

Limbic Encephalitis in Association with Systemic Lupus Erythematosus: A Case Report

Sistemik Lupus Eritematozusun Eşlik Ettiği Limbik Ensefalit: Olgu Sunumu

Hakan SELÇUK, Sait ALBAYRAM*, Sıla ULUS*, Zehra HASILOĞLU*, Osman KIZILKILIÇ*

Bakırköy State Hospital, Department of Radiology, Division of Neuroradiology, İstanbul, Turkey

*Cerrahpaşa Medical School, Department of Radiology, Division of Neuroradiology, İstanbul, Turkey

ABSTRACT

Limbic Encephalitis (LE) is a syndrome manifesting with seizures and delusions, progressive memory loss, and behavioral abnormalities lasting for weeks. Systemic Lupus Erythematosus (SLE) is a chronic autoimmune connective tissue disease that can affect any part of the body. Central nervous system (CNS) involvement has been reported in 14-75% of SLE cases. We present the clinical, immunological, and radiological features of a case of LE occurring in association with SLE. (*Archives of Neuropsychiatry* 2011; 48: 88-91)

Key words: Limbic encephalitis, Systemic Lupus Erythematosus, Magnetic resonance imaging

ÖZET

Limbik ensefalit (LE) sıklıkla nöbetlerin ve sanrıların, ilerleyici hafıza kaybı ve ruhsal anormalliklerin eşlik ettiği haftalar süren bir sendromdur. Sistemik lupus eritematozus (SLE) vücudun tüm parçalarını etkileyen kronik otoimmün konnektif doku hastalığıdır. SLE'de santral sinir sistemi tutulumu %14-75 olguda gösterilmiştir. Bu çalışmada, SLE'li bir hastada limbik ensefalit birlikteliğinin radyolojik, klinik ve immünolojik özellikleri sunulmuştur. (*Nöropsikiyatri Arşivi* 2011; 48: 88-91)

Anahtar kelimeler: Limbik ensefalit, Sistemik Lupus Eritematozus, Manyetik rezonans görüntüleme

Introduction

Subacute limbic encephalitis (LE) was first described as a unique clinical and pathological syndrome by Briery in 1960 (1). Its association with carcinoma was elucidated by Corsellis in 1968 (2). LE is clinically characterized by subacute cognitive dysfunction with memory impairment, seizures, and psychiatric features including hallucinations, anxiety, and depression. Laboratory and radiological findings are usually non-specific. Electroencephalography (EEG) reveals focal involvement of one or both temporal lobes. On magnetic resonance imaging (MRI), the typical lesions demonstrate increased signal intensities on T2-weighted images.

We report the clinical, immunological, and radiological features of a case of LE occurring in association with systemic lupus erythematosus (SLE).

Case Report

A 36-year-old woman with SLE experienced an acute onset of repeated and prolonged seizures. The diagnosis of SLE had been made after complaints of a skin rash, arthropathy of the wrists and knees, nephropathy, and elevated antinuclear antibody (ANA) titers. Methylprednisolone had been administered 1gr per day for three days and 1mg/kg for four weeks. The patient presented to our clinic with repeated generalized tonic-clonic seizures following a dry cough and fever. She was lethargic on initial evaluation, disoriented with respect to time, had a decreased attention span, and had an apparent short-term memory deficit. Non-contrast and contrast-enhanced cranial computed tomography (CT) scans revealed bilateral calcifications of the globus pallidus (Figure 1). Electroencephalography (EEG) monitoring demonstrated electroclinical and subclinical seizures with bitemporal and generalized onset. On cranial MRI, signal

Address for Correspondence/Yazışma Adresi: Dr. Hakan Selçuk, Bakırköy State Hospital, Department of Radiology, Division of Neuroradiology, İstanbul, Turkey
Gsm: +90 532 558 24 44 E-mail: hakanselcuk73@yahoo.com **Received/Geliş tarihi:** 18.06.2010 **Accepted/Kabul tarihi:** 31.08.2010

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intensity was increased bilaterally in the hippocampal and parahippocampal areas, and symmetrical calcification was observed in the globus pallidus (Figures 2a-b). Cerebrospinal fluid (CSF) examination showed white blood cells (WBC), especially lymphocytes, elevated protein levels (75 mg/dl), and normal glucose levels (50 mg/dl). Treatment in the intensive care unit included intravenous administration of phenytoin, methylprednisolone, and acyclovir.

