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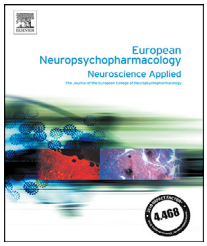

Anti-NMDA-receptor antibody in initial diagnosis of mood disorder

Hiroki Kawai[a], Manabu Takaki[a,*], Shinji Sakamoto[a], Takashi Shibata[b], Ayaka Tsuchida[a], Bunta Yoshimura[c], Yuji Yada[a,c], Namiko Matsumoto[d], Kota Sato[d], Koji Abe[d], Yuko Okahisa[a], Yoshiki Kishi[c], Soshi Takao[e], Ko Tsutsui[f], Takashi Kanbayashi[f,g], Keiko Tanaka[h], Norihito Yamada[a]

[a] *Department of Neuropsychiatry, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, 2-5-1 Shikata-cho, Kita-ku, Okayama 700-8558, Japan*
[b] *Department of Child Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan*
[c] *Department of Psychiatry, Okayama Psychiatric Medical Center, Japan*
[d] *Department of Neurology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan*
[e] *Department of Epidemiology, Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences, Japan*
[f] *Department of Neuropsychiatry, Akita University Graduate School of Medicine, Japan*
[g] *International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, Japan*
[h] *Brain Research Institute, Niigata University Graduate School of Medicine, Japan*

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Catatonia;
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

* Corresponding author.
E-mail address: manabuta@cc.okayama-u.ac.jp (M. Takaki).

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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

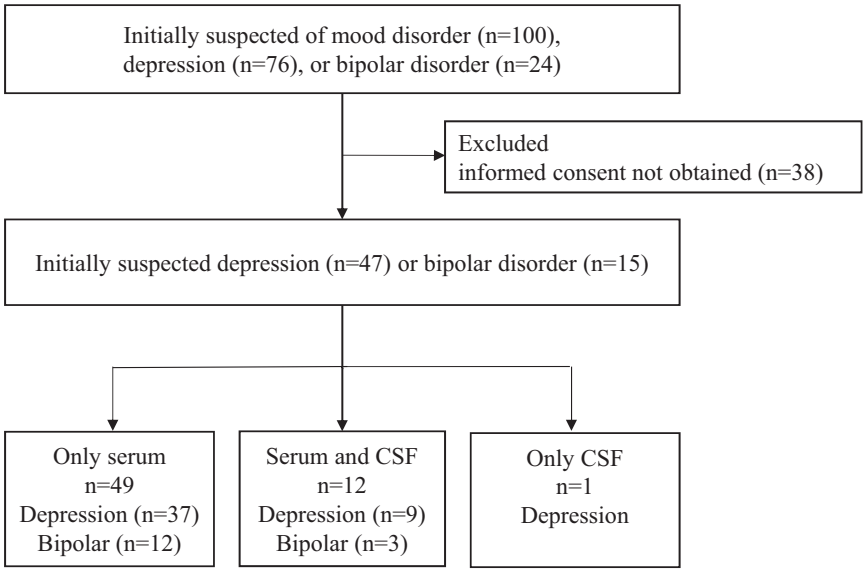

Fig. 1 Selection of subjects.
Sixty-two patients initially suspected of MD were newly hospitalized in Okayama University Hospital between March 2017 and May 2018. After obtaining informed consent from the patient or near relatives, 62 patients were included in this study. We assessed the presence of anti-NR1/NR2B IgG antibodies in serum and/or CSF by CBA. The entire sample study consisted of 61 serum and 13 CSF samples.

Table 1 Comparison of patients with or without NMDAR antibody at first admission.

Age	NMDAR Ab (+) ($n=4$)		NMDAR Ab (−) ($n=58$)		*P* value
	26.5 ± 14.0		40.2 ± 14.7		
	n	%	*n*	%	
Sex (Female)	3	75	37	63.8	0.553
Age (under 21 y.o.)	1	25	3	5.2	0.239
Severe psychosis (not moderate)	3	75	21	36.2	0.156
Duration (less than 3 months)	3	75	26	44.8	0.258
Heredity of psychosis	1	25	15	25.9	0.727
During pregnancy	0	0	3	5.2	0.815
History of ovarian teratoma	1	25	0	0	0.064
Prior infection	1	25	3	5.2	0.239
Super or abnormal sensitivity	4	100	8	13.8	**0.00088***
Catatonia	3	75	13	22.4	**0.049***

during pregnancy, history of ovarian teratoma, infection prior to previous psychiatric episode, super- or abnormal sensitivity, and catatonia. Super- or abnormal sensitivity excluded the hallucinations that patients with schizophrenia show (DSM-IV). Catatonia was defined according to DSM-V. We also independently assessed 18 psychiatric symptoms using the Brief Psychiatric Rating Scale (BPRS) score at first admission (Table 2).

