Nosocomial Herpes Encephalitis: Rare but Treatable with Early MR Diagnosis

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SUMMARY – *Nosocomial/hospital acquired herpes encephalitis is rare and is usually undiagnosed in its early phase because of the non-specific clinical picture and low level of clinical and neuroimaging suspicion. There is a paucity of data in radiology literature for this entity, specifically in the settings of surgery and trauma. We describe two cases of nosocomial herpes simplex encephalitis to demonstrate the imaging clues that might lead to an early diagnosis of this disease.*

Introduction

Herpes encephalitis (HSE), the most common cause of sporadic encephalitis worldwide, is potentially treatable when diagnosed and treated early, and is fatal or results in serious neurological sequelae if left untreated. Though rare, early diagnosis of nosocomial/hospital acquired herpes encephalitis (NHSE) both clinically and radiologically could improve patient prognosis. However due to paucity of clinical and imaging literature describing NHSE to date, its early diagnosis has been elusive. Our report of two cases is an attempt to create awareness of NHSE by describing early imaging clues for this disease.

Case Reports

Patient 1. A seven-year-old boy with a history of primitive neuroectodermal tumor in the left parietal lobe, status post resection, radiation and chemotherapy, presented with expressive aphasia, altered mental status and generalized tonic-clonic seizures. He was started on anti-seizure medication and subsequently intubated due to respiratory compromise. Initial brain MRI (Figure 1A,B) showed a new mass with homogeneously enhancing solid and peripherally enhancing cystic components along the posterior aspect of the surgical cavity.

Findings were suggestive of recurrent tumor and the patient underwent resection one week later following stabilization of his seizures. Onset of protracted focal seizures despite treatment marked postoperative day 1, followed by reintubation, midazolam drip and better control of seizures on postoperative day 2. Brain MRI on postoperative day 2 in hospital (Figure 1C-E) showed a high T2/FLAIR signal with mild restricted diffusion in both frontal temporal cortical and insular regions, more on the left side, in the posterior limb of the left internal capsule, effacement of the sulci with gyri-form enhancement in the left frontotemporal region. A differential diagnosis of seizure/post seizure-related signal changes versus hypoxic ischemic/hypotensive injury was made. Clinical and radiological suspicion for NHSE was low at this time. Continuous fever and change in secretions from endotracheal tube on postoperative day 4 prompted initiation of antibiotics, with later cultures positive for *Klebsiella* from urine and endotracheal tube secretions. Brain MRI on postoperative day 8 (Figure 2A-D) showed a more extensive, symmetric abnormal T2/FLAIR signal and restricted diffusion involving both frontotemporal cortices including the medial temporal lobes and hippocampi and cingulate gyri. A subtle high T1 signal in gyri-form pattern was seen in both frontal lobes. Effacement of sulci with more gyri-form enhancement was seen in the left frontotem-

Figure 1 A-E) Case 1. A 7-year-old boy with a history of primitive neuroectodermal tumor. A,B) Preoperative axial post contrast T1W and DWI images show a mass with homogeneously enhancing solid and peripherally enhancing cystic components along the posterior aspect of the surgical cavity with diffusion restriction (thick arrows). C,D) Postoperative axial FLAIR and DWI images show a high signal in both cortical and insular regions, more on the left side (thick arrows). E) Postoperative coronal T1W post contrast image shows a gyriform pattern of enhancement in the left frontotemporal region (thick arrow).

poral region. Radiological features strongly pointed to an infectious etiology, likely herpes encephalitis considering involvement of both medial temporal lobes and hippocampi. Lumbar puncture the next day on postoperative day 9 was positive for HSV DNA in CSF by PCR and in Dnase test agar, negative in blood. Immunohistochemistry on brain tissue obtained at surgery was negative for HSV. The patient was started on IV Acyclovir. Lumbar puncture performed on the 38th day of hospitalization was negative for HSV DNA in CSF by PCR. Seizures were gradually controlled. However, the patient continued to deteriorate clinically with autonomic dysfunction including increase in blood pressure and heart rate and continuous fever. Brain MRI on the 39th day in hospital (Figure 2E-H) showed an extensive abnormal high T2/FLAIR signal involving both cere-

bral hemispheres, basal ganglia, thalami, mid-brain, with gyriform high T1 signal suggesting laminar necrosis. Sulcal and extra-axial space widening suggestive of diffuse parenchymal atrophy was seen. The radiological picture was compatible with extensive herpes encephalitis in the evolving phase.

