**Case vignettes**

**Patient 1**

A previous healthy 13 year old male without past medical history of interest, was admitted for fever, headache and emesis. Over the next 2 days he developed aphasia, refractory seizures, and decreased level of consciousness. A brain MRI revealed extensive left frontotemporal and mild right frontobasal T2 and fluid-attenuated inversion recovery (FLAIR) abnormalities, with mass effect and restricted apparent diffusion coefficient (ADC) (Figure 3, panel A). Intravenous (IV) acyclovir was initiated for suspected herpes simplex encephalitis (HSE) although the lumbar puncture was not performed due to increased intracranial pressure. Cerebrospinal fluid (CSF) obtained three days later during placement of an external ventricular shunt confirmed the viral infection (PCR positive for Herpes simplex virus 1, [HSV1]). During the patient’s stage at the ICU, he developed severe hypotension, becoming pulseless and requiring cardiopulmonary resuscitation. Acyclovir was discontinued after 21 days at which time the CSF showed 27 white blood cells (WBC)/l, protein concentration 51 mg/dL and the PCR was negative for HSV1. Studies for N-methyl-D-aspartate receptor (NMDAR) and other antibodies to cell surface antigens were negative. During the next 2 weeks he had progressive slow improvement but on day 42 post-HSE he developed a drastic change in behavior including prominent sexual disinhibition, cursing and insulting people, and aggressive behavior, biting the pillow and objects. These behavioral changes were felt to be sequelae of the HSE and he was started on risperidone. He also developed refractory hypertension, requiring four antihypertensive drugs (labetalol, amlodipine, enalapril and hydralazine). The patient was discharged home two months after onset of HSE but he was re-admitted 4 months later (6 months after HSE onset), due to persistent and severe behavioral problems. An MRI without contrast showed encephalomalacia in the previous areas of viral involvement without new necrotic regions but with expansion of the surrounding white matter changes (Figure 3, panels A and B). The CSF showed mild pleocytosis (7 WBC/L) with normal protein concentration, negative PCR to HSV1, and high titers of NMDAR antibodies (CSF titer 1:160; serum titer 1:800). He was treated with 5 daily doses of high dose IV methylprednisolone with rapid recovery of the behavioral abnormalities. Fifteen months after onset of HSE he has stable motor and cognitive deficits considered residual from the viral infection.

**Patient 2**

A previously healthy 15 year-old male presented with headache, focal seizures, and encephalopathy. MRI showed bilateral right greater than left frontotemporal T2-FLAIR hyperintensities with ADC restriction. The CSF had 2 WBC/L, mildly elevated proteins (50 mg/dL) and the PCR was positive for HSV1; NMDAR antibodies were not tested. He completed a 21 day course of IV acyclovir and had a complete recovery. Fifty-two days after HSE onset he developed agitation, memory and cognitive deficits, and inappropriate behavior including aggressiveness. A relapse of the HSE was suspected but the CSF showed 0 WBC/L, normal protein concentration and the PCR was negative for HSV1. The MRI showed encephalomalacia of the previous right frontotemporal viral involvement, no new necrotic lesions, but mild worsening of T2/FLAIR white matter changes bilaterally affecting the frontal lobes (Figure 3, panel C and D), with mild contrast enhancement when compared to the prior MRI taken during the HSE. Re-evaluation of the CSF showed high titers of NMDAR antibodies (1:80) that were not detected in serum. He was treated with one course of intravenous immunoglobulins (IVIg) and IV methylprednisolone followed by oral methylprednisolone that was tapered and discontinued over 2 weeks. A repeat CSF study showed decrease in NMDAR antibody titers (1:20). The patient had good clinical response and at last follow up, 12 months after HSE onset, he is at baseline with no neuropsychiatric symptoms or behavioral problems.

