CASE REPORT

# Anti-N-methyl-D-aspartate receptor encephalitis in a young woman with an ovarian tumour

**Joyce WT Lo** 勞慧婷
**Eric YC Leung** 梁仁政
**Betty LH Ng** 吳麗嫻
**MH Fu** 傅明虹
**KK Yip** 葉建強
**Raymond TM Chan** 陳德文
**CM Chang** 張茲勳

**Anti-N-methyl-D-aspartate receptor encephalitis is characterised by psychiatric and neurological abnormalities and occurs in frequent association with ovarian teratoma. We report the first confirmed case of teratoma-associated anti-N-methyl-D-aspartate receptor encephalitis in Hong Kong in a young woman presenting with confusion and prominent dyskinesia, followed by a review of the current literature.**

## Introduction

Most encephalitides are caused by viruses but a few have an immunological basis, such as paraneoplastic encephalitis, with specific antibodies identified. One recently characterised encephalitis caused by antibodies is anti–N-methyl-D-aspartate (NMDA) receptor encephalitis. The NMDA receptor is formed from heteromers of NR1 subunits which bind glycine and NR2 subunits which bind glutamate, mediating excitatory neurotransmission. It is important for synaptic plasticity, and in turn, for higher functions, such as learning and memory. Anti-NMDA receptor encephalitis is mediated by immunoglobulin (Ig) G antibodies against the NR1/NR2 subunits of this receptor. This disorder is severe but potentially reversible, predominantly affects young adults with or without tumour, and should be considered in the differential diagnosis of encephalitis, especially in those presenting with prominent behavioural changes and dyskinesia.

## Case report

A 21-year-old Chinese woman was admitted to Ruttonjee Hospital in July 2008. She presented with a history of headache for 10 days, fever for 8 days, mild cough, and vomiting and diarrhoea a few times. On admission, she was fully conscious with no neurological deficits. Complete blood count, renal and liver biochemistry, serum glucose and thyroid hormones results were normal.

She developed mental confusion 1 day after admission. Computed tomography (CT) of the brain did not reveal any abnormality. Lumbar puncture yielded clear cerebrospinal fluid (CSF) with normal opening pressure, lymphocytic pleocytosis (white blood cell count 286/mm$^3$, lymphocytes 98%), protein 0.87 g/L, and glucose 2.6 mmol/L (serum 5.4 mmol/L). Intravenous acyclovir was given for possible herpes simplex encephalitis. Over the next few days, the woman's mental confusion worsened and she became increasingly agitated. Recurrent attacks of generalised tonic-clonic seizures occurred but repeated electroencephalograms (EEG) and continuous EEG monitoring showed only generalised slow-wave activity in both cerebral hemispheres and no epileptiform discharge. She developed aspiration pneumonia requiring mechanical ventilation and cranial diabetes insipidus. A further CT brain scan with contrast on day 13 showed no abnormality.

On day 14, the patient began to have recurrent, almost continuous, facial grimacing, lip smacking, chewing, and tongue protrusion movements, resulting in severe lip and tongue injury and damage to her lower incisor teeth. Frequent tremor and choreoathetotic, myoclonic and dystonic movements of all four limbs and trunk appeared. A few episodes of oculogyric crisis were also observed. Abnormal movements persisted despite treatment with trihexphenidyl, tetrabenazine, haloperidol, piracetam and bromocriptine, but decreased with high-dose intravenous propofol infusion. Lumbar puncture repeated on day 21 showed a decreasing CSF white blood cell count (12/mm$^3$, with 80% lymphocytes) and normal CSF protein. Brain magnetic resonance imaging (MRI) with contrast performed in week 4 showed no abnormality. Repeated MRI in week 9 showed only non-specific changes over the left corona radiata. An extensive septic work-up for bacteria, mycobacteria, fungi, herpes simplex, varicella zoster, enterovirus, cytomegalovirus, Japanese encephalitis, Epstein-Barr virus, influenza, coxsackie virus, measles, mumps, rabies, human immunodeficiency virus, lymphocytic choriomeningitis, West Nile encephalitis, and rickettsia were all negative. Anti–double-stranded DNA, antinuclear antibody, thyroid

**Key words**
Encephalitis; Ovarian neoplasms; Paraneoplastic syndromes; Receptors, N-methyl-D-aspartate; Teratoma

*Hong Kong Med J 2010;16:313-6*

**Ruttonjee Hospital, Wanchai, Hong Kong:**
**Department of Medicine**
**JWT Lo,** MB, BS, MRCP
**EYC Leung,** BM, MRCP
**BLH Ng,** MRCP, FHKAM (Medicine)
**MH Fu,** MB, BS, MRCP
**KK Yip,** MRCP, FHKAM (Medicine)
**CM Chang,** FRCP (Lond), FHKAM (Medicine)
**Department of Diagnostic Radiology**
**RTM Chan,** FRCR, FHKAM (Radiology)

