CASE REPORT

Anaesthetic management of a patient with a unique combination of anti-N-methyl-D-aspartate receptor encephalitis and stiff-person syndrome

Mohammad Hadi Gharedaghi,[1] Arjang Khorasani,[2] Nebojsa Nick Knezevic,[2] Farzad Ebrahimi[2]

[1]Department of Anesthesiology, Advocate Illinois Masonic Medical Center, Chicago, Illinois, USA
[2]Department of Anesthesiology, University of Illinois at Chicago College of Medicine, Chicago, Illinois, USA

Correspondence to
Professor Farzad Ebrahimi, ebrahimi@uic.edu

Accepted 23 March 2018

SUMMARY

Stiff-person syndrome (SPS) and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis are rare paraneoplastic syndromes caused by antibodies that target the central nervous system. Here, we describe a 26-year-old woman who presented with psychosis, amnesia, rigidity and fever. After extensive diagnostic and laboratory workup, she was diagnosed with an ovarian teratoma which was causing the symptoms of anti-NMDAR encephalitis and SPS. The patient was successfully treated with laparoscopic removal of the ovarian tumour under general anaesthesia. She was placed on immunosuppressant medications preoperatively and postoperatively, and her symptoms gradually resolved. Although there are case reports regarding the anaesthetic management of SPS and anti-NMDAR encephalitis, our study is the first report of a patient afflicted with both conditions.

BACKGROUND

Stiff-person syndrome (SPS) is an autoimmune disease caused by antibodies against the γ-amino butyric acid (GABA) synthesising enzyme, glutamic acid decarboxylase 65 (GAD65). Patients with this condition experience episodes of muscle rigidity and haemodynamic instability.[1] Intubation and neuraxial anaesthesia can be challenging in patients with SPS because of their abnormal posture. Moreover, many of these patients use antispasmodics which can increase the risk of postoperative muscle weakness.[2]

Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis is a paraneoplastic syndrome accompanied by changes in behaviour, amnesia, psychosis, seizures, autonomic derangements and central hypoventilation. It results from immunologically mediated inhibition of NMDARs by antibodies formed against the neurons of amygdala, hippocampus and insular cortex. Therefore, it has been suggested that the use of NMDA inhibitors such as nitrous oxide and ketamine might aggravate the symptoms in patients with this condition.[3 4]

Here, we present the first reported case of a patient afflicted with both anti-NMDAR encephalitis and SPS. We also discuss the unanticipated challenges that anesthesiologists might face when taking care of a patient suffering from both conditions concurrently.

CASE PRESENTATION

A 26-year-old Vietnamese-American woman was admitted to our hospital with a 2-day history of headache, bizarre behaviour, paranoia and delusion. On admission, the patient was alert and oriented to person and time but not to place. Her family denied any history of medical or psychological disorders. A psychiatrist was consulted on admission. Head CT scan, complete blood count, basic metabolic panel and urine toxicology tests were performed in the emergency department, and the findings were unremarkable. Psychotic mania was considered as the possible diagnosis, and hence, the patient was started on haloperidol (5 mg, orally, every 6 hour), lithium carbonate (150 mg, orally, every 8 hour), lorazepam (1 mg, orally, every 6 hour) and quetiapine (50 mg, orally, every 12 hours).

On postadmission day (PAD) 2, the patient became febrile (temperature of 38°C) and tachycardic (heart rate of 142 beats per min), and her blood pressure increased to 164/118 mm Hg. Since the symptoms did not improve with antipsychotic medication and the vital signs deteriorated following the treatment, a neurologist was consulted. Urinalysis, serum thyroid-stimulating hormone, serum antinuclear antibody and serum creatine phosphokinase (CPK) levels were requested. All laboratory findings were within normal limits, except for the serum CPK level, which was elevated (1114 U/L). Neuroleptic malignant syndrome was suspected based on the elevated serum CPK level. Consequently, all antipsychotic medications were stopped and treatment with dantrolene (25 mg, orally, every 6 hour for 2 days) was initiated. Despite treatment with dantrolene, the CPK level continued to increase.

