Neurological picture

Anti-NMDA-receptor encephalitis: unusual presentation of an uncommon condition

A 19-year-old woman with no significant past medical history presented to the hospital after a 1-week illness. Her symptoms began with 2 days of vomiting, diarrhoea and decreased sensation in the fingertips. She subsequently developed emotional labiality and auditory hallucinations characterised by a persistent background humming. On the fifth day of her illness, she developed dysarthria and expressive aphasia. Initial examination approximately 1 week from symptom onset was significant for expressive and receptive aphasia, inattention and disorganisation, and fluctuating mental status consistent with delirium, with no obvious motor deficits. Brain MRI revealed a left medial temporal T2 hyperintensity without enhancement on FLAIR (figure 1A). Cerebrospinal fluid (CSF) revealed 129 nucleated cells with a lymphocytic predominance and no red blood cells. Extensive serum and cerebrospinal fluid testing, including CSF PCR for herpes simplex virus (HSV) 1 and 2, was unremarkable. Given her clinical presentation and MRI findings, paraneoplastic limbic encephalitis was suspected, and CT scan of the chest, abdomen and pelvis revealed a 1.9 cm right ovarian dermoid (figure 2), as well as ground-glass opacities in the lungs, later determined to be mycoplasma pneumonia. The teratoma was removed within 24 h, and five plasmapheresis treatments were completed over the following 2 weeks. Serum and CSF anti-N-methyl-D-aspartate (NMDA)-receptor antibodies later returned positive by immunofluorescence (1:960 serum, 1:8 CSF). Serum striational antibodies were also found as part of a comprehensive paraneoplastic antibody panel; these striational antibodies were present in the absence of acetylcholine-receptor modulating antibodies, which is a non-specific finding suggestive of autoimmunity.[1 2] She had no clinical symptoms suggestive of a myasthenic disorder, and the striational antibodies were no longer present on follow-up testing after treatment. A full paraneoplastic antibody panel was otherwise negative in CSF and serum.

Examination was normal 1 month after discharge with the exception of mild calculation difficulties, and follow-up MRI showed resolution of abnormalities (figure 1B). Paraneoplastic limbic encephalitis was once considered a rare entity, but is becoming recognised as a relatively frequent disorder, and is often responsive to treatment.[3 4] Atypical features of this patient's presentation were the absence of dyskinesia, movement disorder, central hypoventilation or autonomic instability.[5] Additionally, she did not present with seizure activity or non-convulsive status epilepticus, and only experienced one clinical seizure over the course of her illness (within 48 hours after surgical removal of the dermoid) despite a typical EEG pattern consisting of δ and θ slowing with central bisynchronous spike-wave complexes.

The literature contains reports of other partial phenotypes, including one report of an isolated hemidystonia associated with NMDA-receptor antibodies in a 19-year-old female,[6] as well as a prospective report of four patients (out of 46 analysed) who presented with first time psychosis and were found to have anti-NMDA-receptor antibodies.[7] A report by Niehusmann and colleagues prospectively identified five young women (out of 19 analysed) with new-onset unexplained epilepsy to have anti-NMDA-receptor antibodies, all of whom were found to have EEG findings suggestive of extratemporal epilepsies and 4/5 of whom had prominent psychiatric symptoms.[8] Speech dysfunction and decreased level of consciousness were also noted in the anti-NMDA-receptor patient group, but the report did not further specify the exact symptoms or frequency in the cohort. In an overview of clinical experience with over 400 anti-NMDA-receptor positive patients, Dalmau *et al* estimated that pure monosymptomatic syndromes arise in

