**SUPPLEMENTAL INFORMATION**

Laboratory studies

All patients underwent extensive laboratory studies that included, blood and urine cultures, CSF PCR for Epstein Barr virus, herpes simplex virus, enterovirus, and varicella zoster virus; serum testing for syphilis, Lyme disease, Mycoplasma, arboviral panel, adenovirus, and CMV. In addition, 12 patients were investigated for one or more of the following: West Nile virus, HIV, HHV-6, cat scratch disease, rabies, and Legionella. Urine toxicology screen was obtained in 22 patients. All patients from CHOP were tested for anti-nuclear antibody, angiotensin converting enzyme, rheumatoid factor, beta 2 glycoprotein, anti-cardiolipin antibody, anti-ribosomal P antibody, and complement levels. Six patients from CHOP had comprehensive metabolic panels including ammonia, ceruloplasmin, serum and CSF amino acids, acylcarnitine, serum and CSF lactate/pyruvate, and urine organic acids. Similar autoimmune and metabolic panels were obtained in 18 patients from other institutions.

Results from laboratory studies

Five patients had transient elevated levels of serum CK (415-18,000 U/L, median 1,500). Two patients had renal failure attributed to initial empiric treatment with acyclovir, from which they recovered. Viral, immunological, toxicological, and metabolic studies were negative in most patients except for five (4 without teratoma) who had elevated serum antibody titers to Mycoplasma (2 IgG and IgM, 3 IgG only); 2 had elevated serum titers to adenovirus, and 1 to HHV6. In all these patients the CSF studies were negative for Mycoplasma and the indicated viruses. Four patients had serum autoantibodies (1 transient detection of ANA, 1 ANA and antistreptolysin, 1 ANA and thyroid peroxydase, and 1 thyroid peroxydase) without evidence of related autoimmune disease or organ dysfunction.

DESCRIPTION OF PATIENTS

Patient 2

A two and a half year old girl presented with a prolonged, unprovoked episode of right face and arm clonic movements associated with unresponsiveness, suggestive of focal seizures. The movements subsided following administration of lorazepam and a loading dose of phenobarbital. EEG, brain MRI, and CSF were normal. After discharge from the hospital, she continued to have brief episodes of right face, arm, and occasionally leg clonic rhythmic movements with rightward eye deviation despite escalating doses of oxcarbazepine and levetiracetam. The episodes lasted seconds after which she returned to baseline; sometimes, the movements were bilateral. Her parents also noted new nocturnal enuresis. A repeat EEG two weeks after symptom onset revealed diffuse slowing, left greater than right, and excessive beta activity without epileptiform abnormalities. Twenty days after her first seizure, she developed a right-sided limp and right arm dystonia with extensor posturing. Over the next week, she used her right arm progressively less, and sometimes refused to walk. One month from the onset of symptoms, her parents noted slurred speech and progressive decrease of verbal output. She was readmitted and found to have labile mood, chewing movements, right facial grimacing, and explosive, telegraphic, unclear speech, mostly consisting of single words. She responded intermittently to simple commands. Frequent episodes of right facial twitching were observed and there were also stereotyped, complex movements including repeatedly grasping at the blanket with her right hand. During these movements, she was tachycardic to a maximum rate of 140 and had systolic blood pressures above 130. She had increased tone on the right side with cortical fisting, hyperreflexia, and a positive Babinski. Video EEG monitoring confirmed an ictal electrographic correlate to the clonic movements of the face, arm, and leg but not with her mouth movements and dystonic posturing. The EEG background was slow and disorganized with multifocal sharp waves. On the 35th day of the illness a repeat brain MRI including angiography and MR spectroscopy were normal. CSF analysis revealed 2 WBC/microliter, normal protein concentration, and positive oligoclonal bands. On day 42 she received intravenous methylprednisolone for possible immune-mediated encephalitis. Over the next several weeks, her abnormal movements resolved and she began to increasingly use her right arm; her speech improved but she remained difficult to understand. She continued to have episodic tantrums including screaming and thrashing movements. When her CSF tested positive for NMDAR antibodies, she was readmitted for five days of IVIg and repeat methylprednisolone on day 87. At that time, her gait was almost normal and she spoke with 50% of her normal fluency. At her most recent follow up examination 5 months after symptom onset, she had completely recovered to her pre-illness baseline.

