination he had hyperreflexia in the left lower extremity, but otherwise unremarkable. Brain MRI and EMG examination were normal. On the day of admission, from the morning he had multiple attacks of painful tonic spasms in the left leg, and at 11 pm he had secondarily generalized tonic seizure starting as focal painful tonic spasm in the left lower extremity, and then he was brought to our hospital. He had a past history of second degree AV bock. His family history was unremarkable.

On arrival, the temperature was 37.0°C, the blood pressure 139/73 mmHg, and the pulse 67 beats per minutes. He had multiple seizures, which began with a short-lasting painful tonic seizure of the left lower extremity with extension of the knee and planter flexion of the foot, followed by generalized tonic seizure with head extension and loss of consciousness. Cyanosis and sinus bradycardia developed transiently associated with breath holding during the attack of seizure. After receiving intravenous injection of diazepam, the patient regained his consciousness and he was admitted to our hospital.

On admission (day 1) the patient was alert, cooperative, and well oriented to time and place. No psychiatric symptom was seen, but he had decreased attention span and short-term memory loss. He also had numbness and mild weakness in the left lower extremity, and he occasionally had tonic spasm in the left leg. The deep tendon reflexes were exaggerated in all extremities, more marked in the left lower extremity with Babinski sign. The coordination was normal but he couldn't stand or walk without assistance. The neck was supple. The results of the blood tests on admission, including ANA, antibodies against dsDNA, MPO-ANCA, SSA/Ro, SS-B/La, and GAD, were normal, except elevated level of CK (380 U/L), uric acid (9.7 mg/dl), and lactate (38.8 mg/dl). CSF examination on admission showed mild pleocytosis (WBC 12/μL; mono 100%), normal protein level (35 mg/dl) and normal glucose level (57 mg/dl). The IgG index was normal, and OCBs were

not detected. The result of PCR for HSV-1 was negative. MRI of the brain and cervical cord were normal. An EEG showed mild slowing activities in the right cerebral hemisphere.

The patient was initially treated with intravenous administration of phenytoin and oral levetiracetam, but began to receive IVMP (1000 mg/day, 5 days) twice from day 6, and day 21, respectively. On day 28 NMDAR antibodies were confirmed in CSF obtained on admission (negative in serum). Based on the result, the patient additionally received one course of IVIg with taper of prednisone. After these immunotherapies with antiepileptic agents, all symptoms improved, and he was discharged 2.5 months later. After this he had no recurrence of seizure for 2 years and 9 months. No brain atrophy was seen at last follow-up MRI. He had full recovery without any neurological deficit at the last follow-up (mRS 0).

Patient 12

A 46-year-old man was transferred to our hospital from another hospital in July 2013 for further evaluation of meningoencephalitis.

This patient had been well until one month before admission to our hospital, when he had headache. Eighteen days before admission, he visited a local hospital where he underwent a brain CT, which was reportedly normal. He was given loxoprofen and acetaminophen, but headache persisted. Nine days before transfer, he began to have diarrhea with vomiting, and he was first admitted to another hospital. After admission, headache spontaneously resolved but gastrointestinal tract symptoms persisted. Three days before transfer he was discharged but on the next day he became confusional state with prominent psychiatric symptoms, and then he was re-admitted to the hospital. A brain MRI showed multiple increased T2/FLAIR signals in the right putamen. A lumbar puncture revealed mild pleocytosis (WBC 28/μL; mono 73%), normal protein level (30 mg/dl), and normal glucose level (55 mg/dl). On the next day, he was transferred to our hospital. He had no past medical history of seizure or psychiatric illness.

On admission (day 1), the temperature was 36.2°C, the blood pressure 174/95 mmHg, the pulse 63 beats per minute, the respiratory rate 17 breaths per minute, and the oxygen saturation 97% while the patient was breathing ambient air. The physical examination was unremarkable, but he had prominent psychiatric symptoms, requiring continuous infusion of propofol and restraint. Neurologic examination showed rigidity in the left lower extremity, hyperreflexia on the left side with Babinski sign, and nuchal rigidity. On day 2, bizarre orofacial-limb movements gradually developed; he showed excessive eye blinking followed by sustained wrinkling forehead, choreic twisting movements in the left lower extremity, and paroxysmal eye deviation to the left, but no central hypoperfusion developed. The results of the blood tests on admission, including ANA, MPO-ANCA, SSA/Ro antibodies, SS-B/La antibodies, and thyroid function, were normal. A lumbar puncture revealed mild pleocytosis (WBC 30/μL; mono 97%), normal protein level (38 mg/dl) and normal glucose level (59 mg/dl), with OCBs. IgG index 0.85. PCR testing for HSV-1 was negative. A brain MRI showed multifocal non-enhancing lesions in the right basal ganglia and corona radiata, but there was no visible lesion in the

limbic system (eFigure 1C). An EEG showed diffuse slowing activity with high amplitude delta waves in the right fronto-temporal regions, and recruiting rhythm. A whole CT scan did not disclose radiological evidence of tumor.

