Limbic encephalitis: Clinical spectrum and long-term outcome from a developing country perspective

Sujit Abajirao Jagtap, Gopal Krishna Das, Harsha J. Kambale, Ashalatha Radhakrishnan, M.D. Nair

Departments of Neurology, and Imaging Sciences and Intervention Radiology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India

Abstract

Introduction: Limbic encephalitis (LE) is characterized by rapidly progressive short-term memory loss, psychiatric symptoms and seizures. We describe the clinical spectrum, underlying etiology and long-term follow-up of patients with LE from India. Materials and Methods: This prospective study included patients during the period of January 2009 and December 2011 with the clinical features consistent with LE with one or more of the following: (1) Magnetic resonance imaging (MRI) evidence of temporal lobe involvement; (2) cerebrospinal fluid inflammatory abnormalities, or (3) detection of antineuronal antibodies. Patients with metastasis, infection, metabolic and nutritional deficits, stroke, were excluded. Results: There were 16 patients (9 females), mean age of presentation was 36.6 years (range 15-69 years). The mean duration of symptoms before presentation was 11 months (range 5 days-2 years). The most common symptom at presentation was short-term memory impairment in 7 patients followed by seizures in 5 and behavioral changes in three. Nine patients had seizures, 11 had change in behavior, language involvement in eight, cerebellar features in 3 and autonomic dysfunction in two. Four patients had associated malignancy, 3 of four presented with neurological symptoms and on investigations found to be have malignancy. Antineuronal antibody testing was done in 6 of 12 non paraneoplastic and two paraneoplastic patients, one positive for N-methyl-D-aspartate and one for anti-Hu antibody. MRI brain showed typical fluid attenuated inversion recovery or T2 bilateral temporal lobe hyperintensities in 50% of patients. At a mean follow-up of 21 months (3-36 months), 10 patients improved, 4 patients remained same and two patients expired. Conclusion: Early recognition of LE is important based upon clinical, MRI data in the absence of antineuronal surface antibody screen in developing nations. Early institution of immunotherapy will help in improvement in outcome of these patients in long-term.

Key Words

Antineuronal antibodies, limbic encephalitis, paraneoplastic syndrome

For correspondence:
Dr. Ashalatha Radhakrishnan, Department of Neurology, Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum - 695 011, Kerala, India.
E-mail: drashalatha@sctimst.ac.in

Ann Indian Acad Neurol 2014;17:161-5
Exclusion of metastasis, infection, metabolic and nutritional deficits, stroke and side-effects of therapy that may cause limbic encephalopathy and (d) At least one of the following: (i) Cerebrospinal fluid (CSF) with inflammatory findings, (ii) magnetic resonance imaging (MRI) fluid attenuated inversion recovery (FLAIR) or T2 uni or bilateral temporal lobe hyperintensities and (iii) electroencephalography (EEG) with epileptic or slow activity locally involving the temporal lobes. The diagnosis of LE is no longer dependent on the pathologic confirmation of inflammation involving the limbic system. LE may improve after immunotherapy or removal of a tumor and hence early diagnosis is important. There are few case reports from developing nations due to lack of availability of immunological investigations. We describe the clinical spectrum, underlying etiology and long-term follow-up of patients with LE.

Materials and Methods

This prospective study included patients who were seen between January 2009 and December 2011 at Sree Chitra Tirunal Institute for Medical Sciences and Technology, Trivandrum, Kerala, India. The inclusion criterion was clinical features consistent with LE, like short-term memory loss confusion, seizures, or psychiatric symptoms in association with one or more of the following: (1) Neuroimaging (MRI) evidence of temporal lobe involvement; (2) CSF inflammatory abnormalities (pleocytosis, increased protein concentration or oligoclonal bands), or (3) detection of antibodies that occur in association with LE. All patients were examined for systemic cancer using whole-body computed tomography (CT) and studied for autoimmune disorders with the following tests: Antinuclear antibody, anti-double-stranded deoxyribonucleic acid (DNA), Smith/Rnp, Sjogren’s (SSA, SSB), anti-neutrophilic cytoplasmic antibodies, antcardiolipin, antithyroglobulin and antimicrosomal (thyroperoxidase) antibodies. Patients with metastasis, infection, metabolic and nutritional deficits, stroke and side-effects of therapy that may cause limbic encephalopathy were excluded.