During the clinical course (Table 3), we applied the diagnostic criteria of anti-NMDAR encephalitis (Graus et al., 2016) and assessed a patient as category 1 if he or she had at least four of the following six signs and symptoms: (1) abnormal behavior (psychosis, delusions, hallucinations, agitation, aggression, or catatonia), (2) speech dysfunction (pressured speech, verbal reduction, mutism), (3) seizures, (4) movement disorder (dyskinesia or rigidity/abnormal postures), (5) decreased level of consciousness, and (6) autonomic dysfunction or central hypoventilation. Patients were assessed as category 2 if they had at least one of the following two signs and symptoms: (1) abnormal EEG (focal or diffuse slow or disorganized activity, epileptic activity, or extreme delta brush) and (2) CSF with pleocytosis or oligoclonal bands. Other disorders including neuroleptic malignant syndrome were excluded.

2.3. Statistical analysis

The difference between patients with positive or negative anti-NR1/NR2B IgG antibodies (Tables 1–3) was analyzed by Fisher's exact test, and a Bonferroni correction was conducted for 18 multiple comparisons ($P < 0.0028$, Table 2), and nine multiple comparisons ($P < 0.0056$, Table 3). The relationship between the anti-NMDAR antibody titer and BPRS score was evaluated by linear regression analysis. We conducted these analyses using SPSS Statistics software version 19.0 (SPSS Japan Inc., Tokyo, Japan). In the post hoc power analysis, we used G*Power: Statistical Power Analyses for Windows (Heinrich Heine) and found that our sample size had >0.80 power in any association analysis.

Table 2 Brief Psychiatric Rating Scale of patients with or without NMDAR antibody at first admission.

		NMDAR Ab (+) ($n=4$)		NMDAR Ab (−) ($n=58$)		*P* value
		n	%	*n*	%	
1	Somatic concerns	2	50	57	98.3	0.0093
2	Anxiety	3	75	57	98.3	0.1258
3	Emotional withdrawal	1	75	57	98.3	**<0.0001***
4	Conceptual disorganization	3	75	0	0	**<0.0001***
5	Guilt feelings	2	50	57	98.3	0.0093
6	Tension	4	100	14	24.1	0.0054
7	Mannerisms and posturing	0	0	0	0	-
8	Grandiosity	1	25	1	1.7	0.1250
9	Depressive mood	2	50	58	100	0.0031
10	Hostility	3	75	2	3.4	**0.0010***
11	Suspiciousness	3	75	1	1.7	**<0.0001***
12	Hallucinatory behavior	0	0	0	0	-
13	Motor retardation	1	25	57	98.3	**<0.0001***
14	Uncooperativeness	3	75	15	25.9	0.0698
15	Unusual thought content	0	0	0	0	-
16	Blunted affect	0	0	0	0	-
17	Excitement	3	75	4	6.9	0.0035
18	Disorientation	3	75	12	20.7	0.0407

* *P* value was adjusted for 18 multiple comparisons by Bonferroni method ($P < 0.0028$).

Table 3 Comparisons of patients with or without NMDAR antibody during clinical course by Graus et al., 2016.

	NMDAR Ab (+) ($n=4$)		NMDAR Ab (−) ($n=58$)		*P* value
	n	%	*n*	%	
<Category 1> (at least 4 within the following 6)					
(1) Abnormal behavior	4	100	14	24.1	**0.0054***
Catatonia	4	100	13	44.8	**0.0042***
(2) Speech dysfunction	4	100	9	15.5	**0.0012***
(3) Seizures	1	25	0	0	0.064
(4) Movement disorder	4	100	4	6.9	**<0.0001***
(5) Decreased level of consciousness	3	75	0	0	**<0.0001***
(6)Autonomic dysfunction or central hypoventilation	2	50	26	44.8	0.616
<Category 2> (at least 1 within the following 2)					
(1) Abnormal EEG	3	75	0	0	**<0.0001***
(2) CSF (pleocytosis or oligoclonal bands)	4	100	0	0	**<0.0001***

* *P* value was adjusted for 18 multiple comparisons by Bonferroni method ($P < 0.0056$).

