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A severe anti-NMDA-receptor encephalitis case with extensive cortical and white matter changes, cerebral atrophy and communicating hydrocephalus

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Abstract

A 21-year-old woman presented with a viral prodrome, abnormal behaviours, confusion and short-term memory loss, followed by status epilepticus that later evolved to orofacial dyskinesias, autonomic dysfunctions and hypoventilation requiring prolonged ventilator support and ICU admission. Cerebrospinal fluid (CSF) and serum analysis confirmed the presence of anti-NMDAR autoantibodies. A left salpingoopherectomy was performed on day 35 of admission revealing an immature ovarian teratoma. Following surgical and two courses of intravenous immunoglobulin therapy, her response remained poor. Initial brain magnetic resonance imaging (MRI) during the acute stage showed enlarged left hippocampus. Further MRI follow-up 13 weeks after admission showed unusual findings of extensive cortical and white matter changes, generalised cerebral atrophy, dilated ventricles and possible transependymal CSF seepage of communicating hydrocephalus. A ventriculo-peritoneal shunt was performed subsequently and she was discharged 6 months after admission without significant change in her clinical status. Follow-up 4 months later showed some improvement but patient remained severely disabled.

Keywords

Anti-NMDA-receptor, encephalitis, cortical and white matter changes, cerebral atrophy, hydrocephalus

Introduction

Anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis is a rare immune-mediated syndrome that is predominantly described in young females with ovarian teratoma. Since its discovery in 2007,[1] it is increasingly recognised as an important cause of autoimmune encephalitis. Patients typically present with neuropsychiatric symptoms, often with viral prodrome, that evolves to include seizures, dyskinesias, autonomic dysfunctions and decreased consciousness level.

This disorder is severe, yet potentially treatable. The best outcome depends on prompt immunotherapy and complete tumour removal. However, its diverse presentations and low awareness among clinicians often cause delay in diagnosis and treatment. Standard laboratory and radiologic investigations including brain magnetic resonance imaging (MRI) have limited role in diagnosis, given the non-specific and often negative findings.

We report a severe and protracted clinical course of anti-NMDAR encephalitis in a young woman with ovarian teratoma who had unusual findings of extensive parenchymal abnormalities, generalised cerebral atrophy and ventricular dilatation with potential presence of communicating hydrocephalus on her brain MRI.

Written informed consent for patient information was obtained from a legal authorised representative.

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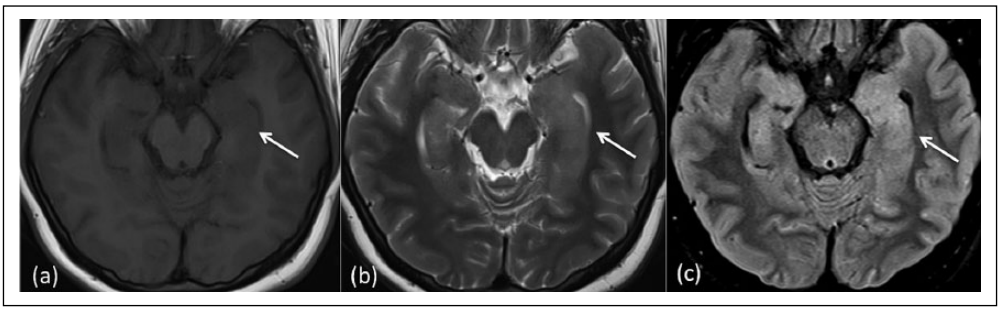

Figure 1. Magnetic resonance imaging scan of the patient at symptom presentation. Axial (a) T1 (b) T2 and (c) FLAIR images demonstrates enlarged left hippocampus which appears mildly hyperintense on T2/FLAIR and hypointense on T1 (white arrows).

