Mood Disorder Due to Herpes Simplex Encephalitis with Neuroimaging Findings Limited to the Right Hemisphere and Cerebellum: Case Report

Sağ Hemisfer ve Serebellumla Sınırlı Görüntüleme Bulguları Olan Herpes Simpleks Enfesaltından Sonra Gelişen Duygudurum Bozukluğu

ABSTRACT Herpes simplex (HSV) encephalitis may cause psychiatric syndromes including mood disorder episodes. A case of secondary mood disorder after HSV encephalitis is reported in this paper. The aim of this case presentation is to discuss the neuroanatomic regions of the brain associated with secondary mood disorders in the light of the patient’s neuroimaging findings. A 62-year-old patient with HSV encephalitis developed a depressive episode for the first time followed by a manic episode. The patient’s magnetic resonance imaging scan showed cerebral atrophy mainly affecting the right temporal lobe and cerebellar atrophy as well as perfusion defects in the right amygdala, right basal ganglion and right temporal cortex as seen in the single-photon emission computed tomography (SPECT). The findings were consistent with defects located exclusively in the right cerebral hemisphere. To the best of our knowledge, the cerebellar pathology has been demonstrated for the first time in a mood disorder case secondary to HSV. Neuroimaging findings of the secondary mood disorder cases may contribute to a better understanding of the neuroanatomical regions of this, yet not fully understood mood disorder.

Key Words: Encephalitis, herpes simplex; bipolar disorder; aged


Anahtar Kelimeler: Enfesaltı, herpes simpleks; bipolar bozukluk; yaşlı


Central nervous system (CNS) lesions are often accompanied by abnormal mood, behavior, cognition and physiological functioning. CNS infections may lead to lesions which can cause these symptoms. Mood disturbances related to such disturbances have been defined by Diagnostic and Statistical Manual of Mental Disorders (DSM)-IV-TR as Mood Disorder due to a General Medical Condition. DSM emphasizes that
evidence from history, physical examination or laboratory findings must be present indicating that the disturbance is a direct physiological consequence of a general medical condition. Studies showed that bipolar patients due to organic lesions were usually older than patients with primary bipolar disorder and have no prior mood episodes and less family history of bipolar disease. Mania associated with various neurological and systemic diseases or drugs was defined as secondary mania by Krauthammer and Klerman. Neurologic insults such as stroke, epilepsy, neoplasms, head trauma, brain surgery and infections have been related with a manic episode. Secondary mania is frequently diagnosed in geriatric patients with new-onset mania. Relatively late onset of illness, absence of both family psychiatric history and past psychiatric history are characteristics of this syndrome.

Herpes simplex virus (HSV) is one of the most frequent and potentially dangerous causes of sporadic and focal encephalitis. HSV typically invades the inferior frontal and anterior temporal lobes via cell to cell spread along branches of the trigeminal nerve. Fever, headache, hallucinations, behavioural disturbances, personality changes, anosmia and simple or complex partial seizures are among the typical findings. Long-standing sequelae of HSV encephalitis may include personality alterations, affective disturbances, amnestic syndrome and dementia. Patients presenting with hypomanic or manic symptoms secondary to HSV encephalitis have formerly been reported.

In this paper, a case of secondary mood disorder due to HSV encephalitis is reported. The aim of this case presentation is to discuss the neuroanatomic regions of the brain related to secondary mood disorders in the light of the patient’s neuroimaging findings.

