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CASE REPORT

Anaesthesia for a patient with paraneoplastic limbic encephalitis with ovarian teratoma: relationship to anti-*N*-methyl-D-aspartate receptor antibodies

H. Kawano,[1] E. Hamaguchi,[2] S. Kawahito,[3] Y. M. Tsutsumi,[3] K. Tanaka,[4] H. Kitahata[5] and S. Oshita[6]

1 Chief Anesthesiologist, 2 Staff Anesthesiologist, Department of Anesthesiology and Clinical Research, National Hospital Organization Zentsuji Hospital, Zentsuji, Japan
3 Assistant Professor, 4 Associate Professor, Department of Anesthesiology, 5 Professor and Chairman, Department of Dental Anesthesiology, 6 Professor and Chairman, Department of Anesthesiology, Institute of Health Biosciences, University of Tokushima Graduate School, Tokushima, Japan

Summary

Paraneoplastic limbic encephalitis associated with ovarian teratoma has recently been related to the development of antibodies to specific heteromers of the *N*-methyl-D-aspartate receptor and exhibits various manifestations including psychiatric symptoms, hypoventilation, seizures and derangement of autonomic nervous system function. Although recovery can sometimes occur spontaneously, early tumour resection with immunotherapy facilitates earlier recovery. Herein, we describe anaesthetic management of a 20-year-old woman who developed general convulsions and decreased level of consciousness, whom we suspected of having paraneoplastic limbic encephalitis and was scheduled for left ovarian tumour resection. Anaesthetic management was successful with no complications but the case acts as focus of discussion for the potential interaction of *N*-methyl-D-aspartate receptors and anaesthetic sensitivity.

Correspondence to: Hiroaki Kawano
Email: hirkawa@jun.ncvc.go.jp
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A unique limbic encephalitis that predominantly affects young women and results in a characteristic syndrome that presents with prominent psychiatric symptoms, central hypoventilation, seizures, involuntary movements and autonomic dysfunction has been noted [1, 2]. Recently, a causal relationship between such encephalitis and ovarian teratoma has been proposed [3–5], and in patients with this disorder, antibodies binding to NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR) have been identified [1]. This disorder is, therefore, called anti-NMDAR encephalitis, and tumour resection along with aggressive immunotherapy can facilitate earlier functional recovery [3, 5].

Although cases of anti-NMDAR encephalitis have been previously reported, we could not find any study of anaesthetic management of patients with this disorder. In this report, we describe a patient with paraneoplastic limbic encephalitis (PLE) with ovarian teratoma and discuss the anaesthetic management of patients with anti-NMDAR antibodies.

Case report

A 20-year-old woman (155 cm, 57 kg) with no remarkable medical history developed low-grade fever that lasted for a few days and was then admitted to another hospital with high-grade fever. Meningitis was initially suspected and appropriate antibiotic treatment started, but 3 days later, she suffered general convulsions and decreased level of consciousness. The following day, she developed diplopia, dysarthria, upper limb tremor and lower extremity weakness. Consequently, she was transferred to our hospital for further evaluation.

On admission, she was lethargic with Glasgow Coma Score of 13. Magnetic resonance imaging of the brain

was normal. Pelvic computed tomography revealed a calcified lesion in the left adnexa (41 × 23 mm). Cerebrospinal fluid (CSF) analysis showed the following: cells, $330 \times 10^3.ml^{-1}$ (normal values $0–5 \times 10^3.ml^{-1}$); lymphocyte 57% (normal values 49–73%); neutrophil 42% (normal values 0–2%); histiocyte 1.2% (normal values 0–2%); glucose, 2.6 $mmol.l^{-1}$ (normal values 2.8-4.4 $mmol.l^{-1}$); protein, 1.6 $g.l^{-1}$ (normal values 0.1–0.4 $g.l^{-1}$); and positive CSF oligoclonal bands. Tests for paraneoplastic antibodies including Hu, Yo, Ri, amphiphysin, Ma1 and Ma2 were all negative. She was suspected of having anti-NMDAR encephalitis, and intravenous methylprednisolone was initiated at a dose of 1 $g.day^{-1}$ for 3 days. On day 7, she developed high-grade fever, and ceftriaxone and arbekacin were administered intravenously. Thereafter, her level of consciousness and other symptoms gradually improved; therefore, additional interventions, including plasma exchange, were not initiated.