Case presentation

A 21-year-old previously healthy Malay woman presented to a district hospital with 3-day history of bizarre behaviours, confusion and short-term memory loss preceded by a 1-week history of fever and headache. At the emergency department, she developed generalised tonic-clonic seizures that were treated with intravenous phenytoin. Her general examination, routine blood studies and computed tomography (CT) brain were unremarkable. Cerebrospinal fluid (CSF) was clear with high opening pressure (27cm H_2O), 0 cell count and normal protein and glucose level. Extensive bacterial, viral and fungal studies were unrevealing. Thyroid profile, complement C3 and C4, anti-nuclear antibodies, anti-nuclear-cytoplasmic antibodies and tumour markers were negative. Intravenous acyclovir was started for presumed viral-herpes encephalitis, which was subsequently discontinued after negative herpes simplex virus polymerase chain reaction (PCR). Further brain MRI imaging was obtained, which showed enlarged left hippocampus with subtle T2 hyperintensity (Figure 1).

The patient deteriorated rapidly within days. Her generalised seizures progressed to status epilepticus for which she required intubation and intensive care unit (ICU) admission. In ICU, the generalised seizures had improved; however, frequent facial grimacing, lip smacking and intermittent dystonic posturing of upper limbs were observed. These orofacial dyskinesias were initially interpreted as refractory seizures, leading to escalation of high doses of antiepileptics (i.e. intravenous phenytoin, sodium valproate, levetiracetam and carbamazepine) and use of anaesthetic agents (i.e. thiopental and propofol). Electroencephalograms (EEG) were performed six times in ICU, which demonstrated diffuse slow delta wave activities without epileptiform discharge despite the presence of the abnormal movements. The antiepileptics and anaesthetic drugs later were gradually deescalated. She also manifested autonomic instabilities including hypotension, bradycardia, hypersalivation and hypoventilation. At this stage, a diagnosis of anti-NMDAR encephalitis was suspected. The presence of anti-NMDAR autoantibodies was later confirmed in the CSF and serum. The antibody titre, however, was not available as our local laboratory did not routinely perform the test. Given the frequent association between NMDAR antibodies and ovarian teratoma, a pelvic ultrasound was performed, which showed a large left ovarian cyst. She was then urgently transferred to our tertiary institution's ICU for further expert management.

A left salpingoopherectomy was performed on day 35 of admission (from symptom onset) revealing a large left ovarian mass. Histopathological examination confirmed an immature ovarian teratoma. She also received intravenous immunoglobulin (IVIG) 0.4g/kg body weight/day for 5 days. Despite medical and surgical therapy and discontinuation of sedations, the patient remained unresponsive. Her eyes would remain open without blinking to threat, blankly staring into space. There was no response to intensive pain stimuli. She also had frequent apnoeic episodes, making it difficult to wean her off the ventilator. Due to poor response, a second round of IVIG was given. In the following 6 weeks, she started showing some improvement. The dyskinesias and dysautonomias gradually subsided. Spontaneous blinking, attempts at head movements, and grimacing to pain were also noted. She was successfully weaned off the ventilator during this period (after 3 months admission). Her progress afterwards, however, remained unchanged. Her clinical course was complicated by recurrent sepsis; corticosteroid and second-line immunotherapy were thus not given.

Follow-up MRI brain performed 13 weeks after admission showed extensive cortical and white matter changes and generalised cerebral atrophy with asymmetrical loss at the temporal lobes (Figure 2). All ventricles were dilated with evidence of periventricular white matter changes, in which transependymal CSF seepage of communicating hydrocephalus was considered as a differential (Figure 2). Clinical assessment of raised intracranial pressure was difficult to perform due to the patient's unresponsiveness. CSF analysis revealed normal opening pressure, pleocytosis (white cell count 20 cells/ml, predominantly polymorphonuclear), elevated protein (1.73g/l) and normal glucose. She was empirically treated for tuberculous meningitis after exclusion of bacterial and fungal aetiologies. CSF tuberculosis, PCR and culture later returned negative. Repeat clinical assessment by fundoscopy after 1 week revealed evidence of papilloedema. Based on this sign and the poor clinical status in a high-risk patient together with the radiological findings, the decision to perform ventriculo-peritoneal (VP) shunt for hydrocephalus treatment was made by the neurosurgical team. A follow-up CT brain 4 days post-VP shunt showed a reducing degree of communicating hydrocephalus. However, there was no significant change in her clinical