Patient #3

A sixteen-year old female with a history of encephalopathy and temporal lobe seizures in 2005 presented with the return of bizarre behavior in 2008. Her initial presentation was associated with episodes of lip smacking, tangential speech, paranoia, and hallucinations. Her speech remained fluent but became more bizarre, paranoid, and hyperreligious. She was found on video EEG to have intermittent temporal lobe seizures and was started on oxcarbazepine. While her seizures appeared to be controlled, she continued to have auditory and visual hallucinations, paranoid ideation, word repetition, and aggression. Abnormal movements such as grasping at the air, leg shaking, and pill-rolling hand movements were observed without EEG correlate. She also had episodes of tachycardia and hypertension with blood pressures approaching 170/100. Although she had a history of pulmonary stenosis, cardiology did not feel the autonomic lability could be attributed to her cardiac anatomy. She was given haloperidol for agitation and became more lethargic with drooling and then developed dystonic upper extremity posturing and tightening of the mouth that resolved with benztropine and discontinuation of the haloperidol. She was started on quetiapine for her psychotic symptoms and zolpidem for frequent awakenings throughout the night. An MRI and MRA of the brain were normal. The CSF revealed 2 WBC. She was empirically given a five day pulse of solumedrol. Cognitively, over the next few weeks she returned to baseline. A normal mental status examination was documented at a routine clinic visit in 2006.

In June, 2008, she had the return of behavioral outbursts, insomnia, and trembling episodes without loss of consciousness. On the night of admission, she threw a glass at her parents and threatened to jump from a second story window. She had not slept for several days. During her admission, she had episodes of attempting to leave her room, throwing objects, spitting, and screaming profanities for which security was called and physical restraints were placed. Visual hallucinations of “men in gray beards walking on all fours” were reported. A video EEG was normal with an appropriate background. She was tried on multiple antipsychotics including quetiapine, olanzapine, and ziprasidone and periods of hypertension and tachycardia which resolved during sleep were attributed to the antipsychotic medications. She was transiently admitted to a psychiatric facility with a diagnosis of mania and re-admitted the following month for an episode of eye fluttering and tachycardia thought to be seizure. She was being treated at that time with lithium and olanzapine and was about to start electroconvulsive therapy (ECT) for refractory psychosis. When she arrived in the emergency department, she was extremely agitated and biting herself. On repeat CSF examination, she had 14 WBC. She was initially admitted to the adolescent floor but was transferred to the ICU when her creatinine kinase was found to be 18,000. Her temperature was not elevated. She had extreme hypertension requiring rescue doses of labetalol. Repeat video EEG monitoring revealed background slowing but no epileptiform abnormalities and episodes of agitation, pupillary dilatation, and tachycardia did not have EEG correlates. MRI of the brain did not reveal any abnormalities. As her evaluation was unrevealing, she was discharged to a psychiatric facility where she received ECT treatments and continuing psychiatric care.

Several weeks later, she was found to have antibodies to the NMDAR present in the CSF that was collected in 2005. As her mental state was improving other than deficits in memory, no further treatment was initiated. However, her symptoms again worsened in late 2008 with episodes of agitation and violence. A repeat lumbar puncture revealed persistence of antibodies and she received both IVIg and methylprednisolone that resulted in substantial neurological improvement over the next 3 weeks. Currently, 8 weeks after immunotherapy, she has no focal neurological deficits, cognitive functions are close to normal baseline but she remains home-schooled due to episodes of agitation and aggression that are progressively subsiding.

