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CASE REPORT

Anesthetic Management of Patients with Anti-N-methyl-D-aspartate Receptor Encephalitis: A Report of Two Cases

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ANTI-N-METHYL-D-ASPARTATE (NMDA) receptor encephalitis is a newly recognized autoimmune disease. It is predominantly described in young women with a series of symptoms, including personality change, memory loss, seizures, involuntary movements, autonomic dysfunction *et al*.[1] It is commonly associated with mature ovarian teratomas.[2] Since its first denomination by Dalmau *et al*,[1] many scientific publications have emerged on anti-NMDA receptor encephalitis, but only a few focused on the anesthetic management of patients with this disease.[3-5] Herein we reported two cases with anti-NMDA receptor encephalitis in association with ovarian teratoma and discussed the anesthetic management and the outcomes of these patients.

CASE DESCRIPTION

Case 1

A 20-year-old woman (157 cm, 51 kg) was admitted to the neurologic ward because of intermittent headache and dizziness, followed with convulsion and visual hallucination over the last two weeks. Previous history revealed a left ovarian teratoma, which was diagnosed one and a half years ago. During the following week after admission, she manifested agitation, orofacial dyskinesias, incoherent speech and involuntary movements of the upper extremities. Generalized tonic-clonic seizures with transient loss of consciousness were also observed. Her physical examination showed normal temperature without focal neurologic deficits or meningeal irritation signs. The score of mini-mental state examination (MMSE) was 26. Results of brain magnetic resonance imaging (MRI) were unremarkable. Electroencephalography (EEG) revealed diffuse slowing wave. She was treated with valproate sodium, olanzapine and midazolam. A diagnosis of anti-NMDA receptor encephalitis was suspected and later confirmed by the positive test results of anti-NMDA receptor antibody in both the cerebral spinal fluid (CSF) and the serum. On the 11th day of admission, she was scheduled for a laparoscopic oophorocystectomy under general anesthesia.

The patient arrived at the operating room with intravenous infusion of midazolam (4 mg/h). Intraoperative monitoring included electrocardiography, invasive blood pressure, capnography, pulseoximetry, and bispec-

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tral index. Total intravenous anesthesia was induced with midazolam (0.04 mg/kg), propofol (2 mg/kg), sufentanil (0.2 μg/kg) and rocuronium (0.8 mg/kg), and maintained with propofol (100-150 mg/h), remifentanil (effect-site target controlled infusion at 1-1.5 ng/ml) and midazolam (4 mg/h). The bispectral index was maintained between 40 and 60 during surgery. The tumor (left ovary mature cystic teratoma, 3.6 cm×2.3 cm) was resected uneventfully within 1 hour. She was transferred to the intensive care unit with endotracheal intubation and was extubated on the next day, but her psychiatric symptoms persisted. She was treated with valproate sodium and glucocorticoids after surgery. The patient was discharged on the 11th day after surgery. At 3 months after surgery, she still had insomnia, memory disorders, and occasional episodes of agitation. At 6 months and 1 year after surgery, her MMSE score had recovered to 30. She had no psychotic symptoms and had returned to normal daily life.

Case 2

A 22-year-old woman (168 cm, 70 kg) was admitted for surgery because of the left ovarian cyst. She was noticed with behavioral change several days ago before hospital admission. In the afternoon of the admission day, her psychiatric symptoms (agitation, uncontrolled emotion and short-term memory disorders) appeared again. The cerebral MRI showed normal results. EEG examination was not performed. After consulting a psychiatrist, she was treated with valproate, olanzapine and oxazepam in order to relieve her symptoms. Then she was suspected anti-NMDA receptor encephalitis and later confirmed by detection of anti-NMDA receptor antibodies both in the CSF and the serum. On the third day after admission, she was scheduled for open abdominal left oophorectomy under general anesthesia.

On arrival to the operating room, the patient was calm and conscious, and could answer questions and follow instructions. Intraoperative monitoring was the same as the case 1. General anesthesia was induced with midazolam (2 mg), propofol (0.5 mg/kg), sufentanil (0.1 μg/kg) and rocuronium (0.6 mg/kg), and maintained with remifentanil (effect-site target controlled infusion at 2-3 ng/ml), propofol (150-200 mg/h) and dexmedetomidine (0.5 μg/kg loading dose in 10 minutes followed by 0.2 μg/kg·h infusion). The bispectral index was maintained between 40 and 60 during the surgery, and the surgery lasted 1 hour and 55 minutes. The resected left ovary tumor was confirmed as immature cystic teratoma with a diameter of about 17 cm. She was transferred to the intensive care unit with endotracheal intubation and sedated with dexmedetomidine and midazolam until the 7th day after surgery because of severe agitation. Other postoperative treatments included intravenous administration of immunoglobulin, corticosteroids and antiepileptics. She regained consciousness and was able to follow simple instructions after extubation, but psychiatric symptoms occurred intermittently. She was transferred to general ward on the 8th day after surgery and discharged to home the next day with continued treatment of corticosteroids and antiepileptics although post-operative serum test of anti-NMDA receptor antibody showed negative result. At 3-month follow-up, she complained of sleep disturbance and memory disorders with a MMSE score of 30 without obvious psychotic symptoms.

