Viral encephalitis: A mere evil doppelganger or a mini-me of glioblastoma

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INTRODUCTION

The clinical features of viral encephalitis include headache, confusion, seizures, cognitive issues and fever. The most common cause of viral encephalitis is herpes simplex virus type (HSV) I, and the gold standard laboratory test for the diagnosis of HSV encephalitis is viral culture of cerebrospinal fluid (CSF) done by polymerase chain reaction (PCR). The most common site of infection is the mesial temporal lobes and the insular cortices. The virus lodges in these areas and causes focal encephalitis, test for the diagnosis of HSV encephalitis is viral culture of cerebrospinal fluid (CSF) done by polymerase chain reaction (PCR). The most common site of infection is the mesial temporal lobes and the insular cortices. The virus lodges in these areas and causes focal encephalitis,
which carries a relatively poor prognosis. Although the confirmatory laboratory test for the diagnosis of viral encephalitis is the detection of HSV in the CSF, it is very well known that the virus is not always detected in CSF. This is the reason why viral encephalitis is often treated empirically based on imaging and clinical features alone, and the most commonly used antiviral drug in such cases is acyclovir. Although magnetic resonance imaging (MRI) can distinguish glioma from encephalitis, there are times when such differentiation is not very clear. This is especially true when gliomas develop in those regions which have a predilection for encephalitis, like the mesial temporal lobes.

MATERIAL AND METHODS

We retrospectively studied the quality analysis records of our image databank to search for cases with an initial suspicion of viral encephalitis based on imaging, clinical features and laboratory parameters. Cases with initial suspicion of viral encephalitis on MRI at the time of presentation with supporting clinical and laboratory features in whom follow-up MRI was done at our institute were included. Patients lost to follow-up; patients in whom final histopathology was not available were excluded from the study. The study was approved by Institutional Ethics Committee (IEC/2021/ SPO/005 Dt 26-11-2021).

These cases were closely followed-up and later were finally diagnosed with glioblastoma on final histopathology. The initial imaging at the time of presentation was reviewed by three radiologists. The follow-up imaging data were also reviewed by the same set of radiologists, and the results were recorded. Age- and sex-matched controls were taken for these three patients. These controls were diagnosed cases of viral encephalitis based on imaging, laboratory and clinical findings.

RESULTS

Our retrospective analysis of the imaging database from 2010 to 2020 revealed seven patients who were initially treated with a working diagnosis of encephalitis but later turned out to be glioblastomas. Out of these four patients were lost to follow-up and their imaging was not available in our database. Hence, only three patients were included in our study. All these three patients presented with acute symptoms such as confusion, fever and seizures and had a short duration of illness. The CSF was negative for HSV in all cases at the time of initial presentation. They had similar high signal intensity abnormality in the medial temporal lobes and the adjacent regions of the brain, which showed subtle or no enhancement on post-contrast sequences. The diagnosis of HSV encephalitis was made based on clinical and radiological findings, and these patients received intravenous (IV) acyclovir. All three patients showed initial clinical improvement after acyclovir administration.

No patient received corticosteroids at presentation and the improvement in patients 1 and 2 presumably occurred as a consequence of achieving seizure control. It was only when the PCR tested negative that the initial diagnosis was reconsidered. Patient 1 showed deterioration in symptoms 4 Wk after discharge from the hospital, whereas patient 2 deteriorated after 3 weeks. Patient 3 was clinically stable till 6-month post-discharge.

In cases 1 and 2, a high-grade temporal lobe glioma was diagnosed by guided stereotactic biopsy within 4–6 weeks of the original presentation. The third patient, however, remained undiagnosed for over 6 months when the final biopsy was carried out. Follow-up MRI showed that the lesion had increased in size. Presumably, the tumour had undergone transformation from low grade to high grade in a short span of time.

While in cases 1 and 2, the MRI showed the abnormality in the left medial temporal lobe, whereas case 3 had abnormal high signal intensity in the right temporal lobe. The patients had an average age of 60 years. All of these patients were males. All these patients had a very short history of their present illness (less than a week).

Age- and sex-matched control patients who were laboratory-confirmed cases of viral encephalitis showed similar imaging findings with the involvement of the medial temporal lobes and the adjacent regions of the brain. All the controls showed an expected clinical course, improved on antiviral therapy and were finally discharged from the hospital.

