Clinical commentary

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Possible induction of multiple seizure foci due to parietal tumour and anti-NMDAR antibody

Riki Matsumoto [1], Nobuhiro Mikuni [2,8], Keiko Tanaka [4], Kiyohide Usami [5], Kenjiro Fukao [3], Takeharu Kunieda [2], Yukitoshi Takahashi [6], Susumu Miyamoto [2], Hidenao Fukuyama [7], Ryosuke Takahashi [5], Akio Ikeda [1]

[1] Department of Epilepsy, Movement Disorders and Physiology, Kyoto University Graduate School of Medicine, Kyoto
[2] Department of Neurosurgery, Kyoto University Graduate School of Medicine, Kyoto
[3] Department of Psychiatry, Kyoto University Graduate School of Medicine, Kyoto
[4] Department of Neurology, Kanazawa Medical University, Ishikawa
[5] Department of Neurology, Kyoto University Graduate School of Medicine, Kyoto
[6] National Epilepsy Center, Shizuoka Institute of Epilepsy and Neurological Disorders, Shizuoka
[7] Human Brain Research Center, Kyoto University Graduate School of Medicine, Kyoto
[8] Department of Neurosurgery, Sapporo Medical University, Sapporo, Japan

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ABSTRACT – "Formes frustes" of encephalopathy associated with anti-NMDAR antibody have been recently described in cases of chronic epilepsy. We report a young woman with a parietal lesion and anti-NMDAR antibody who acquired bilateral, secondary epileptogenesis in the temporal lobes within a period as short as six years. Removal of the primary epileptogenic lesion of oligoastrocytoma in the right parietal lobe resulted in seizure freedom, disappearance of secondary foci, and substantial decrease of the antibody titre. Chronic exposure to anti-NMDAR antibody, albeit at a low titre, may have resulted in a smoldering chronic course and relatively early acquisition of "reversible" secondary foci without development of a high degree of epileptogenicity and structural changes.

Key words: anti-NMDAR antibody, secondary epileptogenesis, oligoastrocytoma, autoimmune epilepsy

Correspondence:
Riki Matsumoto
Department of Epilepsy,
Movement Disorders and Physiology,
Kyoto University Graduate School of Medicine,
54 Kawahara-cho, Shogoin,
Sakyo, Kyoto,
606-8507 Japan
<matsumot@kuhp.kyoto-u.ac.jp>

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In the past decade, the importance of autoimmune antibodies in the generation of CNS disorders has been increasingly recognized. Antibodies to the N-methyl-D-aspartate subtype of glutamate receptors (anti-NMDAR antibodies) have been associated with a newly described encephalopathy that has been usually identified in young females (Dalmau *et al.*, 2007). The syndrome is typically characterized by an acute onset of psychiatric disorder, seizures, dyskinesias, autonomic instability, decreased level of consciousness, and central

hypoventilation, suggesting diffuse hyper- and dysfunction of both the cortical and subcortical structures (Dalmau *et al*., 2007; Iizuka *et al*., 2008). Many patients are reported to have an ovarian tumour and experience remarkable improvement after tumour removal and subsequent immunotherapy (Dalmau *et al*., 2007). However, with increasing recognition of this entity, patients without ovarian tumour or with atypical symptoms have been reported (Dalmau *et al*., 2008; Iizuka *et al*., 2008; Irani *et al*., 2010). More recently, patients with milder forms, with epilepsy as the single or only major symptom, have been reported (Niehusmann *et al*., 2009; Irani *et al*., 2010). These patients were reported to have lower titres of anti-NMDAR antibody and had minimal or no cognitive involvement, and did not develop any movement disorders or other features consistent with the later stage of the disease (Irani *et al*., 2010). Here, we report a patient with epilepsy who had a parietal lesion and a low titre of anti-NMDAR antibody. The patient subsequently acquired bilateral, secondary epileptogenesis in the temporal lobes within a period as short as six years, and later developed psychosis. The removal of the primary epileptogenic lesion of oligoastrocytoma in the right parietal lobe resulted in seizure freedom, disappearance of secondary epileptogenesis, and psychosis.

