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Short communication

N-Methyl d-aspartate receptor antibody encephalitis associated with myelitis

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ABSTRACT

Encephalitis associated with antibodies to the *N*-methyl D-aspartate receptor (NMDA-R) was first described in young women with ovarian teratoma [1]. It has subsequently been described in men, children and in those without an underlying tumour [2]. Characteristic clinical features include neuropsychiatric symptoms, seizures, movement disorders, hypoventilation and autonomic instability. Spinal cord disease in association with other typical clinical features has been described in only one patient previously [3,7].
We report a patient presenting with myelitis, with typical features of NMDA-R associated encephalitis manifesting 3 months later.

1. Introduction

The *N*-methyl D-aspartate receptor (NMDA-R) is involved in excitatory synaptic transmission, neuroplasticity and excitotoxicity in the central nervous system. Antibodies to the NMDA-R classically present with psychiatric symptoms, followed by seizures, encephalopathy and autonomic instability [1,5]. Associated myelitis has only been described in one prior case, [3,7] and it has not previously been seen as a presenting feature. We report a patient presenting with myelitis, with more typical features of NMDA-R encephalitis only manifesting three months later.

A 31-year old female was reviewed at a fast-track neurology clinic with a six-week history of sensory symptoms in the feet, gradually progressing to involve both legs symmetrically and then the lower abdomen.

Clinical examination demonstrated decreased appreciation of light touch and pin prick up to L1 level, with impaired distal proprioception but intact vibration sense. Motor examination of legs was normal with symmetrical deep tendon reflexes and flexor plantar responses. Remaining neurological examination was normal.

Prior medical history included an episode of post-bereavement depression three years previously. The patient had suffered a first trimester miscarriage a year prior to neurological symptom onset.

Spinal cord demyelination was suspected by the assessing clinician. Magnetic resonance imaging (MRI) of the spinal cord was arranged. However, the patient deferred investigation on discovering she was pregnant. The patient suffered a first trimester miscarriage and therefore resumed neurological investigation.

During this interval, the sensory symptoms had partly resolved, but the patient had developed memory and concentration problems, low mood, and sleep talking and walking. Her husband felt that these symptoms had appeared in a subtle manner in the interval between onset of sensory symptoms and her miscarriage, but had become prominent after the miscarriage.

MRI of the spinal cord four months after symptom onset demonstrated multiple small focal and larger segmental areas of high signal on the T_2-weighted scans within the cord below C5 (Fig. 1). There was mild cord swelling at C6–C7. MRI of the brain demonstrated a few focal T2 hyper-intense lesions peri-ventricularly and in the adjacent white matter (Fig. 1).

The patient was admitted to the day ward (five months after symptom onset) for further assessment and a lumbar puncture. Routine blood tests including full blood count, urea and electrolytes, liver function tests, C reactive protein, erythrocyte sedimentation rate, calcium and phosphate were normal. Cerebrospinal fluid (CSF) analysis demonstrated 11 white cells (morphologically normal lymphocytes) and 121 red cells/mm^3, with a protein of 0.49 g/l and glucose of 3.4 mmol/l (concurrent serum glucose 4.2 mmol/l). CSF viral and bacterial serology was negative. Oligoclonal bands were present in CSF but were not detected in serum, indicating intrathecal synthesis of immunoglobulins.

Immediately following the day ward assessment, the patient experienced two complex partial seizures and one secondary generalised seizure prompting an admission to the neurology unit.

On assessment it was noted that there had been personality change since her miscarriage with emotional lability, hostility and impaired memory and concentration. She was uncooperative, irritable, anxious

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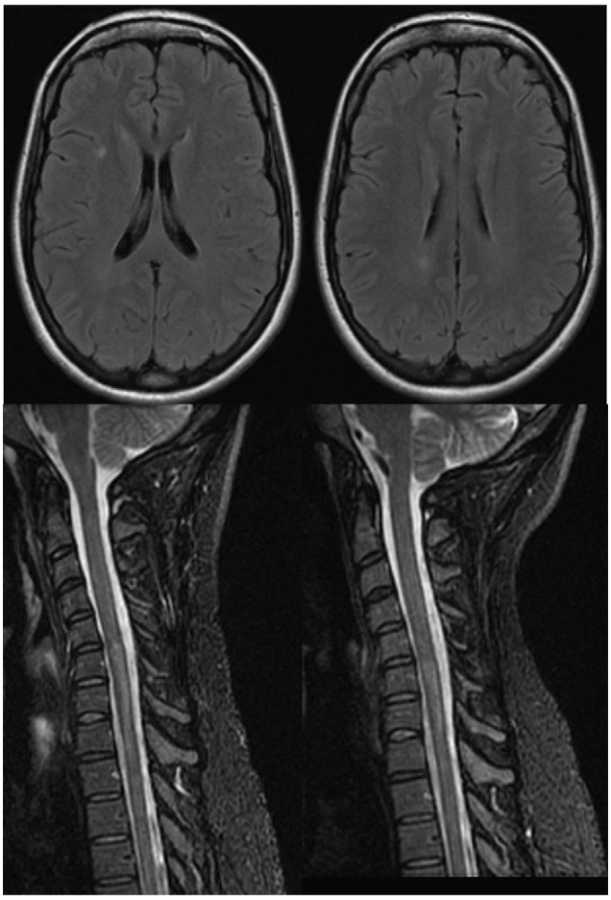

