Uncommon presentation of autoimmune limbic encephalitis: a case report

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Abstract

Autoimmune limbic encephalitis is an inflammatory condition of the brain that presents as an acute psychotic disorder. Investigations to confirm this diagnosis often have normal results, and so discriminating between a functional psychiatric presentation and autoimmune neurological disorders can be difficult. In this case report, we present a complex case where multiple repeat investigations were normal and the subsequent diagnosis of autoimmune limbic encephalitis was made due to a strong clinical picture of glutamatergic psychosis that improved with treatment of limbic encephalitis following local guidelines. Traditional investigative findings of autoimmune encephalitis were not present, such as positive findings on magnetic resonance imaging (MRI) of the brain or pelvis, and autoimmune panels to screen for autoimmune antibodies such as anti-NMDA receptor antibodies. The diagnosis and management of this case involved input from a multi-disciplinary team that included internal medicine, neurology, and consult-liaison psychiatry. This case touches on the importance of understanding the clinical picture of autoimmune limbic encephalitis to ensure prompt diagnosis and treatment. Medical students in New Zealand can learn from this case study that,

despite best efforts, many tools in medicine have subpar sensitivities and specificities, and that clinical gestalt and experience are necessary when interpreting normal results. This case highlights that autoimmune limbic encephalitis can occur despite normal MRI, EEG, and CSF results, and that early specialist input and empiric immunotherapy should be considered when clinical suspicion remains high.

Introduction

Autoimmune limbic encephalitis (ALE) is a multi-stage inflammatory condition of the brain that typically presents as an acute psychotic disorder. Although the prevalence of ALE in New Zealand in unspecified, a local 2009–2018 study of the Auckland and Northland region estimated an annual incidence of 1.10 cases per 100,000 person-years.[1] Despite this low incidence, ALE is life-threatening and has a variable prognosis ranging from full recovery (75% of all patients)[2,3,20] to persistent neurological impairment. This is particularly true because of the nonspecific constellation of symptoms of ALE that can make it challenging to diagnose, such as psychosis, insomnia, memory and behavioural disturbances, seizures, dyskinesias, and autonomic dysfunction.[2]

The most common subtype of ALE is anti-NMDA-R (N-methyl-D-aspartate receptor) encephalitis, which is specifically when autoimmune antibodies target NMDA receptors at both synaptic and extra synaptic sites on neurons responsible for binding glutamate. This glutaminergic effect decreases the total levels of glutamate in the central nervous system, resulting in cognitive impairments and a characteristic psychosis.[11,12] Investigations to diagnose anti-NMDA-R encephalitis have low sensitivity, but often a full battery of tests will yield positive findings.

Here, we present a case of ALE where multiple repeat investigations were normal and the final diagnosis was made due to a strong clinical picture of glutamatergic psychosis that improved with treatment of ALE. The diagnosis and management of this case involved input from a multi-disciplinary team that included internal medicine, neurology, and consult-liaison psychiatry. This was a case where traditional investigative findings of ALE were not present, such as positive findings on magnetic resonance imaging (MRI) of the brain or pelvis. Autoimmune panels to screen for autoimmune antibodies such as anti-NMDA receptor antibodies were also negative.

Case history

Ms. BM was a 22-year-old female who was brought to the psychiatric in-patient unit for a crisis assessment. She presented with a floridly psychotic picture and collateral history detailed two to three days of increasingly bizarre behaviour. Interestingly, she had minimal past medical history of note. She was previously fit and well, with no interactions with the mental health system prior. On discussing with her family, she had features of generalised anxiety, but nothing that would be diagnosable as per DSM-V criteria.

On initial assessment, she displayed psychotic features including dyspraxia, thought disorder, auditory hallucinations, seizure-like episodes, and disorganised behaviour. Ms. BM was sectioned under the New Zealand Mental Health Act[4] and was admitted to the psychiatric in-patient facility. However, the psychiatric in-patient team felt that due to her acute deterioration of mental state, fluctuation of her psychoses during 24 hours of observation, and seizure-like episodes, investigation of an organic cause was necessary. Ms. BM was consequently transferred to the acute medical unit and transitioned to the care of the internal medicine service. A referral was made by the internal medicine service to the neurology and consult-liaison psychiatry (CLP) services for their review.

