Acute psychosis in anti-NMDA-receptor encephalitis

Psychose aiguë par encéphalite avec anticorps anti-récepteur NMDA

We observed anti- N-methyl-D-aspartate (NMDA) receptor encephalitis with inaugural acute psychosis in two young French women.

Case 1

In December 1999, a 22-year-old woman presented with stooped posture, amimia and a reduced speech fluency with disorganized content. She had complained of fatigue and headache for four weeks. Acute psychosis was diagnosed by a psychiatrist and treated with haloperidol, cyamemazine and loxapine. High-grade fever occurred and over 10 days, she became mute and akinetic, with rigidity, and catalepsy. She was intubated because of hypoventilation. Off sedation, she was unresponsive to voice and pain. She developed severe movement disorders characterized by rhythmic movements with complex patterns of mouth opening, chewing, palatal elevation and asymmetric grimacing, rotation of shoulders, elbow flexion, spreading of fingers superimposed to dystonic posturing of the right arm and neck and trunk hyperextension. Routine laboratory testing was unremarkable except for elevated blood creatine phosphokinase (CPK) level. A comprehensive blood immunological and microbiological tests panel was negative. Cerebrospinal fluid (CSF) revealed a pleocytosis (51 cells/microliter, 90% mononuclear cells) with normal protein and glucose levels. Extensive CSF analysis for bacterial, viral and fungal agents and cytology were unrevealing. Brain MRI was normal. Electroencephalogram demonstrated a 6 Hz polymorphic theta activity without epileptiform features.

Neuroleptic treatment was stopped. After failure of amoxicillin and acyclovir therapy, treatment with intravenous high-dose prednisolone was started. The patient dramatically improved within a few days and was weaned from mechanical ventilation after one month. Eight months after discharge, she was under low-dose oral prednisone and had fully recovered.

In June 2003, as she was treated with 7 mg prednisone daily, she had a single generalized seizure, then developed dramatic mood swings, echophenomena and orofacial dyskinesia. Brain MRI was normal. EEG showed a bitemporal polymorphic theta waves with ictal discharge in the left temporal lobe. CSF revealed an isolated pleocytosis (26 cells/microliter, 90% mononuclear cells). Treatment with intravenous methylprednisolone 500 mg/d for three days followed by prednisone 50 mg daily was started with oral methotrexate 15 mg/week. Methotrexate therapy was begun because of the severity of neurological symptoms and because of the relapse of symptoms under corticosteroid therapy. Psychiatric signs and dyskinesia improved slowly. In September 2003, she was considered normal. Methotrexate was stopped in November 2006.

In January 2009, while she was treated with 5 mg/d of prednisone, there was a recurrence of emotional disturbances and depression, rapidly followed by cognitive decline and prominent schizophrenia-like symptoms. The patient was admitted in a psychiatry department and was treated with haloperidol. Psychiatric signs worsened and high-grade fever occurred. Physical examination showed generalized hypertonia, frequent facial grimacing, and intermittent dystonic postures of the arms. Brain MRI was normal. CSF analysis showed a white blood cell count of five cells/mL with normal glucose and protein levels. An 18 FDG PET-scan was not performed. The diagnosis of encephalitis associated with anti-N-methyl-D-aspartate (NMDA)-receptor antibodies was suspected. Antibodies to NMDA-receptor were disclosed in CSF [1]. Whole body CT scan and pelvic MRI were normal. At that time, evaluation of cognitive functions was not performed. Haloperidol was stopped. Intravenous immunoglobulin (IVIG) 0.4 g/kg body weight/day for five days every three weeks was started. The patient rapidly improved. After six months, psychiatric and neurological evaluation (including cognitive functions) were normal and testing for anti-NMDA-receptor was negative in CSF. Eighteen months after the third relapse of the disease, the patient was symptom-free under 10 mg/d of prednisone and has returned to full-time work.

Case 2

In October 2009, a 32-year-old woman suffered gradual memory loss with schizophrenia–like symptoms. She was agitated with bizarre behavior including personality changes, sexual-like activity, visual hallucinations with paranoid and persecution thoughts. Ten days before, she had had fever, headaches and fatigue and had been treated seven days with amoxicillin.

Agitation alternating with sleepiness, mutism, short-term memory impairment and anorexia occurred. One month later, because of pseudo catatonic state, persistent fever and fatigue, she was referred to the emergency unit. On examination, she had myoclonic movements of the eyelids, facial and limbs dyskinesia, hyper-salivation and decreased level of consciousness. Eventually, coma required intensive care unit and she was intubated. Electroencephalogram showed diffuse slowing with no epileptic activity. CSF analysis showed lymphocytic pleocytosis (16 leukocytes/µL) with normal protein and glucose levels. She was initially treated by intravenous acyclovir, tazocillin, ciprofloxacin and sodium valproate. Extensive CSF (including PCR for HSV, VZV, CMV, enterovirus, EBV, tuberculosis, tropheryma whipplei), and blood tests (including a large panel for auto-antibodies) were negative. Brain MRI (T2 flair-weighed images) displayed high-signal small lesions in the frontal cortex. Total body CT-scan showed a right ovarian cyst, with

no peritoneal effusion or enlarged lymph node. An 18 FDG PET-scan was not performed. Infection was ruled out, and antibiotics and antiviral treatment were stopped. Intravenous methylprednisolone (one gram per day for three days) pulse therapy was followed by oral prednisone 60 mg per day. Anti-NMDA-receptor antibodies were detected in the CSF. Anti-NMDA receptor limbic encephalitis was then treated with IVIG (2 g/kg over two days), repeated every three weeks. The ovarian tumor was removed on December 2009 and histopathological analysis showed a complex mature teratoma.