2.4. Cell-based assay (CBA)

Details are given in Appendix 1.

3. Results

3.1. Clinical summary of anti-NR1/NR2B antibody-positive patients (Fig. 2)

Of 62 patients who were initially diagnosed with MD, CSF was obtained from 13. Four patients had anti-NR1/NR2B IgG antibodies in CSF as identified by CBA, and three of the four patients also had anti-NR1/NR2B IgG antibodies in serum. Anti-NR1/NR2B IgG antibody-positive patients had more frequent super- or abnormal sensitivity ($P=0.00088$) and catatonia ($P=0.049$) than negative patients. During the clinical course, their moods were mixed, and the degrees of their symptoms were severe (3) or moderate (1). One patient (#3) had a family history of bipolar disorder. One patient (#4) had non-specific flu-like symptoms before the psychiatric symptoms. One patient (#1) had bilateral ovarian teratomas, and one patient (#2) had a heterotopic pregnancy. Antipsychotics and/or a mood stabilizer (valproic acid) were administered to alleviate their manic symptoms but were not effective. At first admission, they showed only psychiatric symptoms without neurological signs. They all showed super- or abnormal sensitivity. Three patients (#1, 2, 3) met the diagnosis criteria of catatonia of DSM-5 at first admission, and all four met the criteria of catatonia later.

Clinical summary of anti-NR1/ NR2B antibody positive patients

Patient # (Age/Sex)	#1 (22/F)	#2 (49/F)	#3 (25/M)	#4 (13/F)
NR1/ NR2B Ab (CSF / serum)	1 : 1280 / +	1 : 160/ -	1 : 1280/ +	1 : 320/ +
Initial psychiatric diagnosis	Bipolar	Bipolar	Bipolar	Depression
Duration only with psychiatric symptoms	17 days	3 years	33 days	40 days
Heredity of psychosis	-	-	Bipolar	-
Prior infection	-	-	-	+
Tumor or pregnancy	Ovarian teratoma (22 y.o.)	Heterotopic pregnancy (20 y.o.)	-	-
Psychotropic	Not effective	Not effective	Not effective	Not administrated
Super or abnormal sensitivity	Abnormal vision Music hallucination	Hypersensitivity to noise	Hypersensitivity to noise	Hypersensitivity to noise and light
Catatonia (DSM-V)	+	+	+	+
Abnormal behavior	Aggression, agitation, excitement, severe tension	Hypersexuality, regression, excitement, suicide attempt	Hypersexuality, regression, excitement, euphoria	Regression, excitement (later), euphoria (later)
Speech dysfunction	Mutism	Pressured speech Mutism	Pressured speech	Mutism
Seizures	+	-	-	-
Movement disorder	Tongue dyskinesia	Dysarthria Horizontal nystagmus	Dysarthria	Dysarthria Right cheek numbness
Decreased level of consciousness	+	-	+	+
Autonomic dysfunction or central hypoventilation	+	-	-	-
Abnormal EEG	+	-	+	+
Abnormal MRI	+	+	-	-
CSF (pleocytosis / monocyte)	8/μl	5/μl	7/μl	3/μl
CSF (oligoclonal bands)	+	+	+	N/A
CSF (protein)	48 mg/dl	71 mg/dl	55 mg/dl	24 mg/dl
other autoimmune Ab	aCL	AQP4	-	TPO, GAD
Immunotherapy	Tumor resection, mPSL pulse, IV Ig, PE	mPSL pulse, IV Ig, PE	mPSL pulse, PE	mPSL pulse, IV Ig, PE, rituximab
NR1/ NR2B Ab after immunotherapy	1 : 1280 (CSF)	1 : 20 (CSF)	-	-

Fig. 2 Clinical summary of four anti-NR1/ NR2B antibody-positive patients.
Super- or abnormal sensitivity excluded the hallucination that patients of schizophrenia show (DSM-IV), and catatonia was defined by DSM-V. CSF: cerebrospinal fluid, EEG: electroencephalogram, MRI: magnetic resonance imaging, TPO: thyroid peroxidase, GAD: glutamic acid decarboxylase, AQP4: aquaporin 4, mPSL: methylprednisolone, PE: plasma exchange, IVIg: intravenous immunoglobulin.