Results

There were 16 patients comprising of 9 females and 7 males. The mean age of presentation was 36.6 years (range 15-69 years). The mean duration of symptoms before presentation was 11 months (range 5 days-2 years). The most common symptom at presentation was short-term memory impairment in 7 patients followed by seizures in 5 and behavioral changes in three. Eight patients had complex partial seizures, one had generalized seizure and seven did not have any seizure. Seizures were infrequent but two patients had status epilepticus. 11 patients had change behavior, predominant symptom was apathy followed by irritability and depression. Language was affected in eight patients and one became mute who improved subsequently. Catatonia was present in two patients, which improved with treatment. Cerebellar features were seen in three patients and autonomic dysfunction was present in two one of which expired due to autonomic storm [Figure 1]. Four patients had associated malignancy, small cell carcinoma lung in 2, one had thymoma and one had renal cell carcinoma (RCC). Patients with SCLC and RCC presented with memory impairment and seizures while patient with thymoma presented with ataxia. Three of four presented with neurological symptoms and on investigations found to be have malignancy. One patient expired during hospital admission while two underwent tumor removal with improvement in symptoms. Antineuronal antibody testing was done in 6 of 12 non paraneoplastic and two paraneoplastic patients, one positive for NMDA and one for anti-Hu antibody. EEG showed epileptiform abnormalities in eight patients, focal slowing in six and was normal in two. Electrographic seizures were present in two patients on presentation. MRI brain showed typical FLAIR or T2 bilateral temporal lobe hyperintensities in eight patients, unilateral in three, cerebellar involvement in two, subcortical white matter in two and normal in one [Figure 2]. All patients were treated with intravenous methylprednisolone, two patients received intravenous immunoglobulin and two received plasma exchange additionally. At a mean follow-up of 21 months duration (3-36 months), 10 patients improved, 4 patients remained same and two patients expired.

Figure 1: Column chart and bar chart showing clinical and imaging features in patients with limbic encephalitis

Figure 2: (a) Magnetic resonance imaging brain axial T2-weighted (b) axial fluid attenuated inversion recovery (FLAIR) image showing bilateral amygdala, hippocampal hyperintensity (c) axial FLAIR images showing hyperintensity in bilateral hippocampi and posterolateral aspect of bilateral putamen in patient with non paraneoplastic limbic encephalitis (d) axial FLAIR image showing bilateral amygdala, hippocampal hyperintensity (e) coronal post contrast T1w thoracic image revealing large right upper lobe lung mass in patient with paraneoplastic limbic encephalitis
**Discussion**

LE was initially described as a rare complication of cancer, now non-paraneoplastic form of LE associated with antibodies to neuronal proteins are being well recognized. They generally have a better prognosis than that of patients with the paraneoplastic form. Paraneoplastic limbic encephalitis (PLE) preceded the diagnosis of cancer in 60% of cases by an average of 3½ months in the largest published series, similarly in our all patients with PLE. This is important in treatment point of view, as they have a better prospect for curative therapy of the underlying tumor if it is detected early and has not metastasized. PLE seems likely to be immune mediated, the mechanism by which distant malignancies cause LE is not clear. The antineuronal antibodies associated with PLE may only be markers of cell mediated immunopathology, rather than pathogenic per se.

NMDA receptor encephalitis is usually associated more frequently with an ovarian teratoma in women older than 18 years, approximately 55%, compared with only 15% of women younger than 14 years. Hence, screening for ovarian teratoma in females with NMDA receptor encephalitis is important. The most useful screening tests include MRI, CT scan and pelvic and transvaginal ultrasound. Our NMDA receptor encephalitis patient did not have ovarian teratoma. NMDA receptor encephalitis patient have higher titers when compared with non-paraneoplastic encephalitis with mean of 7855 (948-17,070) and 2255 (0-16,208) fluorescent units precipitated, respectively although increased chance of relapse is seen in non-paraneoplastic autoimmune encephalitis. Patients treated with tumor resection and immunotherapy (corticosteroids, intravenous immunoglobulin, or plasma exchange) respond faster to treatment and less frequently need second-line immunotherapy (cyclophosphamide or rituximab, or both) than do patients without a tumor who receive similar initial immunotherapy. More than 75% of all patients have substantial recovery that occurs in inverse order of symptom development and is associated with a decline of antibody titers.

