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Clinical-radiological-pathological correlation in an unusual case of refractory epilepsy: a two-year journey of whodunit!

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ABSTRACT – New-onset refractory focal epilepsy poses significant challenges to the clinician in the absence of specific diagnostic biomarkers. Differential diagnoses based on imaging may be expanded by a veritable spectrum of peri-ictal imaging findings that may mask the underlying substrate. We report a 13-year-old girl who presented with refractory focal seizures of left parieto-occipital origin with cytotoxic gyral oedema noted over the same region on imaging. Despite an initial negative autoantibody profile, the patient was treated with immunosuppression, followed by serial relapses requiring immune-modulation. Over the next year, her syndrome persisted as focal left posterior cortex epilepsy that necessitated occipital lobectomy, following a relapsing-remitting radiological profile, consistent with peri-ictal MRI changes. Histopathology was inconclusive for any definitive substrate. After a period of quiescence, she developed focal motor seizures of right hemispheric origin with progressive encephalopathy, at which point a repeat cerebrospinal fluid anti-N-methyl-D-aspartate receptor antibody profile returned positive. The patient was managed with steroids and rituximab with a good clinical outcome. We hypothesise that persistent or relapsing-remitting focal gyral oedema in unexplained refractory focal epilepsy mandates consideration of focal encephalitis secondary to autoimmunity, and late appearance of intrathecal auto-antibody synthesis correlates with evolution into a more diffuse disease.

Key words: refractory focal epilepsy, peri-ictal oedema, N-methyl-D-aspartate receptor (NMDAR) antibody, focal encephalitis pathology

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Despite major advances in the areas of multimodal neuroimaging, a significant subset of patients with new-onset refractory focal epilepsy is deemed cryptogenic. With an expanding spectrum of clinical manifestations, autoimmune epilepsies pose a major challenge for diagnosis, especially when available investigating modalities show conflicting results (Armangue *et al*., 2013). We present this serial radiopathological study to highlight the dynamic evolution, diagnostic and management dilemmas in a case of *de novo* refractory focal epilepsy.

Case study

A 13-year-old girl with no antecedent illness, developed recurrent complex partial seizures in December 2013, characterised by visual aura of coloured halos over the right visual field and right focal motor seizures, with and without impaired awareness, with frequent secondary generalisation. Following the seizures, right hemianopia and subtle right hemiparesis was noted. Based on the initial MRI, she was treated at a local hospital with a course of acyclovir along with antiepileptics. However, following a period of quiescence for two months, she suffered a relapse of her seizures after which she was referred to our comprehensive epilepsy care in February 2014. Neurological examination at presentation revealed congruous right homonymous hemianopia with impaired left-sided pursuit and right hand epilepsia partialis continua (EPC). The investigation results are detailed in *table 1*. Based on the electro-clinico-radiological findings, the possibility of focal encephalitis of possible autoimmune aetiology was entertained first and foremost while considering a radiological differential of a focal cortical dysplasia (FCD) with peri-ictal changes. A five-day course of intravenous methyl prednisolone followed by oral prednisolone was initiated. MRI after one month revealed reduction in cortical hyperintensities, gyral oedema, as well as improved perfusion patterns. Although she remained cognitively intact, she had serial relapses with admission for simple and complex partial status epilepticus/seizure clusters despite maintenance on oral prednisolone, trials of intravenous immunoglobulin, and mycophenolate mofetil as a steroid-sparing agent. The serial images during these periods are shown in *figure 1A-C*. During a relapse in November 2014 with persistence of right hemianopia, despite adequate immunosuppression, MRI demonstrated reappearance of cytotoxic oedema over the left posterior cortex (*figure 2A*). At this juncture, we retained consideration of antibody-negative focal encephalitis, including an atypical and highly focal presentation of Rasmussen's encephalitis versus FCD. Electro-clinical concordance was established on video-EEG (*figure 2B*), wherein the ictal-onset irritative zones were located over the left parieto-occipital cortex, and left posterior cortex dysfunction

Table 1. Summary of initial investigation findings.