During the clinical course, they showed speech dysfunction (4), seizure (1), movement disorder (4), decreased level of consciousness (3), central hypoventilation (1), abnormal EEG (3), or pleocytosis or oligoclonal bands in CSF (3). Patients 1, 2, and 3 also had autoimmune antibodies to thyroid peroxidase (TPO), glutamic acid decarboxylase (GAD), aquaporin 4 (AQP4), or cardiolipin.

First-line (methylprednisolone (mPSL) pulse therapy, plasma exchange (PE), intravenous immunoglobulin (IVIg)) immunotherapies, or second-line immunotherapy (rituximab) were administered to the antibody-positive patients; the neurological and psychiatric symptoms of the three patients improved dramatically, and anti-NR1/NR2B IgG antibodies in CSF of two patients became negative. Even after immunotherapies, patient #1 still had anti-NR1/NR2B IgG antibodies (>x1280) and her consciousness and EEG findings had not improved after one year. A typical case (patient #3) is shown in Appendix 2 and the Supplemental figure.

3.2. Comparisons of patients with or without NMDAR antibody at first admission (Table 1)

The moods of the 58 antibody-negative patients were depression (56) or a mixed state (2), and the degrees of the symptoms were severe (21) or moderate (37). Twenty-six patients had a previous psychiatric episode within three months. Three negative patients were pregnant. Three negative patients had an episode of non-specific flu-like symptoms before psychiatric symptoms. Nine patients had super- or abnormal sensitivity (hypersensitivity to light and/or noise (5), visual hallucination (2), or auditory hallucination (2)). Thirteen patients met the diagnostic criteria of catatonia of DSM-5. The anti-NR1/NR2B IgG antibody-positive patients showed more super- or abnormal sensitivity ($P = 0.00088$), catatonia ($P = 0.049$).

3.3. BPRS of patients with or without NMDAR antibody at first admission (Table 2)

We compared psychiatric symptoms at the first admission higher than score 2 (mild symptom) on BPRS. Anti-NR1/NR2B IgG antibody-positive patients showed more conceptual disorganization ($P < 0.0001$), tension ($P = 0.0054$), hostility ($P = 0.0010$), suspiciousness ($P < 0.0001$), excitement ($P = 0.0035$), and disorientation ($P = 0.0407$) than negative patients, but the differences in tension, excitement, and disorientation were lost after Bonferroni correction for

post hoc comparisons. Anti-NR1/NR2B IgG antibody-positive patients showed fewer somatic concerns ($P = 0.0093$), less emotional withdrawal ($P < 0.0001$), fewer guilt feelings ($P = 0.0093$), less depressive mood ($P = 0.0031$), and less motor retardation ($P < 0.0001$) than the nine negative patients, but the differences in somatic concerns, guilt feelings, and depressive mood were lost after Bonferroni correction for post hoc comparisons.

3.4. Comparisons of patients with or without NMDAR antibody during clinical course according to criteria of Graus (Table 3)

During the clinical course, anti-NR1/NR2B IgG antibody-positive patients met diagnosis criteria categories 1 and 2 of anti-NMDAR encephalitis (Graus et al., 2016), but negative patients did not. Negative patients showed abnormal behavior (14): catatonia (13), manic symptoms (1), speech dysfunction (9): mutism (8), pressured speech (1), movement disorder (4): dysarthria (1), myoclonus (1), eye blinking (1), dyskinesia (2), autonomic dysfunctions (26): fever (17), hypertension (14), tachycardia (10), and hypersalivation (1)). Negative patients showed no seizure, decreased level of consciousness, or abnormal EEG or MRI findings. The CSF of the nine anti-NMDAR antibody-negative patients who had CSF taken had a protein increase (7) but didn't have pleocytosis and OCB.

After the statistical analysis, anti-NR1/NR2B IgG antibody-positive patients showed more abnormal behavior ($P = 0.0054$), catatonia ($P = 0.0042$), speech dysfunction ($P = 0.0012$), movement disorder ($P < 0.0001$), decreased level of consciousness ($P < 0.0001$), abnormal EEG ($P < 0.0001$), CSF with pleocytosis, and oligoclonal bands ($P < 0.0001$) than negative patients.