The patient was empirically treated with intravenous administration of acyclovir, ceftriaxone, vancomycin, and phenytoin with continuous infusion of propofol. On day 8, he began to receive IVMP (1000 mg/day, 5 days) with prednisone under the possible diagnosis of anti-NMDAR encephalitis. On day 22, NMDAR antibodies were detected in serum/CSF obtained on admission. The patient was treated with IVIg from day 19, and IVCPA on day 34, resulting in resolution of symptoms, and he was discharged on day 60. Follow-up MRI did not show brain atrophy.

At the last visit he remained to have mild memory impairment, but otherwise he had no neurological deficits (mRS 1). In this patient myelin oligodendrocyte glycoprotein (MOG) antibodies were also subsequently confirmed in serum/CSF obtained at presentation.

Patient 13

A 20-year-old man was initially admitted to another hospital with loss of consciousness in May 2014, and 6 weeks later he was transferred to our hospital for further treatment. This patient had been well until 3 days before admission when he had headache and nausea. On the day of admission, he went to his company. At 9 am he was found unconscious in the rest room of the company. He was brought to the emergency room at another hospital. He had no past medical history of epileptic seizure, and no history of the use of elicit drugs. His family history was unremarkable.

On admission to the hospital, the temperature was 36.4°C, the blood pressure 116/60 mmHg, the pulse 110 beat per minute, and the oxygen saturation 96% while the patient was breathing ambient air. The physical examination was unremarkable. On neurologic examination he was drowsy and disoriented to date, but otherwise unremarkable. A brain CT was normal. The results of the blood tests, including NH3, IgG, ANA, lactate, anti-TPO or anti-Tg antibodies, were all normal except elevated serum CK level (470 IU/L) and anti-SSA/Ro antibodies (21.2 U/ml). CSF examination on admission revealed mild pleocytosis (WBC 13/μL; mono; 97%) with normal protein level (33 mg/dl) and normal glucose level (59 mg/dl). OCBs were detected.

On admission (day 1) the patient began to receive intravenous acyclovir but on the next day, he developed generalized tonic clonic seizures, followed by prominent disinhibited psychiatric symptoms, which required continuous infusion of propofol and midazolam. He was also treated with intravenous phenytoin. After that, high fever developed. The follow-up lumbar puncture on day 4 revealed pleocytosis (WBC 91/μL; mono: 79%), with elevated protein level (62 mg/dl), and normal glucose level (69 mg/dl). An EEG on day 5 showed sporadic or multiple spikes in the right occipital region with background slowing activity. A brain MRI on day 6 showed no significant changes. On day 8 he became incoherent with prominent psychiatric symptoms and oral dyskinesias. He was treated with IVIg and transferred to ICU. Afterwards various involuntary movements became marked with development of prominent visual and auditory hallucination. On day 11, he was also treated with IVMP (1000 mg/day, 3 days). He still remained in ICU but not required mechanical ventilation support. A CT scan of the whole body did not show

evidence of tumor. On day 39 NMDAR antibodies were confirmed in CSF/serum obtained on day 8. Six weeks after symptoms presentation he was transferred to our hospital on June 2014.

Following the treatment with additional 3 courses of IVMP, 2 courses of IVIg, and 3 courses of monthly IVCPA, and oral prednisone and azathioprine, the symptoms had gradually improved. During his hospitalization he was also treated with carbamazepine (300 mg) and levetiracetam (2000mg). The patient was discharged to a rehabilitation hospital 4 months after admission (hospitalization was 5.4 months). On discharge the MMSE was 29/30. At the last follow-up (10 months after symptoms presentation), he had full recovery, without any neurological deficit (mRS 0). No brain atrophy or tumor was found during the course of the disease.

Patient 14

A 29-year-old woman was referred to our hospital on May 2014 for further evaluation of residual neurological deficits of encephalitis.

This patient had been well until 4 years earlier, at the age of 25 years, when she had first convulsive seizure after having cold-like symptoms in May 2010. The patient was brought to the emergency room at a local hospital; on arrival no abnormal findings were noted and then she returned home. However, after that she began to have prominent schizophrenia-like psychiatric symptoms, behavioral changes and seizures. She was first admitted to a psychiatry hospital and treated by psychiatrist under the diagnosis of dissociative disorder. One month later she was discharged and refereed to psychiatry department at another hospital; she was given valproate and diazepam, but she quit taking the drugs and stopped regular medical check after the last visit on August 2010. Her mental status was stable without mood stabilizer for 6 months.