Case study

The patient was a 29-year-old, right-handed woman. The delivery, early development and past history were unremarkable. At 18 years of age, she first had an aura with an apparent "dizzy sensation", *i.e.*, she could not reach objects with her hand due to blurred vision. At 21 years old, she started to have auras of *déjà vu* and epigastric rising sensation, and developed complex partial seizures (CPSs) following auras. Since seizures were intractable to antiepileptic medication (carbamazepine, gabapentin and topiramate), she was referred to our hospital at age 24 for the evaluation of intractable focal epilepsy. Three-tesla MRI revealed a well-demarcated calcified lesion in the right lateral parietal area and normal temporal lobes, including bilateral hippocampi (*figure 1A*). Video-EEG monitoring showed frequent independent spikes in the bilateral temporal areas, and ictal discharges arising from the right or left temporal area (*figure 2A, B*). In half of the seizures, rhythmic alpha activity preceded in the right central area, most likely spreading from the right parietal lesion (*figure 2C*). Regarding semiology, those originating from the right hemisphere (either from the right central or temporal region) were CPSs that consisted of unresponsiveness, motion arrest, and bilateral leg automatisms, followed by the bilateral hand dystonic postures.

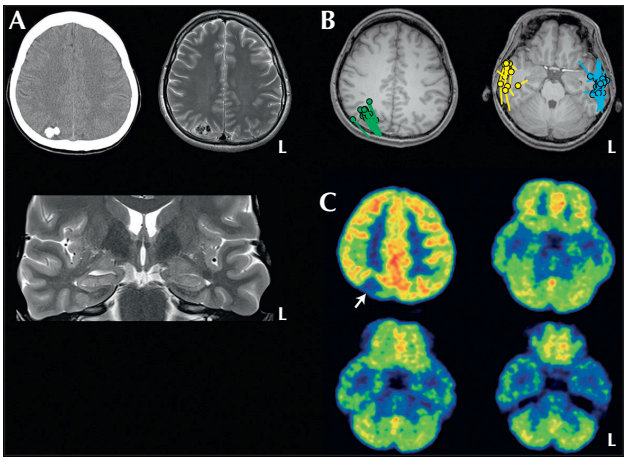

Figure 1. Triple pathology in the present patient. (A) Brain MRI and CT showed a well-demarcated calcified lesion in the right parietal lobe (pathologically oligoastrocytoma). Note normal structures in the bilateral temporal lobes including the hippocampi. (B) MEG analysis delineated three independent spike foci at the tumour (green) and in the bilateral temporal lobes (yellow and blue). (C) Interictal FDG-PET study showed hypometablic areas in the tumour (arrow) and the bilateral temporal areas.

An aura of "dizzy sensation" preceded in half of these seizures. In seizures starting from the left temporal region, the patient showed unresponsiveness and left hand automatism, followed by right hand dystonic posture. Magnetoencephalography (MEG) revealed three independent dipole clusters of the interictal spikes; one cluster at and around the right parietal lesion and the other two in the left and right temporal lobes (*figure 1B*). Temporal spikes were not preceded by spikes in the right parietal area. Interictal FDG-PET showed hypometabolic regions in the right parietal area, as well as in the bilateral temporal lobes (*figure 1C*). The primary focus was considered at and around the parietal lesion because of the initial aura of "dizzy sensation" with which the patient could not reach an object properly, the MRI finding, and ictal EEG pattern. Furthermore, judging from the EEG, MEG, and functional imaging studies, the patient likely developed secondary epileptogenesis in the bilateral temporal lobes within six years from the seizure onset. The unexpected, relatively early acquisition of "triple" pathology, *i.e.* bilateral, secondary epileptogenesis in the temporal lobes, led us to investigate CSF for possible immunological modification of the epileptic condition. While cell counts, protein, glucose, and IgG index were within normal range, anti-NMDA glutamate receptor (GluR) epsilon 2 antibody (IgG type) was positive in the CSF (and negative in the serum) (Takahashi *et al*., 2003). Antibodies for systemic autoimmune diseases were negative. Because anti-GluR epsilon 2 antibody that reacts with NR2B linear epitopes or peptides is reported to be found in a relatively broad

