果がなければ他剤に切り替える。それでも効果がみられなければ多剤治療へ切り替えていく。Kwanらによると、１種類目の抗てんかん薬治療で発作が抑制されたのは患者全体の47%、２種類目で13%であるのに対し、３種類目では１%、２種類の併用療法では３%で発作が抑制されたにすぎない。したがって、２種類の抗てんかん薬を使用して発作が抑制できなければ他の治療法、特にてんかん外科治療を考慮する。

Wiebeらによると、側頭葉てんかんでは外科治療群は薬物治療群と比較して発作が抑制されるものが有意に多かった。特に、海馬硬化を伴う内側側頭葉てんかんや皮質形成異常などの器質性病変を伴う症候性部分てんかんは外科治療の適応とされている。

てんかんには身体・精神的合併障害、あるいは心理社会的問題が伴うことが多い。これらの問題がてんかんのある人のQOLや日常・社会生活に大きな影響を及ぼす。てんかん治療では、薬物治療や外科治療などの狭義の医療だけでは不十分であり、てんかんのある人のさまざまな問題に対応する包括医療が重要である。例えば、患者・家族教育、心理的支援、生活支援、就労支援などのリハビリテーションが行われる必要がある。

経過・予後

てんかん症候群により発作予後はさまざまである。小児の特発性部分てんかんは多くが思春期以降に自然寛解する。若年ミオクロニーてんかんなどの特発性全般てんかんは抗てんかん薬による治療が奏効することが多いが、断薬後の再発のリスクが高く注意が必要である。症候性全般てんかんの予後は概して悪く、発作が完全に抑制されることは少ない。症候性部分てんかんの予後はさまざまである。

前述のように、てんかんでは発作以外の合併障害や諸問題が出現することが多いことから、てんかんの予後は、発作予後のみならず生命予後、知的予後、障害予後、精神医学的予後、心理社会的予後など包括的に考慮する必要がある。

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A Novel Treatment-Responsive Encephalitis with Frequent Opsoclonus and Teratoma

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Among 249 patients with teratoma-associated encephalitis, 211 had N-methyl-D-aspartate receptor antibodies and 38 were negative for these antibodies. Whereas antibody-positive patients rarely developed prominent brainstem–cerebellar symptoms, 22 (58%) antibody-negative patients developed a brainstem–cerebellar syndrome, which in 45% occurred with opsoclonus. The median age of these patients was 28.5 years (range = 12–41), 91% were women, and 74% had full recovery after therapy and tumor resection. These findings uncover a novel phenotype of paraneoplastic opsoclonus that until recently was likely considered idiopathic or postinfectious. The triad of young age (teenager to young adult), systemic teratoma, and high response to treatment characterize this novel brainstem–cerebellar syndrome.

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The discovery of anti–N-methyl-D-aspartate receptor (NMDAR) encephalitis in 2007[1] has brought attention to a relationship between systemic teratomas and autoimmune encephalitis. Since 2007, we have studied 249 patients with teratoma-associated encephalitis; most of these patients had antibodies against the NR1 subunit of the NMDAR, but 38 were NMDAR antibody negative. When these 38 patients were compared with those with NMDAR antibodies, a novel brainstem–cerebellar syndrome that frequently associates with opsoclonus emerged. The current study describes the clinical differences between NMDAR antibody-positive and antibody-negative patients with systemic teratoma, and focuses on the novel brainstem–cerebellar syndrome and the subgroup of patients with opsoclonus.

Patients and Methods

From January 2007 until September 2012, serum and CSF of 249 patients with teratoma-associated encephalitis were studied at the Department of Neurology, Hospital of the University of Pennsylvania and at the Neurology Service, Hospital Clinic, August Pi i Sunyer Biomedical Research Institute, University of Barcelona. The presence of a systemic teratoma was confirmed pathologically in 234 patients and radiologically in 15. Information was obtained by the authors or provided by referring physicians at symptom onset and at regular intervals during the course of the disease using a comprehensive questionnaire that includes all symptoms shown in the Figure.[2] Sera and cerebrospinal fluid (CSF) were examined for antibodies to NMDA, α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, γ-aminobutyric acid (B), and mGluR5 receptors, LGI1, Caspr2, onconeuronal proteins (Hu, CRMP5, Ma1–2, amphiphysin), and GAD65, using reported techniques including brain immunohistochemistry, immunoblot, and cell-based assays.[3–5] Patients without NMDAR antibodies were further studied for antibodies to dipeptidyl-

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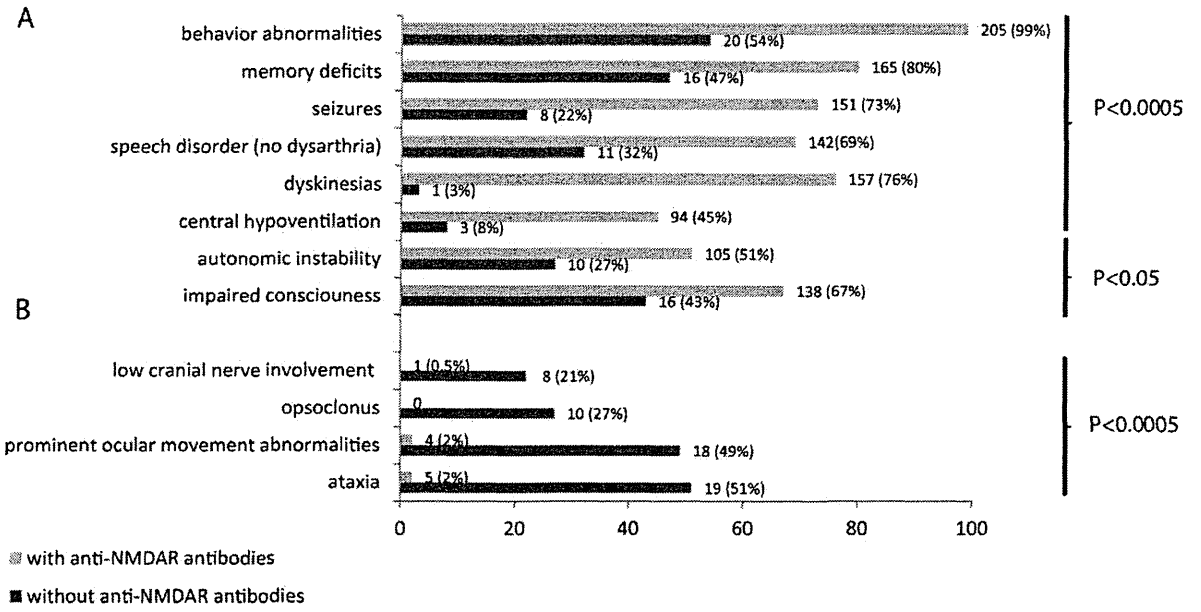

FIGURE 1: Comparison of symptoms of patients with teratoma-associated encephalitis and N-methyl-D-aspartate receptor (NMDAR) antibodies with those without NMDAR antibodies. (A) Patients without NMDAR antibodies (indicated in dark gray) less frequently developed symptoms considered characteristic of anti-NMDAR encephalitis (behavioral abnormalities, memory deficits, seizures, dyskinesias, speech disorder, and central hypoventilation, all $p<0.0005$, and impaired level of consciousness and autonomic dysfunction, $p<0.05$). (B) In addition, patients without NMDAR antibodies more frequently developed brainstem–cerebellar symptoms and opsoclonus, which are rare in anti-NMDAR encephalitis (all $p<0.0005$). From 1 patient without NMDAR antibodies and 4 with antibodies, detailed clinical information was not available, and these patients were excluded from analysis; in 3 additional patients without NMDAR antibodies, information for memory deficits and speech disorder was not available.

peptidase-like protein-6 (DPPX), α1-glycine receptor, D2 subunit of the dopamine receptor, and unknown cell-surface antigens using reported techniques.[3–5]

Outcome was assessed with the modified Rankin scale (mRS),[6] grading it as full recovery (mRS = 0), substantial improvement (mRS = 1–2), partial improvement (mRS > 2 after having had at least 1 point of improvement), and no improvement. Three patients without NMDAR antibodies have been previously reported.[7–9] Studies were approved by the internal review boards of the University of Pennsylvania and University of Barcelona.