Physical examination revealed alopecia and malar rash; blood pressure was 110/70 mmHg, pulse was 96 beats/min, and her heart and breath sounds were normal with the exception of a 2/6 systolic murmur at the apex. A hepatomegaly of 4 cm was noted, but there was no splenomegaly. Active arthritis was not detected. On neurological examination, cranial nerves were intact, mental status was normal, as well as motor and sensory functions. The other systems showed no abnormality. Laboratory studies revealed erythrocyte sedimentation rate (ESR) of 87 mm/h, C-reactive protein (CRP) level of 100.2 ng/l, WBC count of 2800/mm³ with lymphocytopenia, and hemoglobin level of 9.9 g/dl. ANA test was positive with homogeneous pattern. The levels of specific antibodies were as follows: anti-double-stranded DNA (dsDNA) - 13.47 (N<0.90), anti-Smith (Sm) - 1.15 (N: 0.9-1.0), anti-cardiolipin IgM - 4.6 MPL (N: 0-8), anticardiolipin IgG - 24.7 GPL (N: 0-8); the C3 level was 0.713 g/l (N: 0.9-1.8) and the C4 level was 0.109 g/l (N: 0.1-0.4). Herpes simplex virus antibodies were not detected in serum or CSF (titers <1/10), and neither type 1 nor 2 virus DNA were detected by polymerase chain reaction (PCR) in CSF obtained after a week of acyclovir treatment. In addition, whole body PET-CT was performed to rule out paraneoplastic limbic encephalitis, and it was normal. The levels of antineuronal antibodies specific for paraneoplastic limbic encephalitis were not studied due to technical reasons. Seizure control was achieved with carbamazepine. An intravenous cyclophosphamide pulse therapy was given on day 14 for possible lupus cerebritis. Three months later, MRI showed atrophy of the temporal lobes, especially in the hippocampal and parahippocampal areas, with dilated temporal horns of the lateral ventricles (Figure 3). Any findings related to seizures, neurocognitive sequelae or paraneoplastic process was not seen at the one- and three-year follow-up visits.

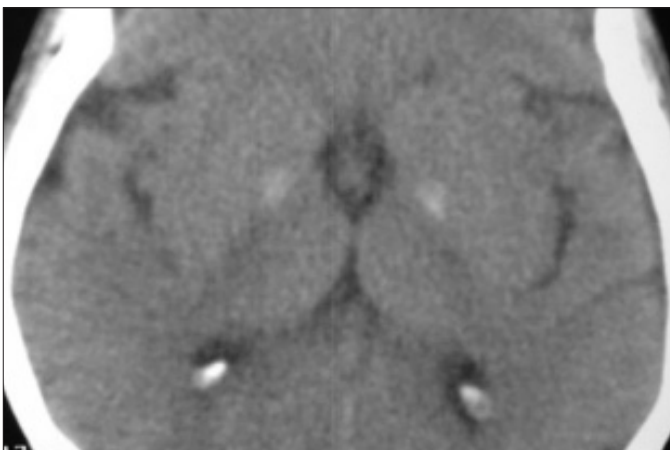


Figure 1. Axial CT image shows bilaterally symmetric calcification of the globus pallidum

Discussion

LE is a syndrome manifested by progressive memory loss and behavioral abnormalities over the course of many weeks, often accompanied by delusions and seizures. Tendency for involvement of limbic structures is the most important trait of herpes simplex encephalitis. In addition, this site is also preferentially affected in a subgroup of patients with SLE and in some cases of systemic malignancy (3). Paraneoplastic LE is a rare non-metastatic complication of malignant tumors. It can occur either alone or in combination with other paraneoplastic syndromes, such as paraneoplastic cerebellar degeneration (4). In 75% of cases, the primary tumor is small cell carcinoma of the lung, but an association with many other tumors, including thymoma, lymphoma, colon adenocarcinoma, testicular tumors, breast cancer, and renal cell carcinoma, has been reported (5-11). Paraneoplastic LE may precede the diagnosis of underlying tumor by several months. In rare instances, an underlying malignancy is never found.

