Journal of Neuroimmunology 330 (2019) 44–47

Contents lists available at ScienceDirect

Journal of Neuroimmunology

journal homepage: www.elsevier.com/locate/jneuroim

Short communication

Electroclinical insights into autoimmune epilepsy

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ARTICLE INFO

Keywords:
Stereo electroencephalography
Autoimmune
Epilepsy

ABSTRACT

Purpose: Chronic autoimmune epilepsy is an increasingly recognised entity however its clinical and electrographic features remain poorly understood. We present a case undergoing diagnostic Stereo-electroencephalography implantation that was found to have a multifocal perisylvian epilepsy with unique electrographic features and is now seizure free with immunotherapy.

Methods: The patient had antibody negative refractory perisylvian epilepsy and underwent implantation of the perisylvian-temporal networks. Immunomodulatory treatment was administered during SEEG.

Results: SEEG demonstrated a multifocal perisylvian epilepsy with strong involvement of the posterior insula. There was almost continuous spiking seen interictally from multiple foci within the right hemisphere and independent seizures were generated from 5 locations. After treatment with intravenous methylprednisone and immunoglobulin during SEEG, spiking and seizures terminated while still off anti-seizure medications. The patient remains seizure free on immunotherapy.

Conclusion: This case highlights the importance of considering autoimmunity in the differential diagnosis of refractory epilepsy, especially perisylvian epilepsy. It also highlights the need to define a clinical phenotype associated with autoantibodies in epilepsy, as there are likely many cases who are not positive for one of the commercially available tests. This case also provides insights into the possible features of an electroclinical syndrome associated with autoimmunity.

1. Introduction

Chronic autoimmune epilepsy is an increasingly recognised entity however its clinical and electrographic features remain poorly understood. There are many antibodies associated with epileptogenesis, however this is typically recognised to cause an acute encephalopathic/encephalitic syndrome (Bakpa et al., 2016). However, patients can also present as chronic medically refractory epilepsy of unknown aetiology.

We present a case undergoing diagnostic Stereo-electroencephalography (SEEG) implantation which demonstrated multifocal perisylvian epilepsy with unique electrographic features and is now seizure free with immunotherapy.

2. The case

A 28-year-old female presented with 13 years of epilepsy. Seizures began with a metallic taste, feeling of rapid internal body movement, nausea and an abdominal sinking feeling. There could also be déjà vu, with a dream-like quality. There was also a second but less common seizure type which caused bilateral hand and perioral paraesthesia's which progressed to anarthria and gagging. This semiology type began only after several years of epilepsy. Seizures occurred monthly. There were no other symptoms at disease onset, specifically no neuropsychiatric changes, fevers or viral prodrome, movements disorder or autonomic changes.

Background was complicated by severe depression and prior deliberate self-harm. Current anti-seizure medications were levetiracetam 1 g twice daily, carbamazepine controlled release 400 mg twice daily, lamotrigine 100 mg twice daily.

Video Electroencephalography captured 4 seizures of her typical semiology and secondary generalisation with signs of right hemisphere lateralisation. Importantly interictal sharp waves and spikes were absent. MRI and Voxel Based Morphmetry were unrevealing. An FDG-PET scan demonstrated hypometabolism in the right temporo-perisylvian region. Neuropsychology was normal.

Given the strong perisylvian features she underwent autoimmune screening after presentation to our service (Gillinder et al., 2017). Serology revealed non-specific findings: ANA titre 1:80, TPO 304 IU/mL and CRP 15 mg/L. Cerebrospinal fluid (CSF) was also non-specific (white cell count 8, OCB + ve, protein 300 mg/L). Intracellular antineuronal antibodies (including PCA-1/Anti-Yo, PCA-2, ANNA-1/Anti-Hu, ANNA-2/Anti-Ri, anti-Ma, GABAa, GABAb, AMPA1/2), anti-*N*-

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https://doi.org/10.1016/j.jneuroim.2019.02.005
Received 3 January 2019; Received in revised form 14 February 2019; Accepted 14 February 2019

