End of the bed (end of the video) diagnosis

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The supplementary videos are available to view online at http://pn.bmj.com/content/12/2.toc.

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A 23-year-old woman, who had been previously well, developed three generalised tonic-clonic seizures in 24 hours. For 5 days, she had complained of headache and fever, and her family had noted a personality change with unusual hypomanic behaviour (she cleaned the house persistently and wanted to stay out and party all night). She was admitted initially to a general medical ward, where she exhibited bizarre behaviour. She made strange noises, laughed inappropriately and performed repetitive stereotyped movements such as picking at her clothes. She had periods of agitation and at one point almost jumped out of the window. Brain imaging (CT and MRI) was normal. Cerebrospinal fluid (CSF) examination showed a raised lymphocyte count (140 lymphocytes/μL (≤5)) with normal CSF protein and glucose, and oligoclonal bands in CSF but not in serum. Blood cultures were sterile. Routine bloods and inflammatory markers, including serum C reactive protein, were normal. She was transferred to a neurology ward for further investigation. On the fifth day of her hospital admission, she appeared alert and was able to walk with support but had no verbal output and did not obey commands. She had limited visual tracking of people around her. She displayed waxy flexibility but with no abnormality in tone, power or reflexes. She continued with episodes of agitation, with reduced alertness, lip smacking and eye-uprolling, each lasting several minutes.

Question 1

What is the differential diagnosis?

Headache followed by altered level of consciousness and seizures together with normal imaging and lymphocytic CSF suggests an encephalitic process. Infection, particularly viral encephalitis, would need to be considered. Bacterial meningoencephalitis, such as infection with *Neisseria meningitides*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Listeria moncytogenes* or *Mycobacterium tuberculosis*, is possible though unlikely, but the normal CSF protein, normal peripheral blood count and lack of acute phase reaction were strongly against a bacterial cause. In the absence of an infective cause, and given the prominent behavioural changes, autoimmune limbic encephalitis should be considered. Other autoimmune conditions such as central nervous system vasculitis or cerebral lupus were also possible. Non-convulsive status epilepticus or postictal psychosis could also potentially have contributed to her altered level of consciousness and agitation, but would not have explained the lymphocytic CSF.

Question 2

How would you manage this patient?

Comment

Our patient received intravenous aciclovir (for presumed viral encephalitis) and phenytoin (for seizures). Prolonged EEG recording captured episodes where her eyes would roll back and her conscious level would drop, but the recording only showed diffuse slow waves in the δ range, without epileptiform features.

On the eighth day of admission she was catatonic. She had stopped speaking except for a few incomprehensible sounds, and showed no

reaction to pain. Her tone was normal and there was persistent waxy flexibility in the upper limbs. She received nasogastric feeding. On day 10, she developed autonomic instability and was transferred to a high dependency unit. She had episodes of fever (up to 40°C) with no clear focus of infection, fluctuations in blood pressure (with readings up to 170/100 mm Hg) and heart rate (with tachycardia up to 130 beats per minute), and apnoeic spells with oxygen desaturation during these episodes.

She developed continuous stereotyped movements, slapping her tongue against her hard palate, and repeated lateral eye deviation (see supplementary online video 1). She had subtle repetitive head nodding and frequent blinking. Although she appeared catatonic and would stare ahead most of the time, very occasionally she had spontaneous side-to-side head movements or would sit up suddenly.

Prolonged EEG recording during these episodes showed no epileptiform abnormalities. Routine blood investigations and copper studies were normal. Her serum was negative for antibasal ganglia antibodies and antivoltage-gated potassium channel antibodies. CSF PCR was negative for Herpes simplex, Varicella zoster, cytomegalovirus, Epstein–Barr virus, human Herpes virus 6 and 7 and enterovirus. CT imaging of her chest, abdomen and pelvis was normal.

Question 3

What is the diagnosis and treatment?

