## **Appendix e-1: Case Reports**

*Patient #1*. An 8-year-old girl developed typical symptoms of anti-NMDAR encephalitis. She was misdiagnosed of encephalitis lethargica and treated with a 5-day course of 1g methylprednisolone. Brain MRI was normal and CSF showed lymphocytic pleocytosis of 40 cells/mm3. She completely recovered over the ensuing two months. A second typical episode occurred 8 years later when NMDAR-ab were detected for the first time. She went into complete remission after a 6-day course of intravenous steroids. Imaging studies to detect an ovarian teratoma were negative.

*Patient #2.* A 13-year-old girl developed typical symptoms of anti-NMDAR encephalitis that were also misdiagnosed of lethargic encephalitis. She completely improved one month after treatment with a 5-day course of intravenous immunoglobulins and corticosteroids. Thirty months later, she developed subacute headache, abulia, and speech dysfunction with difficulty to pronounce certain words and striking reduction of verbal output (comprehension remained preserved). No other psychiatric or neurological symptoms were observed. Brain MRI and CSF analysis were normal. She completely improved after a 5-day course of 1g of methylprednisolone. During this first relapse NMDAR-ab were found positive. Screening for ovarian teratoma was negative.

*Patient #3*. An 18-year-old girl developed a typical syndrome of anti-NMDAR encephalitis. She was diagnosed of probable viral encephalitis and without immunotherapy she slowly improved with mild residual speech and behavioural dysfunction. One year later, she had a relapse of the encephalitis. Brain MRI was normal. CSF analysis disclosed lymphocytic pleocytosis of 10 cells/mm3. She improved without immunotherapy and recovered to baseline functional state. A second relapse occurred 5 years after the initial episode with bradypsychia and clear worsening of her speech, behavior and attention. NMDAR-ab were detected during this relapse. The patient was treated with oral steroids (60 mg/day for 5 months and slow decrease over 7 months) and with three 5-day courses of intravenous immunoglobulins for 1 year. In less than one month she recovered her previous baseline state. During corticosteroid tapering and nine months after the third and last course of immunoglobulins (6.6 years after the disease onset) she suffered a third relapse characterized by subacute worsening of her speech, bradypsychia and decreased attention that improved to previous state with a single pulse of intravenous corticosteroids. She continued with oral steroids and immunoglobulin cycles (1 cycle/ 3 months). Search for ovarian teratoma was negative.

*Patient #4*. A 22-year-old woman was diagnosed of secondarily generalized partial epilepsy after suffering 3 episodes of focal sensory symptoms with secondary generalization. Interictal EEG and brain MRI were normal. CSF analysis was not performed. Symptoms resolved with antiepileptic treatment. Sixteen months later, she developed progressive speech abnormalities and focal seizures with impaired consciousness. At this time, an ovarian teratoma was diagnosed and removed. No immunotherapy was given and she slowly recovered. Five years after the onset of the disease she suffered a second relapse corresponding to a typical NMDAR-encephalitis syndrome. NMDAR-ab were detected for the first time. She was treated with a 5-day course of intravenous methylprednisolone and immunoglobulins with complete recovery over the ensuing weeks.

*Patient #5*. This 30-year-old woman suffered 4 relapses in a period of three and a half years despite of treatment with steroids, intravenous immunoglobulins, azathioprine, plasma exchange and cyclophosphamide. In the initial episode she complained of generalized hyperesthesia, memory and speech disorder, and decrease of consciousness. Brain MRI was abnormal with bilateral diencephalic and brainstem hyperintensities and CSF analysis was normal. She was left with residual abulia and a severe amnestic syndrome despite treatment with intravenous immunoglobulins. The first three relapses were milder and after immunotherapy she recovered to baseline. The predominant clinical symptoms were subacute drowsiness, psychotic depression and sleep disturbance in the first relapse, isolated acute psychotic depression in the second and subacute drowsiness, behavioral disorder, autonomic dysfunction, and coma in the third. The fourth episode was atypical with isolated subacute cerebellar ataxia and diplopia. As reported by referring physicians, these symptoms appeared in isolation and insidiously, they were mild and improved with oral steroids. No ovarian teratoma was found.

*Patient #6.* A 35-year-old woman developed typical symptoms of anti-NMDAR encephalitis. Brain MRI disclosed right temporal hyperintensity and CSF analysis showed lymphocytic pleocytosis of 20 cells/mm3. She was not treated with immunotherapy and she made and slow and partial recovery with mild frontal cognitive deficits. Thirteen years later, she was readmitted for subacute dysarthria and dysphagia. Symptoms improved without treatment in two months. One year later, she suffered an atypical relapse of new onset cerebellar ataxia and limb tremor. The patient was treated with intravenous corticosteroids and immunoglobulins, with good outcome and return to the functional status after the first event. NMDAR-ab were detected for the first time during this second relapse. No tumour was identified.