

# Secondary Mania: An Uncommon Late Sequelae of Herpes Simplex Encephalitis

Prathama Guha<sup>1</sup>, Malay Ghoshal<sup>2</sup>, Rajarshi Das<sup>3</sup>

<sup>1</sup>Assistant Professor, Dept. of Psychiatry, Medical College, Kolkata.

<sup>2</sup>Associate Professor & Head, Dept. of Psychiatry, Medical College, Kolkata.

<sup>3</sup>Post graduate trainee, Dept. of Psychiatry, Medical College, Kolkata.

Corresponding author: Malay Ghoshal, Associate Professor and Head, Dept. of Psychiatry, Medical College, Kolkata. 68 B.N. Road, Uttarpara, Hooghly, West Bengal, India, Email: malayghosal@yahoo.co.in

## Abstract

*Herpes simplex encephalitis is associated with marked psychological disturbances both in the acute phase and as a chronic sequelae. Mania has been reported as an acute phase manifestation of HSE, but not as long term consequence. Here we report two cases of mania developing as a long term complication of HSE, in the absence of any other predisposing factor. The possible mechanisms underlying the development of secondary mania as a long term consequence of this condition are discussed (German J Psychiatry 2005;8:94-97).*

*Keywords: Secondary mania, herpes simplex encephalitis, Klüver-Bucy syndrome*

*Received: 4.6.2005*

*Revised version: 24.7.2005*

*Published: 1.10.2005*

## Introduction

**H**erpes simplex encephalitis (HSE), one of the commonest causes of severe sporadic encephalitis, has often been associated with marked psychological disturbances both in the acute phase and as a major sequelae.

The association of psychiatric symptoms can be traced to the involvement of basal frontal and temporal lobes in the disease. The initial presentation of HSE may consist of marked behavioral abnormalities like restless hyperactivity, hallucinations, anosmia, Klüver-Bucy Syndrome, and acute manic or hypomanic symptoms. (Lishman, 1997; Fisher, 1996; Koehlar & Guth, 1979). Long term psychiatric sequelae would include prolonged anxiety and depression, dementia, amnesic syndromes, personality changes and behavioural disorders in children.

In this article, we report two cases of HSE who presented with Klüver-Bucy syndrome in the first few weeks, and after a period of two to three months, developed typical mania. Both the cases were followed up for two years. To our knowledge, mania as a consequence of HSE is rare (Fisher,

1996; Koehlar & Guth, 1979), and its development as a late sequelae of this condition has not been reported so far.

These case studies are unique in the sense that a long term psychiatric follow up has been carried out in HSE, and development of affective illness as a chronic sequelae has been clearly established, a fact not reported so far in literature.

## Case 1

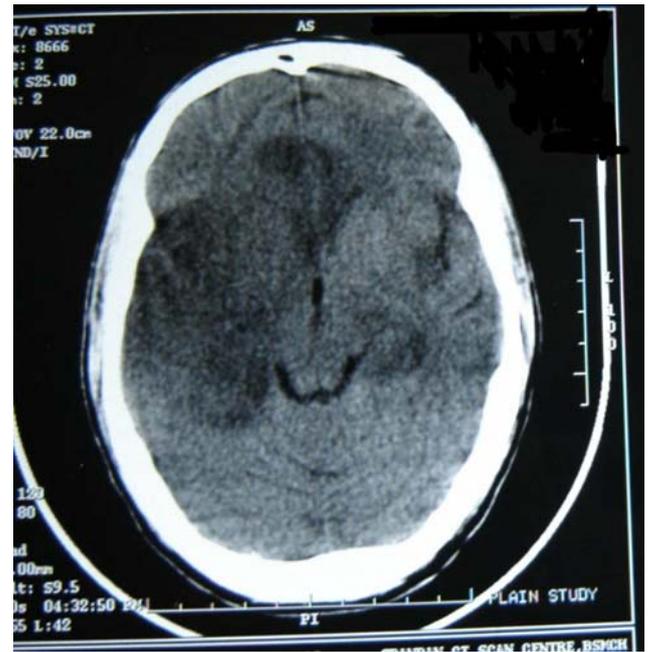
A 12 year old girl without any significant past or family history of neuropsychiatric illness was admitted in our hospital with high fever, headache, seizure and altered sensorium. Her CSF study corroborated with viral encephalitis, viz. cell count= 90/cumm (predominant lymphocytes), RBC positive, protein= 90mg/dl, glucose= 65mg/dl. Estimations of antibody titre and CSF PCR for HSV in the acute phase were not done as patient could not afford these. Brain CT revealed subarachnoid haemorrhage and intraparenchymal bleed in right basal ganglia. MRI brain showed bilateral (right > left) medial temporal hyperintensities with involvement of