Paraneoplastic neurological syndromes (PNS) occur in about 1% of patients with malignant diseases. They have usually a severe course and sometimes can be lethal. The pathogenesis of most PNS is thought to be immune mediated (12). The most common antibodies are anti-Hu antibodies, which are well-known antineuronal antibodies. They have a specificity of 99% and a sensitivity of 82% in detecting PNS (13).

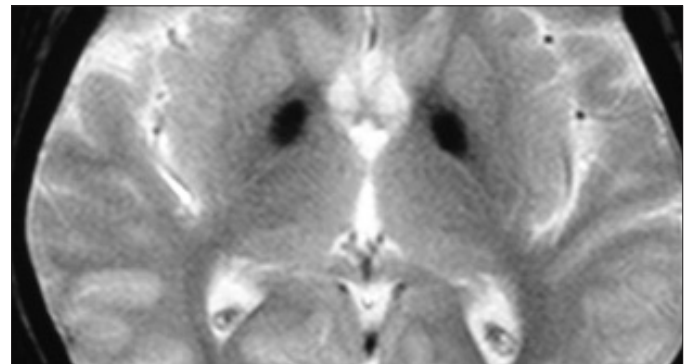


Figure 2a. Axial T2 weighted image shows symmetric calcification of the globus pallidum

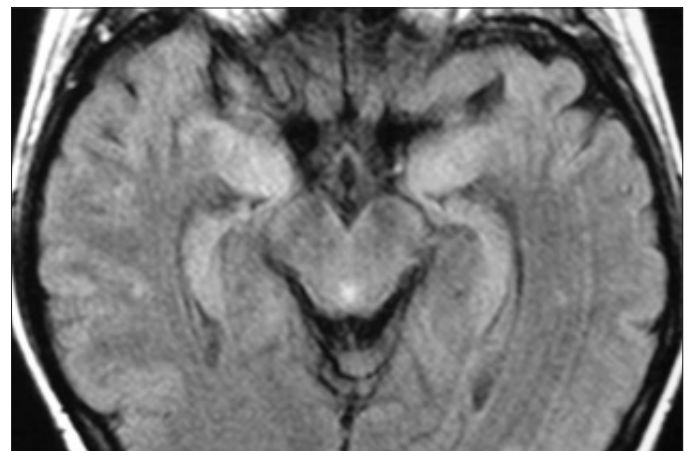


Figure 2b. Axial FLAIR image shows increased signal intensity in bilateral hippocampal and parahippocampal areas

SLE is a chronic autoimmune connective tissue disease that can affect any part of the body. Central nervous system (CNS) involvement is reported to occur in 14-75% of patients with SLE (14). Neurological presentation appears in approximately 3% of cases (14-15). The broad spectrum of neurological involvement comprises psychosis, seizures, visual disturbances, organic brain syndromes, cerebrovascular disease, migraine, cranial neuropathies, myelopathy, and focal neurological findings (14-15).

SLE cases can present with limbic findings. However, medial temporal lobe involvement, as in our case, is quite rare. Very few SLE cases with this pathological feature are reported in the literature. In addition, recently, neuromyelitis optica (NMO) has been reported as a distinct diagnostic entity in patients with SLE and other rheumatic diseases (16).

The classic histopathological study of the nervous system in SLE was initially reported by Johnson and Richardson in 1968 (17). They observed microinfarcts particularly in the cerebral cortex and brainstem that correlated well with the clinical features in most of the cases. Different pathogenetic mechanisms including B-cell/auto-antibody mediated nervous system compromise, immune complex deposition and vasculitis, microthrombosis and vasculopathy, aberrant MHC Class II antigen expression with T-cell mediated disease, and cytokine-induced brain inflammation might be involved in nervous system lupus (18). The detection of autoantibodies such as anti-neuronal, anti-ribosomal-P, anti-synaptosomal, and anti-ganglioside in serum/CSF support the autoimmune theories (19).

However, a possible explanation for these observations is that antineuronal antibodies bind to neuronal membranes and cause transient alteration of cell function without cell death or inflammation. Antineuronal antibodies can be found in both serum and spinal fluid of patients with CNS lupus. In addition, they have been associated with a variety of behavioral and neurological defects that developed in experimental animals injected with these antibodies (14).