The spectrum of clinical features of VGKC associated LE continues to be evolved. Antibodies against VGKCs in fact target associated channel proteins – i.e., leucine-rich glioma inactivated 1 (LGI1) and contactin associated protein-like 2 (Caspr2) rather than the potassium channel itself. Antibodies against VGKC complexes can have different clinical manifestations, LE is the most common syndrome followed by neumyotonia, Morvan's syndrome, epilepsy only or uncategorized central nervous system (CNS) features. High titers (>400 pmol/L) were detected in the serum, at the rate of about 1-2/million/year in the study by Vincent et al. Anti-LGI1 LE is seen in middle aged patients more predominant in men than women (2:1 ratio) and is not associated with cancer. Hyponatraemia can sometimes be diagnostic for this encephalitis. LE associated with anti-VGKCs can present with rapid eye movement sleep behaviour disorder, severe insomnia and neumyotonia, which is a well-known symptom of Morvan’s syndrome. Morvan’s syndrome have been reported in patients with tumors, particularly in those with thymoma or lung or other carcinomas. One of our patients with thymoma presented with features similar to Morvan’s syndrome. In some patients brief, frequent episodes of abnormal unilateral and bilateral movements of the arms, sometimes the ipsilateral muscles of the face and more rarely the leg also called as faciobrachial dystonic seizures precede LE associated with LGII antibodies. Video EEG monitoring is important as EEG with scalp electrodes might not reveal an ictal pattern and the epileptic origin of these myoclonic-like movements.

Brain MRI is normal in 50% of patients and in the other 50%, T2 or FLAIR signal hyperintensity might be seen in the hippocampus, cerebellar or cerebral cortex, frontobasal and insular regions, basal ganglia, brainstem and infrequently, the spinal cord. The findings are usually mild or transient and can be accompanied by subtle contrast enhancement in the affected areas or the meninges. Follow-up MR is either remain normal or show minimum change despite the severity and duration of symptoms. In our series only one patient had normal MRI and 50% had bilateral hippocampal abnormalities. This high percentage of positive imaging findings may be due to small sample size as well as referral bias. In most patients, EEG are abnormal usually showing non-specific, slow and disorganized activity sometimes with electrographic seizures. Nearly 80% of patients have abnormal CSF initially and becomes abnormal later in the disease in most other patients in the form of moderate lymphocytic pleocytosis, normal or mildly increased protein concentration. NMDAR antibodies might be detected only in CSF, If diagnosis is delayed or patients have received treatment with plasma exchange or IV immunoglobulin. During follow-up 62% of our patients showed improvement emphasizing on early detection and treatment. The mortality in our study was due to autonomic storm in non paraneoplastic group and infection in paraneoplastic group with advanced cancer. Long-term follow-up is available in very few studies, which emphasizes on early immunomodulatory treatment as tumor detection with removal as important prognostic factor.

The differential diagnosis for LE includes metabolic or toxic encephalopathy which presents as an acute confusional state, difficult to distinguish from LE. Some infections of the CNS such as herpes simplex virus (HSV), human herpes virus type 6 (HHV6), Japanese encephalitis and flavi virus infections are difficult to distinguish from autoimmune LE. The polymerase chain reaction (PCR) assay for HSV DNA in the CSF is highly specific and sensitive for herpes simplex encephalitis and helps to distinguish from LE as both has a predilection to involve the temporal lobes with behavioral change and seizures. Similarly, HHV6 can be easily identified with positive CSF PCR assay. Hashimoto's encephalopathy, systemic autoimmune disorders such as Sjogren's syndrome, systemic lupus erythematosus, primary CNS vasculitis and brain tumors like primary CNS lymphoma and gliomatosis cerebri, can have a clinical presentation and MRI appearance that resembles LE. The hormonal assay, antibody titers, brain biopsy and imaging features helps to distinguish these conditions from LE.
The treatment consists of tumor removal with intravenous methyl prednisolone and intravenous immunoglobulin or plasma exchange in paraneoplastic LE while intravenous methyl prednisolone (1 g daily for 3 days) and intravenous immunoglobulin (0.4 g/kg/day for 5 days), or plasma exchange in non paraneoplastic LE, which is considered as first line immnosuppressive therapy. If patient had good response to first line treatment then supportive care and yearly tumor surveillance for 5 years is required. If there is no response to first line treatment then immunosuppression with second line treatment is with rituximab or cyclophosphamide or both, followed by supportive care and yearly tumor surveillance for 5 years. Patients who had relapse of symptoms after improvement may require long-term pulse therapies and continuous low grade immnosuppression. If there is no response to second line immunosuppression then other immnosuppressive agents like mycofenolate mofetil, azathioprine are used but still there are no clear guideline about treatment resistant LE[8,9,18-22] [Figure 3].

