



Anti-NMDA-receptor antibody in initial diagnosis of mood disorder

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Super- or abnormal sensitivity

Abstract

Anti-NMDAR encephalitis is increasingly recognized as one etiology of psychiatric symptoms, but there is not enough evidence on patients with mood disorder. We assayed anti-NR1/NR2B IgG antibodies in serum and/or cerebrospinal fluid of 62 patients initially diagnosed with mood disorder by a cell-based assay. We also investigated the specific patient characteristics and psychotic symptoms. At first admission, the patients showed only psychiatric symptoms without typical neurological signs or abnormal examination findings. Four of the 62 patients had anti-NR1/NR2B IgG antibodies. The anti-NR1/NR2B IgG antibody-positive patients showed more super- or abnormal sensitivity ($P=0.00088$), catatonia ($P=0.049$), and more conceptual disorganization ($P < 0.0001$), hostility ($P=0.0010$), suspiciousness ($P < 0.0001$), and less

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emotional withdrawal ($P < 0.0001$) and motor retardation ($P < 0.0001$) on the Brief Psychiatric Rating Scale than the antibody-negative patients. During the clinical course, anti-NR1/NR2B IgG antibody-positive patients showed more catatonia ($P = 0.0042$) and met Graus's criteria for diagnosis of anti-NMDAR encephalitis, but negative patients did not. Immunotherapy was effective for anti-NR1/NR2B IgG antibody-positive patients, and there was the weak relationship ($R^2 = 0.318$) between the anti-NR1/NR2B IgG antibody titer in the cerebrospinal fluid and the Brief Psychiatric Rating Scale score.

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1. Introduction

Anti-N-methyl D-aspartate receptor (NMDAR) encephalitis is caused by interaction between the NMDAR subunits NR1/NR2B and specific IgG antibodies (Dalmau et al., 2007). Anti-NMDAR encephalitis has become an increasingly recognized etiology of psychiatric symptoms (Kayser and Dalmau, 2016), and 76% of patients with anti-NMDAR encephalitis are first examined by psychiatrists (Dalmau et al., 2008). The typical course of anti-NMDAR encephalitis is divided into five phases: prodromal, psychotic, unresponsive, hyperkinetic, and gradual recovery (Dalmau et al., 2011; Iizuka et al., 2008). In the psychotic phase, patients with anti-NMDAR encephalitis demonstrate various psychiatric symptoms, such as anxiety, depression, aggression, mania, hallucination, or delusion (Dalmau et al., 2011; Iizuka et al., 2008; Kayser et al., 2013). Neurological or physical symptoms such as convulsion, impaired consciousness, hypoventilation, involuntary movement, and autonomic nervous symptoms subsequently appear (Dalmau et al., 2007; Iizuka et al., 2008). Some patients (about 4%) show no neurological or physical symptoms and develop predominantly or apparently only isolated psychiatric symptoms (Kayser et al., 2013), and there are several reports of chronic patients with initially diagnosed psychosis who had anti-NMDAR encephalitis (Senda et al., 2015; Tsutsui et al., 2012; Yoshimura and Takaki, 2017). Abnormalities in cerebrospinal fluid (CSF) (92%) and on electroencephalogram (EEG) (91%) are reported in patients with anti-NMDAR encephalitis (Schmitt et al., 2012; Viaccoz et al., 2014). Though quick diagnosis and initiation of appropriate immunotherapies and tumor removal produce a good outcome in 94% patients (Titulaer et al., 2013), the examinations for diagnosis of anti-NMDAR encephalitis may be difficult to perform on patients with severe psychosis or without neurological signs.

Mood disorder (MD) is a common, chronic, and debilitating disorder with a complicated and multifactorial etiology. The lifetime prevalences of major depressive disorder (14.4%) and bipolar disorder (4.1%) are relatively high (Kessler et al., 2012). Functional impairment due to MD causes social and economic difficulties (Simon, 2003). Suicidal ideation and suicide attempts by patients with MD have a very high frequency (Sokero et al., 2003; Valtonen et al., 2005). Though the pharmacotherapy of depression has been improved by more selective antidepressants such as selective serotonin reuptake inhibitors (SSRI) and selective serotonin-norepinephrine reuptake inhibitors (SNRI) (Malhi et al., 2013), the remission rate due to the first administered antidepressant is only about 30% (Gaynes et al., 2009).

Thus, non-monoamine-based etiological hypotheses of MD (e.g., glutamate hypothesis) have been proposed (Sanacora et al., 2012).

Several studies previously reported that anti-NMDAR antibodies have a potential to cause schizophrenia-like symptoms (Hammer et al., 2014; Lennox et al., 2017; Steiner et al., 2013, 2014). By contrast, there are a few studies of the relationships between anti-NMDAR encephalitis and other psychiatric disorders, especially MD in serum (Hammer et al., 2014; Steiner et al., 2013, 2014) but the results were not consistent. Though all subunits of anti-NR1 antibodies are reported to have pathogenic potential (Castillo-Gómez et al., 2017), anti-NR1 IgG antibodies, which are highly specific (Armangue et al., 2014), induce internalization of NMDAR (Hughes et al., 2010) and decrease NMDAR, but IgM, and IgA do not (Hara et al., 2018). In addition, anti-NMDAR antibodies recognize the conformational heteromers of NR1/NR2B or NR1/NR2A/NR2B and the conformations of NR1 and NR2B are thought to be important for more syndrome-specific detection (Dalmau et al., 2007; Sansing et al., 2007).

In order to distinguish pure MD and anti-NMDAR encephalitis, we assayed anti-NR1/NR2B IgG antibodies in serum and/or CSF of patients initially diagnosed with MD by a cell-based assay (CBA). We also investigated the specific patient characteristics and psychotic symptoms that may be indications for lumbar puncture.

2. Methods

2.1. Subjects (Fig. 1)

This study was a prospective study approved by the Okayama University ethics committee. One hundred patients initially suspected of MD were newly hospitalized in Okayama University Hospital between March 2017 and May 2018. After obtaining informed consent, 62 patients who or whose families agreed to this study were included. We assessed the presence of anti-NR1/NR2B IgG antibodies in serum and/or CSF by CBA. The entire sample study consisted of 61 sera and 13 CSF samples. Two trained psychiatrists (M.T. and S.S.) assessed the clinical records of patients and diagnosed them based on the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).

2.2. Comparison of clinical characteristics

At first admission (Table 1), the backgrounds of 62 patients with an initial diagnosis of mood disorder were assessed, including sex, age, severe psychosis (not moderate) (DSM-IV), and duration (less than 3 months) of any previous psychiatric episode, history of psychosis

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