Refractory chronic epilepsy associated with neuronal auto-antibodies: could perisylvian semiology be a clue?

Lisa Gillinder 1,2, Linda Tjoa 1,2, Basil Mantzioris 1,2, Stefan Blum 1,2, Sasha Dionisio 1,2
1 Mater Advanced Epilepsy Unit, Mater Adults Hospital, 2 Princess Alexandra Hospital, Department of Neurology, Brisbane, Australia

Received August 02, 2017; Accepted October 07, 2017

ABSTRACT – Aims. We report a case series of 10 patients with chronic medically refractory antibody-positive autoimmune epilepsy and assess their common clinical features. Immune-mediated seizures are most commonly reported in the context of encephalitis or encephalopathy, with few reports focusing on lone, chronic epilepsy in the outpatient setting. Our aim was to define the potential diagnostic clues that might be present in these cases, leading to consideration of an autoimmune cause of the epilepsy.

Methods. We performed a retrospective review of all patients presenting to the outpatient department of our unit who underwent autoimmune screening. All patients with chronic epilepsy and a positive result for an antibody known to be associated with epilepsy were included.

Results. Sixty-three patients underwent testing. Thirteen returned a positive result, however, only 10 of these were patients which chronic epilepsy who did not present with an acute illness. Common features in these cases included: perisylvian semiology, EEG abnormalities in the mid temporal region, normal or non-specific MRI findings, depression, and head injury.

Conclusion. In cases of medically refractory, lesion-negative epilepsy, with predominantly perisylvian semiology, clinicians should have a high level of suspicion for the diagnosis of autoimmune aetiologies and a low threshold to perform autoantibody screening. This is especially true if there are atypical electrographic findings, a previous history of head injury, or co-morbid depression.

Key words: autoimmune epilepsy, perisylvian semiology, insula, antiglycine antibody, GAD-65 antibody

Autoimmune epilepsy is an increasingly recognised entity, with many known causative antibodies now identified and a progressively broadening range of clinical presentations. It is now clear that these antibodies, while frequently producing an encephalopathic syndrome in addition to epilepsy, can also result in chronic epilepsy which
is not associated with the acute neuropsychiatric and behavioural changes or cognitive issues that have been classically described (Bakpa et al., 2016). Instead, these patients will present as chronic medically refractory epilepsies, of unknown aetiology, and be considered potential candidates for epilepsy surgery. The mainstay of clinical recognition for patients with autoimmune epilepsy remains based on peculiar presentations and encephalitic features in the acute setting (Baysal-Kirac et al., 2016). Several groups have published guidelines proposing clinical criteria for identification of these patients, however, these are all heavily weighted towards acute/subacute phenotypes (Irani et al., 2011; Zuliani et al., 2012; McKeon, 2017). In fact, there are no clear guidelines for the identification of cases of chronic autoimmune epilepsy, especially in the outpatient setting. Furthermore, there are no studies published in which the common elements seen in these cases have been analysed, especially in relation to seizure semiology, which is often the first clinical information obtained. The diagnosis of autoimmunity in these cases is especially important given that early identification and treatment in these cases produces better outcomes (Bakpa et al., 2016). Therefore, there is an obvious need for clarity in this area to define the clinical syndrome, making it easier to differentiate in the outpatient setting and facilitating faster detection and treatment.

We report a series of cases with immune-mediated seizures that presented with perisylvian semiology. Perisylvian epilepsy is rarely reported in the literature and results in semiology which commonly mimics seizures of mesial temporal epilepsy (Penfield and Herbert, 1954). However, there are certain aspects of the semiology which may be subtle, but specific enough to identify involvement of the perisylvian region. This, in turn, could provide a diagnostic clue to identify which patients are most appropriate for antibody screening, especially in the absence of neuroimaging abnormalities.

The perisylvian region is a unique area with a complex structure and high connectivity. It is comprised of the frontal, temporal, and parietal opercular regions, as well as the insula. These regions are highly integrated with numerous and versatile roles. Seizures arising from these areas can involve autonomic, gustatory, auditory, vestibular, somatosensory, and visceral features (Stefan and Buchfelder, 2007), which are outlined in Table 1. From this, it is easy to appreciate the complex nature of the symptomatology of this epilepsy and that many of these features would be easy to overlook in semiological classification, or even go unrecognised by both patient and clinician. The diversity of symptoms seen in perisylvian epilepsy are particularly attributable to the insula. It has been described as a limbic network integrator, allowing communication of pre-processed sensory, autonomic, and complex motor information between multiple networks (Augustine, 1996; Nieuwenhuys, 2012). We propose that a high level of clinical suspicion for the diagnosis of an autoimmune aetiology should exist for patients presenting with lesion-negative, chronic refractory epilepsy with predominantly perisylvian semiology. Furthermore, we speculate on the potential causes for this association, with a particular focus on the insula and the evolution of our understanding of its unique functions, principally related to its role in immunity.

