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Adel Ekladious *

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Review Article

Autoimmune Limbic Encephalitis

Abd Razak [1], Adel Ekladious [2,3*], Farhan Ahmad Aizaz [4]

[1] John hunter hospital, Hunter new England Health,

[2] faculty of Health and Medical Sciences, University of Western Australia, 35 Stirling Hwy, Carwley, 6009, Western Australia.

[3] Royal Hobart Hospital, 48 Liverpool Street, Tasmania 7000, Australia.

[4] general practitioner , Perth Western Australia.

Corresponding Author: Adel Ekladious. Associate Professor, Faculty of Health and Medical Sciences University of Western Australia. Email: ekladiou@gmail.com.

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Abstract

We present a case of Herpes Simplex encephalitis which evolved into autoimmune limbic encephalitis. With ongoing follow-up and re-assessment of the patient, the diagnosis was refined and specific treatment could be initiated with very good outcome.

This case illustrates the diversity of presentation of this disease. In this case, it presented with neuropsychiatric manifestations and followed a Herpes Simplex viral infection rather than it being caused by a paraneoplastic syndrome.

Keywords: neuropsychiatric encephalitis; limbic autoimmune encephalitis; herpes encephalitis

Case Presentation

A 34-year-old female teacher presented to the Emergency Department (ED) with an acute onset of confusion, insomnia, headache, and delusional thoughts. She had recently returned back to Australia after visiting her parents in London in the United Kingdom.

Her past medical history was unremarkable apart from a diagnosis of hypothyroidism. At the time of diagnosis, her TSH receptor antibodies were positive. She was treated with thyroxine 50 micrograms. At the time of review, she was clinically euthyroid and recent TSH, T3 and T4 were normal.

She was a non-smoker and drank two approximately glasses of red wine per day. She did not use recreational drugs. She was married to a teacher and had a 10-year-old, healthy son. She played netball twice a week. Her family medical history was unremarkable.

While in ED, the patient developed generalised seizures. Repeated doses of diazepam failed to control the seizure, so the patient was intubated, mechanically ventilated, and admitted to the Intensive Care Unit (ICU).

On arrival to the ICU, she was febrile at 38 degrees Celsius, and her blood pressure was 110/60. There was no neck stiffness, no rash and no localising neurological signs. There were cold sores visible on her lower lip.

Cardiac auscultation revealed a pan-systolic murmur over the mitral area with radiation to the left axilla. The chest examination and the remainder of the examination was otherwise unremarkable.

As advised by the Infectious Disease team, the patient was started empirically on Acyclovir 10mg/kg IV TDS, in addition to Vancomycin 15 mg/Kg TDS, Ampicillin 2grams /4hours, Ceftriaxone 2grams/12 hours and Dexamethasone 10 mg QID for four days.

An array of tests was subsequently ordered. Blood tests included FBC, UEC, LFTs, coagulation screens, blood cultures. Throat and vaginal swabs were taken, and PCR for Herpes simplex, Herpes zoster, Enterovirus, Streptococcus, Staph aureus, Neisseria gonococcus and Haemophilus influenza were sent. A CSF study was performed and analysed for cells, protein and viral and bacterial PCR and serology.

A transthoracic echo did not show vegetations. An MRI with and without Gadolinium showed a high signal area involving medial temporal lobes and the insula cortex bilaterally in T2 and Flair images. DWI/ADC confirmed mild restricted diffusion and cytotoxic oedema.

In Day 3 in the ICU, the fever resolved. By now, PCR confirmed Herpes simplex encephalitis. All antibiotics were subsequently discontinued, and Acyclovir was continued. The patient was eventually extubated and remained haemodynamically stable. The patient regained consciousness but was delirious with confusion, agitation and sleepiness.

A repeated MRI showed resolution of the cytotoxic oedema. The patient was discharged from the ICU on Day 8 under General Medicine. A repeat

septic screen was negative for any infection, however the patient remained confused. Dietary support was offered via a nasogastric tube (NGT) and supervised by a dietitian. Refeeding syndrome was ruled out with daily electrolytes (including phosphate) and repeat B12, folate, copper and ECGs. Despite this treatment, the patient remained confused. A repeat Transthoracic Echocardiogram and Trans-oesophageal Echocardiogram was normal.