**Correspondence to: Dr WT Lo**
**Email: joycelowt@gmail.com**

## 一名有卵巢癌的年輕女子患上抗NMDA受體腦炎

抗NMDA受體腦炎經常與卵巢畸胎瘤相關聯，病人的臨床特徵有類似精神分裂症狀及意識障礙。一名年輕女子出現神經紊亂及運動神經功能障礙，後被證實患上與其卵巢畸胎瘤有關的抗NMDA受體腦炎。這是本港首宗有關病例報告，並進行文獻回顧。

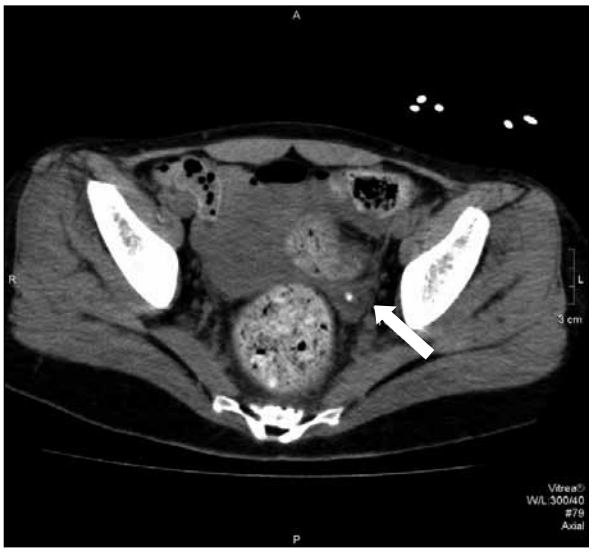


FIG. A computed tomogram of the abdomen and pelvis showing a 1.3-cm heterogeneous lesion (arrow), with fat density and calcification, in the left ovary

antimicrosomal and antithyroglobulin antibodies, carcinoembryonic antigen, alpha-fetoprotein, cancer antigens 125 and 19.9, anti-Ri, anti-Yo and anti-Hu antibodies were all negative. A CT scan of the abdomen and pelvis performed at 2 months for possible paraneoplastic tumour showed a 1.3-cm heterogeneous lesion with fat density and calcification in the left ovary, suggestive of a teratoma (Fig). The patient was finally taken off mechanical ventilation at 3 months and maintained on sodium valproate, clonazepam, haloperidol, piracetam, and trihexphenidyl. A few weeks after this, at the request of her parents, the patient was transferred to a hospital in mainland China for a trial of alternative therapy.

In January 2009, the patient's remaining CSF held at Ruttonjee Hospital was sent to the Center for Paraneoplastic Neurological Disorders, University of Pennsylvania for NMDA receptor antibody testing. The result was positive for antibodies to the NMDA receptor NR1 subunit. Doctors in mainland China were informed and removal of the ovarian tumour was advised. Initially, the patient was not considered fit to undergo surgery because of her poor physical condition. Her movement disorder later largely disappeared. The operation for removal of the ovarian teratoma, which by then measured 3.5 cm, was performed in October 2009, 15 months after the onset of her illness. Histology confirmed a mature teratoma. She was discharged from hospital and seen for follow-up in mainland China. The woman has residual orofacial dyskinesia, dysarthria, a severe cognitive impairment, and requires the use of a wheelchair.

## Discussion

The patient first presented with fever, confusion, and seizures. Initially, viral encephalitis was suspected, but viral testing was negative. Studies for other infective, metabolic, and autoimmune encephalopathies were also negative. There was no EEG or imaging evidence of limbic involvement. The prominent orofacial and limb dyskinesias are noted, in retrospect, to be typical for anti-NMDA receptor encephalitis rather than other limbic encephalitides. The ovarian teratoma detected is also a well-known association.

The association of psychiatric and neurological symptoms in patients with ovarian teratoma had been observed as early as 1997 in Japan[1] and in other populations, including Hong Kong.[2] However, it was not until 2007 that the antibodies against NR1/NR2 heteromers of the NMDA receptor were identified as the cause, and the disease was named anti-NMDA receptor encephalitis.[3] More than 100 patients with anti-NMDA receptor encephalitis have now been identified, some without any underlying tumour.