Comment

Our presumed diagnosis was immune-mediated encephalitis and on day 12 of her admission, she received treatment with high dose corticosteroids (1 g of intravenous methylprednisolone for 3 days, followed by oral prednisolone 1 mg/kg). The next day, she had a tracheostomy for episodes of hypoventilation with oxygen desaturation. On day 19, her clinical state changed. She was no longer catatonic but agitated, kicking out and climbing out of bed. She had rapidly changing facial emotional expressions, ranging from crying one moment to laughing uncontrollably the next (see supplementary online video 2). She required significant sedation (up to 60 mg of diazepam daily), primarily to prevent her from harming herself. Her motor agitation gradually settled over 2 weeks and she entered a phase where she became rigid in all four limbs. While she remained unresponsive to verbal stimuli, she grimaced to painful stimuli. She was no longer agitated or requiring sedation. This coincided with confirmation of antibodies to the N-methyl-D-aspartate receptor (NMDAR) in serum and CSF. The neurology team initiated treatment with plasma exchange. After just one treatment, she had improved visual tracking, and after three sessions of plasma exchange over 6 days she was obeying commands. Figure 1 illustrates the changes in her serum anti-NMDAR antibody titres during her illness, correlating with her clinical improvement. CSF on two occasions was positive for NMDAR antibodies, although levels were significantly lower than in serum and did not correlate with her clinical status. CT imaging of chest, abdomen and pelvis was normal; specifically, her ovaries were normal. She continued to improve rapidly and 1 month after plasma exchange, she was well enough to be discharged home. She had minimal immediate and delayed memory impairment and mild deficits of new learning.

The corticosteroid dose was gradually tapered and stopped. At follow-up 3, 6 and 12 months after discharge, her condition was stable and she returned to part-time work as a shop manager. Her neuropsychological assessment remained essentially unchanged. Repeat CT scan of chest, abdomen and pelvis was again normal. Nevertheless, there was a small rise in her latest serum anti-NMDAR antibodies (figure 1). We plan to monitor her closely for evidence of tumour development.

Final comment

Many patients present with features of an encephalitic illness. Frequently, the aetiology is viral but once excluded, an autoimmune or paraneoplastic illness should be suspected. A proportion of patients present with limbic encephalopathy secondary to antivoltage-gated potassium channel antibodies, which responds to immunosuppressive therapy.[1] Anti-NMDAR encephalitis is a relatively recently described autoimmune encephalitis, with antibodies against the NR1–NR2 heteromers of the NMDAR.[2] Compared with other immune-mediated encephalitides, anti-NMDAR encephalitis is relatively common.[3]

The NMDAR is a ligand-gated cation channel that is responsible for synaptic transmission and plasticity. Receptor overactivity causes excitotoxicity, for example, in the context of epileptic seizures, while receptor underactivity occurs in schizophrenia.[4] Both underactivity and overactivity occur in this encephalitic illness. Laboratory

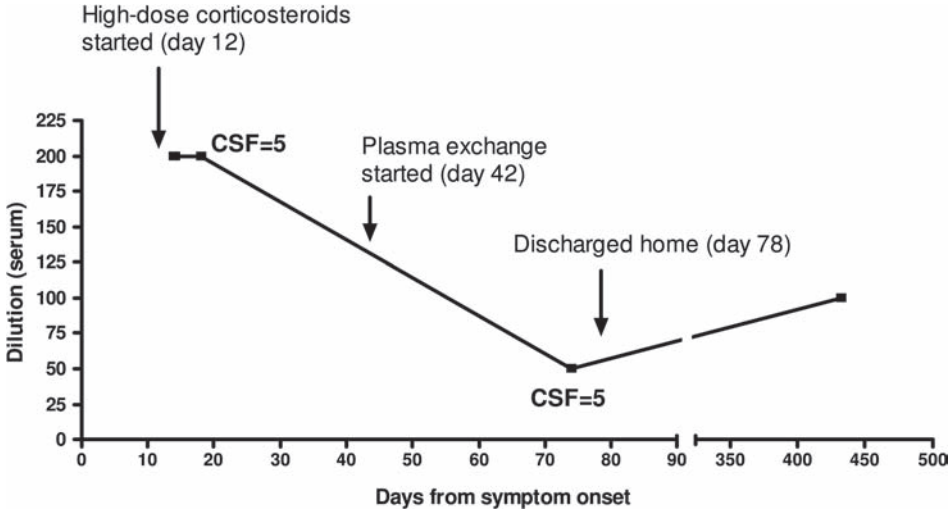

Figure 1 Changes in serum N-methyl-D-aspartate receptor antibody levels with time. The antibody levels are shown as endpoint dilutions (lowest dilution producing a score of 1.5, on the range of 0–4, normal value <1, median 0). The serum levels appeared to correlate with the disease course, but cerebrospinal fluid (CSF) antibody levels did not change between the two samples studied.

