Autoimmune limbic encephalitis with neurogenic stunned myocardium

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ABSTRACT

Autoimmune encephalitis can present itself in a wide multitude of ways, and it is often low on the clinician's differential diagnosis list. Varied presentations make the diagnosis challenging and a definitive diagnosis is only achieved by autoimmune antibody studies. Limbic encephalitis, a sub-type of autoimmune encephalitis, occurs due to inflammation of the limbic system of the brain and this could have either paraneoplastic or non-paraneoplastic aetiology. It often presents with rapid onset of confusion, memory impairment, mood changes and frequently seizures. An unusual phenomenon rarely observed in autoimmune limbic encephalitis is the malfunction of the autonomic nervous system with a catecholamine surge that damages the myocardium to cause a neurogenic stunned myocardium. We present a case of a 48-year-old gentleman presenting with rapid cognitive decline and clinical evidence of heart failure, subsequently diagnosed as limbic encephalitis and neurogenic stunned myocardium. This clinical picture is exceedingly rare with only two previous cases reported in the literatures.

Key Words: *Dizziness; Insulin; Strains; Myocardium*

INTRODUCTION

ALE is an inflammatory disease of the limbic system which is often misdiagnosed as infectious encephalitis due to its infrequent occurrence and diverse clinical presentations. Increasing the awareness among general physicians will help to ensure prompt diagnosis and accurate treatment, helping to improve outcomes for even paraneoplastic cases and preventing the long-term sequalae. As ALE is a diagnosis of exclusion, HSV encephalitis treatment should be continued until a definitive diagnosis can be made. Limbic encephalitis, just like many other brain insults, can cause neurogenic stunned myocardium with a characteristic reversible left ventricular dysfunction and heart failure.

CASE PRESENTATION

A 48-year-old gentleman presented with symptoms of feeling generally unwell, dry cough, dizziness, and confusion. The duration of the symptoms was unclear, as he was markedly confused. Later, it was observed that his confusion was primarily caused by a short-term memory loss. He had a background of type 1 diabetes mellitus for nearly 40 years and had been self-administering Lantus insulin and Novorapid insulin (basal bolus regimen). At the time of presentation, his blood glucose levels were remarkably high (37 mmol/L), and it continued to remain high during his admission, as he had lost his insulin administration skills. He had a history of an unprovoked Deep Vein Thrombosis (DVT) 3 months ago during which he was investigated with a whole-body Computed Tomography (CT) scan which was normal. He was prescribed with warfarin for the DVT, but due to the issues with short-term memory loss, he was not taking it-evidenced by an international normalized ratio (INR) of 1.1 on admission.

On examination he had crackles in both the right middle and lower lung zones. Notably, neither cardiovascular, central or peripheral nervous system examinations demonstrated any abnormality, with exception of a Glasgow Coma Scale score of 14/15 (due to confusion). An Electrocardiogram (ECG) done at the time of admission showed presence of T wave inversions in lead 1, aVL and V3-V6–all presumed to be new changes. A chest radiograph reported a small right-sided pleural effusion with overlying consolidation, suggesting the presence of an infection. The heart size was seen to be normal in the chest radiograph. Basic blood tests were also conducted (Table 1).

The ongoing memory issues initiated a series of brain imaging studies; whilst a CT image of the brain including both angiography and venography failed to demonstrate an acute intracranial pathology, a subsequent Magnetic Resonance Imaging (MRI) scan of the brain showed a hyper-intensity on T2-weighted Fluid-Attenuated Inversion Recovery (FLAIR) sequences involving the bilateral hippocampi with mild restricted diffusion, suggestive of limbic encephalitis (Figures 1 and 2). On the basis of these findings, a lumbar puncture was planned. The patient, however, declined to undergo the procedure-a capacity assessment at the time deemed the patient to have capacity despite being mildly confused (Figures 3).

Given the raised troponin levels and ECG changes on admission, a possibility of Acute Coronary Syndrome (ACS)-Non-ST Elevation Myocardial Infarction (NSTEMI) was considered and hence anti-platelet therapy was initiated. Within a few days of hospitalisation, he developed shortness of breath with both clinical and radiological features of acute heart failure. An Echocardiogram (ECHO) showed severely impaired Left Ventricular Systolic Function (LVSF) with an Ejection Fraction (EF) of 26%. He was commenced on diuretics following a cardiology review. The heart failure was thought to be caused by the acute coronary syndrome (Table 2).

Based on the clinical signs and initial investigation results, the patient was admitted to a medical ward and managed for pneumonia, NSTEMI and poorly controlled diabetes. Following imaging results, the diagnosis remained unclear. The differential diagnosis was expanded to include viral encephalitis, auto-immune encephalitis, stroke or postictal change.