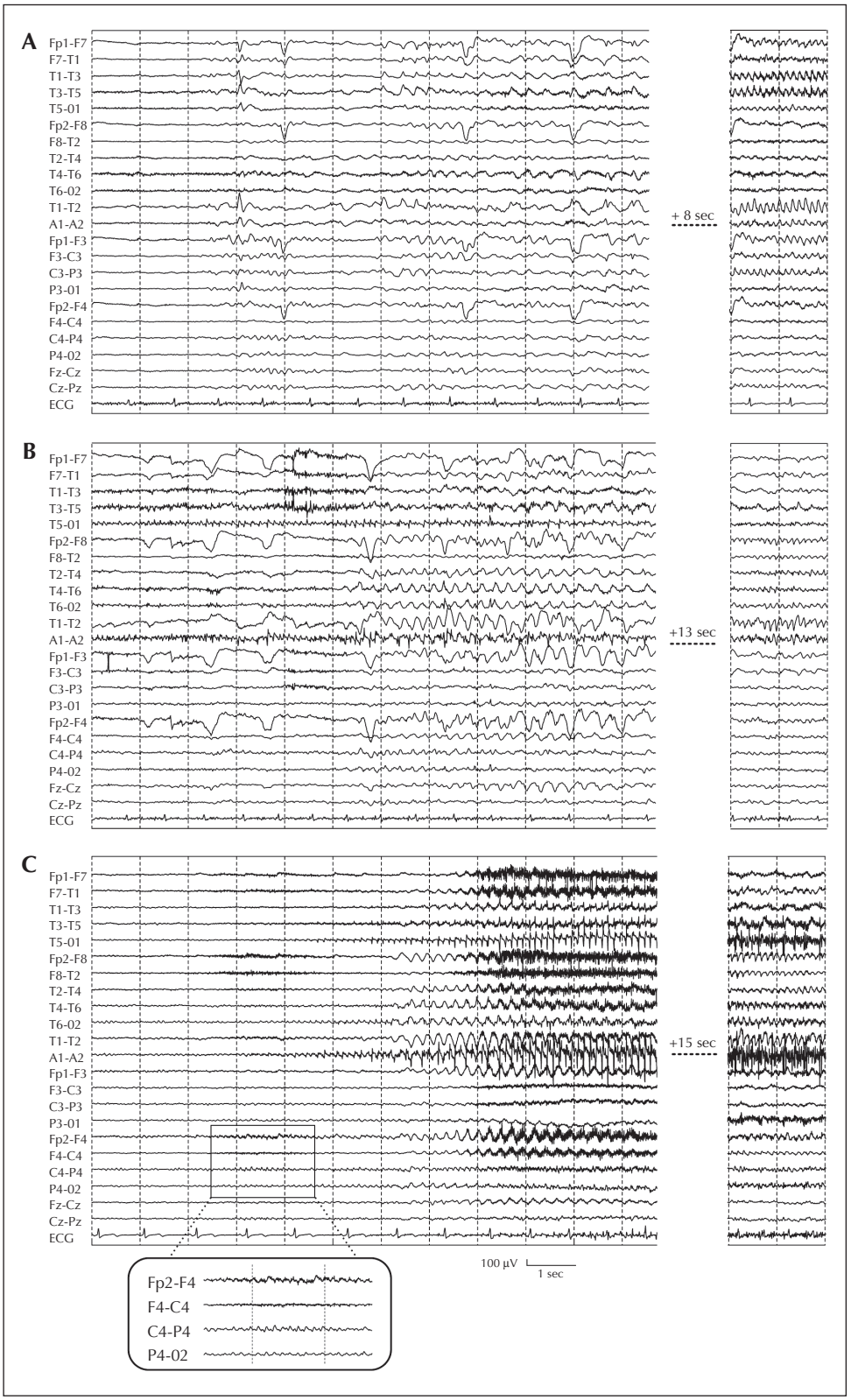

Figure 2. Three different ictal EEG patterns were documented during the video-EEG monitoring. (A) An ictal EEG pattern arising from the left hemisphere, maximum at the left temporal region. Note that the ictal pattern evolved later into clear rhythmic theta activity, maximum in the left temporal region. (B) An ictal EEG pattern arising from the right temporal region. (C) An ictal EEG pattern arising from the right central region (rhythmic alpha). Only the beginning of the ictal EEG is shown.

