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Neuropsychiatric and seizure outcomes in nonparaneoplastic autoimmune limbic encephalitis

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ABSTRACT

Introduction: Autoimmune limbic encephalitis is an inflammatory condition often associated with an underlying neoplasm. However, a subset of patients does not have an underlying tumor and have a nonparaneoplastic form of this condition. The focus in the literature has been on the acute phase of this illness, but long-term follow-up is lacking.
Methods: A retrospective chart review, over a period of 15 years, of patients carrying a diagnosis of encephalitis was performed. Inclusion criteria included a clinical presentation consistent with limbic encephalitis (subacute behavioral change, seizures, or anterograde memory decline) and an identifiable autoantibody, inflammatory CSF (>5 white blood cells/mm^3), or limbic hyperintensities on MRI. Readmission rates and long-term psychiatric, psychosocial, and seizure outcomes were evaluated.
Results: A total of 16 patients were identified. Clinical presentation included new-onset seizures in 14 (88%), behavioral changes in 7 (44%), and memory decline in 5 (31%). Four (25%) patients presented with status epilepticus. Five patients had antibodies against NMDAR (N-methyl-D-aspartate receptor) and four against VGKC (voltage gated potassium channel) complex. An inflammatory CSF was noted in 7 (44%) and MRI changes in 9 (56%). Four were readmitted during the follow-up period. Around half the patients continued to have medically drug/treatment-refractory seizures, while 7 (44%) had a new psychiatric diagnosis (mood disorder, anxiety disorder, or impulse control disorder). The majority of the patients continued to reside at home, while 43% of previously employed patients lost employment.
Conclusion: Nonparaneoplastic autoimmune limbic encephalitis is a neuropsychiatric condition presenting with a combination of seizures (sometimes status epilepticus), behavioral changes, and memory decline. After the acute phase, patients are at risk of readmissions, medically refractory seizures, chronic mood and anxiety disorders, and loss of employment.

1. Introduction

Limbic encephalitis is an inflammatory condition affecting the limbic system, usually presenting with a combination of seizures, short-term memory loss, and behavioral disturbances [1].

An underlying neoplasm is sometimes identified suggesting a paraneoplastic syndrome, but this is not always the case [2]. A growing number of antibodies are described as causing nonparaneoplastic autoimmune encephalitis with membrane or intracellular antigen targets [3]. The current list of antibodies includes the following: anti-GAD [4], anti-NMDAR [5], anti-VGKC complex (LGI1, CASPR2, contactin-2) [6], anti-AMPAR [7], and anti-GABA$_B$R [8,9]. Despite this, a subset of patients does not have an identifiable antibody and tend to have a worse prognosis [10]. There are currently no established criteria for the diagnosis of nonparaneoplastic autoimmune limbic encephalitis. Criteria were proposed by Bien and Elger [11] and include a recent-onset limbic syndrome (<5 years) and one out of the 4 following criteria: an identifiable autoantibody, unexplained temporomedial T2/FLAIR changes on MRI, histopathological evidence of lymphocytic–micronodular encephalitis, and identification of a tumor for the paraneoplastic limbic encephalitis. Other proposed criteria for paraneoplastic limbic encephalitis have also included neurophysiologic and CSF markers [12].

It is now thought that after the initial illness, patients may go on to develop medically refractory epilepsy [13] or return to the hospital with behavioral relapses [14].

Abbreviations: AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; CASPR2, contactin-associated protein-like 2; GABABR, gamma hydroxybutyrate B receptor; GAD, glutamic acid decarboxylase; LGI1, leucine-rich glioma inactivated 1; NMDAR, N-methyl-D-aspartate receptor; VGKC, voltage gated potassium channel.

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The current literature has mainly focused on the identification and treatment of nonparaneoplastic autoimmune limbic encephalitis (NPALE) in the acute period. Long-term follow-up looking at seizure, psychiatric, and psychosocial outcomes remains limited.

2. Material and methods

A retrospective chart review using an institution-based search engine of all inpatient and outpatient encounters at the Massachusetts General Hospital was performed, looking for patients carrying an ICD9 diagnosis consistent with encephalitis over a 15-year period (1999–2014). The study was approved by the hospital's institutional review board.

Inclusion criteria included a clinical presentation consistent with new-onset seizures, anterograde memory loss, and behavioral disturbances over a period of days up to 3 months in addition to 1 out of the following 3: an identifiable autoantibody, MRI T2 hyperintensities involving the limbic system, or CSF inflammatory findings (>5 white blood cells/mm^3).

Patients with structural lesions on MRI, a tumor diagnosed within 4 years of diagnosis, or infectious etiologies were excluded.

The patients' clinical presentation, initial hospital course, and treatments were evaluated. Hospital readmissions and the reason for hospitalization were also noted during the follow-up period.

At the last follow-up, the patients' psychiatric status, specifically a diagnosis of anxiety or mood disorder; thought disorder; suicide attempts; and use of psychotropic medications were recorded in addition to epilepsy status with seizure types; history of status epilepticus; surgical evaluations; number of antiseizure medications; as well as psychosocial metrics of employment, and living conditions were assessed.