**Patient 3**

A previously healthy 45 year old man developed sudden onset headache, fever, confusion, and speech problems. A brain CT showed a left temporal hypointense lesion with mass effect suspected to be a glioma but the MRI demonstrated left temporal T2/FLAIR hyperintensities with ADC restriction and mild contrast enhancement suggestive of HSE encephalitis (Figure 3, panel E). The CSF showed 110 WBC/L, increased protein concentration (74 mg/dL), and PCR positive for HSV1; NMDAR and other antibodies to cell surface antigens were negative. He was started on IV acyclovir and repeat CSF two weeks later showed 56 WBC/L, protein of 78 mg/dL and the PCR was no longer positive for HSV1 (NMDAR antibodies not tested in this CSF sample). After completing 21 days of acyclovir the MRI showed stability of the previously noted brain lesions and the patient was discharged with residual global aphasia. Ten days after discharge (44 days after HSE onset) he was admitted to a local community hospital for acute onset headache, confusion, agitation, severe insomnia, and delusional thoughts. MRI showed slight progression of the T2/FLAIR hyperintensities in the left temporal lobe with intense contrast enhancement and new involvement of the right temporal lobe (Figure 3, panels F and G) that was not present in the MRI performed 2 weeks earlier. Acyclovir was restarted for presumed HSE relapse but it was discontinued 5 days later when the CSF PCR came back negative for HSV; this revealed 5 WBC/L, and protein concentration of 93 mg/dL (NMDAR antibodies were not tested). He improved with no further treatment and was discharged with his baseline aphasia. Three months after this episode (and as part of a prospective study of patients with HSE) he was re-evaluated in our center. The MRI showed marked improvement of the previous contrast-enhancing temporal lobe abnormalities (Figure 3, panel H), and the CSF showed 10 WBC/L with normal protein concentration, unmatched oligoclonal bands, negative PCR for HSV-1, and positive NMDAR antibodies (1:40; serum negative), suggesting that the episode he developed after the HSE was NMDAR-antibody related. At the last follow up, 6 months after HSE onset, he had residual baseline aphasia due to HSE but no neuropsychiatric symptoms or behavioral problems.

**Patient 4**

A previous healthy 50 year old male was admitted for subacute onset of fever, speech difficulties and memory deficits. Brain MRI showed right greater than left temporal and hippocampal T2/FLAIR hyperintensities with ADC restriction without contrast enhancement (Figure 3, panel I and K). The CSF showed 239 WBC/L, increased protein (66 mg/dL), and PCR positive for HSV1 (NMDAR antibodies were not tested). He received IV acyclovir for 14 days with good recovery. One month after discharge (40 days after HSE onset), he developed severe headache and abnormal behaviors. He was depressed with suicidal ideation and episodes of aggression. He had an intention tremor with no other abnormal movements. These symptoms were initially attributed to the previous HSE and risperidone was started. He was admitted 2 months later with refractory headaches and behavioral symptoms. The MRI showed mild progression of the previous T2/FLAIR white matter bilateral temporal lobe hyperintensities with new intense contrast enhancement (data not shown). The CSF showed 27 WBC/L, increased proteins 107 mg/dL, and the PCR was negative for HSV1. NMDAR antibodies were not tested. Although a viral relapse was not confirmed by PCR, he empirically received IV acyclovir for two weeks without improvement, and his symptoms were attributed to residual deficits of HSE. Due to persistent symptoms he was re-evaluated 12 month after HSE onset. The MRI showed more intense contrast enhancement compared to the prior study (Figure 3, panels J and L). The CSF showed mild pleocytosis (15 WBC/L), high protein concentration (88 mg/dL), negative HSV1 PCR and low titers of NMDAR antibodies (1:2) (serum negative). He was treated with IV corticosteroids and IVIg with substantial but not complete recovery of the headache and psychiatric symptoms, and he is currently receiving rituximab and cyclophosphamide.

**Patient 5**

A previous healthy 34 year old woman was admitted for subacute onset of fever, speech difficulties, memory deficits, and focal seizures. An MRI without contrast showed left temporal and hippocampal T2/FLAIR hyperintensities with ADC restriction. The CSF showed 460 WBC/L, increased protein (51 mg/dL), PCR positive for HSV1, and absence of NMDAR and other autoantibodies. She was discharged after completing 14 days of intravenous acyclovir with residual aphasia and memory deficits. Twenty-three days after discharge (38 days after HSE onset) she developed progressive behavioral abnormalities, including anxiety, restlessness, delusional thoughts, irritability and insomnia. In a routine follow up visit sixty days after HSE onset, her change of behavior led to consider an autoimmune relapse and she was re-admitted. The CSF PCR was negative for HSV, but showed 10 WBC/L, protein concentration of 65 mg/dL, and NMDAR antibodies (CSF titer 1:40; serum titer 1:200). She was started on IV methylprednisolone with rapid improvement of the behavioral abnormalities, returning to her pre-relapse level. A brain MRI performed 5 days after methylprednisolone was initiated showed mild expansion of the T2/FLAIR white matter changes in the left temporal lobe compared with the MRI obtained during the HSE.