adjacent basifrontal region and subacute haemorrhage in right median temporal lobe. Gyriform enhancements were present in post contrast study, findings in favour of HSV 1 encephalitis. EEG showed diffuse slowing with sharp waves in the right temporal region. Based on these reports, a provisional diagnosis of herpes simplex encephalitis was made by the neurology department. She was treated with prednisolone and acyclovir. Features of CNS infection started improving but she developed hyperorality and hypersexuality in the form of stroking genital organs and hypermetamorphosis. There was significant attention deficit and recent memory impairment. We prescribed risperidone in usual dosages. During the next couple of months she developed excessive talkativeness, cheerfulness, grandiosity, increased psychomotor activity, and diminished need for sleep. Her mood varied between elation to irritability. Cognitive deficits persisted. Interestingly, though, hypersexuality and hyperorality gradually faded. The transformation from Klüver–Bucy syndrome to a clear manic presentation was complete in two to three months. She was then prescribed valproate in therapeutic doses which controlled her manic symptoms. Attempts to withdraw medication several months later resulted in partial relapse, hence valproate was reinstated. The patient was followed up for two years with good response to valproate alone.

## Case 2

A 20 year old male having no past psychiatric and medical illness came to our hospital with low grade fever, headache, dizziness and syncope, progressing to seizures and unconsciousness. CSF study showed cell count of 85/cumm (all lymphocytes and traces of RBC), sugar - 90 mg/dl, protein - 95 mg/dl. The CT scan revealed patchy non-enhancing hypodense areas in right fronto-temporo-parietal and left temporal area. Periodic lateralized epileptiform discharges were present in EEG. Though PCR could not be done owing to financial constraints, the condition improved with acyclovir, corticosteroids and carbamazepine (600 mg/day). Within a week he showed hyperorality and hypersexuality in the form of frequent genital stimulation, and sang meaningless, self-composed lyrics. There was perseveration, impaired recent and remote memory and irritable mood. He was prescribed olanzapine (10 mg/d) in addition to carbamazepine. Several weeks on with the aforesaid medication, he showed increased talkativeness, irritability, distractibility, grandiose delusions, increased appetite, diminished need for sleep and hypersexuality. The manic features were severe enough to warrant admission. The transformation from KBS to a manic presentation took about 8 to 10 weeks. At this stage we added valproate (1000 mg/d) and discontinued olanzapine. The patient showed remarkable improvement in the following 4 wks period. The case was followed up for two years with good response to valproate and carbamazepine.

Figure 1. Case 2; T scan (plain study) showing patchy non-enhancing hypodense areas in the right fronto-temporo-parietal region, right frontal area (falx adjacent)



## Discussion

Herpes simplex encephalitis has always intrigued neuropsychiatrists because its clinical features and pathogenesis seem to bridge some of the grey areas of brain behaviour relationship. The diagnosis of HSE is based on clinical features, EEG, brain imaging and PCR studies of CSF (Dominguez et al., 1997; Cinque et al., 1996).

In our cases, diagnosis has been presumed on the basis of clinical picture, CSF, EEG and imaging reports. Estimations of antibody to HSV and CSF-PCR studies were not possible due to financial constraints.

CSF-PCR is considered to be the gold standard in the diagnosis of HSE. Nonetheless, we have also come across cases of PCR negative HSE in recent times (Allreza and Allen, 2001). Tebas et al in their review have compared the diagnostic sensitivity of PCR based approach with empirical therapy using acyclovir. Though the former is associated with better diagnostic efficacy, empirical diagnosis sans PCR has its own clinical value (Tebas et al., 1998). In our cases, both patients showed a speedy neurological recovery within days of commencing acyclovir therapy, suggesting a near definite diagnosis of HSE.

But their psychological-behavioural profile continued to show significant abnormality in the long term follow up. What intrigued us most was the development of the clinical picture of mania, quite indistinguishable from what we see in our typical psychiatric patients. The episodes lasted the usual course of 6 to 8 weeks. No underlying predisposition to an affective illness could be identified in either. Family history was negative. The patients' limited medication played no part

in the production of symptoms. There was no history of any substance use as well.

HSE is associated with haemorrhagic necrosis of the inferior and medial parts of the temporal lobe and medial orbital parts of the frontal lobe. They may extend upwards along the cingulate gyri and to the insula or the lateral parts of the temporal lobe or caudally into the midbrain. It is likely that such extensive lesions will leave their footprints even after the acute phase subsides. That explains the serious long term neurological sequelae of this condition like Korsakoff syndrome, dementia, seizure, and aphasia (Lishman, 1997).

