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Psychiatric symptoms delay the diagnosis of anti-LGI1 encephalitis

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ABSTRACT

The aim of this study was to analyze the detailed characteristics of the psychiatric symptoms in patients with anti-LGI1 encephalitis. Of 16 patients, ten showed psychiatric symptoms as the initial manifestations. All 10 patients experienced mood-related symptoms. The time to immune therapy was longer in those with initial psychiatric symptoms compared to those without them. Initial manifestation of psychiatric symptoms in patients with anti-LGI1 encephalitis may be a poor prognostic factor, at least in the short term, in that it misleads both the patients and the clinicians to neglect the typically accompanied symptoms of the disease such as faciobrachial dystonic seizure, delaying the timing of immune therapy.

1. Introduction

Discovery of autoimmune synaptic encephalitis has opened a new era of autoimmune neurology in that it sheds a light on the diagnosis and treatment of many undiagnosed patients. As the diagnostic criteria of autoimmune encephalitis have been documented, psychiatric symptoms have been recognized as one of the key clinical manifestations of the disease (Graus et al., 2016). Recently, patients formerly misdiagnosed as having psychiatric disorders such as bipolar disorder and schizophrenia, have been identified as having autoimmune inflammatory encephalitis. For example, anti-*N*-methyl D-aspartate receptor (NMDAR) encephalitis can occur with isolated psychiatric symptoms seen as an initial manifestation in 4% of the patients (Kayser et al., 2013), and > 65% of the patients with anti-NMDAR encephalitis have psychiatric features as accompanying symptoms (Titulaer et al., 2013). Furthermore, 6.5% of patients that fulfilled the DSM-IV criteria for schizophrenia were found to have the anti-NMDAR antibody (Pollak et al., 2013). The psychiatric symptoms of autoimmune encephalitis are perilous not only because they mislead clinicians to the wrong diagnosis but also because classic management such as dopaminergic blockers results in uniquely unfavorable side effects, such as rhabdomyolysis as seen in anti-NMDAR encephalitis (Lim et al., 2016).

Anti-leucine-rich glioma inactivated 1 (LGI1) encephalitis is the second most common type of autoimmune synaptic encephalitis (Shin et al., 2013; van Sonderen et al., 2017). LGI1 is a secreted protein that is a component of the voltage gated potassium channel-complex which is involved in neural excitatory signals (van Sonderen et al., 2017), and the antibody against LGI1 is associated with unique human leukocyte antigen subtypes, which disrupt the complex provoking several distinct clinical manifestations represented as memory impairment, faciobrachial dystonic seizure (FBDS), sinus bradycardia, and neuropsychiatric symptoms (Irani et al., 2011; Kim et al., 2017; Lancaster, 2015; Naasan et al., 2014), Shin et al., 2013). Imaging studies with magnetic resonance imaging (MRI) and positron emission tomography (PET) have revealed that the medial temporal lobe and the basal ganglia are the major targets of the antibody and are thought to be the origin of the characteristic symptoms (Chiriboga et al., 2017), Shin et al., 2013, (Wegner et al., 2014). FBDS, the specific involuntary movement affecting the arms and the face, has been well characterized for anti-LGI1 encephalitis including therapeutic response to immunotherapies and the long-term follow up results with cognitive impairment (Irani et al., 2011). However, despite the importance of psychiatric symptoms in autoimmune encephalitis, detailed profiles and prognostic meaning of psychiatric comorbidities in anti-LGI1 encephalitis have not been elucidated.

Here, we analyzed the detailed characteristics of the psychiatric

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symptoms in patients with anti-LGI1 encephalitis. This study includes the therapeutic response of psychiatric symptoms to immunotherapies and their prognostic meaning. This is an institutional prospective cohort study that provides thorough profiles of the anti-LGI1 encephalitis symptoms.

2. Methods

2.1. Enrollment of the patients and review of medical records

We operated a prospective cohort for all patients with autoimmune encephalitis in our institution since June 2012, and identified 18 patients who were diagnosed with anti-LGI1 encephalitis from June 2012 to March 2017 at the Seoul National University Hospital, a tertiary referral hospital. The antibody was confirmed by the protocol as described in previous studies (Lancaster et al., 2010; Lee and Lee, 2016). In brief, we assayed the patients' cerebrospinal fluid (CSF) and serum by immunostaining the rat brain section to ascertain the presence of the brain-reactive autoimmune antibodies. Then a cell-based immunocytochemistry kit (Euroimmun AG, Lübeck, Germany) was utilized to find synaptic autoimmune antibodies such as anti-LGI1, NMDA, contactin-associated protein-like 2 (CASPR2), anti-α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid 1 (AMPA1), AMPA2, and γ-aminobutyric-acid type B (GABA-B) receptor. To screen other paraneoplastic antibody (anti-Hu, Yo, Ri, Ma2, CV2, Amphiphysin, Recoverin, Sox1, and Titin antibodies), an immunoblotting kit (Euroimmun AG) was used.

We described the patients' symptoms into three categories: The onset of the disease, Chief Complaint, Initial presentation at the time of diagnosis of anti-LGI1 encephalitis. The onset of the disease is the first symptom that the patient or his/her family noticed to have changed in the patient's state. The chief complaint is a symptom for which the patient or his/her family decided to visit a doctor. Initial presentation at the time of diagnosis of anti-LGI1 encephalitis is the symptoms that the patients manifested at the time of anti-LGI1 encephalitis diagnosis.