**Methods**

A retrospective review of case data was performed for all patients presenting to the outpatient department of the Mater Epilepsy unit, a tertiary referral centre, who underwent autoantibody screening between May 2015 and May 2017.

**Table 1.** Summary of the semiological features of perisylvian seizures, which are largely classified into five groups.

<table>
<thead>
<tr>
<th>SOMATOSENSORY*</th>
<th>VISCERO-SENSITIVE</th>
<th>AUDITORY</th>
<th>LANGUAGE</th>
<th>AUTONOMIC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Parasthesias</td>
<td>Pharyngeal discomfort</td>
<td>Auditory hallucinations</td>
<td>Dysarthria</td>
<td>Tachycardia</td>
</tr>
<tr>
<td>Pain</td>
<td>Abdominal discomfort**</td>
<td>Palinaeousis</td>
<td>Dysphasia</td>
<td>Bradycardia</td>
</tr>
<tr>
<td>Warmth</td>
<td>Thoracic sensations</td>
<td>Tinnitus</td>
<td>Hyperventilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Taste</td>
<td>Vertigo</td>
<td>Hypoventilation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tenesmus</td>
<td></td>
<td>Piloerection</td>
<td></td>
</tr>
</tbody>
</table>

*Somatosensory symptoms may be unilateral or bilateral and localised or diffuse.

**Abdominal sensations are the most frequent cause of confusion with mesial temporal seizures, and comprise localised discomfort, rising sensation, nausea, constriction, or pain.
Case selection
Cases were considered for analysis in the study if they had chronic epilepsy (duration > two years at presentation to our unit) and underwent a panel of autoantibody screening. Patients were included if they returned a positive result with serum or cerebrospinal fluid (CSF) for any antibodies which have been previously described in cases of autoimmune encephalitis resulting in seizures. These being: anti-glutamic acid decarboxylase Ab (GAD-65), anti-N-methyl-D-aspartic acid Ab (NMDAR), anti-voltage-gated potassium channel Ab (VGKC) including LGI1 and CASPR2, anti-glycine Ab (GLY-R), and anti-neuronal nuclear/cytoplasmic antibodies (panel includes PCA-1/anti-Yo, PCA-2, ANNA-1/anti-Hu, ANNA-2/anti-Ri, anti-Ma, GABAa, GABAb, and AMPA). Cases with positive results for non-specific antibodies that have an unclear correlation with encephalidities and seizures were not included. These being: anti-nuclear antibody (ANA), extractable nuclear antigens (ENA), antineutrophil cytoplasmic antibody, and thyroid antibodies, including TPO and TGA. Patients were not excluded on the basis of neuroimaging findings or the presence of known risk factors associated with epileptogenesis. Only adult cases were considered in the analysis, and patients who were pregnant at the time of testing were excluded. Patients who had been diagnosed and treated in the acute phase of their illness were not included.

Data collection
A data search was performed using the electronic medical records system at our institution (Verdi, IP Health Pty Ltd, North Melbourne, Australia) and from the patient database held in the Advanced Epilepsy Unit, Mater Adult Hospital, Brisbane. Demographic information was collected and tabulated, including age at epilepsy onset, epilepsy duration, seizure frequency, current and prior antiepileptic drugs (AEDs), response to immunotherapy, epilepsy risk factors, prior autoimmune diagnoses, and the results of the antibody panel tested. A review of prior investigations was also performed to determine the specific seizure semiology in each case, the epileptic network, interictal abnormalities, and ictal onset patterns. Neuroimaging and neuropsychiatric data was also collected. Institutional approval was obtained.