Statistical Analysis

Comparative analyses between patients with and without NMDAR antibodies were performed with SPSS version 20 (IBM, Armonk, NY), using the Fisher exact test for contingency tables and Mann–Whitney *U* tests for continuous variables.

Results

Two hundred eleven patients were found to have NMDAR antibodies, and 38 were negative for these antibodies. Compared with antibody-positive patients, the 38 patients without NMDAR antibodies showed no differences with respect to gender and age of symptom onset (NMDAR antibody-negative patients: 92% female, median age = 28 years [interquartile range (IQR) = 20–32, range = 12–55] vs antibody-positive patients: 99% female, median age = 25 years [IQR = 19–30, range = 7–65], $p = 0.05$ and $p = 0.11$, respectively). However, significant differences were identified with respect to symptom presentation and repertoire of symptoms during the first month of the disease (see Fig 1). Whereas 18 (47%) patients without NMDAR antibodies initially presented with brainstem–cerebellar dysfunction, this presentation did not occur in any of the patients with NMDAR antibodies ($p < 0.0005$). In contrast, whereas 144 of 211 (68%) patients with NMDAR antibodies presented with psychosis and behavioral abnormalities, this presentation occurred only in 4 of 38 (11%) patients without these antibodies ($p < 0.0005$).

The Figure shows that during the first month of the disease, 76% of the patients with NMDAR antibodies developed dyskinesias, often involving the face and mouth, whereas only 1 (3%) patient without these antibodies developed dyskinesias, without affecting the face and mouth ($p < 0.0005$); similar differences were seen for most symptoms typical of anti-NMDAR encephalitis. In contrast, 22 of 38 (58%) patients without NMDAR

TABLE 1. Clinical Features in Patients with Brainstem–Cerebellar Syndrome and Systemic Teratoma without N-Methyl-D-Aspartate Receptor Antibodies

Opsoclonus	Patient No.	Age, yr/Sex	Main Symptoms	Neurologic Symptoms before Tumor Diagnosis	Brain MRI	CSF	Treatment	Response to Treatment	Immunological Studies with Cultures of Neurons
With	1	20/F	Opsoclonus–myoclonus, limb ataxia, dysarthria, meningeal signs, drowsiness, tonic seizures, autonomic instability (ileus, urinary retention)	Yes	Meningeal enhancement	182 WBC/μl (87% L), 99mg/dl protein; repeat study: 326 WBC/μl, 159mg/dl protein	Tumor removal, steroids	Complete, related to immunotherapy	Negative
	2	15/F	Opsoclonus–myoclonus, ataxia, drowsiness, vomiting, blurred vision	Yes	Normal	37 WBC/μl, 64mg/dl protein	Tumor removal, steroids, IVIg	Complete, related to tumor removal	Negative
	3	26/F	Opsoclonus–myoclonus, ataxia, dysarthria, aphasia, 3 days after tumor removal	No	Normal	72 WBC/μl (69% L), 49mg/dl protein, OB positive	Steroids, IVIg, plasma exchange (3×), rituximab (3 cycles); 1 cycle of bleomycin, etoposide, and carboplatin; 3 cycles of etoposide and cisplatin	Partial response to steroids, IVIg, plasma exchange; complete recovery after chemotherapy and rituximab	Negative
	4	31/F	Opsoclonus–myoclonus, ataxia, tinnitus	Yes	Normal	Mild pleocytosis with increased lymphocytes and protein concentration	Tumor removal (bilateral), steroids, IVIg, plasma exchange, chlorambucil	Complete, related to immunotherapy and tumor removal; relapsed 7 years later with mild ataxia and memory deficits	Reactivity of serum with cell surface of neurons
	5	22/F	Opsoclonus–myoclonus, ataxia, abnormal behavior, impaired consciousness; severe bradycardia requiring sinus pacemaker	Yes	Normal	10 WBC/μl, 57mg/dl protein, OB positive	Tumor removal, steroids	Partial, related to immunotherapy; complete after tumor removal	Negative
	6	24/F	Opsoclonus without myoclonus, truncal ataxia, vertigo, abdominal pain, generalized weakness, hyporeflexia	Yes	Normal[a]	<5 WBC/μl, <45mg/dl protein	Tumor removal, steroids, IVIg	Complete, related to immunotherapy	Negative
	7	30/F	Opsoclonus without myoclonus, dizziness, meningeal signs, seizures, abnormal behavior (not psychotic), weakness, hyporeflexia, central hypoventilation	Yes	1st normal; repeat study: brainstem edema and meningeal enhancement	134 WBC/μl (88% L), 88 mg/dl protein; repeat study: 414 WBC/μl (97% L), 110mg/dl protein	Steroids, IVIg, plasma exchange	Complete, related to immunotherapy; remained with motor weakness 3 months after disease onset	Negative
	8	29/F	Opsoclonus–myoclonus, sense of unsteadiness and body "shakiness" (26th week of pregnancy)	No	Not done	<5 WBC/μl, <45mg/dl protein, OB positive	Tumor removal, steroids	Complete, related to immunotherapy	Negative

TABLE 1. (Continued)

Opsoclonus	Patient No.	Age, yr/Sex	Main Symptoms	Neurologic Symptoms before Tumor Diagnosis	Brain MRI	CSF	Treatment	Response to Treatment	Immunological Studies with Cultures of Neurons
	9	28/F	Opsoclonus–myoclonus, dysarthria, ataxia, behavioral disinhibition, hypersexuality, hyperphagia, cognitive decline	No	Normal	12 WBC/μl, <45mg/dl protein	Tumor removal, steroids, IVIg, plasma exchange, azathioprine	Partial, related to immunotherapy; improved dysarthria and opsoclonus; ataxia still improving at last follow-up (15 months)	Reactivity of serum with cell surface of neurons
	10	32/F	Opsoclonus–myoclonus, dysarthria, diplopia, ataxia	Yes	Normal	30 WBC/μl, <45mg/dl protein	Tumor removal, steroids, IVIg, rituximab (4 doses)	Partial, related to immunotherapy and tumor removal; mild ataxia and dysarthria at last follow-up (13 months)	Negative
Without	11	19/F	Right hand tremor, ataxia, bilateral dysdiadochokinesia, dysmetria	Yes	Normal	124 WBC/μl, <45mg/dl protein	Tumor removal, steroids	Complete, related to immunotherapy and tumor removal	Negative
	12	32/F	Subacute tremor, unsteady gait	Yes	Normal	<5 WBC/μl, <45mg/dl protein	Tumor removal	Complete, related to tumor removal	Negative
	13	31/F	Subacute onset of vomiting, nystagmus, ataxic gait, dysarthria, myoclonus; all symptoms resolved after removal of ovarian teratoma, but the patient developed abnormal behavior, memory deficit, labile affect, and optic neuritis; recurrence of symptoms and oculomotor paresis 4 months later	Yes	1st normal; at clinical relapse 7 months later: abnormality at the level of oculomotor nuclei	16 WBC/μl, <45mg/dl protein, OB negative	Tumor removal, steroids, IVIg	Partial with tumor removal, complete with immunotherapy; relapse 8 months later (4 months after recovery)	Negative
	14	23/M	Cerebellar ataxia	Yes	NA	NA	NA	NA	Negative
	15	33/F	Severe cerebellar ataxia	Yes	NA	NA	Tumor removal	NA	Negative
	16	15/F	Left side ataxia, dysarthria, paresthesias, dysdiadochokinesia with left hand (onset 1.5 months after tumor removal)	No	Normal brain MRI and PET scan	<5 WBC/μl, <45mg/dl protein	Not treated	Symptoms stable with no improvement 4 months after presentation	Reactivity of CSF with cell surface of neurons

