**Appendix 2**

**Development of anti-NMDAR encephalitis after (HSE)- Clinical Case**

A 2-year-old previously healthy Caucasian girl presented with partial seizures and fever. CSF studies showed 180 white blood cells/microliter (69% lymphocytes), normal protein and glucose concentrations and the PCR for herpes simplex virus -1 (HSV-1) was positive. Brain MRI showed increased T2/FLAIR signal in opercular regions, medial temporal lobes, and posterior aspect of the basal ganglia (Figure 3, A-D). She was treated with intravenous acyclovir during three weeks, resulting in substantial recovery but with residual bilateral facial weakness and anarthria secondary to bilateral opercular encephalomalacia (Foix-Chavany-Marie syndrome). One week after being discharged home (one month after HSE onset) she developed diarrhea and low grade fever followed by behavioral abnormalities, including agitation, inability to sleep, and periods of hyperexcitability alternating with somnolence. The patient was admitted to the Pediatric Intensive Care Unit for extreme agitation, and treatment with midazolam was initiated. While waiting for the CSF results, treatment with acyclovir was started for suspicion of HSV reactivation. CSF analysis showed a normal white blood cell count and protein concentration, and the PCR for HSV was negative. Over the next days she developed choreathetosis in the limbs, orofacial dyskinesias, generalized tonic-clonic seizures, and decreased level of consciousness. Severe tachychardia and transient hypoventilation were noted during the episodes of agitation, but mechanical ventilation was not required. A repeat brain MRI showed areas of encephalomalacia in opercular regions where the MRI obtained 1 month earlier had demonstrated the most prominent FLAIR/T2 signal abnormalities other previously noted abnormalities were unchanged or improved, without new findings identified (Figure 3, E-H). The EEG demonstrated diffuse but asymmetric slow activity (more evident in the right hemisphere), without evidence of epileptic activity. The absence of new MRI findings or areas of necrosis, negative HSV testing in CSF studies, and the clinical picture of choreoathetosis and orofacial dyskinesias that did not respond to ayclovir, led to a diagnosis of post-HSV “choreoathetosis”, which is a disorder suspected to be immune mediated. Therefore, treatment with methylprednisolone (30mg/k/day for three days) and IVIg (0,4g/k/day for 5 days, 2 courses) was started, followed by a 4 week taper of steroids. Additional symptomatic medication included, midazolam for agitation, and valproate for seizures. However, her symptoms did not improve and she continued with prominent choreaoathetosis (Video 1), catatonic features, and episodes of tachycardia. Four months after onset of this new episode of encephalitis, testing for antibodies to cell surface or synaptic proteins demonstrated high levels of NMDAR antibodies in serum and CSF. The patient was then started on 5 monthly courses of IVIg along with second line immunotherapy, including rituximab (375 mg/m2 weekly, 4 doses), and cyclophosphamide (monthly IV pulses, 1st dose: 500 mg/m2, 2nd and subsequent doses: 750 mg/m2). Screening for an underlying ovarian teratoma with abdominal and pelvic ultrasound was negative. Five weeks after second line drugs were started (5 months since the onset of anti-NMDAR encephalitis), the first signs of improvement were noted. The patient’s level of consciousness as well as the involuntary movements and abnormal behavior started to improve (Video 2). At the last follow-up, 9 months after onset of anti-NMDAR encephalitis she is still improving and is now completing the fourth cycle of cyclophosphamide. Because of the residual opercular syndrome (sequelae of HSE), she cannot speak or swallow and her feedings are via a percuatenous endoscopic gastrostomy tube. Her gait is mildly dystonic/ataxic but she is able to walk with mild support. Her cognition is intact, she follows commands appropriately, and communicates by signs (Video 3).