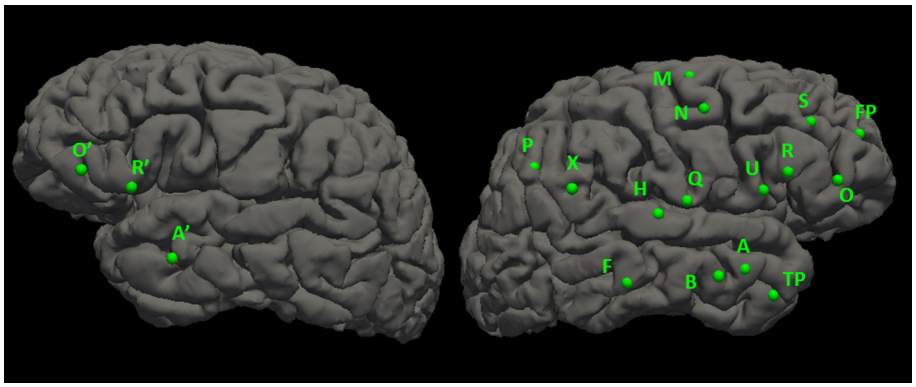

Fig. 1. SEEG implantation surface map representing lateral electrode locations.
Electrode coding: O – Orbitofrontal, FP – Frontal pole, S – Cingulate gyrus, R – Anterior Insula, U – Anterior Insula, Q - Posterior Insula, X – Posterior cingulate, P – Precuneus, N – Pre-Supplementary motor area, M – Mid-Cingulate sulcus, TP – Temporal pole, A – Amygdala, B – Hippocampus, F – Fusiform Gyrus, H – Heschl's Gyrus. STG – superior temporal gyrus, MTG – middle temporal gyrus. 'indicates left sided electrodes. Full electrode contact map is located in reference (Gillinder, 2019).

methyl-D-aspartate receptor antibody, anti-Voltage Gated Potassium channel antibody (including LG1 and CASPR2), anti-glutamic acid decarboxylase antibody, anti-Glycine receptor antibody and Dipeptidyl-peptidase-like protein 6 antibody were not detected in serum or CSF and decision was made to progress to SEEG.

2.1. SEEG

The patient underwent bilateral temporo-perisylvian implantation and was recorded for 5 days off medications. The Implantation surface map is seen in Fig. 1 (and full SEEG map in print (Gillinder, 2019)). Interictal abnormalities were most prominent in the right perisylvian region and were seen independently with a highly localised field (Fig. 2A). This manifest as almost continuous independent multi-regional slow repetitive spiking (1 Hz). The spiking seen in the posterior insula was the only activity to spread to other regions (anterior insula, insula apex). Frequent repetitive spiking also affected the right temporal operculum, posterior middle temporal gyrus (MTG) and the supramarginal gyrus (SMG). Of note there was no epileptic fast activity seen in the insula or elsewhere.

Frequent non-clinical seizures were recorded which could continue for a prolonged period. When progressing to clinical symptoms these were consistent with the two seizure types described from the history and clinical onset of both semiologies coincided with seizure spread to the posterior insula despite EEG onset arising from different locations. Both seizure types could result in secondary generalisation after many minutes.

The ictal EEG revealed a multifocal epilepsy in the right hemisphere. Independent seizures were seen to arise from the right posterior insula, temporal operculum, posterior MTG and SMG (Fig. 3). These all began with slow repetitive spiking in a highly restricted area. After many minutes this would spread to other regions. Despite arising from different locations, all foci spread to affect the posterior insula which coincided with clinical symptoms. Even the seizures arising from the posterior insula began with slow repetitive spiking, evolving over many minutes, and did not involve fast activity (Gillinder, 2019). The left hemisphere electrodes were not affected by slowing or epileptiform activity.

