**Cases**

**1) Case 3: NMDAR encephalitis**

A previously well seven year old girl had a prodromal illness of headache, fevers, vomiting and abdominal pain followed by right leg pain and difficulties with fine motor skills. Memory impairment and cognitive decline followed. Three weeks into her illness she developed an absence-like seizure with unresponsiveness and salivary drooling that lasted for 10 minutes. She had more episodes suggestive of focal dyscognitive seizures and was admitted to hospital, and treated with phenytoin and levetiracetam. She developed abnormal movements in the form of orobuccal dyskinesia, excessive blinking, non purposeful limb movements and excessive thrashing movements in her bed. Her behaviour was altered with agitation, irritability, inappropriate affect and mood swings. She had slurred and reduced speech and became confused and disoriented.

Neuropsychological assessment showed significant impairment in language and verbal intellect as well as mild impairment in processing speed and fluctuation in attention. EEG showed left temporal slowing and no epileptiform activity. CSF analysis revealed 15white cells/mm3 and MRI revealed hyperintensities in the right frontal, left temporal and insular cortex. Ovarian ultrasound was normal. NMDAR Abs were positive in serum and CSF and VGKC-complex Abs were negative.

She was treated with intravenous pulse 30 mg/kg/day methylprednisolone for five days followed by oral prednisolone weaning regimen over four weeks in addition to intravenous immunoglobulin at a dose of 2g/kg. Three weeks later she was reported by her family to be 90% back to normal and had no ongoing seizures or abnormal movements. Further doses of monthly IVIG over 3 months were given and associated with a full recovery.

This patient had positive NMDAR antibodies and positive response to immunotherapy and applying the guidelines’ classification she has “definite” autoimmune epilepsy.

**2) Case 4: VGKC-complex Abs associated encephalitis**

A previously well 15 month old girl presented after an upper respiratory tract infection with a 30 minute new onset focal seizure involving the left side of the face and the left arm. At the hospital she had a low grade fever and was floppy, unresponsive and staring into space. She had more episodes of focal seizures consisting of facial twitching, staring and lip smacking. Seizures were treated with phenytoin, phenobarbitone and midazolam and stopped within five days of onset. Encephalopathy, cognitive or behavioural alterations were not prominent features of her illness once the seizures were controlled.

EEG showed diffuse slowing of the background with superimposed fast activity and no epileptiform activity. CSF analysis revealed 6 white cells/mm3 and raised neopterin of 205 nmol/L (normal <30). CSF culture and viral PCR were negative. Mycoplasma IgM was positive using complement fixation test and there was no hyponatremia. MRI of the brain revealed T2 high signal in right basal ganglia, both temporal lobes and in the right parietal lobe. Testing of her serum from the acute illness revealed positive VGKC-complex Abs at 421 pM (normal <100pM) but negative antibodies against CASPR2, LGI1, NMDAR and GAD.

Four months following her illness she was back to normal and continued to achieve developmental milestones appropriate to her age. She had no further seizures and her anti-epileptic drugs (AEDs) have been withdrawn.

This patient was positive for a known NSAb (VGKC-complex Ab) but did not receive immunotherapy therefore she has “probable” autoimmune epilepsy.

**3) Case 6: Limbic encephalitis with negative NSAbs**

A previously well 12 year old girl presented to the local hospital with frequent “funny episodes” over six week period. The episodes started with nausea followed by confusion and disorientation, and lasted 60-90 seconds. She had lethargy, intermittent headache and behaviour alteration with episodes of agitation, screaming and confusion. The episodes were initially thought to be psychological until an EEG performed four weeks after discharge showed epileptiform activity in the right temporal region and MRI brain then showed swelling in the right hippocampus . She was commenced on carbamazepine and referred to our hospital. She had ongoing temporal lobe seizures when she was reviewed at our hospital a few months after her acute illness. Repeated MRI scan at this time showed resolution of the right temporal lobe swelling and it was concluded that she had limbic encephalitis. Academic decline and emotional and behavioural abnormalities were reported, and neuropsychological testing showed difficulties in higher level thinking skills, attention, behaviour and emotional function.

