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THE HIDDEN ROLE OF EPSTEIN-BARR VIRUS IN ENCEPHALITIS: CASE STUDIES OF DIAGNOSTIC DILEMMAS

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ABSTRACT

Epstein-Barr virus (EBV), typically associated with infectious mononucleosis and various malignancies, is an uncommon cause of encephalitis. The role of EBV in conjunction with other central nervous system (CNS) infections remains unclear, though its detection may provide critical insights into immune status and patient prognosis. This article presents three cases where EBV coexisted with primary CNS infections, complicating diagnostic and treatment processes.

Case 1: A 38-year-old male with a six-month history of intermittent fever, altered sensorium, and seizures was diagnosed with disseminated tuberculosis and EBV encephalitis. Initial MRI of brain suggested viral encephalitis, and CSF analysis revealed Mycobacterium tuberculosis. CSF PCR confirmed EBV, leading to successful treatment with antiepileptics, antitubercular therapy, and acyclovir.

Case 2: A 32-year-old male presented with fever, headache, vomiting, and altered sensorium. CSF analysis showed Strep-

tococcus pneumoniae and EBV. MRI indicated extensive CNS involvement. The patient responded well to antibiotics, acyclovir, and dexamethasone.

Case 3: A 47-year-old female presented with 10 days of fever, severe headache, and 2 days of altered sensorium. Examination revealed meningitis with positive Kernig's sign. CSF PCR confirmed Mycobacterium tuberculosis and Epstein-Barr virus, and MRI showed leptomeningeal enhancement with infarcts. She responded well to antitubercular therapy, acyclovir and steroids, and was discharged in a fully conscious and oriented state.

These cases highlight EBV's potential to exacerbate CNS infections, evidenced by significant MRI changes and diagnostic challenges. Despite its rarity, EBV encephalitis should be considered in differential diagnoses, particularly in immunocompromised individuals. The primary diagnostic tool remains CSF PCR, while treatment efficacy varies, necessitating further research for standardized guidelines.

Declaration of patient consent – The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/ have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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INTRODUCTION

Epstein-Barr virus (EBV), also known as human herpesvirus 4, is a common cause of infectious mononucleosis and certain types of malignancies including Hodgkin' lymphoma, non-Hodgkin's lymphoma, Burkitt's lymphoma etc. [1] but it is very rarely reported as a causative agent of encephalitis [2]. EBV Encephalitis can either occur because of primary infection or reactivation of the latent virus [3]. Relevance of detection of EBV in CSF along with other central nervous system (CNS) infection is still unclear but as more and more cases are being detected it appears that EBV is not merely a silent spectator in the whole pathogenesis of encephalitis and its detection actually gives an important clue regarding immune status and prognosis of the patient [3,4]. Here we present three cases of encephalitis in which EBV posed a diagnostic dilemma regarding etiology of encephalitis.

Case 1 – This patient, 38year old heterosexual male not a known case of any medical illness, butcher by occupation presented to us in October 2023 with chief complaints of intermittent fever for past 6 months, altered sensorium for past 4 days and 3 episodes of generalized tonic-clonic seizure in past 3 days. There was no history of weight loss, cough, sputum, night sweats, skin rash, joint pain or pus discharge from any site. For last 6 months patient had consulted multiple physicians and had been prescribed multiple antibiotics like ciprofloxacin, azithromycin, cefixime etc. but there was no improvement in the symptoms. On examination patient was stuporous with Glasgow Coma Scale (GCS) of E2V2M5 and febrile to touch with temperature of 102 F. There was no lymphadenopathy, hepatosplenomegaly or skin rash. neck rigidity was present and bilateral plantar reflex were flexor. Rest of the examination was unremarkable.