The largest published case series to date by Dalmau et al[4] included 100 patients with anti-NMDA receptor encephalitis. This reported that 90% of the patients were women, with a median age of 23 years (range, 5-76 years). Children as young as 2 years old with anti-NMDA receptor encephalitis have been reported in the literature.[5] Many patients have non-specific prodromal symptoms of fever, fatigue, and headache in the preceding 2 weeks, as seen in our patient. This suggests that an infectious process may trigger an immunological response. A majority of patients (77%) reported by Dalmau et al[4] presented to psychiatrists because of prominent anxiety, paranoia or hallucinations, while 23% presented with memory loss or seizures, with or without psychiatric manifestations. Young children have been noted to present with temper tantrums, agitation, and progressive speech deterioration.[5] One characteristic feature of the disease is the severe, often treatment refractory movement disorder,[6] as was seen in our patient. Orofacial dyskinesias, with jaw opening and closing, chewing, teeth clenching, facial grimacing, lip pouting, and tongue protrusion are characteristic features. Tremors, dystonic,

choreoathetotic, myoclonic, ballistic movements of the limbs are also common. Oculogyric crises, tonic gaze deviation, truncal hyperextension and opisthotonic posturing have also been described.[7] These movements are repetitive, persisting even during depressed consciousness and may lead to self-injury.[7] Autonomic instability—such as blood pressure fluctuations, arrhythmias, hyperthermia and diaphoresis—may occur.[4] Many patients have central hypoventilation and require prolonged ventilatory support.[4] Our patient exhibited hypersalivation and diaphoresis, but not hypoventilation before intubation or labile blood pressure. Iizuka et al[6] have grouped the symptoms of anti-NMDA receptor encephalitis into five characteristic phases—prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery phase.

Most patients have lymphocytic pleocytosis and elevated protein in their CSF.[4] Epileptiform activity on EEG was seen in only 21% of patients as reviewed by Dalmau et al[4]; the usual finding noted on EEG being generalised or predominantly frontotemporal slow waves. Increased signal on fluid-attenuated inversion recovery or T2 sequences on MRI occurred in 55% of patients, involving the mesial temporal lobes, cerebral cortex, cerebellum, brainstem and basal ganglion (in decreasing order of frequency), but these findings were non-specific and correlated poorly with patients' symptoms. Contrast enhancement of the MRI abnormalities was uncommon, transient, and faint only.[4]

To establish the diagnosis, NMDA receptor antibodies by definition must be detected in the CSF, but are sometimes also detected in the serum.[8] Titres in the CSF are higher than in the serum and appear to correlate with clinical activity. No false positives to the test have been reported to date.[8] The antibodies are IgG antibodies[9] and the major antigens are the NR1/NR2B heteromers of the NMDA receptor, though reactivity with other NR1/NR2 heteromers is also seen.[4] Binding to different receptor subtypes may lead to different clinical manifestations; for example, binding to the NR1 subunit may be related to hypoventilation,[6] while binding to the NR2A subunit may be related to amnesia.[7] It is possible that inhibition of NMDA receptors by the antibodies causes a reduction in gamma-aminobutyric acid release in presynaptic neurons, which leads to disinhibition of postsynaptic glutamate release in the prefrontal or subcortical structures, contributing to the development of psychosis and dyskinesias.[6] Similar symptoms of dyskinesia and psychotic behaviours are found in dysfunction of NMDA receptors caused by drugs, such as ketamine and phencyclidine.[7] Sixty percent of patients have an underlying tumour, most commonly an ovarian teratoma, but other tumours, such as testicular teratoma[10] and small cell lung cancer, have been found. These tumours contain neural tissue which expresses NMDA NR1 and NR2 subunits.[9] Most of these tumours are benign and may not be detected on positron emission tomography scanning, requiring ultrasound, CT or MRI for their detection. The heterogeneous appearance of the tumour, with fat and calcification inside, seen on the CT scan of our patient suggested an ovarian teratoma, and this was confirmed by histological study. In Dalmau et al's study,[4] no tumour was found in 40% of patients. A recent study[5] showed that the incidence of teratoma appears to correlate with the age of the patient, with a lower incidence of teratoma in younger patients.

Other than infective, metabolic and toxic causes, the differential diagnoses to consider for encephalopathies with fever, change of mental status, and abnormal movements include serotonin syndrome and neuroleptic malignant syndrome in patients on serotonergic agents or dopamine receptor blocking agents. Serotonin syndrome is suggested by a shivering-type tremor, myoclonus, hyperreflexia, diarrhoea, and mydriasis. Neuroleptic malignant syndrome patients have muscle rigidity and an elevation in creatine kinase. Other diseases to be excluded are the rare but important rapidly degenerative diseases, such as prion diseases, autoimmune causes of primary vasculitis, systemic autoimmune diseases and steroid responsive encephalopathy associated with autoimmune thyroiditis. The latter presents with cognitive changes, seizures, tremor, myoclonus, stroke-like symptoms and a relapsing course.