CSF	2 cells, Protein: 30 mg/dl, Sugar: 55 mg/dl (random blood sugar: 82 mg/dl)
CSF PCR	TB, HSV, Enterovirus, Jap B, West Nile: negative
MRI	(*figure 1*)
EEG	Frequent left posterior cortex spikes, focal delta slowing, and very frequent electrographic seizures of left posterior head region origin (*figure 2*)
Anti-NMDA	Negative (CSF & serum) (indirect immunofluroscence on transfected cells)
Anti-VGKC	Negative
Anti-microsomal	Negative
CSF lactate	14.76 mg/dl (10-22 mg/dl)
Mitochondrial genome sequencing for known mutations	No pathogenic variants identified
MRI	Increased gyral oedema with restricted diffusion, prominent vessels to lesion, elevated lactate peak at 1.3 ppm
Anti-tissue transglutaminase Ab for celiac disease	Negative
Digital subtraction angiography	Normal

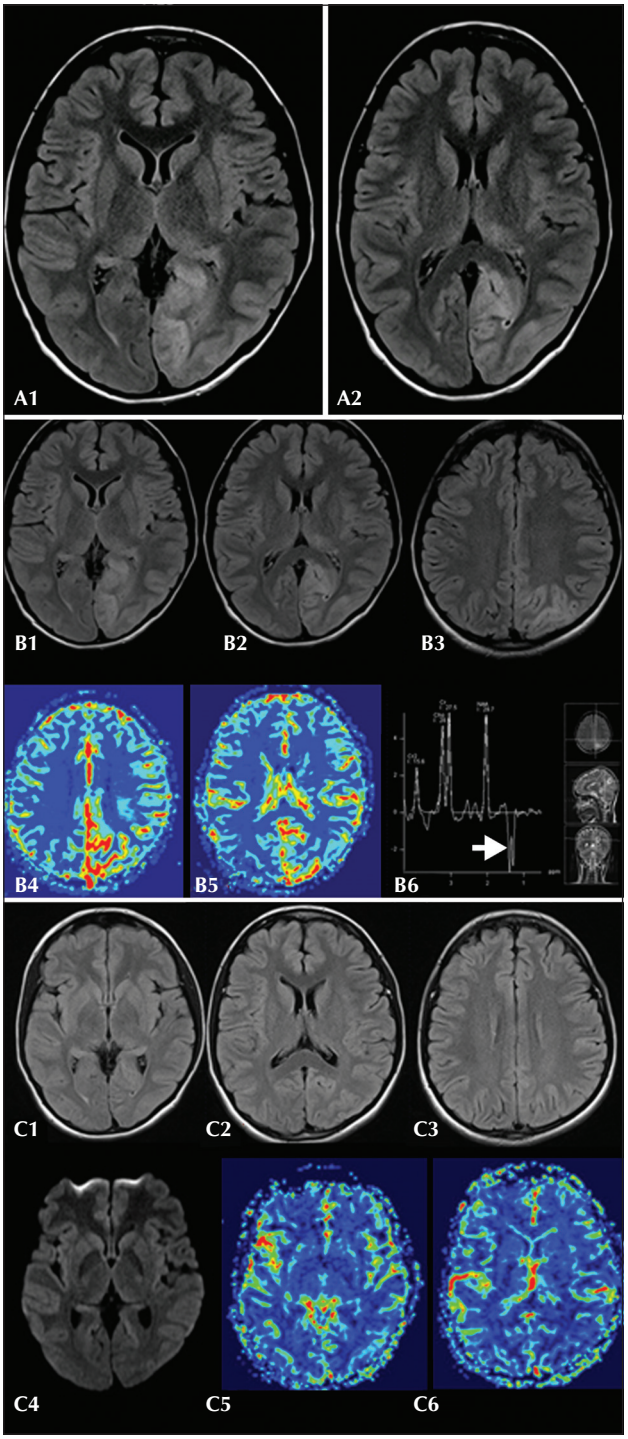

Figure 1. (A) FLAIR axial MRI from November 2013, showing left parieto-occipital gyral swelling (A1 and A2). (B) Images from April 2014 showing the persistence of focal left parieto-occipital gyral oedema (B1-B3) with increased perfusion in the peri-ictal image (B4-B5) and double inverted lactate peak, as indicated by the white arrow (B6). (C) Images from July 2014 demonstrating the disappearance of gyral oedema (C1-C4) and normal perfusion pattern (C5-C6).