Over the following 5 days, the condition of the patient continued to deteriorate. Her level of consciousness decreased, she was unable to talk and she developed dystonic movements, strange facial gestures, rigidity of the upper and lower extremities, axial spasticity and dysphagia (figure 1A,B). Brain MRI showed small areas of signal hyperintensity in the frontal region on T2 fluid attenuation inversion recovery images (figure 2). Electroencephalography (EEG) was inconclusive due to the patient's movement and lack of cooperation. Lyme disease serology was negative. A cerebrospinal fluid (CSF) virology panel was requested to rule out encephalitis due to viruses such as herpes simplex virus,

To cite: Gharedaghi MH, Khorasani A, Knezevic NN, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-223261

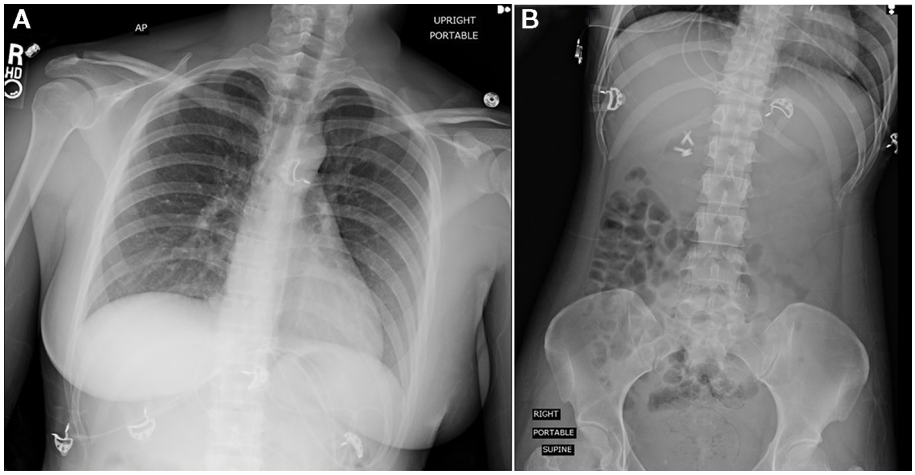

Figure 1 (A) Chest and (B) abdominal X-ray findings showing lateral curvature of the vertebral column due to axial muscle spasticity.

HIV and West Nile virus. The CSF virology was also negative. Analysis of CSF showed a mild increase in white cell count (clear colour, glucose 61 mg/dL, protein 20 mg/dL, polymorphonuclear cells $3.4x10^7$ cells/L, red blood cells $2x10^6$ cells/L, lymphocytes $9.4x10^7$ cells/L, monocytes $6x10^6$ cells/L). The patient was placed on acyclovir (550 mg, intravenously, every 8 hour), ceftriaxone (2 g, intravenously, every 12 hours) and vancomycin (1250 mg, intravenously, every 8 hour) for 3 days. Since the patient did not respond to these treatments and the initial CSF culture results were negative, autoimmune encephalitis was suspected. The patient was empirically placed on methylprednisolone (1000 mg, intravenously, daily for 5 days) and a paraneoplastic antibody panel test was requested. The patient was positive for serum anti-NMDAR antibodies (titre of 1:320) which suggested a diagnosis of anti-NMDAR encephalitis. Transvaginal and pelvic ultrasonography revealed an 11 cm right ovarian teratoma, thus confirming the diagnosis of paraneoplastic anti-NMDAR encephalitis (figure 3). The patient was started on intravenous immunoglobulin (IVIG; 1 g/kg for 5 days) treatment. Since the treatment of choice for anti-NMDAR encephalitis is resection of the underlying tumour, the patient was scheduled for laparoscopic removal of the ovarian teratoma.

