

## Supplementary Online Content

Joubert B, Kerschen P, Zekeridou A, et al. Clinical spectrum of encephalitis associated with antibodies against the  $\alpha$ -amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor: case series and review of the literature. *JAMA Neurol*. Published online August 17, 2015. doi:10.1001/jamaneurol.2015.1715.

### **eAppendix.** Clinical Vignettes

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

## eAppendix. Clinical Vignettes

**Patient 1.** A 58-year-old male patient without a previous significant medical history was admitted to the emergency care unit because of the sudden onset of confusion. At examination, the patient was mildly febrile and disoriented in time and space. Severe anterograde memory impairment, marked dysexecutive symptoms and mild aphasia were observed. Neuropsychological testing confirmed global amnesia, constructive apraxia and the alteration of executive functions. Cerebrospinal fluid (CSF) analysis was normal. Extensive infectious screenings including human immunodeficiency virus (HIV) serology, blood tests for *Plasmodium falciparum*, and polymerase chain reaction (PCR) for enterovirus, herpes virus simplex (HSV) 1 and 2 and varicella zoster virus (VZV) in the CSF were negative. Brain magnetic resonance imaging (MRI) showed a bilateral increase in the hippocampal FLAIR signal. Scalp electroencephalography was unremarkable. Whole body tomodensitometry (TDM) displayed infra-centimetric mediastinal adenopathies with normal metabolism in fluorodeoxyglucose positron emission tomography (FDG-PET) and non-specific interstitial pneumonia. Immunological studies revealed positive antinuclear antibodies (ANA) and anti-intrinsic factor antibodies. Antibodies against Hu, Yo, CV2, amphiphysin, Ma2, Ri, Tr, GAD65, NMDAR, GABAB-R, Lgi1, Caspr2 and VGCC were negative in both serum and CSF. Conversely, antibodies against the GluR1/2 subunits of the AMPAR (AMPAR-Ab) were found in the CSF. The patient was treated with intravenous steroids starting from 3 weeks after onset, followed by 9 courses of intravenous immunoglobulin (IVIg) and 6 courses of cyclophosphamide. Improvement was noted 6 weeks after onset. At 15 months, neurological status had improved, but the patient still suffered from important amnesic and executive defects compromising his autonomy. The modified Rankin scale (mRS) was rated at 3. Control brain MRI showed vascular leukopathy and slight bilateral hippocampal atrophy, which was stable from month 12 to month 15.

**Patient 2.** A 74-year-old male patient, a heavy smoker without a previous significant medical history, was admitted to the department of neurology for recent abnormal behavior. Examination revealed spatio-temporal disorientation, confusion, alternating states of agitation and somnolence, hemi-body polymodal sensory deficits, and dysexecutive symptoms. The patient complained of headache, insomnia and of a severely depressed mood. Brain MRI and EEG. CSF analysis displayed a lymphocytic pleiocytosis ( $38 \text{ WBC/mm}^3$ ), elevated protein level at  $0.56 \text{ g/l}$  and oligoclonal bands at isofocalization. Infectious analysis including PCR for HSV and enterovirus were negative. Eventually, CSF was found to be positive for Hu and AMPAR-Ab. Oncological screening revealed a hypermetabolic pulmonary lesion. Surgery and radiation therapy were rejected due to general physical deterioration. Considering the high probability of lung cancer, five courses of chemotherapy (carboplatin and VP16) were performed, leading to radiological remission. Regarding autoimmune encephalitis, plasma exchanges were performed four weeks after disease onset followed by 6 courses of IVIg. At the last evaluation at 9 months after onset, behavioral disorders had disappeared, but the patient maintained right hemiparesis and neuralgic pain, severe anterograde amnesia and dysexecutive symptoms. The mRS was then rated at 3.