Fig. 1. MRI of the cervical spine (STIR sequences), performed on admission (above left) and two months later (above right). High signal in a segmental distribution and mild cord swelling can be seen on the left, which partly resolved on the follow-up image. MRI of the brain on admission (sagittal T2 FLAIR images) showing areas of high signal in the white matter and peri-ventricularly (admission imaging bottom left, follow up imaging bottom right).

and tearful with a child-like affect. There was a varying degree of hostility to medical staff. Neurological examination demonstrated mild left partial ptosis. Pupillary reflexes and fundoscopic examination were normal. Examination of arms and legs demonstrated normal tone, power and symmetrical deep tendon reflexes with flexor plantar responses. There was altered appreciation of touch and pin prick sensation in the legs but it was difficult to ascertain a level of sensory disturbance due to lack of patient cooperation. Joint position sense in the legs was normal. "Twitching" and "tremor" of the hands and feet had been reported by the patient's husband but were not observed during her hospital admission. No autonomic or respiratory disturbance was seen.

Neuropsychological assessment was limited due to non-cooperation but demonstrated evidence of a frontal lobe syndrome with perseveration and dysexecutive problems, in particular marked difficulties on clock face construction. Addenbrooke's Cognitive Examination-Revised [4] demonstrated a score of 48/100 with deficits in all domains, particularly memory and fluency.

Based upon clinical presentation, neuroimaging and CSF results a presumptive diagnosis of a neuroinflammatory illness was made with systemic lupus erythematosus (SLE) and anti-NMDA receptor antibody associated encephalitis considered as a possible basis for the presentation. The patient was administered intravenous Methylprednisolone 1 g/day for 3 days. Levetiracetam was commenced as anticonvulsant therapy.

Repeat MRI of the cervical and upper thoracic cord demonstrated partial resolution of the lesions within the lower cervical and upper thoracic cord (Fig. 1). Repeat MRI brain demonstrated that all the previously visualized lesions were less prominent and a new lesion (5 mm diameter) was seen within the white matter in the right frontal lobe. Incidental note was made of a thyroid nodule (5 cm diameter).

An extensive panel of blood tests searching for inflammatory or autoimmune disease was performed and was normal (Table 1). Aquaporin 4 antibodies were not detected. Electroencephalography (EEG) showed encephalopathic changes. Visual evoked responses were delayed bilaterally.

Anti-nuclear antigen antibodies were detected at a low titre of 1 in 40 with a homogenous pattern. Anti double-stranded DNA (anti-dsDNA) antibodies were detected on enzyme-linked immunosorbant assay (ELISA). There was no involvement of other organs. Therefore, in the absence of suggestive clinical features and given the negative *Crithidia* immunofluorescence assay, a diagnosis of SLE was considered unlikely.

Over the following three weeks, there was some improvement in emotional lability but continuing significant neuropsychological impairment. There were no further seizures. At this juncture, laboratory results confirmed the presence of NMDA-R antibodies in the serum sample sent for analysis on the day of admission. Analysis of the CSF sample detected NMDA-R antibodies at a titre of 1:2. 11 lymphocytes and 121 red cells/mm^3 with a protein of 0.49 g/l were also seen in the CSF. It was therefore possible that the presence of NMDA-R antibodies in the CSF represented breakdown of blood brain barrier rather than intrathecal synthesis.

The diagnosis of a NMDA-R antibody mediated neurological syndrome was established on the basis of the above investigations. The patient received 5 cycles of plasmapheresis over approximately 10 days. This was followed by initiation of oral azathioprine. This coincided with slow but steady improvement in behaviour, emotional lability and memory leading to discharge from hospital 6 weeks after admission.

Screen for possible underlying malignancy was performed. Computed tomographic (CT) examination of chest, abdomen and pelvis was normal besides a multi-nodular goitre. No evidence of malignancy was found on fine-needle aspirate of the thyroid nodule.

Over the course of the following 12 months, the patient has continued to improve but has residual mild emotional dysregulation and mild cognitive deficits. Repeat serum NMDA-R antibodies tested 5 months after the first test were positive with a titre of 1:100.

2. Discussion

This patient presented with myelitis, consistent with spinal cord demyelination. Over the following three months, she developed mild and then significant neuropsychiatric symptoms consistent with NMDA-R antibody mediated encephalitis. NMDA-R antibody testing was performed using a cell based assay of high sensitivity performed at a reference laboratory in the United Kingdom [8]. Positive

Table 1
Negative or normal investigations.