TABLE 1. (Continued)

Opsoclonus	Patient No.	Age, yr/Sex	Main Symptoms	Neurologic Symptoms before Tumor Diagnosis	Brain MRI	CSF	Treatment	Response to Treatment	Immunological Studies with Cultures of Neurons
	17	33/F	6-week episode of severe cerebellar ataxia that resolved without any specific treatment; relapse 2 years later: ataxia and memory problems; ovarian teratoma found	Yes	Normal	<5 WBC/μl, <45mg/dl protein	Not treated	Complete without treatment, but relapsed 2 years later	Negative
	18	36/F	Subacute ataxia, memory problems, confabulation, bilateral intention tremor, bilateral gaze directed nystagmus	Yes	Diffuse bilateral atrophy, enlarged ventricles (history of alcohol abuse)	<5 WBC/μl, <45mg/dl protein, OB negative	NA	NA	Negative
	19	28/F	Suspected viral meningoencephalitis (drowsiness, fever, headache), followed by seizures, brainstem symptoms, ataxia, cognitive and behavioral abnormalities	Yes	1st normal; 1 year later: diffuse brain atrophy (predominant in cerebellum)	66 WBC/μl, 126mg/dl protein	Tumor removal	No response; dependent for activities of daily living (dressing, feeding, ambulation) due to cognitive deficits and tetraparesis	Negative
	20	12/M	Left side ataxia, bilateral tremor, weakness, short-term memory loss; status epilepticus after testis teratoma removal	Yes	FLAIR hyperintensities in limbic region; right cortical atrophy	13 WBC/μl, <45mg/dl protein, OB positive	Tumor removal, steroids, IVIg	Partial, ataxia and coordination problems 4 months after onset	Negative
	21	41/F	Subacute diplopia, ophthalmoplegia, impaired consciousness; left ovarian teratoma discovered at workup of encephalitis (history of a right ovarian teratoma removed 10 years earlier)	Yes	Normal	25 WBC/μl, 85mg/dl protein	IVIg, plasma exchange	Complete, related to immunotherapy	Reactivity of serum with cell surface of neurons
	22	31/F	Myoclonus of lips, diplopia, confusion, catatonia, orthostatic hypotension	Yes	Increased FLAIR signal in medial temporal lobes	106 WBC/μl (98% L), 63.2mg/dl protein	Tumor removal, steroids	Complete, related to tumor removal and immunotherapy	Negative

[a]Normal brain MRI, but decreased degree of tracer accumulation in the brainstem and bilateral cerebral hemispheres on single photon emission computed tomography.
CSF = cerebrospinal fluid; F = female; FLAIR = fluid-attenuated inversion recovery; IVIg = intravenous immunoglobulin; L = lymphocyte; M = male; MRI = magnetic resonance imaging; NA = not available; OB = oligoclonal bands; PET = positron emission tomography; WBC = white blood cell count.

antibodies developed brainstem–cerebellar symptoms during the first month of the disease, 10 (45%) of them with opsoclonus, whereas these symptoms rarely occurred in patients with NMDAR antibodies. The identification of a predominant brainstem–cerebellar syndrome led us to focus on this disorder and the subgroup of patients with opsoclonus, both described below (the other 16 patients are shown in the Supplementary Table).

Brainstem–Cerebellar Syndrome

The median age of the 22 patients with brainstem–cerebellar symptoms was 28.5 years (IQR = 22–32, range = 12–41). Twenty (91%) were female, all with ovarian teratoma; 2 male patients had testicular teratoma. Main symptoms included ataxia in 86%, opsoclonus–myoclonus in 45% (described below), dysarthria in 36%, decreased level of consciousness in 32%, diplopia or ophthalmoparesis in 18%, and seizures in 18%. Other symptoms are listed in the Table 1.

Neurological symptoms developed before tumor diagnosis in 18 patients (82%; median = 1 month, IQR = 0.9–2 months, range = 3 days to 24 months) and after tumor diagnosis in 4 (10 days and 1.5, 2, and 3.5 months, respectively). Two of these 4 patients had the tumor removed 3 days and 1.5 months before developing encephalitis, respectively. All patients had mature teratomas, except 1 who had an immature ovarian teratoma. Serum of 3 patients (2 with opsoclonus) and CSF of another patient showed weak immunolabeling of cultures of rat neurons (data not shown); no antibodies were identified in the other patients.

Treatment and follow-up information was available for 19 (86%) patients, including all patients with opsoclonus (described below). Fifteen (79%) received immunotherapy, 13 of them with tumor resection; 2 had tumor resection without immunotherapy, and 2 were not treated (1 had tumor removal before developing encephalitis). With a median follow-up of 15 months (range = 3–84), 14 patients (74%) had full recovery, 3 (16%) had partial improvement, and 2 had no improvement (1 of them was not treated). Two patients with complete recovery and 1 with partial recovery relapsed 2 years, 7 years, and 8 months after disease onset, respectively.

Opsoclonus–Myoclonus Syndrome

Ten women (median age = 27 years, IQR = 22–30, range = 15–32) with brainstem–cerebellar syndrome developed opsoclonus; accompanying symptoms are listed in the Table 1. Four had prodromal fever or viral-like symptoms, and another one was 26 weeks pregnant. Symptoms developed before the tumor diagnosis in 7 (median = 1 month, IQR = 0.1–1.5 months, range = 3 days to 2 months) and after tumor diagnosis in 3 (10 days, 2 months, and 3.5 months, respectively). One of these 3 patients had undergone tumor resection 3 days before developing opsoclonus; the other 2 patients had not had tumor treatment.

At symptom onset, 7 patients had CSF lymphocytic pleocytosis (median = 37 white blood cells/μl, range = 10–182), 6 had increased protein concentration (median = 64/dl, range 49–100), and 3 of 3 had oligoclonal bands. Brain magnetic resonance imaging and electroencephalographic studies were abnormal in 2 of 9 and 3 of 5 patients (see Table 1).

All patients were treated with methylprednisolone: 3 alone, 3 combined with intravenous immunoglobulin (IVIg), and 4 with IVIg and plasma exchange. Two patients received rituximab after failing initial immunotherapy, and 1 received azathioprine (see Table 1). Nine patients had resection of the teratoma; pathological studies showed mature teratoma in 8, including 1 with bilateral teratomas, and immature teratoma in 1. Chemotherapy was used in 2 patients (see Table 1). Valproic acid, clonazepam, levetiracetam, or phenobarbital did not control the opsoclonus–myoclonus (data not shown).

The median time of follow-up was 19.5 months (IQR = 6–39, range = 3–84). Eight patients had full recovery, and 2 had mild residual dysarthria and ataxia at 13- and 15-month follow-up, respectively. Six of the 8 patients with full recovery became asymptomatic within the first 3 months of treatment, and the other 2 patients within 6 and 12 months, respectively.