3.5. Relationship between anti-NMDAR antibody titer and Brief Psychiatric Rating Scale

In anti-NR1/NR2B IgG antibody-positive patients, tension (3), hostility (3), uncooperativeness (3), and excitement (3) were frequent and higher than score 4 (moderate) on BPRS. Mannerisms and posturing, hallucination, unusual thought content, and blunted affect were not present (Table 4). BPRS scores of three of the four patients were reduced after immunotherapies, and there was a weak relationship ($R^2 = 0.318$) between the anti-NR1/NR2B IgG antibody titer in CSF and the BPRS score (Fig. 3).

4. Discussion

Four patients initially suspected of MD had anti-NR1/NR2B IgG antibodies in their CSF. They showed only psychiatric symptoms without typical neurological signs at first admission. During the clinical course, they developed typical neurological signs and abnormal examination findings of anti-NMDAR encephalitis. When we distinguish anti-NMDAR encephalitis from pure MD during the period with no typical neurological sign, super- or abnormal sensitivity, catatonia, conceptual disorganization, hostility, and suspiciousness may be suggested to be specific symptoms of anti-NMDAR encephalitis.

This is the first study to consider super- or abnormal sensitivity in anti-NMDAR encephalitis. Forms of super- or abnormal sensitivity like hypersensitivity to light and/or noise, visual hallucination, or auditory hallucination in this study were observed in both anti-NR1/NR2B IgG antibody-positive and -negative patients. We consider that these psychiatric symptoms are induced by anxiety, tension, or depressive mood. They may be extrapyramidal side effects induced by antipsychotics, although one anti-NR1/NR2B IgG antibody-positive patient (patient #4) and four negative patients who showed super- or abnormal sensitivity were not administered antipsychotics. Patients with epilepsy are reported to show abnormal sensitivity as seizures (Wolf, 2016). Patient #1 in this study showed music hallucination, abnormal vision, and thought a room looked dazzling. This may be not atypical for psychiatric symptoms and may represent seizures arising from Heschl's gyrus (Milner, 2017) and/or the ventral stream (Dierks et al., 1999).

Catatonia occurs in patients with schizophrenia and MD or in association with neurological diseases and other general medical conditions (Tandon et al., 2013) and is reported recently to be an important symptom of NMDAR encephalitis (Warren et al., 2018). One study reported that 32.7% (Warren et al., 2018) and 70.6% (Espinola-Nadurille et al., 2019) of patients with anti-NMDAR encephalitis showed catatonia. Another study indicated that catatonic patients with anti-NMDAR encephalitis fulfill the diagnostic criteria of delirium, which means a decreased level of consciousness (Espinola-Nadurille et al., 2018). In our study, one anti-NR1/NR2B IgG antibody-positive patient didn't meet the diagnosis of catatonia at first admission, but all four patients showed catatonia later, and four of 17 catatonia patients had anti-NR1/NR2B IgG antibodies in CSF. Three of the four anti-NR1/NR2B IgG antibody-positive patients in this study had abnormal EEG, but negative patients did not. When patients show catatonia, EEG may be important to distinguish between MD-induced catatonia and anti-NMDAR encephalitis-induced catatonia.

Among the psychiatric symptoms of anti-NMDAR encephalitis, abnormal behavior, agitation, aggression, hallucination, delusions, mood (manic or depression), and unusual thoughts are frequently reported (Al-Diwani et al., 2019; Ando et al., 2016; Espinola-Nadurille et al., 2018; Kayser et al., 2013; Sarkis et al., 2019; Wang et al., 2017; Warren et al., 2018). This study first evaluated the psychiatric symptoms of anti-NMDAR encephalitis using BPRS. Because we initially diagnosed MD in this study, schizophrenia-like symptoms such as hallucinatory behavior, unusual thought content, and blunted affect are thought to be negligible. On the other hand, conceptual disorganization, hostility, and suspiciousness may not be frequent in MD and become statistically more frequent in patients with anti-NMDAR encephalitis.

Ando et al. reported the possible relationship of anti-NMDAR antibody titers and their psychiatric symptoms (Ando et al., 2016). Unfortunately, they used only serum and didn't use any evaluation scales. Our data indicates a weak relationship between decreasing titers of anti-NR1/NR2B IgG antibodies in CSF and psychiatric symptoms. On the other hand, Dalmau et al. suggested a correlation

Table 4 Brief Psychiatric Rating Scale of anti-NMDAR antibody positive patients.