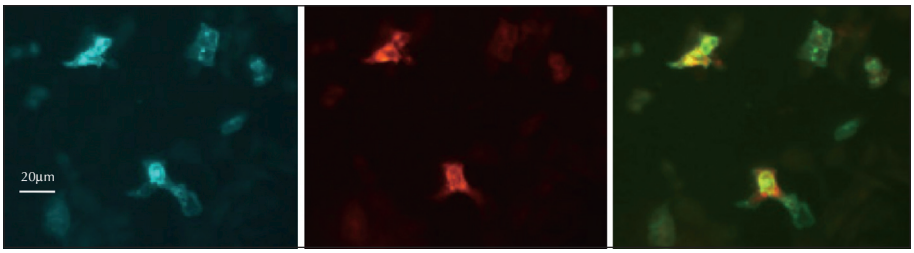

Figure 3. (A) NMDAR NR1 and NR2-transfected HEK cells were incubated with the patient's CSF and stained with FITC-anti-human IgG (green) (untransfected cells did not show any immunostaining; data not shown). (B) The same cells were incubated with rabbit anti-NR1 antibody and stained with PE-anti-rabbit IgG (red). (C) Merged figure (yellow) of the left (green) and middle (red); note that the degree of co-staining varied among cells due to rapid decay of PE. Scale bar: 20 μm.

spectrum of encephalitis (Kimura *et al*., 2007), we further tested additional autoimmune antibodies. Anti-VGKC complex antibody and onconeuronal antibodies (Yo, Hu, Ri, MA1, MA2, CV2/CRMP5, and amphiphysin) were all negative in the serum. We also analyzed anti-NMDAR antibody using a cell-based assay with human embryonic kidney 293 (HEK 293) cells co-transfected with NMDAR NR1 and NR2 cDNA (Zhang *et al*., 2012); the target of the antibody was confirmed to be NR1 (*supplementary figure 1*[1]). Anti-NMDAR antibody was positive with a low titre (1:64) in the CSF and negative in the serum (*figure 3*). Tumour investigation with whole-body FDG-PET and contrast-enhanced CT was negative. In terms of treatment, epilepsy or lesion surgery was not promptly recommended in the patient management conference because of the triple epileptic foci. With the positive evidence of possible immunological involvement for the epileptic condition, we instead performed steroid pulse therapy (methylprednisolone at 1 mg/3 days) for frequent CPSs at age 25 years. The steroid therapy decreased seizure frequency (auras from 10-15/month to 5/month, and CPSs from 5-8/month to 3/month). The second steroid pulse therapy was performed six weeks later. The patient, however, subsequently developed a psychotic episode. The episode consisted of an outburst of emotion and agitation along with aura continua of *déjà vu*. No auditory or visual hallucination occurred, but the patient could not differentiate the experimental aura or delusion from reality, in other words, she was in a kind of dreamy state. The episode subsided after one week. Despite discontinuation of steroid treatment, the patient further developed two episodes of psychosis. One was similar to the first episode and lasted one week. The other was triggered by a family problem. The psychosis consisted of outburst of emotion and agitation, but was neither associated with a *déjà vu* feeling, delusion, nor hallucination. The patient was urgently admitted to the psychiatric ward and the episode subsided in two weeks. All of the three episodes were successfully treated with temporary administration of antipsychotics (risperidone) and valproate. Although the patient had already developed two secondary foci or triple pathology at age 26, the resection of the primary focus at and around the right parietal lesion was finally recommended at the patient management conference. It was discussed that the resection of the primary focus would at least improve intractable CPSs resulting from the primary focus, and may improve the epileptic state associated with anti-NMDAR antibody if the lesion was associated with antibody production. The patient underwent craniotomy while awake and the electrocorticogram showed frequent spikes at and around the lesion. Tailored resection of the lesion and surrounding tissue was performed, and the pathology was oligoastrocytoma grade II. Immunochemical staining of the surgical tissue with anti-NMDAR NR1 subunit was positive along the neuronal axons and glial cells in the tumour tissue (*supplementary figure 2*[2]). After surgery, the patient was seizure-free for three years without any psychotic episodes. Two-day video-EEG monitoring one year after surgery showed neither interictal epileptiform discharges nor subclinical EEG seizure patterns at all in any of the previous foci. Follow-up measurement of anti-NMDAR antibody one year after surgery revealed substantial decrease (1:2) in the CSF.