Discussion

This study shows that patients with systemic teratoma can develop several forms of encephalitis without NMDAR antibodies, among which a syndrome that associates with brainstem–cerebellar symptoms stands out. Almost 50% of patients with this syndrome developed opsoclonus in association with the triad of young age (teenager to young adult), presence of an ovarian teratoma, and high response to treatment. The subacute presentation of symptoms, frequent CSF pleocytosis, and response to immunotherapy coupled with the detection of antibodies to neuronal cell-surface antigens in some patients suggest an immune-mediated pathogenesis.

All patients with opsoclonus were young women (aged 15–32 years), considered too young for carcinoma-associated opsoclonus, which usually occurs in patients >50 years old,[10] and too old for neuroblastoma-associated opsoclonus, which usually affects children <5 years old.[11] It is likely that this type of opsoclonus has been previously considered idiopathic or postinfectious and

that the presence of a teratoma was missed or not felt to be related.

Compared with patients with anti-NMDAR encephalitis, those without these antibodies were less likely to initially present with psychosis and behavioral change. Although there was overlap of some symptoms, such as limbic dysfunction and psychiatric manifestations, the frequency of other symptoms, such as dyskinesias, rarely occurred in patients without NMDAR antibodies. In contrast, patients with anti-NMDAR encephalitis did not initially present with brainstem–cerebellar dysfunction or opsoclonus. Of note, ataxia can be a presentation of anti-NMDAR encephalitis in children[2,12]; this is not reflected here, because young children usually do not have teratomas.

This study has several practical implications. Any teenager or young adult, especially if female, who develops subacute brainstem–cerebellar symptoms or opsoclonus–myoclonus suspected to be immune-mediated (because of the rapid onset of symptoms and/or CSF pleocytosis) should be investigated for a teratoma in the ovary (or testes for male patients). Detection of a teratoma should prompt its removal along with the use of immunotherapy (most patients described here received steroids, IVIg, and/or plasma exchange). A limitation of this study is that it is retrospective; future studies will establish the frequency of these disorders and may identify patients with higher levels of cell-surface antibodies that could lead to the characterization of the antigens.

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Potential Conflicts of Interest

J.D.: grants/grants pending, Euroimmun, NIH; patents, royalties, Athena Diagnostics Euroimmun; editorial board, *Up-To-Date*.

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Brain perfusion SPECT in limbic encephalitis associated with autoantibody against the glutamate receptor epsilon 2

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Keywords:
Non-herpetic limbic encephalitis
Autoantibody against the glutamate receptor epsilon 2
Brain perfusion SPECT
eZIS analysis

ABSTRACT

Objectives: The aim of this study was to elucidate the single-photon emission computed tomography (SPECT) pattern at the acute stage of disease in non-herpetic limbic encephalitis (NHLE) patients associated with the N-methyl-D-aspartate-type glutamate receptor epsilon 2 (GluR ϵ2) autoantibody using *Z*-score imaging system (eZIS) analyses.

Methods: Brain magnetic resonance imaging (MRI) and brain perfusion SPECT using technetium-99 ethyl cysteinate dimer (^{99m}Tc-ECD) were performed in eight patients with NHLE (5 men and 3 women; mean age 48.8 ± 22 years) within 20 days after clinical onset.

Results: All patients had various clinical limbic-associated symptoms and no evidence of herpes simplex infection or systemic malignancies. Two of eight patients showed abnormally hyperintense lesions on diffusion-weighted images and significant hyperperfusion in ipsilateral cerebral cortex on eZIS analysis, whereas other patients showed normal MRI findings and significant hypoperfusion in one or both sides of the limbic and paralimbic areas.

Conclusion: We suggest that ^{99m}Tc-ECD SPECT study using eZIS analyses may be helpful to detect the neuronal dysfunction, particularly in NHLE patients without abnormal MRI findings.

1. Introduction

Limbic encephalitis is clinically characterized by limbic-associated symptoms, such as confusion, short-term memory loss, psychiatric symptoms, and seizures, in addition to acute encephalitis symptoms, and includes a paraneoplastic and non-herpetic limbic encephalitis (NHLE) [1–7]. NHLE was recently identified as a new type of limbic encephalitis in Japan, and is characterized by the lack of evidence of herpes simplex virus (HSV) infection and paraneoplastic disease process [4,5]. Some patients with NHLE show positive autoantibody against the N-methyl-D-aspartate-type glutamate receptor epsilon 2 (GluR ϵ2) in cerebrospinal fluid [6,7]. GluR ϵ2 channels have been implicated in synaptic plasticity and localization associated with neural development and learning [8]. Although it remains unclear whether the autoantibody against GluR ϵ2 is the cause or the result of NHLE, the presence of this antibody suggests the autoimmune pathogenic mechanism [6,7]. Accurate and early diagnosis of NHLE is important for deciding on treatment and management. Brain magnetic resonance imaging (MRI) is highly sensitive for detecting early changes in NHLE and shows abnormal findings in one or both medial temporal lobes [6,7,9]. Some patients, however, have normal MRI findings and it is difficult to diagnose these patients based solely on clinical examination. Therefore, other sensitive methods to detect the neuronal dysfunction in limbic system are needed. Brain perfusion single-photon emission computed tomography (SPECT) provides an indirect marker of neuronal function. SPECT studies in HSV encephalitis reported the abnormal uptake of technetium-99 ethyl cysteinate dimer (^{99m}Tc-ECD) or technetium-99m hexamethylpropylamine-oxime (^{99m}Tc-HMPAO) in affected regions [10,11]. To our knowledge, few SPECT imaging studies have been performed in NHLE patients associated with GluR ϵ2 autoantibody.

Here we evaluated cerebral blood flow during the acute stage in NHLE patients associated with GluR ϵ2 autoantibody using *Z*-score imaging system (eZIS). The eZIS programs are statistical analysis techniques for diagnosis of brain perfusion SPECT images that can be used to objectively evaluate rCBF [12]. The aim of this study was to elucidate SPECT pattern in NHLE patients associated with GluR ϵ2 autoantibody.

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Table 1
Summary of the clinical and demographic characteristics.

Patient	Age/sex	Psychiatric symptoms	Convulsive state	CSF		SPECT study[a]
				Cells (mm^3)	Protein (mg/dl)	
1	30/M	Memory loss and agitation	+	9	57	15
2	58/M	Hallucination and delirium	+	1	20	13
3	36/F	Disorientation, delirium, agitation, and generalized seizures	–	55	45	10
4	80/M	Delirium, agitation, and generalized seizures	–	1	35	9
5	57/M	Disorientation and agitation	–	26	84	2
6	76/F	Memory loss, disorientation, and delirium	–	4	134	13
7	24/M	Agitation and generalized seizures	–	30	27	4
8	29/F	Disorientation, anxiety, delirium, and generalized seizures	–	1	31	20

M, male; F, female; CSF, cerebrospinal fluid.
[a] Duration from clinical onset to study (days).

2. Methods

2.1. Subjects

Eight patients with NHLE (5 men and 3 women; mean age 48.8 ± 22 years) were admitted to the Department of Internal Medicine III, Oita University, and both brain MRI and brain perfusion SPECT were performed between 2007 and 2010. Autoantibody against GluR ϵ2 in cerebrospinal fluid (CSF) was detected in all patients using enzyme-linked immunosorbent assay (ELISA). The diagnosis criteria of NHLE was based on the previous reports as follows [4,5]: (1) encephalitis symptoms, such as fever and disturbed consciousness, (2) limbic-associated symptoms, such as short-term memory loss, seizure, and various psychiatric symptoms, (3) negative HSV DNA in CSF by polymerase chain reaction and negative antibodies in the CSF for HSV, varicella-zoster virus, Epstein-Barr virus, and human herpes virus-6 determined by the ELISA, (3) lesions of the temporal lobe on MRI, (4) absence of systemic malignancy and collagen disease, (5) no bacteria or fungi in CSF culture, and (6) the exclusion of all other neurologic, vascular, metabolic, toxic, and drug-induced disorders. Moreover, we included patients without abnormal MRI findings, regardless of the presence of limbic-associated symptoms. All patients showed no malignancy on contrast enhanced computed tomography (CT) of the chest, abdomen, and pelvis. Information regarding age, sex, neurologic symptoms, laboratory tests, including the complete blood count, urine components, blood biochemistry, thyroid function, and tumor markers, and CSF analysis and electroencephalography findings were extracted from the medical records. Brain MRI and brain perfusion SPECT were performed in the interictal state. The electroencephalogram was not performed at the time of SPECT study.