Antibody testing
All patients had undergone plasma testing for intracellular anti-neuronal antibodies (including PCA-1/anti-Yo, PCA-2, ANNA-1/anti-Hu, ANNA-2/anti-Ri, anti-Ma, GABAa, GABAb, and AMPA) by indirect immunofluorescence using a composite slide of primary cerebellum/cerebrum and murine gastric tissues (Inova Diagnostics, USA). Anti-NMDAR antibodies were detected using a commercial assay containing four biochips of primate hippocampus, primate cerebellum, and NMDAR-transfected HEK293 cells and non-transfected control HEK293 cells (Euroimmun, Germany). Antibodies directed against VGKC were detected using a commercial radio-immunoassay (RSR, UK). This quantitative assay utilizes detergent-solubilized VGKCs extracted from rabbit brain tissue and complexed with 125 I-labelled α-dendrotoxin. Positive sera on the radio-immunoassay were then tested by indirect immunofluorescence on biochips of LG1 and CASPR2-transfected HEK293 cells (Euroimmun, Germany). GAD-65 antibodies were detected using a commercial quantitative immunoassay (RSR, UK). The assay utilizes GAD-65 coated onto the wells of an ELISA plate. Sensitivity was increased using a second step that included the addition of GAD-biotin and a streptavidin detection step. Results are expressed in U/ml. Anti-GLY-R antibodies were tested by the Oxford Neuroimmunology testing service, Oxford University Hospitals NHS trust (Oxford, UK).

Results
A total of 63 patients were identified who had undergone autoantibody screening. Thirteen of these returned a positive result in serum or CSF for one of the listed antibodies. Three were excluded as they had presented to hospital in the acute phase of an encephalitic illness and were formally diagnosed and treated during that admission. The demographics of the 10 cases (eight female) reviewed in this article are summarised in table 2. The mean age was 37 (range: 22-43 years). Mean duration of epilepsy was 14.2 years (range: 2-36 years). Risk factors for epilepsy were documented in seven cases. Five (50%) had prior head injury, however, the timing for three of the patients was unknown; these were all moderate impact (loss of consciousness but not brain injury). There were also four cases (40%) in which other autoimmune conditions were already diagnosed, including Cases 2 and 3 which had prior diagnosis of type 1 diabetes mellitus (T1DM) with GAD-65 antibodies present in CSF. Nine of the cases had already failed with three or more AEDs. All cases received immunotherapy and nine demonstrated partial or substantial reduction in seizure frequency. A significant reduction in seizure severity was observed for Case 8, although seizure frequency was unchanged. The response for Case 4 is still pending. A significant reduction in seizure severity was observed for Case 7, although reduction in seizure frequency was...
Table 2. Summary of patient demographics and clinical findings.

