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Autoimmune encephalitis and anti-GAD/GABA-A receptor antibodies

To the Editor,

We refer to the publication of Kojima *et al* 2014: "*PET-positive extralimbic presentation of anti-glutamic acid decarboxylase antibody-associated encephalitis*". Neurological disorders associated with antibodies against cell surface and synaptic proteins are fascinating diseases that have changed paradigms in neurological practice, mainly because these disorders were previously unknown and/or mischaracterized (Leypoldt *et al*., 2014). In a recent report, Kojima et al. (2014) described a patient with limbic encephalitis and refractory status epilepticus attributed to the presence of low-titer anti-glutamic acid decarboxylase (GAD) antibodies. The authors did not perform comprehensive autoantibody studies, and therefore, the attribution of the patient's syndrome to GAD65 autoimmunity is highly questionable. Indeed, antibodies against gamma-aminobutyric acid (GABA)-A receptor should have been examined. This is important, since the patient had several findings very similar to other patients with encephalitis associated with GABA-A receptor antibodies.

The GABA-A receptor is one of the most recently identified antigens (Petit-Pedrol *et al*., 2014) within the category of autoimmune encephalitis associated with antibodies against synaptic receptors. High-titer serum and CSF GABA-A receptor antibodies were recently reported in six patients with autoimmune encephalitis associated with seizures or status epilepticus, four of whom required pharmacologically induced coma. Epileptic symptoms were preceded by, or associated with, a change in behaviour or level of cognition in all patients. Brain MRI showed extensive multifocal abnormalities on FLAIR and T2 imaging, with cortical and subcortical involvement without contrast enhancement, which highly resembled the findings for the patient reported by Kojima *et al*. (2014). Patients often had coexistent autoantibodies against less relevant or intracellular proteins, including anti-thyroid peroxidase antibodies (three patients), anti-GAD65 antibodies (one patient), and anti-GABA-B receptor antibodies (one patient). Importantly, the antibodies of the patients altered the levels of GABA-A receptors in cultured neurons, and most patients improved after treatment.

The patient reported by Kojima *et al*. had a history of thymoma, although no relapsing neoplasia was found. Interestingly, two cases of anti-GABA-A receptor antibody-associated encephalitis were recently reported in association with thymoma (Ohkawa *et al*., 2014), one of whom had concomitant anti-LGI1 antibodies, while the other had anti-Caspr2 antibodies.

Altogether, the clinical picture, MRI findings, and history of thymoma in the patient reported by Kojima and colleagues are suggestive of anti-GABA-A receptor antibody-associated encephalitis, a disorder that may occur in patients with a propensity for autoimmunity and sometimes co-existent anti-GAD65 antibodies.

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References

Kojima G, Inaba M, Bruno MK. PET-positive extralimbic presentation of anti-glutamic acid decarboxylase antibody-associated encephalitis. *Epileptic Disord* 2014; 16(3): 358-61.

Leypoldt F, Armangue T, Dalmau J. Autoimmune encephalopathies. *Ann N Y Acad Sci* 2014, In press.

Ohkawa T, Satake S, Yokoi N, *et al*. Identification and characterization of GABAA receptor autoantibodies in autoimmune encephalitis. *J Neurosci* 2014; 34(24): 8151-63.

Petit-Pedrol M, Armangue T, Peng X, *et al*. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol* 2014; 13(3): 276-86.

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Authors' response

To the Editor,

We thank Dr. Simabukuro for his interest in our case report (Kojima *et al*., 2014) and appreciate his insightful comment. We agree that the classification of autoim-

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mune encephalopathy associated with antibodies to the cell surface or synaptic proteins is evolving as new antibodies are discovered.