2.2. Brain MRI

MRI was performed with a 1.5 T scanner (Excelart Vantage; Toshiba Medical System Corp., Tokyo, Japan), using spin echo sequences. T1-weighted image, T2-weighted image, and diffusion-weighted image were obtained on axial slices. The pulse sequence being repletion time (TR) 500–550 ms/echo time (TE) 12 ms for T1-weighted image, TR 4000–5000 ms/TE 90 ms for T2-weighted image, and TR 5000–6000 ms/TE 100 ms for diffusion-weighted image. The section thickness was 5 mm with an intersection space of 1.2 mm.

2.3. Brain SPECT imaging

Patients were asked to assume a comfortable supine position with eyes closed in quiet surroundings. After intravenous injection of ^{99m}Tc-ECD (600 MBq, FUJIFILM RI Pharma Co., Tokyo, Japan), its passage from the heart to the brain was monitored using a rectangular large field gamma camera (E. Cam Signature, Toshiba Medical, Tochigi, Japan). Data comprising a sequence of 120 frames was acquired at a rate of one frame per second with a 128 × 128 matrix. Ten minutes after the angiography, SPECT images were obtained using a rotating, dual-head gamma camera (E. Cam Signature) equipped with low energy, high resolution, and parallel hole collimators. The energy windows were set at 140 keV ± 20% and 90 views were obtained throughout 360° of rotation (128 × 128 matrix, 1.95 mm/pixel) with an acquisition time of 140 s/cycle repeated 6 times. Data processing was performed on a GMS-7700A/EI (Toshiba Medical, Japan). All images were reconstructed using a ramp-filtered back projection and then three-dimensionally smoothed with a Butterworth filter (order 8, cutoff 0.25 cycles/pixel). The reconstructed images were corrected for gamma ray attenuation using the Chang method ($\mu = 0.09$).

2.4. SPECT image analysis using eZIS

We used the eZIS program to supplement the diagnosis and to detect abnormal blood perfusion in each patient. A *Z*-score map for each SPECT image was extracted from the comparison with the mean and standard deviation (SD) of SPECT images of age-matched normal controls that had been incorporated into the eZIS program as a normal control database. A voxel-by-voxel *Z*-score analysis was performed after voxel normalization to global means or cerebellar values; *Z*-score = ([control mean] – [individual value])/(control SD). These *Z*-score maps were displayed by overlaying them on tomographic sections and projecting the averaged *Z*-score of a 14-mm thickness-to-surface rendering of the anatomically standardized MR imaging template [12].

3. Results

Table 1 summarizes the clinical and demographic characteristics of the NHLE patients associated with autoantibody against the GluR ϵ2. All patients showed various clinical limbic-associated symptoms, such as memory loss, disorientation, hallucination, agitation, delirium, and anxiety. Patients 1 and 2 experienced convulsions during the illness, whereas patients 3, 4, 7, and 8 had generalized seizures at least once at the onset. The electroencephalogram showed a bihemispheric ictal discharge in the bilateral temporal regions in patient 1, and periodic lateralized epileptiform discharges in the left temporal area in patient 2, whereas the other patients had diffusely intermittent slow waves. CSF analysis revealed an increased cell count (normal range: <5 /mm^3) in four patients and increased protein level (normal range: <45 mg/dl) in four patients. Brain MRI showed high signal intensities on T2- and diffusion-weighted images in the bilateral medial temporal lobes, cingulate gyri, and insulae in patient 1 (Fig. 1A), in the right temporal and occipital lobe in patient 2 (Fig. 1B). These lesions showed iso-intensity signals on T1-weighted images and the lack of low apparent diffusion

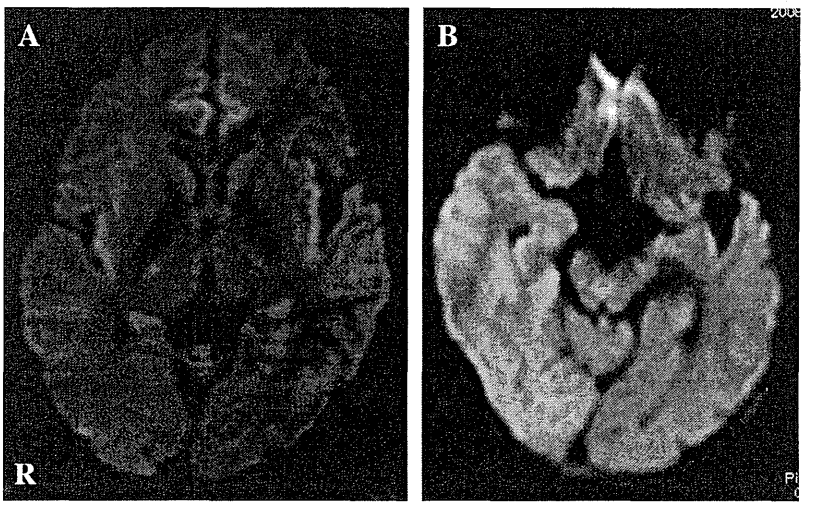

Fig. 1. Diffusion-weighted MR images (axial images) in NHLE patients (patients 1 and 2). Brain MRI shows high signal intensities on diffusion-weighted images in the bilateral medial temporal lobes, cingulate gyri, and insulae in patient 1 (A; cited from reference [21]. Adapted with permission.) and in the right temporal and occipital lobes in patient 2 (B).

coefficient values and gadolinium enhancement. Brain perfusion SPECT was performed in all patients within 20 days (mean duration 10.8 ± 5.8 days) of clinical onset. The eZIS analysis detected significantly increased or decreased regional cerebral blood flow in all patients (Fig. 2, Table 2). Two patients with abnormal MRI findings showed significant hyperperfusion in ipsilateral cerebral cortices. Patient 1 had hyperperfusion in the medial temporal lobes, left putamen, and left insula, and hypoperfusion in the bilateral frontal lobes (Fig. 2A). Patient 2 showed hyperperfusion mainly in the right lateral temporal and occipital lobes and hypoperfusion mainly in