Patient #4

One week prior to presentation, this six-year old boy began having frequent behavioral outbursts that would last minutes. He spontaneously started screaming, kicking, and demanding that a loose tooth be removed. A few days later, he became hypersomnolent, sleeping frequently during the day and waking for only 15 to 30 minutes at a time. He also had daytime urinary incontinence which was unusual for him. The day prior to admission, he developed right facial twitching, lip smacking, unsteady gait, and confusion. He walked into a closet thinking it was the shower then entered the shower with his clothes on. He could not name familiar objects. He became increasingly unresponsive and unable to follow commands. He had several episodes of emesis a few days prior to admission but no other recent illnesses. On evaluation his affect was flat alternating with agitation. He was only able to speak a few words which were slurred and difficult to understand. He inconsistently followed simple commands. There was occasional right facial twitching with intermittent violent bicycling movements of the legs and writhing, choreiform movements of the shoulders, particularly on the right. He did not withdraw consistently to pain. He was symmetrically hyperreflexic with an absent Babinski. On transfer to the pediatric intensive care unit (PICU), he had one elevated temperature of 38.3oC but no further hyperthermia. He had a few recorded periods of tachycardia to a maximum heart rate of 150 which correlated with periods of agitation and desaturations to 80% on room air, one of which required brief supplementary oxygen. There was no blood pressure lability. Routine EEG demonstrated a slow, poorly organized background, left greater than right, with no epileptiform discharges. A lumbar puncture revealed 11 WBC. A nasal aspirate was adenovirus positive but other infectious studies were negative. MRI of the brain showed subtle bilateral T2/FLAIR high signal in the posterior periventricular white matter and within the hippocampi without enhancement thought to within the range of normal but possibly secondary to encephalitis or seizure activity. Over the next few days he progressed to complete unresponsiveness. His eyes were open but he would not fix or follow. He was very agitated at times with pronounced shoulder writhing, dystonic neck extension, frequent tongue thrusting, drooling, chewing, and “kissing” mouth movements. Video EEG monitoring was performed and runs of bifrontal rhythmic low amplitude delta activity without clinical correlate were seen (Figure 4). These runs were considered suspicious for seizure but there was no observed change with levetiracetam. Valproic acid was initiated for the choreiform movements with minimal improvement. A repeat lumbar puncture 7 days after admission revealed 4 WBC. A repeat MRI the same day showed improved hippocampal signal with residual obscuration of the architecture of the right hippocampus. MR angiography was normal and MR spectroscopy revealed a nonspecific slight elevation of choline and reduction of NAA. On day 17 of hospitalization, he was discovered to have oligoclonal bands in the CSF and antibodies to the NMDAR for which he received a five day course of methylprednisolone followed by five days of IVIg. His symptoms stabilized and then he was transferred to the neurology floor.

One month after presentation the choreiform movements had improved but he continued to have occasional chewing movements and right mouth twitching. At this time, he also began reciting numbers, echoing, and yelling profanities and eventually produced short sentences with pressured, difficult to understand speech. He had one episode of prolonged right gaze deviation and one evening developed desaturations to 60% and a respiratory of rate of 6 and mild hyperthermia to a maximum of 38.4oC. A third MRI of the brain was unchanged. A repeat 5 day course of IVIg was administered without alteration in symptoms. He was transferred to the rehabilitation service where his speech and movements normalized approximately three months after presentation, however, his behavior remained disinhibited and hyperactive and he was occasionally violent. Psychiatry suggested risperidone, clonidine, lorazepam, and a methylphenidate patch for his episodes of agitation with risperidone being the most effective. He was recently discharged to home with rare behavioral outbursts on a standing dose of risperidone.

Patient #5

A six year old boy with no past medical history presented with seizures. In June, 2008, he had a brief, self-limited febrile illness. In early August, he developed low-grade fevers and left-sided focal seizures which were treated with phenytoin and oxcarbazepine. A lumbar puncture revealed 18 WBC and an MRI of the brain was normal. An infectious evaluation was negative and he was discharged home. One month from symptom onset, the seizures worsened and he developed behavioral changes including agitation, difficulty sleeping, and paranoia. He was readmitted to an outside hospital for seizures and severe episodes of agitation. A video EEG revealed only right sided slowing and a repeat lumbar puncture confirmed the pleocytosis with 20 WBC. He was started on risperidone and valproic acid without change in behavior and was transferred to our institution. On arrival, his exam was significant for dystonic posturing, particularly in the left arm and leg which persisted despite the discontinuation of risperidone. He had periods of agitation with opisthotonic posturing (Figure 3), purposeless opening of the mouth, chorea of the hands and arms, pressured speech, and tachycardia alternating with periods of calm. He received a five day course of methylprednisolone without change in symptoms. On the third day of methylprednisolone, he developed status epilepticus with eye deviation and left sided extremity shaking requiring several doses of lorazepam. Respiratory depression ensued and he was intubated and transferred to the PICU. He was extubated the following day and had no further periods of respiratory compromise. On return to the pediatric floor, he would sleep only for brief periods at a time. One dose of olanzapine was given which his parents felt worsened the dystonia and abnormal movements. Clonazepam allowed him to sleep through the night but resulted in excessive somnolence and he was switched to lorazepam with good result. Occasional drooling was noted and, due to continual mouth movements and arching while attempting to eat, nasogastric tube feeding was initiated. Levetiracetam was added for intermittent seizures which were recorded on video EEG and found to have definite electrographic correlate. His EEG background was slow. A repeat MRI of the brain revealed abnormal, nonspecific posterior subcortical and periventricular white matter signal thought to be secondary to periventricular leukomalacia. MRA of the head was normal. After eight days in the hospital, he was found to have antibodies to the NMDAR and a five day course of IVIg was administered. One week later, there was notable improvement in his agitation and dystonia. He had no speech production but intermittently followed commands. He seemed restless and, without warning, would attempt to run out of the room.