3. Results

A total of 755 patients carrying the diagnosis of encephalitis during the study period were identified. Out of the 755 patients, 18 patients fulfilled criteria for NPALE. Two patients were later excluded because of in-hospital death. All patients had at least a paraneoplastic panel, CSF viral studies, and a whole-body PET–CT performed.

3.1. Diagnosis and clinical presentation

Details about the patients' presentation at diagnosis are described in Table 1. The presentation consisted of new-onset seizures in 14 (88%) patients, of whom 3 were in nonconvulsive status epilepticus, and 1 was in convulsive status epilepticus. Seven (44%) patients had new-onset behavioral changes, including psychosis in 6 patients and severe anxiety in one case. Five (31%) patients had progressive anterograde memory loss. Four patients were diagnosed with an autoimmune disorder prior to their admission: hypothyroidism, rheumatoid arthritis (2 cases), and Wegener granulomatosis. Seven (44%) patients did not have an identifiable autoantibody, although two of them did not have NMDA antibody testing as the test had not been available yet.

All patients in the studied sample with anti-NMDAR antibodies for encephalitis had psychosis upon presentation, and one of them developed tremors during the admission. Three of these patients had detectable antibodies in the CSF, while one of them did not, and one of them did not have the antibody tested.

Meanwhile, patients with antibodies against VGKC complex were noted to have hyponatremia (Na: 123–133) on presentation to the hospital. Oligoclonal bands in the CSF were tested in 7 patients and were negative.

Prior to the hospital admission leading to their diagnosis, 1 patient with NMDA autoantibodies presented with encephalitis and psychosis (4 years prior), 1 patient with NMDA antibodies presented with psychosis 7 months prior, and 1 patient had presented with encephalitis 3 months prior to recurrence.

Brain FDG-PET studies were performed in 5 patients. Results were as follows: one case showed temporal hypermetabolism, while hypometabolism was noted in 3/5 cases, and one was normal. The electroencephalogram documented seizures from the temporal or frontotemporal regions in 7 patients. Five patients had theta or delta slowing in the temporal regions, and 3 patients had a normal EEG. Eleven patients received immunomodulatory treatments during their acute hospital admission (Table 1).

3.2. Clinical follow-up

The mean follow-up duration was 3.0 years (of 0.5 to 14.0 years). At the last follow-up, 4 patients required readmission: two patients were readmitted because of delirium in the setting of an infection, one patient with psychosis, and one patient with worsening cognitive decline.

At the last follow-up, 50% of the patients who presented with seizures were seizure-free (Table 2). The remaining half sample size included 2 cases with rare isolated auras and focal seizures with altered consciousness (once a year), 1 patient with monthly focal seizures, 2 patients with weekly to daily auras, and 2 with frequent (weekly to monthly) generalized tonic–clonic seizures (GTCS) and focal seizures

Table 1
Clinical and diagnostic characteristics of the cohort upon presentation.

	Clinical presentation	Age at onset/ gender	MRI (T2/FLAIR hyperintensities)	LP (WBC/mm^3, Ptn mg/dl, Glu mg/dl)	Antibodies	Immune treatments	Start of treatment[a]
1	B, S	32/M	Subcortical	Not available	NMDA	IVIG, MP, Ritux	1 wk
2	B	59/F	Subcortical	2, 93, 40	NMDA	MP	1 y
3	B	39/F	Negative	8, 12, 70	NMDA	IVIG, MP	12 wk
4	B, S (SE)	41/M	Negative	20, 35, 79	NMDA	IVIG	1 y
5	B, S	45/F	Negative	20, 60, 60	NMDA	IVIG, MP, Ritux	2 wk
6	M, S	76/M	L temporal	8, 79, 69	VGKC	IVIG, MP	2 wk
7	S	42/M	L temporal	4, 14, 66	VGKC	IVIG, MP	2 wk
8	M, S (SE)	80/M	L temporal	4, 46, 75	VGKC	None	
9	M, S	29/F	Bitemporal	1, 16, 65	VGKC	IVIG, MP	2 wk
10	B, M, S	82/F	Bitemporal	2, 34, 60	Idiopathic	MP	1 wk
11	B, S	58/M	Small L hippocampus	0, 61, 37	Idiopathic	MP, Ritux	1 wk
12	S	33/F	Negative	8, 62, 63	Idiopathic	IVIG	6 wk
13	M, S	58/F	Bitemporal	1, 36, 114	Idiopathic	None	
14	S	49/F	Bitemporal	0, 36, 63	Idiopathic	None	
15	S (SE)	39/F	R temporal	15, 20, 73	Idiopathic	MP, Ritux	8 wk
16	S (SE)	22/F	Bithalamic	51, 30, 89	Idiopathic	None	

B = behavioral changes, Glu = glucose, IVIG = intravenous immunoglobulin, L = left, M = memory loss, mo = month, MP = methylprednisolone (IV), Ptn = protein, R = right, Ritux = rituximab, S = seizures, SE = status epilepticus, WBC = white blood cell count, wk = week, y = year.

[a] Duration of symptoms prior to the initiation of treatment.