2.2. Treatment

Due to multifocality this epilepsy was determined to be non-operable. Given the atypical electrographic patterns and strong perisylvian involvement, intravenous methylprednisone (IVMP) and IVIg were administered before explantation. After 24-h the degree of spiking from each region was significantly reduced (Fig. 2B). No anti-seizure

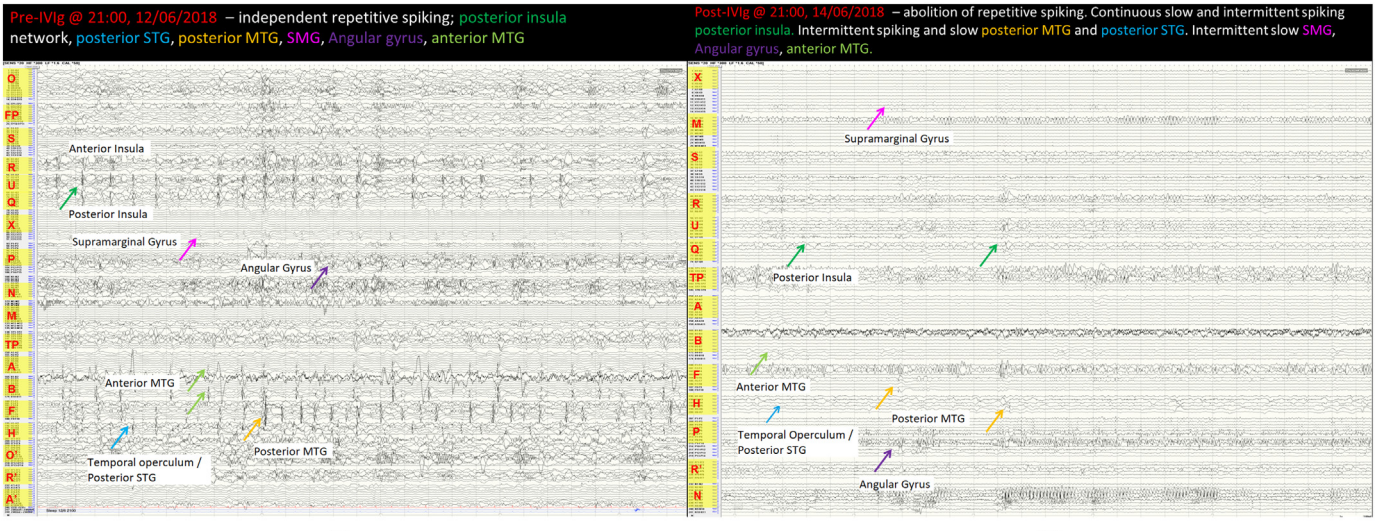

Fig. 2. Interictal pages. A) Multiregional epileptiform abnormalities within the right hemisphere with almost continuous slow repetitive spiking. B) Resolution of epileptiform activity 24 h post treatment with intravenous immunoglobulin and methylprednisone while still of anti-seizure medication.
Electrode coding: O – Orbitofrontal, FP – Frontal pole, S – Cingulate gyrus, R – Anterior Insula, U – Anterior Insula,Q - Posterior Insula, X – Posterior cingulate, P – Precuneus, N – Pre-Supplementary motor area, M – Mid-Cingulate sulcus, TP – Temporal pole, A – Amygdala, B – Hippocampus, F – Fusiform Gyrus, H – Heschl's Gyrus. STG – superior temporal gyrus, MTG – middle temporal gyrus. 'indicates left sided electrodes. Full electrode contact map is located in reference (Gillinder, 2019).