was noted on neuropsychological examination. A standard left occipital lobectomy was decided upon as a diagnostic and potential therapeutic option, which was conducted in December 2014. Histopathology (as detailed in *figure 3*) was more consistent with a postictal oedema without the typical features of autoimmune/Rasmussen's encephalitis or FCD. Following surgery, prednisolone was gradually tapered off, with maintenance on the four antiepileptic drugs initiated earlier. Six months post-op, the patient's family noticed progressive logopenia and anomia, progressing to impaired comprehension. She also started experiencing oro-bucco-lingual and upper limb choreoathetoid movements along with bilateral hand and lingual epilepsia partialis continua (EPC). Repeat MRI (*figure 2C*) revealed a new hyperintensity over the right inferior frontal gyrus. EEG revealed right fronto-parietal PLEDs with right hemispheric slow waves. Considering a new site of cortical involvement, a genetic/metabolic cause, such as mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS), was also considered, however, the genetic and metabolic evaluation was negative. Given the high index of suspicion, a repeat serum and CSF anti N-methyl-D-aspartate receptor (NMDAR) antibody panel was performed which returned strongly positive (*figure 4*). She was then initiated on Rituximab in April 2015. Clinical and radiological remission was achieved (*figure 2D*). Two years into follow-up, she remains seizure-free, has right hemianopia and mildly reduced fluency of language, and is on a maintenance dosage of low-dose prednisolone with resumption of schooling.

Discussion

New-onset focal epilepsy presenting with seizure clusters and recurrent complex focal status epilepticus can be extremely challenging to manage. At various time points during the course of illness, a number of possibilities emerged varying from focal encephalitis, cortical dysplasia, to mitochondrial cytopathy, with the initial consideration of autoimmune encephalitis finally established, subsequent to the delayed appearance of intrathecal anti-NMDAR antibodies.

The recurrent seizures throughout the relapsing-remitting course of the illness inevitably result in postictal changes on MRI and can thus further complicate the picture. Various abnormalities described include cortical and subcortical striatal/cerebellar/brainstem hyperintensities, leptomeningeal or parenchymal contrast enhancement, and positron emission tomography (PET) hypermetabolism during acute stages, followed by hypometabolism during the subacute stage, reversible brain atrophy, and more recently,

