CASE REPORT

Primary lateral sclerosis-like picture in a patient with a remote history of anti-N-methyl-D- aspartate receptor (anti-NMDAR) antibody encephalitis

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SUMMARY

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a well-recognised disorder, first fully characterised in 2007. The long-term sequelae reported thus far include relapses with typical, as well as partial aspects of the well-defined neuropsychiatric syndrome. Rarely, isolated atypical symptoms (diplopia, ataxia and tremor) have been reported as relapse phenomenon. We report a case of a patient with a remote history of likely anti-NMDAR encephalitis with the longest follow-up reported in the literature to date (22 years). The relapse presentation was of a purely upper motor neuron syndrome with a primary lateral sclerosis-like picture.

BACKGROUND

The case is unique as it represents the longest follow-up of a historical anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis patient with a unique long-term sequelae/relapse presentation, not previously reported in the literature. The case also implicates the possibility of anti-NMDAR antibodies having a role in neurodegenerative processes and the need for clinicians to consider the expansion of the spectrum of presentations related to these antibodies.

CASE PRESENTATION

A 39-year-old woman was referred for evaluation of progressive gait decline over the preceding 6 months. The reviewing neurologist had been involved in her care during a severe illness in August 1994, when she was 17 years old. At that time, she presented with a 2-day history of altered behaviour, inappropriate laughing and change of personality. She had no previous psychiatric history and was not known to use illicit substances. Shortly after presenting, she had two consecutive generalised tonic-clonic seizures with incomplete recovery requiring intubation. She was transferred to the intensive care unit and subsequently had recurrent motor events that were varied according to a review of her historical records. These included twitches, eyelid flickers, facial movements, lip smacking, generalised spasms, prolonged tonic spasms and generalised seizures. There was also fluctuating tone, marked hypersalivation as well as other autonomic disturbances.

At the time, CT of her brain was normal. Initial electroencephalogram showed generalised slowing

with no epileptiform abnormalities. Initial cerebrospinal fluid examination revealed a white cell count of 130, with a mononuclear predominance, and a protein of 0.75 g/L. Extensive work-up for herpes simplex virus and other infectious, inflammatory and metabolic causes was negative. Early in her admission, she empirically received a full treatment course of acyclovir in addition to antibacterial therapy and anticonvulsants, with no improvement. An MRI scan with contrast of the brain was normal. The ICU admission was prolonged and had multiple complications. She started to slowly improve and was eventually extubated and transferred to a medical ward after 89 days.

During the next 5 months of hospitalisation, she continued to suffer generalised and focal myoclonic jerks, dystonic spasms, facial grimacing, extensor posturing, restlessness and fevers. She remained totally disabled requiring full-time nursing care and percutaneous endoscopic (PEG) feeding. Eight months into the illness, she was discharged home to the care of her parents still fully dependent. She was assessed 9-months postdischarge in a tertiary rehabilitation centre and was documented to be both cognitively and physically disabled.

However, 3 years following onset of illness, she gradually improved and was able to return to part-time employment, although she was still using a wheelchair. Five years after the onset of her illness, she was walking independently. She had seen a neurologist for driving licencing assessment and was approved as fit to drive. She was ambulant with only mild residual pyramidal signs in lower limbs. Her cognitive function was normal.

She had no further neurological issues and was discharged from the neurology clinic. Of note, in 2005, she underwent resection of a left ovarian teratoma. She then remained well working for nearly 10 years as a teacher's aide. As recently as 2014, she travelled overseas and worked for a year in a physiotherapy practice that included walking to and from work every day.

In March 2017, 6 months after the onset of the recent decline, she was referred to the neurologist who had been involved in her original illness for an assessment of progressive deterioration of gait. She reported increasing difficulty with her balance, multiple falls and leg stiffness. She had started using a walking stick for extra support but still felt unsteady and subsequently transitioned

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to a frame but was only managing short distances. She denied any functional problems with upper limbs. She had also noticed bladder urgency and frequency. She did not report any seizures or memory complaints. She was now significantly disabled and was finding it difficult to cope with activities of daily living.

On examination she had difficulty in transferring; her gait was very slow and unsteady. She was using bilateral crutches and had scissoring spastic gait. Speech and cognition were normal. She had mild emotional lability and positive palmomental reflexes. Myerson's sign was negative. The jaw jerk was not increased. Cranial nerve examination was normal. In addition to severe spasticity of the lower limbs, there was mild-to-moderate hypertonia of the upper limbs. Power was normal in upper limbs but difficult to accurately assess in lower limbs due to severe spasticity, although there was definite weakness of dorsiflexion of the ankles. She had marked generalised hyper-reflexia, ankle clonus with bilateral extensor plantar responses. Sensation to all modalities was normal.

INVESTIGATIONS

MRI of the brain and full spine were normal. Electromyography studies did not show any peripheral or lower motor neuron abnormalities. Blood paraneoplastic antibody panel was negative. Pelvic ultrasound revealed changes in her remaining right ovary which, on MRI, appeared to be cysts of benign appearance. Anti-NMDAR antibody in cerebrospinal fluid was strongly positive with normal cell counts and biochemistry. No cerebrospinal fluid samples had been stored from her original illness for comparison. Due to increased cytoplasmic staining of the N-methyl-D-aspartate receptor (NMDAR) cell substrate, anti-NMDAR antibodies could not be excluded in the serum sample. Positron emission tomography scan done revealed focus of fluorodeoxyglucose (FDG) uptake within the fibroglandular tissues of the left breast which, on biopsy, revealed benign fibroadenoma.

TREATMENT

A hypothesis was made of her current progressive primary lateral sclerosis (PLS)-like picture being an outcome of persisting or relapsing anti-NMDAR autoimmunity. As the patient's major limiting symptom was severe spasticity, she was given baclofen. A course of intravenous immunoglobulin therapy at 2 g/kg (Privigen 10%) was given over 5 days.