Clinical course was characterized by echolalia, anterograde amnesia, unresponsive phases (with mutism, resistance to eyes opening) alternating with hyperkinetic phases with agitation. Autonomic instability was persistent with tachycardia. Ventilatory support was pursued for one month.

After ventilation weaning, she was transferred to the Internal Medicine Department. She was still confused with agitation, persistent licking and chewing dyskinesia, short term memory loss, frontal lobe syndrome (constructive apraxia, concentration troubles, inversion of circadian rhythm, perseverations) and language disorders (logorrhea and paraphasia). A neuropsychological evaluation was performed and found a decline of level of consciousness, a decreased responsiveness to stimulation, a decline in expressiveness of language with amnestic aphasia, cognitive disorders in social interactions, and emotional disturbances with anxiety.

She received five monthly IVIG infusions and was included in a memory and language rehabilitation program. Six months after disease onset, the patient had partially recovered with severe persisting cognitive dysfunction. A CSF analysis was performed and revealed no pleocytosis. Anti-NMDA receptor antibodies were still present in CSF.

Discussion

We describe two cases of young French women with anti-NMDA-receptor antibodies encephalitis, heralded by acute psychosis. Anti-NMDA-receptor encephalitis has been described as a cause of paraneoplastic and auto-immune limbic encephalitis. Its frequency is probably underestimated. As in patient 2, teratoma of the ovary is the main tumor associated with anti-NMDA-receptor encephalitis (53 of 58 cases associated with tumors in a series of 98 patients) [2].

This disorder mainly affects young women (sex ratio 9F:1 M) and usually presents with a prodromic episode of fever, headache, or malaise followed a few days later by mood or behavioural changes, psychiatric symptoms suggesting schizophrenia or catatonia, decline of level of consciousness, hyperkinesias with severe movement disorders. After excluding viral and systemic auto-immune disorders, limbic encephalitis – paraneoplastic or not – diagnosis is based on cerebrospinal fluid inflammatory findings, EEG or MRI abnormalities in the temporal lobes, and antineuronal antibodies testing.

Our first case demonstrates that relapses over a very long period of time do not rule out the diagnosis of anti-NMDA-receptor encephalitis. In the largest case-series published with a median follow-up of 17 months, relapses occurred in 15% of cases and appeared less frequent when anti-NMDA-receptor encephalitis was paraneoplastic [2]. The mean time between first flare and last relapse was 18 months. It was much longer in our patient, with 42 and 67 months between relapses, respectively.

At disease onset, patients are frequently admitted in a psychiatry department due to the acute psychiatric presentation. In the largest case-series reported to date, patients with anti-NMDA-receptor encephalitis were first seen by psychiatrists in 77% of cases [2]. Of note, anti-NMDA-receptor encephalitis is increasingly recognized in children. In 32 cases reported in children or adolescents aged less than 18 years, the vast majority presented with behavioural or personality changes, and sleep dysfunction [3].

As in our two patients, symptoms include anxiety, agitation, bizarre behaviour, delusional or paranoid thoughts, and visual or auditory hallucinations. Short-term memory loss or seizures may occur. Periods of akinesia alternate with agitation. Decreased responsiveness to stimulation may progress to a catatonic-like state. The association with various, severe abnormal movements may provide a clue for diagnosis: orofacial dyskinesia including grimacing, chewing-like movements, clenching of the teeth, forceful jaw opening with tongue protrusion, abnormal postures of the limbs and trunk (dystonic extension) and muscle rigidity. Orolingual dyskinesias with abnormal postures, associated with bizarre involuntary movements may resemble complex partial seizure status epilepticus or mimic psychogenic disorder. Many patients suffer generalized tonic-clonic or partial complex seizures in the first three weeks of illness. Electroencephalogram is abnormal in more than 90% of the cases, showing either diffuse delta slowing or paroxysmal discharges. Brain MRI is abnormal in 55% of cases. CSF is abnormal in 95% of cases with lymphocytic pleocytosis in 91% of cases.

NMDA receptors are ligand-gated cation channels involved in synaptic transmission and plasticity. Testing for anti-NMDA receptor antibodies in CSF (or blood) appears both sensitive and specific for the diagnosis. Antibody titers are measured with ELISA on transfected cells that express NMDA (NR1/NR2 heterodimers) receptors [1]. In patients with antibodies tested both in blood and CSF, all had higher antibodies titres in CSF than in sera suggesting intrathecal synthesis of anti-NMDA-receptor antibodies [2].

