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BRIEF COMMUNICATION

Anti-*N*-methyl-D-aspartate receptor antibody limbic encephalitis

G. M. Khadem, S. Heble, R. Kumar and C. White

Department of Medicine and Psychiatry, Taranaki Base Hospital, New Plymouth, New Zealand

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Correspondence
Golam Moinuddin Khadem, Consultant Physician, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, QLD 4102, Australia.
Email: Golam_khadem@health.qld.gov.au

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Abstract

We report the case of a 57-year-old woman who developed acute psychiatric symptoms, behavioural disturbances, insomnia and dystonia resembling a catatonic state. During the course of her illness she developed hypoventilation and required monitoring in the intensive care unit. Her serum and cerebrospinal fluid showed antibodies to the NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR). Anti-NMDAR encephalitis is a severe form of autoimmune encephalitis, which has only recently been described in the published work. Most patients improve with immunosuppressive treatment. Raising awareness of this rare but increasingly reported condition is important, as it is responsive to treatment and potentially reversible.

A previously well 57-year-old receptionist was admitted to Taranaki Base Hospital with symptoms of elevated mood, insomnia, restlessness, overfamiliarity, sexual disinhibition and bizarre behaviour such as coprophagia.

Two weeks before presentation, she had a viral-like illness with arthralgias, frontal headache and a transient rash on her back. Her general practitioner had treated her with analgesics, doxycycline, lisinopril, prednisone, zopiclone, fluoxetine and clonazepam without a satisfactory response and referred her to mental health services.

An initial diagnosis of psychosis was made. She was treated with lithium carbonate, risperidone, sodium valproate and olanzapine but her condition rapidly deteriorated. At times she was restless, agitated, uncooperative and at other times she appeared catatonic: alert and attending to visual stimuli but staring, mumbling, dystonic, hyper-reflexic and needing assistance to stand. She developed fever and periods of apnoea causing respiratory acidosis and was transferred to the medical service.

Her medical history included thyrotoxicosis, which has been treated with radioactive iodine and carbimazole. She also had hypertension, mild chronic intermittent neutropenia and a benign breast lump. She had taken over-the-counter melatonin.

Routine laboratory work-up was unremarkable. Full blood count, erythrocyte sedimentation rate and C-reactive protein were normal. Thyroid function tests were normal, antithyroglobulin and antimicrosomal antibodies were negative. Syphilis serology was negative. Tumour markers (β-hCG, α-fetoprotein, carcinoembryonic antigen and CA125) were normal. Serum B12, folate, calcium, ceruloplasmin and ammonia were normal. Cerebrospinal fluid (CSF) analysis showed normal cell count, protein and glucose and herpes simplex virus polymerase chain reaction (HSV PCR) were negative. Computed tomography (CT) and magnetic resonance imaging (MRI) of the brain were normal. CT of the chest, abdomen and pelvis was negative apart from a possible small hypoechoic cyst adjacent to the right ovary. Electroencephalogram (EEG) was markedly abnormal, with generalized slow wave activity, which was more marked over the left hemisphere. The first EEG was recorded after electroconvulsive therapy (ECT), but a repeat EEG 2 weeks later showed similar changes.

She was treated with i.v. lorazepam and had 12 sessions of ECT. She required close monitoring and a propofol infusion in the intensive care unit (ICU), but did not require mechanical ventilation. She also appeared to have seizure activity with muscle twitching and jerking of

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fingers and was treated with carbamazepine. She received 1000 mg i.v. methylprednisolone for three doses without improvement of her clinical condition. After 17 weeks in hospital she was transferred to a residential care unit. At the time of transfer she continued to have periods of agitation, anxiety, aimless pacing in the ward and outbursts of inappropriate laughter, alternating with prolonged periods of rigidity and dystonia. She was managed with benzodiazepines and haloperidol. She was mostly incoherent although occasionally she spoke recognizable words.

At that stage, antibodies to the NR1/NR2 heteromers of the *N*-methyl-D-aspartate receptor (NMDAR) were found in her serum and CSF (Dr Josep Dalmau, University of Pennsylvania). Transvaginal ultrasound and MRI pelvis did not show an ovarian lesion, although an earlier CT scan suggested a small hypoechoic lesion in the right ovary. The patient was postmenopausal, clinically deteriorating and had anti-NMDAR antibodies and after discussion with her family, she underwent bilateral oophorectomy. The ovaries were macroscopically and histologically normal. She received a 5-day course of i.v. immunoglobulins (Ig) (0.4 mg/kg per day) and four cycles of 750 mg/m^2 of cyclophosphamide. There was a definite improvement in her condition over the next 8 months. Her mental status fluctuated, but sometimes she responded and answered questions appropriately and spoke spontaneously. Her dystonia disappeared. She slept better at night, but still had episodes of insomnia. Her level of self-care also improved, but she still had difficulty managing tasks of daily living.