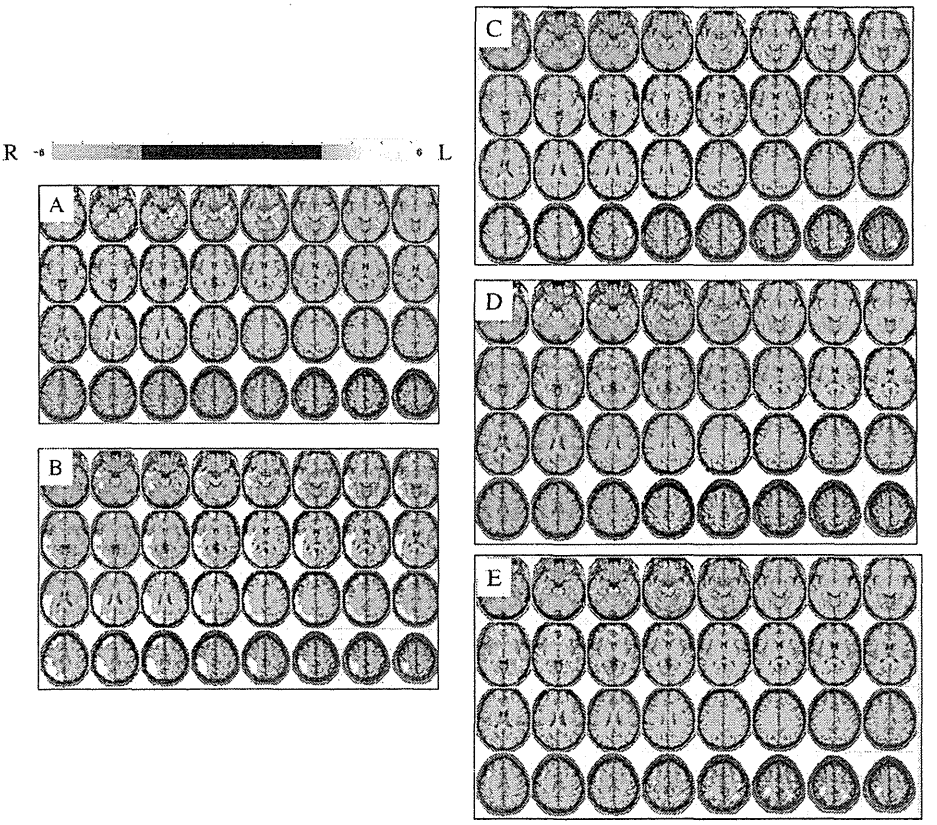

Fig. 2. Easy *Z*-score imaging system (eZIS) images in patients with NHLE (patients 1, 2, 5, 6, and 7). The color images represent the statistical significance (*Z*-score) of the increase (red) and decrease (blue) in regional cerebral blood flow. Patient 1 shows hyperperfusion in the bilateral medial temporal lobes, left putamen, and left insula, and hypoperfusion in the bilateral frontal lobes (A; cited from reference [21]. Adapted with permission.). Patient 2 shows hyperperfusion in the right lateral temporal and occipital lobes and hypoperfusion in frontal, parietal, and lateral temporal lobes, insula on the left hemisphere (B). Patients 5 (C), 6 (D), and 7 show hypoperfusion on one or both sides in the limbic system, such as cingulate gyrus, insula, and orbitofrontal cortex, as well as basal ganglia and brainstem (E). Moreover, hyperperfusion was identified in the focal cortical regions. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

Table 2
Summary of the SPECT findings.

Patient	SPECT	
	Hyperperfusion areas	Hypoperfusion areas
1	Medial temporal, Lt putamen, and Lt insula	Frontal
2	Rt lateral temporal and Rt occipital	Lt frontal, Lt parietal, Lt lateral temporal, Lt insula, Lt caudate, and cingulate
3	Frontal	Rt medial temporal
4	Rt temporal	Lt insula
5	Lt frontal and Lt temporal	Rt orbitofrontal, Rt isula, Lt putamen, and brainstem
6	Rt lateral temporal	Insula, cingulate, and caudate
7	Frontal and parietal	Rt insula, cingulate, fusiform, and brainstem
8	Frontal and lateral temporal	Fusiform and cerebellum

Rt: right; Lt: left; frontal: frontal lobe; parietal: parietal lobe; lateral temporal: lateral emporal lobe; medial temporal: medial temporal lobe; occipital: occipital lobe; orbitofrontal: orbitofrontal gyrus; cingulate: cingulate gyrus; caudate: caudate nucleus; fusiform: fusiform gyrus.

the insula, caudate nucleus as well as left lateral temporal, parietal, and occipital lobes on the left hemisphere (Fig. 2B). Although the other six patients had normal MRI findings, significant hypoperfusion was identified mainly in one or both sides of the limbic system, such as medial temporal lobe, cingulate gyrus, insula, and orbitofrontal cortex (Fig. 2C–E). In some patients, the regions of hypoperfusion extended to the basal ganglia, brainstem, or cerebellum. Significant hyperperfusion was identified in focal cortical regions and its distribution was different in each patient.

4. Discussion

We examined brain perfusion changes in eight NHLE patients using eZIS analyses. All patients showed typical neurologic symptoms of NHLE and positive autoantibody against the GluR $\epsilon 2$ in cerebrospinal fluid. HSV encephalitis and paraneoplastic limbic encephalitis were excluded by the lack of evidence for HSV infection and systemic malignancies. We suggest that NHLE in our patients may be caused by a transient autoimmune response, rather than by direct viral infection based on the presence of autoantibody.

Previous SPECT imaging studies in patients NHLE associated with the GluR $\epsilon 2$ antibodies showed hyperperfusion in temporal lobe corresponding to the abnormally hyperintense lesions on MRI [6,7]. Our results indicated a significant hyperperfusion that corresponded to hyperintense lesions on diffusion-weighted image and a significant hypoperfusion, predominantly in the limbic system, in the patients without abnormal MRI findings. Two of eight patients showed abnormal hyperintensity in the temporal and occipital lobes, cingulate gyrus, and insula on diffusion-weighted image. These lesions were inconsistent with the ischemic changes because of the normal apparent diffusion coefficient values. The eZIS analysis showed a significant hyperperfusion corresponding to the hyperintense lesions on diffusion-weighted image. These patients developed a convulsive state over the course of the disease. Hyperintense lesions on diffusion-weighted image in convulsive state reflect the cytotoxic edema caused by neuronal excitotoxicity [13,14]. Brain perfusion SPECT in a convulsive state shows compensatory hyperperfusion due to the increased glucose and O_2 required during prolonged overactivation of epileptic neurons. Subsequently, cerebral blood flow is no longer sufficient to prevent local hypoxia, and these events lead to cytotoxic edema and reduced extracellular volume [13,14]. We suggest that hyperintense lesions on diffusion-weighted image with hyperperfusion may be related to not only the inflammatory process itself, but also a prolonged convulsive state.

The most interesting findings in patients without abnormal MRI findings were hypoperfusion predominantly in the medial temporal lobe, cingulate gyrus, insula, and orbitofrontal cortex on eZIS analysis. The limbic system is generally thought to include the hippocampus, amygdale, anterior thalamus, hypothalamus, mammillary bodies, basal forebrain, cingulate gyrus, orbitofrontal cortex, and parahippocampal cortex [15]. Moreover, the insula has a vital role as a limbic integration cortex [16]. These regions are associated with vegetative and survival behaviors, emotions, learning, and memory [17]. Therefore, NHLE patients without abnormal MRI findings showed hypoperfusion predominantly in one or both sides of the limbic and paralimbic areas corresponding to the clinical symptoms. ^{99m}Tc-ECD, which is a lipid soluble tracer, undergoes ester hydrolysis and the acid metabolite is trapped intracellularly for a prolonged period. The distribution of ^{99m}Tc-ECD might reflect not only brain perfusion, but also the reduction of the enzymatic process due to neuronal dysfunction [18–20]. Our results suggest that the ^{99m}Tc-ECD SPECT study may be able to detect neuronal dysfunction in NHLE, even before any morphologic abnormalities become detectable on MRI.

The present study has several limitations. NHLE in our patients may be caused by an undetected infectious agent. The diagnosis was made without examination of other antineuronal antibodies against the anti-NMDA receptor and the anti-VGKCs or pathologic confirmation. The electroencephalogram was not performed at the time of SPECT study. We could not define whether brain perfusion changes specifically related to NHLE or seizure activity, including subclinical seizure. Moreover, the number of patients was small and further studies with larger samples, are needed to confirm our results.

