Original Article

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

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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

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Introduction

Limbic encephalitis (LE) is characterized by rapidly progressive short-term memory loss, psychiatric symptoms and seizures.[1] The term "LE" was coined by Corsellis *et al*. in 1968 to describe memory loss and dementia in association with bronchial carcinoma.[2] Initially LE was considered a rare disorder in association with cancer; most commonly associated with small cell lung cancer (SCLC), breast cancer, testicular tumors, teratomas, Hodgkin's lymphoma and thymomas but can occur in the absence of malignancy also.[3-5] About 60-75% of patients neurological symptoms precedes the diagnosis of malignancy.[6] LE can have varied presentation and delayed diagnosis is common. The improvements in neuroimaging and identification of antineuronal antibodies in patients with LE have facilitated recognition of the disorder. These antineuronal antibodies are directed against (1) intracellular or classic paraneoplastic antigens, including Hu, Ma2, CV2/collapsin response-mediator protein 5 and amphiphysin among others and (2) cell membrane antigens, including voltage-gated potassium channels (VGKC), N-methyl-D-aspartate (NMDA) receptor and others expressed in the neuropil of hippocampus and cerebellum.[3-8]

The diagnostic criteria by Gultekin *et al*.[5] is more frequently used which includes (1) Pathological demonstration of LE; or (2) All 4 of the following: (a) Symptoms of short-term memory loss, seizures, or psychiatric symptoms suggesting involvement of the limbic system, (b) <4 year between the onset of neurological symptoms and the cancer diagnosis, (c)

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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 focally involving the temporal lobes. The diagnosis of LE is no longer dependent on the pathologic confirmation of inflammation involving the limbic system.[9] LE may improve after immunotherapy or removal of a tumor and hence early diagnosis is important.[7] There are few case reports from developing nations due to lack of availability of immunological investigations.[10-16] 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, anticardiolipin, 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.

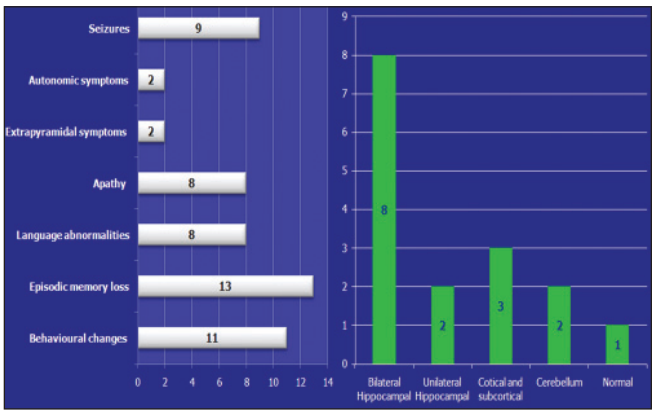

Figure 1: Column chart and bar chart showing clinical and imaging features in patients with limbic encephalitis

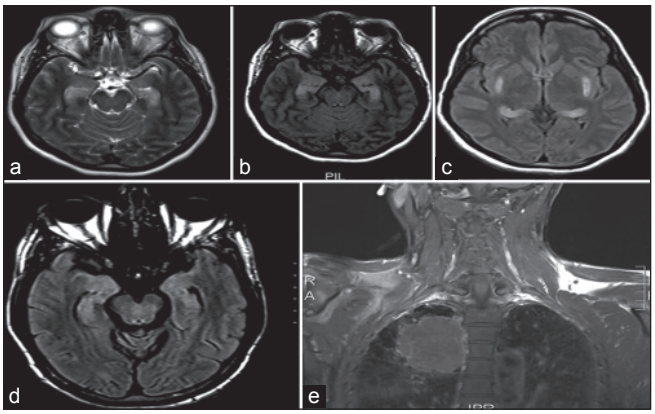

Figure 2: (a) Magnetic resonance imaging brain axial T2-weighted (b) axial fluid attenuated inversion recovery (FLAIR) image showing bilateral amygdala, hippocampal hyperintensity (c) axial FLAIR images showing hyperintensity in bilateral hippocampi and posterolateral aspect of bilateral putamen in patient 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.[17] 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.[5] 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*.[18,19]

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 NMAD receptor encephalitis is important.[8] 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 in association with testicular germ-cell tumors or other neoplasms has been reported in approximately 5% of men. Fluorescent immunoprecipitation assay are used for detection of antibodies to N-methyl-D-aspartate receptor (NMDAR). Patients with paraneoplastic encephalitis 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.[20] 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.[21] 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 rather than the potassium channel itself.[21] Antibodies against VGKC complexes can have different clinical manifestations, LE is the most common syndrome followed by neuromyotonia, Morvans' syndrome, epilepsy only or uncategorized central nervous system (CNS) features.[22] High titers (>400 pmol/L; normal values <100 pmol/L) were detected in the serum, at the rate of about 1-2/million/year in the study by Vincent *et al*.[19] 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.[23] LE associated with anti-VGKCs can present with rapid eye movement sleep behaviour disorder, severe insomnia and neuromyotonia, which is a well-known symptom of Morvan's syndrome.[24] 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 LGI1 antibodies.[25] 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 hippocampi, 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.[21,26] 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.[18] 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.[27] 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.[26] 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.[8,9,14,16,22] 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 predinisolone and intravenous immunoglobulin or plasma exchange in paraneoplastic LE while intravenous methyl predinisolone (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 immunosuppressive 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 immunosuppression. If there is no response to second line immunosuppression then other immunosuppressive 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.