**Patient 3.** A 56-year-old woman without a significant prior medical history was admitted in the emergency care unit for acute-onset anterograde amnesia with a night-day cycle inversion. Confusion and agitation arose in the following days. Two weeks after onset, those behavioral disorders worsened, and right upper limb cerebellar dysmetria, vertical nystagmus and opsoclonus appeared. Agitation was easily controlled with antipsychotic drugs, but severe anterograde amnesia persisted. Brain MRI displayed FLAIR hyperintensities in the hippocampi and gyri recti of both sides and in the right precentral area. An EEG was not performed. CSF analysis at onset showed marked pleiocytosis (220 WBC/mm<sup>3</sup>, 100% lymphocytes) and normal protein levels. CSF protein isofocalization was not performed. CSF lymphocyte immunophenotyping was normal. Bacterial cultures and repeated PCR for HSV in the CSF were negative. Antibodies against Hu, Yo, CV2, amphiphysin, Ma2, Ri, Tr, GAD65, NMDAR, GABAB-R, Lgi1, Caspr2 and VGCC were negative in both serum and CSF, but AMPAR-Abs were found in the CSF. Oncological screening (tumor markers, TAP TDM, PET FDG) only found mild ovarian hypermetabolism, for which a hysteroscopy and ovariectomy revealed only benign adenomyosis. Mild but persisting hyponatremia was noted (131 – 135 mM). She was treated with IVIg from 12 days after disease onset, followed by high dose intravenous steroids 3 weeks after disease onset. Rituximab was administered as a long-term immunomodulatory treatment. Memory function improved following corticosteroid administration. At 2 months of evolution, the mRS was rated at 3.

**Patient 4.** A 43-year-old woman without prior medical history complained of recurrent, sudden-onset stereotyped attacks, consisting of a feeling of chest and abdominal tightness, sometimes followed by hemi-body paresthesia and tachycardia. Two weeks later, the patient developed bilateral tremor and mild cerebellar signs. She also complained of nocturnal insomnia and memory impairment. Neuropsychological tests revealed short-term memory impairment and alteration of executive functions. Right temporal lobe seizures were recorded on EEG. A brain MRI showed increased bilateral hippocampal T2 signal. CSF analyses, including protein level and cytology, oligoclonal bands and HSV PCR, were negative or normal. Serum onconeural antibodies, including Hu, Yo, Ri, Ma1, Ma2, amphiphysin and Tr antibodies, and anti-thyroid antibodies were all negative. Conversely, anti-AMPA, anti-leucine-rich, glioma inactivated 1 (LGI1) and anti-glutamic acid decarboxylase 65 kDa (GAD65) antibodies were found both in serum and CSF. Anti-islet cell antigen 512 (IA2) antibodies were also found in the serum. Repeated oncological screening, including whole-body CT scan, whole-body FDG-PET and mammography only found thymus hyperplasia, which remained stable through follow-up. A brain FDG-PET showed hypermetabolism in the right mesial temporal lobe and striatum.

The clinical situation worsened despite triple antiepileptic therapy (clobazam, valproate, oxcarbazepine). High-dose corticosteroids were administered 3 weeks after onset and were followed by 6 courses of IVIg. At the end of the third course, epileptic seizures dramatically reduced. Antiepileptic treatment was lowered to lacosamide only. Control brain MRI at 6 months showed prominent right hippocampal atrophy. Upon neuropsychological testing 5 months later, there was a dramatic improvement in verbal and non-verbal memory. Neuropsychological outcome remained stable, and negative myoclonus disappeared. At the last evaluation at 31 months, the patient was considered seizure free. She maintained only slight anterograde memory impairment and has resumed a normal life (mRS = 1).

**Patient 5.** A previously healthy 21-year-old patient was admitted in the intensive care unit for a rapidly developing coma with fever, diffuse hypertonia and ocular deviation. He was reported to have been complaining of headache for three days and memory problems for several weeks before. Intubation was performed due to respiratory failure. Vigilance improved after 4 weeks of coma. Examination at this time showed massive anterograde amnesia, dysexecutive symptoms, behavioral disorders and psychiatric symptoms (depressed mood, delusions and hallucinations). Brain MRI displayed bilateral striatal FLAIR hyperintensities. EEG demonstrated bifrontal sharp and slow waves without organized seizures. CSF analyses showed a mildly elevated protein level (0.7 g/l) and lymphocytic pleiocytosis at 28 WBC/ml. No oligoclonal bands were observed. Bacterial, viral and parasitic investigations were negative. Oncological screening led to the discovery of a thymic carcinoma with pleural extension and mediastinal lymph node metastasis. AMPAR-Abs were found in the CSF. Surgical resection of the carcinoma coupled to anti-cancerous chemotherapy and radiation therapy was performed three months after disease onset. Anti-AMPAR encephalitis was treated with antiepileptic drugs (levetiracetam), steroids and IVIg starting from 6 weeks after disease onset. The patient improved slowly. At the last evolution 18 months after disease onset, only mild deficits in working memory persisted, while the control brain MRI was normal.