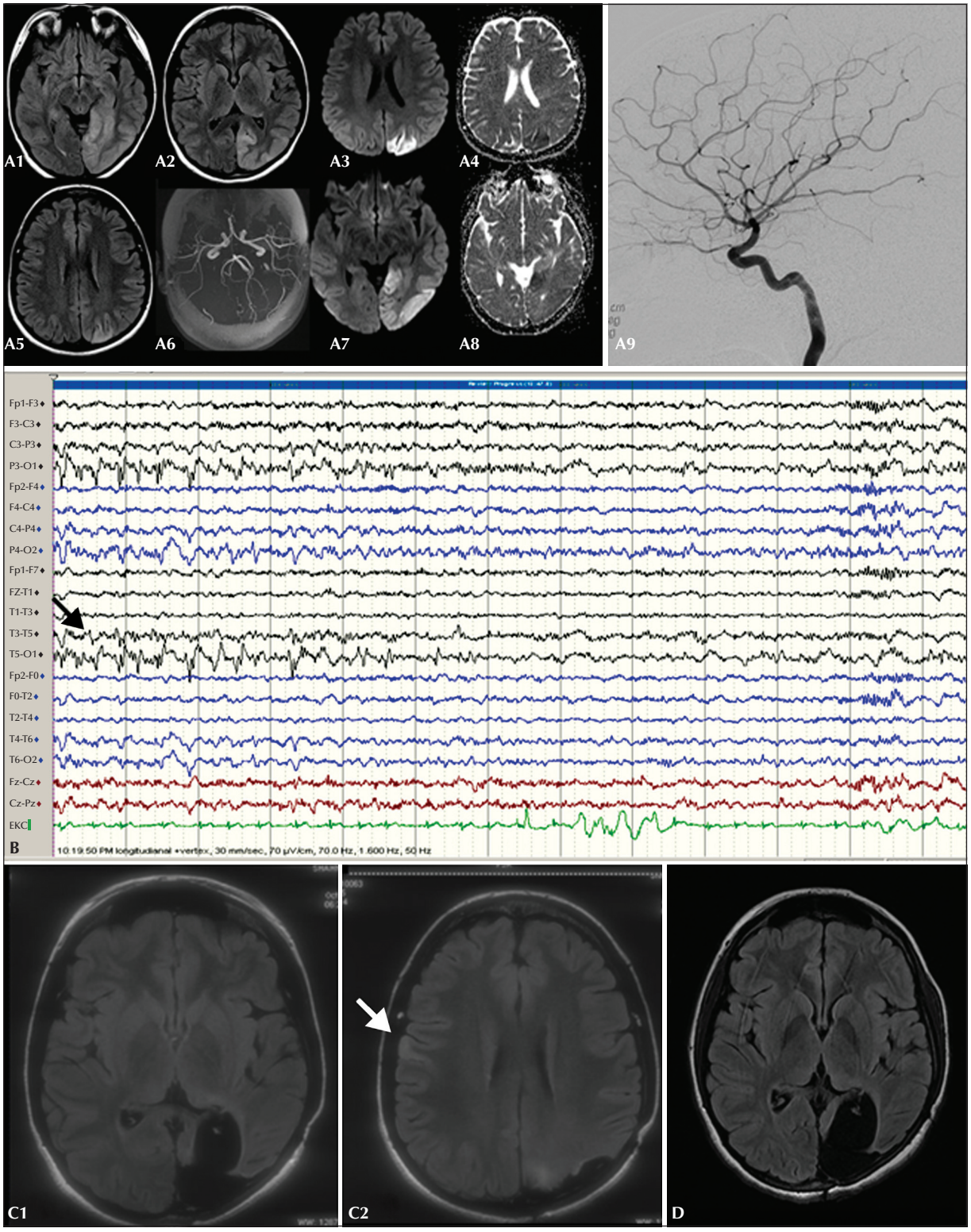

Figure 2. (A) Pre-operative MRI from November 2014 showing FLAIR hyperintensities over the left parietal and entire left occipital region (A1, A2, A5) with diffusion restriction over the left parietal cortex (A3-A4) and left medial parieto-occipital junction (A7-A8), with normal TOF MR angiogram (A6) and digital subtraction angiogram (A9). (B) Ictal EEG showing a focal ictal rhythm over the left posterior cortex (arrow) (bipolar montage; sensitivity: 7 µV/mm; low-pass filter: 50 Hz; high-pass filter: 1.6 Hz; notch filter: 50 Hz). (C) Post-operative FLAIR image showing scar of the left occipital lobectomy (C1) and new hyperintensity over the right frontal region (C2; May 2015). (D) Scar of left occipital lobectomy in MRI performed in February 2016 following treatment with steroids and rituximab showing disappearance of right frontal hyperintensity.

