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Findings that shed new light on the possible pathogenesis of a disease or an adverse effect

NMDA receptor encephalitis – expanding the clinical spectrum

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Summary

A young woman presented with memory problems of subacute onset. Imaging was normal. She was admitted with severe complex partial status epilepticus requiring intensive care support and ventilation. Fits proved difficult to control requiring high dose anticonvulsants. She developed a profound amnesic syndrome. A clinical diagnosis of autoimmune encephalitis was considered and she was treated with intravenous steroids with an excellent cognitive outcome. She continues to have occasional seizures.

BACKGROUND

It is important to consider this diagnosis in patients who present with an illness that can mimic an encephalitis but in which no infective cause is found.

CASE PRESENTATION

A 34-year-old customer services advisor presented with myalgia, headaches and loss of appetite. She had depression and weight loss following the birth of her daughter 8 months previously. She reported some memory problems for example, forgetting family phone numbers, in the month prior to presentation. Her husband added that on one occasion she had been unable to recall her daughter's birth date. CT head and MRI brain were normal. Five days after presentation she developed severe secondary generalised seizures and was admitted to intensive care in complex partial status epilepticus, initially requiring sedation and ventilation. She was treated with intravenous acyclovir, phenytoin and levetiracetam to control the seizures. She showed features of delerium with paranoia, hallucinations and extreme anxiety. She required haloperidol for sedation. She was noted to have a profound retrograde and anterograde amnesia. She was unable to recall her own wedding or the birth of her baby and had a 10 s retention span for new memories. She developed a left upper limb tremor with a burning sensation in that limb.

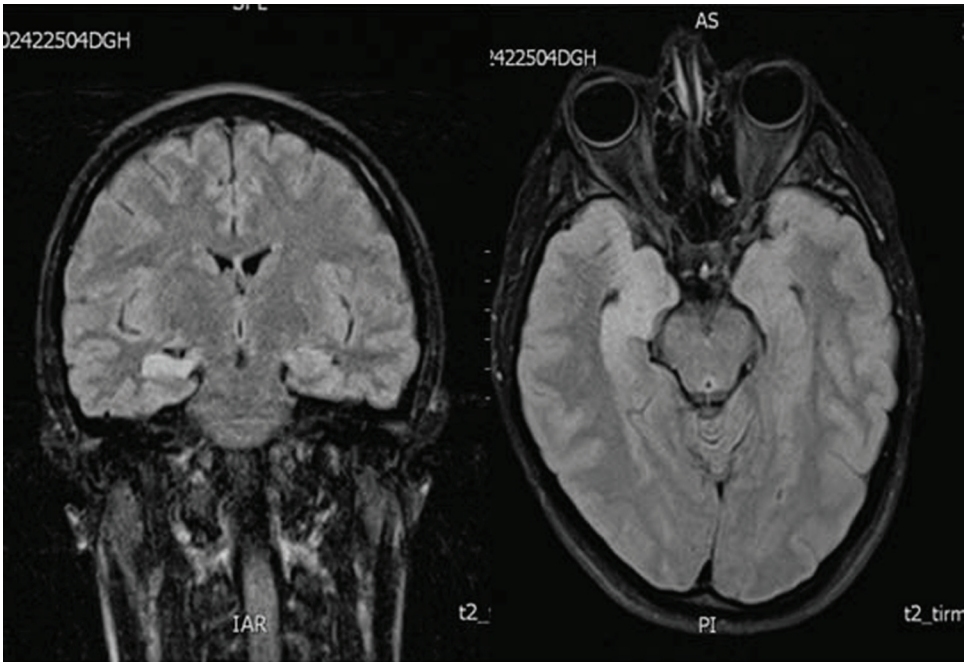

Figure 1 MRI images of patient with NMDA encephalitis.

INVESTIGATIONS

Routine bloods on admission showed mild bone marrow suppression felt to be consistent with a viral response. Renal, liver, bone and thyroid biochemistry was normal. Lumbar puncture initially showed a mildly raised cerebrospinal fluid (CSF) protein of 0.58 g/l with 6 x 10^6/l white blood cells, and on repeat testing 6 days later the protein had normalised with a white cell count of 16 x10^6/l. Herpes simplex PCR in CSF was negative. EEG confirmed complex partial status with a right temporal focus and a slow background rhythm. Two repeat MRI brain scans showed gradually evolving high signal in both hippocampi (figure 1). The following investigations were normal or negative: autoantibody screen, anti-neutrophil cytoplasmic antibody, extractable nuclear antigen, serology for brucella, lyme, mycoplasma, cytomegalovirus, enterovirus, Epstein–Barr virus and HIV; neuronal, voltage gated potassium and thyroid antibodies, CA-125 and α feto protein. CT chest, abdomen and pelvis and pelvic ultrasound were normal. N-methyl D-aspartate receptor (NMDAR) antibodies were low positive.