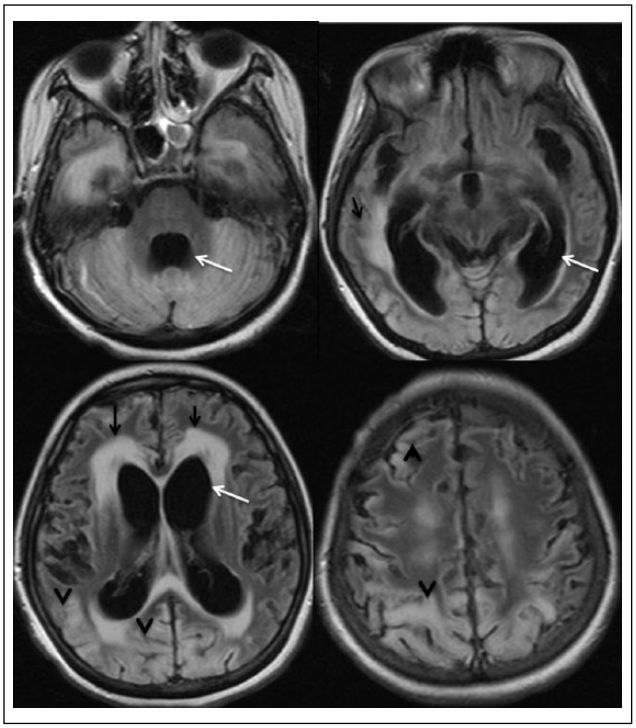

Figure 2. Magnetic resonance imaging scan of the patient 13 weeks after admission. Axial FLAIR images of the cerebral hemispheres demonstrate extensive FLAIR hyperintensities involving the cerebellum, temporal, parieto-occipital and right frontal regions (arrowheads) with generalised cerebral atrophy. The atrophy loss is more prominent in the left parieto-occipital lobe. All ventricles are dilated (white arrows) with evidence of periventricular hyperintensities (black arrows); the main differential is transependymal CSF seepage seen in communicating hydrocephalus, which is difficult to diagnose in the setting of brain atrophy.

status post-shunt insertion. Six months after admission, she was eventually discharged.

At follow-up 4 months after discharge, she remained severely disabled. However, some improvements were noted: she could smile, cry, move her eyes and head and intermittently raise her arms spontaneously. Dykinesias and dysautonomias were resolved completely. She is still on regular follow-up by our neurology and neurosurgical team.

Discussion

Anti-NMDAR encephalitis is an autoimmune disorder mediated by antibodies against the NR1 subunits of the receptor in the hippocampus and forebrain.[2] Although the exact incidence is unknown, previous study suggested it may be the second most common immune-mediated cause after acute demyelinating encephalitis.[3] The majority of cases involved young females (median age 23 years) with an underlying tumour (59%; most commonly an ovarian teratoma),[2] with a more recent study[4] indicating a lower tumour incidence (38%). The tumour presence is more frequent in older women (age >18 years) and in African-American and Asian patients,[4,5] possibly suggesting genetic predisposition.

Clinical manifestations occur in phases.[6] This initially involves prodromal flu-like symptoms before invariably progresses to a psychotic period including mood and behavioural disturbances, cognitive decline, amnesia and psychosis followed by decreased responsiveness. Later, development of seizures, abnormal movements especially orofacial dyskinesia and autonomic instabilities manifesting as hyper-hypotension, tachy-bradycardia, cardiac dysrhythmias, hyperthermia and hypoventilation can ensue. Our patient followed these stereotypical clinical stages. She had a severe and protracted clinical course that was complicated by status epilepticus, recurrent sepsis, prolonged ventilator support and VP shunt insertion for communicating hydrocephalus.