Ms. BM was investigated thoroughly for an organic cause of her delirium. Encephalitis is an important differential diagnosis for causes of organic psychosis, and ALE was therefore an early consideration. However, NMDA-R antibodies and other autoimmune antibodies were absent from cerebrospinal fluid (CSF) per lumbar puncture, and a follow-up MRI showed no features suggestive of encephalitis. Repeat computer tomography (CT) brain scans were performed two weeks apart, both of which showed no intracranial pathology to account for her symptoms. Abdominal and pelvic ultrasound scan (USS) and MRI pelvis showed no ovarian abnormality or ovarian pathology.

Multi-disciplinary advice was sought, and the team opted to treat for ALE after deliberation about other causes. Ms. BM was commenced on a five-day course of intravenous immunoglobulin-G (IVIG) and IV methyl-prednisone and rapidly improved in the first 48 hours. At the end of the five-day course, the battery screen for common neuroimmune antibodies returned as negative.

Despite some improvement, Ms. BM still displayed ongoing psychotic features, including delusions of reference, thought disorder, and catatonia, and the CLP service commenced the anti-psychotic medication olanzapine at 5 mg nocte and increased the dose to 10 mg nocte one week later. After some improvement in Ms. BM's presentation, and a further battery of investigations (see Tables 1–2 and supplementary material) that yielded no positive findings, it was decided by the primary team to discharge Ms. BM.

Ms. BM was discharged on olanzapine 5 mg daily but was brought back to the emergency department two days later. Her mother reported that she had suffered another seizure-like episode where her back had "contorted" and she had dropped to the bathroom floor at home. Ms. BM was incontinent during this episode and experienced focal amnesia after regaining consciousness.

After consulting the general medical service, a repeat MRI, electroencephalogram (EEG), and herpes simplex virus (HSV) screen were completed. These were unremarkable. This second admission on the ward came with new onset psychiatric symptoms which consisted of a fluctuating mental state, characterised by hypo- and hyperkinetic movements such as mutism, catatonia, and periods of excitement and bizarre behaviour. On repeat lumbar puncture, the CSF showed a pleocytosis of 9 white cells per mm^3. Discussion of plasma exchange ensued but due to her continued recovery, this treatment option was withheld.

After Ms. BM recovered to her baseline mental state, further history was able to be elicited and Ms. BM informed the team that she had suffered a prodromal viral illness two weeks prior to her presentation. Ms. BM was discharged with out-patient follow-up scheduled from both the neurology and CLP services. She was also discharged under the care of a community mental health team.

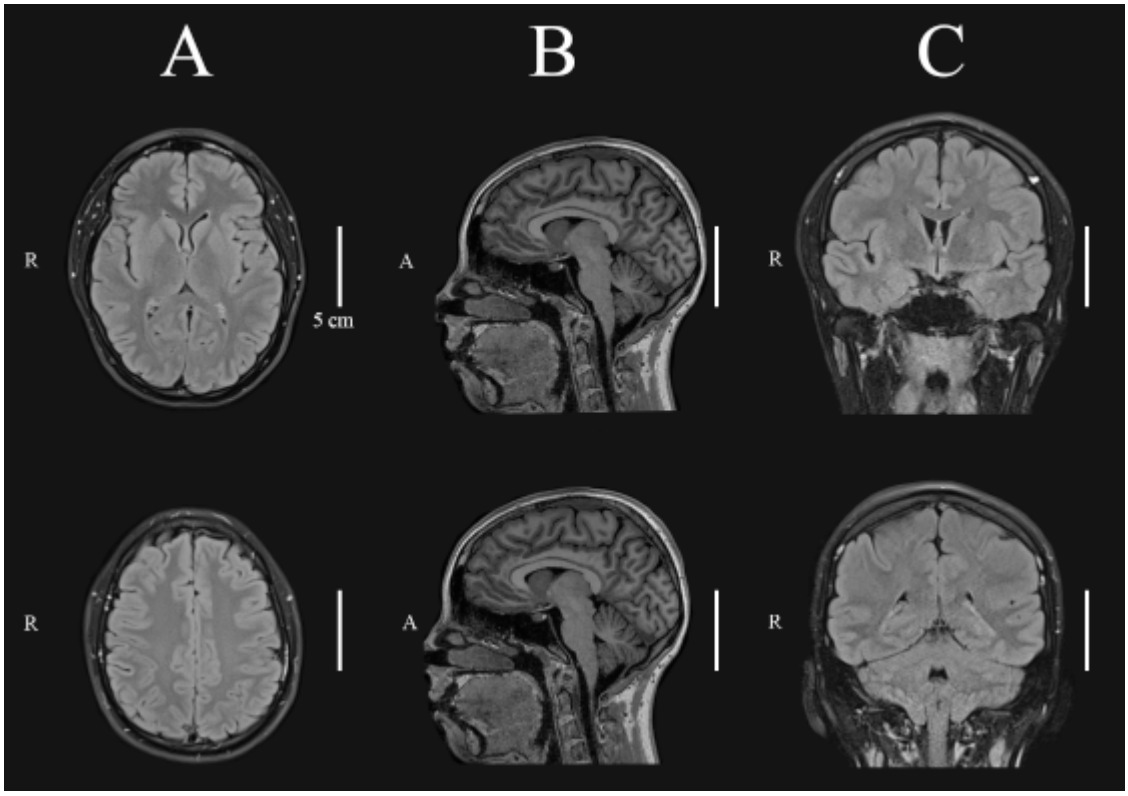
Table 1: Imaging investigations performed during BM's admission.