Treatment

The patient was commenced on antibiotics for pneumonia, anti-platelets for ACS and a variable rate intravenous insulin infusion for poorly controlled

TABLE 1
Laboratory results on admission to the hospital

Lab tests	Results	Range	Lab tests	Results	Range
Sodium	129 mmol/L	133-146	Troponin T	1273 ng/L	0-15
Potassium	5.6 mmol/L	3.5-5.3	NT-pro BNP	1786 ng/L	0-300
Urea	17.9 mmol/L	2.5-7.8	Haemoglobin	127 g/L	132-170
Creatinine	114 umol/L	59-104	WBC count	12.5 10^9/L	4.3-11.2
eGFR	65 ml/min	90-200	Platelets	158 10^9/L	150-400
Glucose	37.0 mmol/L	3.0-6.0	INR	1.1	0.8-1.2
CRP	90 mg/L	0-5	pH	7.44	7.35-7.45
CK	17273 U/L	40-320	Ketones	1.6 mmol/L	0.0-0.6
HbA1c	62 mmol/mol	20-41	Lactate	2.1 mmol/L	0.5-1.0

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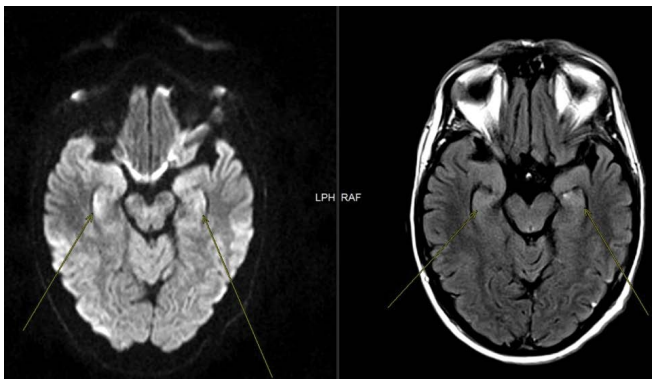

Figure 1) *MRI brain showing hyper-intensities on T2-weighted FLAIR images involving the bilateral hippocampi with mild restricted diffusion suggestive of limbic encephalitis (marked by arrows).*

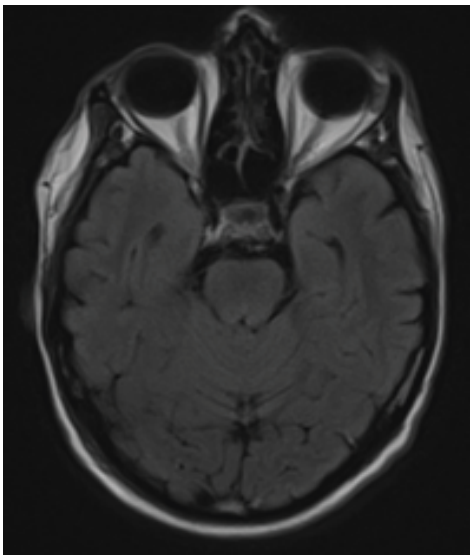

Figure 2) *MRI brain showing near complete resolution of previously seen signal abnormality in bilateral hippocampi.*

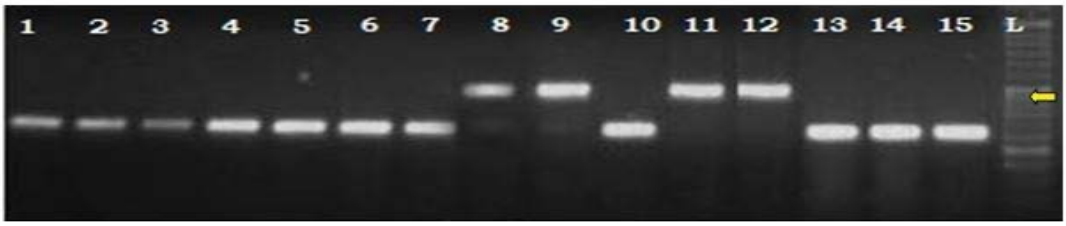

Figure 3) *Amplification of 540 bp xa13 resistance allele using the primer xa13 (Prom). Arrow represents the position of 540 bp allele. Numbers 1-15 corresponds to varieties 1) IR24, 2) IR36, 3) Carolina Gold, 4)IR64, 5)JALDI 13, 6) IRBB21, 7) IRRI146 8) BJ1, 9) IRBB60, 10) IR29, 11) IRBB59, 12) IRBB13, 13) IR72, 14) Swarna, 15) Vandana.*

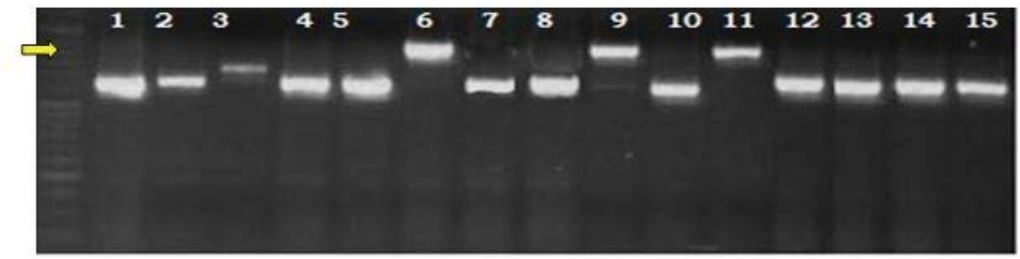

Figure 4) *Amplification of 950 bp Xa21 resistance allele using the primer pTA248. Arrow represents the position of 950bp allele. Numbers 1-15 corresponds to varieties 1) IR24, 2) IR36, 3) Carolina Gold, 4)IR64, 5)JALDI 13, 6) IRBB21, 7) IRRI146 8) BJ1, 9) IRBB60, 10) IR29, 11) IRBB59, 12) IRBB13, 13) IR72, 14) Swarna, 15) Vandana*