and clinical data support the pathogenic role of NMDAR antibodies and the reversible nature of the encephalitis. In vitro studies showed that adding patients' immunoglobulin G to rat hippocampal neuronal cultures gave a concentration-dependent decrease of NMDARs. Adding CSF from healthy controls to these cultures quickly restored the number of NMDARs.[2] The serum and CSF antibody titres correlated with illness severity.[2 3 5] Patients who improved had a parallel reduction in serum titres of anti-NMDAR antibodies, as in our patient, while those who did not improve maintained high serum titres.[2 3 5]

Anti-NMDAR encephalitis occurs mainly in females.[2 3 5] Its clinical picture is very characteristic and comprises five distinct phases:

- Patients present first with a prodrome of headache and fever, followed by psychobehavioural symptoms.
- During the psychotic phase, patients demonstrate emotional disturbance, cognitive decline and schizophrenia-like symptoms. They may present at this stage to a psychiatrist rather than a neurologist.
- In the third phase, patients are unresponsive or catatonic, with typical orofacial dyskinesia. There is often autonomic instability during this phase. Patients may require prolonged intensive care support, commonly for management of hypoventilation, which is central in origin.
- The fourth phase is the hyperkinetic phase.
- Patients finally enter a slow recovery phase and can progress back through these stages.[3] Although it is treatable and reversible in about 75% of cases, some patients are left with residual cognitive deficits. Relapses occasionally occur [3] and in a minority it is fatal.[2]

EEG typically shows non-specific diffuse slowing. Brain imaging can be normal or may show increased T2 or FLAIR (fluid attenuated inversion recovery) signal on MRI, in one or several brain regions.[2]

The phases of this syndrome could be explained by the effect of the reduction in NMDARs on various brain pathways.[3] This includes inactivation of GABAergic neurons (ie, neurons producing gamma-Aminobutyric acid), which disinhibits excitatory pathways. There is also involvement of the brainstem central pattern generator and the pontine–medullary respiratory network. Because NMDARs also occur within dopaminergic, cholinergic and adrenergic systems, the disorder results in autonomic manifestations.

The clinical presentation, characterised by the described stages of the illness, is an important clue to the diagnosis. The supplementary online video clips accompanying this case report illustrate some of these phases. Antibody testing is now widely available, facilitating diagnosis of this treatable and reversible encephalitic illness. Moreover, it can be associated with underlying neoplasm, particularly ovarian teratoma in young females. Occasionally, other tumours may cause the syndrome, especially those expressing NMDARs, such as testicular teratoma and small cell lung cancer.[2] However, some patients (particularly children[5]) may not harbour a tumour; the pathophysiology in these cases may be postinfective. *Mycoplasma pneumoniae*[6] and *Campylobacter jejuni*[7] are the common offending agents. A recent review of 400 cases associated the rate of tumour detection with age and sex.[3] Dalmau *et al*[2] found 59% of 98 cases were

Practice points

1. Anti-NMDAR encephalitis presents with a characteristic clinical picture, including catatonia, orofacial dyskinesias and other extrapyramidal features.
2. Immunotherapy should be initiated and escalated early.
3. Investigation should include a search for an underlying neoplasm.

paraneoplastic.[2] In contrast, in a recent study of 44 cases only 20% had a tumour.[5]

Treatment strategies aim first at removing any tumour, and then at immunosuppression or immunomodulation.[3] There are no systematic studies of treatment outcomes. However, patients undergoing prompt surgical removal of an associated ovarian teratoma do better than those without a tumour.[8] Corticosteroids, immunoglobulin and plasma exchange are most commonly used.[2] Early immunotherapy appears to improve clinical outcome; occasionally patients respond promptly to treatment with rituximab.[5 9] A recent treatment algorithm[3] suggested using rituximab and cyclophosphamide as second line agents in resistant cases. Our patient dramatically responded to plasma exchange, although we cannot rule out the possibility that her recovery was through a delayed response to corticosteroid treatment or indeed was the natural course of the illness. Other case reports suggest that plasma exchange gives better outcomes than immunosuppression.[10]

Competing interests None.

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