However, 9 months after initial presentation, she began to have multiple attacks of seizures that were initially considered as psychogenic origin. Three days later she was admitted to psychiatry hospital with a diagnosis of dissociative disorder. After admission; however, the temperature rose up and multiple convulsive seizures developed, ultimately leading to status epilepticus, and she was transferred to the other hospital in February 2011.

On arrival the patient was in convulsive status epilepticus; the temperature was 40.0°C, the blood pressure 153/66 mmHg, the pulse 137 beats per minute, the respiratory rate 17 breaths per minutes, and the oxygen saturation 89%. The trachea was intubated, and the patient was admitted to ICU with mechanical ventilatory support (for 5 weeks). The blood test-results on admission (day 1) showed rhabdomyolysis with multiple organ dysfunction syndrome, with a peak serum CK level of 43,363 IU/L, for which the patient underwent continuous hemodiafiltration. CSF examination revealed pleocytosis (WBC 41/uL; mono 100%), normal protein level (42 mg/dl), and normal glucose level (110 mg/dl). She was treated with intravenous diazepam and phenytoin, and continuous infusion of midazolam and thiamylal. She also received intravenous acyclovir. A brain MRI on day 3 showed transient symmetric DWI/FLAIR high intensities in the medial temporal lobes (eFigure 1A). The patient began to receive IVMP (1000 mg/day, 3 days). An EEG on day 2

showed periodic synchronous discharges with burst-suppression pattern. She was treated with valproate and lamotrigine, but these drugs were subsequently discontinued due to skin eruption.

During approximately 18-month hospitalization she was treated with a total of 7 courses of IVMP (1000 mg/day, 3 days). She also received IVIg 6 months after admission because NMDAR antibodies were confirmed approximately 19 weeks after admission. The clinical course was complicated by recurrent infection, rhabdomyolysis, and multiple organs dysfunction syndrome. Severe dyskinesias persisted for the initial 4 months but afterwards these movements had subsided gradually. She regained consciousness and became able to eat by assistance. In late August 2012, she was discharged from the hospital to home nursing care in a bed-ridden state with a gastrostomy and tracheostomy. Follow-up MRI showed diffuse cerebral atrophy with progressive cerebellar atrophy (eFigure 2). Follow-up antibody testing performed approximately 2 years after presentation of the second episode was reportedly negative in serum/CSF. She gradually became able to recognize spoken and written language despite no spontaneous speech, but she remained confined to a wheel chair or remained in a bed-ridden state due to marked disability.

Approximately 3 years after the onset of the second episode, she was referred and admitted to our hospital. On admission to our hospital (May 2014), she was awake and cooperative, but emotionally labile and childish; she was able to understand simple commands or short sentence, but did not talk at all, due to severe spasmodic dysphonia. She had dysphagia but she was able to eat by assistance. She had orofacial dystonia, saccadic smooth pursuit eye movements but no gaze-evoked nystagmus was evoked. Volitional saccadic eye movements were markedly impaired, but the vestibulo-ocular reflex was well preserved in all direction. She was able to raise both upper and lower extremities, but her motor performance was extremely poor due to choreoathetoid-dystonic movements during voluntary movements, but no involuntary movements were seen at rest, and muscle tone was normal at rest. Her fingers movements were also dystonic and limited due to contracture. Sensory examination was normal. Coordination was severely impaired. The deep tendon reflexes were slightly hyperactive in the upper extremities but more hyperactive in the lower extremities with bilateral Babinski sings. She was confined to a

wheel chair and remained in a bed-ridden state. The mRS was graded as 5. CSF examination was unremarkable (WBC 1/μL) with elevated protein level (49 mg/dl), without OCBs. An EEG was unremarkable. A brain MRI revealed no marked changes except mild cerebral atrophy and prominent cerebellar atrophy, but no hippocampal atrophy was seen (not shown). NMDAR antibodies were not detected in serum/CSF obtained when the patient was referred to our hospital 3 years and 3 months after onset of second episode.

Four years and 6 months after the second episode the patient relapsed again, representing as recurrent vomiting with increasing dyskinesias and dystonia. A brain MRI showed splenial hyperintensity (eFigure 1B), which is compatible with mild encephalopathy with a reversible splenial lesion (MERS). CSF examination revealed a few cells (WBC 5/uL; mono 100%) with slightly elevated protein level (49 mg/dl). NMDAR antibodies were detected in both serum and CSF. She is in our hospital, with severe neurological deficits, including severe dysphonia, dysphagia (requiring gastrostomy), slow saccade without nystagmus, facial dystonia, limb dystonia, marked truncal and limb ataxia, and severe cognitive dysfunction (mRS 5).