Ten weeks after onset of symptoms, he was transferred to the inpatient rehabilitation service. As his movements became more purposeful, he became more impulsive and hypersexual. He made marked gains in language and was able to speak in full sentences. He continued to have unnatural pauses between sounds in words and decreased coordination of breath support. His movements became more fluid however he remained restless and had some difficulty with balance, partly due to distractibility and inattention. He was discharged after over 2 months in the hospital and, on last report, continues to improve at home.

Patient #6

This fourteen-year old girl presented with two days of right hand numbness, right arm pain, and uncharacteristic school-related paranoia. Three days prior she had mild upper respiratory symptoms but was otherwise healthy. On examination, her temperature was not elevated but she appeared ill. She had slurred speech and seemed to have difficulty finding words. She was admitted to the PICU where she developed involuntary, repetitive, pill-rolling hand movements predominately on the right (Figure 3, inset), and distinct periods of agitation with unresponsiveness, mutism, flailing of the right arm, drooling, and enuresis. She appeared lucid between these episodes, attempting to form words but without speech production. The CSF revealed 63 WBC/ l, with normal protein and glucose concentrations. Routine EEG demonstrated left sided background slowing. MRI of the brain showed minimal sulcal enhancement after contrast administration. She was started on haloperidol for agitation, but four days later she developed hyperthermia 38.9oC and was transferred to CHOP. On arrival, she had neck dystonia and full body rigidity approaching opisthotonic posturing. Serum creatinine kinase was normal. During the periods of agitation the systolic blood pressure raised to 150. She had no speech production, appeared frightened, and was intermittently able to follow simple commands. Her reflexes were brisk with unsustained clonus bilaterally, and at times, she had waxy catatonia. Status epilepticus was suspected and she was given ativan and a loading dose of levetiracetam. A video EEG was performed showing left sided slowing without epileptiform abnormalities. Episodes of right mouth twitching, chewing movements, and right eye deviation were captured without electrographic correlate. There were also periods of normal EEG. Repeat CSF analysis showed 4 WBC, and MRI and MRA of the brain were normal. Treatment with diazepam was initiated for continued truncal and extremity dystonia. She had infrequent episodes of oxygen desaturation into the 80th percentile, which self-resolved without requiring intubation. On day 15 of the illness, NMDAR antibodies were detected in her CSF. She was given five days of simultaneous IVIg and methylprednisolone. Within one week, the dystonia improved allowing her to stand and walk with a shuffling gait. She remained impulsive, disinhibited, hyperoral, and hypersexual. She started to speak a few words and become more interactive with her family. Her speech started as echolalia and incoherent babbling but progressed to appropriate, full sentences. She remained emotionally labile with frequent tearfulness and appeared fearful of the hospital staff. Her sleep schedule became more erratic with nighttime awakenings that improved with clonidine. On day 20 of the illness, she was transferred to an inpatient rehabilitation facility. She continued to have episodes of agitation, crying, and screaming which at times were redirectable without intervention. Six weeks after symptom onset, her speech, behavior, and mobility were considered at 75% of her normal baseline. Neuropsychological testing by the time of discharge from rehabilitation, 8 weeks after symptom onset, revealed mild deficits in processing speed but preserved, advanced intellectual ability.