Patient investigations showed hemoglobin of 10g/dl, total leucocyte count (TLC) of 12000/mm3 with 75% polymorphs, platelet count of 1lac/mm3, erythrocyte sedimentation rate (ESR) of 120mm in 1st hour with normal blood glucose, liver function tests and kidney function tests. Workup for tropical febrile illness including serology for typhoid fever, leptospira, brucella, scrub typhus, Peripheral blood film for malarial parasite, blood cultures, urine culture, chest X-ray were within normal limits. Patient HIV test by ELISA were found to be positive with CD4 count of 330/mm3. In view of suspected meningoencephalitis, CSF analysis and MRI scan of brain were done. CSF analysis revealed TLC of 40 cells with lymphocytic predominance, protein of 300mg/dl, sugar of 23mg/dl (blood sugar – 109mg/dl), ADA – 9IU/dl, cryptococcal antigen was negative and Cartridge-Based Nucleic Acid Amplification Test (CBNAAT) was positive for *Mycobacterium tuberculosis*. MRI brain revealed gyral edema with subcortical FLAIR hyperintense signals along bilateral frontal regions at parafalcine location with involvement of adjacent cingulate gyrus, showing no diffusion restriction or significant post contrast enhancement suggesting of viral encephalitis as shown in fig 1a.

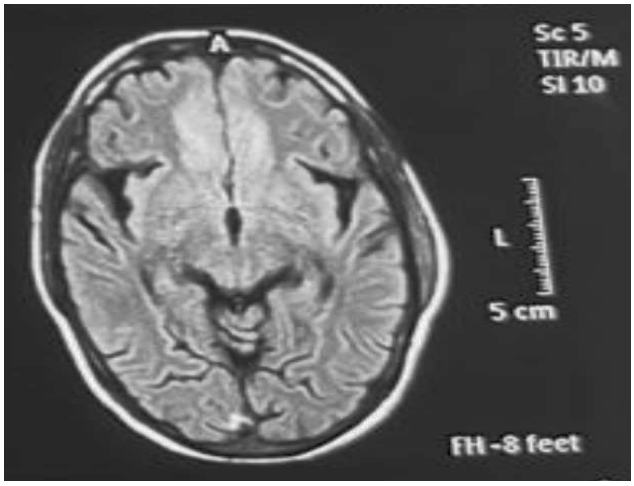


Fig – 1a



Fig – 1b

Electroencephalography (EEG) showed an epileptogenic focus in right frontal lobe. CSF PCR was done in view of possibility of viral etiology which revealed detection of Epstein Barr virus. Patient was started on antiepileptics, dexamethasone, antitubercular therapy consisting of isoniazid, rifampicin, pyrazinamide and streptomycin along with acyclovir considering the possibility of both tubercular and EBV encephalitis. Patient improved dramatically within 5 days and became completely oriented to time, place and person. For finding out primary focus of tuberculosis, Computed tomography (CT) scan of chest and abdomen was done which revealed multiple tiny hyperdense lesions in liver and spleen suggestive of granulomas as shown in fig 1b. It confirmed the diagnosis of HIV/AIDS with disseminated tuberculosis along with tubercular and EBV encephalitis.

Case 2 – 32year old married male without any significant past medical history presented with chief complaint of fever for last 2 days and altered sensorium for last 1 day. Fever was high grade (102degree F), associated with headache and multiple episodes of vomiting. No associated history of chills, rigors, skin rash, joint pain, jaundice, cough, burning micturition or diarrhoea. For last one day patient was in altered sensorium. On examination patient was stuporous with a GCS of E3V1M4. Neck rigidity was present and Kernig's sign was positive with bilateral normal size and reactive pupils. There was no hepatosplenomegaly, lymphadenopathy or skin rash. Rest of the systemic examination was unremarkable.

On investigation patient was having hemoglobin of 14.4g/dl, TLC count of 23000/mm3 with 90% polymorphs and platelet count of 2.2lacs/mm3. LFT, KFT, chest X ray and urine complete examination were within normal limits. CSF analysis revealed TLC of 9000cells/mm3 with 82 percent neutrophils, protein of 300mg/dl and sugar of 15mg/dl (blood sugar – 109mg/dl). CSF culture was sterile and hence CSF PCR was done which revealed presence of *Streptococcus pneumoniae* along with Epstein Barr virus. MRI of the brain revealed multiple ill defined non enhancing patchy and confluent areas of altered signal intensity in bilateral cerebral hemisphere, bilateral basal ganglia and thalamus without any diffusion restriction as shown in fig. 2