Patient 15

A 37-year-old woman was admitted to the department of gynecology at our hospital in August 2014 with rapidly progressive bulbar palsy. This patient had been in her usual state of health until 10 days before admission, when she began to have numbness in her face and tongue. One day before admission, she began to feel difficulty in talking and swallowing, and then she was admitted at 35 weeks of gestation. She had no past medical history, including epilepsy, seizure or mental disorder. Her family history was unremarkable.

On admission (day 1), physical examination was unremarkable except marked obesity (BMI 38.2/m^2) and pitting edema in the legs. The temperature was 37.5°C, the blood pressure 107/73 mmHg, the pulse 69 beats per minute, the respiratory rate 24 breaths per minute, and the oxygen saturation 94% while she was breathing an ambient air. Gynecological examination was unremarkable.

After admission dysphagia and dysarthria deteriorated. On day 3, the patient was referred to our department of neurology. On examination, the patient was alert, cognitively and emotionally intact. She had severe dysphagia; she did not swallow her saliva. She had mild dysarthria but not aphasia or hoarseness. She could not stick out her tongue despite ability of moving her tongue in her oral cavity. She had numbness in her face on both sides. She had no ptosis or eye movement abnormalities. The remaining neurologic examination was unremarkable. The blood test-results, including thyroid function, CRP, ACA, ANA, and ANCA, were unremarkable except normocytic normochromic anemia (Hb 8.2 g/dl), and mild elevation of BNP. CSF examination on day 3 revealed only mild pleocytosis (WBC 13/μL; mono 98%), normal protein level (22 mg/dl), without OCBs. HSV-1 PCR testing was negative. A brain MRI was unremarkable.

She underwent caesarean section in the evening of day 3, and she was started on IVIg under ventilatory support for possible immune-mediated disorder, including anti-GT1a antibody-associated pharyngeal weakness, myasthenic crisis, or brainstem encephalitis. On day 4, horizontal gaze-evoked nystagmus was seen under continuous infusion of propofol (50 mg/h). An electromyography examination did not show decremental response, but blink reflex test did not provoke early (R1) and late (R2) blink

reflex responses. An EEG revealed no paroxysmal discharges. Delirium began to develop at night of day 4, for which the patient required high dosage of propofol and midazolam. Oral dyskinesia was transiently seen but not severe. On day 6, the trachea was once extubated but severe bulbar palsy and hypersalivation remained required continuous suction and oxygen delivery. In the evening of day 6, the patient began to receive IVMP (1000 mg/day, 3 days); however, episodic delirium during night and sinus bradycardia (41-46 beats per minutes) developed. Despite immunotherapy with IVIg and IVMP, bulbar palsy did not improve. On day 10, the trachea was re-intubated due to transient airway obstruction, after that she required mechanical ventilatory support. Although nocturnal central apnea developed under ventilatory support with continuous infusion of sedative drugs, she was able to follow commands. Follow-up MRI did not show changes in the brain, including the medulla and limbic system. A pelvic MRI did not show an evidence of ovarian teratoma.

On day 20, high titers of CSF anti-NMDAR antibodies were confirmed in the CSF obtained on day 3. On day 21, she received IVCPA (500 mg/m^2). On day 24, the patient became able to stick out her tongue, but mental status fluctuated and apnea still developed at night, requiring continuous ventilation support at ICU. On day 26, both R1 and R2 blink responses remained absent. On day 32, she received additional IVMP and IVIg. On day 39, she was started on tacrolimus 3 mg daily. On day 41, she was weaned from mechanical ventilation. CSF examination on day 47 revealed mild pleocytosis (WBC 8/μL). On day 47, both R1 and R2 blink reflex responses became normal. On day 48, the patient received the second course of IVCPA. On day 69, the patient was discharged without neurological deficit. Following immunotherapy, the antibody titers declined in CSF (from 1:1280 on day 3 to 1:80 on day 47) but remained unchanged in serum (1:400). She remained free of symptoms, without any neurological deficits (mRS 0) at last follow-up (14 months after symptoms presentation).