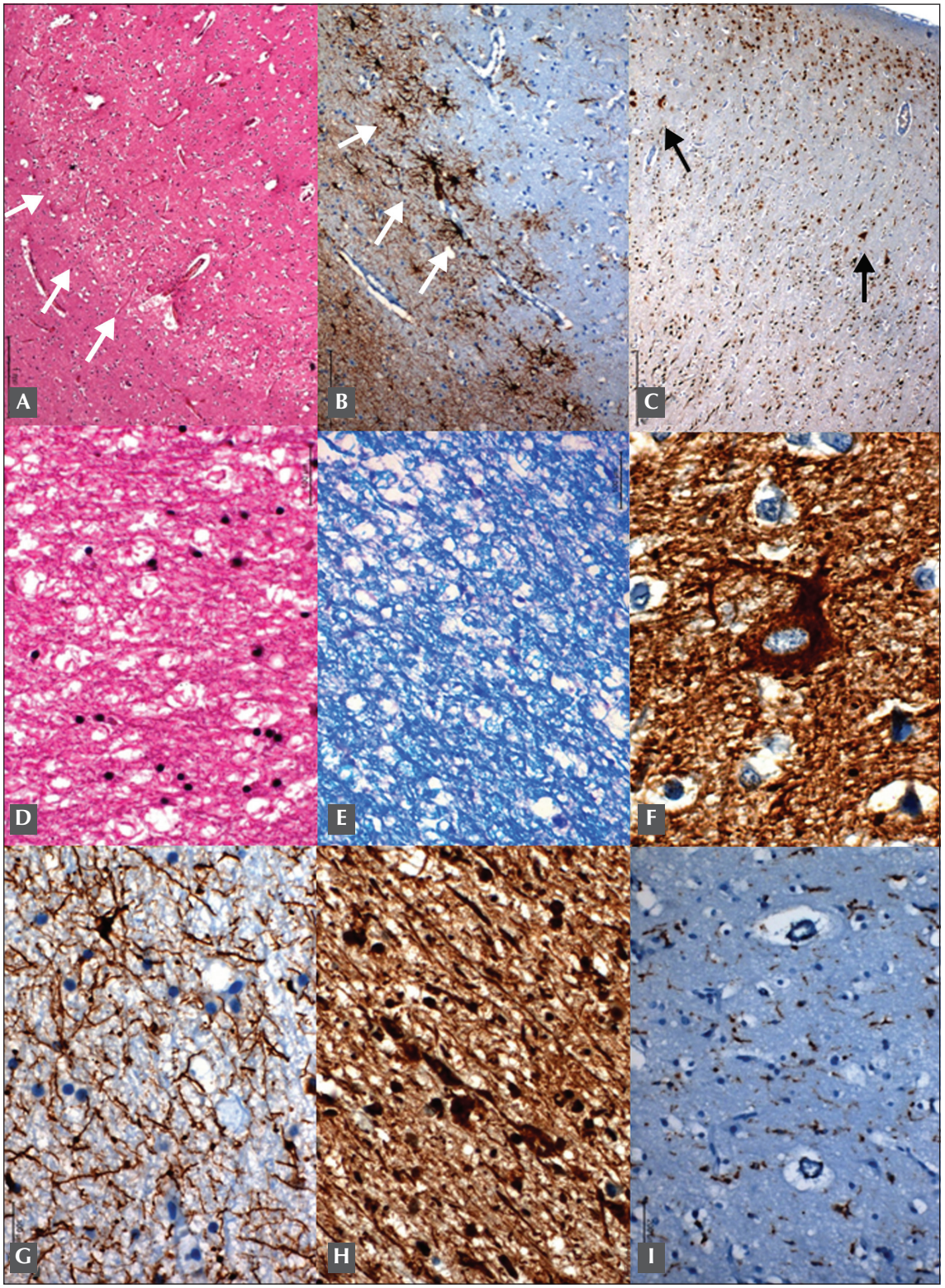

Figure 3. Histopathology of lobectomy specimen. (A) H&E and (B) GFAP stain showing oedematous vacuolation of lower layers corresponding to "laminar necrosis" with a band of reactive astrocytes along this zone, as indicated by the arrows. (C) Focal loss of neurons in layer 3 with few enlarged neurons, as indicated by arrows. (D, E) White matter vacuolation of myelin sheaths, suggestive of intramyelinic oedema (H&E and Luxol blue stain). (F) Enlarged neurons with neurofilament accumulation and abnormal branching (dystrophic change). (G, H) Beaded and dystrophic changes in glial processes and axons. (I) Diffuse microglial response without microglial nodule formation.