On PAD 15, the patient was transferred to the preoperative area, with stable vital signs (blood pressure of 140/85 mm Hg, heart rate of 92 beats per minute, respiratory rate of 16 breaths per minute, pulse oximetry oxygen saturation of 99% in room air, temperature of 37°C). She was not responding to any questions and exhibited drooling secondary to dysphagia. She was unable to lie on her back because of muscle rigidity and axial dystonia. She maintained a sitting position, and her head, neck and upper body were turned to the right side. The patient had a functional preexisting 20-gauge intravenous catheter. Preoperative benzodiazepine treatment was avoided since the patient was disoriented. Because of her lack of cooperation, unusual posture, dysphagia, drooling and high risk of aspiration, neuraxial anaesthesia, awake fiberoptic intubation and inhalational induction appeared to be unsuitable choices. The patient was transferred to the operating room, placed on standard American Society of Anesthesiologists monitors and preoxygenated with a face mask. Anaesthesia was induced with lidocaine (1 mg/kg, intravenously) and propofol (2 mg/kg, intravenously), following which the muscle rigidity gradually resolved and the patient was positioned supine on the surgical table. A soft suction catheter was used to

Figure 2 Brain MRI showing two small areas of hyperintensity in the left frontal subcortical region (arrows).

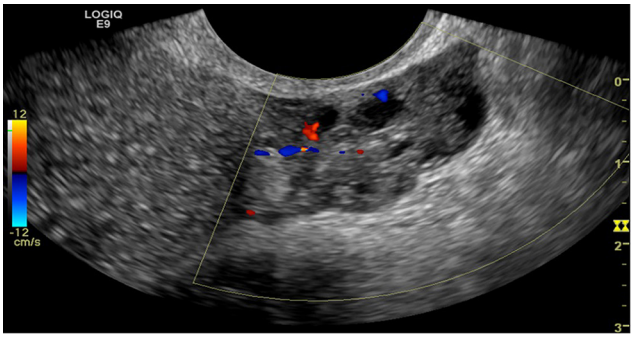

Figure 3 Transvaginal pelvic ultrasonography findings showing an 11 cm right adnexal tumour with complex mixed echogenicity and regions with cystic appearance.

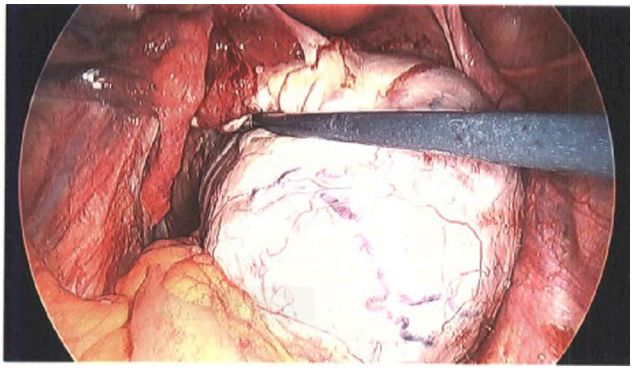

Figure 4 Laparoscopic view of an 11 cm right ovarian teratoma.

suction out the existing saliva in the oral cavity, pharynx and oesophagus. Ventilation was easily achieved with a face mask. Fentanyl (1 µg/kg, intravenously) and rocuronium (0.6 mg/kg, intravenously) were administered for pain control and paralysis, respectively. Endotracheal intubation was performed using video laryngoscopy. Anaesthesia was maintained with sevoflurane (one minimum alveolar concentration (MAC)), oxygen (1 L/min) and air (1 L/min). A radial arterial line was placed for continuous blood-pressure monitoring. The ovarian teratoma was removed (figure 4). At the end of surgery, the train of four was above 0.9, and muscle paralysis was reversed with neostigmine (0.05 mg/kg, intravenously) and glycopyrrolate (0.01 mg/kg, intravenously). The patient emerged from anaesthesia and was extubated uneventfully. Postoperative pain was controlled with ketorolac (30 mg, intravenously, every 6 hour), morphine (1 mg, intravenously, every 2 hour) and acetaminophen–hydrocodone (325–5 mg, orally, every 6 hour).