That a full fledged affective illness can develop as a chronic complication of HSE was hitherto unreported. However, a closer look into the pathogenesis of secondary mania may help us understand the relationship between the two. Krauthammer and Klerman, in their article introducing the concept of secondary mania, were of the opinion that mania is a clinical syndrome of multiple causes. They included three cases of secondary mania related to encephalitis and four cases associated with brain tumor (Krauthammer and Klerman, 1978). Cummings and Mendez described two patients aged 63 and 61, who developed acute mania with small right-sided cerebral infarctions. The authors concluded that focal lesions associated with secondary mania usually involved diencephalic structures or adjacent regions of the basal forebrain and the lesions were more often on the right side than the left (Cummings and Mendez, 1984). Starkstein et al., in their first study, found secondary mania correlating with anterior subcortical atrophy and focal lesion of a limbic or limbic-connected region of the right hemisphere (Starkstein et al., 1990). In their second study of secondary mania the causative brain lesions were mainly located in limbic and limbic-related areas (orbitofrontal and basotemporal cortex, head of caudate, and thalamus) that have strong connections with the frontal lobes. Lesions were located primarily in the right hemisphere (Starkstein et al., 1991). Several other studies, some of them quite recent, have also suggested that right sided lesions in the limbic system, temporobasal areas, basal ganglia and thalamus can induce secondary mania (Robinson et al., 1988; Soares and Mann, 1997).

PET studies showed a major role for the right basotemporal lobe in mania (Starkstein et al., 1990). <sup>123</sup>I labelled SPECT studies indicated high uptake in right anterior temporal lobe compared to left in depressive *and* manic states of patients and not during periods of euthymia (Gyulai et al., 1997).

To illustrate that exceptions occur, Jampala and Abrams reported secondary mania with dominant hemisphere damage (Jampala and Abrams, 1983). A study by Drake et al. mentioned two cases of secondary mania after ventral pontine infarction, one having an infarct on the right side, the other on the left (Drake et al., 1990). Our case studies seem to contribute to the school professing lateralization of brain lesion in secondary mania, since the lesions in both cases are predominantly right sided. The areas involved are also as could be expected, viz. the medial temporal and frontal regions with affection of the basal ganglia.

It is possible that subtle alteration in structure or function of brain areas that participate in mood regulation contribute to the development of mood disorders. The relevant areas are

the prefrontal cortex; subcortical structures like the basal ganglia, thalamus and hypothalamus; white matter pathways connecting these to one another and to the cerebral cortex (e.g. limbic-thalamic-cortical circuit, limbic-striatal-pallidal-thalamo-cortical circuit), and possibly the cerebellum (Soares and Mann, 1997).

These two case studies may add modest evidence to the growing body of literature supporting the organic basis for understanding affective illness.

## References

- Cinque P, Cleator GM, Weber T, Monteyene P, Sindic CJ, van Loon AM. The role of laboratory investigation in the diagnosis and management of patients with suspected herpes simplex encephalitis: a consensus report. *J Neurol Neurosurg and Psychiat* 1996; 61: 339-345
- Cummings JL, Mendez MF. Secondary mania with focal cerebrovascular lesions. *Am J Psychiatry* 1984; 141: 1084-1087
- Domingues RB, Tsanaclis AM, Pannuti CS, Mayo MS, Lakeman FD. Evaluation of the range of clinical presentations of herpes simplex encephalitis by using polymerase chain reaction assay of cerebrospinal fluid samples. *Clin Infec Dis* 1997; 25:86-91. ‘
- Drake NE. Secondary Mania after ventral pontine infarction. *J of Neuropsychiatry Clin Neuroscience* 1990; 2:322-325.
- Fathi A, Lendr A. PCR Negative herpes simplex encephalitis: A case presentation. *International Pediatrics* 2001; 16: 1-4
- Fisher CM. Hypomanic symptoms caused by herpes simplex encephalitis. *Neurology*, Dec 1996; 47(6):1374-1378
- Gyulai L, Alavi A, Broich K, et al. I-123 iofetamine single photon computed emission tomography in rapid cycling bipolar disorder: a clinical study. *Biol Psychiatry* 1997; 41: 152-161
- Jampala VC, Abrams R. Mania secondary to left and right hemispheric damage. *Am J Psychiatry* 1983; 140:1197-1199.
- Koehler K, Guth W. The mimicking of mania in "benign" herpes simplex encephalitis. *Biol Psychiatry* 1979; 14(2):405-11.
- Krauthammer C, Klerman GL. Secondary mania. *Arch Gen Psychiatry*. 1978; 35: 1333- 1339
- Lishman WA 1997 *Organic Psychiatry: the psychological consequences of cerebral disorder III* Ed. Blackwell Scientific Publication, Oxford.

## SECONDARY MANIA

- Robinson RG, Bostan JD, Starkstein SE, et al. Comparison of mania and depression after brain injury. *Am J Psychiatry* 1988; 145: 172-175
- Soares JC, Mann JJ. The anatomy of mood disorders- review of structural neuroimaging studies. *Biol Psychiatry* 1997; 41:86-106
- Starkstein SE, Federoff P, Berthier ML, Robinson RG. Manic-depressive and pure manic states after brain lesions. *Biol Psychiatry* 1991; 29:149-158.
- Starkstein SE, Mayberg HS, Berthier ML, Robinson RG. Mania after brain injury: neuroradiological and metabolic findings. *Ann Neurol* 1990; 27:652-659
- Tebas P, Nease RF, Storch GA. Use of the polymerase chain reaction in the diagnosis of herpes simplex encephalitis: a decision making model. *Am J Med* 1998; 105: 287-95