<table>
<thead>
<tr>
<th>PATIENT AGE</th>
<th>EPILEPSY DURATION (YEARS)</th>
<th>RISK FACTORS</th>
<th>SEIZURE FREQUENCY</th>
<th>ANTI-BODY</th>
<th>NETWORK</th>
<th>SEMIOLOGY</th>
<th>INTERICTAL FINDINGS</th>
<th>Ictal FINDINGS</th>
<th>IMAGING</th>
<th>PSYCHIATRIC CO-MORBIDITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>40</td>
<td>20</td>
<td>Head injury (moderate), hypothyroid</td>
<td>10/month</td>
<td>GAD</td>
<td>R insular-opercular</td>
<td>Slow R temporal SW R frontotemporal and temporal SW L mid temporal</td>
<td>33 seizures: R frontotemporal, non-localisable</td>
<td>Normal</td>
<td>Depression (severe)</td>
</tr>
<tr>
<td>2</td>
<td>43</td>
<td>27</td>
<td>Head injury (moderate), T1DM, Coeliac</td>
<td>8/month</td>
<td>GAD</td>
<td>Non-dominant insular-opercular</td>
<td>Slow L FCT Slow, generalised Slow R temp SW L temporal (complex), SW L parietal, SW R mid temporal</td>
<td>12 seizures: R mid temporal</td>
<td>Normal</td>
<td>Depression</td>
</tr>
<tr>
<td>3</td>
<td>41</td>
<td>13</td>
<td>T1DM</td>
<td>1/month</td>
<td>GAD</td>
<td>Non-dominant perisylvian</td>
<td>SW R mid temporal</td>
<td>No VEEG</td>
<td>Normal</td>
<td>Depression</td>
</tr>
<tr>
<td>4</td>
<td>38</td>
<td>3</td>
<td>Head injury (moderate) pernicious anaemia</td>
<td>300/month</td>
<td>Glycine</td>
<td>Non-dominant perisylvian</td>
<td>Slow L mid temporal</td>
<td>10 seizures: non-localisable, L mid temporal, 35 auras</td>
<td>Normal</td>
<td>Depression (severe)</td>
</tr>
<tr>
<td>5</td>
<td>41</td>
<td>36</td>
<td>Febrile seizures</td>
<td>30/month</td>
<td>Glycine</td>
<td>Non-dominant perisylvian</td>
<td>Slow bilateral temporal (independent), SW L mid temporal</td>
<td>4 seizures: non-localisable</td>
<td>R MTS</td>
<td>Nil</td>
</tr>
<tr>
<td>PATIENT AGE</td>
<td>EPILEPSY DURATION (YEARS)</td>
<td>RISK FACTORS</td>
<td>SEIZURE FREQUENCY</td>
<td>ANTIBODY</td>
<td>NETWORK</td>
<td>SEMIOLOGY</td>
<td>INTERICITAL FINDINGS</td>
<td>Ictal FINDINGS</td>
<td>IMAGING</td>
<td>PSYCHIATRIC CO-MORBIDITY</td>
</tr>
<tr>
<td>-------------</td>
<td>--------------------------</td>
<td>--------------</td>
<td>-------------------</td>
<td>----------</td>
<td>---------</td>
<td>-----------</td>
<td>----------------------</td>
<td>----------------</td>
<td>---------</td>
<td>----------------------------</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>Nil</td>
<td>1/month</td>
<td>GAD</td>
<td>Dominant temporal-opercular</td>
<td>Palinacousis (reflexive), Whole-body parasthesias, Déjà Vu, Water drinking, GTC</td>
<td>Slow L mid temporal</td>
<td>3 seizures: L mid temporal</td>
<td>Normal</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>7</td>
<td>26</td>
<td>Head injury (moderate)</td>
<td>12/month</td>
<td>Glycine</td>
<td>Dominant perisylvian</td>
<td>Somatosensory (feeling in head), Humming, Aphasia, Eye twiching</td>
<td>SW L mid temporal</td>
<td>2 seizures: L mid-temporal</td>
<td>Normal</td>
<td>Nil</td>
</tr>
<tr>
<td>8</td>
<td>35</td>
<td>Head injury (moderate)</td>
<td>12/month</td>
<td>NMDA</td>
<td>Dominant posterior perisylvian</td>
<td>Piloerection in both arms, Sensation in head, Verbalisation, fear</td>
<td>Slow L temporal SW L mid temporal</td>
<td>No VEEG</td>
<td>Normal</td>
<td>Depression, anxiety</td>
</tr>
<tr>
<td>9*</td>
<td>31</td>
<td>Nil</td>
<td>70/month*</td>
<td>GAD</td>
<td>Bilateral mesial temporal-insula-Heschl network</td>
<td>Auditory (musical) Experiential (déjà vu, jamais vu)</td>
<td>Slow L hippocampus, R hippocampus, amygdala, temporal pole, SW L hippocampus, amygdala, SW R hippocampus, amygdala</td>
<td>12 seizures on SEEG: bilateral mesial temporal-insula-Heschl network</td>
<td>L MTS</td>
<td>Depression</td>
</tr>
<tr>
<td>10</td>
<td>43</td>
<td>Nil</td>
<td>150/month*</td>
<td>VGKC</td>
<td>Perisylvian</td>
<td>Piloerection on either limb or hemibody, Parasthesias, GTC</td>
<td>Nil abnormalities</td>
<td>6 seizures: non-localisable</td>
<td>Normal</td>
<td>Depression</td>
</tr>
</tbody>
</table>

*Patient 9 was the only patient to undergo SEEG.

#Predominantly auras.

*sharp waves were predominantly low in amplitude.

SW: sharp waves; R: right; L: left; FCT: frontocentral and temporal; VEEG: Video-electroencephalogram; SEEG: stereo-electroencephalogram.