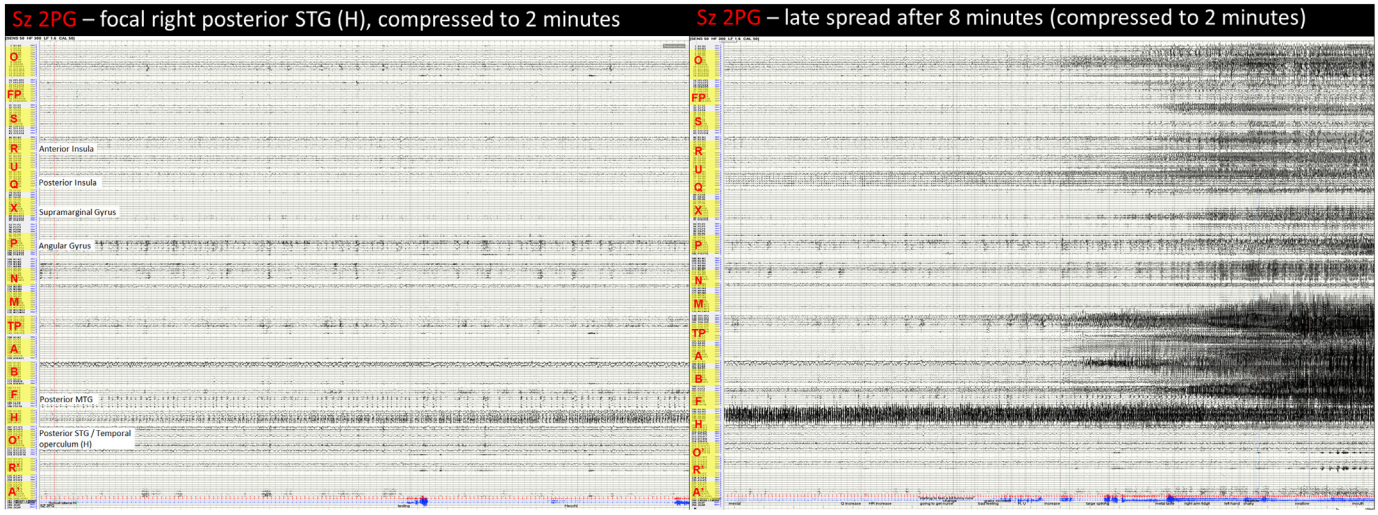

Fig. 3. Seizure arising in the right temporal operculum/posterior superior temporal gyrus, beginning with slow repetitive spiking which remains localised and does not spread to affect other regions for many minutes.
Electrode coding: O – Orbitofrontal, FP – Frontal pole, S – Cingulate gyrus, R – Anterior Insula, U – Anterior Insula, Q - Posterior Insula, X – Posterior cingulate, P – Precuneus, N – Pre-Supplementary motor area, M – Mid-Cingulate sulcus, TP – Temporal pole, A – Amygdala, B – Hippocampus, F – Fusiform Gyrus, H – Heschl's Gyrus. STG – superior temporal gyrus, MTG – middle temporal gyrus. 'indicates left sided electrodes. Full electrode contact map is located in reference (Gillinder, 2019).

medications were given during this time. The patient continues to have 3 days of 1 g IVMP every 3 months and 24 g IVIg every two weeks. She is now over 6 months post SEEG and remains seizure free. Her mood disorder has also improved.

3. Discussion

Multifocal seizure onset and slow repetitive spiking were striking features of this epilepsy which profoundly improved after administration of immunotherapy while still off anti-seizure medications. This epilepsy strongly involved the perisylvian region, particularly the posterior insula. These features are unique and provide potential insights into the nature of the aetiology of this epilepsy.

There were many foci which were affected independently within a defined region of the right hemisphere involving and surrounding the perisylvian structures. Both interictally and at seizure onset, these regions would be affected by highly localised activity that was seen universally as slow repetitive spiking, with no fast activity and would increase very gradually and only spread after many minutes. This is unusual for these regions, particularly the insula, which has highly connected networks and often spreads rapidly and generates very fast frequencies given its ability to support a wide bandwidth (Laoprasert et al., 2017). Furthermore, all of the seizures spread to the posterior insula, resulting in clinical symptoms. While the left hemisphere electrodes were not affected, it is possible given the highly localised features seen in the right hemisphere that there were epileptiform changes in the left hemisphere that were not detected with only sentinel electrodes.