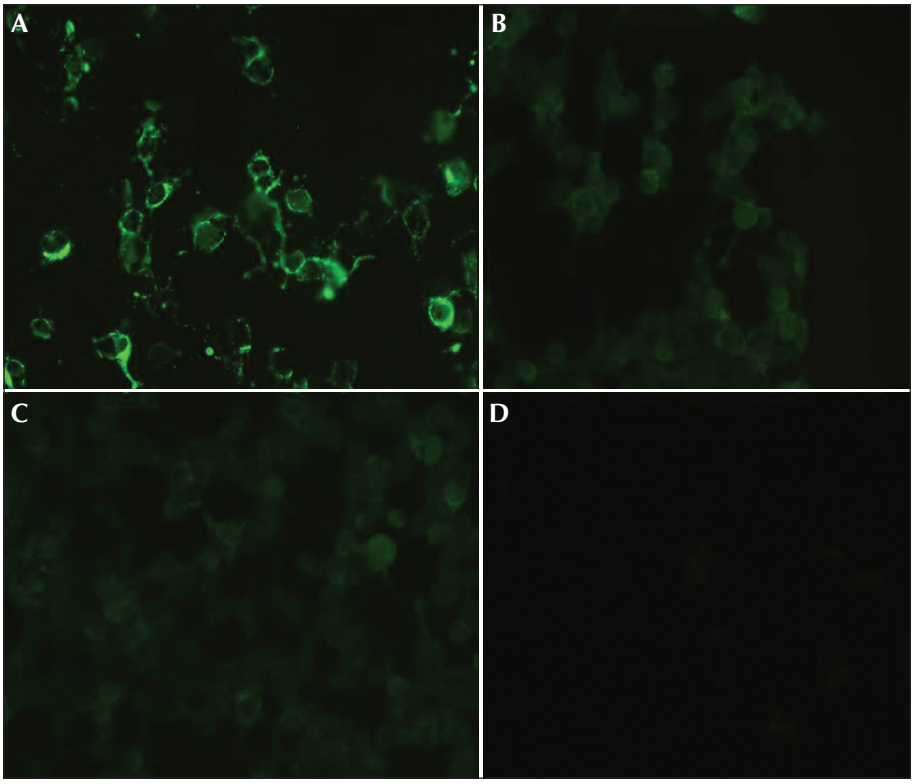

Figure 4. NMDAR IgG auto-antibody in CSF. Using a cell-based assay, NMDAR IgG auto-antibody in CSF with reflex to titre was detected using a commercial anti-glutamate receptor NR1 subunit kit (Euroimmune AG. Luebeck, Germany) by indirect immunofluorescence. The CSF sample of the patient was incubated with NMDAR substrate antigen on the biochip slide in the following dilutions: undiluted, 1:10, 1:20, and 1:40 in PBS-Tween at room temperature for 30 minutes. After the incubation, the biochip slides were washed with PBS-Tween to remove any unbound antibodies. The biochip slide was again incubated with fluorescent-labelled anti-human IgG for 30 minutes at room temperature and washed with PBS-Tween and mounted in buffered glycerin. The reaction was made visible under a fluorescence microscope. The presence of anti-NMDAR antibody is shown as smooth fine granular fluorescence in the cytoplasm of transfected HEK 293 cells, while there is no fluorescence in the negative control. Positive fluorescence was demonstrated in (A) undiluted CSF; (B) 1:10 diluted CSF; and (C) 1:20 diluted CSF; no fluorescence was present in the negative control (CSF, undiluted), supplied with the kit (D).

arterial spin labelling-estimated hyperperfusion, secondary to ongoing inflammation/seizures (Dalmau *et al*., 2011; Ramanathan *et al*., 2014; da Rocha *et al*., 2015; Kumar *et al*., 2017). The pathophysiological basis is postictal neuronal damage, secondary to cytotoxic oedema following a breakdown of cerebral autoregulation in the context of reduced metabolic reserve (McLeoad *et al*., 2012).

By one year from the initial contact, our patient had sustained multiple focal seizure clusters despite trials of immunosuppressive agents. In the presence of established right hemianopia, absence of sustained remission despite immunosuppression/immunomodulation, and considering the pre-eminent electro-clinical possibility of a highly focal and restrictive form of autoimmune encephalitis (including atypical Rasmussen's encephalitis without the typical caudate atrophy, insular, or pan-hemispheric involvement), left occipital lobectomy was performed as a potential therapeutic and diagnostic intervention but proved to be unrewarding on both fronts. On critical hindsight, our decision to offer epilepsy surgery may seem inappropriate, however, this was the only tenable disease-modifying intervention at that point in time, as consideration of an empirical trial of other potent cytotoxic agents with a negative serology is debatable.

Biopsy findings in autoimmune encephalitis are non-specific and include perivascular lymphocytic cuffing (predominantly of B cells), sparse parenchymal T-cell infiltrates, or microglial activation along with plasma cells and rare or absent neuronophagic nodules (Dalmau *et al*., 2011). In our patient, there was mild dyslamination in the presence of large neurons with abnormal branching and accumulation of dystrophic neurofilament. Many of the findings, such as intramyelinic oedema and dystrophic beading, could suggest postictal changes. Considering diffuse microglial nodules and intra-myelinic oedema, autoimmune encephalitis with postictal

radiopathological changes was considered, and FCD was considered unlikely.

The summary of differentiating features on MRI between potential aetiologies is highlighted in *table 2*. The appearance of a new lesion guided us to re-explore the auto-antibody profile, which finally clinched the diagnosis.