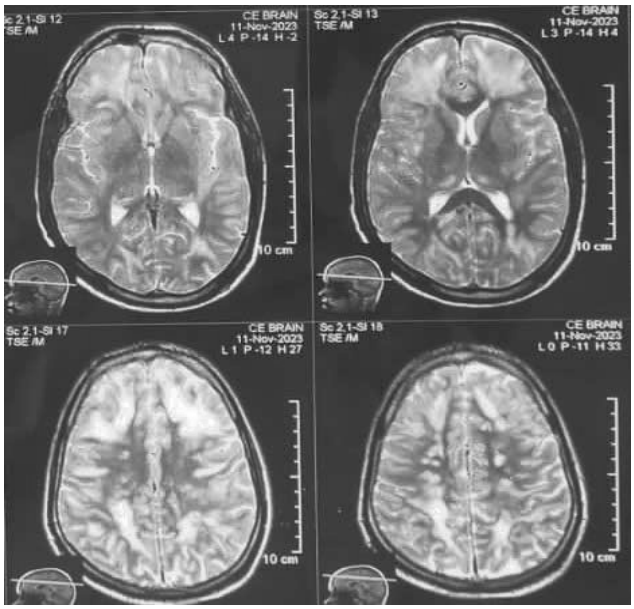


Fig – 2

Patient was started on vancomycin, acyclovir and dexamethasone. Patient responded well to treatment and discharged after 14 days of treatment without any complication.

Case 3 – 47year old female, not a known case of any chronic disease, presented to emergency department with chief complaint of fever for last 10 days and altered sensorium for last 2 days. Fever was high grade (102degree F) and associated with diffuse, severe headache. No associated history of chills, rigors, skin rash, joint pain, jaundice, cough, burning micturition, vomiting or diarrhoea. For last two days patient was in altered sensorium. On examination patient was conscious but not oriented to time, place and person. Neck rigidity was present and Kernig's sign was positive with bilateral normal size and reactive pupils. There was no hepatosplenomegaly, lymphadenopathy or skin rash. Rest of the systemic examination was unremarkable.

On investigation patient was having hemoglobin of 11.1g/dl, TLC count of 9300/mm3 with 92% polymorphs and platelet count of 2.3lacs/mm3. ESR was raised with value of 40mm in 1st hour. LFT, KFT, chest X ray and urine complete examination were within normal limits. CSF analysis revealed TLC of 490cells/mm3 with 70 percent lymphocytes, protein of 300mg/dl and sugar of 11mg/dl (blood sugar – 102mg/dl). CSF culture was sterile and hence CSF PCR was done which revealed presence of *Mycobacterium tuberculosis* along with Epstein Barr virus. MRI of the brain revealed diffuse leptomeningeal enhancement along bilateral cerebral convexity with multifocal patchy areas of acute infarcts in bilateral frontal region in parasagittal location as shown in fig 3. Patient was started on dexamethasone, acyclovir and antitubercular therapy consisting of isoniazid, rifampicin, pyrazinamide and streptomycin. Patient showed dramatic response to treatment and was discharged in fully conscious, oriented state after 5 days.

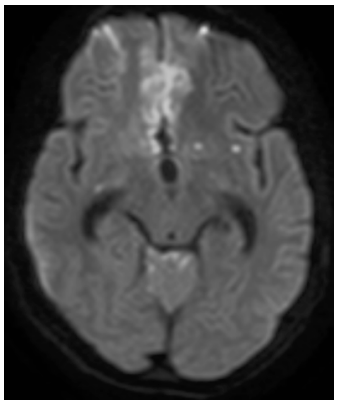


Fig – 3

DISCUSSION

EBV is a double stranded DNA virus belonging to herpesvirus family, also known as human herpesvirus 4. It is highly prevalent worldwide Affecting >90% population [5]. The EBV predominantly targets B lymphocytes by interacting with two key receptors. Firstly, it binds to the CD21 receptor located on the surface of B cells via the major viral envelope glycoprotein, gp350. Secondly, it utilizes a co-receptor mechanism by binding another glycoprotein, gp42, to human leukocyte antigen (HLA) CLASS II molecules [6]. After binding EBV transforms resting B cells into permanent latently infected lympho-plasmacytoid cell lines (LCL). These LCLs expresses limited set of viral gene products compromising of EBV nuclear antigens (EBNAs) and latent membrane proteins (LMPs) along with high levels B-cell activation markers like CD23, CD30, CD39 and CD70 which by altering the cellular signaling pathway enables EBV to persist indefinitely within the memory B-cells of the immunocompetent host [6]. EBV has been associated with a variety of diseases ranging from benign infectious mononucleosis to highly aggressive non-Hodgkin's lymphoma, primary CNS lymphoma, Burkitt's lymphoma and nasopharyngeal carcinoma [2] but rarely recognized as causative agent of encephalitis with less than 5% cases of viral meningoencephalitis attributed to it [7].