eTable. Clinical Features, Laboratory Data, and Long-term Outcome

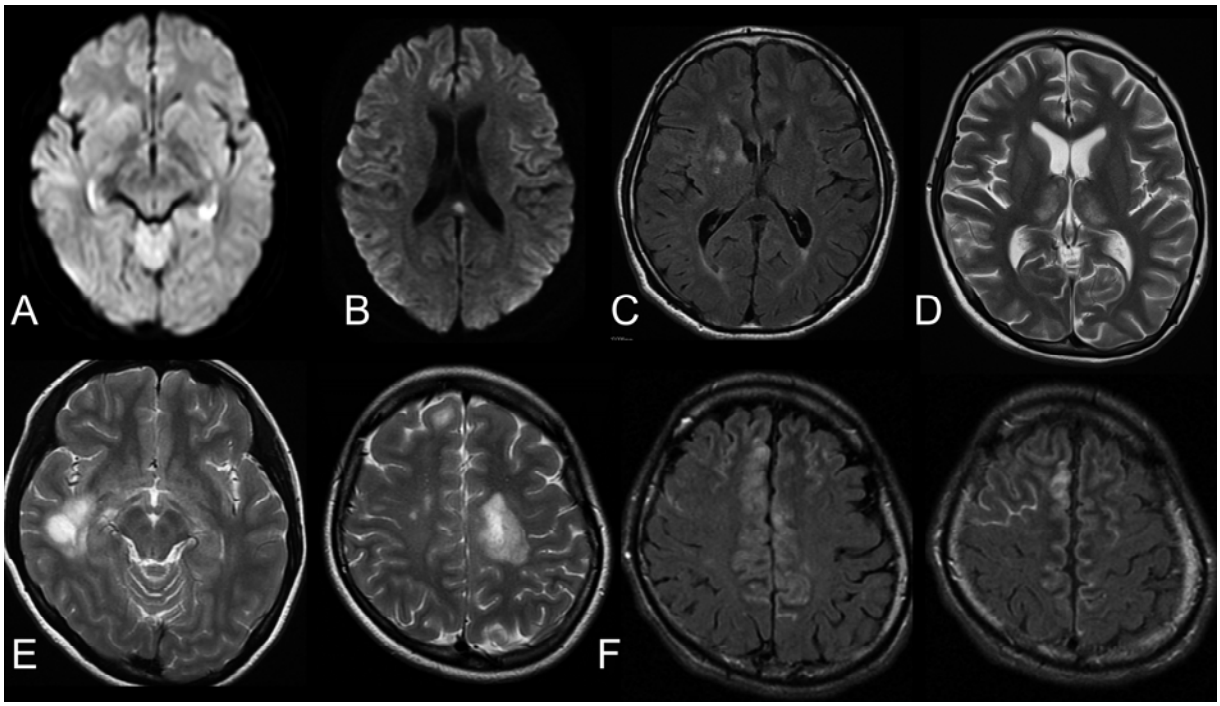
No.	Age, y/ sex/ date of onset, y	Clinical spectrum	CSF: WBC per µL/ OCB	Brain MRI		Tumor/ tumor removal	Immunotherapy [a]/ time to immunotherapy	Ventilator support/ duration, weeks	Hospitalization, mos/ clinical course/ serious complications	Time to diagnosis [b] (CSF/serum)	Long-term outcome [c] (mRS) / duration, mos
				At presentation	DCA/ CA/ follow-up duration, mos						
1	21/ M/ 1999	Typical spectrum	28/ +	FLAIR high signal in B. MTL	No/ No/ 7	None	IVMP/ 17 days	Yes/ 6	5.7/gradually improved/ none	123 mos (+/+)	Good (mRS 1)/ 126
2	26/ F/ 1999	Typical spectrum	17/ –	NR	No/ No/ 7	R. OT/ after recovery	None	Yes/ 10	3.1/gradually improved/ none	84 mos (+/+)	Good (mRS 0)/ 94
3	27/ F/ 2000	Typical spectrum	8/ –	NR	No/ No/ 20	R. OT/ after recovery	None	No	1.5/ gradually improved/ none	82 mos (n.d./+)	Good (mRS 0)/ 88
4	17/ F/ 2001	Typical spectrum	51/ +	FLAIR high signal in B. MTL	Yes/ No/ 90	None	IVMP, IVIg/ 8 days	Yes/ 36	13.7/ apallic for 18 mos, but gradually improved/ DIC, DVT, septic shock, arterial thrombosis requiring above-knee amputation	71 mos (n.d./+)	Good (mRS 4 due to leg amputation, otherwise near full recovery)/ 179
5	33/ F/ 2003	Typical spectrum	32/ –	NR	Yes/ No/ 70	R. OT/ after recovery	IVIg, IVMP/ 5 days	Yes/ 24	9.3/ apallic for 7 mos, but gradually improved/ none	49 mos (+/+)	Good (mRS 0)/ 156
6	21/ F/ 2009	Typical spectrum	26/ n.d.	NR	No/ No/ 4	L. OT/ at 1 week)	IVMP with PDN taper, IVIg, PLEX/ 7 days	Yes/ 10	4.1/ gradually improved after immunotherapy with tumor removal/ none	22 days (+/+)	Good (mRS 0)/ 77
7	27/ F/ 2009	Typical spectrum	97/ –	FLAIR high signal in B. MTL	Yes/ No/ 24	R. OT/ 9 mos later	IVMP, IVIg, PLEX/ 8 mos	Yes/ 40	11.1/ apallic for 8 mos, but rapidly improved after immunotherapy with tumor removal/ PE, DVT	9 mos (+/-)	Good (mRS 2)/-84
8	18/ M/ 2010	Isolated convulsive seizure	9/ +	Enhancement of frontal cortex	No/ No/ 59	None	IVMP, PDN/ 12 days	No	1.1/ improved after immunotherapy/ none	9 weeks (+/+)	Good (mRS 0)/ 60