Similar to other cases, the distribution of pathological changes in our case was correlated with the clinical presentation. Mental confusion, impairment of recent memory with normal cognitive

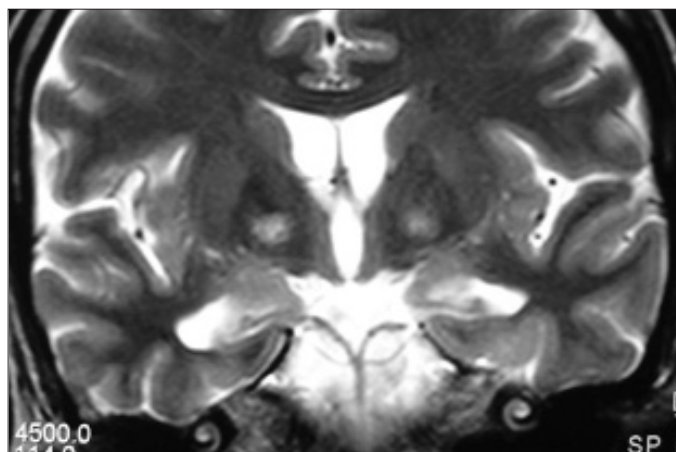


Figure 3. Coronal T2 WI shows especially in the hippocampal and parahippocampal areas, with dilated temporal horns of the lateral ventricles in the control MRI after 3 months

function, hallucinations, depression, personality change, and sleep disturbances were consistent findings. In the literature, these symptoms have been reported in various combinations in more than 90% of all patients (3); however, temporal lobe seizures occurred in few of them (19).

The diagnosis of LE can be difficult if based on clinical and laboratory findings alone, particularly when a neoplasm has not yet been diagnosed, because metabolic, infective, and neoplastic conditions can mimic the clinical features. Routine laboratory studies are usually of little help in the diagnosis of LE; CSF analysis reveals only mildly elevated WBC count and slightly elevated protein levels. The detection of antineuronal antibodies is highly specific for paraneoplastic neurological disorders (7). These antibodies are related to a paraneoplastic syndrome associated with small cell carcinoma of the lung, and are implicated in the pathogenesis of LE as they have the ability to bind to brain neuronal antigens (20). Plasmapheresis, used to remove the antibodies from the blood, can be helpful in the treatment of these patients.

Neuropathological studies have showed chronic perivascular inflammatory changes in the meninges, encephalitis with lymphocytic infiltrates of the medial temporal lobes (7, 21). The histological and clinical findings were possibly due to an autoimmune phenomenon. The pathogenesis of LE-complicating malignancy is not clear. Correllis et al. speculated that a slow viral infection might be responsible (2).

Imaging studies has an important role in the diagnosis of LE, especially in eliminating the need for brain biopsy (11, 21, 22, 23). CT findings are often normal, but have occasionally shown a hypodense lesion in the medial aspect of one or both temporal lobes (24). MRI studies have demonstrated hyperintense signal abnormalities in the temporal lobe on T2-weighted images in the acute phase (11, 22,23-25). In our case, the MRI studies revealed bitemporal lobe hyperintense signal abnormalities on T2-weighted images in the acute phase. Stübgen (19) described one case of nervous system lupus, in which MRI showed bitemporal nonenhancing lesions, predominantly in the gray matter. Involvement of the cortex was consistent with an antineuronal antibody hypothesis of cerebral lupus (CL), because the gray matter consists largely of the target neurons. In our case, symmetric calcifications in bilateral basal ganglia were detected in addition to the lesions in the limbic area. This suggests that CNS involvement had taken place in the past and, thus, deposition of dystrophic calcification had occurred in the damaged area. Intracerebral calcification is not a common finding in SLE, and has only been reported following episodes of CL. The pathogenesis of cerebral calcification in CL is unknown. Basal ganglia calcifications can be physiological, however, bilateral basal ganglia calcifications have been reported in SLE patients. We think that the bilateral dense calcifications in our case are dystrophic rather than physiological because of the patient's age. CL must now be included in the differential diagnosis of intracerebral calcification (25-28).

As a conclusion, nervous system lupus is an important consideration in the differential diagnosis of LE since the nervous system involvement may be the presenting manifestation of SLE.

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