Three years following her acute illness the seizures have settled and carbamazepine was stopped. Repeat neuropsychological assessment showed persistent cognitive impairment. Autoimmune screen showed very high ANA titres at 1: 2560 (normal <1:40) with a strong centromere staining pattern, although further immunological investigations and clinical assessments failed to confirm a diagnosis of systemic autoimmune disease. Antibodies against VGKC-complex, NMDAR and GAD tested on serum collected three years after onset of her seizures were negative.

This patient illness is consistent with autoimmune limbic encephalitis based on clinical presentation, MRI abnormality, and the associated high titre of ANA which supported an autoimmune tendency.

Despite the clinical suspicion of limbic encephalitis, using the classification she has “unknown” autoimmune epilepsy as she was NSAbs and GAD Abs negative and received no immunotherapy.

**4) Case 8: Fever-Infection Related Epilepsy Syndrome- FIRES**

A previously well three year old boy presented with fever and blanching rash for a few days followed by irritability and reduced level of consciousness. He was semi-comatose on presentation to hospital and required intubation and ventilation. He had status epilepticus with frequent and prolonged focal seizures which were refractory to AEDs.

CSF analysis revealed 4 white cells/mm3 and elevated neopterin at 264 nmol/L (normal <30). Extensive serological, microbial, metabolic and genetic testing did not reveal aetiology. EEG showed diffusely slow background with quasiperiodic multifocal high voltage epileptiform activity followed by periods of electrical attenuation and frequent multi-focal electrical and clinical seizures. MRI was normal apart from nonspecific signal abnormality in the white matter of the frontal and occipital lobes. Subsequent MRI showed loss of white matter volume and increased signal in the periventricular areas. Antibodies against VGKC-complex, LGI1, CASPR2, NMDAR and GAD were negative.

Intensive care treatment with multiple antiepileptic drugs and barbiturate induced coma as well as ketogenic diet did not help control his seizures. Early immunotherapy in the form of high dose intravenous pulse methylprednisolone at 30 mg/kg/day for three days followed by oral prednisolone for eight weeks and adjunctive intravenous immunoglobulin 2 g/kg followed by anti-CD20 antibody rituximab had no effect.

After 64 days in intensive care he was discharged to the ward, and continued to have refractory focal seizures and significant neurological impairment. He was discharged home after eight months. Sixteen months later he had severe cognitive and developmental impairment, refractory focal epilepsy on six AEDs and prolonged hypogammaglobulinemia presumed secondary to rituximab treatment and requiring IVIG replacement.

**5) Case 9: FIRES**

A previously well eight year old girl presented with high fever, headache and lethargy, confusion with altered level of consciousness and proceeded to have frequent focal seizures which evolved into generalised seizures requiring intubation and ventilation.

CSF analysis revealed 5 white cells/mm3 and elevated neopterin at 296 nmol/l (normal <30) but negative oligoclonal bands, viral PCRs and bacterial cultures. Extensive work up for infectious agents, immune screen and metabolic investigations were negative. Initial EEG showed diffuse high-voltage slowing consistent with encephalopathic process. Subsequent EEGs showed burst suppression, multifocal epileptiform activity and focal electrical seizures alternating from both hemispheres. Initial MRI was normal and subsequent acute MRIs revealed meningeal enhancement, patchy areas of cerebral oedema and high signal in bilateral thalami and hippocampi. Subsequent MRI showed global cerebral and cerebellar atrophy and periventricular white matter high signal.

Intensive care treatment with mechanical ventilation, thiopentone and multiple antiepileptic drugs did not control her seizures. She received ketogenic diet and electroconvulsive treatment (ECT) without effect. She was given high dose intravenous methylprednisolone 30 mg/kg/day over 3 days with negative response. No other forms of immunotherapy were given.

After eight months in intensive care she was discharged to the ward where she continued to have multiple daily focal seizures. She was discharged home after 20 months in hospital in vegetative state. Four years after her illness she remained in “minimally conscious state” with refractory focal seizures on multiple AEDs.

Retrospective testing of serum stored form the acute illness for antibodies against VGKC-complex, LGI1, CASPR2, NMDAR and GAD were negative.

Using the classification these two cases with FIRES have “unlikely” autoimmune epilepsy as they are negative for known NSAbs and GAD Abs and were unresponsive to immune therapy.