Moderate head injury indicated events causing loss of consciousness but not brain injury.
Table 3. Treatment and outcomes.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Current AEDs</th>
<th>Prior AEDs</th>
<th>Immunotherapy</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LTG 100 mg BD, LCS 100 mg BD, LEV 500 mg BD</td>
<td>TPM, OxC, CBZ, perampanel</td>
<td>IVIg Jan 2017, RTX July 2017</td>
<td>50% reduction</td>
</tr>
<tr>
<td>2</td>
<td>LTG 300 mg BD, TPM 100 mg BD, Pb 60 mg BD, CBZ 200/400 mg BD</td>
<td>CBZ, LEV, clobazam, VPA, OxC, GBP, LCS, ZNS, clonazepam, perampanel</td>
<td>IVIg Aug 2016, MMF Dec 2016</td>
<td>Seizure-free since commencing MMF</td>
</tr>
<tr>
<td>3</td>
<td>OxC 450 mg BD, Clonazepam PRN</td>
<td>VPA, LEV, CBZ, TGB, GBP, LTG, LCS, TPM, ZNS</td>
<td>IVIg Jan 2017, MMF July 2017</td>
<td>50% reduction since MMF</td>
</tr>
<tr>
<td>4</td>
<td>LEV 1.5 g BD, LCS 100 mg BD, OxC 300 mg BD, clobazam 10 mg BD</td>
<td>VPA, LTG, ZNS</td>
<td>IVIg March 2017, MMF July 2017</td>
<td>Pending further escalation</td>
</tr>
<tr>
<td>5</td>
<td>LCS 200 mg BD, LEV 1.5 g BD</td>
<td>CBZ</td>
<td>IVIg June 2016</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>6</td>
<td>LEV 1.5 g BD, CBZ 400 mg BD, VPA 500 mg BD</td>
<td>LTG, perampanel</td>
<td>IVIg April 2017</td>
<td>Seizure-free</td>
</tr>
<tr>
<td>7</td>
<td>LTG 200 mg BD, LEV 1.5 g BD, ZNS 100 mg BD, CBZ 400 mg BD</td>
<td>LCS, TPM, VPA, perampanel</td>
<td>IVIg May 2017</td>
<td>80% reduction</td>
</tr>
<tr>
<td>8</td>
<td>LTG 200 mg BD</td>
<td></td>
<td>IVIg May 2017</td>
<td>50% reduction</td>
</tr>
<tr>
<td>9</td>
<td>LEV 1.5 g BD, TPM 125/150 mg, LTG 100 mg BD, clobazam 10 mg BD, MAD</td>
<td>VPA, ZNS, CBZ</td>
<td>Steroids, IVIg, MMF, RTX June 2015, PLEX March 2017</td>
<td>70% reduction</td>
</tr>
<tr>
<td>10</td>
<td>LTG 100 mg BD</td>
<td>TPM, LEV</td>
<td>IVIg May 2017</td>
<td>70% reduction</td>
</tr>
</tbody>
</table>

Treatment response indicates % reduction in seizure frequency from before treatment to next review after starting treatment. AEDs were not titrated during commencement of immunotherapy. Dates indicate time of commencement for each treatment option.

LEV: levetiracetam; LTG: lamotrigine; LCS: lacosamide; TPM: topiramate; VPA: valproate; CBZ: carbamazepine; OxC: oxcarbazepine; ZNS: zonisamide; Pb: phenobarbitone; MAD: modified Atkins diet; IVIg: intravenous immunoglobulin; MMF: mycophenolate mofetil; RTX: rituximab; PLEX: plasma exchange.

less impressive. Intravenous immunoglobulin (IVIg) was administered in all cases according to our institutional protocol (induction dose: 2 g/kg in five divided doses; maintenance dose: 0.4 g/kg, once each month). MMF dosing was calculated by patient weight and adjusted according to lymphocyte count. Treatments and outcomes are summarised in Table 3. All patients were reviewed by the neuropsychiatrist and diagnosed according to Diagnostic and Statistical Manual (DSM) criteria. Psychiatric co-morbidity was found in eight cases (80%), all of whom had depression, and two cases were so severe that these patients had required inpatient treatment for suicidal ideation.

GAD-65 was present in five cases (50%), all with a titre >2,000 U/ml, GLY-R was positive in three patients (30%), NMDAR in one (10%), and VGKC (LG11) in one (10%). Malignancy was not found in any patients (this was excluded in all patients based on computed tomography of chest abdomen and pelvis, and ultrasound pelvis in females). Seven patients also underwent PET scanning. Lumbar puncture was performed in seven cases (all except Case 7, 8 and 10), however, CSF pleocytosis was only found in one case and oligoclonal...
bands were detected in trace amounts in three cases. Protein was normal in all cases. There were no cases in which antibodies were detected in serum but absent in CSF. ANA was detected in Case 5, with GLY-R positivity (titre: 160). TPO was detected in Case 2 and 3, both with GAD-65 positivity (titres: 768 and 208, respectively). All cases had chronic refractory epilepsy with predominantly perisylvian semiology. The dominant features included laryngeal sensation (parasthesias), auditory hallucinations, piloerection and autonomic symptoms, and whole-body somatosensory symptoms. This is outlined in table 2.