Patient 2. A 40-year-old woman presented with altered mental status and generalized tonic-clonic seizures 2.5 months after partial resection of a left cavernous sinus meningioma (Figure 3A,B). Initial brain CT (Figure 4A,B) showed moderate communicating hydrocephalus and the patient underwent shunting. This was followed by fever and respiratory failure with collapse of the right lung due to mucus plug likely from aspiration related to seizures. Bronchoalveolar lavage (BAL) culture revealed

Figure 2 A-H) Case 1. A,B) Axial FLAIR images show a more extensive, symmetric abnormal high signal involving both frontotemporal cortices including the medial temporal lobes and hippocampi (thin arrow). C) Diffusion restriction is seen in both frontotemporal regions (thin arrow). D) Axial post contrast T1W image shows effacement of sulci with more gyriform enhancement in left frontotemporal region (thin arrow). Follow-up MRI. E,F) Axial FLAIR images show an extensive abnormal high FLAIR signal involving the cerebral hemispheres, basal ganglia and thalami. G) The DWI image shows diffusion restriction in both frontal and parietal lobes and basal ganglia with a resolution of restriction in the temporal lobes. H) Axial T1W post contrast images show a gyriform pattern of contrast enhancement in both cerebral hemispheres (thin arrow). The prominence of cortical sulci is suggestive of diffuse parenchymal atrophy

heavy growth of *Staphylococcus aureus* and *Candida albicans* and treatment for the same was initiated. On the seventh day following hospitalization, viral cultures from BAL grew herpes simplex virus (HSV). IV Acyclovir was started and CSF was sent for further confirmatory studies. CSF grew gram negative bacteria but was negative for herpes simplex virus. The patient's prognosis remained poor with a Glasgow coma score of 3. Brain CT on the 11th day following hospitalization and shunting (Figure 4C,D) showed diffuse, patchy hypodensities involving the bilateral frontal, parietal, temporal and occipital lobes, and basal ganglia. Diffuse sulcal effacement and increasing edema were seen. The possibility of these findings being due to infectious encephalitis in this patient with known disseminated herpes infection as

well as *Staphylococcus* and *Candida* infection was suggested. Brain MRI performed on the same day (Figure 5A-D) showed diffuse high T2/FLAIR signal intensities with restricted diffusion involving the cortices of both cerebral hemispheres including the hippocampi, cingulate gyri and thalami. A high T1 gyriform signal was seen in the bilateral frontotemporal lobes. Diffuse avid leptomeningeal enhancement was seen.

The constellation of MR findings strongly favored diffuse encephalitis due to HSV infection. Brain MRI performed on the 26th day post hospitalization (Figure 5E,H) showed more extensive signal and enhancement changes compared to the MRI performed 15 days earlier with a decrease in the high diffusion-weighted signal compared to earlier scans.

Discussion

Viral encephalitis complicating early postoperative or post traumatic course is rare. Most common but non-specific clinical features include high-grade fever, impairment of consciousness, and seizures. Viral encephalitis may result from: 1) primary HSV infection; 2) reactivation of latent infection in the sensory ganglia or brain parenchyma; 3) invasion of central nervous system through olfactory pathway; 4) spread from hospital personnel to patient or cross infection among patients^{1-5,7}. The mechanism of reactivation is unclear, but stress, trauma, immunosuppression and radiation are possible causes^{1,2,5}.