## CASE REPORT

A 62-year-old man was admitted to a neurology unit with fever, confusion and light headedness approximately 6½ months before his presentation to the psychiatric emergency unit in our hospital. His fever was 38.4°C. His complete blood count showed a mild increase in white blood cells. There were no lateralizing or localizing signs on neurological examination, as reported. Electroencephalography (EEG) showed slowing in bilateral frontal and temporal regions. Cranial magnetic resonance imaging (MRI) revealed infarctions in right temporal lobe and insular cortex (Figure 1a, b). Cerebrospinal fluid was positive for HSV-DNA. With these find-

![Figure 1: The arrows on T2- sagittal magnetic resonance image of the patient indicate the infarction in right insular cortex (A), and the infarction in right temporal lobe with cerebellar atrophy (B).](image-url)
ings, the patient was diagnosed with HSV encephalitis and treated with acyclovir. His present-
ings complaints disappeared in three weeks time. It was learned that after a three-week well-being pe-
riod, he had developed depressed mood, excessive worrying about his children’s health, anhedonia, unwillingness to leave home, psychomotor retar-
dation, fatigue and difficulty in concentration. These symptoms had lasted for three months and he did not receive any treatment.

The depressed phase was followed by abrupt onset of manic symptoms without any euthymic pe-
riod in between. During the manic phase, which lasted about two months before the psychiatric con-
sultation, the patient exhibited unusual behaviours such as smoking (he did not smoke before), non-
compliance to his diabetic diet, unnecessary shopping leading to loss of large amounts of money and had very poor sleep. He made a number of trips to other cities, during one of which his leg was broken in a car accident while he jumped in a street with a busy traffic. On admission, the mental state exami-
nation revealed elevated mood, psychomotor over-
activity, pressured speech, concentration difficulties, visual hallucinations and impairment in judgement. No delusions were elicited. He had no personal or family history of mood disorders. He was diabetic for 10 years and was rece-
viving oral antidiabetics. His neurological examination and EEG were normal. He scored 27 out of 30 on the Mini Mental State Exam-
ination (MMSE). Cranial MRI revealed cerebral and cerebellar atrophy, cortical and subcortical ischemic glosis in the right temporal lobe. Cranial single-
photon emission computed tomography (SPECT) showed perfusion defects in right temporal cortex, right temporoparietal region, right basal ganglion and right thalamus. His condition was diagnosed with manic episode and he fulfilled the diagnostic criteria according to DSM-IV for mood disorder due to a general medical condition. He was prescribed valproate 1000 mg/day and quetiapine 400 mg/day. His manic symptoms were responsive to this treat-
ment. Serum valproate levels of the patient were 72.3 mg/dL on the 10th day of the treatment and 80.6 mg/dL after one month. Quetiapine was ta-
pered as mood symptoms disappeared gradually in two months. During his seven year-follow up pe-
riod, he never demonstrated any significant depres-
sive or manic episode. The evaluation was performed clinically according to the DSM-IV cri-
teria. Patient’s treatment with valproate was con-
tinued because there were periods of affective dysregulations not reaching the intensity and dura-
tion of a major affective episode. Quetiapine was added to valproate during these minor affective dys-
regulations and the antipsychotic was discontinued once the symptoms disappeared. The informed con-
sent of the patient was obtained for the publication.

DISCUSSION

The patient was diagnosed with mood disorder due to a general medical condition. He had his first manic episode ever in his life after having HSV en-
cephalitis. The patient experienced a depressive episode which preceded the manic episode. The short time interval between the neurologic illness and the mood episodes supports the possibility of the etiological link and precludes the possibility of a coincidental relationship. The onset of the pa-
tient’s mood disorder at the age of 62 compared to the usual early onset of bipolar disorder at the age of 20s or 30s, lack of psychiatric history before the HSV infection, along with the absence of family psychiatric history are all consistent with a mood disorder secondary to organic illness as also ex-
pected in secondary mania. Elderly onset bipolar disorder was ruled out in the patient. Some bipolar disorder cases in advanced age are early onset bipolar patients, which continue into the old age. A significant number of elderly bipolar pa-
tients live their first depression in their 40s and convert to a manic state after having gone through a couple of depressive episodes. The remaining bipolar cases in older age are either early-onset unipolar mania cases or secondary mania patients. History obtained from the patient does not fit any of the above groups. In terms of the treatment em-
ployed, the patient was prescribed valproate as a mood stabilizer. Valproate is replacing lithium car-
bonate as the mood stabilizer of choice for elderly manic patients and in patients with organic mental disor-
ders. Lithium has a narrower therapeutic
window and high toxicity risk for the elderly. Valproate causes less cognitive impairment compared to lithium, which is an important concern in the geriatric population. The patient responded quite well to valproate. Da Rocha et al. similarly reported a successful outcome with valproic acid in a case of mania secondary to stroke.