Anti-NMDAR encephalitis is a severe form of autoimmune encephalitis, but patients often improve with treatment.[1] NMDAR antibody-associated encephalitis typically occurs in young women. Characteristic clinical features include prominent psychiatric manifestations, which often resemble acute psychosis. These patients are often admitted to a psychiatric ward. Most patients with anti-NMDAR encephalitis have an ovarian teratoma, which often is a benign or mature dermoid cyst. Pelvic CT and intravaginal ultrasound usually show the tumour, but as 70% of the tumours are benign, positron emission tomography can be negative.[2] Recurrent and bilateral tumours can occur and the teratoma may be located at another site.[3] Anti-NMDAR encephalitis has a better prognosis than most forms of paraneoplastic encephalitis.[4] The disorders most frequently considered in the differential diagnosis of patients with anti-NMDAR encephalitis are toxic and metabolic disorders, other causes of autoimmune encephalitis, viral encephalitis and patients with true psychiatric disorder.[5] In this case, the toxic and metabolic disorders were excluded by the patient's history and by blood testing. The patient had taken melatonin but after a search of published work we have not found any evidence that melatonin can lead to a similar clinical presentation. Paraneoplastic limbic encephalitis in women is mostly associated with lung and breast cancer and antineuronal antibodies can often be detected in the serum or CSF.[6] Our patient had a normal CT chest and mammogram. Acute encephalitis due to HSV was suspected, but HSV PCR of CSF was negative. Recently non-herpetic acute limbic encephalitis has emerged as a subgroup of limbic encephalitis.[7] Most patients present with acute or subacute development of amnesia, disorientation and epilepsy and are characterized by MRI abnormalities in the bilateral medial temporal lobes.[8] Encephalitis lethargica syndrome associated with basal ganglia autoimmunity has been recently described with evidence of an autoimmune, possibly post-streptococcal infection. Patients usually present with rapid-onset parkinsonism, sleep disorder, lethargy and neuropsychiatric disturbances. MRI typically shows high-signal lesions in the basal ganglia and deep grey matter region.[9]

How are patients of anti-NMDAR encephalitis distinguished from patients with a true psychiatric disorder? Anterograde amnesia (impairment of short-term memory) is usually present in patients with NMDAR antibody-associated encephalitis, but it often is overshadowed by the psychiatric and behavioural manifestations of the disorder. The development of dystonia, seizures, decreased level of consciousness, and central hypoventilation requiring mechanical ventilation are important clinical clues that help to distinguish these patients from those with a true psychiatric illness.

Commercially available paraneoplastic antibody tests do not detect anti-NMDAR antibodies. Until this test becomes commercially available, serum and CSF should be sent to a research laboratory that carries out analysis of antibodies to NR1/NR2B of the NMDA receptor. These antibodies can be detected using immunohistochemistry with rat brain and hippocampal neuronal cultures, but the identity of the antigens can only be established using cells transfected to express NR1/NR2B heteromers. The antibody is present in serum and CSF, but sometimes it is only detected in the CSF. The antigen is predominantly expressed in the hippocampus and forebrain.

The optimal management of anti-NMDAR encephalitis is tumour resection and immunotherapy. ICU care for ventilatory support, seizures and autonomic instability can delay tumour removal. Treatment with methylprednisolone, plasma exchange or i.v. Ig might result in partial neurological improvement or stabilization. In some patients tumour removal results in noticeable neurological improvement within days to several weeks [1].

Our case differed from most of the other reported cases in that our patient is older, the CSF examination and MRI was normal and an underlying primary tumour has not

been found. Normal MRI and CSF examination has been reported in other published cases.[2] The patient had serum and CSF antibodies that reacted with both NR1/NR2 heteromers (NR2A-2B) of N-methyl-D-aspartate receptor (NMDAR), which is considered to be highly specific for the condition. No false positive test was found in ~400 controls studied with diverse neurological disorders (J. Dalmau, pers. comm., 2008). Approximately 30% of patients have no detectable tumour (J. Dalmau, pers. comm., 2008). Whether these patients have an underlying tumour that will manifest several months or years later is unclear. Increased awareness of this condition is very important, as effective treatment is available.

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