OUTCOME AND FOLLOW-UP

On postoperative day (POD) 4, the dysphagia resolved and the patient became alert and oriented. However, she continued to exhibit spasticity and axial dystonia. Therefore, a second round of treatment with methylprednisolone (500 mg, intravenously, every 12 hours for 5 days) was initiated. Since SPS was considered as an overlapping pathology, treatment with baclofen (20 mg, orally, every 12 hours for 4 days) was also started. Additionally, the patient was tested for serum anti-GAD65 antibodies, which revealed positive results (concentration of 129.6 IU/mL). Following treatment with baclofen, the spasticity and axial dystonia significantly improved. The patient was transferred to a rehabilitation facility, and physical and occupational therapy were initiated. She was eventually discharged on POD 24 with a final diagnosis of concurrent anti-NMDAR encephalitis and SPS.

DISCUSSION

The NMDAR is composed of NR_1 and NR_2 subunits. Antibodies targeted against the extracellular portion of the NR_1 subunit are responsible for the majority of cases of anti-NMDAR encephalitis. There is evidence indicating that the severity of symptoms is directly correlated with the serum or CSF concentration of anti-NMDAR antibodies.[5] Although many patients with anti-NMDAR encephalitis have areas of hyperintensity on brain MRIs, this finding is non-specific and can be seen in many other central nervous system disorders.[6] Most patients with anti-NMDAR encephalitis have abnormal EEG findings, and around 30% of them will demonstrate extreme delta brush waves on EEG which is very specific for this disease.[7] On the other hand, SPS is caused by antibodies produced against proteins of the inhibitory GABAergic pathway in the brain, most notably GAD65.[8] This results in continuous firing of the downstream spinal motor neurons, which can cause muscle rigidity.[9] Although an electromyography study was not done in our patient, it typically shows continuous muscle activity in patients with SPS.[10] Antibodies against NMDAR and GAD65 are produced as a result of cross-reactivity between tumour antigens and the central nervous system.[5 8]

Preoperative considerations in patients with anti-NMDAR encephalitis and SPS

Because of the altered mental status and lack of cooperation of patients with anti-NMDAR encephalitis, optimal preoperative airway assessment is not feasible in these patients, and therefore, it is prudent to be prepared for difficult airway management in these settings. Precautionary measures such as video laryngoscopy, laryngeal mask airway and availability of an otolaryngologist for possible surgical airway placement should be considered for these cases. Although preoperative use of benzodiazepines might provide some degrees of muscle relaxation and reduced agitation, it can potentially aggravate the altered mental status, prolong the effects of narcotics and increase the risk of postoperative respiratory failure.[11 12] For this reason, benzodiazepines should be used judiciously in patients who suffer from anti-NMDAR encephalitis and SPS.

Preoperative placement of an arterial line allows for beat to beat blood pressure monitoring during induction of anaesthesia. In addition, close monitoring of the haemodynamics and maintaining the blood pressure within normal limits is of utmost importance in patients with encephalitis who might have increased intracranial pressures. However, due to the muscle rigidity, altered mental status and agitation of patients with anti-NMDAR encephalitis and SPS, this might not be feasible and placement of an arterial line might have to be done after the induction of anaesthesia. Of note, we did not observe any evidence of increased intracranial pressure on brain MRI of our patient. Considering this fact, we decided to place an arterial line after induction of anaesthesia.