The detection of antineuronal surface antibodies is important in patient presenting with features of LE as it has both diagnostic and prognostic value. Depending on clinical features antibody testing should be planned as it is requires special techniques and done only in few laboratories world-wide. Due to non-availability and economic constraints very few reports have been came from developing countries, although it is increasingly recognized.

Figure 3: Diagnostic approach and management algorithm for limbic encephalitis HHV6 - human herpes virus 6, HSV - herpes simplex virus, VGKC - voltage gated potassium channel, NMDAR - N-methyl-D-aspartate receptor, CV2/CRMP5 - collapsin response-mediator protein 5, PET - positron emission tomography, LGI1 - leucine-rich, glioma-inactivated 1, CASPER2 - contactin associated protein 2. 1st line immunosuppression-intravenous methyl prednisolone and intravenous immunoglobulin or plasma exchange, 2nd line immunosuppression-rituximab or cyclophosphamide or both.
Conclusion

Early recognition of LE is important based upon clinical, MRI data in the absence of antineuronal surface antibody screen in developing nations. Early institution immunotherapy will help improvement in clinical conditions of these patients in long-term.

References

1. Tüzün E, Dalmau J. Limbic encephalitis and variants: Classification, diagnosis and treatment. Neurologist 2007;13:261-71.
2. Corsellis JA, Goldberg GJ, Norton AR. “Limbic encephalitis” and its association with carcinoma. Brain 1968;91:481-96.
3. Bakheit AM, Kennedy PG, Behan PO. Paraneoplastic limbic encephalitis: Clinico-pathological correlations. J Neurol Neurosurg Psychiatry 1990;53:1084-8.
4. Manley GT, Smitt PS, Dalmau J, Posner JB. Hu antigens: Reactivity with Hu antibodies, tumor expression, and major immunogenic sites. Ann Neurol 1995;38:102-10.
5. Gultekin SH, Rosenfeld MR, Voltz R, Eichen J, Posner JB, Dalmau J. Paraneoplastic limbic encephalitis: Neurological symptoms, immunological findings and tumour association in 50 patients. Brain 2000;123 (Pt 7):1481-94.
6. Buckley C, Oger J, Clover L, Tüzün E, Carpenter K, Jackson M, et al. Potassium channel antibodies in two patients with reversible limbic encephalitis. Ann Neurol 2001;50:73-8.
7. Thieben MJ, Lennon VA, Boeve BF, Aksamit AJ, Keegan M, Vernino S. Potentially reversible autoimmune limbic encephalitis with neuronal potassium channel antibody. Neurology 2004;62:1177-82.
8. Dalmau J, Tüzün E, Wu HY, Masjuan J, Rossi JE, Voloschin A, et al. Paraneoplastic anti-N-methyl-D-aspartate receptor encephalitis associated with ovarian teratoma. Ann Neurol 2007;61:25-36.
9. Alamowitch S, Graus F, Uchuya M, Renié R, Bescansa E, Delattre JY. Limbic encephalitis and small cell lung cancer. Clinical and immunological features. Brain 1997;120 (Pt 6):923-8.
10. Wani MA, Dar JA, Khan MA, Rehman A. Paraneoplastic limbic encephalitis associated with bronchogenic carcinoma: A case report. Neurol India 2001;49:185-7.
11. Ghosh KC, Biswas S, Misra AK, Dhibar T, Das SK. Limbic encephalitis – An uncommon presentation of systemic malignancy. J Assoc Physicians India 2007;55:731-3.