Imaging modality and site	**Result**
CT Head	No abnormalities detected
MRI Brain	No abnormalities detected
USS Pelvis	No abnormalities detected
MRI Chest/Abdo/Pelvis	No abnormalities detected
EEG	No abnormalities detected
MRI Brain repeat	No abnormalities detected

Table 2: Modified extract from Ms. BM's Mental State Examination clinical notes on day 12 of admission

Ms. B is a 22-year-old female who appears her stated age. She is dressed in hospital attire with marked evidence of poor self-cares, including overgrown fingernails and dishevelled, unkempt hair. Ms. B is wearing her hospital gown back to front and inside out with one sleeve rolled up, she is oddly positioned in her hospital bed with one leg folded underneath her and her left arm unnaturally wrapped behind her back, as if reaching for her right scapular region. She appears to have a pill-rolling tremor in her right hand, and she looks perplexed. Ms. BM is staring at the team and displaying abnormal physical jerking movements throughout the consult. Her speech lacked spontaneity and is disturbed with retardation of rate, quiet volume, and a monotonous tone. Her mood appears euthymic; her affect is flattened. Attending clinician is unable to access her thought form. Her thought content is difficult to assess as she is a poor historian. She appears to be responding to non-apparent stimuli. She is not oriented to time or place. Her cognition appears impaired, and she is unable to complete a formal cognitive examination. She displays no insight into current admission. Her judgement is poor. There is a high risk of self-neglect and of absconding from the ward.

Figure 1: Ms. BM's MRI Brain scan taken on day 12 of hospital admission. Column A: Axial T2 FLAIR BLADE. Column B: Sagittal T1 MPRAGE. Column C: Coronal T2 FLAIR. Label R: Right. Label A: Anterior.



Discussion

ALE is a multi-stage syndrome that can present with psychosis, insomnia, memory and behavioural disturbances, seizures, dyskinesias, and autonomic dysfunction.[2] While it was first described by Dalmau and colleagues in 2005,[2] the condition is now better characterised and this case report details a typical clinical picture that was missing positive investigative findings to confirm the diagnosis of ALE.