9	14/ F/ 2010	Typical spectrum	6/ n.d., (2/ +) [d]	NR	Yes/ Yes/ 47	None	IVMP, IVIg, PLEX, PDN/ 20 days	Yes/ 2	9.3/ not responded for 13 mos, but partially improved after IVCPA/ septic shock, transient cardiac arrest, DVT	7 weeks (+/+)	Poor (mRS 4)/ 55
10	17/ F/ 2011	MS mimicking spectrum	2/ –	Multifocal FLAIR high signals	No/ No/ 51	None	IVMP, IVIg, PLEX, PDN, AZA/ 21 days	No	1.9/ improved/ none	13 weeks (+/+)	Good (mRS 1)/ 51
11	21/ M/ 2012	Isolated convulsive seizure	12/ –	NR	No/ No/ 7	None	IVMP with PDN taper-off, IVIg/ 18 days	No	2.5/ improved/ none	6 weeks (+/-)	Good (mRS 0)/ 33
12	46/ M/ 2013	Typical spectrum	30/ +	Multifocal FLAIR high signals	No/ No/ 18	None	IVMP, IVIg, IVCPA, PDN/ 9 days	No	1.9/ improved/ none	23 days (+/+)	Good (mRS 1)/ 27
13	20/ M/ 2014	Loss of cons, followed by typical spectrum	13/ +	NR	No/ No/ 3	None	IVMP, IVIg, IVCPA, PDN, AZA/ 7 days	No	5.4/ gradually improved/ none	38 days (+/+)	Good (mRS 0)/ 10
14	25/ F/ 2010	Psychosis at first episode, typical spectrum at relapse	41/ n.d.	FLAIR high signal in B. MTL	Yes/ Yes/ 55	None	IVMP, IVIg/ 7 days	Yes/ 5	18.2/ not responded to first-line immunotherapy/ multiple organ dysfunction syndrome, rhabdomyolysis	19 weeks [e] (+/+)	Poor (mRS 5)/ 68
15	37/ F/ 2014	Acute bulbar palsy followed by typical spectrum	13/ –	NR	No/ No/ 2	None	IVMP, IVIg, IVCPA, TAC/ 13 days	Yes/ 5	2.2/ rapidly improved after IVCPA/ none	30 days (+/+)	Good (mRS 0)/ 14

Patients 7, 9 and 14 were initially treated at another hospital during 8-18 months before referral to our hospital. [a] Immunotherapy initiated within one year of symptoms presentation is shown; immunotherapy, including IVCPA, started one year after presentation is not shown *in Patient 9.* [b] Time to diagnosis is defined as a time from symptoms presentation until detection of NMDAR antibodies. Antibody assay was subsequently carried out in 5 patients (*Patients 1-5)* using archived CSF and/or serum obtained at symptoms presentation and kept in frozen until assay. The CSF was only positive when examined at 8 months in *Patient 7* and at symptoms presentation in *Patient 11*. [c] Good outcome was defined as a mRS score of 0-2 at the last follow-up, and poor outcome was defined as a mRS score of 3 or higher (except *Patient 4*) [d] OCBs were detected one year later. [e] Time from symptoms onset at relapse is shown.