**Patient 6**

A 69 year old female was recently admitted for speech difficulties and an acute confusional syndrome associated with fever. A brain CT was normal but the CSF showed 32 WBC/L, normal protein level, and the PCR was positive for HSV1. NMDAR and other antibodies to cell surface antigens were not tested. IV acyclovir was started and over the next 6 days she developed simple partial seizures that were initially well controlled with levetiracetam and valproate. Brain MRI performed 8 days after HSE onset showed left temporal and hippocampal T2/FLAIR hyperintensities without ADC restriction but with intense contrast enhancement. Over the next days the patient had a progressive increase in frequency of seizures that evolved to a non-convulsive status epilepticus. The patient was readmitted to the ICU for refractory status epilepticus receiving treatment with continuous infusion of midazolam and propofol, followed by barbiturate coma. After completing 21 days of acyclovir the CSF showed absence of WBC, normal protein concentration, and the PCR was negative for HSV1. Antibodies to unknown neuronal cell surface antigens were identified in CSF and serum. She was then started on IV methylprednisolone, IVIG, and plasma exchange resulting in a transient improvement of the EEG pattern. Four weeks after first line immunotherapies she was started on rituximab leading to complete seizure control. Currently, 3 months after HSE onset, the patient has moderate aphasia and proximal weakness due to critical illness neuropathy.

**Patient 7**

A previously healthy 29 year old male was admitted for fever, seizures, and abnormal behavior. After admission he developed respiratory failure requiring mechanical ventilation. A brain CT showed a right frontotemporal hypointensity. The CSF demonstrated 49 WBC/L, protein concentration 60 mg/dL and positive PCR for HSV1. NMDAR and other neuronal cell surface autoantibodies were not tested. He was treated with 2 weeks of IV acyclovir with improvement but one week later developed abnormal behavior which was thought to be secondary to the HSE. He was discharged one month after admission requiring haloperidol and risperidone and was then re-admitted 1 month later due to the development of decreased level of consciousness and fever. At admission he was noted to have blepharospasm without other abnormal movements. An MRI without contrast showed extensive bilateral right greater than left frontotemporal T2/FLAIR hyperintensities. There was no prior MRI for comparison. The CSF showed 2 WBC/L and increased proteins (112 mg/dL). He was re-treated with IV acyclovir for 21 days for a suspected viral relapse although the CSF PCR for HSV1 was negative. He did not improve and progressed to a comatose state that required mechanical ventilation. Re-evaluation of the CSF showed 12 WBC/L, increased proteins (63 mg/dL) and antibodies to unknown neuronal cell surface antigens; the serum was not studied. He was treated with IV methylprednisolone for 5 days and his level of consciousness improved as did the abnormal behavior. Persistent blepharospasm was treated with botulin toxin. At the last follow up 12 months after the initial admission he is almost fully recovered and has returned to work.

**Patient 8**

A healthy 56 year old female developed low grade fever and diarrhea followed the next day by apathy and somnolence. She was seen by a psychiatrist and diagnosed with reactive depression due to the recent death of her father. She was started on citalopram but several days later she became catatonic. An MRI of the brain showed bilateral T2/FLAIR abnormalities without contrast enhancement in the temporal lobes, right greater left. The CSF showed 250 WBC/L, increased proteins (62 mg/dL), positive PCR for HSV1 and absence of antibodies to cell surface antigens. The patient received 15 days of IV acyclovir and was discharged to a rehabilitation center with severe anterograde amnesia. Repeat CSF obtained one day before the acyclovir was discontinued showed 90 WBC/L, protein concentration 61 mg/dL, negative HSV1 PCR, and absence of antibodies to neuronal cell surface antigens. Over the next 2 weeks she developed emotional lability, continuous crying, and suicidal ideation. She was treated with quetiapine, citalopram and paroxetine with partial improvement, but continued having episodes of severe agitation, and confrontational and oppositional behavior. Five months after onset of HSE the patient was seen in a follow up visit of a prospective study of patients with HSE in our center. She had stable, severe anterograde amnesia, and was disoriented to place, time and person (Minimental State Examination 19/30) and continuously confused (Figure 1, panels A, D and G). MRI showed slight progression of T2/FLAIR hyperintensity in the temporal lobes with new contrast enhancement. Repeat CSF studies showed 10 WBC/L, normal protein concentration, negative HSV1 PCR, unmatched oligoclonal bands, and antibodies to unknown neuronal cell surface antigens that were not present in serum. Although her symptoms were stable, based on these laboratory findings she was treated with 5 days of IV methylprednisolone. Within the next three weeks her severe behavioral problems resolved and became oriented to person and place (Minimental State Examination 22/30) (Figure 1, panels B, E and H). Her anterograde amnesia and orientation to time remained unchanged, but overall she was able to return home and participate in conversations with her family and friends. She received 2 additional monthly cycles of methylprednisolone. At the last follow 15 months after HSE, she was clinically stable (Figure 1, panels C, F, I) and the MRI showed resolution of the contrast enhancement.