		Patient 1		Patient 2		Patient 3		Patient 4	
		Initial	Follow-up	Initial	Follow-up	Initial	Follow-up	Initial	Follow-up
1	Somatic concerns	1	N/A	7	4	1	1	3	1
2	Anxiety	6	N/A	7	4	1	1	2	1
3	Emotional withdrawal	1	N/A	1	1	1	1	5	1
4	Conceptual disorganization	3	N/A	3	2	3	1	1	1
5	Guilt feelings	1	N/A	4	2	1	1	2	1
6	Tension	7	N/A	7	3	4	1	2	1
7	Mannerisms and posturing	1	N/A	1	1	1	1	1	1
8	Grandiosity	1	N/A	1	1	6	1	1	1
9	Depressive mood	1	N/A	6	3	1	1	3	1
10	Hostility	7	N/A	6	2	5	1	1	1
11	Suspiciousness	4	N/A	3	1	4	1	1	1
12	Hallucinatory behavior	1	N/A	1	1	1	1	1	1
13	Motor retardation	1	N/A	1	1	1	1	3	1
14	Uncooperativeness	6	N/A	4	2	5	1	1	1
15	Unusual thought content	1	N/A	1	1	1	1	1	1
16	Blunted affect	1	N/A	1	1	1	1	1	1
17	Excitement	7	N/A	6	3	7	1	1	1
18	Disorientation	4	N/A	1	1	2	1	3	1
	Total	54	N/A	61	34	46	18	33	18

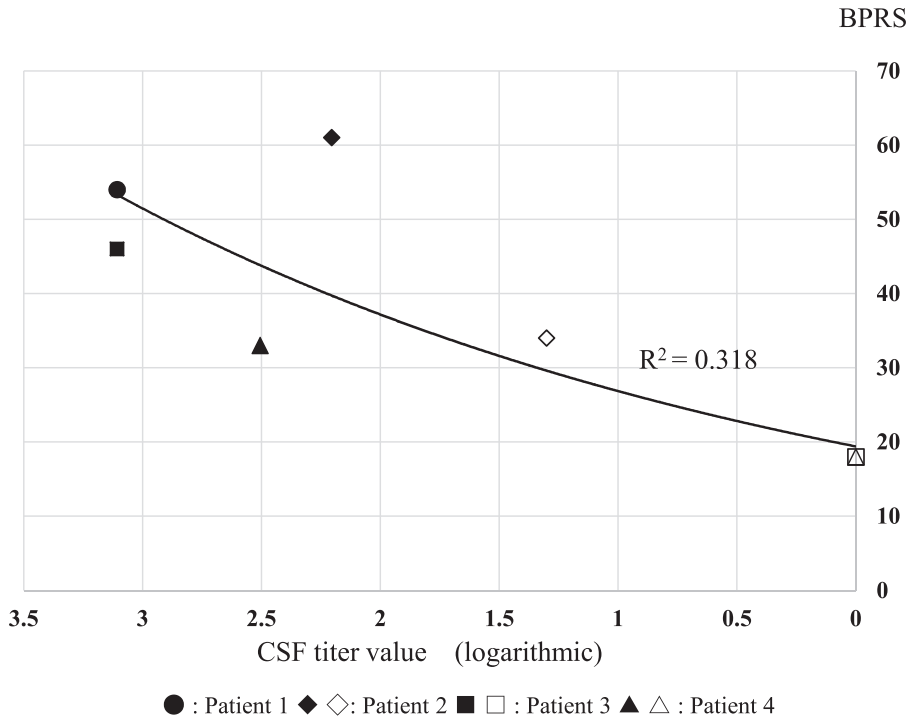

Fig. 3 Relationship between anti-NMDAR antibody titer and Brief Psychiatric Rating Scale score.
The relationship between the anti-NMDAR antibody titer and BPRS score was analyzed by linear regression analysis. We conducted all analyses using SPSS Statistic software version 19.0 (SPSS Japan Inc., Tokyo, Japan). BPRS scores of the three patients were reduced after immunotherapies, and there was a weak relationship ($R^2 = 0.318$) between the anti-NR1/NR2B IgG antibody titer in CSF and BPRS. ● (before immunotherapy) of Patient #1, ♦ (before immunotherapy) ⋄ (after immunotherapy) of Patient #2, ■ (before immunotherapy) □ (after immunotherapy) of Patient #3, ▲ (before immunotherapy) △ (after immunotherapy) of Patient #4. BPRS: Brief Psychiatric Rating Scale, CSF: cerebrospinal fluid.

between anti-NMDAR antibody titers and neurological outcomes (Dalmau et al., 2011; Gresa-Arribas et al., 2014). It may be difficult to measure psychiatric symptoms because the neurological symptoms of anti-NMDAR encephalitis are not qualified as psychiatric symptoms. The anti-NMDAR antibody titers of the two patients who were in complete remission became negative. Thus, we should increase the sample size for clarity.