Mean seizure frequency was 59 seizures per month (range: 1-300/month). There were interictal abnormalities in the mid temporal region for all cases except Case 10, in which there were no abnormalities. These changes consisted of slowing and epileptiform discharges, often in the mid temporal region and were found bilaterally in three patients (30%). Interestingly, in seven of the cases, there were either no interictal epileptiform discharges, or when they occurred they were small in amplitude. These changes are detailed in table 2. Seizures were captured in eight patients with findings consisting of either temporal onset, frontotemporal onset, or non-localisable ictal onset. One case (Case 9) underwent SEEG evaluation which showed a bilateral mesial temporal - anterior insula - Heschl’s gyrus network, with primarily perisylvian semiology (auditory hallucinations). Observationally, many of these seizures had similarities on scalp EEG. The activity was often seen as a low-amplitude, theta/alpha-band discharge and evolved maximally in the mid temporal region on either side. An example of this is shown in figure 1.

Neuroimaging findings were either normal or non-specific in eight cases. There were two cases of mesial temporal sclerosis. The first was Case 9 (discussed above) and the other had epileptiform abnormalities originating from the contralateral temporal region to the MRI abnormality (Case 5). All patients underwent epilepsy protocol MRI brain sequencing on a 3T scanner.

Of the 50 patients who were tested but did not return a positive result, this was confirmed in CSF in 18 patients. The indications for testing were broad. The most common indication was for chronic epilepsy with atypical features (44 cases). These included: semiology not localisable to one region, frequent seizures, bilateral or multifocal seizure onset, lack of interictal epileptiform abnormalities, or non-localisable seizure onset. Testing was also performed commonly when a patient had a comorbid psychiatric diagnosis, especially if multiple psychiatric diagnoses were present. This included psychosis (six cases), dissociative attacks (seven cases), and/or depression (11 cases). There were also three cases with established autoimmunity of other organ systems that were tested. Six cases were tested for other non-epileptic indications including stiff person syndrome, myoclonus, and spasticity. In eight cases, there was a prior history of head injury (16%).

The most common seizure classification in the chronic epileptic group was temporal (25 cases), however, these were often reported as network epilepsies. There were five cases with either perisylvian or opercular epilepsy, however, again, four of these were networks that involved other regions (frontal or temporal) and perisylvian features were not the dominant semiology.
Discussion

Clinical features of an immune-mediated epilepsy phenotype

In this study, we have specifically analysed the common elements in seizure semiology for patients presenting with chronic autoimmune epilepsy. Semiology analysis is a powerful clinical tool that is an important piece of the puzzle for identifying the epileptogenic zone (Bancaud, 1980; Tufenkjian and Luders, 2012). In the outpatient setting, this approach may help to rapidly identify patients appropriate for autoantibody screening.

While the appreciation of underlying anatomical networks corresponding to seizure semiology is very complex and may be overlooked, our findings highlight the importance of considering these clinical features, particularly looking for markers of perisylvian involvement. There are still issues with a lack of standardisation, and variation can exist between clinicians (Tufenkjian and Luders, 2012). This is further complicated by semiological mimicry due to perisylvian-temporal networks (Penfield and Herbert, 1954). However, identifying the specific features highlighted above allows more accurate epilepsy classification, and this differentiation in patients with chronic autoimmune epilepsy will allow early intervention and the avoidance of potentially unnecessary invasive investigations or even surgery.

It is not uncommon that research in autoimmune epilepsy has led to reports of EEG abnormalities in the temporal region, and our study has been no different (Dubey et al., 2015; Malter et al., 2016; von Rhein et al., 2017). Of particular interest in the cases identified here are the electrographic features of these abnormalities. Many had either no interictal epileptiform discharges, or if present had a characteristic low-amplitude, mid temporal focus. These findings would be atypical for mesial temporal epilepsy. Furthermore, seizure onset was commonly accompanied by a low-amplitude discharge and was mid temporal in location or non-localisable, which is again atypical. This may indicate that the epileptogenic zone is located in a deep mesial structure and may mimic a temporal onset. Considering the complex anatomical arrangement of this area, it is not necessarily the case that all abnormalities in this region are attributable to structures in the temporal lobe itself. Furthermore, in much of the current literature, there is a paucity of information regarding how the diagnosis of “temporal lobe epilepsy” was formulated. If the diagnosis was based primarily on interictal or ictal abnormalities from this region, it is conceivable that extra-temporal regions may not have been appreciated. We know that abnormalities arising from the insula-opercular region will also create EEG abnormalities in the mid temporal region, thus not all temporal abnormalities can be considered synonymous with “temporal lobe epilepsy” (Munari et al., 1980). Additionally, the perisylvian structures are highly connected to the mesial temporal region and limbic network, so their involvement in such epilepsies would not be unexpected (Ostrowsky et al., 2000).