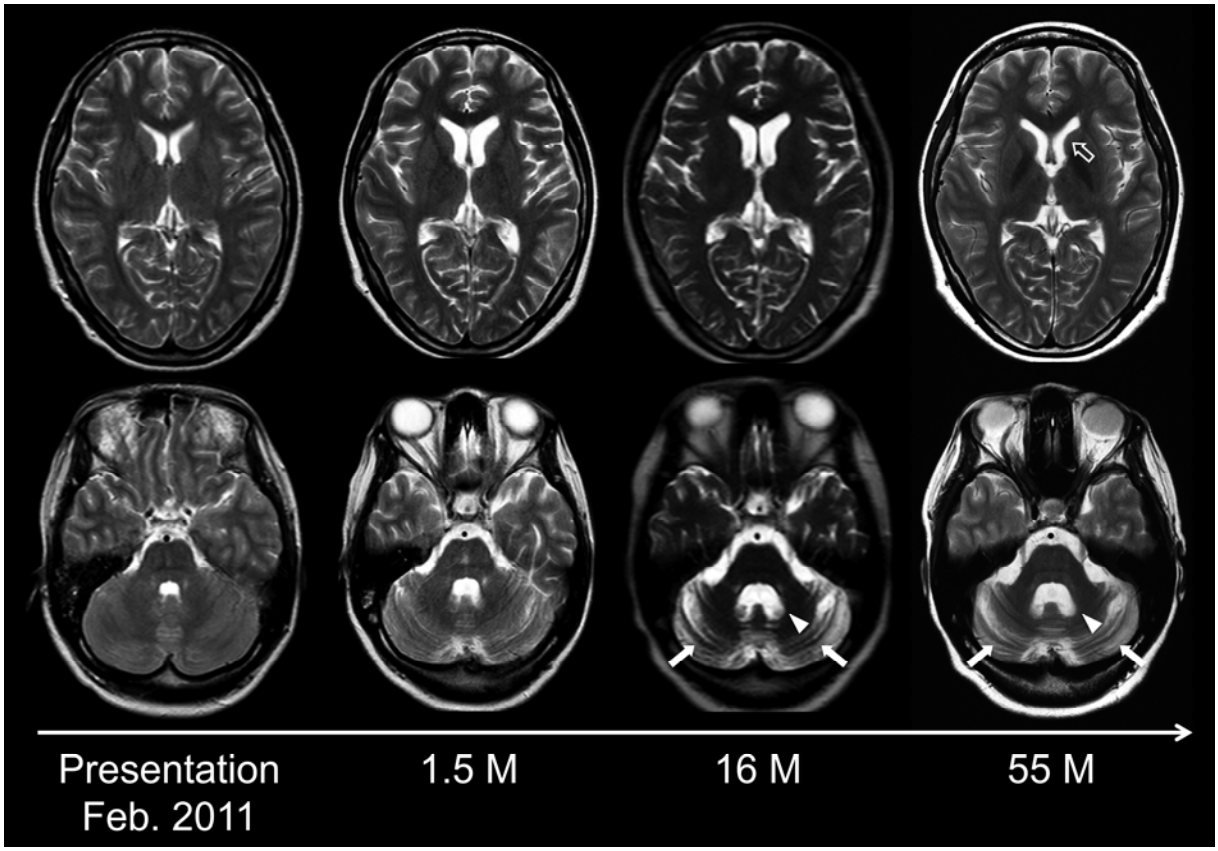
AZA: azathioprine; B.: bilateral; CA: cerebellar atrophy; cons: consciousness; DCA: diffuse cerebral atrophy; DIC: disseminated intravascular coagulation; DVT: deep vein thrombosis; F: female; FLAIR: fluid-attenuated inversion recovery; IVCPA: intravenous cyclophosphamide; IVIg: intravenous immunoglobulin; IVMP: intravenous high-dose methylprednisolone; L.: left; M: male; mos: months; mRS: modified Rankin Scale; MS: multiple sclerosis; MTL: medial temporal lobes; n.a.: not applicable; n.d.: not done; NR: not revealing; OCB: oligoclonal bands; OT: ovarian teratoma; PDN: prednisone; PE: pulmonary embolism; PLEX: plasma exchange; R.: right; TAC: tacrolimus; WBC: white blood cell