TABLE 2
Scoring of genotypes for disease response

Antibodies	Clinical features apart from limbic encephalitis	Dysautonomia	MRI changes	Female: Male	Response	Relapse rate
LGI1	Faciobrachial dystonic seizures, insomnia, hyponatremia, autonomic dysfunction	15%	>80%	01:21	80%	35%
CASPR2	Morvan's syndrome, neuromyotonia, neuropathy, myasthenia, dysautonomia	32%	~40%	01:41	70%	25%
AMPAR	Predominant psychosis, movement disorders, seizure, ataxia, optic neuritis	9%	90%	09:11	71%	16%
NMDAR	Psychosis, movement disorder, seizure, autonomic dysfunction, catatonia	69%	33%	04:11	80%	12%
$GABA_BR$	Status epilepticus, psychosis, ataxia, opsoclonus-myoclonus, mild spasticity	5%	>60%	01:11	90%	8%

TABLE 3
Markers used for identifying three resistant genes towards BLB

Genes	Chromosome	Primers	Sequences	Reference
Xa4	11	RM224F	atcgatcgatcttcacgagg	Sun et al. (2003)
		RM224R	tgctataaaaggcattcggg	
xa5	5	xa5s-F (Multiplex)	gtctggaatttgctcgcgttcg	Pradhan et al. (2015)
		xa5s-R (Multiplex)	tggtaaagtagataccttatcaaactgga	
		xa5sr/R-F(Multiplex)	agctcgccattcaagttcttgag	
		xa5sr/R-R(Multiplex)	tgacttggttctccaaggctt	
xa13	8	Xa13 Prom-F	ggccatggctcagtgtttat	Sundaram et al. (2011)
		Xa13 Prom-R	gagctccagctctccaaatg	
Xa21	11	pTA248 F	agacgcggaagggtggttcccgga	Pradhan et al. (2015)
		pTA248 R	agaccggtaatcgaaagatgaaa	

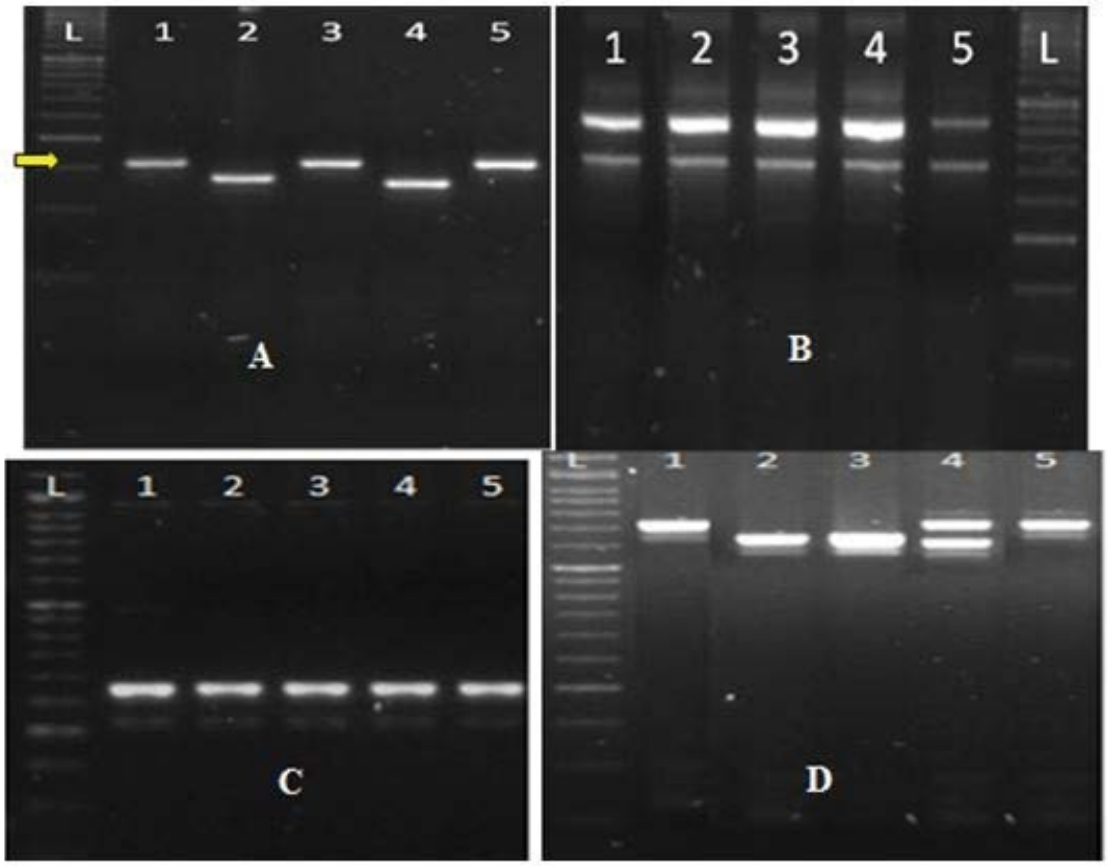

Figure 5) *Indigenous landraces being tested using molecular markers linked with resistance genes Xa4, xa5, xa13 and Xa21. A: 160 bp resistance allele for Xa4 (marked by arrow) being amplified using RM224; B: Amplification of 310 bp susceptible alleles for xa5 using the marker xa5s (multiplex); C: Amplification of 280 bp susceptible allele for xa13 using the marker xa13 (Prom); D: Amplification of 650/750 bp susceptible alleles for Xa21 using the marker pTA248. [Numbers 1 to 5 represents the landraces Kalabhat, Kalonunia, Chamarmani Kerala Sundari and Dudheswar]*