Discussion

A recent systematic survey of 44 non-paraneoplastic patients with anti-NMDAR antibody revealed the presence of atypical or mild forms of the disease associated with anti-NMDAR antibody (Irani *et al*., 2010). In this study, four patients were reported to have focal epilepsy as an exclusive symptom. Two male patients had drug-resistant temporal lobe epilepsy, while two female patients presented with acute onset of complex partial *status epilepticus*. Existence of this subgroup

[1] Available on www.epilepticdisorders.com

[2] Available on www.epilepticdisorders.com

was also described in a report of another prospective cohort study of women with new-onset epilepsy at age 15-45 years. Five patients were found to have a positive titre of anti-NMDAR antibody with the primary focus located outside the temporal lobe in all (Niehusmann *et al*., 2009). No evident mesiotemporal MRI abnormalities were found. The high frequency of acute psychotic episodes (four of five patients) was noteworthy. The psychotic symptoms included depression, liability of mood, pathological crying and laughter, agitation, hallucination, delusions, and confusion. In the majority of the patients, the titre or binding score of anti-NMDAR antibody was reportedly low in this subgroup of patients. The majority of the patients responded to immunotherapy. Our patient shares common features with this subgroup of patients:

(1) focal epilepsy and later development of mild episodic psychosis;

(2) low-titre anti-NMDAR antibody;

(3) response to immunotherapy.

Besides the common features, long-term follow-up over 12 years enabled us to describe the unique characteristics of the present patient:

(1) early acquisition (≤six years) of bilateral, secondary foci in the temporal lobes in the absence of structural changes;

(2) seizure freedom and disappearance of temporal spikes after resection of the primary focus (oligoastrocytoma) alone;

(3) substantial decrease, if not disappearance, of anti-NMDAR antibody titre after resection.

In this patient, secondary epileptogenesis was considered to be in an intermediate stage, where interictal or ictal discharges occur independently in the secondary foci but disappear after removal of the primary focus (Morrell, 1985). The present case could indicate a possible role of immunological modulation by autoimmune antibodies in the generation of dual pathology or secondary epileptogenesis in general. It is tempting to hypothesize that chronic exposure to anti-NMDAR antibodies, albeit at a low titre and possibly with occasional flare-up, resulted in functional impairment of the temporal lobes, presumably the mesial structures, leading to early acquisition of "reversible" secondary foci in the bilateral temporal lobes without development of structural changes, such as hippocampal sclerosis. This hypothesis appears plausible since reversible decrease of synaptic NMDAR is the presumable mode of action for anti-NMDAR antibody (Dalmau *et al*., 2011), and that neuropathological findings in brain biopsy specimens were indeed without distinctive parenchymal inflammatory changes even in the full-blown typical cases (Dalmau *et al*., 2007).

To date, only tumours outside the CNS are reported to be associated with encephalopathy, with positive anti-NMDAR antibody. Our patient had a parietal oligoastrocytoma as a primary epileptogenic lesion. Immunohistochemical staining of the surgical specimen was positive for NMDAR NR1. Since both neurons and glial cells can harbour NMDAR, it is too early to conclude that this brain tumour is involved in production of anti-NMDAR antibody. The substantial decrease, however, of the antibody titre after tumour removal indicates that this tumour was at least associated with maintenance of the milieu necessary for chronic production of anti-NMDAR antibody in our patient. The existence of very low-titre antibody after surgery could be ascribed to residual production of the antibodies under the effects of memory T cells.

A few limitations should be addressed in the present case study. First, we were not able to fully document the development of secondary epileptogenesis since the detailed work-up was performed only after the secondary foci were identified. Second, we could not completely rule out the possibility of the spreading phenomenon from the primary parietal focus to the temporal areas, although MEG revealed dipole clusters of the spikes in the left and right temporal areas, being spatio-temporally independent from those of the right parietal spikes around the tumour. Further case accumulation is warranted to establish the effects of anti-NMDAR antibody on secondary epileptogenesis, as well as direct or indirect association of brain tumour with anti-NMDAR antibody. □

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TEST YOURSELF

(1) Which antibody is not related to autoimmune epilepsy?
A. Anti-NMDAR antibody
B. Anti-VGKC complex antibody
C. Anti-GAD antibody
D. Anti-MuSK antibody
E. Anti-GABA(B) antibody

(2) How does anti-NMDAR antibody affect focal epilepsy (select the two most appropriate choices)?
A. Provocation of psychosis
B. Spontaneous remission
C. Promotion of secondary epileptogenesis in the hippocampus
D. Generation of faciobrachial dystonic seizures
E. Hyponatraemia

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".