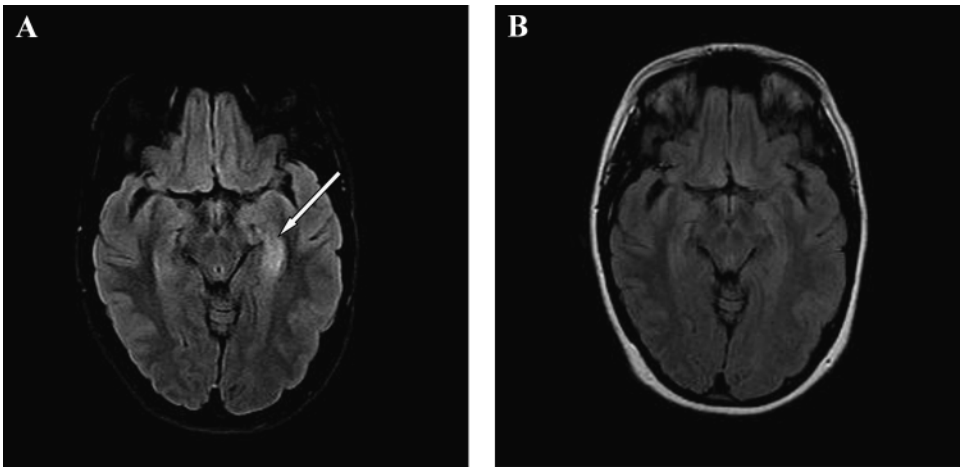

Figure 1 MRI of the brain revealed a left medial temporal T2 hyperintensity without enhancement on FLAIR image (A), with resolution of the hyperintensity at 2-month follow-up (B).

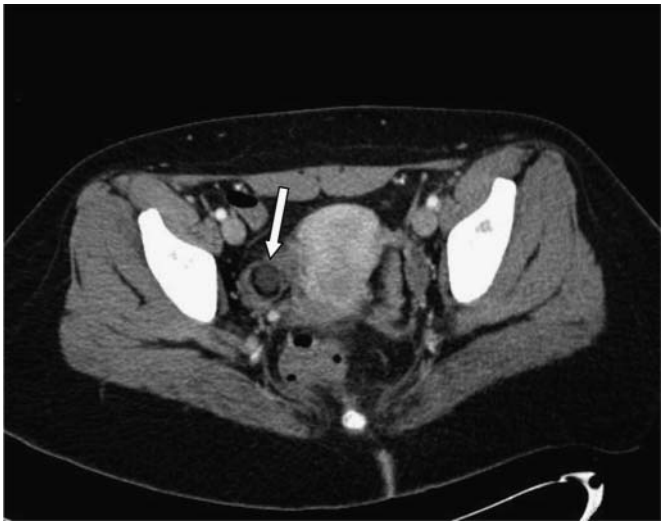

Figure 2 CT scan of the chest, abdomen and pelvis revealed a 1.9 cm right ovarian dermoid, later pathologically identified as a mature teratoma.

<5% of patients, and suggest that perhaps more commonly patients may present with a predominant symptom and milder manifestations of other elements of the syndrome.[9] This case describes a unique example of an early and/or less severe phenotype in the clinical spectrum of anti-NMDA-receptor encephalitis. Early recognition of such phenotypes could have positive clinical implications.

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Multiple Choice Question:

A 19 year old female presents to the Emergency Department with a one week history of emotional labiality and auditory hallucinations characterized by a persistent background humming which began following a two day prodromal illness of vomiting, diarrhea, and decreased sensation in the fingertips. On exam, she demonstrates moderate expressive and receptive aphasia and fluctuating mental status. Her imaging, including MRI of the brain and CT scan of the pelvis, is shown below (see attachments). What is the most likely diagnosis?

Ischemic stroke
Acute Disseminated Encephalomyelitis (ADEM)
Herpes Encephalitis
Anti-NMDA receptor encephalitis
Multiple Sclerosis
Mesial Temporal Sclerosis

Anti-NMDA receptor encephalitis represents one type of limbic encephalitis. Anti-NMDA receptor antibodies are often found in association with underlying malignancy, often an ovarian teratoma. A high index of suspicion should be present in acute psychiatric symptoms, often preceded by a prodromal -viral-like illness, in a previously healthy patient with no clear precipitating cause. Common associated symptoms include seizures, decreased consciousness, dyskinesias, autonomic instability, and hypoventilation.

Brain MRI revealed a left medial temporal T2 hyperintensity without enhancement on FLAIR. MR Spectroscopy revealed a decreased NAA peak in the left hippocampus, suggestive of neuronal injury. With appropriate clinical suspicion, investigation for an occult neoplasm should be undertaken, as in this patient where a CT scan of the chest, abdomen and pelvis revealed a 1.9 cm right ovarian dermoid.

Treatment involves removal of the underlying tumor (if present), followed by a combination of corticosteroids, plasma exchange, and/or intravenous immunoglobulin. Management of complex cases or chronic maintenance therapy often also includes a combination of cyclophosphamide and/or rituximab.

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