Paraneoplastic limbic encephalitis is characterised by short-term memory impairment, temporal lobe seizures, and psychiatric symptoms. Patients with encephalitis associated with voltage-gated potassium channel antibodies have neuromyotonia and hyponatraemia. Our patient did not have demonstrable evidence of limbic dysfunction. It has been proposed that the disease should be called limbic encephalitis only if it has a classic presentation, and encephalitis if the clinical or imaging features do not fulfill the criteria for limbic encephalitis.[11,12] The wide range of abnormal movements, which are semi-arrhythmic in character, with prominent orofacial involvement, persistence during depressed consciousness and resistance to treatment, together with psychiatric symptoms, autonomic features and central hypoventilation, distinguish anti-NMDA receptor encephalitis from other paraneoplastic encephalitis.

Treatment of anti-NMDA receptor encephalitis is best achieved by combined tumour removal and immunotherapy. Immunomodulatory agents, including corticosteroids, intravenous Ig, plasma exchange, cyclophosphamide, azathioprine and the monoclonal antibody rituximab have been used.[4,13] Overall, the prognosis is good, with nearly half of

patients making a full recovery and a quarter having mild residual deficits; a quarter of patients are left with severe deficits or die.[4] The outcome is better for those who undergo tumour removal, especially if this is completed within 4 months of neurological symptom development, with the antibody titre decreasing after surgery.[4] Without surgery or with late tumour treatment, the clinical course may be fatal or prolonged, as shown by Iizuka et al's study[6] and in our case. Relapses may occur, especially with late tumour removal, tumour recurrence, or in those with no associated tumour.[4]

Although this is the first reported case of teratoma-associated anti-NMDA receptor encephalitis in Hong Kong, we think it is likely that there have been previous cases which were not diagnosed because the antibody test was not available. Recently, a case of a girl aged 3 years and 9 months, with positive antibodies but no teratoma, was reported in our locality.[14] Clinicians should be aware of this distinctive presentation of encephalitis and severe movement disorder, particularly in young women with an 'incidental' ovarian tumour because timely treatment can reduce long-term disability and improve survival. Local laboratories should consider developing the anti-NMDA receptor antibody test so that the diagnosis can be confirmed and proper treatment instituted early. With wider recognition of this disease, more diagnoses of anti-NMDA receptor encephalitis are expected in the future.

## References


1. Nokura K, Yamamoto H, Okawara Y, Koga H, Osawa H, Sakai K. Reversible limbic encephalitis caused by ovarian teratoma. Acta Neurol Scand 1997;95:367-73.
2. Lee AC, Ou Y, Lee WK, Wong YC. Paraneoplastic limbic encephalitis masquerading as chronic behavioural disturbance in an adolescent girl. Acta Paediatr 2003;92:506-9.
3. Dalmau J, Tüzün E, Wu HY, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
4. 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.
5. Florance NR, Davis RL, Lam C, et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. Ann Neurol 2009;66:11-8.
6. Iizuka T, Sakai F, Ide T, et al. Anti-NMDA receptor encephalitis in Japan: long-term outcome without tumor removal. Neurology 2008;70:504-11.
7. Kleinig TJ, Thompson PD, Matar W, et al. The distinctive movement disorder of ovarian teratoma–associated encephalitis. Mov Disord 2008;23:1256-61.
8. Goodman A. Clinical symptoms and test described for detecting anti-NMDA receptor encephalitis. Neurology Today 2008;8:18-9.
9. Tüzün E, Zhou L, Baehring JM, Bannykh S, Rosenfeld MR, Dalmau J. Evidence for antibody-mediated pathogenesis in anti-NMDAR encephalitis associated with ovarian teratoma. Acta Neuropathol 2009;118:737-43.
10. Eker A, Saka E, Dalmau J, et al. Testicular teratoma and anti-N-methyl-D-aspartate receptor–associated encephalitis. J Neurol Neurosurg Psychiatry 2008;79:1082-3.
11. Graus F, Saiz A. Limbic encephalitis: an expanding concept. Neurology 2008;70:500-1.
12. Tüzün E, Dalmau J. Limbic encephalitis and variants: classification, diagnosis and treatment. Neurologist 2007;13:261-71.
13. Ishiura H, Matsuda S, Higashihara M, et al. Response of anti-NMDA receptor encephalitis without tumour to immunotherapy including rituximab. Neurology 2008;71:1921-3.
14. Chan HS, Fung CW, Yung WY, et al. Anti-NMDA-R encephalitis—an encephalitis lethargica-like illness. Proceedings of the 1st Hong Kong Neurological Congress cum 22nd Annual Scientific Meeting of the Hong Kong Neurological Society; 2009 November 6-8; Hong Kong. Hong Kong Med J 2009;15(Suppl 7):47S.