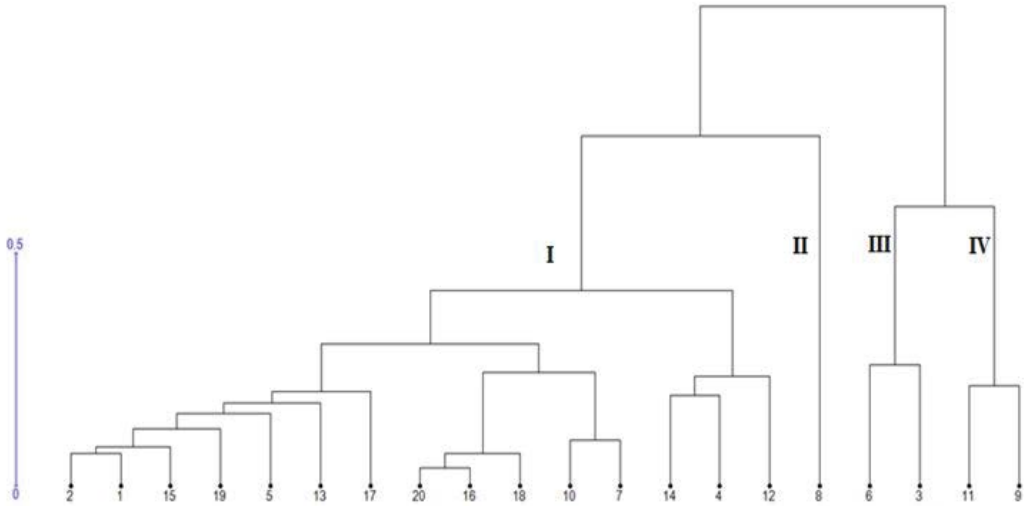

Figure 6) *Dendrogram showing four clusters, calculated on the basis of genetic differences in terms of resistance conferring genes Xa4, xa5, xa13 and Xa21. Numbers 1 to 20 corresponds to genotypes: 1)IR24, 2) IR36, 3) Carolina Gold, 4) IR64, 5) JALDI 13, 6) IRBB21, 7) IRRI146, 8) BJ1, 9) IRBB60 , 10) IR29, 11) IRBB59 , 12) IRBB13, 13) IR72, 14) Swarna, 15) Vandana, 16) Kalabhat, 17) Kalonunia, 18) Chamarmani, 19) Kerala Sundari, 20) Dudheswar*

Figure 7) *(A) and (B) represents images of infected leaves of IRBB13 and IRBB21 exhibiting complete susceptibility and moderate susceptibility respectively against the strain IX027. (C) represents image of the infected leaf of IRBB60 infected by IX027*

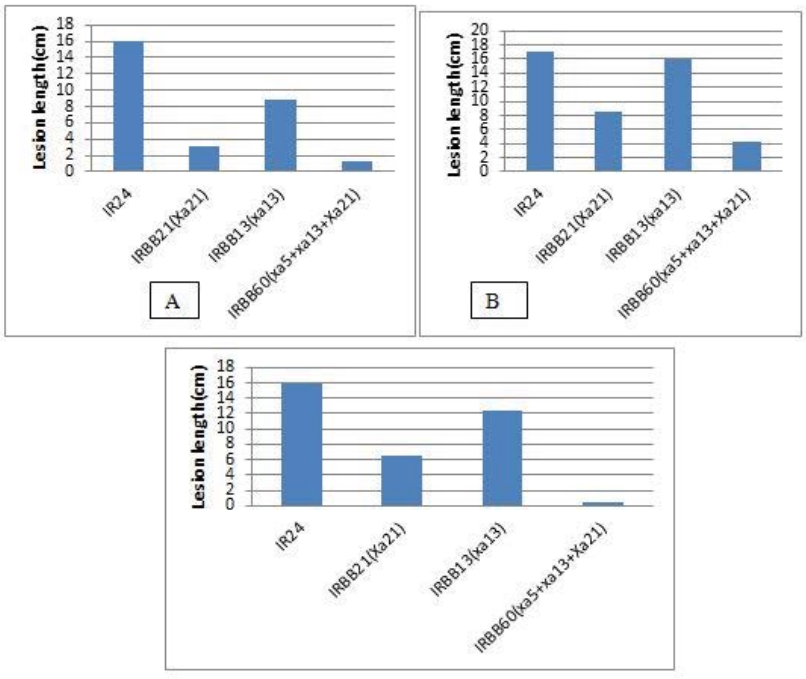

Figure 8) *Disease response of IR24 and the near isogenic lines IRBB13, IRBB21 and IRBB60 carrying varied Xa-gene combinations being inoculated by BLB strains (A) IX021, (B)IX027, (C)CUXo1*

diabetes. Subsequently, he received intravenous acyclovir for a presumed diagnosis of viral encephalitis-a diagnosis of which could not have been ruled out in the absence of Cerebrospinal Fluid (CSF) studies. As a whole-body CT scan was previously performed when he developed DVT 3 months prior, this was not repeated. A stroke team review deemed it unlikely for the patient to have had an acute stroke. The neurology team felt a diagnosis of non-paraneoplastic limbic encephalitis to be more in-keeping with the presentation and consequently commenced him on a five-day course of intravenous methyl prednisolone, 1-gram once-daily-this was later followed by a tapering dose of oral prednisolone (initially 20 mg) together with gastric protection. Serum markers for limbic encephalitis including anti-CASPR2 (Contactin-Associated Protein 2) and anti-LGI (Leucine-rich Glioma Inactivated 1) antibody results were found to be negative (Figures 4 and 5).