DISCUSSION

Anti-NMDA receptor encephalitis has been diagnosed in patients of all ages, but more frequently in young adults and children with or without teratoma.[2] It is supposed that anti-NMDA receptor antibodies deactivate the surface NMDA receptors by binding with them and causing internalization. The main resulting effects are altered synaptic transmission and synaptic plasticity, which may cause psychotic symptoms as well as learning and memory dysfunction. However, the precise mechanism remains unclear.

Anti-NMDA receptor encephalitis should be suspected in an individual (especially a young adult or a teenager) with ovarian teratoma, when he/she developed a rapid change of behavior or a new-onset episode of psychosis. Clinical manifestations may include psychiatric symptoms, abnormal movements (mostly orofacial and limb dyskinesias), seizures, hypoventilation, or variable signs of autonomic instability.[6] Diagnosis can be confirmed with positive anti-NMDA receptor antibodies detected in the serum and/or the CSF. In approximately 15% of patients, antibodies can only be detected in the CSF. During the acute phase, most patients have diffuse slowing or occasionally epileptiform abnormalities on surface EEG with normal or atypical brain MRI. Some neurologists believe that continuous EEG monitoring may be helpful in making the diagnosis and even in predicting the course of the disease. In our series, the cerebral MRI of the two cases was normal, and the EEG of case 1 showed a diffuse slowing wave. Once the diagnosis is confirmed, treatment should begin promptly. For patients with a detectable tumor, tumor resection should be performed because that will expedite improvement and decrease symptom recurrence.[1,7] First-line immunotherapy includes intravenous

methylprednisolone, immunoglobulin G and/or plasmapheresis. Second-line immunotherapy like rituximab or cyclophosphamide should be considered if no improvement is noted after 10 days of first-line treatment, especially for those without detectable tumors.

Anesthetic management of patients with anti-NMDA receptor encephalitis remains challenging for anesthesiologists. First, these patients usually have psychotic symptoms and require treatment of anticonvulsants, antipsychotics or sedatives. The effects of these preoperative medications must be considered since they may potentiate the effects of anesthetics. Second, many anesthetics with known NMDA receptor effects (such as ketamine, nitrous oxide, xenon, methadone, dextromethorphan and volatile anesthetics) should be avoided during anesthesia.[8] This may interfere with the conduct of anesthesia.

In our cases, we avoided the use of any anesthetics with known NMDA receptor effects despite of the facts that inhalational anesthetics were used and well tolerated in some case reports.[9] It is reported that propofol, of which the primary effect is produced by enhancing GABAergic transmission, can also act on NMDA receptors and may produce potential side effect in patients with anti-NMDA receptor encephalitis.[3] In order to decrease the dose of propofol during anesthesia, we co-administered benzodiazepines, opiates, and dexmedetomidine (for the second case) under the guidance of bispectral index monitoring. Dexmedetomidine is a selective α2 adrenoceptor agonist with the effects of sedation, hypnosis and antianxiety. Studies showed that comparing with benzodiazepine, dexmedetomidine sedation might decrease the occurrence of delirium and shorten the duration of mechanical ventilation.[10] And dexmedetomidine may be effective in delirious patients with ongoing physiological instability. However, whether dexmedetomidine can relieve the psychiatric symptoms in patients with anti-NMDA receptor encephalitis remains unknown.

Although rapid psychiatric improvement has been reported, but usually recovery is a slow process and may require 3 to 4 months of hospitalization followed by several months of rehabilitation, especially in patients with undetectable or recurrent tumors. A study showed that the detection of teratoma was a good prognostic factor for anti-NMDA receptor encephalitis. The time interval from symptom onset until initiation of treatment and the length of stay in ICU were also regarded as significant prognostic factors. In our patients, psychiatric symptoms persisted during hospitalization after surgery. However, at 3- or 6-month follow-up, their MMSE score had recovered to 30 and one of them had resumed a normal life.

Herein, we reported the successful anesthetic management of two cases with anti-NMDA receptor encephalitis. Similar to most of the previous case reports, we avoided using the anesthetics with known NMDA receptor effect. Considering the potential antipsychotic effect, we applied dexmedetomidine in one patient and didn't observe any side effect, however, the benefit of dexmedetomidine for these patients still need further research.

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