The diagnosis of anti-NMDAR encephalitis is often difficult and requires exclusion of other mimics including infectious, endocrine and other immune-mediated aetiologies. The typical CSF analysis for anti-NMDAR encephalitis is lymphocytic pleocytosis with either normal or elevated protein,[2,7] which was absent in our case. Demonstration of anti-NMDAR autoantibodies in the CSF and serum confirm the diagnosis. EEG is abnormal in 90% of cases, usually showing non-specific generalised slowing activities[2,7] which do not correlate with abnormal movements and do not respond to antiepileptics,[5] as presented in our case.

Brain MRI is often unrevealing, although some patients (55%) have T2/FLAIR hyperintensity in variety of regions including the hippocampi, cerebellar and cerebral cortex. These findings are non-specific, correlate poorly with symptoms and usually mild and transient.[2] In our case, the patient's MRI during the acute disease stage initially showed left hippocampal involvement. Her MRI follow-up 13 weeks after admission showed extensive cortical and white matter changes with generalised cerebral atrophy – findings that are unusual and have never been reported before in the literature. There was a previous report of brain atrophy cases in patients with severe clinical course;[8] however, the atrophy was focal and was not associated with extensive parenchymal changes as seen in our case. Another rare finding in this case is the communicating hydrocephalus. A similar case of communicating hydrocephalus in anti-NMDAR encephalitis has been reported recently.[9] In our patient, the potential presence of communicating hydrocephalus based on the ventricular dilatation and periventricular white matter changes (possible transependymal CSF seepage) was a challenge to diagnose in the setting of brain atrophy. Clinical assessment for hydrocephalus in an unresponsive patient is difficult. Moreover, the patient may present insidiously in chronic cases. The decision to treat was made based on the radiological features and poor clinical status in a high-risk patient with autonomic condition and recurrent infections. The cause of hydrocephalus could not be found, although it may be related to parainfectious aetiology causing blood–brain barrier leakage and disturbance of CSF homeostasis, resulting in excess production and decreased absorption of CSF. It may also result in the elevated CSF protein that can cause obstruction of the arachnoid granulations leading to the communicating hydrocephalus. Whether or not the elevated CSF protein and the hydrocephalus (if present) are directly related to anti-NMDAR encephalitis is unknown. To our knowledge, there has been no report in the literature on late CSF findings in anti-NMDAR encephalitis. More late laboratory and neuroimaging studies to look into the pathophysiological mechanism behind these find-

ings as well as risk and long-term outcome of brain abnormalities in anti-NMDAR encephalitis are suggested.

Despite the severity, anti-NMDAR encephalitis is potentially treatable. Treatment strategies consist of tumour removal with corticosteroid and IVIG or plasmaphoresis as first-line therapy and rituximab and cyclophosphamide as second-line therapy. Titulaer et al. showed that immunotherapy and tumour removal result in improvement in 81% of patients with anti-NMDAR encephalitis after a median follow-up of 24 months.[4] This study also showed that second-line therapy is usually effective when first-line therapy fails. Relapses occur in 12% of patients, often in those undetectable, recurrent or without tumour.[4] Our patient did not receive corticosteroid or second-line immunotherapy due to active infection in the initial and later stage of disease.

The prognosis of anti-NMDAR encephalitis depends on early recognition, prompt immunotherapy and complete tumour removal if present. Its diverse clinical presentations and the protracted courses of symptom development often impose a challenge in diagnosis, as observed in our case. Many clinicians are not aware or have limited knowledge of this disorder, causing delay in diagnosis and treatment. Most often, it is dismissed initially as a psychiatric symptom or viral encephalitis. Screening for anti-NMDAR autoantibodies should be considered in young women with acute neuropsychiatric symptoms and abnormal movements to allow for early detection and treatment.

Conclusion

Magnetic resonance imaging abnormalities seen in anti-NMDAR encephalitis are generally mild and non-specific. Findings of extensive cortical and white matter changes with cerebral atrophy and communicating hydrocephalus as presented in our case, however, have never been described before in the literature. Future neuroimaging studies are needed to understand the pathophysiological mechanism behind these changes. Despite an expanding body of literature, anti-NMDAR encephalitis remains under-recognised. Heightening the awareness among clinicians is imperative to ensure prompt recognition and treatment, since this disorder is potentially reversible.

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Declaration of conflicting interests

None declared.

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