N-methyl-D-aspartate receptor antibody-mediated encephalitis

Introduction

Failing to diagnose and treat a potentially curable condition can result in a catastrophic outcome for a patient. Encephalitis is a pathological process, which has many causes. In some cases the aetiology remains unclear or is hard to ascertain, meaning that patients are treated in a purely supportive fashion. A recently described form of autoimmune encephalitis mediated by N-methyl-D-aspartate (NMDA) receptor antibodies accounts for 1–4% of all cases presenting with encephalitis. Its association with malignant and immunological phenotypes offers potential therapeutic options. It is vital that physicians know about this condition to allow its inclusion in a differential diagnosis, facilitate earlier detection and institute suitable treatment where appropriate. This article presents the case of a young woman who was diagnosed with and treated for NMDA receptor encephalitis.

Discussion

Encephalopathy associated with antibodies against NMDA receptors has only been recently described. In a retrospective German study it represented 1% of encephalopathies of unknown origin in 505 patients admitted to the intensive care unit (Prüss et al, 2010). A 2-year UK prospective encephalitis study recruiting 203 patients identified 48 patients with immune-mediated encephalitis of which nine were NMDA-R antibody mediated (Granerod et al, 2010). The condition is associated with a neoplasm, commonly a teratoma, in 59% of cases and patients are characteristically young females presenting with psychiatric and memory problems (Dalmau et al, 2008; Irani et al, 2010). Seizures occur in 76% of cases, loss of consciousness in 88% and movement disorder in 86%.

Other features include autonomic instability and hypoventilation (Dalmau et al, 2008). Prodromal viral-like illness has been reported (Irani et al, 2010). Imaging is often non-diagnostic although magnetic resonance imaging T2 fluid-attenuated inversion recovery images may show non-specific enhancement. This should be treated with caution as it may represent propofol anaesthesia or supplemental oxygen ubiquitous in intensive care patients. Electroencephalography is usually abnormal showing slow rhythmic delta-theta activity (Dalmau et al, 2008; Irani et al, 2010) that may unusually represent non-convulsive status epilepticus (Kirkpatrick et al, 2011). Frank epileptiform discharges can be seen early in the disease in 50% of patients (Irani et al, 2010). NMDA-R encephalitis can be the underlying cause of new onset epilepsy in a significant proportion of young women (Niehusmann et al, 2009). CSF is abnormal in 80% of cases with moderately raised white cell count, protein and, if tested, positive for NMDA receptor antibodies.

The main epitope targeted by the antibodies is variably reported as either the extracellular N-terminal domain of the

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Case Report

A 21-year-old woman presented to the accident and emergency department with confusion and strange behaviour. She was disoriented, uncooperative and experiencing delusional beliefs and visual hallucinations. Her initial Glasgow Coma Scale was 15, she was afebrile and haemodynamically stable. Routine serum laboratory analysis was unremarkable. Initially, she was referred to a psychiatrist and admitted for investigation under the Mental Health Act. However, subsequent mutism, odd posturing and choreoathetoid movements of the limbs prompted further investigations under an acute medical team.

While undergoing a computed tomography scan of the brain she became agitated with a drop in Glasgow Coma Scale precipitating intubation in the radiology department and admission to the intensive care unit. The computed tomography scan was non-diagnostic as was subsequent magnetic resonance imaging. CSF analysis yielded a white cell count of 10 x10^9/litre, glucose 4.6 mmol/litre and total protein 0.2 g/litre. Viral polymerase chain reaction and culture of the CSF were negative. Other investigations including urine toxicology, porphyria screen, vasculitic screen, Borrelia, syphilis and HIV serology were all negative. Electroencephalography showed excess rhythmic slow activity with no evidence of seizure activity. During the recording the patient experienced rhythmic limb and orofacial movements which bore no relationship to the electroencephalogram. The electroencephalogram findings were felt to be consistent with encephalopathy. During sedation holds while intubated and ventilated the patient would have her eyes open but would not follow commands. On day 10 of the admission during one of the sedation holds the patient suffered a grand-mal seizure that was terminated with propofol. She was subsequently commenced on phenytoin. Assays for CNS auto-antibodies were performed as well as a transvaginal ultrasound examination. Ultrasound scan confirmed the presence of an ovarian mass, which following laparoscopic resection proved to be a teratoma. Antibody screen was negative for neuronal, Purkinje cell and myelin antibodies, but strongly positive for N-methyl-D-aspartate-receptor antibodies. A diagnosis of N-methyl-D-aspartate-receptor antibody-mediated encephalopathy was confirmed.