EBV has been associated with a variety of CNS disorders including Alzheimer's disease, Parkinson's disease, multiple sclerosis, acute cerebellar ataxia, meningitis, acute disseminated encephalomyelitis and brain tumors [1]. Exact pathogenesis of CNS manifestations of EBV is poorly understood but Research indicates that EBV has the capability to reproduce within the CNS and compromise the integrity of the blood-brain barrier (BBB). Damage to the BBB is linked with neurocognitive deficits, neuronal harm, and inflammation. Latently infected memory B-cells

by EBV undergo the lytic cycle triggered by early viral proteins BZLF1 and BRLF1, resulting in the discharge of viral particles. These particles can infiltrate the CNS through infected lymphocytes and the bloodstream, initiating pathogenic processes [1].

Regarding meningoencephalitis, both primary infection and reactivation in the presence of other CNS infections can contribute to this condition. CNS coinfection with EBV have been found in both immunocompetent and immunocompromised hosts in varying frequencies. Bacterial meningitis induced disruption of BBB leads to entry and reactivation of latently infected lymphocytes into the CSF which leads to their detection in CSF and this process appears to be more frequent in immunocompromised host. Whether EBV remains silent or have a causative role in meningitis is doubtful but as it has been shown that CSF EBV load is associated with increased mortality in bacterial meningitis it appears that EBV itself causes neurological damage by direct infection of brain cells or with immune mediated injury [3].

Regarding diagnosis of EBV encephalitis, EBV Polymerase chain reaction (PCR)test on CSF sample appear to be most important test for etiological diagnosis [2]. Currently there is no set threshold of viral loads in CSF to determine association with the disease. Moreover, viral loads showed a wide variation in different patients. EBV serology in blood including anti-VCA IgM antibody can be used to complement EBV PCR tests on CSF samples [2].

Regarding imaging, magnetic resonance imaging (MRI) abnormalities has been detected in around 27- 80% of cases [5]. Cortical/subcortical, white matter and basal ganglia involvement appear to be more common followed by thalamus, brain stem, substantia nigra, cerebellum and spinal cord [7]. Our all patients have MRI changes that are difficult to explain only on the basis of primary infection and it appears that EBV has played a causative role up to some extent in the pathogenesis.

Treatment of EBV encephalitis is still a matter of debate. Acyclovir, ganciclovir, corticosteroids and plasmapheresis, all have been tried with varying results. We used acyclovir in all of our patients and all of them responded well to the treatment. But at present it is very difficult to compare different therapeutic options due to lack of standardized guidelines.

CONCLUSION

EBV appear to be a much more cause of encephalitis than once thought. In the absence of standardized guidelines, diagnosing it requires high degree of suspicion along with CSF PCR test and MRI as it can complicate the course of bacterial meningitis if not managed properly.

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TITLE: SURGICAL OUTCOMES IN CEREBELLOPONTINE ANGLE TUMORS: A RETROSPECTIVE ANALYSIS OF 30 CASES

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ABSTRACT:

Introduction: Cerebellopontine angle (CPA) tumors present unique challenges due to their complex anatomy and proximity to critical neurovascular structures. This study aimed to analyze the clinical, demographic, and radiological characteristics of CPA tumors, identify pathological types, assess surgical resectability, and evaluate postoperative outcomes.

Methods: We conducted a retrospective analysis of 30 patients who underwent surgical intervention via the retrosigmoid suboccipital approach for CPA tumors at Sadar Vallabh Patel Medical College, Ahmedabad, between May 2021 and May 2024.

Results: Vestibular schwannomas constituted the majority (73.3%) of tumors, with most cases presenting in the third to sixth decades of life. Common symptoms included sensorineural hearing loss (83.3%), tinnitus (70%), vertigo (56.6%), headache (30%), and gait disturbance (33.3%). Total tumor resection was achieved in 76.6% of cases, with facial nerve preservation in 86.7% [5]. Postoperative complications included CSF leak