The history taking was done by three neurologists (S.L, K.C., S.K.L.). Among 16 patients, the psychiatric symptoms of 3 patients were further analyzed by consultation of the psychiatric department of Seoul National University Hospital. All medical records were reviewed from the onset of the disease until the final clinic visit (April 2017) of the patients by four neurologists (Y.J., S.L., J.L., J.J.). Then, five neurologists (J.L., T.K., J.M., K-I.P., K.J.) classified the psychiatric symptoms of the patients according to the checklist of the Vanderbilt-Kennedy center. Two patients were excluded: one patient had medical records that did not fully describe the psychiatric symptoms, and the other patient had psychosis, which was revealed to be the side effect of levetiracetam and disappeared fully after the termination of this antiepileptic drug. The Autoimmune Encephalitis Cohort Study was approved by the Institutional Review Board of the Seoul National University (2520140040). Written informed consent was obtained from all patients that were registered into the cohort.

2.2. Classification of psychiatric symptoms

The psychiatric symptoms of the patients were classified into five categories related to anxiety, mood, sleep issues, psychosis, and impulsivity according to the Psychiatric symptoms and Behavior check list of the Vanderbilt-Kennedy center. (The Vanderbilt-Kennedy center) The psychiatric symptoms were categorized into the three time points based on when the patient received immune therapies (IT): before the IT, after the first-line IT, and after the second-line IT. In all cases, the first-line IT was immediately administered when the patient was diagnosed with anti-LGI1 encephalitis, and the time to the IT was calculated as the duration from the onset of any clinical symptoms that patients manifested to the first day of the administration of the steroid, the plasma exchange, or the intravenous immunoglobulin (IVIG). The second-line IT was Rituximab (RTX), or Tocilizumab (TCZ). No patient was treated with cyclophosphamide in this institution.

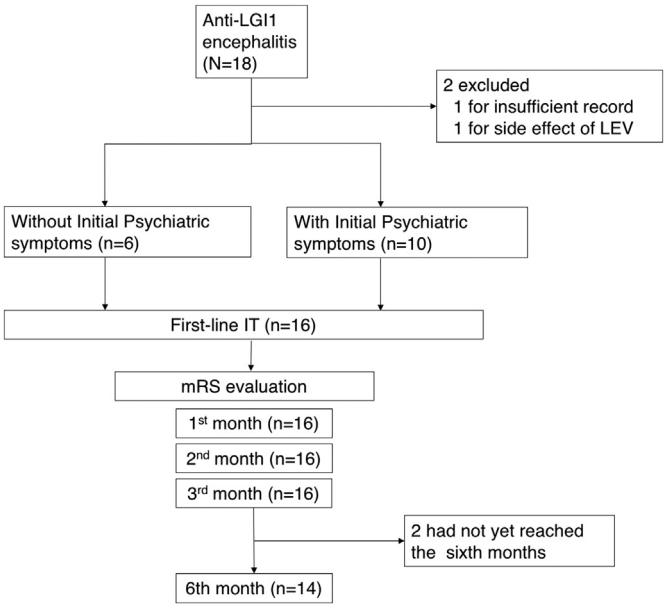

Fig. 1. Study population profile and the evaluation time of the modified Rankin scale (mRS) for the patients with anti-LGI1 encephalitis. LEV = levetiracetam; IT = immune therapy.

2.3. The evaluation of the prognosis

The prognosis of the patients with anti-LGI1 encephalitis was investigated by examining the modified Rankin scale (mRS). The mRS of the patients was evaluated at six time points: the initial and final visit of the clinic, and the first, second, third, and sixth month from the first day of the administration of the IT. Two patients had not yet reached the sixth month mark of the first-line IT; therefore, they were excluded in the analysis of the prognosis at this time point (Fig. 1). Relapse was diagnosed based on whether the patient showed worsening of symptoms at the following visit to the clinic after stabilization or improvement.

2.4. The statistical analysis

Fisher's exact test was applied for the analysis of the binary and higher order data. Ordinal and numerical data were evaluated by the Mann-Whitney *U* test. Generalized estimating equation was performed accounting for correlation in repeated measured mRSs. STATA 14 (StataCorp LLC., Texas, USA) was used for all the analyses, and a *p*-value $< .05$ was considered as statistically significant.

3. Results

3.1. Detailed profiles of the psychiatric symptoms

Of the 16 patients with anti-LGI1 encephalitis, 12 (75%) experienced psychiatric symptoms during the course of the disease. All the patient with psychiatric symptoms accompanied other typical manifestations of anti-LGI1 encephalitis such as FBDS, partial/generalized seizure, and cognitive impairment. Ten (62.5%) had the symptoms at the time of diagnosis of anti-LGI1 encephalitis, and they all manifested at least one of the mood-related symptoms. Depressed mood was the most common symptom that six (37.5%) patients had. Four (25%) suffered from general anxiety, three (18.75%) had sleep issues, and five (31.25%) showed psychosis (Table 1, Supplementary Table 1). One of the five patients who experienced psychosis had hallucination on two