Scenarios have been described previously wherein the development of high levels of NMDAR antibodies followed herpes simplex virus encephalitis with response to immunotherapy, however, this possibility was excluded on the initial presentation in our patient (Mohammad *et al*., 2014). A detailed review of literature revealed only a single case report of anti-NMDAR encephalitis with similar presentation (Goldberg *et al*., 2011). However, in that case, at the initial evaluation itself, the patient had a very high CSF titre of anti-NMDAR antibodies. The initial negative serological results for the IgG anti-NMDA antibody cell-based assay and later positivity at high titres both in serum and CSF represent an unusual scenario (Dalmau *et al*., 2011). A similar phenomenon has been reported wherein NMDAR antibody detection followed plasma exchange as well as surgery for ovarian teratoma (Wali *et al*., 2011). Neuronal antibodies have been reported at low levels in a subset of children with new-onset epilepsy, but did not necessarily persist over time, and the *de novo* development of antibodies on serial testing could be indicative of a secondary response to neuronal damage or inflammation (Wright *et al*., 2016). From our own published data on 39 cases of autoimmune encephalitis, including 14 cases of NMDAR antibody-mediated disease, five cases demonstrated delayed positivity as late as two years from the acute event (Cyril *et al*., 2015). It is conceivable that secondary intrathecal synthesis of NMDAR antibodies and oligoclonal bands are required before there is more global cerebral disease evolution (Irani *et al*., 2014). This was apparent in our case following the development of encephalopathy, EPCs, and right frontal involvement on MRI. Autoantibody detection may have been accentuated by the release of these antibodies into circulation following surgery. While EPCs merited the consideration of Rasmussen's encephalitis, bi-hemispheric involvement and histopathological features favoured a non-Rasmussen's autoimmune encephalitis. It is notable that in recent proposed guidelines for the diagnosis of autoimmune encephalitis, serology was not given as a priority in any of the criteria (Graus *et al*., 2016). The newly recognized forms can develop with core symptoms resembling infectious encephalitis, as well as neurological and psychiatric manifestations without fever or CSF pleocytosis. Antibody testing is not readily accessible in many centres, furthermore, it may take weeks to obtain results; an absence of antibodies does

Table 2. Distinguishing multi-modal neuroimaging features of various disorders, similar to those of the index case.

Imaging characteristics	Focal encephalitis	Focal cortical dysplasia	Postictal changes	MELAS	Current case
FLAIR	Grey matter hyper-intensity with gyral swelling	Loss of grey-white matter distinction and cortical thickening	Grey and white matter hyper-intensity, swelling	Grey matter hyperintensity	Left occipital; right frontal hyperintensities
Diffusion	No restriction	No restriction	Restricted in acute setting	No restriction (vasogenic oedema)	Minimal/none
Perfusion	Reduced	Reduced	Increased perfusion	Low	Increased
Contrast	+/-	None	Lepto-meningeal	+/-	None
MR spectroscopy			NAA reduced, choline increased	Lactate peak at 1.3 ppm	Lactate peak
Others	Normal in 60%	Focal	Preferential peri-rolandic involvement; localized with recurrence	Not site-restricted	Prominent vessels to the lesion

+/-: gadolinium contrast enhancing or not.

not exclude an autoimmune origin in an appropriate scenario. Moreover, response to immunotherapy as part of the diagnostic criteria is not practical because many patients do not respond to the most frequently used first-line immunotherapies (steroids, intravenous immunoglobulin, and plasma exchange) or the response may take several weeks, potentially delaying the diagnosis. Anti-NMDAR encephalitis is frequently thus recognizable on clinical grounds.

Conclusion

This case study presents a rare opportunity to document the dynamic evolution of NMDAR encephalitis initially presenting as *de novo* refractory focal epilepsy. A hitherto unreported situation is also considered wherein the CSF antibody assay was negative and subsequently positive when tested at a later stage, in the absence of classic features of NMDAR antibody-mediated encephalitis. Physicians should consider the diagnosis of autoimmune epilepsy even if the CSF or serum antibody panels are negative, based on the clinical evolution in the setting of focal cortical and persistent postictal MRI changes which could serve as a surrogate marker of focal encephalitis. Aggressive immunosuppression, despite auto-antibody negativity, may prove to be a disease-modifying intervention prior to consideration for epilepsy surgery, with consideration for serial CSF antibody testing during relapses. □

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None of the authors have any conflict of interest to declare.

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TEST YOURSELF

(1) What is the differential diagnosis of focal unilateral gyral oedema on peri-ictal MRI in patients with new-onset focal epilepsy?

(2) What causes postictal oedema on MRI?

(3) In an appropriate clinical scenario, does a failure to demonstrate intra-thecal auto-antibody synthesis on CSF examination reliably exclude anti-NMDAR antibody-mediated encephalitis?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".