The fact that in such setting the anti-NMDA receptor antibodies are associated with features of acute psychosis fits well with the ''NMDA-receptor hypofunction hypothesis'' of schizophrenia. Indeed, NMDA receptor antagonists such as ketamine – an anesthetic drug – may exacerbate psychiatric symptoms in schizophrenia or induce schizophrenic symptoms in healthy

individuals, whereas agents that enhance NMDA receptor function improve schizophrenic symptoms. The psychomimetic effect of NMDA receptor antagonists has been attributed to the functional blocking in NMDA receptor in pre-synaptic gamma-aminobutyric acid-mediated (GABAergic) interneurons of the thalamus and frontal cortex, causing a decrease of release of GABA [4,5].

Treatment strategy for anti-NMDA-receptor encephalitis is based on immunotherapy, including corticosteroids, IVIG, plasma exchange, cyclosphosphamide or rituximab, and removal of the ovarian when it exists. Of note more than half of patients do not have detectable tumor.

Outcome variability is illustrated by our observation. In both patients, untreated disease led to autonomic instability (hyperthermia, hypothermia, tachycardia, tachypnea, hypertension alternating with hypotension), progressing to a catatonic like state with paradoxical response to stimuli (for example no response to pain but resisting eye opening), and a decline of consciousness with central hypoventilation. In our first case, encephalitis relapsed twice over 10 years, was not associated with tumor, and was completely responsive to high dose steroids and IVIG. On the other hand, in the second case severe sequellae occurred despite ovarian teratoma removal, corticosteroids and immunoglobulins therapy.

Anti-NMDA receptor encephalitis may be highly misleading, as it may mimic acute psychosis. Moreover, in treated psychotic patients symptoms such as diaphoresis, fever, confusion, autonomic dysfunction, dyskinesia and movement disorders, seizures and hypoventilation may be ascribed to anti-psychotic therapy toxicity, such as neuroleptic malignant syndrome [6]. Our first patient suffered from fever and rhabdomyolysis, and events chronology strongly suggested neuroleptic syndrome that was confusing. Hence, because anti-NMDA features may be mistaken for drugs-related symptoms and brain MRI is normal in half of patients, the disease may go undiagnosed and patients referred to the ICU with severe untreated encephalitis.

In conclusion, anti-NMDA receptor encephalitis causes both acute psychosis and symptoms that mimic neuroleptic malignant syndrome. The association with various, severe abnormal movements, mainly orolingual dyskinesias with abnormal postures, may provide a clue for diagnosis. Such misleading features should be acknowledged by clinicians, in order to avoid a life-threatening delay in diagnosis and specific treatment. Testing for anti-NMDA receptor antibodies in CSF appears both sensitive and specific for the diagnosis.

Disclosure of interest : The authors declare they have no conflicts of interest regarding this article.

Acknowledgments : The authors thank Pr Jerome Honnorat and Dr Adrien Didelot (UMR-INSERM U842, Claude Bernard University, Lyon, France) for measuring NMDA-R antibodies and Doctors Sandrine Deltour and Francis Bolgert (Neurology Intensive Care Unit, Salpêtrière Hospital, Paris, France) for clinical care of the first patient in 1999.

References

[1] Dalmau J, Tuzun E, Wu HY, Masjuan J, Rossi JE, Voloschin A *et al.* Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61(1):25-36.

[2] Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M *et al.* Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. Lancet Neurol 2008;7(12):1091-8.

[3] Lorance NR, Davis RL, Lam C, Szperka C, Zhou L, Ahmad S *et al.* Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66(1):11-8.

[4] Olney JW, Newcomer JW, Farber NB. NMDA receptor hypofunction model of schizophrenia. J Psychiatr Res 1999;33(6):523-33.

[5] Coyle JT. Glutamate and schizophrenia: beyond the dopamine hypothesis. Cell Mol Neurobiol 2006;26(4–6):365-84.

[6] McAllen KJ, Schwartz DR. Adverse drug reactions resulting in hyperthermia in the intensive care unit. Crit Care Med 2010;38 (6 Suppl):S244-252.

Karim Sacré[1,a], Olivier Lidove[1,a], Noémie Chanson[1], Jean Laganier[1], Marie Vidailhet[2], Michel Lejoyeux[3], Thomas Papo[1]

[1]Paris-7 University, Paris-Diderot University, Bichat Hospital, Department of Internal Medicine, Paris, France
[2]Pierre et Marie Curie University, Salpêtrière Hospital, Federation of Neurology, CRICM UPMC/Inserm UMR-S975 CNRS UMR7225, Paris, France
[3]Paris-Diderot University, Bichat Hospital, Department of Psychiatry, Paris, France

Correspondence: **Olivier Lidove**, Bichat-Claude-Bernard Hospital, Department of Internal Medicine, 46, rue Henri-Huchard, 75877 Paris cedex 18, France.
[a]KS and OL contributed equally to this work.
olivier.lidove@bch.aphp.fr

Received 10 January 2011
Accepted 2 May 2011
Available online 14 July 2011

doi: 10.1016/j.lpm.2011.05.010