Cases

Case 1

A 56-year-old male presented with seizures, confusion and fever for 1 day. MRI done at the time of admission showed high signal intensity abnormality in the left temporal lobe on T2-weighted and fluid-attenuated inversion recovery (FLAIR) images with subtle abnormal enhancement on post-contrast images (Figure 1). CSF examination was normal. He was started on antiviral therapy with IV acyclovir with a presumptive diagnosis of herpes simplex encephalitis (HSE). CSF report of PCR for HSV deoxyribonucleic acid (DNA) that became available later had tested negative. The patient showed initial clinical improvement and was discharged after a few days. However, 4 weeks after discharge, his generalised condition deteriorated with increased seizures and drowsiness,
and his follow-up MRI showed an increase in the size of the temporal lesion and development of a peripherally enhancing lesion at the site of initial abnormality (Figure 2). The patient was managed with corticosteroids and supportive treatment and was discharged in a stable condition with the advice to undergo biopsy for the confirmation of diagnosis. While still at home, the patient’s neurological condition further deteriorated, and he underwent another follow-up MRI after 1 month, which showed a further increase in the size of the enhancing left temporal lobe lesion with an increase in mass effect and left-sided uncal herniation (Figure 3). The patient underwent a decompressive craniotomy and debulking

![Figure 1: Sequential axial FLAIR (a-c), T2-weighted (d-f) and post-contrast (g and h) MRI done at the time of initial presentation showing an ill-defined area of high signal intensity involving the left temporal lobe. Subtle ill-defined enhancement is noted on post-contrast images (g and h). FLAIR = Fluid-attenuated inversion recovery; MRI = Magnetic resonance imaging.](image-url)

![Figure 2: Sequential axial FLAIR (a-c), T2-weighted (d-f) and post-contrast (g and h) MRI done after 4 week showing an increase in the area of involvement of the abnormal high signal intensity in the left medial temporal lobe with new-onset ring-enhancing lesion at the site of the original abnormality in the previous MRI. FLAIR = Fluid-attenuated inversion recovery; MRI = Magnetic resonance imaging.](image-url)
surgery. The final histology of the lesion was glioblastoma multiforme.

**Case 2**

A 64-year-old male presented with high-grade fever, acutely onset confusion and seizures for 2 days. MRI revealed patchy areas of high signal intensity in the left temporal and parietal lobes with no enhancement on post-contrast images (Figure 4). There was no mass effect on the surrounding structure. The adjacent sulci spaces and the Sylvian fissure were not effaced. CSF examination was normal. He was also treated with antiviral therapy with iv acyclovir and showed some clinical improvement. However, soon after, he had tonic-clonic seizures and a decrease in the level of consciousness. A repeat MRI done at 3 weeks from the initial presentation showed an increase in the size of the high signal abnormality in the left temporal and parietal lobes (Figure 5). These lesions showed patchy areas of enhancement on post-contrast images. There was no mass effect on the ventricle and the sulcal spaces. A stereotactic-guided brain biopsy was done, and the final histopathological diagnosis was glioblastoma multiforme.

**Case 3**

A 70-year-old male presented with 2 days history of drowsiness and confusion. MRI at the time of admission revealed a focal area of high signal intensity on T2-weighted and FLAIR images in the right temporal lobe (Figure 6). Mild mass effect was noted along with mild contrast enhancement. No definite rim-like enhancement could be seen. CSF examination was reported normal; PCR for HSV
had tested negative. He was also treated with iv acyclovir and showed clinical improvement. He was fine till 6-month post-discharge from the hospital when he had a recurrence of seizures and memory impairment. Follow-up MRI showed a well-defined enhancing lesion at the site of the initial abnormality (Figure 7). This was followed by open biopsy and decompression, which on histopathological evaluation revealed a high-grade glioma.

DISCUSSION

In our search of the literature, we came across a few case reports and case series where patients with symptoms similar to HSE were diagnosed with having glioblastomas. Majority of these patients were given antiviral therapy and few of them did show clinical improvement as well. However, the imaging did not show any improvement in all these cases, which makes MRI a robust follow-up modality to monitor such cases where clinical features could be misleading. Furthermore, the fact that the final glioblastoma developed at the same site where the initial encephalitic-like abnormality was found in the MRI suggests a relationship between these two diseases.

