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PET-positive extralimbic presentation of anti-glutamic acid decarboxylase antibody-associated encephalitis

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ABSTRACT – Anti-glutamic acid decarboxylase (GAD) antibody-associated autoimmune encephalitis has been reported mostly as limbic encephalitis. Only few cases with extralimbic involvement are reported with limited investigation. Here, we report an extensive investigation with MRI, PET, and pathological examination. A 66-year-old Japanese female with a history of hypothyroidism, colon cancer, pheochromocytoma, and thymoma-associated myasthenia gravis presented with generalised tonic-clonic seizures. MRI showed multiple hyperintense lesions and PET showed hypermetabolic lesions in the brain. Biopsy showed non-specific gliosis, microglial proliferation, and perivascular lymphohistiocytic infiltrates. Various neuronal antibodies were negative, except for anti-GAD antibody. Anti-GAD antibody-associated encephalitis is an increasingly recognised CNS disease. Pathophysiology of this encephalitis is unclear. While PET showed hypermetabolic lesions, the biopsy showed non-specific changes. The treatments may include immunosuppressants, IVIg, and plasma exchange. One should consider to measure this antibody, in addition to others, when autoimmune encephalitis is suspected [*Published with video sequences*].

Key words: generalized seizure, autoimmune encephalitis, anti-GAD antibody, palatal myoclonus, limbic encephalitis, glutamic acid decarboxylase

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Various paraneoplastic and non-paraneoplastic neuronal autoantibodies have recently been discovered to be associated with neurological syndromes (Vincent *et al*., 2011). These antibodies include anti-voltage-gated potassium channel (VGKC) antibody, anti-N-methyl-D-aspartate receptor (NMDAR) antibody, anti-gamma-aminobutyric acid-B receptor antibody, and anti-glutamic acid decarboxylase (GAD) antibody (Vincent *et al*., 2011). Among them, anti-GAD antibodies have been identified in neurological diseases

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such as stiff-person syndrome, cerebellar ataxia, and palatal myoclonus (Nemni *et al*., 1994; Saiz *et al*., 2008; Ishida *et al*., 2008; Squintani *et al*., 2012). Rare cases of anti-GAD antibody-associated encephalitis are also reported as limbic encephalitis involving the limbic system (Vincent *et al*., 2011). Extralimbic lesions are uncommon and have been demonstrated only in a limited number of reports (Peltola *et al*., 2000; Malter *et al*., 2010; Cianci *et al*., 2010; Najjar *et al*., 2011). This is the first report to present an extensive investigation, including MRI, PET, and pathological examination, of a rare case of anti-GAD antibody-associated encephalitis with extralimbic involvement, in which the patient had refractory seizures and developed palatal myoclonus.

Case study

A 66-year-old Japanese female developed a new onset of generalised tonic-clonic seizures, preceded by three days of auditory hallucinations. After a brief post-ictal state, she became alert and oriented without neurological deficits. Her medical history included multiple cancers (colon cancer and pheochromocytoma, both in remission after resection seven years ago, and thymoma-associated myasthenia gravis, also in remission after thymectomy 18 months ago), hypothyroidism, and osteoporosis. She was an active smoker (50 packs/year) and used alcohol occasionally. Laboratory and cerebrospinal fluid (CSF) examinations were unremarkable except for low thyroid stimulating hormone at 0.19 μIU/mL, with normal free T4 at 1.4 ng/mL. MRI of the brain revealed T2-fluid-attenuated inversion recovery sequence (FLAIR) hyperintense mass-like lesions without gadolinium enhancement in the right temporal lobe and left anterior superior frontal gyrus (*figure 1A*). The right temporal lobe lesion was extensive and involved the right internal and external capsules. Magnetic resonance angiogram of the brain was normal. Brain PET showed multiple hypermetabolic lesions in bilateral frontal, right temporal, and right parietotemporal lobes corresponding to the MRI lesions (*figure 1B*). Whole-body PET was negative for occult malignancy. Brain biopsy was performed on the right temporal lobe lesion based on suspicion of brain metastasis in the light of the imaging findings, as well as her previous history of multiple malignancies. The pathology showed only non-specific changes including mild gliosis, microglial proliferation (*figure 1C*), and perivascular lymphohistiocytic infiltrates (*figure 1D*). No overt demyelination, neoplasm, microglial nodule, neuronophagia, or viral inclusion were observed and the bacterial and fungal cultures were negative. Serum titres for anti-N-type and anti-P/Q-type calcium channel antibody, anti-Purkinje cell cytoplasmic antibody (type 1, 2, and Tr), anti-collapsin response-mediator protein-5 antibody, anti-neuronal nuclear antibody 1, 2, and 3, anti-amphiphysin antibody, and anti-neuronal ganglionic acetylcholine receptor antibody were all negative. Antibodies against acetylcholine receptor and striated muscle were detected, which were already known to be positive. She was neurologically stable and discharged with levetiracetam.