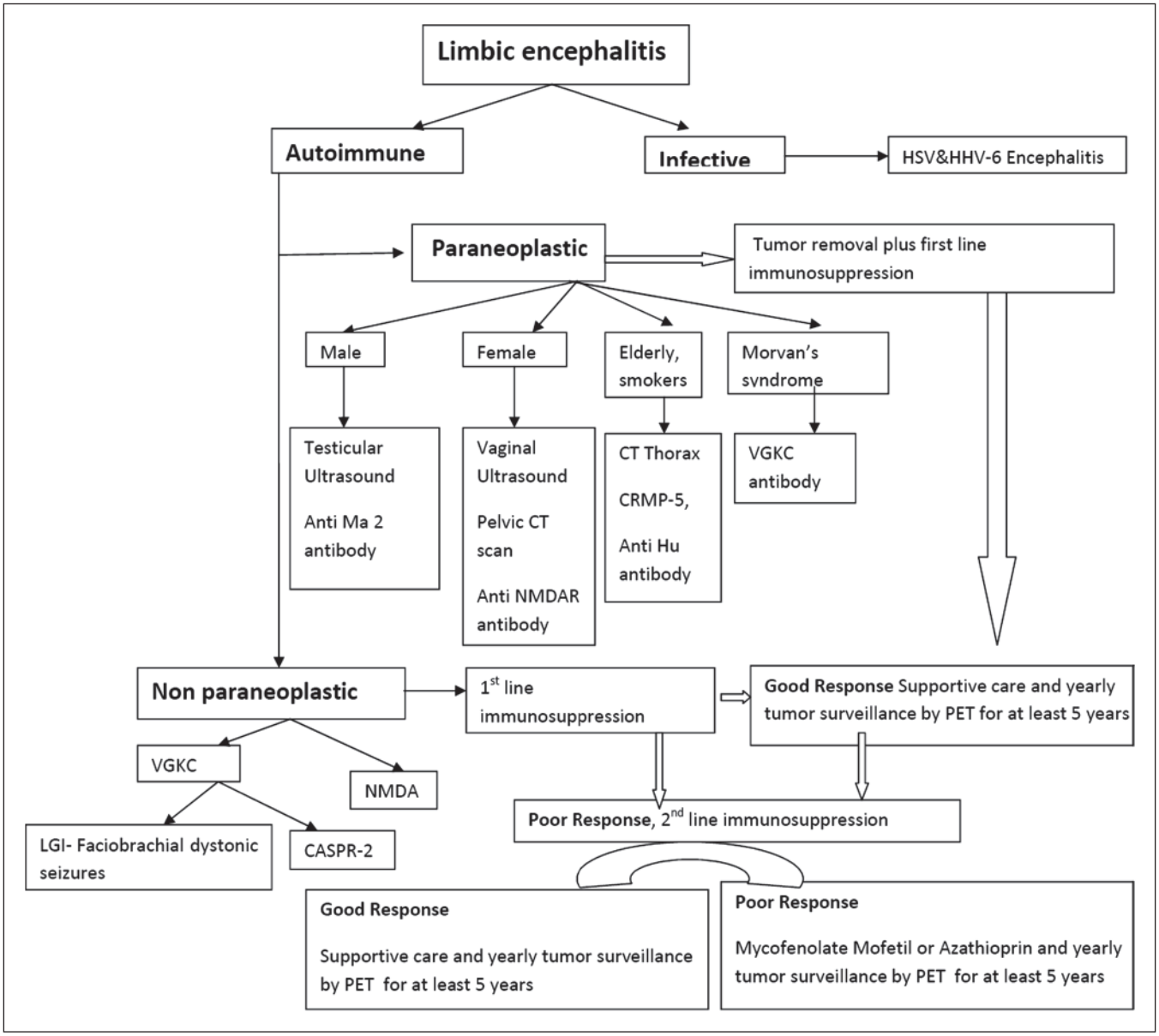

Figure 3: Diagnostic approach and management algorithm for limbic encephalitis HHV6 - human herpes virus 6, HSV - herpes simplex virus, VGKC - voltage gated potassium channel, NMDAR - N-methyl-D-aspartate receptor, CV2/CRMP5 - collapsin response-mediator protein 5, PET - positron emission tomography,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

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