On day 24, she was scheduled for left ovarian tumour resection. Pre-anaesthetic medication was not administered. On arrival in the operating room, her blood pressure was 117/69 mmHg, heart rate was 79 $beats.min^{-1}$ and arterial oxygen saturation was 99% breathing room air. General anaesthesia was induced with intravenous remifentanil ($0.5\ \mu g.kg^{-1}.min^{-1}$), thiamylal (150 mg) and rocuronium (30 mg), and was maintained with oxygen ($1\ l.min^{-1}$), air ($2\ l.min^{-1}$), sevoflurane (1.0%) and remifentanil ($0.3\ \mu g.kg^{-1}.min^{-1}$). Neuromuscular blockade was maintained with intermittent rocuronium and monitored with train-of-four responses at the adductor pollicis muscle. The patient was monitored with electrocardiography, non-invasive blood pressure, capnography, pulse oximetry and bispectral index (BIS). The patient's intra-operative systolic blood pressure was 70–100 mmHg, heart rate was 55–65 $beats.min^{-1}$ and BIS was 35–45. Surgery was completed without complications, and the patient emerged from anaesthesia uneventfully. We reversed neuromuscular blockade and extubated the trachea when the patient regained consciousness and was able to follow easy commands. Duration of surgery and anaesthesia were 1 h:59 min and 2 h:51 min, respectively. Intra-operative total blood loss was just 10 ml, urine output was 630 ml and total infusion volume was 1000 ml. Her physical examination remained unchanged pre-operatively and no postoperative complications were evident. The tumour was solid and included hair and cartilage. The pathological diagnosis was mature teratoma.

After surgery, IgM and IgG auto-antibodies against glutamate receptor (GluR) ε2 and δ2 were identified in the samples of serum and CSF obtained on admission. The postoperative course was uneventful, and the patient was discharged on the 42nd postoperative day. At the 1-month follow-up, she was symptom-free and without any postoperative complications.

Discussion

Paraneoplastic limbic encephalitis is a rare neurological syndrome characterised by short-term memory impairment, seizures and various psychiatric disturbances due to a misdirected tumour-activated antibody response that damages host neural tissue. It has been commonly associated with small cell lung cancer, germ cell tumours of the testis and breast cancer, but rarely with ovarian teratoma [6]. Recently a causal relationship between such encephalitis and ovarian teratoma has been proposed [3–5], and in patients with this disorder antibodies binding to NR1/NR2 heteromers of the NMDAR have been identified [1]. This disorder is, therefore, called anti-NMDAR encephalitis, and it represents a new category of severe, potentially lethal, but treatment-responsive encephalitis [4]. It usually develops in young women, who typically present with the above features and decreased level of consciousness that often results in a requirement for ventilatory support.

Treatment of anti-NMDAR encephalitis includes immunotherapy and/or tumour resection. Immunotherapy is principally necessary and effective because autoimmune responses are responsible for the pathogenic mechanism. Immunotherapy includes corticosteroids, intravenous immunoglobulin, plasma exchange and cyclophosphamide; of these, corticosteroids and intravenous immunoglobulin are the most frequently used agents. Tumours occur in approximately 59% of all cases of anti-NMDAR encephalitis [1], and it has been suggested that prompt resection of tumour expedites recovery [5]. Although recovery also occurs without tumour resection, the severity and extended duration of symptoms support tumour resection. However, patients with this disorder usually require ventilatory support and intensive care for seizures and autonomic instability, which can delay tumour resection. Management in the intensive care unit (ICU) is currently limited to a relatively non-specific, symptom-based approach. Most patients admitted to ICU for mechanical ventilation receive sedatives such as propofol and analgesics such as

opioids, but complications related to these anaesthetics have not been reported.