Patient #7

A sixteen-year old female with a history of bipolar disorder was admitted to a psychiatric facility with worsening symptoms. For the past 4 years, she had been managed on quetiapine for mood lability. Several days after a quetiapine wean, she became more anxious with intense mood swings, crying episodes, and perseveration. She repeatedly asked, “Why is this happening?” She recently had some low grade elevations in temperature without any other signs of illness. Shortly thereafter, she had an episode of incontinence at school and developed pressured speech and tangential ideas. Despite increasing her quetiapine to the original dose, the new symptoms persisted. She then began complaining of left hand and lip numbness. She presented to a crisis center where she required sedation for agitation and was transferred to an inpatient psychiatric facility. Multiple medications were administered including ziprasidone and thorazine without effect. She had two episodes of unresponsiveness concerning for seizure involving speech arrest, staring and facial twitching lasting ten minutes followed by disorientation and confusion that improved over hours. She was brought to the emergency department where a lumbar puncture revealed 73 WBC and a routine EEG was normal. On admission, mental status exam revealed pressured speech with perseveration, tangential content, emotional lability, and impairment of short-term memory. She was diaphoretic with an elevated temperature to 38.5oC. Video EEG captured episodes of facial twitching and rhythmic leg shaking without electrographic correlate. An MRI of the brain was normal. Her agitation continued with periods of unresponsiveness, extremity trembling, jaw deviation to the left, and protrusion of the tongue. These lasted several minutes and resolved spontaneously. Administration of ativan and trazodone did not alter her behavior. Her clinical status gradually declined with development of psychomotor slowing (at times consistent with a waxy catatonic state), bizarre arm movements (floating and hand wringing), mutism, and dysphagia necessitating nasogastric tube feeding. Her agitation escalated involving pelvic thrusting, extremity stiffening, screaming, tachycardia, and pupilary dilatation lasting hours. She perseverated that she was giving birth and repeatedly arched her back or panted on all fours. She reported visual hallucinations of babies in her room. At times, she stated that she was “wet all over”, “dead”, or “naked” when she was gowned and dry. There were two recorded episodes of oxygen desaturation to the 80th percentile which were thought due to “breath-holding”. These events resolved spontaneously and respiratory support was never required. When not agitated, she appeared alert and had intact visual tracking. Her speech was absent or inappropriate and slurred and she only intermittently followed commands. She awoke frequently during the night despite escalating doses of lorazepam. Repeat lumbar puncture two weeks into her hospitalization revealed 28 WBC and NMDAR antibodies. A five day course of methylprednisolone was initiated on day 15 of admission. She had gradual improvement with fewer episodes of agitation and unresponsiveness, less psychomotor slowing, improved interactions and resolution of dysphagia. When she had not returned to her baseline two weeks after completion of IV steroid therapy a course of IVIg was initiated and within days she began speaking in full sentences and her agitation resolved. She was transferred to an inpatient rehabilitation facility where she made rapid, dramatic improvement. Neuropsychological testing on discharge revealed only deficits in processing speed.

Patient #8

A nine-year old male was admitted with the onset of isolated left leg dystonia. MRI of the brain and creatinine kinase were normal. The following week, he developed extreme episodes of agitation with choreoathetoid movements of his face and legs. His speech production progressively decreased to only single words and he would only follow simple commands. Although initially admitted to the pediatric floor, he required transfer to the PICU and intubation secondary to his severe agitation and elevated creatinine kinase to 4500. During agitation only, he had elevated blood pressure to a maximum systolic of 156 and infrequent tachycardia to a rate of 120 and elevations of temperature. A routine EEG was abnormal due to diffuse low amplitude background slowing, excess beta activity, no response to stimulation and/or state change, and frequent vertex sharp waves. He was initially managed on ketamine, olanzapine, valproic acid, and pentobarbital which improved the agitation. He did not exhibit hypoventilation or respiratory distress and was easily extubated two days later. One week after admission, he was found to have NMDAR antibodies in the CSF and he began a five day course of treatment with IVIg which did not alter his symptoms. He was transferred to the neurology floor and continued to have distinct episodes of pupil dilation followed by unresponsiveness, violent movements of all extremities including leg bicycling, and “floating”of the arms. The episodes lasted 10 minutes and then he was calm and occasionally able to speak single words. His agitation was minimally responsive to risperidone or olanzapine with some response to quetiapine. His sleep was severely disordered, sleeping no more than three consecutive hours in over a week despite treatment with melatonin, gabapentin, clonidine, and lorazepam. Repeat EEG 3 weeks from symptom onset revealed diffuse slowing bilaterally and frequent sharps in the left parietal region. He completed a five day course of methylprednisolone which initially appeared to lessen his agitation. He then started to desaturate with a decreased respiratory rate requiring a second intubation and return to the ICU. He was extubated within two days but remained in the PICU for over a week secondary to extreme agitation requiring a fentanyl infusion and additional doses of pentobarbital. Over the past few weeks, his agitation has calmed and he has returned to the neurology floor. He continues to have stereotypic movements and does not react to his environment. The parents are currently considering further immunotherapy.