Outcome and follow-up

A repeat MRI of the brain following completion of the 5-day course of intravenous methyl prednisolone showed a near complete resolution of the previously seen signal abnormality in the bilateral hippocampi (Figure 6). A cardiac MRI performed 4 weeks following discharge showed a non-dilated left ventricle with normal EVSF and an EF of 56%. In his outpatient follow up, he showed reasonable recovery in cognition though there were some ongoing memory issues. Encouragingly, he was able to self-administer his insulin therapy safely (Figures 7 and 8).

RESULTS AND DISCUSSION

Autoimmune Limbic Encephalitis (ALE), an inflammatory disease affecting the bilateral medial temporal lobes, is commonly misdiagnosed due to its varied neuropsychiatric presentations and its infrequent occurrence [1]. However, early diagnosis and prompt immunotherapy can significantly improve the outcomes by avoiding the long-term sequalae including chronic temporal lobe epilepsy and psycho-cognitive deficits [2]. ALE is a rare disease with a prevalence of 2 cases per 100,000 people and an incidence of 0.2 cases per 100,000 people [3]. Though it can occur at any age, it is often diagnosed in the middle-aged. Clinically, ALE is characterised by a subacute onset with a median time from "the onset of symptoms to the time of diagnosis" of several weeks [4]. As such, it should be considered in anyone presenting with subacute onset of memory/behavioural changes, psychiatric symptoms, and/or unexplained seizures (Table 3).

ALE could have either paraneoplastic or non-paraneoplastic aetiology, both of which present with similar clinical features except for the presence or absence of malignancy [5]. Paraneoplastic ALE was thought to constitute 60%-70% of all ALE cases, but non-paraneoplastic ALE is becoming as common, if not more common, as paraneoplastic ALE. ALE can precede malignancy by several months to years [6]. Various autoimmune diseases like type 1 diabetes mellitus [7] and autoimmune thyroid disease [8] have been associated with ALE. Moreover, autoimmune diseases like Bechet's disease, Sjogren syndrome, lupus, antiphospholipid antibody syndrome, primary CNS angiitis and relapsing polychondritis can cause clinical and radiological features of limbic encephalitis.

At time of presentation, it is often difficult to differentiate whether the limbic encephalitis is infectious or autoimmune in origin, as prodromal symptoms like fever, gastroenteritis or flu like symptoms often happen in many patients with ALE [9]. Moreover, Herpes Simplex Virus (HSV) encephalitis can trigger NMDAR (N-methyl-d-aspartate receptor) encephalitis, a type of autoimmune encephalitis [10]. The latter explains a relapse of encephalitis within few weeks in a patient receiving antiviral therapy for HSV encephalitis. ALE is primarily a diagnosis of exclusion. HSV encephalitis should therefore be considered with antiviral therapy continued until a definitive diagnosis of ALE can be made. ALE can be diagnosed when all four of the following criteria have been met:

- Subacute onset of seizures, memory deficit or psychiatric symptoms.
- Bilateral medial temporal lobe signal changes on T2-weighted FLAIR MRI.
- At least 1 of the 2
- CSF pleocytosis (WCC>5 cells/mm^3).
- Typical EEG changes (slow wave activity and epileptiform discharges).
- Reasonable exclusion of alternative diagnoses.

MRI in the diagnosis and differential diagnosis of ALE

The characteristic MRI finding in a patient with ALE is bilateral symmetrical involvement of the medial temporal lobe (including hippocampus and amygdala), hypothalamus, cingulate gyrus of frontal lobe and limbic cortex in the form of hyperintense signal in T2 weighted FLAIR. MRI can be normal in nearly 25% of cases of ALE [11]. The major differential diagnoses for medial temporal lobe changes include HSV encephalitis, medial temporal glioma, mesial temporal sclerosis, posticta oedema, and medial temporal ischaemic stroke. These conditions can present with either unilateral1 or bilateral but asymmetric [12] involvement of medial temporal lobes. Nearly 90% of patients with HSV encephalitis have bilateral asymmetrical medial temporal lobe involvement on T2 weighted FLAIR images within initial 48 hours of illness onset, reaching sensitivity of 100% by 3-10 days [13].

Temporal lobe tumours are usually unilateral, though bilateral involvement can occur with gliomatosis and lymphomatosis cerebri [14]. Moreover, in one trial, nearly 54% of patients with possible ALE having bilateral temporal lobe involvement were later confirmed to have glioblastoma multiforme [15]. Hence, a possibility of glioblastoma multiforme should always be considered

TABLE 4
Average Lesion length (cm) observed in twenty genotypes inoculated by three strains of s across two years