Although the results of the tests for antibodies to NMDARs remained unknown, we strongly suspected this patient of having anti-NMDAR antibodies from the clinical features and eventual outcome. It is also unclear whether our patient had antibodies to NR1/NR2 heteromers of the NMDAR. However, auto-antibodies against GluRε2 and GluRδ2 were detected. One subtype of ionotropic glutamate receptors, NMDARs, is formed by at least two families of subunits, i.e. ε1–4 (NR2A-D) and δ1 (NR1). Thus, the GluRε2 antibody and the NMDAR NR1/NR2 heteromer antibody are both antibodies to NMDA type glutamate receptors. In Japan, young women with acute non-herpetic limbic encephalitis have been studied as acute juvenile female non-herpetic encephalitis (AJFNHE). Although antibodies against GluRε2 have been frequently found in the sera and CSF of patients with AJFNHE [2], they have been also detected in patients with Rasmussen's encephalitis and epilepsia partialis continua [7]. Of these diagnoses, AJFNHE fits well with the presentation of our patient. This clinical picture of AJFNHE closely resembles that of anti-NMDAR encephalitis, and Iizuka et al. reported that anti-NMDAR encephalitis and AJFNHE are the same disorder [3].

The pathogenesis of anti-NMDAR encephalitis remains unknown, but recent studies indicate that NMDAR antagonists can exacerbate psychiatric schizophrenia-like symptoms and induce schizophrenic behaviour in healthy individuals, whereas agents that enhance NMDAR function ameliorate such symptoms [8–10]. Thus, NMDAR antibodies may cause inhibition, rather than activation, of the NMDAR, thereby contributing to the development of schizophrenia-like symptoms. Furthermore, antibodies of patients with anti-NMDAR encephalitis cause a specific and reversible loss of NMDARs [11]. Therefore, the psychosis and cognitive and behavioural deficits in patients with anti-NMDAR encephalitis may result from NMDAR hypofunction.

Recent molecular strategies have demonstrated that general anaesthetics act on one or more superfamilies of ligand-gated ion channels that include γ-aminobutyric acid type A ($GABA_A$), glycine, nicotinic acetylcholine and 5-hydroxytryptamine 3 receptors, along with the α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)-, kainate- and NMDA-sensitive subtypes of ionotropic glutamate receptors [12, 13]. Although effects of general anaesthetics on the $GABA_A$ receptors have received the most attention, various electrophysiological studies suggest that ketamine and nitrous oxide minimally affect $GABA_A$ receptors but inhibit NMDARs [14–16]. Anis et al. reported that ketamine acts as a non-competitive NMDAR antagonist to inhibit the influx of Na^+ and Ca^{2+} through these channels [17]. Similar to other NMDA antagonists, nitrous oxide also inhibits the ionic current induced by NMDA [14, 15].

Volatile anaesthetics exhibit a wide range of NMDAR inhibitory potencies and immobilising activities, but they act on various channels such as those mentioned above and show little selectivity for NMDARs. By contrast, propofol is considered to be less likely to produce anaesthetic effects through an NMDAR-dependent mechanism. This is because a large number of studies have shown that propofol anaesthetises via enhancing GABA-ergic transmission [18, 19]. Therefore, propofol may be a more appropriate anaesthetic for such patients. On the other hand, volatile anaesthetics may suppress the immune response more potently compared with propofol [20, 21] and this may be a different, favourable effect in this condition.

If antibodies attenuate receptor function in a manner similar to anaesthetics, then we might predict that patients are more susceptible to anaesthetic effects. However, in our patient, the BIS values ranged from 35 to 45 at 1.0% sevoflurane concentration during surgery, generally regarded as adequate [22]. Therefore, we conclude that the sensitivity to volatile anaesthetics on the patients with anti-NMDAR encephalitis is not attenuated. This may be because volatile agents act by a non-NMDAR receptor mechanism.

However, sensitivity may be increased to agents that inhibit NMDARs such as ketamine or nitrous oxide. It would be interesting to test this notion, perhaps in animal studies using knockouts for NMDARs or administration of antibodies to these receptors.

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