Patients suffering from SPS and anti-NMDAR encephalitis have a high risk of aspiration following induction of anaesthesia. This is because of the presence of an intra-abdominal tumour, dysphagia, drooling and altered mental status. From a practical standpoint, oral non-particulate antacids cannot be readily used due to the presence of dysphagia and altered mental status in these patients. However, intravenous H_2 blockers can potentially be utilised to minimise the risk of aspiration pneumonia in this set of patients.[13] Although metoclopramide can reduce the risk of aspiration pneumonia, it should be avoided in patients who already suffer from muscle rigidity. This is due to the fact that metoclopramide possesses antidopaminergic properties and can potentially lead to dystonic muscle contractions.[14] Finally, preoperative use of antisialagogues, such as glycopyrrolate, can be beneficial in patients who experience drooling due to dysphagia secondary to SPS and anti-NMDAR encephalitis.

Considerations for induction of anaesthesia in patients with anti-NMDAR encephalitis and SPS

Considering the unusual posture of patients with SPS, airway management during induction of anaesthesia can be challenging in these patients. Awake fiberoptic intubation has been considered as a plausible option for endotracheal intubation in such patients.[15] However, this option is not feasible when SPS is accompanied by disorders such as anti-NMDAR encephalitis that

result in decreased consciousness and/or lack of cooperation. Use of induction agents that maintain spontaneous breathing, such as ketamine or inhalational agents, might seem appealing.[16] However, ketamine, nitrous oxide and inhalational agents (at concentrations >1 MAC) possess NMDAR antagonistic effects and can worsen the symptoms of anti-NMDAR encephalitis.[17 18]

Because of their prolonged respiratory depressant effects and possibility of muscle rigidity at high doses, narcotics are not considered ideal for induction of anaesthesia in patients with SPS.[19] Propofol, another intravenous anaesthetic agent with respiratory depressant effects, seems to be a promising choice in patients with SPS because of its short-lived effects and its ability to counteract the inhibition of GABA receptors and muscle rigidity observed in these patients.[20] Propofol has been extensively used as an anaesthetic agent in patients with anti-NMDAR encephalitis without significant complications. To date, there have only been two case reports of severe hypotension in patients with anti-NMDAR encephalitis following induction of anaesthesia with propofol. The exact mechanism of this process is not clear. Moreover, neither of these studies reported any haemodynamic instability following induction of anaesthesia with propofol during subsequent surgeries in these patients.[21 22]

Considering the presence of an intra-abdominal tumour and dysphagia, our patient had a high risk of aspiration following induction. Therefore, one could argue that a modified rapid sequence intubation using 1–1.2 mg/kg of rocuronium should have been done during induction. Despite this fact, we decided to limit the dose of rocuronium to 0.6 mg/kg to minimise the risk of postextubation respiratory failure in our patient.

Considerations for maintenance of anaesthesia in patients with anti-NMDAR encephalitis and SPS

Although halogenated anaesthetic gases possess anti-NMDAR activity at high MAC, they are considered safe for maintenance of anaesthesia at low MAC in patients with anti-NMDAR encephalitis.[4 18 23] This might be explained by the presence of amnesia and reduced pain perception in these patients.[24 25] Halogenated anaesthetic gases can potentiate the effect of antispasmodic medications in patients with SPS, which could lead to significant respiratory muscle weakness after surgery.[2] In the present case, since the diagnosis of SPS was made after surgery, our patient did not receive any antispasmodic medication preoperatively. This explains why she did not show any signs of residual muscle weakness after extubation despite the use of sevoflurane.

Total intravenous anaesthesia appears to be an alternative method for maintenance of anaesthesia in patients with SPS and anti-NMDAR encephalitis.[26] Propofol, remifentanil and sufentanil infusions have been used to maintain anaesthesia in patients with anti-NMDAR encephalitis without significant adverse effects.[27]

Although neuraxial anaesthesia has been successfully used in patients with anti-NMDAR encephalitis,[28] it can be challenging in patients with SPS. The spinal deformity and muscle rigidity in patients with SPS makes positioning difficult and can result in an unpredictable level of neuraxial blockade. Moreover, pain from needle placement and emotional stress might trigger muscle spasms in patients with SPS, which makes neuraxial anaesthesia less appealing.[2]