5. Conclusion

NHLE patients associated with GluR $\epsilon 2$ autoantibody showed brain perfusion changes on eZIS analysis. NHLE patients with abnormal MRI findings showed hyperperfusion that corresponded to hyperintense lesions on diffusion-weighted image, whereas those without abnormal MRI findings showed hypoperfusion, predominantly in the limbic and paralimbic areas. We speculate that hyperperfusion in hyperintense lesions reflects compensatory hyperperfusion relating to a prolonged convulsive state, whereas hypoperfusion, predominantly in the limbic system may indicate neuronal dysfunction. We suggest that ^{99m}Tc-ECD SPECT study using eZIS analysis might be helpful to detect the neuronal dysfunction, particularly in NHLE patients without abnormal MRI findings.

Disclosure

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INTERNAL MEDICINE

□ CASE REPORT □

Multifocal Encephalopathy and Autoimmune-mediated Limbic Encephalitis Following Tocilizumab Therapy

Yuko Yamaguchi[1], Koji Furukawa[1], Toru Yamamoto[1], Yukitoshi Takahashi[2], Keiko Tanaka[3] and Makio Takahashi[4]

Abstract

A 63-year-old man with rheumatoid arthritis developed multifocal encephalopathy and limbic encephalitis following therapy with tocilizumab, a humanized anti-interleukin-6 receptor antibody. Anti-glutamate receptor ε2 antibodies were later found to be positive in both the serum and cerebrospinal fluid. This case highlights the possibility of the development of encephalopathy after treatment with tocilizumab, which may also induce autoimmune limbic encephalitis.

Key words: autoantibody, anti-glutamate receptor (GluR), multifocal encephalopathy, limbic encephalitis, tocilizumab, interleukin-6

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Introduction

Recently, several emerging biological agents have been increasingly used in the treatment of collagen-vascular and hematological disorders. However, several reports have shown that these agents can induce encephalopathy (1-3), the underlying mechanisms of which are currently unknown. We herein report the case of a patient presenting with multifocal encephalopathy and limbic encephalitis following treatment with tocilizumab, a humanized monoclonal antibody against interleukin (IL)-6 receptor (IL-6R). In this case, autoantibodies against the N-methyl-D-aspartate (NMDA)-type glutamate receptor (GluR) subunit were detected. The GluR antibodies, which were possibly induced by treatment with tocilizumab, may have contributed to the pathogenesis of multifocal encephalopathy and limbic encephalitis.

Case Report

A 63-year-old man with rheumatoid arthritis (RA) was initially prescribed 7 mg/day of oral prednisolone (PSL) and 8 mg/week of methotrexate (MTX) at 60 years of age. Since the disease activity of RA was uncontrollable, he was treated with TNF-α antagonists, including 0.4 mg/kg of etanercept twice a week for five months followed by 40 mg of adalimumab every other week for 13 months, in addition to PSL and MTX. However, these agents were ineffective for treating the RA.

One month after the cessation of adalimumab therapy, the regimen was changed to 8 mg/kg of tocilizumab every four weeks (Fig. 1). Three months after the initiation of tocilizumab, the patient gradually developed cognitive impairment and weakness of the right arm. Total knee joint replacement was planned, and tocilizumab was discontinued. Two months later, he further developed weakness of the right leg and disorientation and his verbal communication progressively deteriorated. The Mini-Mental State Exam score was 4/30. Dysphagia, right-side dominant muscle weakness and rigidity in the extremities were later detected.

Laboratory blood tests showed an elevated C-reactive protein level (5.84 mg/dL) and erythrocyte sedimentation rate (105 mm/hr). The levels of angiotensin-converting enzyme and thyroid hormones were within the normal ranges. Serological tests were negative for syphilis and human immunodeficiency virus. No antinuclear, anti-SS-A, SS-B antibod-

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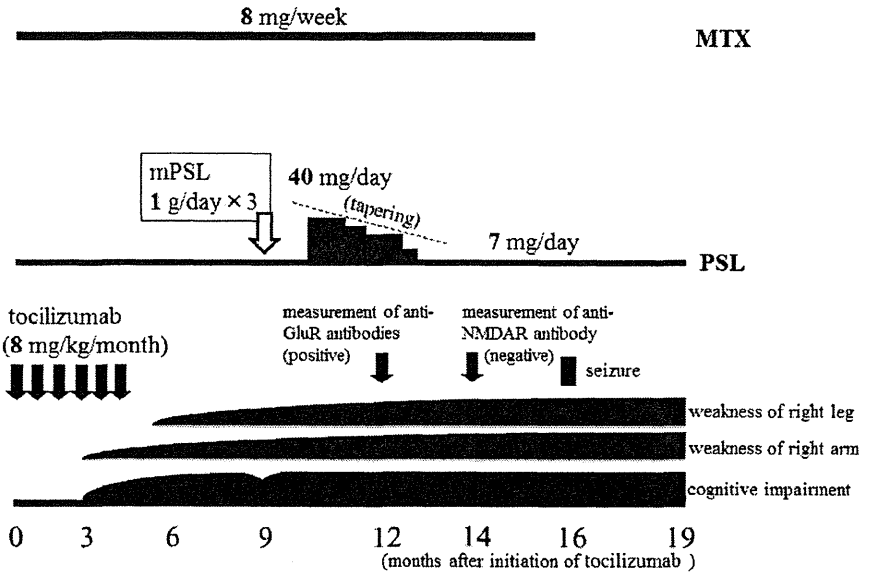

Figure 1. Schematic diagram of the patient's clinical course and treatment in the present case. The X axis indicates the number of months after the initiation of tocilizumab. MTX: methotrexate, PSL: prednisolone, mPSL: methylprednisolone, GluR: glutamate receptor, NMDAR: N-methyl-D-aspartate receptor

ies, MPO-ANCA or PR3-ANCA antibodies were detected. A cerebrospinal fluid (CSF) examination revealed slight lymphocytic pleocytosis (6/μL) and an elevated protein concentration (57 mg/dL). No bacteria were cultured in the CSF, and viral studies were negative, including polymerase chain reaction for herpes simplex virus, human herpes virus-6 and JC virus DNA. No malignancy was detected on esophagogastroduodenoscopy, colonoscopy or a whole-body CT scan.

Fluid-attenuated inversion recovery (FLAIR) MRI of the brain revealed high intensity lesions within the left frontoparietal and bilateral temporal white matter seven months after the administration of tocilizumab (Fig. 2a). These lesions were partially contrasted with gadolinium. ^{99m}Tc-ethylcysteinate dimer SPECT showed a decreased uptake in both the lesions observed on MRI and bilateral limbic areas (data not shown).

A needle brain biopsy of the right temporal lobe lesion adjacent to the lateral ventricles showed definitive perivascular lymphocytic infiltration and abundant reactive astrocytes (Fig. 2a, arrow, Fig. 2c). Immunohistochemical staining with lymphocyte markers showed perivascular inflammatory infiltrates of both T- (CD3) and B- (CD20) cells (Fig. 2d, e), while fibrinoid necrosis, characteristic of RA associated angiitis, was absent, thus indicating nonspecific encephalitis. The administration of methylprednisolone pulse therapy (1 g/day for three days) and subsequent oral steroids (PSL, tapered from 40 mg/day) temporarily ameliorated the patient's symptoms; however, his condition deteriorated (Fig. 1). Furthermore, he experienced recurrent generalized tonic-clonic seizures 16 months after treatment with tocilizumab. An interictal EEG showed periodical lateralized epileptiform discharges in the right hemisphere. MRI performed nine months later demonstrated the disappearance of enhancement in the left parietal and right temporal white matter lesions, although new lesions were observed in the right frontal lobe in addition to marked atrophy in the bilateral mesial temporal areas, suggesting limbic encephalitis (Fig. 2b). Autoantibodies against the N- and C-termini of NMDA type GluRε2 (homologs to NR2B) were detected in both the serum and CSF collected 12 months after the initiation of tocilizumab; the antibody titer was higher in the CSF than in the serum. The IL-6 level was simultaneously elevated (35 pg/mL) in the CSF. However, anti-NMDA receptor (NMDAR) antibodies were negative in the CSF collected 14 months after the administration of tocilizumab using a cell-based assay with human embryonic kidney 293 cells (Fig. 1).