Ten days following the onset of seizures she was given intravenous methylprednisolone 1 g for 3 days. She improved significantly and generalised seizures became infrequent with only occasional complex partial seizures. Her Addenbrookes' cognitive examination was 66/100 with particularly poor memory/recall subsets. After 2 weeks she developed recurrence of headache and left upper limb tremor. She was commenced on intravenous immunoglobulin (IVIG) but this was stopped due to an allergic reaction. She underwent plasma exchange with improvement in her symptoms. Two months following her admission her Addenbrookes score was 96/100. This is considered within normal limits. Repeat NMDA receptor antibodies 10 weeks after plasma exchange were negative.

TREATMENT

Over the following few months she suffered two relapses requiring further courses of plasma exchange, occurring on attempted steroid dose reduction.

OUTCOME AND FOLLOW-UP

The relapses presented as a recurrence of complex partial seizures with déjà vu, left upper limb tremor, headaches, weight loss (despite high dose steroids) and depression. She also reported in her diary, odd symptoms of craving to eat coal, and superhearing (auditory hallucinations during which she could hear clearly voices in the car park over half a mile away). These symptoms could last for hours and were present when ictal activity was not found on EEG. Insight was otherwise retained. Gradually more of her autobiographical memory returned and she was eventually able to fix these memories in the correct time period. She became able to successfully lay down and retain new memories. Repeat pelvic imaging 6 months after presentation showed no tumour. One year later her memory had almost fully recovered but she suffers occasional seizures and is managed on steroids, azathioprine and levetiracetam. She has remained steroid dependent and attempted reduction below 30 mg leads to severe headaches and worsening left sided tremor though no significant memory problems. She has now developed rapid eye movement sleep behaviour disorder. NMDA antibodies are still negative in March 2011.

DISCUSSION

The diagnosis was felt to be NMDAR limbic encephalitis (LE). LE has a number of causes including infectious, paraneoplastic, autoimmune and connective tissue diseases. NMDAR LE was first described in 2007 as an encephalitis presenting with psychiatric disturbance and dyskinesias associated with hypoventilation, seizures, amnesia, autonomic disturbance, reduced consciousness and positive NMDA receptor antibodies.[1] The antibodies are directed against a subunit of the NMDA receptor.[2] This is thought to reduce the gamma-aminobutyric acidergic inhibition of glutamatergic cells resulting in excessive glutamatergic excitation of prefrontal and subcortical structures.[3] The antibody is pathogenic and tends to fall with effective treatment.

A recent series of 100 cases of NMDA encephalitis reported that characteristic presenting features included dyskinesias, hypoventilation and profound psychiatric and autonomic disturbance, not present in our case.[2] Jerky tremor was present however which has not, as far as we are aware, been previously described. She did exhibit a typical viral prodrome. NMDAR LE typically has 5 phases, the prodromal, psychotic, unresponsive, hyperkinetic and gradual recovery phase.[4] It is possible that our patient did not develop some of the reported features due to early treatment. Initial low antibody levels in our patient did not correlate with her severe disease presentation but did fall after treatment. It is possible that another antibody was responsible for her condition which has not yet been characterised but more likely that the spectrum of clinical disorders associated with these antibodies is wider than previously identified. NMDAR antibodies have recently been identified in five of 19 young females with new onset epilepsy often with prominent psychiatric symptoms and pleocytosis in the CSF.[5]

NMDAR LE usually affects young women and teratoma, usually ovarian, is found in 60% of cases.[2] In this case a search for cancer was negative despite interval scans, but she will need further imaging as tumours have been detected a number of years after presentation.[4] It is increasingly recognised that the disorder may have a non-paraneoplastic basis. Those cases without underlying malignancy are felt to have a better prognosis.

The main stay of treatment is immunotherapy and tumour removal if detected. Steroids and IVIG have most commonly been used but there are reports of treatment with plasma exchange, cyclophophamide and rituximab.[6] This case highlights the importance of considering autoimmune disorders as a differential for encephalitis particularly in younger patients. Early treatment is associated with better long-term outcome. It is therefore well worth treating empirically before waiting for antibody results.

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Learning points

- NMDA receptor encephalitis is an important, potentially underrecognised cause of confusion and seizures.
- Initial investigations including imaging can be normal. Fluid-attenuated inversion-recovery imaging should be requested to look at temporal lobes.
- Early treatment may be associated with better long-term outcome hence a high index of suspicion is needed to recognise cases early
- NMDA antibodies are associated with epilepsy
- NMDA antibodies are not always associated with underlying malignancy.

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Competing interests None.

Patient consent Obtained.

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