Neuroimaging is of varying clinical utility in these cases. A review by Bakpa et al. (2016) of the diagnostic features of various antibody associated epilepsies found that MRI brain findings were either normal or demonstrated non-specific changes in the mesial temporal lobe (Bakpa et al., 2016). However, again, much of these data is taken from patients presenting in the acute phase of an encephalitic illness. In our cohort, there were two cases with mesial temporal sclerosis. The remainder of our cases had essentially normal MRI scans. This suggests that routine MRI has limited clinical utility for the diagnostic exclusion of autoimmune epilepsy in the chronic setting.

The cases reviewed in our series were chronic and refractory in nature. Conversely, the bulk of the literature published to date has focussed on acute subacute presentations with an encephalopathic/encephalitic prodrome. Clinical criteria for identifying such patients is strongly weighted towards the identification of acute cases (Irani et al., 2011; Zuliani et al., 2012; McKeon, 2017). This highlights the need for another set of criteria, specifically targeted to identify this separate subset of patients who do not present in the classic way. When taken together, the features outlined above might represent an electroclinical syndrome which potentially indicates an underlying autoimmune process. We propose that an autoimmune aetiology should also be suspected in cases of chronic refractory lesion-negative epilepsy, with a perisylvian semiology, even in the absence of encephalopathy or prior encephalitis.

Interestingly, there was also a high prevalence of depression in our patients. It has been long established that patients with epilepsy have higher rates of depression. However, rates reported in the literature range from 9 to 37% (Kwon and Park, 2014), and in the cohort which tested negative to antibodies, this was 25%. In the antibody-positive cohort, 80% of cases were affected, two of which had major depressive episodes. The literature also reports a relationship between seizure frequency and depression, however, this was not demonstrated in our cohort. It seems possible that, although patients presenting with autoimmune epilepsy within this part of the spectrum do not suffer acute neuropsychiatric, behavioural, and cognitive changes, there may still be an element of this
as part of the condition, such that refractory epilepsy with comorbid depression may represent a syndrome of chronic autoimmunity. The insula, which is located in the perisylvian region, has been increasingly implicated in the pathophysiology of depression, and might, at least in part, explain this association (Nagai et al., 2007).

The prevalence of comorbid autoimmunity has been previously described and was a common feature in four of our cases (Vincent and Crino, 2011). Two of these had pre-existing T1DM, but were subsequently found to have GAD-65 antibodies in CSF. This is not a novel finding, and in fact the development of epilepsy has even been documented in a case with long-standing GAD-65 antibodies but no clinically evident endocrinopathy or encephalitis (Fauser et al., 2015). This perhaps suggests a second hit is required to allow passage of antibodies intrathecally. Similar suggestions have been made regarding the pathophysiology of NMDAR encephalitis, that the passage of autoantibodies occurs via damage to the blood/brain barrier (BBB) (Martinez-Hernandez et al., 2011).

The perisylvian region, a unique island within the brain

The cases presented here demonstrate diverse and rich semiology, which is typical of perisylvian epilepsies. The broad range of symptoms seen in perisylvian epilepsy is attributable to the abundant functions and connections of this area, particularly the insula. The insula is still not fully understood, and further studies continue to explore this diversity. It has been described as a limbic network integrator, allowing communication of pre-processed sensory, autonomic and complex motor information between different networks (Augustine, 1996). This is supported by invasive studies using SEEG and cortical stimulation, which reveal a wide range of clinical symptoms that can be elicited by stimulation of the insula, as it synchronises with its network connections (Penfield and Herbert, 1954). Connectivity studies of both human insula efferents confirm this structure to be a major multi-modal network hub within the cerebral cortex (Almashaikhi et al., 2014). The sheer amount of connections explains the complex neurophysiological function and that it is a key region involved in both functional and effective connectivity (Almashaikhi et al., 2014).