As Dr. Simabukuro points out, anti-GABA-A receptor antibody was not discovered at the time of our patient's presentation and, therefore, was not measured. We agree that there are similarities between our case and recently reported cases of encephalitis with GABA-A receptor antibodies (Petit-Pedrol *et al*., 2014; Ohkawa *et al*., 2014). Notably, the MRI findings of extensive multifocal abnormalities on FLAIR and T2 imaging, with cortical and subcortical involvement without contrast enhancement (Petit-Pedrol *et al*., 2014; *figure 4* [Index Patient 1]), are strikingly similar to those of our patient (Kojima *et al*., 2014). Petit-Pedro *et al*. divides the patients into two groups: (1) patients with high serum and CSF titers of anti-GABA-A receptor antibodies (six patients) and (2) patients with a low serum titer of anti-GABA-A receptor antibodies (12 patients). The clinical outcome and subsequent CSF, EEG, and MRI results of the latter group are relatively variable. Many patients in both of these groups had co-existing antibodies, including thyroid auto-antibodies and anti-GAD, anti-GABA-B receptor, and anti-NMDAR antibodies, among which anti-GAD antibodies were most commonly detected in 6 of 18 patients (Petit-Pedrol *et al*., 2014). Another shared clinical presentation is neurological symptoms which precede seizure episodes; our patient had auditory hallucination for three days before the onset of seizures (Kojima *et al*., 2014) and all of six patients with high titers had epileptic symptoms preceded by, or associated with, a change in behaviour or level of cognition (Petit-Pedrol *et al*., 2014). In addition, hemiparesis prior to seizure was observed both in our patient (before the second seizure attack) (Kojima *et al*., 2014) and in one of the six patients (Petit-Pedrol *et al*., 2014).

Whether the low-titer group can be attributed to anti-GABA-A receptor antibody-related encephalitis, or whether anti-GABA-A receptor antibody is a marker of autoimmunity in these cases needs further study (Suleiman and Dale, 2014). Of the two patients reported by Ohkawa *et al*., one patient did not have seizures (Ohkawa *et al*., 2014). Both of them had invasive thymomas, but our patient's thymoma (benign) was resected years ago, and the patient was in remission at the time of presentation. While these two patients had co-existing anti-LGI1 or anti-CASPR2 antibodies, anti-GAD antibody and thyroid auto-antibody were not mentioned. It would be interesting to determine what the PET scan and pathology would have shown for these patients with anti-GABA-A receptor antibody-associated encephalitis. If there is a discrepancy, as in our case (PET positive but very little inflammation on pathology), this may support the notion that synaptic, but not intracellular, antibodies are causative and that they induce transient neuronal dysfunction, but not overt inflammation and cell death. However, because of the novelty and a very small number of anti-GABA-A receptor antibody-associated encephalitis cases, it is still too soon to attribute the syndrome to anti-GABA-A receptor antibodies. More studies and immunological understanding of the pathogenesis of autoantibody-induced encephalitis will be needed to finalize how we would classify these various syndromes associated with neuronal autoantibodies. It is possible that some of the previous cases of anti-GAD antibody-associated encephalitis with extralimbic involvements may have been associated with anti-GABA-A receptor antibody.

In summary, as in any case report, we acknowledge that we cannot provide final answers on every aspect of this patient, but we still feel our case provides valuable clinical information on pathology, PET imaging, and MRI. We do acknowledge that anti-GAD antibody may not have been pathogenic in our case, and may have simply been a marker of autoimmunity. However, this information was still valuable, because it led to the successful treatment of our patient. As this field of neuroimmunology and neuronal autoantibodies evolves, the nomenclature and classification will be clearer. We do agree that our case may indeed harbour anti-GABA-A receptor antibody and we would like to pursue this possibility in our patient. We thank Dr. Simabukuro for initiating a very fruitful correspondence.

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References

Kojima G, Inaba M, Bruno MK. PET-positive extralimbic presentation of anti-glutamic acid decarboxylase antibody-associated encephalitis. *Epileptic Disord* 2014; 16(3): 358-61.

Ohkawa T, Satake S, Yokoi N, *et al*. Identification and characterization of GABA(A) receptor autoantibodies in autoimmune encephalitis. *J Neurosci* 2014; 34(24): 8151-63.

Petit-Pedrol M, Armangue T, Peng X, *et al*. Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABAA receptor: A case series, characterisation of the antigen, and analysis of the effects of antibodies. *Lancet Neurol* 2014; 13(3): 276-86.

Suleiman J, Dale RC. The recognition and treatment of autoimmune epilepsy in children. *Dev Med Child Neurol* 2014, in press.

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