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ANTI-LGI1 AUTOIMMUNE LIMBIC ENCEPHALITIS: AN EASY-TO-MISS DIAGNOSIS

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ABSTRACT

Background: Autoimmune limbic encephalitis (ALE) is a rare inflammatory disorder characterised by a subacute onset, usually within weeks. The presence of multiple neuropsychiatric symptoms such as seizures, short-term memory deficits, anxiety and depression often leads to misdiagnosis as another medical condition, contributing to poor prognosis and reduced long-term survival.

Case description: A 60-year-old man, with no chronic illnesses, presented at the emergency department with daily episodes of palpitations, shivering, piloerection and a sense of impending doom lasting two months. Initially diagnosed with anxiety disorder and treated with venlafaxine 50 mg daily, he showed no improvement and developed memory loss. Hospitalised three months later, he exhibited both temporal and spatial disorientation, along with short-term memory loss. Key findings included elevated serum sedimentation rate, hyponatraemia, increased cerebrospinal fluid (CSF) protein levels and cranial magnetic resonance imaging evidence of bilateral temporal intra-parenchymal lesions, suggesting limbic encephalitis. After ruling out alternative diagnoses, screening of autoantibodies in the CSF was requested, which was positive for anti-LGI1 antibodies. The diagnosis of anti-LGI1 ALE was assumed, and treatment was initiated with significant clinical and imaging improvement.

Conclusions: ALE's broad clinical spectrum contributes to underdiagnosis. Therefore, in patients with new onset of neuropsychiatric symptoms and no prior psychiatric history, ALE should be considered, as prompt diagnosis and treatment are pivotal to achieve a good prognosis.

KEYWORDS

Autoimmune diseases, limbic encephalitis, anti-LGI1 antibodies, psychiatric symptoms

LEARNING POINTS

- Autoimmune limbic encephalitis is a rare inflammatory neurological disease that affects the limbic system particularly the hippocampus, leading to memory impairment and neuropsychiatric symptoms.
- Due to its wide range of neuropsychiatric symptoms, the diagnosis of autoimmune limbic encephalitis may go unnoticed, leading to misdiagnosis as another medical disorder.
- Early diagnosis is essential to prevent potential neurological sequelae through appropriate treatment.

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INTRODUCTION

Autoimmune limbic encephalitis (ALE) is a rare inflammatory disorder involving the medial temporal lobes, where the limbic system is located. It presents subacutely (within weeks) with varied neuropsychiatric symptoms, including short-term memory deficit, seizures, anxiety and depression[1]. Over the past decade, ALE's incidence has been rising due to the discovery and improvement of antineuronal antibody detection techniques. Anti-leucine-rich glioma-inactivated protein 1 antibody (anti-LGI1) ALE, first described in 2010 by Lai et al.[2], was initially thought to be a paraneoplastic phenomenon[3]. However, thanks to long-term follow-up of these patients, it is now known that only 10% of cases are linked to neoplastic processes. The rare and subacute nature of ALE, coupled with diverse neuropsychiatric manifestations, often leads to underdiagnosis and worse outcomes.

Here, we present a case of anti-LGI1 ALE, illustrating the diagnostic challenges posed when neuropsychiatric symptoms are the primary presentation.

CASE DESCRIPTION

A 60-year-old male, previously healthy and independent, presented to the emergency department (ED) with a two-month-long history of daily episodes of palpitations, shivering, piloerection and sense of impending death. Blood tests and electrocardiogram were unremarkable. After psychiatric examination, he was diagnosed with generalised anxiety disorder and discharged with venlafaxine (50 mg daily). Three months later, due to a lack of improvement and the emergence of memory loss affecting his independence, he returned to the ED. The patient was alert and afebrile with stable vital signs but showed disorientation in time and space along with severe short-term memory deficits, unable to recall events from the day or the previous six months, was constantly repeating the same questions and unable to form any new memories. As seen in *Table 1*, initial tests revealed an elevated serum sedimentation rate (56 mm), mild hyponatraemia (130 mEq/l) and a normal C-reactive-protein value. The patient underwent a cranial computerised tomography scan and an electroencephalogram, both without pathological findings. A lumbar puncture showed clear CSF with increased protein levels (57.5 mg/dl), two mononuclear cells and a glucose level of 129 mg/dl. After being admitted for further investigation, brain magnetic resonance imaging revealed bilateral intraparenchymal temporal

Blood analysis	Results	Reference value
Haemoglobin (g/dl)	14.8	13.7–17.3
White blood cell count (10^3/µl)	8	4.8–10.8
Platelets (10^3/µl)	339	144–440
Sedimentation velocity (mm)	56	< 20
Creatinine (mg/dl)	0.62	0.7–1.2
Blood urea nitrogen (mg/dl)	25	16.6–48.5
Sodium (mmol/l)	130	136–145
Potassium (mmol/l)	3.5	3.5–5.1
Glutamic pyruvic transaminase (U/l)	25	< 33
Glutamic-oxaloacetic transaminase (U/l)	28	< 32
Alkaline phosphatase (U/l)	70	35–104
Gamma-glutamyl transferase (U/l)	12	5–36
Total bilirubin (mg/dl)	0.5	< 1.2
Lactate dehydrogenase (U/l)	230	< 250
C-reactive protein (mg/dl)	< 0.6	< 5
Creatine kinase (U/l)	95	< 170

Table 1. Initial blood test requested in the emergency department.