A more novel concept is the insula’s role in immunity. There has been evidence for some time that the insula is critically involved in conditioned immunosuppression and that this region is involved in the neuronal mechanisms important for evoking an immune response (Ramirez-Amaya et al., 1996, 1998). More recently, there has been a number of studies suggesting that the insular cortex is also involved in perception and transmission of information from the peripheral immune system (Harrison et al., 2009; Serrats et al., 2010; Doenlen et al., 2011; Kullmann and Schedlowski, 2011; Hannestad et al., 2012). Other studies have demonstrated that systemic inflammation has direct physiological effects on the insular cortex, inducing rapid changes in microstructure and metabolism (Harrison et al., 2009; Hannestad et al., 2012; Benson et al., 2015; Karshikoff et al., 2016). How this is mediated remains unclear, but it has been postulated to involve both autonomic and neuroendocrine pathways via the hypothalamic pituitary axis (Ader et al., 1995). However, given the consistent involvement of the insular-opercular areas in the autoimmune epilepsies reviewed in our series, it seems possible that there is a more direct immunological communication with this area, which when disrupted could result in area-specific autoimmunity. A more controversial idea would be that an affected insula could in fact upregulate auto-destructive antibodies by aberrant signalling to the immune system. Both ideas are of course speculative and require further targeted research.

Another common element in the cases reviewed in our series was prior brain insult. This might explain how antigenic exposure and immune sensitisation is occurring in these patients. In the normal brain, the BBB is protective, preventing the passage of immune cells and antibodies into the brain parenchyma. Where there is BBB disruption, there can be infiltration of these cells leading to inflammation and autoantigen exposure. This has been demonstrated in patients with Herpes encephalitis, which leads to development of NMDAR antibodies (Arangue et al., 2014, 2015). Furthermore, in animal studies, it has been shown that sensitised T cells can increase BBB permeability, ultimately compounding the problem (Lassmann et al., 1988). Currently, the evidence for this is not well established enough to draw conclusions. Furthermore, this relationship in epilepsy is unclear. Head injury is a known risk factor for epilepsy and this finding on its own cannot be causally linked. However, this was less common in the antibody-negative group, occurring in only 16% of cases.

Accumulation of insults might result in a multi-hit model of disease acquisition and could explain prior findings that antineuronal antibodies exist in a certain percentage of patients that do not express the typical diseases associated with them (Hammer et al., 2014). There is also evidence to suggest that the presence of antibodies, especially to intracellular targets, represents an epiphenomenon of another disease process (Fang et al., 2017). If this is the case, then the remaining question is which one of these insults predisposes the perisylvian region to be affected in autoimmune
epilepsy. Is the BBB in this location more susceptible to injury, or do immune cells aggregate here due to some structural or anatomical difference? Or perhaps there is some more specific difference in the insula, which is involved in its immunological communication that also makes it more susceptible to immune attack. This might explain why in other immune-mediated conditions such as Rasmussen’s encephalitis and FIRES, inflammation is seen to begin in the perisylvian region (Nabbout et al., 2011; Varadkar et al., 2014). It might also provide insights into other observations in immuno-mediated conditions, such as multiple sclerosis, in which epilepsy is seen to occur most commonly in patients with lesions in the insula and mesial temporal regions (Rizzi, 2009).

Limitations

There are some clear limitations of this study due to its retrospective design and small sample size. We have included a heterogeneous group of seropositive patients with a diversity of neuronal autoantibodies. We have not considered antibody-negative cases with presumed limbic encephalitis, cases presenting in the acute phase, or cases of non-specific antibody positivity. Our results are based on observational data and these findings need to be confirmed in a prospective controlled trial with systematic testing and analysis of a large group of patients. This would also help confirm the possible associations with head injury and increased rates of depression. These findings in epilepsy are not an uncommon constellation, and the link with autoimmunity in these cases remains unclear.

Conclusion

In cases of medically refractory, lesion-negative epilepsy, with predominant perisylvian semiology, clinicians should have a high level of suspicion for the diagnosis of autoimmune aetiologies and a low threshold to perform autoantibody screening. This is especially true if there are electrographic abnormalities in the mid temporal region, a previous history of head injury, or co-morbid depression.

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

Acknowledgements and disclosures.
Kirsty Rickett, Librarian, University of Queensland, Mater Adults Hospital.
Nicholas Murray, Research assistant, Mater Advanced Epilepsy unit, Mater Adults Hospital.
None of the authors have any conflict of interest to declare.

References


Chronic autoimmune epilepsy


Rizzi R. Cortical-subcortical lesions near the temporal pole, the medial temporal and the insular cortex are associated with epileptic seizures in patients with MS. *Epilepsia* 2009; 50: 54.