Sl.no.	Genotypes	IX021	Response	IX027	Response	CUX01	Response
1	IR24 (SC)	16	S	17.16	S	15.8	S
2	IR36	15.33	S	16.16	S	15.93	S
3	Carolina Gold	6.83	MR	10.16	MS	8.73	MR
4	IR64	9	MR	17.26	S	16.2	S
5	JALDI 13	15.33	S	14.2	MS	16.33	S
6	IRBB21	3.16	R	8.5	MR	6.5	MR
7	IRRI146	13.33	MS	12.93	MS	17.46	S
8	BJ1	16.5	S	3.33	R	15.06	S
9	IRBB60 (RC)	1.33	R	4.16	R	0.46	R
10	IR29	12.33	MS	13.86	MS	16.43	S
11	IRBB59 (RC)	2.83	R	0.86	R	0.86	R
12	IRBB13	8.83	MR	16.03	S	12.33	MS
13	IR72	17.5	S	14.7	MS	13.9	MS
14	Swarna	7.66	MR	14.26	MS	15.96	S
15	Vandana	16.66	S	16.23	S	15.03	S
16	Kalabhat	7.20	MR	9.50	MS	4.10	R
17	Kalonunia	16.43	S	17.63	S	18.43	S
18	Chamarmani	6.03	MR	8.83	MS	2.13	R
19	Kerala Sundari	17.23	S	16.03	S	17.13	S
20	Dudheswar	12.70	MS	13.80	MS	12.50	MS
	LSD at 5% probability	3.511		3.814		1.519	

in patients who do not satisfy the criteria for definite ALE and who do not respond adequately to immunotherapy. In MRI, the grey-white matter distinction at the cortical-subcortical interface is lost in the case of medial temporal gliomas whereas it is maintained in ALE, a useful differentiating feature from ALE [16]. Moreover, spread along the nerve tracts and parenchymal enhancement rather than cortical enhancement is found to occur with tumours (Table 4).

Temporal lobe epilepsy can be caused by mesial temporal sclerosis due to idiopathic neuronal loss and is evident on MRI as increased signal on T2 weighted FLAIR images along with loss of architecture and atrophy of hippocampus. There can be involvement of ipsilateral fornix, parahippocampal gyrus and mammillary bodies. Though the involvement is usually unilateral, it can be bilateral in up to 10 % of cases. Absence of atrophy, presence of extra-temporal and extensive limbic system involvement differentiates ALE from mesial temporal sclerosis.

Status epilepticus can cause postictal oedema involving cortex, subcortical white matter, hippocampi, medial temporal lobes, and thalamus. The points that differentiate this postictal oedema from ALE are absence of prodromal neuropsychiatric symptoms and the resolution of temporal lobe changes after cessation of status epilepticus. Acute onset of illness and MRI changes restricted to a vascular territory helps distinguish ischaemic stroke from ALE.

A retrospective review of adult encephalitis patients with temporal lobe involvement on MRI from the California encephalitis project showed that nearly 43% were caused by infections, in which nearly half were by HSV infection followed by tuberculosis, and Varicella Zoster Virus (VZV) [17]. Rare infectious causes in a descending order of occurrence were mycoplasma pneumoniae, enterovirus, balamuthia mandrillaris, Human Herpes Virus 6 (HHV6), Creutzfeldt-Jakob disease, west nile virus, rocky mountain spotted fever, influenza, syphilis, chlamydia pneumoniae, coccidioidomycosis, nocardia, adenovirus and aspergillus.

In the above study, nearly 16% were caused by non-infectious causes with more than half by autoimmune limbic encephalitis. Other non-infectious causes were glioma, lymphoma, vasculitis, lupus, sarcoidosis, and toxic or metabolic or Hashimoto's encephalopathy. Finally, in nearly 41% of cases, no specific aetiology were noted. The study found that unilateral rather than bilateral temporal involvement, presence of insular and cingulate involvement, and absence of basal ganglia involvement were points in favour of HSV encephalitis. In another study, HSV encephalitis had a diffuse temporal lobe involvement (with insular involvement but sparing basal ganglia) whereas ALE had selective medial temporal involvement [18].

18-FDG PET in the diagnosis of ALE and detection of malignancy

MRI of the brain is the primary neuroimaging technique in the workup of a suspected ALE. However, brain 18-Fluoro Deoxy Glucose Positron Emission Tomography (18-FDG PET) can demonstrate glucose hypermetabolism in bilateral medial temporal lobes and extra-temporal structures of active ALE patients with even normal MRI, indicating that 18-FDG PET has a better sensitivity compared to MRI [19]. An integrated PET and MRI could improve the overall detection rates of ALE, especially the ability to exclude paraneoplastic ALE [20].

Antineuronal antibodies in the diagnosis of ALE

The criteria proposed for the diagnosis of ALE do not require the documentation of positive antibodies. Moreover, antibody tests are not readily available in many centres and the results can take up to several weeks. A positive antibody, by itself, does not imply and a negative test does not rule out the diagnosis. However, a positive testing is useful to confirm the diagnosis in a patient who would not otherwise satisfy the criteria. Moreover, detection of antibodies would predict the presence of certain malignancies, the detection of which might improve outcomes. Two types of antibodies, one that targets intracellular proteins and another that targets extracellular proteins, can be found in patients with ALE (Table 5).

In general, the antibodies targeting the extracellular proteins are likely pathogenic and the antibodies targeting the intracellular proteins are likely non-pathogenic for ALE [21]. Antibodies that target intracellular proteins, exemplified by Hu antibodies, Ma2 antibodies, amphiphysin antibodies, and CRMP5 antibodies (collapsin response mediator protein 5) had frequent association with various tumours; only exception being GAD antibodies (glutamic acid decarboxylase). On the other hand, antibodies to cell surface and synaptic proteins which were variably associated with malignancy include LGI1 antibodies, CASPR2 antibodies, GABABR antibodies (γ-aminobutyric acid B receptor), AMPAR antibodies (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor), and NMDAR antibodies (N-methyl-d-aspartate receptor). The common tumours that are associated with various antibody subtypes are given in Table 2. LGI1 and CASPR2 are antigens belonging to Voltage-Gated Potassium Channel (VGKC) complex. Anti-LGI1 and anti-CASPR2 are more sensitive than anti-VGKC and hence the latter should not be routinely used.