Considerations for emergence from anaesthesia in patients with anti-NMDAR encephalitis and SPS

Central hypoventilation is a significant clinical feature of anti-NMDAR encephalitis. The risk of central hypoventilation increases with an increase in anti-NMDA autoantibody concentrations and decreases with corticosteroid or IVIG treatment.[5 29] Patients suffering from anti-NMDAR encephalitis are prone to hypoventilation and respiratory compromise, and therefore, they should be monitored closely in the intensive care unit following surgery. In patients with SPS treated with antispasmodic medications, use of neuromuscular blockers might increase the risk of respiratory failure after endotracheal extubation.[2] Our patient did not show any respiratory muscle weakness at the end of surgery and was extubated without any complications. This might have been due to the fact that she had not received any antispasmodic medications and had received corticosteroid and IVIG treatment preoperatively.

In conclusion, previous case reports have demonstrated the anaesthetic challenges observed in patients with SPS or anti-NMDAR encephalitis.[2–4] In our report, we discussed a number of perioperative difficulties that anesthesiologists might encounter when taking care of patients afflicted simultaneously with both disorders.

Learning points

- Propofol appears to be a promising anaesthetic agent for patients with Stiff-person syndrome (SPS) and anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis.
- Total intravenous anaesthesia is safe for maintenance of anaesthesia in patients with SPS and anti-NMDAR encephalitis.
- Patients with SPS and anti-NMDAR encephalitis are at an increased risk of respiratory failure after endotracheal extubation.

Contributors AK and FE took care of the patient and wrote the manuscript. MHG and NNK contributed to the writing and reviewing of the manuscript.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Sidransky MA, Tran NV, Kaye AD. Anesthesia considerations in stiff person syndrome. *Middle East J Anaesthesiol* 2013;22:217–21.
2 Hylan K, Vu AD, Stammen K. Anesthetic considerations of stiff-person syndrome: a case report. *Aana J* 2016;84:181–7.
3 Pryzbylkowski PG, Dunkman WJ, Liu R, *et al*. Case report: Anti-N-methyl-D-aspartate receptor encephalitis and its anesthetic implications. *Anesth Analg* 2011;113:1188–91.
4 Kawano H, Hamaguchi E, Kawahito S, *et al*. Anaesthesia for a patient with paraneoplastic limbic encephalitis with ovarian teratoma: relationship to anti-N-methyl-D-aspartate receptor antibodies. *Anaesthesia* 2011;66:515–8.
5 Dalmau J, Gleichman AJ, Hughes EG, *et al*. Anti-NMDA-receptor encephalitis: case series and analysis of the effects of antibodies. *Lancet Neurol* 2008;7:1091–8.
6 Ternifi R, Cazals X, Desmidt T, *et al*. Ultrasound measurements of brain tissue pulsatility correlate with the volume of MRI white-matter hyperintensity. *J Cereb Blood Flow Metab* 2014;34:942–4.
7 Schmitt SE, Pargeon K, Frechette ES, *et al*. Extreme delta brush: a unique EEG pattern in adults with anti-NMDA receptor encephalitis. *Neurology* 2012;79:1094–100.
8 Levy LM, Dalakas MC, Floeter MK. The stiff-person syndrome: an autoimmune disorder affecting neurotransmission of gamma-aminobutyric acid. *Ann Intern Med* 1999;131:522–30.
9 Sharma CM, Pandey RK, Kumawat BL, *et al*. A unique combination of autoimmune limbic encephalitis, type 1 diabetes, and Stiff person syndrome associated with GAD-65 antibody. *Ann Indian Acad Neurol* 2016;19:146–9.
10 Hadavi S, Noyce AJ, Leslie RD, *et al*. Stiff person syndrome. *Pract Neurol* 2011;11:272–82.