**6) Case 11: Epilepsy, type 1 diabetes mellitus (T1DM) and autoimmune thyroid disease**

A 13 year old girl with well controlled T1DM presented with early morning episodes of shaking lasting a few minutes and often followed by confusion and fatigue. She developed early morning myoclonic jerks in the absence of hypoglycaemia and some of the episodes were associated with loss of consciousness. At this time she was noted to have recent loss of weight and had tachycardia, hypertension and goitre on examination.

Thyroid function tests were consistent with hyperthyroidism. Thyroid antibodies were elevated including anti thyroglobulin antibodies 1314 U/ml (<60), anti thyroid peroxidise antibodies 105 U/ml (<35) and anti thyrotropin receptor antibodies 35.7 U/L (0 – 2). EEG showed generalised spike and wave discharges suggestive of idiopathic generalised epilepsy but MRI brain was normal.

She was diagnosed with Graves’ disease and juvenile myoclonic epilepsy (JME), commenced on carbimazole for the treatment of thyrotoxicosis and her epilepsy was successfully treated with AEDs.

Retrospective testing of her serum collected at the time of seizure onset was negative for VGKC-complex, LGI1, CASPR2, NMDAR and GAD antibodies.

This child had negative NSAbs and GAD Abs and received no immunotherapy and applying the guidelines she has “unknown” autoimmune epilepsy.

**7) Case 12: Anti MuSK myasthenia gravis and epilepsy**

A previously healthy three year old girl presented with a four month history of ptosis and non-conjugate eye movements with diurnal variation. Examination confirmed a fatigable ptosis and variable ophthalmoplegia, but no generalised muscle weakness. Mestinon test was associated with clinical improvement confirming the diagnosis of myasthenia. Serum AChR antibodies were negative however MuSK antibodies were positive with a titre of 0.87 nmol/L (normal <0.09). At the same time as the myasthenia she started to have staring episodes, occurring multiple times per day. Her EEG showed bilateral occipital epileptiform discharges (L>R) without photosensitivity consistent with a focal epilepsy. Her MRI brain was normal and autoimmune screen was negative. Antibodies against VGKC-complex, NMDAR and GAD were negative.

She was treated with carbamazepine and low dose oral prednisolone at 5 mg daily for four weeks with partial improvement then increased to 2 mg/kg/day with complete resolution of myasthenic and epileptic symptoms. Initial attempt to wean off steroid was associated with recurrence of ocular symptoms as well as seizures while she remained on AED thus steroids were weaned slowly over six months. After 17 months of disease, she is steroid dependent despite adding azathioprine, but her ocular myasthenia gravis and seizures are in remission. Long term steroid treatment was associated with behavioural adverse side effects.

Both the patient’s epilepsy and myasthenia gravis responded to immunotherapy particularly steroids. She was negative for NSAbs and GAD Abs and applying the guidelines to this case she has “possible” autoimmune epilepsy.

**8) Case 13 T1DM, Epilepsy, ataxia and high titre GAD antibodies**

A 4 year old girl with chronic ear infection, grommets, hearing impairment and speech delay presented with acute unsteadiness of gait, lethargy and irritability. She was febrile and had a rash thought to be consistent with a viral exanthem. She had difficulty obeying commands, was ataxic and had mild hand tremor; but no other focal neurologic findings.

MRI brain was normal and EEG showed paroxysmal epileptic discharges during sleep. CSF analysis showed no cells, normal glucose, protein and lactate and negative culture. Her symptoms recovered during her hospital stay over 5 days however she was noted to have infrequent staring episodes at the time of discharge. Her illness was thought to be consistent with an immune mediated ataxia with complete recovery.

Five years following her acute ataxia she presented with new onset T1DM. She was reassessed by her neurologist for concerns about ongoing absence episodes that were associated with eye deviation, and thought to be consistent with focal seizures. However, the events were infrequent and required no treatment. The child had cognitive impairment and was attending a support class at school. EEG was normal and Video EEG was not performed. Testing of serum collected at the time of onset of DM showed highly elevated GAD antibody titre at 3000 U/mL and negative antibodies against VGKC-complex, LGI1, CASPR2 and NMDAR.

Applying the guidelines this patient has “possible” autoimmune epilepsy as she was negative for NSAbs but positive for GAD Abs and received no immunotherapy.