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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.

Table 2
Long-term seizure, psychiatric, and functional outcomes.

	Readmission	Seizure-free	Antiseizure med, n	New psychiatric diagnoses	Functional status change	Antibodies
1	N	No	1	None	Employed → employed	NMDA
2	Y	N/A		None	Employed → unemployed	NMDA
3	N	N/A		None	Employed → employed	NMDA
4	N	No	3	Anxiety disorder	Employed → unemployed	NMDA
5	N	Yes	1	None	Employed → unemployed	NMDA
6	Y	Yes	1	None	Retired → retired	VGKC
7	Y	Yes	0	Impulse control disorder	Employed → employed	VGKC
8	Y	No	2	None	Retired → retired	VGKC
9	N	Yes	2	Mood disorder	Unemployed → unemployed	VGKC
10	N	No	2	Anxiety disorder	Retired → retired	Idiopathic
11	N	Yes	1	None	Employed → employed	Idiopathic
12	N	No	2	Mood disorder	Employed → employed	Idiopathic
13	N	Yes	1	None	Employed → unemployed	Idiopathic
14	N	No	3	Mood disorder	Employed → unemployed	Idiopathic
15	N	Yes	1	None	Employed → employed	Idiopathic
16	N	No	4	Impulse control disorder	Employed → unemployed	Idiopathic

N/A = not applicable, N = no, Y = yes.

with impaired consciousness. One patient underwent an unsuccessful temporal lobectomy with no improvement in seizure frequency.

In the studied sample, seven (50%) patients carried a new psychiatric diagnosis (Table 2), with 3 having a mood disorder (depression), 2 having a generalized anxiety disorder, and 2 having an impulse control disorder. No thought disorders were noted. Suicidal ideation, gestures, plans, or attempts were never reported. Six (46%) out of 13 employed patients had a change in their functional status and became unemployed after their illness. The majority (95%) of the patients continued to reside at home.

4. Discussion

Although limbic encephalitis was previously considered a rare condition closely linked to an underlying malignancy, there is a growing belief that the nonparaneoplastic forms of this disease do exist [3]. The differential diagnosis remains broad and should include at presentation infectious (HSV, HHV6, and CJD) and autoimmune (Sjogren's syndrome, systemic lupus erythematosus, Hashimoto's encephalopathy, CNS vasculitis, and antiphospholipid syndrome) conditions [1] among other etiologies. An extensive diagnostic workup is always recommended, and treatment should not be delayed if the clinical suspicion is high even if neuroimaging or CSF studies are normal.

Najjar et al. [15] described a case of pathologically proven limbic encephalitis with spontaneous resolution and emphasize the existence of a seronegative subtype of these patients with no underlying tumor. Bataller et al. [16] described a cohort of 39 patients with limbic encephalitis and could not identify an underlying tumor in 6 of them. Overall, good outcomes defined as return to work or baseline functioning were achieved in 22, with the most prominent responses in patients with antibodies against surface antigens. The lack of identifiable antibodies may be due to our lack of knowledge of antibodies causing the disease, the transient presence of antibodies, or the possibility that those antibodies are only detected in CSF and are not routinely assayed.

In our cohort, we were able to identify antibodies to NMDAR and VGKC complex in nearly half of our patients. Their clinical presentation often involved new-onset seizures in addition to either psychosis or progressive anterograde memory decline. Two of the patients did not warrant a hospital admission and were managed as outpatients. At the other end of the spectrum, four patients presented with status epilepticus. As part of their diagnostic workup, T2/FLAIR hyperintensities were noted in 56% (Fig. 1) and inflammatory CSF with WBC $>5/mm^3$ in 44%. Our cohort, similar to that of other studies [14], lists low readmission rates limited to only four patients, while the rest seemed to have a monophasic illness with no clear progression.