The more one considers the dilemma of differentiating viral encephalitis from glioblastomas, the more striking and puzzling the unanimous agreement about the close association between these disease entities. Although the exact mechanism is not known, various possible mechanisms are described in the literature, which supports the similar clinical, pathological and radiological presentation of these two different disease entities. On one end of the spectrum is the theory describing the oncomodulatory action of various chronic viral infections such as cytomegalovirus (CMV) infection. While...
on the other end is the oncogenic theory describing a ‘hit-and-run’ transformation by human CMV immediate-early 1 (IE-1) and immediate-early 2 (IE-2) proteins proteins. The possibility of coexisting of viral encephalitis and glioblastoma appears remote as both of these conditions are rare and their co-existence would be even rarer, although there are published case reports describing such coexistence.

The role of human CMV found in glioblastomas in promoting an invasive and vascular phenotype of this tumour has been described. The authors has postulated that human CMV latently infects glioblastomas and causes the release of various growth factors and enzymes, including vascular endothelial growth factor and cyclooxygenase 2. These growth factors and enzymes combined with release of reactive oxygen acts as a catalyst to promote neoangiogenesis and increased vascular permeability. These changes lead to tumour genesis and may also have a role in upscaling the pathological grade of the tumour. This theory is consistent with the fact that many of such patients have a good initial clinical response to antiviral therapy with acyclovir. Even with a false-negative PCR testing, which can happen early in the illness acyclovir should be continued empirically in suspected cases of viral encephalitis and repeat CSF HSV PCR testing should be done within 3–7 days. This algorithmic approach is still followed where treatment with acyclovir is continued irrespective of the findings of CSF HSV PCR test reports. These authors have suggested that alternative differential diagnosis should be considered after two consecutive negative CSF HSV PCR tests. The inhibitory effect of interferon-gamma and acyclovir on glioblastoma cell cycle has been reported. Another study further showed inhibition of indoleamine 2,3-dioxygenase (IDO) and an inhibitory effect on regulatory T-cells (Tregs).

Various antiviral drugs such as valganciclovir and cidofovir have also shown promising results in the treatment of glioblastomas. Gidofovir is known to introduce double-stranded cellular DNA breaks, which lead to oncolysis of glioblastomas. These antiviral agents have shown to suppress T-cell function and therefore amplify the immune reaction towards the tumour tissues. The coexistence theory, although sounding remote, finds definite merit with case reports describing such a coexistence of viral encephalitis and glioblastomas. The detection of HSV after excision of tumour specimen on histopathological examination has been reported. The presence of human cytomegalovirus (HCMV) sequences in glioblastomas has also been reported.

The present study adds more weight to the theory regarding the role of a viral aetiology in the pathogenesis of glioblastoma. The exact mechanism of such a role would need further studies for confirmation. Although it is not clear whether glioblastoma developed as a sequel to HSV encephalitis or viral encephalitis was a superadded infection in cases of pre-existing glioblastoma. At one point, at least, almost all the commentators of the viral aetiopathogenesis theory agree that short-term follow-up MRI could have been useful.

More prospective studies are required to be done to strengthen the association between these two conditions. We could find only three cases in a 10-year period, so we suggest pooling of data from multiple centres to reach an adequate sample size. Studies should also be performed on post-operative or post-mortem glioma specimens for extraction of viral components and vice-versa.

A malignant brain tumour can present acutely with clinical features such as fever, confusion, memory disturbances and encephalopathy along with abnormalities on MRI of the head. This can confuse the treating physician, and the diagnosis of a malignant glioma may be missed in the list of differential diagnosis. Such an omission would prove disastrous as it would entail institution of incorrect treatment and the consequent medicolegal issues. Hence, use short-term follow-up MRI of the head and further pursuit of ascertaining tissue diagnosis in cases where there is a progression on follow-up MRI can be helpful. Furthermore, with the recent advances in CSF analysis, especially the PCR analysis, invasive brain biopsy is seldom being done for confirming the diagnosis of viral encephalitis. Still, we suggest that stereotactic-guided biopsy should be considered in all patients with temporal lobe mass lesions if the patient’s clinical condition is deteriorating and when no definitive diagnosis is made even after the result of PCR testing. One of the reasons for doing so is the very little risk of this procedure and the other one is that potentially treatable infectious conditions such as fungal or bacterial abscesses and tuberculosis would otherwise be missed.

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REFERENCES
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