A latent period of four to ten days is common for onset of HSE following surgery and should be considered in the differential for cause of fever of unknown origin specifically after neurosurgical procedures². Lack of response to medical treatment for bacterial infections should raise the suspicion for alternative diagnoses including herpes encephalitis. Early MRI and HSV PCR help to establish diagnosis in a timely fashion. HSE primarily affects neurons reflected by its cortical distribution with only secondary involvement of white matter. Noguchi et al.⁸ divided the MR findings into early period (within two days of onset of neurologic symptoms), middle period (three to 30 days after onset of symptoms) and late period (more than 30 days after onset of symptoms). Low T1 signal abnormality with parenchymal swelling is usually seen in the early period with high T1 signal in the affected cortex in the middle and late periods. Abnormal gyral enhancement may be seen in the early period, more often in middle period. MRI including diffusion-weighted images (DW-MRI) can demonstrate signs of HSVE as early as 40 h after the onset of symptoms. DW-MRI shows diffusion abnormality in the cerebral cortex and may be more sensitive than T2-weighted sequences⁹. Whereas the diffusion abnormality seems to subside after 14 days, T2 signal changes and contrast persist for more than two weeks⁹. We speculate that a high T2/FLAIR signal seen in the temporal and extratemporal lobes usually persists due to neuronal loss and necrosis and is associated with progressive atrophy as in our cases. Involvement can be unilateral initially but subsequent involvement of the contralateral side is highly suggestive of the disease. CSF PCR for HSV DNA which is 96-98% sensitive and 95-99% specific in adults can be used for confirmation⁵.

Figure 3 A-B) Case 2. A) Preoperative axial post contrast T1W image shows an enhancing left cavernous sinus meningioma (thin arrow) with mass effect on the left anterolateral pons. B) Postoperative axial post contrast T1W image shows partial resection of meningioma (thin arrow).

Figure 4 A-D) Case 2. A,B) Non contrast CT scan shows moderate communicating hydrocephalus. C,D) Non contrast CT scan post shunting shows diffuse, patchy hypodensities involving both frontal, parietal, temporal and occipital lobes (arrows). Diffuse sulcal effacement is seen.

Figure 5 A-H) Case 2. A) Axial FLAIR image shows diffuse high signal intensity involving cortices of both cerebral hemispheres. B) Axial pre-contrast T1W image shows a high T1 gyriform signal in the bilateral insular cortex and temporal lobes (thin arrow). C) Axial post-contrast T1W image shows diffuse avid leptomeningeal enhancement (thin arrow). D) DWI images show diffusion restriction in areas of FLAIR signal abnormality. Follow-up MRI. E) Axial FLAIR image with persistent high signal in both cerebral hemispheres with Axial post-contrast T1W (F) and sagittal post-contrast T1W (G) images showing more extensive gyriform enhancement (arrow). H) Axial DWI images show a decrease in the high DWI signal compared to earlier studies.

MRI provides the most sensitive method of detecting early lesions and is the imaging of choice in HSE¹. In our two patients, lack of clinical suspicion and presence of systemic bacterial infections led to other alternate differential diagnosis on initial imaging. Follow-up imaging showing characteristic imaging findings of HSV bilaterally with high T2/flair signal and restricted diffusion in frontotemporal cortices including medial temporal lobes and hippocampi helped towards the diagnosis. Hence it is important to recognize this disease entity in such situations and imaging findings help to clarify the diagnosis.

Conclusion

While rare, HSE can develop in the hospital and should be considered when new and rapidly evolving parenchymal abnormalities (especially temporal lobe) incongruous with the patient's admitting diagnosis are seen on imaging, especially in the settings of neurosurgical interventions and trauma. Early neuroradiological suspicion for NHSE can be achieved using MR, alerting the clinician to this diagnosis, which can be further confirmed by CSF analysis, resulting in the institution of appropriate medical therapy and improved patient outcome.

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