In a retrospective study of 163 ALE patients, the frequency of antibodies were as follows: LGI1 (44%), GABABR (16%), AMPAR (7%), CASPR2 (7%), Ma2 (8%), and Hu (7%). Nearly 7% were negative for all antibodies [22]. These seronegative ALE patients were older males (mean age of 62 years, female:male ratio of 1:3) who presented with predominant or isolated short-term memory loss. Though seronegative, they responded to immunotherapy and 42% of them had underlying cancer. The antibody testing should ideally be done in both serum and CSF as some give more yield from serum (LGI1) whilst others give yield only from CSF (GABABR).

Antineuronal antibodies in the sub-classification of ALE

Anti-CASPR2 ALE is characterised by increased peripheral nerve excitability (neuromyotonia), which can lead to a misdiagnosis as atypical motor neuron disease. This condition is associated with myasthenia gravis (MG) with positive antibodies to Muscle Kinase (MuSK). In anti-LGI1 ALE, cognitive deficits are preceded by frequent short-lasting myoclonus-like focal seizures that are refractory to antiepileptic drugs involving ipsilateral face, arm and rarely legs [23]. These Facio Brachial Dystonic Seizures (FBDS) are pathognomonic of anti-LGI1 ALE and is seen in around 40% of cases [24]. Another characteristic feature of anti-LGI1 ALE is the intractable hyponatremia secondary to Syndrome of Inappropriate Anti Diuretic Hormone secretion (SIADH) in nearly 60% of cases and is caused by LGI1 antibody that binds to the paraventricular nucleus neurons [25]. Both anti-CASPR2 and anti-LGI1 ALE had a median age of 60 years, and a male preponderance contrary to other ALEs (Table 2) [26-30].

Electroencephalography (EEG) in the diagnosis of ALE

A normal EEG in a patient with ALE does not rule out the diagnosis. Continuous slow wave activity and epileptiform discharges from temporal lobes are commonly seen in ALE patients [31-33]. However, EEG changes alone are not sufficient to make a definitive diagnosis in the absence of either abnormal MRI/FGD-PET or positive antibody test. In a case of abnormal EEG but normal MRI, the MRI should be periodically repeated [34]. A retrospective study of autoimmune encephalitis patients with seizures found that 42% had interictal temporal epileptiform discharges and 63% had seizure onset in the temporal region which closely matched with the MRI changes in 74% and FDG-PET changes in 75% of patients [35]. In

TABLE 5
Fifteen genotypes classified into four clusters along with the range of pathogenicity recorded for the clusters in response to the three strains of *X. oryzae*

Cluster number	Genotypes	Range of pathogenicity for the strains		
		IX021	IX027	CUXo1
I	IR36, IR24, Vandana, Kerala Sundari, Jaldi 13, IR72, Kalonunia, Dudheswar, Kalabhat, Chamarmani, IR29, IRRI146, Swarna, IR64, IRBB13	MR-SC	MR-SC	R-SC
II	BJ1	SC	R	SC
III	IRBB21, Carolina Gold	R-MR	MS-MR	MR
IV	IRBB59, IRBB60	R	R	R

Note: MR= Moderately Resistant, MS= Moderately Susceptible, SC= Susceptible, R=Resistant

patients with LGI1 ALE, nearly 68% of the cases had FBDS and the EEG were normal in all cases during FBDS. Video-EEG showed that there were multifocal epileptiform discharges from frontal, temporal, and apical regions and there was interictal slow wave activity [36].

Cerebrospinal Fluid (CSF) studies in the diagnosis of ALE

CSF abnormalities that are present only in 25%-50% of ALE cases, include mild or moderate lymphocytic pleocytosis, a slight increase in protein and oligoclonal antibodies. Though CSF pleocytosis and oligoclonal bands support a diagnosis of ALE, they have an extremely low sensitivity and there is no CSF specific pattern for ALE. However, CSF testing is still important as a tool to differentiate infectious encephalitis (e.g. HSV encephalitis) from non-infectious with the help of tests like Polymerase Chain Reaction (PCR). However, PCR can be falsely negative early in the course of illness. Repeat CSF analysis should be performed whilst on antiviral therapy [37]. CSF should be sent for antibody tests, especially GABABR as this will only appear positive in the CSF (Table 6).

Screening for and treatment of cancers

All ALE patients should undergo cancer screen with a whole-body CT scan. Women should have a gynaecology examination and ultrasonography of the breast and pelvis and if negative, an MRI of the pelvis. Men should have a urology examination and scrotal ultrasonography. If all negative, a whole-body FDG-PET should be considered. Any malignancy detected should be removed and treated sufficiently to eliminate the antigen that initiate and perpetuate the brain inflammation [38].