The teratoma was removed urgently laparoscopically before the presence of N-methyl-D-aspartate-receptor antibodies was confirmed. This was done purely on clinical suspicion based on her presentation alone. Medical treatment consisted of 3 days of intravenous methylprednisolone (1 g per day) followed by a 5-day course of plasma exchange. Following that she received a 10-day course of intravenous immunoglobulin. Movement disorders and sedation were managed with propofol, clonidine and benzodiazepines.

The patient remained deeply encephalopathic 4 months after presentation in spite of the above treatment.

NR-1 subunit (Irani et al, 2010) or the NR-2 subunit (Dalmau et al, 2007) of the NMDA receptor. The antibodies seem functional in producing symptomatology akin to that of other antagonists at that receptor. Inflammatory response is not the main feature of this type of encephalitis, but inflammation may be present during the prodromal illness and antibodies are able to fix complement (Irani et al, 2010).

NMDA-receptor encephalopathy in association with a tumour may benefit from prompt resection of the lesion (Seki et al, 2008), as this removes the antigenic drive. Pelvic ultrasound, computed tomography, pelvic magnetic resonance imaging or whole body positron emission tomography help localize the neoplasm. Treatment may also include immunosuppressants, e.g. corticosteroids, immunoglobulins, cyclophosphamide or rituximab, as well as plasma exchange (Dalmau et al, 2008; Davies et al, 2010). Use of NMDA receptor-blocking drugs has been reported (Davies et al, 2010; Kirkpatrick et al, 2011). Accompanying movement disorders may prove difficult to treat.

Prognosis is generally good with recovery seen in 75% of cases, although 85% of those have symptoms of frontal lobe dysfunction and a quarter have disordered sleep (Dalmau et al, 2008). Median duration of hospitalization is 2.5 months and relapse is possible, particularly in patients with non-tumour related disease or undetected tumour (Dalmau et al, 2008; Irani et al, 2010). Symptoms of encephalopathy such as confusion, agitation, amnesia and reduced consciousness are more severe and more common in the paraneoplastic patients but tend to improve more rapidly after tumour resection. **BJHM**

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LEARNING POINTS

- N-methyl-D-aspartate receptor encephalopathy is an important, not uncommon and treatable cause of severe encephalopathy.
- Accident and emergency, acute and intensive care physicians should consider this diagnosis, especially in young women presenting with neuropsychiatric symptoms, or if more common infectious causes have been excluded.
- The association with tumours, classically teratomas, should prompt a search for them with subsequent urgent resection.

Amiodarone-induced facial pigmentation

A 79-year-old man was admitted with a history of near collapse with complete heart block on electrocardiography. He had been taking digoxin 125 µg and amiodarone 200 mg for atrial fibrillation for 10 years. He had blue-gray discolouration of his nose, cheeks and lips, sparing the deep skin folds, and also had bilateral ectropion (*Figure 1*). Digoxin levels were normal, both drugs were stopped and the patient was sent for permanent pacemaker implantation.

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Amiodarone photosensitivity is seen in 2–24% of patients (Karrer et al, 1999). It is caused by ultraviolet-induced accumulation of lipofuscin in dermal macrophages depending on both the dose and duration of therapy (Kounis et al, 1996). Skin pigmentation is reversible but may take up to 1 year to completely resolve after the drug is discontinued. Although medically benign, amiodarone-induced pigmentation may be cosmetically disfiguring. It has been successfully treated using the Q-switched ruby laser (Karrer et al, 1999). **BJHM**

Karrer S, Hohenleutner U, Szeimies RM, Landthaler M (1999) Amiodarone-induced pigmentation resolves after treatment with the Q-switched ruby laser. *Arch Dermatol* **135**: 251–3

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Figure 1. Blue-gray discolouration of the nose, cheeks and lips, sparing the deep skin folds, and bilateral ectropion.