At this point, a neurologist opinion was sought. An EEG showed generalised periodic spikes which was interpreted as a non-convulsive status epilepticus. A drug screen for metabolic encephalopathy was negative. The patient was accepted under neurology and started on levetiracetam and sodium valproate. The patient's confusion worsened, and EEG monitoring failed to show improvement. The patient then became un-arousable.

Repeat MRI showed high signals in both mesial temporal lobes and cortical thickening, in addition to increased signal in T2/Flair images, and a new increased signal in the basal ganglia. A CT-PET scan of the entire body showed increased Fludeoxyglucose F 18 Injection (FDG) activity in both temporal lobes.

A repeat lumbar puncture showed lymphocytic pleocytosis. The CSF was sent for onconeural intracellular and neuronal cell surface antibodies. NMDA receptor antibodies and GAD-65 antibodies were positive. At this stage, a diagnosis of autoimmune encephalitis was made, in addition to the diagnosis of treated viral encephalitis. The patient was started on methyl prednisolone 1 gram IV daily for five days, and IVIG 0.4mg/kg for seven days. The patient improved significantly, and EEG abnormalities resolved.

All anticonvulsants were later ceased, and the patient's prednisolone doses were tapered. The patient was started on calcium, vitamin D and Denosumab for bone protection and was referred for rehabilitation and follow-up in a neurology and autoimmune clinic. At the follow-up appointments, the patient remained asymptomatic and all un-necessary medications were ceased.

Discussion

Autoimmune limbic encephalitis (ALE) is an inflammatory disease involving the medial temporal lobes. It classically presents with rapid neuropsychiatric decline. Patients with ALE may present with a diverse array of neuropsychiatric symptoms. The condition was first described as a paraneoplastic phenomenon, however after disease-causing antibodies were found, it was shown to be non-paraneoplastic in many cases. The prevalence and incidence of ALE is comparable to infectious encephalitis and its detection is increasing over time. ALE most frequently occurs in middle-aged adults, but it can affect people of all ages.

In the acute phase, many patients with ALE show disorientation, short-term memory deficits, confusion, confabulation and amnesia, which are features that may relate to the dense expression of many autoantigens in limbic structures, particularly the hippocampus [1]. Typically, within two weeks of onset, prominent psychiatric symptoms and personality changes emerge.

Focal neurological deficits may include seizures, aphasia, and motor and sensory deficits. Patients with brainstem encephalitis may experience oscillopsia, diplopia, vertical and horizontal gaze abnormalities, facial numbness, dysarthria, hearing loss and dysphagia.

Sleep-disorders are frequent and often severe, and usually persist beyond the acute disease stage, interfering with patients' quality of life. These features may initially be masked by other neurological deficits [1].

Hypothalamic dysfunction may also occur and manifest as hyperthermia, somnolence, and endocrine abnormalities. Symptoms typically evolve over days to weeks, but more indolent presentations over months have been described.

The commonest autoantibodies linked to ALE are NMDA-R, LGI1 and GABA-R. These autoantibodies often relate to a certain disease phenotype. For example, NMDA-R antibodies are often found in young female patients who present acutely with psychiatric manifestations and frequent ovarian teratoma, while LGI1 antibody positive cases are often males who present insidiously with frequent focal seizures and amnesia. Despite the prevalence of autoantibodies causing ALE there are also cases of seronegative ALE [2].

While the clinical features of these disorders span the spectrum of neurological symptomatology, patients with autoantibodies against any individual target tend to show a characteristic set of core phenotypic manifestations which may relate to the regional expression, function and relative susceptibility of the target protein.3

Criteria [1,4]

1.Acute or subacute (<12 weeks) onset of symptoms

2.Evidence of CNS inflammation (at least one of):

2.1.CSF (lymphocytic pleocytosis, CSF specific oligoclonal bands or an elevated IgG index);

2.2.MRI (eg, mediotemporal lobes Flair/T2 hyperintensities in case of a ALE-like syndrome— otherwise unexplained (eg, post-seizure); or enhancement of cerebellar sulci) or functional imaging (hypermetabolism on FDG-PET or hyperperfusion on single photon emission computed tomography in the acute–subacute phase);

3. Inflammatory neuropathology (lymphocytic infiltrates or other signs of immune activation) on biopsy.

4. Exclusion of other causes (infective, trauma, toxic, metabolic, tumours, demyelinating or histories of previous CNS disease) [5].

In adult-onset NMDA-R-antibody encephalitis, psychiatric features are typically the presenting complaint. Patients are often assessed by a mental health team before a neurology consultation is sought after. Relatively isolated psychiatric features occur in these patients at disease onset, but after a few days, neurological abnormalities such as delirium, amnesia and seizures may occur. In younger patients, radiological changes are often absent.