Immunotherapy

This should be started with steroids, intravenous immunoglobulins, and plasmapheresis as first-line [39]. Second-line immunotherapy should include rituximab and cyclophosphamide. Alternative regimen includes tocilizumab and low dose interleukin-2 a combination therapy may be needed for some. In steroid-responsive patients, steroid sparing agents like azathioprine or mycophenolate can be used. In ALE with high relapse rates (e.g. LGI1 ALE), long-term/continuous treatment with rituximab or cyclophosphamide should be considered. Relapses should be treated with the same regimen as the first presentation. Antibody levels should not be used for monitoring response during therapy, as levels can persist for years after recovery. However, antibody levels might be useful during a relapse. ALE with antibodies to surface proteins had a better prognosis compared to antibodies to intracellular proteins. The response and relapse rate of immunotherapy if given in Table 3.

Treatment of seizure

This is challenging as levetiracetam, with neuropsychiatric side-effects, should be avoided. Lamotrigine, benzodiazepines and lacosamide, however, can be used.

Treatment of autonomic dysfunction

Cardiac dysautonomia could cause life threatening tachycardia, bradycardia, QT prolongation, hypotension, hypertension, asystole, or sudden cardiac death. Other symptoms include hyperhidrosis, hypothermia, hyperthermia, diarrhoea and urinary or sexual dysfunction. Life-threatening dysautonomia should be detected as intensive care prevents mortality.

Long-term sequalae of untreated or incompletely treated ALE

Immunotherapy could reduce the seizure frequency, recover the memory loss, improve quality of life and overall survival1. During acute phase of ALE, the seizures are caused by the immune-mediated inflammation of medial temporal structures. Though most patients' seizures respond well to immunotherapy, in a proportion, seizures can persist leading to chronic epilepsy. Mild presentation at onset and delay in diagnosis are the main determinants of chronic epilepsy [40].

Even after successful immunotherapy, many often develop hippocampal atrophy and cognitive decline. In a recent study, repeat MRI one year after immunotherapy showed significant medial temporal lobe atrophy. The prevalence of cognitive impairment was 64% [41]. Another recent study showed that nearly 50% of ALE patients after the acute phase developed pathologic tearfulness, a state in which patients were moved to tears easily by a relatively trivial stimulus [42]. This condition was not caused by low mood or cognitive impairment but was found to be caused by significant changes in emotional networks of the brain associated with volume reduction in the right anterior hippocampus, left fusiform gyrus, and cerebellum.

Neurogenic Stunned Myocardium after Limbic Encephalitis (NSMLE)

Various neurological insults including encephalitis, stroke, and traumatic brain injury could be associated with cardiac injury in up to 40% of cases [43]. This condition, known as Neurogenic Stunned Myocardium (NSM) is part of stress-cardiomyopathy syndrome, which includes the more familiar takotsubo cardiomyopathy or broken-heart syndrome. Typical presentation of takotsubo cardiomyopathy is chest pain, ST elevation, severe LV dysfunction, whereas NSM presents with decompensated cardiac failure in context of a neurological insult. These two conditions belong to the same spectrum, as they have similar pathophysiology [44].

The pathophysiology of NSM is thought to be brain injury resulting from dysregulation of catecholamines and confounding sympathetic overdrive [45]. Limbic system components like insula, amygdala and cingulate gyrus are crucial in autonomic regulation. Injury to these structures, can result in an "autonomic storm" which adversely affects the myocardium, as myocytes have high numbers of beta-adrenergic receptors. Tachycardia and increased myofibril contraction caused by the autonomic storm results in increased oxygen demand. Catecholamine surge opens the cardiac myocyte calcium channels and the resultant calcium influx prevents cardiac myocyte relaxation, eventually leading to contraction band necrosis. Catecholamines indirectly causes myocyte damage by inducing coronary vasospasm.

In patients with NSM, blood tests would show raised troponin and NT-proBNP in keeping with myocyte damage. Typical ECG changes would include ST-segment depression, T-wave inversion, QT prolongation, and arrythmias. ECHO would show left ventricular regional wall motion abnormalities, not confined to single vessel distribution. Coronary angiography would show normal coronaries. A follow-up ECHO would often show improvement in LVSD, as NSM is mostly transient. However, some cases may not fully recover [46].

One of the proposed treatment options for NSM was beta-blockers which was supposed to inhibit sympathetic storm and protect cardiac myocytes, however, a recent meta-analysis showed that preadmission beta-blockers failed to reduce cardiac dysfunction in patients admitted with subarachnoid haemorrhage [47]. Treatment of NSM is primarily aimed at treating the underlying neurological disease and administering diuretics for cardiac failure [48].

CONCLUSION

In our case, the patient presented with subacute onset of short-term memory loss. MRI showed features of bilateral medial temporal changes, suggestive of limbic encephalitis. He refused lumbar puncture, which made it difficult to exclude infectious causes and hence treated empirically with intravenous acyclovir. EEG could not be performed. The neurologist, following a discussion with a neuroradiologist and after exclusion of alternative diagnoses, considered the possibility of non-paraneoplastic autoimmune limbic encephalitis as a likely diagnosis. A subsequent commencement of the methyl prednisolone regime showed a significant recovery of short-term memory loss.

Whilst the neuronal antibodies returned negative, this alone does not exclude the possibility of ALE. Without CSF studies and EEG results, a diagnosis of definite ALE could not be made, thereby diagnosing him as possible ALE. Whilst inpatient, he developed a new onset of heart failure with poor LVSF which completely improved on the cardiac MRI done 1 month later, suggesting that the previously impaired LVSF was not secondary to ACS, but due to NSM. Only two previous case reports of NSM with limbic encephalitis are available in the literature.

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