11 Labroo RB, Paine MF, Thummel KE, *et al*. Fentanyl metabolism by human hepatic and intestinal cytochrome P450 3A4: implications for interindividual variability in disposition, efficacy, and drug interactions. *Drug Metab Dispos* 1997;25:1072–80.
12 Crevoisier C, Ziegler WH, Eckert M, *et al*. Relationship between plasma concentration and effect of midazolam after oral and intravenous administration. *Br J Clin Pharmacol* 1983;16(Suppl 1):51S–61.
13 Puig I, Calzado S, Suárez D, *et al*. Meta-analysis: comparative efficacy of H2-receptor antagonists and proton pump inhibitors for reducing aspiration risk during anaesthesia depending on the administration route and schedule. *Pharmacol Res* 2012;65:480–90.
14 Moos DD, Hansen DJ. Metoclopramide and extrapyramidal symptoms: a case report. *J Perianesth Nurs* 2008;23:292–9.
15 Cassavaugh JM, Oravitz TM. Multiple anesthetics for a patient with stiff-person syndrome. *J Clin Anesth* 2016;31:197–9.
16 Stuart MG, Neubert L, Green P. Anesthetic care of stiff person syndrome in the outpatient setting. *J Anesth Clin Res* 2013;2:5.
17 Lapébie FX, Kennel C, Magy L, *et al*. Potential side effect of propofol and sevoflurane for anesthesia of anti-NMDA-R encephalitis. *BMC Anesthesiol* 2014;14:5.
18 Solt K, Eger EI, Raines DE. Differential modulation of human N-methyl-D-aspartate receptors by structurally diverse general anesthetics. *Anesth Analg* 2006;102:1407–11.
19 Çoruh B, Tonelli MR, Park DR. Fentanyl-induced chest wall rigidity. *Chest* 2013;143:1145–6.
20 Hattan E, Angle MR, Chalk C. Unexpected benefit of propofol in stiff-person syndrome. *Neurology* 2008;70:1641–2.
21 Splinter WM, Eipe N. Anti-NMDA receptor antibodies encephalitis. *Paediatr Anaesth* 2009;19:911–3.
22 Dalmau J, Lancaster E, Martinez-Hernandez E, *et al*. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. *Lancet Neurol* 2011;10:63–74.
23 Ding L, Tan H, Li Z, *et al*. Case report: anaesthetic management of radical gastrectomy for gastric cancer associated with anti-N-methyl-D-aspartate receptor encephalitis. *BMC Anesthesiol* 2017;17:90.
24 Chaw SH, Foo LL, Chan L, *et al*. [Anesthesia in anti-N-methyl-d-aspartate receptor encephalitis – is general anesthesia a requisite? A case report]. *Rev Bras Anestesiol* 2017;67.
25 Broderick DK, Raines DE, Nanji KC. Total intravenous anesthesia using N-Methyl-D-Aspartate (NMDA) receptor-sparing drugs in a patient with Anti-NMDA receptor encephalitis. *A A Case Rep* 2014;2:83–5.
26 Liu H, Jian M, Liang F, *et al*. Anti-N-methyl-D-aspartate receptor encephalitis associated with an ovarian teratoma: two cases report and anesthesia considerations. *BMC Anesthesiol* 2015;15:150.
27 Qin X, Wang DX, Wu XM. Anesthetic management of a patient with stiff-person syndrome and thymoma: a case report. *Chin Med J* 2006;119:963–5.
28 Demma L, Norris S, Dolak J. Neuraxial anesthesia in a patient with anti-N-methyl-D-aspartate receptor encephalitis in pregnancy: management for cesarean delivery and oophorectomy. *Int J Obstet Anesth* 2017;31:104–7.
29 Gong YH, Zhang MZ, Zhang XH, *et al*. Potential effect of preoperative immunotherapy on anesthesia of patients with Anti-N-methyl-D-aspartate receptor encephalitis. *Chin Med J* 2015;128:2972–5.