eFigure 1. Various Acute Brain Lesions in Anti-NMDAR Encephalitis



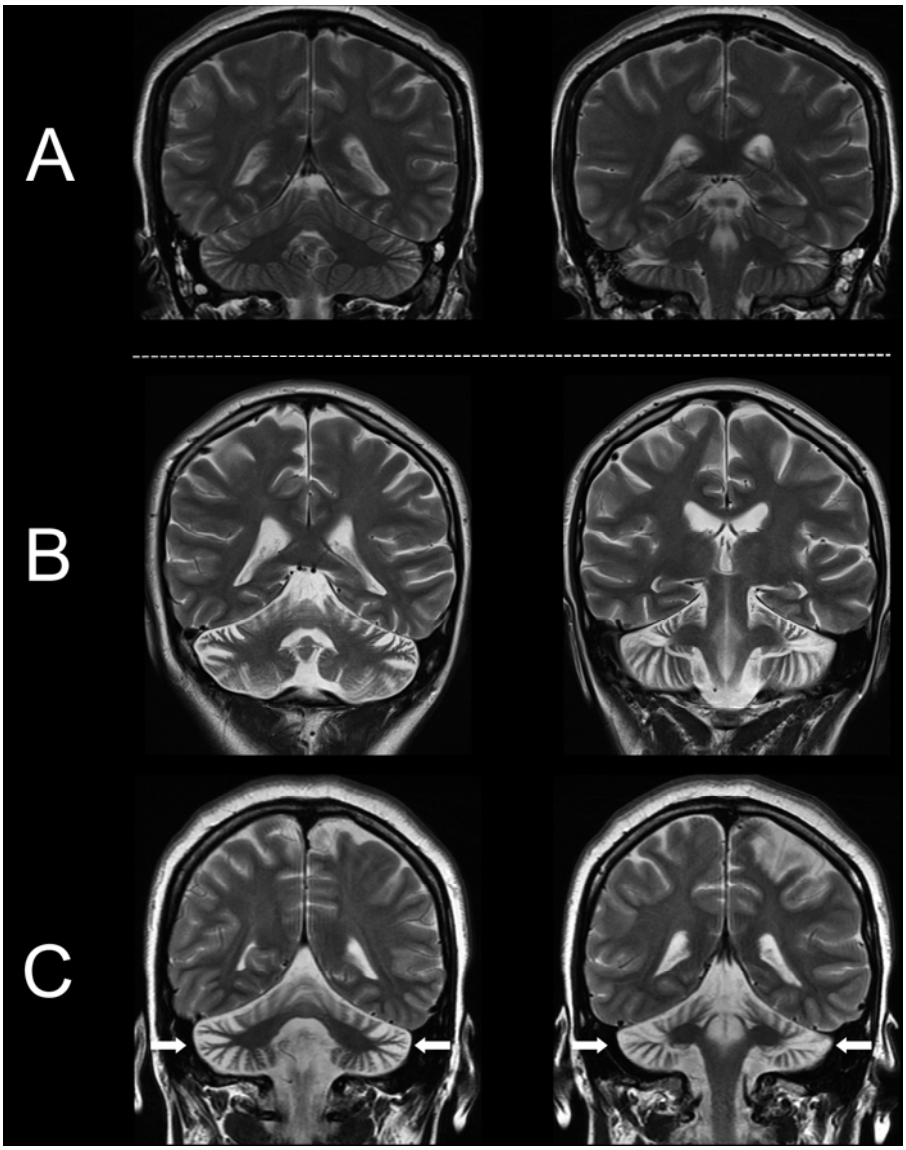
Brain MRIs show various patterns of lesions, including symmetric hippocampal DWI/FLAIR high signals (A: *Patient 14*, 7 days after onset of the second episode), reversible splenial lesion of the corpus callosum (B: *Patient 14,* 2 weeks after onset of the third episode) consistent with mild encephalopathy with a reversible splenial lesion (MERS), multifocal T2/FLAIR high signals (C: *Patient 12,* one month after symptoms onset), symmetric thalamic T2/FLAIR high signals (D: *Patient 9*, 2 months after presentation), multifocal demyelinating T2 high signals (E: *Patient 10*, 3 weeks after presentation), and gadolinium enhancement of frontal cortex with augmented leakage into the sulci of the cortex (F: *Patient 8*, 12 days after presentation). D, E: T2-weighted MRI; A, B: DWI; C: FLAIR; F: Gadolinium enhanced FLAIR.

eFigure 2. Progressive Cerebellar Atrophy and Partial Recovery of Cerebral Atrophy in Patient 14



Follow-up T2-weighted MRIs show gradual development of mild cerebral atrophy and progressive cerebellar atrophy. Cerebellar atrophy is seen at 1.5 months and becomes prominent at 16 months or later, and is irreversible even at 55 months, but cerebral atrophy has partially reversed on the follow-up MRIs. See marked dilatation of the fourth ventricle (arrow head) and cerebellar sulci (arrows), and reversal change of anterior horn dilatation (open arrow). M: months.

eFigure 3. Comparison of Coronal View of the Cerebellum on MRI Between Patients 15 and 9



Coronal MRIs show normal appearance of the cerebellum in *Patient 15* who presented with acute bulbar palsy (A: 2 months after presentation). In contrast, in *Patient 9* with residual cerebellar ataxia, MRIs show progressive symmetric dilatation of the cerebellar sulci (C, arrows), with relatively sparing subcortical white matter (B: 8.5 months after presentation; C: 3 years and 11 months after presentation).