When a patient presents with typical neurological signs and abnormal examination findings, the diagnostic criteria of anti-NMDAR encephalitis (Graus et al., 2016) are definitely useful to distinguish anti-NMDAR encephalitis from pure MD. Autonomic dysfunction was not statistically different between pure MD and anti-NMDAR encephalitis patients in this study. The reasons may be that MD patients frequently have autonomic dysfunction (Sgoifo et al., 2015).

Among the etiological hypotheses of MD, the glutamate hypothesis is recently considered influential (Sanacora et al., 2012). Glutamate is the most plentiful and crucial excitatory neurotransmitter in the brain and plays important roles in nutrition, metabolism, and signaling (Meldrum, 2000). Glutamate transmission is strictly regulated in the brain (Fonnum, 1984), and an excess of synaptic glutamate causes neurotoxicity (Olney and Sharpe, 1969). Glutamate regulation is a key to psychiatric disorders such as schizophrenia (Javitt, 2004). Patients with MD experience dysregulation of the glutamine/glutamate cycle and have significantly higher glutamine levels in CSF than controls (Levine et al., 2000). Levels of glutamate also increase in the frontal cortex of patients with MD (Hashimoto et al., 2007). A significant effect of ketamine in treatment-resistant depression patients is reported frequently, and ketamine can produce a quick reduction of depressive symptoms (Murrough et al., 2013). Memantine, a low-affinity NMDA receptor antagonist is effective in treatment and long-term prevention of treatment-resistant bipolar disorders (Serra et al., 2014).

Electroconvulsive therapy (ECT) is also effective for treatment-resistant bipolar disorder (Fountoulakis et al., 2008) and for psychotic and catatonic symptoms in anti-NMDA receptor encephalitis (Matsumoto et al., 2012). Recently, ECT is reported to be effective in treatment of anti-N-methyl-d-aspartate (NMDA) receptor encephalitis (Warren et al., 2019). In our study, ECT was administered to 13 patients who had pure MD and was effective. We should consider administering it to the one patient who did not respond to previous immunotherapies (patient #1). Though ECT mechanisms are still controversial, prolonged electroconvulsive shock leads to a reduction of NMDA receptor activity and potentiation of AMPA receptors in the rat hippocampus (Fumagalli et al., 2010). Regulation of the functional interaction between AMPA and NMDA is necessary for the antidepressant effect of NMDA receptor antagonists (Maeng et al., 2008).

There are several limitations in this study. The sample size may be too small to demonstrate statistical significance. The sensitivity/specificity of CBA in CSF is higher than in serum (Gresa-Arribas et al., 2014). Though this is the first study demonstrating that some patients with initially diagnosed MD have anti-NR1/NR2B IgG antibodies in serum and/or CSF, many patients with severe grade depression or bipolar disorder did not undergo lumbar puncture. Further studies examining CSF in more cases are necessary to validate our findings.

5. Conclusion

Anti-NMDAR antibody was present in the CSF of four patients initially diagnosed with MD. Patients with anti-NMDAR encephalitis exhibit depression or mania in the early clinical phase and are diagnosed with MD. Because immunotherapies are effective and decreases in anti-NR1/NR2B IgG antibody titers are related to the reduction of psychiatric symptoms, identification of anti-NR1/NR2B IgG antibodies in CSF is important for diagnosis of anti-NMDAR encephalitis of patients with an initially suspected mood disorder, especially those whose clinical course is not typical.

Conflicts of interest

There is no conflict of interests in this work.

Contributors

All authors contributed to the conception or design of the work (M Takaki, S Sakamoto, B Yoshimura, N Yamada), or the acquisition, analysis (H Kawai, M Takaki, S Sakamoto, S Takao), or interpretation of data for the work and drafting of the work (H Kawai, M Takaki, S Sakamoto) or revising it critically for important intellectual content (T Shibata, A Tsuchida, B Yoshimura, Y Yada, N Matsumoto, K Sato, K Abe, Y Okahisa, Y Kishi, K Tsutsui, T Kanbayashi, K Tanaka, N Yamada).

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Supplementary materials

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