An assessment of long-term outcomes in our patients revealed continued seizures in 50% of the patients who initially presented with seizures, treatment for a psychiatric comorbidity in 44%, and a change in employment status in 46%. These findings are significant as they impact a predominantly young patient population with a subset of them fulfilling criteria for dementia, facing a health-care system with limited resources for their age group [17], and needing extended hours of caregiving services. We found that most patients continued to reside at home after their illness. This, by no means, should be meant as a good prognosis. Young people with neurological illness are often hard to place in residential facilities. They continue to live at home with a parent/spouse (often) or sibling (less frequently) as the main caregiver. They require long-term follow-up and psychiatric care because of neuropsychiatric comorbidities resulting from their encephalitis. In addition, they encounter significant psychosocial stressors as they learn to deal with their losses (new sense of diseased self, seizures, loss of employment or educational status), facing, on a daily basis, their limitations with the list of things that they can no longer do as they are used to do them growing every day [18].

4.1. Overall epilepsy outcomes

In our series, only one patient had undergone a temporal lobectomy, and this was unsuccessful. Status epilepticus, whether convulsive or nonconvulsive, can be an initial presentation of nonparaneoplastic limbic encephalitis. Early recognition of the underlying cause is important because of the risk of morbidity and mortality from ongoing seizures even if nonconvulsive [19]. After the initial acute phase and diagnosis, even in the absence of status epilepticus, 50% of patients go on to have medically refractory epilepsy. Epilepsy surgery has been offered in these patients, and on histopathology, lymphocytic parenchymal infiltration is often noted [13]. Some of these patients continue to have isolated auras which are often difficult to treat with medications. It is unclear whether other nonpharmacological approaches would be more successful [20].

4.2. Anti-NMDAR encephalitis

In our cohort of 5 patients with anti-NMDAR encephalitis, seizures were present in 3 patients upon presentation, and only one had medically refractory seizures afterwards. Three of these patients lost employment as a result of their disease.

Anti-NMDAR encephalitis is a form of encephalitis which was initially described in young females with ovarian teratomas. The antibodies that target the NMDA receptor are on the cell surface. In addition to the classic clinical presentation, patients may also have a movement disorder, dysautonomia, and a reduction in their level of consciousness [21]. The age at onset can range widely from 2 up to 76 years of age, and the disease often involves a number of brain regions beyond the

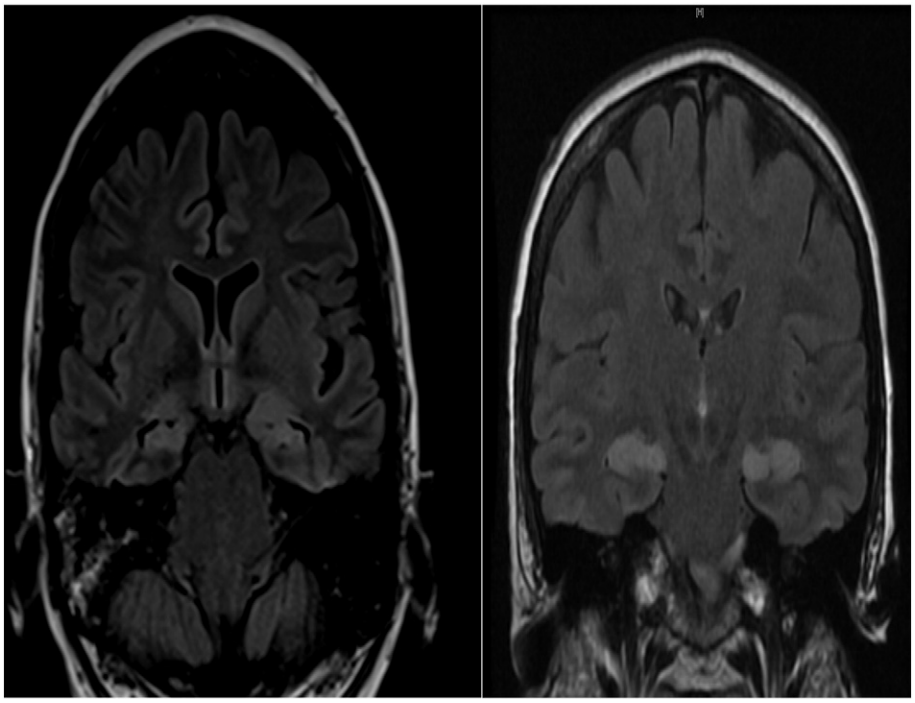

Fig. 1. Coronal FLAIR MRIs showing hyperintensities in the bilateral mesial temporal lobes.

limbic system [22]. As a result, it is a more diffuse encephalitis rather than a purely limbic one.