One week later, she suddenly developed confusion, aphasia, and left-sided weakness. MRI revealed, in addition to enlargement of the previously-demonstrated lesions, multiple new T2/FLAIR hyperintense lesions without enhancement throughout the brain. After admission, she went into status epilepticus. EEG showed periodic lateralising epileptiform discharges from the left temporal area and independent frequent epileptiform discharge from the right temporal area. CSF examination showed 25 leukocytes/mm^3 (97% lymphocytes) with normal glucose and protein, and was negative for gram stain, culture, and herpes simplex virus-1/2 PCR. Serum antibodies against VGKC and NMDAR were negative. Her seizures were refractory to levetiracetam, lacosamide, and fosphenytoin, but ultimately resolved after a five-day course of intravenous methylprednisolone. Repeat MRI of the brain was essentially unchanged; no new lesions were demonstrated. She was discharged with levetiracetam, lacosamide, phenytoin, and tapering steroid.

During the next four months, she was clinically stable but the follow-up MRI demonstrated multiple relapsing-remitting lesions throughout the cortex (*figure 1E and 1F*). Azathioprine was added to monthly methylprednisolone (two days/month). Four months later, she developed a left facial twitch, involving her lips and tongue, with palatal myoclonus (*see videos 1 and 2*). Valproic acid was ineffective and intravenous immunoglobulin at 2 mg/kg resulted in only a partial response. Botulinum toxin injection to the facial muscles resolved the facial twitching.

Eight months after the original presentation, she developed another generalised tonic-clonic seizure. MRI revealed new non-enhancing FLAIR/T2 hyperintense lesion on the left temporal pole. She was again treated with a five-day course of intravenous methylprednisolone, which resulted in dramatic improvement. Additional investigation revealed a weakly positive titre of anti-GAD65 antibody (<1:600), as well as elevated anti-thyroglobulin antibodies (2,660 IU/mL), anti-TPO antibodies (698 IU/mL), rheumatoid factor (114 IU/mL), and anti-cyclic citrullinated peptide antibodies (31.9 IU/mL). Anti-LGI1 antibody and anti-CASPR2 antibody were negative.

Monthly intravenous methylprednisolone was increased to four days/month, in addition to her azathioprine, and she has been neurologically stable without further seizures or residual neurological deficits and the MRI lesions have completely resolved.