Prior to SEEG, autoimmunity was considered, however neuronal autoantibody testing was negative. Findings on serology and CSF, which while non-specific, could implicate an inflammatory process in the aetiology of this epilepsy. Non-specific antibodies (ANA, TPO) are unlikely to be directly pathogenic, however may represent an epiphenomena or marker of autoimmunity (Miro et al., 2014). When administered IVMP and IVIg while still off anti-seizure medications there was a profound improvement in the EEG. This further supports the hypothesis that inflammation and/or autoimmunity is implicated in the pathogenesis of this epilepsy. Alternatively, it is possible that there is an underlying neuroinflammatory process present in many epilepsies that instead of being implicated in the pathogenesis might be responsible for ongoing maintenance of epileptogenesis. Therefore, while this epilepsy responded to immunotherapy, it does not confirm autoimmunity as the aetiology. There have been reports of seizure improvement with the use of steroids/IVIg, however, this has been predominantly in specific childhood syndromes or refractory status epilepticus and was not confirmed in reviews (Geng et al., 2017; Ozkara and Vigevano, 2011). This will only be clarified by further studies.

The understanding of autoimmune epileptogenesis remains poor, however this case potentially provides some insights. There is increasing evidence in the literature that perisylvian symptoms can be a feature in autoimmune epilepsy without encephalitis, and this case supports that association (Gillinder et al., 2017; Baysal-Kirac et al., 2016; Steriade et al., 2018). There is a paucity of intracranial recordings in cases of autoimmune epilepsy and encephalitis. The unique features which were most prominent in this case were its multifocality and the appearance of slow repetitive spiking. While further data is required to make any conclusions, such features might provide clues for a unique electroclinical syndrome associated with autoimmunity. It is possible that autoantibodies can directly modulate neuronal activity and connectivity resulting in epileptogenesis. This might be explained by a synaptopathy which has been implicated in encephalidities (Crisp et al., 2016). It might also explain how the effect is reversible with immunotherapy. Alternatively, the finding of autoantibodies in cases of chronic isolated epilepsy without features of encephalitis might suggest that neural autoimmunity can occur as a chronic ongoing process rather than an acute one, and that autoantibodies might not be directly epileptogenic but that epileptogenesis might be secondary to immune mediated neuronal damage. It is also possible that autoantibodies are generated by chronic refractory seizures and antigenic exposure from blood brain barrier breakdown, resulting in secondary epiletogenesis but are not the primary aetiology. Regardless, a diffuse process could explain how multiple cortical regions are affected simultaneously as seen in this case. This pattern has also been seen in Rasmussen's encephalitis (Varadkar et al., 2014). Why the perisylvian region is implicated and what predisposes it to immune attack is unclear, however there are many unique features of this region which might provide clues.

Surgery is unlikely to be successful in this case (Carreno et al., 2017). Resection of the insula seems imprudent, despite it being the most strongly affected region and responsible for clinical symptoms.

Firstly, it is unlikely to result in seizure freedom, as there are many other active epileptogenic foci which will continue to generate seizures after insula resection. Secondly, epilepsies with multiple recorded ictal patterns, such as this one, and partial resections and have been shown to result in increased rates of GTC seizures post operatively (Sarkis et al., 2012). This phenomenon is thought to be related to modulation of the seizure propagation within the established network, resulting in spread to other regions, particularly suprasylvian regions which are more likely to cause GTC. Also of note, it is possible that an ongoing immune mediated process may lead to secondary epileptogenesis which will not respond to immunotherapy and hence it is essential these cases are identified early and managed appropriately (Gillinder et al., 2018).

4. Conclusion

This case highlights the importance of identifying a clinical syndrome in epilepsies where autoimmunity might be implicated in pathogenesis and supports the hypothesis of perisylvian involvement in autoimmunity. Defining a clinical syndrome is essential to ensure patients are managed appropriately and have the best chance at achieving seizure freedom. There are likely other cases such as this, who are not positive for commercially available tests, and serology alone cannot be relied upon for diagnosis.

Ethical statement

We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Disclosure

None of the authors report any disclosures.

No funding was received for this trial.

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