Alpha feto-protein	Angiotensin converting enzyme (serum and CSF levels)
Anti-cardiolipin antibodies	Anti-neuronal antibodies
Anti-neutrophil cytoplasmic antibody	Anti-phospholipid antibodies
Aquaporin 4 antibodies	B12
Blood film	CA125
Carcinoembryonic antigen	Complement
ESR	Ferritin
Folate	Gangliosides
HIV serology	Immunoglobulins
Lyme serology	Lymphocyte subsets
Protein electophoresis	Rheumatoid factor
Ro, La, Sm, RNP, Jo-1, Scl-70, Centromere and ribosomal antibodies	Thyroid function tests
Very long chain fatty acids	Voltage gated potassium channel antibodies

results were found in two serum samples and in CSF, supporting the diagnosis of a NMDA-R antibody mediated neurological syndrome. To note, several common features of NMDA-R antibody mediated encephalitis such as dyskinesias, autonomic and respiratory disturbances were not seen in our patient.

Alternative diagnoses were considered, including multiple sclerosis, cerebral lupus and neuromyelitis optica. In regard to the possibility of SLE, whilst dsDNA antibodies were positive by ELISA, this is known to potentially give false positive results if there is binding of single stranded DNA. The *Crithidia* immunofluorescence assay was negative; this assay is more specific (but less sensitive) for dsDNA [9]. The low ANA titre also indicated against a diagnosis of SLE. Systemic examination, immunological analysis and CT of chest, abdomen and pelvis did not show any evidence of an inflammatory disorder out-with the nervous system.

It was considered possible that our patient represented a chance association of multiple sclerosis and NMDA-R antibody mediated encephalitis. However, spinal cord involvement has been described before in an individual with NMDA-R encephalitis and myelitis, who presented with encephalopathy, seizures and dyskinesia, with development of myelitis one month later [3]. Our patient developed typical features of NMDA-R associated encephalitis, including anxiety, paranoia, cognitive deficits and seizures three to five months after sensory symptom onset.

In the subsequent year since diagnosis no further features or relapses suggestive of multiple sclerosis have emerged. We therefore consider that our patient does represent myelitis occurring in the context of a NMDA-R mediated neurological syndrome, rather than a chance association of two distinct neurological conditions, although this remains a possibility.

In regard to a possible diagnosis of neuromyelitis optica, there was no clinical evidence of optic nerve inflammation, but visual evoked responses were delayed bilaterally (making it difficult to localise the level of the abnormality). A cell based assay was used to detect aquaporin 4 antibodies, which has a sensitivity of 80% but this was negative [10]. Given the lack of clinical evidence of optic neuritis and negative aquaporin 4 antibodies a diagnosis of neuromyelitis optica was felt to be unlikely.

The NMDA-R is composed of heteromers of NMDA-R subunits 1 (NR1) and 2 (NR2). Studies have demonstrated that the main epitope recognised by pathogenic antibodies lies within the extra-cellular region of NR1 [11]. Adding antibodies to cultured rat hippocampal neurons causes a dose-dependent decrease in the level of receptor present on the cell surface. Early indications that the NMDA-R influences behaviour came from observations of the effects of drugs such as ketamine and phencyclidine, which are non-competitive antagonists. These cause schizophrenic-like features, memory dysfunction, involuntary movements and autonomic irregularities in humans [12], whilst mice lacking the NR1 subunit in their cortical and hippocampal neurons display abnormal behaviour in adulthood [13].

No clear evidence based treatment exists for NMDA-R antibody associated encephalitis. Typical initial immune therapy offered includes corticosteroids, intravenous immunoglobulin and plasma exchange (as utilised in our patient). If initial treatment does not lead to symptomatic improvement, second line agents such as Cyclophosphamide or Rituximab have been used [2]. Oral azathioprine has been used as long-term immune treatment as in our patient. No clear evidence exists to guide duration of such long-term azathioprine therapy but a minimum period of one year has been suggested [6].

Systematic search for underlying malignancy is mandatory and it has been recommended that such search should continue for a period of up to one year following diagnosis. Prognosis varies with the majority of patients recovering with mild or no residual deficits. However, approximately 4% die and up to 25% relapse [6]. Those with a treatable tumour are more likely to have a good outcome than those with no detectable malignancy [2].

In conclusion, we describe a patient with myelitis with subsequent development of neuropsychiatric features in a person with a NMDA-R antibody mediated neurological syndrome. Our case illustrates the possible clinical spectrum of this recently recognised disorder. Clinicians should consider this diagnosis in patients presenting with spinal cord demyelination, especially if neuropsychiatric features and seizures occur concurrently or subsequently. Further work is required to help clarify the potential role of NMDA-R antibodies in spinal cord demyelination.

Consent

Fully informed patient consent obtained.

Conflicts of interest

None of the authors have any conflict of interest to disclose.

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