One of the key features of ALE is its association with a prodromal, non-specific viral illness that may present with headache, fever, vomiting, and upper respiratory tract symptoms.[2,3,5] This illness is typically followed by psychiatric symptoms, with initial presentation to psychiatrists and psychiatric in-patient units being common. It is therefore important for autoimmune encephalitis to remain a differential diagnosis in first presentation psychosis.[6,7]

In this case, Ms. BM displayed psychiatric symptoms which are common in ALE, including anxiety, grandiose delusions, hyper-religiosity, paranoia, social withdrawal, echolalia, mutism, and catatonia.[2,8-11] This particular psychosis is described as glutamatergic, as the autoimmune antibodies target the NMDA receptors responsible for binding glutamate, thus decreasing the levels of glutamate in the CNS.[12,13] A similar presentation has been induced *in vivo* and *in vitro* in animal models using phencyclidine and ketamine, both of which are non-competitive NMDA receptor antagonists and thus mimic the effect of NMDA receptor dysfunction.[2,14] Glutamate hypofunction has also been implicated in schizophrenia, which may explain the similar symptomatic presentation of ANMDAR-E and schizophrenia.[6,11,12,15]

Investigative tests in ALE typically have low sensitivity. Brain MRI will be normal in up to 50% of patients.[2,3] If positive, T2 or FLAIR signal hypersensitivity may be transiently seen in the hippocampi, cerebellar or cerebral cortex, basal ganglia, and the brainstem.[2,3] EEG will be normal in up to 10% of patients,[16] but may show slow, continuous, rhythmic activity in the delta-theta range.[2] CSF will have normal findings in 20% of patients but is likely to become abnormal as the disease progresses.[2,17,18] Importantly, there are likely no clinical features that will differentiate between antibody positive and negative patients.[19] Positive CSF findings include moderate lymphocytic pleocytosis (also seen in Ms. BM), mildly increased protein concentration, and CSF-specific oligoclonal bands.[2,17,18] Brain biopsy does not usually show any positive findings.[20,21]

Standard treatment for autoimmune limbic encephalitis (ALE) is early immunotherapy once infectious causes have been reasonably excluded.[22] First-line therapy typically includes high-dose intravenous corticosteroids, intravenous immunoglobulin, and/or plasma exchange; concurrent tumour screening and treatment is recommended where a paraneoplastic trigger is suspected.[22] Where there is inadequate clinical response, second-line immunotherapy such as

rituximab or cyclophosphamide is commonly used.[22] In Ms. BM's case, repeated investigations did not identify an infectious or structural cause, and her presentation remained compatible with probable autoimmune encephalitis; empiric immunotherapy was therefore justified to reduce the risk of ongoing seizures, cognitive decline, and autonomic complications.

There are many learnings in this case report relevant for current and recent medical students in New Zealand. Firstly, this case highlights the importance of a full battery work-up for first-presentation psychoses to catch more obscure diagnoses such as ALE and anti-NMDA-R encephalitis. This was particularly important for Ms. BM and was supported by epidemiological indicators. For example, females have a four-fold increased risk of ALE than males[3] and half of all females with ALE will have an ovarian teratoma, which is why imaging of Ms. BM's pelvis was relevant.[2] The prevalence of anti-NMDA-R encephalitis also peaks in the 18–25-year-old age group[18] and can be triggered by prior infection such as by HSV encephalitis which is why this was screened for.

Secondly, this case emphasises the benefits of working in a multi-disciplinary, multi-specialty team when tackling complex presentations. Ms. BM's presentation would be considered amongst the statistical minority of ALE presentations where most, if not all, of the investigations were considered unremarkable. Collaborative care was particularly important in this case because, if left untreated, ALE can progress into catatonia, hypoventilation, and coma.[2,3] The prognosis of ALE also improves if treatment is given within the first month of illness[6] which is why a timely diagnosis is important.

Finally, this case shows the difficulty of discriminating between a functional psychiatric presentation and the psychiatric presentations of autoimmune neurological disorders. When non-psychiatric symptoms also manifest (commonly seen in the form of seizures, dyskinesias, and autonomic instability[2,3]) they are often confounding and may lead to erroneous treatment

with anti-epileptics (although it is not erroneous to use anti-epileptics if the patient has a seizure). Specialist neurology input was sought for the repeat electroencephalograms that showed no evidence of seizure-like activity.

Conclusion

This case report highlights the importance of understanding the clinical picture of ALE and enacting prompt and accurate treatment. Although investigative tests in ALE have low sensitivity, the typical clinical picture and awareness of the association with a prodromal viral illness can aid in early diagnosis and treatment. Early intervention can improve prognosis and help prevent the progression of the disease to potentially life-threatening complications.

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Consent

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