The patient’s neuroimaging findings supported the earlier view about the laterality in mood disorders. It was believed that lesions in the left frontal lobe resulted in depression whereas right frontotemporal lesions caused mania. Much of the information regarding brain regions associated with geriatric bipolar disorder comes from the literature on secondary mania. Therefore data from literature on secondary mania has been quoted in the discussion of our case. Starkstein et al. described 12 patients with secondary mania having brain lesions of various nature. Of these 12 patients, 11 had right hemisphere involvement while only one had a left sided lesion. In a recently published case by Goyal et al., a right hemisphere lesion was defined as a prerequisite for secondary mania after stroke. Guha et al., in their case presentation, which happens to be the most recent one on this topic, have demonstrated right hemisphere involvement in two mania cases due to HSV encephalitis. Involvement of the right cerebral hemisphere seems to be almost a prerequisite for secondary mania. In addition to the frequently documented relationship between secondary mania and the right hemisphere involvement, this case gives reason to believe that a similar relationship also exists between manic depressive states secondary to organic illnesses and the right hemisphere.

Secondary mania has been associated with orbitofrontal, basotemporal, basal ganglia and thalamic areas. The brain regions which have been implicated in secondary mania after HSV encephalitis are also the same. Starkstein et al. proposed that lesions involving basal ganglia and thalamus produce a bipolar type of mood disorder whereas lesions of the cortex produce manic syndrome that is not followed by a cyclic mood disorder. This conclusion is consistent with the clinical picture and neuroimaging data of our case.

To the best of our knowledge, this is also the first reported case that demonstrates a cerebellar pathology in a secondary mood disorder case due to HSV encephalitis. Studies on the role of cerebellum in bipolar disorder have an upward trend. DelBello et al. reported volume reductions in the cerebellar vermis of bipolar disorder patients with multiple episodes compared to first episode patients and healthy subjects. Cerebellar atrophy was also found in bipolar patients compared to control subjects in previous studies. Cerebellum was considered as a brain region which was mainly involved in motor control. However, recent findings showed that cerebellum had projections to the limbic brain regions and might take part in emotional regulation. Along with cerebellum, the patient showed structural and functional defects in the temporal cortex, temporoparietal region, basal ganglion structures and thalamus. There are several frontal subcortical circuits in the brain that are believed to control an individual’s emotional, social and cognitive functions. Neuroimaging data which are collected by comparison of bipolar disorder patients to healthy controls and investigation of secondary mania cases show that there is a disconnection in some of these networks in bipolar disorder. In a recent review, Cerullo et al. concluded that altered brain activation in cortico-limbic pathways was also identified in functional MRI studies in bipolar disorder patients. According to the model for bipolar disorder, there is a relative deficiency in the modulation of subcortical and medial temporal limbic areas by the prefrontal cortex. All of the defective brain regions demonstrated in the MRI and SPECT of the patient constitute parts of these frontal-subcortical circuits and associated limbic modulating areas. The pathogenesis of the mood disorder in this HSV encephalitis case may be explained by the frontal-subcortical disconnection as postulated for bipolar disorder patients.

This case not only supports searching for an underlying medical illness in late onset mania, but also suggests that HSV encephalitis patients should be followed up for subsequent psychiatric syndromes including manic depressive states.
our findings employing structural and functional neuroimaging techniques which showed defects located exclusively in the right hemisphere of the patient, it can be suggested that manic-depressive states secondary to organic lesions are more likely to be associated with this hemisphere. Neuroimaging data regarding secondary mood disorder cases may contribute to a better understanding of the neuroanatomical regions as well as the neurophysiology of this yet not fully understood mood disorder.

REFERENCES