Our cohort included 5 patients with identified NMDA receptor antibodies, and they all had prominent behavioral disturbances upon presentation with psychosis. Irani et al. [5] described a large series of patients with this condition in both pediatric and adult patients. They found that male patients tended not to have an underlying tumor. The group with nonparaneoplastic limbic encephalitis tended to have lower antibody levels; lower prevalence of agitation, confusion, and amnesia; and decreased level of consciousness. The authors noted that the majority of patients tended to have improved modified Rankin Scores (mRS) at 4 months, especially if treated within the first 40 days of presentation. In an analysis of 25 patients (5 with teratomas), Gabilondo et al. [14] found a complete recovery in 48% of the patients and mild disability in 32% of the patients. Six patients had a relapse during the follow-up period; the relapses were usually milder than the initial presentation.

4.3. Anti-VGKC complex limbic encephalitis

In our series, we also noted five patients with anti-VGKC complex limbic encephalitis. They all suffered from seizures at their presentation, and one patient had status epilepticus. The CSF WBC count ranged between 1 and 8 cells. At follow-up, one continued to have seizures, one had an impulse control disorder, and one had depression.

Nonparaneoplastic autoimmune limbic encephalitis due to antibodies against VGKC receptor complex components is common. The actual antigens targeted have been identified as LGI1, CASPR2, and contactin-2. It tends to occur in patients older than 40, is male-predominant, and does not tend to have CSF pleocytosis [23]. Initial descriptions of the condition showed mild short-term memory deficits and disabling behavioral deficits at last follow-up despite treatment. In another case series [6], an epilepsy-only presentation was described. Patients treated with immunotherapy in the absence of a tumor tended to have a significant improvement in their outcomes, with around 40% of the patients experiencing an mRS score of 2 or 3 (2 = symptoms lead to some restriction of lifestyle but do not prevent totally independent existence; 3 = symptoms significantly interfere with lifestyle or prevent totally independent existence). In another series of 7 patients, long-term follow-up showed mild cognitive impairment in 4 patients and "disabling" behavioral deficits in 2 patients [24].

5. Limitations

This study spanned a 15-year period leading to the identification of a heterogeneous patient population, so not all known antibodies were tested in the patients who were diagnosed earlier. A number of patients labeled as having "idiopathic" antibodies may have yet unidentified autoantibodies or may have only recently been identified as having one of the syndromes described above. Antibodies were not always tested in the CSF, and we had a single case of serum-positive but CSF-negative NMDA antibodies. Inflammatory cells can also be noted in the CSF during status epilepticus; it is unclear if this may be due to an underlying encephalitis or the seizures themselves. An undiagnosed neoplasm may also be a possibility in a number of these patients. Treatment approaches, diagnostic workup, and follow-up were polymorphic (nonstandardized). Psychiatric diagnoses relied on the chart review rather than on the structured assessments, and there was no control group allowing a better analysis of the employment outcomes.

6. 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. As this disorder affects mostly young people in the height of their productive years, the psychosocial impact of the illness on the individual, his/her family, and community is huge. The financial burden on the system is also considerable. Future studies would need to assess the role of early treatment on these outcomes and address long-term sequelae. We hope that our paper will help open a constructive debate leading to continuous advances in this field of study.

Conflict of interest

We wish to confirm that there are no known conflicts of interest associated with this publication and that there has been no significant financial support for this work that could have influenced its outcome.

We confirm that the manuscript has been read and approved by all named authors and that there are no other persons who satisfied the criteria for authorship that are not listed. We further confirm that the order of authors listed in the manuscript has been approved by all authors.

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