Patients with LGI1-antibody and NMDA-R-antibody syndromes, and other forms of limbic encephalitis, often experience a dense amnesia for the period of acute hospitalisation, especially the nadir of their disease. In LGI1-antibody encephalitis, the amnesia characteristically affects both anterograde and retrograde.

Patients with anti-VGKC antibodies may exhibit classic features of "limbic encephalitis" such as prominent seizures, and uncommonly, extra-limbic involvement [6,7].

Investigations

MRI and PET scan are important modalities for investigating suspected cases of ALE.

As many as 60% cases of autoimmune encephalitis have no imaging findings, particularly early in the course of the disease. This is in contrast to Herpes simplex encephalitis where the MRI is abnormal in most cases. Despite this, MRI with contrast is considered the most sensitive imaging modality for ALE and findings are present in over 50% of cases.8 True diffusion restriction (i.e. low ADC values) and haemorrhage are not common and suggest alternative diagnoses.

Both serum and cerebrospinal fluid testing for the most commonly identified antibodies in ALE (anti-LGI1, GABABR, AMPAR, CASPR2, Hu, Ma2 and GAD) should be considered, to maximize diagnostic yield, as some antibodies (e.g., anti-LGI1) are more sensitive in the serum. Other antibodies (e.g., anti-GABABR) may be identified only in the cerebrospinal fluid. Antibody testing is always worthwhile, even in patients who already meet the Graus criteria for definite ALE, as a positive antibody may indicate the likelihood of a specific tumour and inform malignancy screening.

An EEG may show significant changes. In anti-NMDA autoimmune encephalitis, the EEG may show an extreme delta brush, identified as generalised rhythmic delta activity plus fast activity. There is also a high incidence of seizures among patients with AE. Seizures may exhibit periodic or rhythmic patterns [9].

Management

Managing ALE should be performed as early as possible to allow for the best chance of recovery. The 3 main approaches to management include:

1. Excluding underlying disease such as cancer, infection or autoimmune disease other than ALE. This could involve further pathology testing, imaging or procedures.

2. Treating symptoms such as seizures, psychiatric or neurological deficits.

3. Immune therapy (the mainstay of treatment) which may include steroids, steroid-sparing agents, immunoglobulins or plasma exchange. Treatment should not be delayed and should be initiated once other causes have been excluded.

First-line immunotherapies include corticosteroids alone or in addition to IV immunoglobulin (IVIG) or plasma exchange (PLEX).

Common dosages are IV methylprednisolone 1 g/day for 5 days (or bioequivalent oral corticosteroids) IVIG 0.4 g/kg/day typically divided over 4-5 days Plasma exchange 1 session every other day for 5-7 cycles 1-1.5 plasma volume.10

After the initial 5-day treatment one may consider a tapering regimen with oral glucocorticoids (prednisone) or intermittent IV pulse steroids for 6-12 weeks such as:

- methylprednisolone 1 g once weekly

additional IVIG 0.4 g/kg once weekly (or another round of 2 g/kg divided over 4-5 days.

Second-line therapies (such as rituximab, cyclophosphamide, or combination therapy) should be considered for patients who fail to demonstrate sustained improvement to first-line treatments.11-14

Other treatment strategies are emerging. Immunoadsorption with staphylococcal protein A column has also been tried with some success.15 Tocilizumab might be a good treatment strategy for treating AE refractory to conventional immunotherapies and rituximab.16 Patients not responding to first and second-line therapies should be worked-up for an alternative diagnosis.

A poor response to immunotherapy, mechanical ventilation and autonomic dysregulation are bad prognostic factors in ALE.17 Those who respond may relapse and have higher incidences of cancer in the long term compared to patients with infectious encephalitis [18].

Conclusion

This is another case of post-infective (Herpes Simplex encephalitis) autoimmune encephalitis. The clinical significance of this case is to help illustrate the importance of seeking an alternative explanation if the patient is not improving as suspected after initial treatments. ALE commonly presents with neuropsychiatric features such as seizures, focal neurological signs, and sleep disturbances. MRI, PET scan and brain inflammatory markers including autoantibodies help to fulfill the diagnosis.

Immunotherapy, including steroids, steroid sparing and biological agents are the main therapeutic options. The outcome is worse in patients who do not respond to these therapies.

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