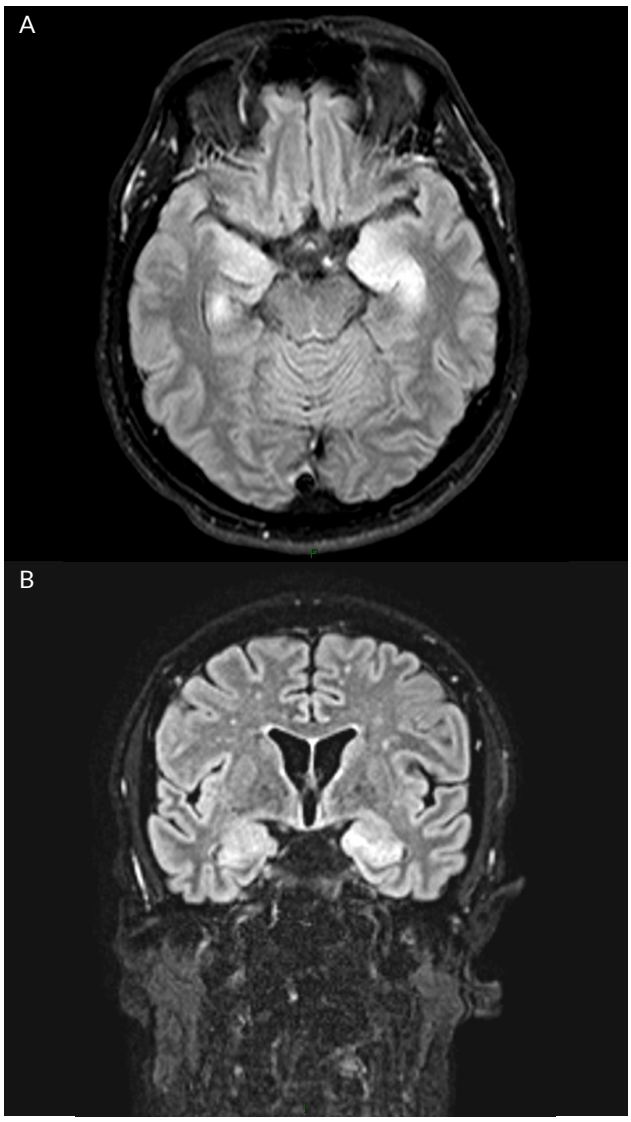

Figure 1. Axial section (A) and coronal section (B) of head MRI imaging showing bilateral intraparenchymal temporal hyperintense lesions on vFLAIR, involving the hippocampi and tonsils.

Laboratory test	Results	Reference value
Serum thyroid function Thyroid stimulating hormone (µUI/ml) Free T4 fraction (ng/dl)	 1.23 1.6	 0.3–4.7 0.6–1.7
Serum immunoglobulins IgG (mg/dl) IgA (mg/dl) IgM (mg/dl)	 1,290 340 66.7	 700–1,600 70–400 40–230
Serum protein electrophoresis	Without alterations	-
Serum vitamin B12 (pg/ml)	547	197–771
Serum folic acid (ng/ml)	4.52	3.89–26.8
Serum antinuclear antibody	Negative	-
Serum antineutrophil cytoplasmic antibodies	Negative	-
Serum Ag/Ac HIV 1/2	Negative	-
Serum RPR (VDRL carbon)	Negative	-
Microbiological examination of CSF	Negative	-
Screening for oligoclonal bands in CSF	Negative	-
Screening for viruses and bacteria by polymerase chain reaction in CSF Enterovirus RNA Herpes simplex virus DNA Epstein-Barr virus DNA Cytomegalovirus DNA Varicella-zoster DNA *Streptococcus pneumoniae* DNA *Neisseria meningitidis* DNA *Haemophilus influenzae* DNA	 Negative Negative Negative Negative Negative Negative Negative Negative	 - - - - - - - -

Table 2. Further blood and CSF tests results, requested during the hospital stay.

lesions involving the hippocampi and tonsils, suggesting limbic encephalitis *(Fig. 1)*. As seen in *Table 2*, additional laboratory tests including thyroid function; vitamin B12 and folic acid were normal. Antinuclear antibodies (ANA) and antineutrophil cytoplasmic antibodies (ANCA), human immunodeficiency virus serology and CSF bacterial and viral studies were also negative. A new lumbar puncture was conducted due to high suspicion of ALE, and the diagnosis was confirmed after screening of anti-LGI1 antibodies was positive on CSF. The patient was then promptly started on immunosuppressive therapy, which included pulses of high-dose intravenous methylprednisolone, multiple sessions of plasmapheresis and subsequent initiation of mycophenolate mofetil. To rule out paraneoplastic ALE, the patient underwent a full body computerised tomography scan plus upper and lower gastrointestinal endoscopies, all without evidence of neoplasia. He was discharged after 25 days of hospitalisation with significant clinical and imaging improvement.

DISCUSSION

Van Sonderen et al. reported an incidence of anti-LGI1 ALE of 0.83 per million inhabitants in the Netherlands[4], with case numbers increasing over the past decade due to diagnostic improvements and heightened awareness regarding this disease. In a retrospective study which assessed the admission diagnoses of 50 patients with diagnosed autoimmune encephalitis, including ALE, 68% (n=34) were initially misdiagnosed as having another condition, commonly with psychiatric or epileptic disorders, and ischaemic brain disease[5]. Even among those with suspected encephalitis from the start, almost half were initially thought to have an encephalitis of infectious aetiology[5]. Delayed ALE diagnosis is – as shown – not uncommon, and may lead to permanent neurological damage, including cognitive impairment and epilepsy, with a serious impact on the patient's autonomy, reduced response to immunosuppressive therapy and a poorer long-term outcome[4].

In summary, this case highlights that any medical practitioner may come across a patient with similar symptoms. Therefore, it is crucial to consider ALE in patients presenting with new, unexplained neuropsychiatric symptoms, especially in the absence of a prior psychiatric history. Early recognition and timely treatment are essential to improve patient outcomes and prognosis.

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