OUTCOME AND FOLLOW-UP

At 3 months after intravenous immunoglobulin, the patient had not shown a clinical response. After discussion and patient indicating no desire to have children, an oophorectomy was performed. The entire ovary was processed for examination, and histopathology revealed benign ovarian follicles and cyst with no evidence of teratoma. She was later commenced on rituximab, followed by bortezomib. At her most recent review, her clinical condition was continuing to deteriorate. She was anarthric, fully wheelchair user and using a hoist transfer.

DISCUSSION

This case presents several interesting, novel aspects in autoimmune encephalitis. To our knowledge, this is the longest anti-NMDAR encephalitis case follow-up with a unique late sequelae. Although there is no definite evidence that her original illness was anti-NMDAR encephalitis, in retrospect, and in context of the more recent findings, there is little doubt that this was indeed the case. Our patient currently shows progressive pure upper motor neuron pathology resembling PLS, with no

clinical evidence of limbic or bulbar involvement but with some emotional lability. Although her initial illness more than 20 years ago had left her with some mild residual lower limb impairment, the marked recent decline in gait and clinically severe spasticity with positive anti-NMDAR antibodies in the cerebrospinal fluid suggests the current presentation could have been a relapse of her original anti-NMDAR disease more than 20 years ago.

Previous case series have analysed relapse profiles. A 2011 Spanish series investigated the relapse profile of anti-NMDAR encephalitis cases. They reported six patients with 13 relapses during a median follow-up of 20 months. In this series, some initial relapses were typical for anti-NMDAR encephalitis (31%), while others showed only partial aspects or isolated symptoms of the typical syndrome. Atypical symptoms were reported in only two relapses including ataxia, diplopia and tremor. The longest delay to relapse analysed was 13 years. None, however, reported a clinical relapse profile identified in our case.¹

This case also exemplifies that a portion of patients undergo spontaneous recovery despite a very severe disease course and untreated teratomas. Ovarian imaging was not done at time of her initial illness as the association of encephalitis with teratoma was unknown in 1994. Her oophorectomy for teratoma was 11 years later. An early case series from Japan reported four women with a previous clinical syndrome consistent with anti-NMDAR encephalitis, with positive anti-NMDAR antibody in archived samples. Three of these had subsequently confirmed teratomas.² Each underwent a similar clinical course to the present case with severe disease, prolonged admission and eventual spontaneous recovery without removal of the teratoma.

The NMDA receptor has a crucial role in maintaining neuronal health and function. Extensive research has been carried out in the last few decades, but the understanding of their function and roles in disease is far from complete. Several different neurodegenerative conditions have been speculated to be linked with NMDAR dysfunction including Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis and schizophrenia.^{3 4} A unifying popular hypothesis involves glutamate excitotoxicity at NMDAR causing excessive calcium influx leading to mitochondrial failure, although other mechanisms of neuronal death or dysfunction also exist. Apart from the role the receptor might play in mediating direct excitotoxicity via calcium influx in neurodegenerative conditions, its absence from neurons or reduced numbers almost certainly has dramatic neuronal effects as exemplified by its association with the now well-characterised anti-NMDAR encephalitis.⁵ These antibodies are known to be pathogenic and cause a selective and reversible decrease in NMDAR surface density and synaptic localisation that correlates with antibody titres. The mechanism of this decrease is via antibody mediated capping and internalisation of surface NMDARs.⁶

Our patient's current presentation raises questions as to its pathogenesis: is this upper motor neuron degeneration as a long term sequelae of anti-NMDAR encephalitis or a partial relapse of the autoimmune disorder developing insidiously, even in the absence of acute or subacute neuropsychiatric features typical of anti-NMDAR encephalitis? Although no such link or case report could be identified in the literature, there has been report of anti-MA2 antibody, which ordinarily also causes a paraneoplastic limbic encephalitis, presenting with a PLS-like picture in a patient who also had co-occurring Sjogren's disease.⁷ The ongoing progression of our patient's symptoms and lack of response to treatment may suggest secondary degeneration rather than a relapse of her autoimmune disorder.

Learning points

- ▶ Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis can present with atypical relapses and, as in our case, as a late sequelae with an upper motor neuron syndrome resembling primary lateral sclerosis decades after initial presentation. More research is needed in the role of anti-NMDAR antibodies in neurodegenerative processes.
- ▶ Although N-methyl-D-aspartate receptor glutamate mediated excitotoxicity is implicated in a wide range of common neurological conditions, an antibody role is also possibly raised with this clinical case.
- ▶ Anti-NMDAR encephalitis can occasionally spontaneously remit without directed therapy.

Given that NMDA receptors are widely located in neocortex and limbic neurons, autoimmune selectivity to the cortico-spinal tract as a relapse phenomenon in a patient with a prior episode of the classic acute encephalitic syndrome remains a puzzle. However, it would be prudent for neurologists to expand their suspicion of the possible pathophysiological role of anti-NMDAR antibodies to a wider clinical spectrum. A case series investigating presence of the antibody in patients with PLS may establish specific possible links with this and other neurodegenerative disorders and the link between neuroinflammation and neurodegeneration.

Contributors MJ reviewed archived medical records, was the author of the initial draft and was involved in patients care as the advanced trainee of the team. WK was the primary neurologist involved in patient's current outpatient and inpatient evaluation/management and the main editor of the manuscript. He was also involved in her original care in 1994. MN was involved in patients follow-up, care and editing of the manuscript. SS was involved in refining and editing of manuscript, contribution to discussion from the neuroimmunology perspective and reviewed previous case series on the topic.

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