12. Rajappa S, Digumarti R, Immaneni SR, Parage M. Primary renal lymphoma presenting with paraneoplastic limbic encephalitis. J Clin Oncol 2007;25:3785-3.
13. Padma S, Sundaram PS, Marmattom BV. PET/CT in the evaluation of anti-NMDA-receptor encephalitis: What we need to know as a NM physician. Indian J Nucl Med 2011;26:99-101.
14. Marmattom BV, Jacob A. N-methyl D-aspartate receptor encephalitis: A new addition to the spectrum of autoimmune encephalitis. Ann Indian Acad Neurol 2011;14:153-7.
15. Kamaleshwaran KK, Iyer RS, Antony J, Radhakrishnan EK, Shinto A. 18F-FDG PET/CT findings in voltage-gated potassium channel limbic encephalitis. Clin Nucl Med 2013;38:392-4.
16. Pandit AK, Ihtisham K, Garg A, Gulali S, Padma MV, Tripathi M. Autoimmune encephalitis: A potentially reversible cause of status epilepticus, epilepsy, and cognitive decline. Ann Indian Acad Neurol 2013;16:577-84.
17. Lancaster E, Martinez-Hernandez E, Dalmau J. Encephalitis and antibodies to synaptic and neuronal cell surface proteins. Neurology 2011;77:179-89.
18. Dropcho EJ. Update on paraneoplastic syndromes. Curr Opin Neurol 2005;18:331-6.
19. Vincent A, Buckley C, Schott JM, Baker I, Dewar BK, Detert N. et al. Potassium channel antibody-associated encephalopathy: A potentially immunotherapy-responsive form of limbic encephalitis. Brain 2004;127:701-12.
20. Irani SR, Bera K, Waters P, Zuliani L, Maxwell S, Zandi MS, et al. N-methyl-D-aspartate antibody encephalitis: Temporal progression of clinical and paraclinical observations in a predominantly non-paraneoplastic disorder of both sexes. Brain 2010;133:1655-67.
21. Dalmau J, Lancaster E, Martinez-Hernandez E, Rosenfeld MR, Balice-Gordon R. Clinical experience and laboratory investigations in patients with anti-NMDAR encephalitis. Lancet Neurol 2011;10:63-74.
22. Vincent A, Blen CG, Irani SR, Waters P. Autoantibodies associated with diseases of the CNS: New developments and future challenges. Lancet Neurol 2011;10:759-72.
23. Irani SR, Alexander S, Waters P, Kleopa KA, Pettingill P, Zuliani L, et al. Antibodies to Kv1 potassium channel-complex proteins leucine-rich, glioma inactivated 1 protein and contactin-associated protein-2 in limbic encephalitis, Morvan’s syndrome and acquired neuromyotonia. Brain 2010;133:2734-48.
24. Hart IK, Waters C, Vincent A, Newland C, Beeson D, Pongs O, et al. Autoantibodies detected to expressed K+ channels are implicated in neuromyotonia. Ann Neurol 1997;41:238-46.
25. Irani SR, Michell AW, Lang B, Pettingill P, Waters P, Johnson MR, et al. Faciobrachial dystonic seizures precede Lgi1 antibody limbic encephalitis. Ann Neurol 2011;69:392-399.
26. Anderson NE, Barber PA. Limbic encephalitis - A review. J Clin Neurosci 2008;15:961-71.
27. Dalmau J, Gleichman AJ, Hughes EG, Rossi JE, Peng X, Lai M, et al. Anti-NMDA-receptor encephalitis: Case series and analysis of the effects of antibodies. Lancet Neurol 2008;7:1091-8.

How to cite this article: Jagtap SA, Das GK, Kambale HJ, Radhakrishnan A, Nair M. Limbic encephalitis: Clinical spectrum and long-term outcome from a developing country perspective. Ann Indian Acad Neurol 2014;17:161-5

Received: 13-10-13, Revised: 05-11-13, Accepted: 08-12-13

Source of Support: Nil, Conflict of Interest: None declared.