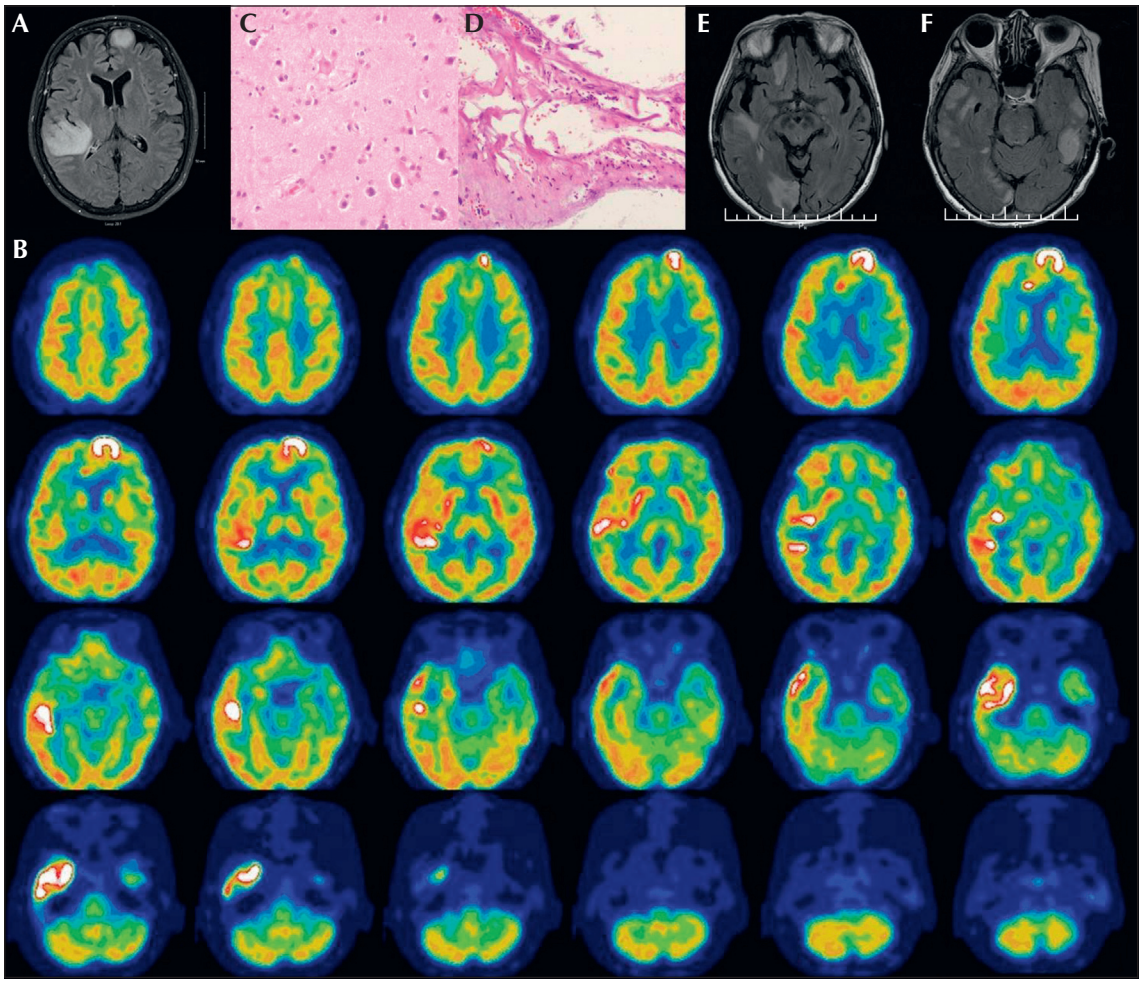

Figure 1. Fluid-attenuated inversion recovery sequence of MRI showed hyperintense lesions in the right temporal lobe and left anterior superior frontal gyrus (A). Brain PET revealed multiple hypermetabolic lesions corresponding to the MRI lesions (B). Biopsy of the right temporal lobe lesion showed non-specific changes including mild gliosis, microglial proliferation (C), and perivascular lymphohistiocytic infiltrates (D) (haematoxylin-eosin staining; original magnification: x10). A series of follow-up brain MRI investigations (fluid-attenuated inversion recovery sequence) showed multiple relapsing-remitting lesions throughout the cortex (E and F).

Discussion

Anti-GAD antibody-associated encephalitis is an increasingly recognised central nervous system disease. In the reported cases of anti-GAD encephalitis, brain lesions are mostly confined to the limbic areas (Cianci *et al*., 2010; Malter *et al*., 2010), commonly presenting with refractory seizures (Malter *et al*., 2010). Other clinical manifestations include dementia, encephalopathy, and rarely palatal myoclonus or extralimbic involvement (Peltola *et al*., 2000; Malter *et al*, 2010; Cianci *et al*., 2010; Najjar *et al*., 2011).

PET and pathological examinations of anti-GAD antibody-associated encephalitis are scarce. In our patient, PET showed very hypermetabolic lesions; this raised concern for metastatic lesions, given her history of multiple cancers, and lead to biopsy. Pathological examination performed before immunosuppressive treatment showed only non-specific changes, without overt inflammation. This discrepancy between PET and pathology may point to a more synaptic mechanism of anti-GAD antibody-associated encephalitis. In the literature, one case of PET demonstrated hypermetabolism at the onset of encephalitis, similar to our patient (Blanc *et al*., 2009). Few pathological examinations of anti-GAD antibody-associated encephalitis cases have shown relatively non-specific encephalitis (Malter *et al*., 2010; Najjar *et al*., 2011), as in our case, but one case showed concomitant encephalitis and vasculitis (Najjar *et al*., 2011).

The clinical course of our patient was relapsing-remitting and it required long-term immunotherapy with azathioprine and monthly intravenous methylprednisolone. Treatments for anti-GAD antibody-associated encephalitis include intravenous methylprednisolone, intravenous immunoglobulin, plasma

exchange, and other immunosuppressive agents, such as azathioprine (Najjar *et al*., 2011), cyclophosphamide, (Malter *et al*., 2010), mycophenolate mofetil (Cianci *et al*., 2010), and rituximab (Cianci *et al*., 2010). Anti-GAD antibody-associated encephalitis also shows variable response and frequently relapses when discontinuing or tapering the therapy (Peltola *et al*., 2000; Malter *et al*., 2010).

In summary, although Anti-GAD antibody-associated encephalitis is rare, measuring anti-GAD antibodies in addition to other autoantibodies should be considered in patients suspected to have autoimmune encephalitis. □

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Legends for video sequences

Video sequence 1

There is a continuous rhythmic 0.5 to 1 Hz involuntary myoclonic retraction of the tongue towards the left, followed by slow protrusion. Myoclonic movements are also noted in her left lip.

Video sequence 2

When she closes her mouth, 0.5 to 1 Hz myoclonic movements are present in her left lower face muscles, pulling the upper corner of the mouth laterally, and upwards. Facial muscles innervated by Zygomatic and Buccal branches of the facial nerve (*Zygomaticus Major/Minor*, *Risorius*, and *Orbicularis Oris*) are involved.

Key words for video research on www.epilepticdisorders.com

Syndrome: focal non-idiopathic (localization not specified)
Etiology: encephalitis
Phenomenology: clonic (non epileptic), dyskinesias (non epileptic), face
Localization: multifocal

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