**Patient 6.** A 22-year-old female patient without prior significant medical history presented with sudden memory deficits, followed the next week by unusual headache and abdominal pain. In a few days, her condition worsened with confusion, behavioral disturbances, dysexecutive symptoms, complete insomnia and massive anterograde amnesia. The patient was then hospitalized, and three days after admission, a coma developed with fever, diffuse hypertonia, ocular deviation and otherwise unexplained rhabdomyolysis. CSF analysis showed normal protein levels, mild lymphocytic pleiocytosis (29 WBC/mm<sup>3</sup>) and no oligoclonal bands. Brain MRI displayed FLAIR and diffusion hyperintensities with restricted apparent diffusion coefficient (ADC) in the left temporomesial areas, cortico-subcortical left temporal, insular and bilateral parietal lobes, as well as in the right caudate nucleus and cerebellum. Brain PET FDG displayed hypermetabolism of the right parietal and occipital lobes, cerebellum and bilateral basal ganglia. The EEG was unremarkable. A cerebral salt wasting syndrome was observed 3 weeks after onset. Extensive bacterial, viral, parasitic, and fungal analyses were negative. Thyroid hormones and anti-thyroid antibodies were negative or normal. Immunological analyses showed positive ANA in the serum and AMPAR-Abs in both the serum and CSF. Immunotherapy was administered starting from 3 weeks after onset and 1 week after hospital admission. It consisted of high-dose steroids and IVIg followed by consecutive courses of cyclophosphamide, plasma exchanges and rituximab. Acyclovir and antiepileptic drugs were administered empirically. The patient began to display signs of awakening four weeks after the onset of coma, but stayed in a minimally conscious state until then. Neurological examination at this time showed tetrapyramidal syndrome, movement disorders (hemidystonia, myoclonus, oculogyric crisis) and down-beat nystagmus. Motor-evoked potentials confirmed the alteration of the pyramidal tracts at the cephalic level. A brain MRI three months after onset demonstrated the development of diffuse and severe cortico-subcortical atrophy. The patient died of urinary sepsis after one year of evolution. An autopsy was not performed.

**Patient 7.** A 92-year-old woman was hospitalized for acute-onset amnesia. She had no previous history of cognitive decline or inadequate behavior; her prior mini mental state examinations (MMSE) performed 6 months before symptoms onset were reported normal (30/30). Clinical examination revealed complete disorientation in space and time with pure anterograde amnesia. There was no executive function disorder, attention deficit or consciousness alteration. No focal neurologic deficit was observed, except for discrete unsteadiness, suggesting a mild axial cerebellar syndrome. Brain MRI showed leucoaraiosis, mild and diffuse cerebral atrophy without predominance to the hippocampi, no micro-bleeds and one small right frontal hyperintensity suggestive of an ancient stroke. An EEG was unremarkable. Routine serum analyses were normal. CSF examination displayed 4 WBC/mm<sup>3</sup>, normal protein levels and one oligoclonal band. Systematic immunological analyses revealed anti-neuropile staining of the CSF. Indirect immunofluorescence was negative for anti-Hu, Yo, CV2, amphiphysin, Ma2, Ri, Tr, GAD65, NMDAR, GABAB-R, Lgi1, Caspr2 and VGCC antibodies but displayed clear positivity for AMPAR-Abs. Six cycles of IVIg were administered. At the last follow-up, at 6 months after diagnosis, her neurological evaluation remained remarkably stable.