The patient suffered from recurrent infections; therefore, only low-dose PSL (7 mg/day) was continued. He died of aspiration pneumonia 19 months after the introduction of tocilizumab. An autopsy was not allowed.

Discussion

Tocilizumab is a humanized monoclonal antibody against IL-6R that was introduced for the treatment of adult RA in 2008 in Japan, 2009 in Europe and 2010 in the U.S.A. More recently, tocilizumab has been shown to be effective for neuromyelitis optica (NMO) (4). In general, tocilizumab attenuates plasma cell differentiation and subsequent autoantibody production, such as that of aquaporin 4 antibodies in patients with NMO (4, 5). It also suppresses IL-21, which is primarily derived from effector/memory CD4-T cells. IL-21

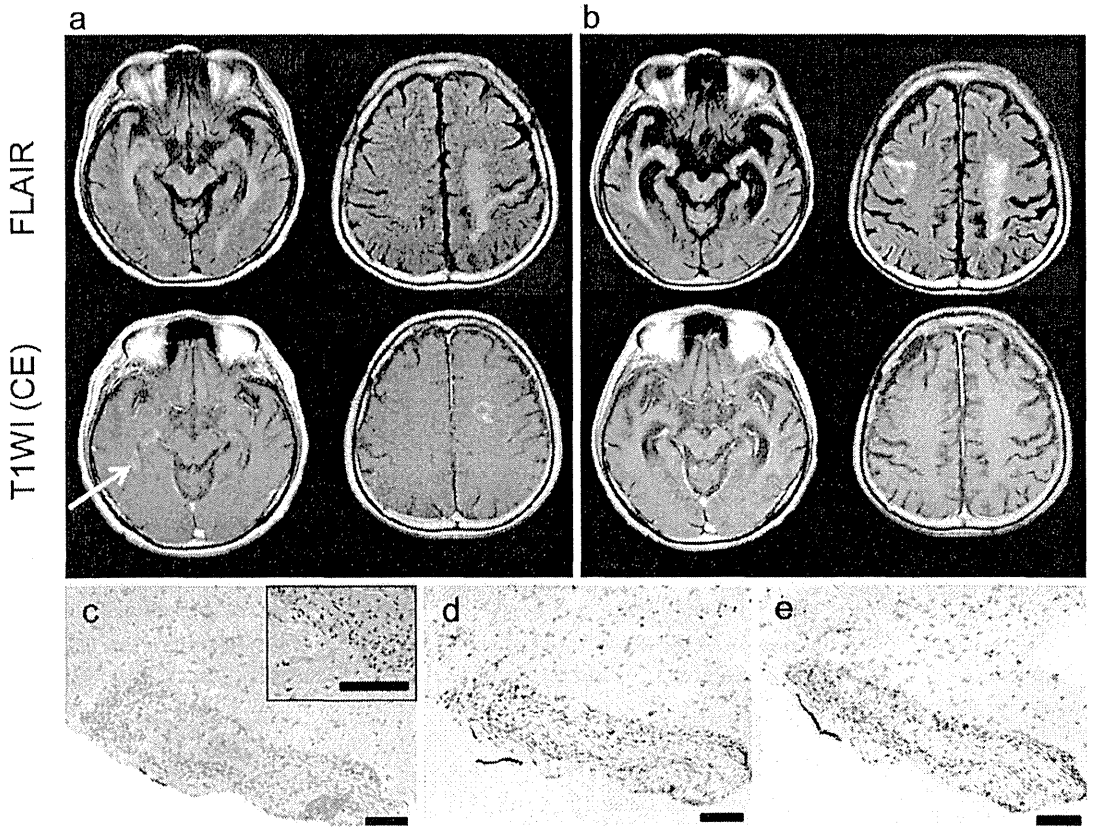

Figure 2. An axial view of FLAIR (upper) and T1-weighted contrast (lower) MRI performed at seven months (a) and 16 months (b) after tocilizumab treatment. FLAIR-MRI revealed high-intensity lesions reflecting leukoencephalopathy within the left frontoparietal, right frontal and bilateral temporal areas (a). Gadolinium-enhanced areas on T1-weighted MRI were partially observed within the lesions. Compared to the image obtained at seven months (a), progressive brain atrophy was conspicuous at 16 months, especially in the bilateral mesial temporal areas (b). A needle brain biopsy of the right temporal white matter adjacent to the lateral ventricles performed at 10 months after the initiation of tocilizumab (Fig. 1a, arrow). The microscopic findings of the obtained tissue showed definitive perivascular lymphocytic infiltration (c) with reactive astrocytes (Hematoxylin and Eosin staining) (c, inset). Immunohistochemical staining with T-(CD3) (d) and B-(CD20) cell (e) markers revealed perivascular inflammatory infiltrates of both T- and B-cells. The scale bar indicates 25 μm (c, inset) and 50 μm (d, e).

plays a pivotal role in the differentiation of plasma cells and production of autoantibodies in patients with RA. Tocilizumab also inhibits IgG4 (not IgG1)-class anti-CCP antibodies by blocking the effects of IL-6 on IL-21 production induced by CD4-T-cells (6). IL-6 exhibits ambivalent effects with respect to inflammation and neurotrophic repair depending on the pathological context in the central nervous system (CNS) (7). Therefore, tocilizumab potentially has both positive and negative effects on the CNS.

Notably, tocilizumab-induced leukoencephalopathy was described in the case of a 72-year-old woman with RA who developed cognitive impairment 40 months after the initiation of tocilizumab (1). FLAIR-MRI demonstrated the dissemination of high-intensity lesions in the bilateral cerebral white matter. The patient's clinical symptoms and MRI abnormalities persisted for five months after the discontinuation of tocilizumab. Unlike that observed in this reported case, which lacked a pathological study, the present patient exhibited progressive dementia, weakness of the extremities and generalized tonic-clonic seizures. MRI of the brain demonstrated both multifocal encephalopathy lesions and bilateral mesial temporal atrophy.

TNF-α antagonists, such as etanercept and infliximab, may cause demyelinating disorders of the CNS and encephalopathy (8). These drugs were administered before the introduction of tocilizumab in the present case. Although several cases of etanercept-related encephalopathy have been previously reported (2), it is unlikely that etanercept caused encephalopathy after at least 16 months of use in our patient. Furthermore, to our knowledge, no cases of encephalopathy induced by adalimumab have been reported. Therefore, we suspect tocilizumab, the last biological agent used,

to be the trigger for the development of encephalopathy in this case (Fig. 1).

Regarding MTX, which was used in the present case in combination with tocilizumab, rare case reports have shown that low doses of this drug can cause blood brain barrier (BBB) disruption and subsequent leukoencephalopathy in RA patients (9). We postulate that MTX disrupted the BBB, which then allowed tocilizumab to exert toxic effects on the CNS.

Furthermore, the detection of autoantibodies against intrathecal GluRε2 in this case warrants comment. Tocilizumab attenuates autoantibody production (4, 10); however, it may also augment serum IL-6 via the suppression of IL-6R signaling (10). Salsano et al. reported a case of autoinflammatory encephalopathy in which the patient exhibited an upregulated IL-6 level in the CSF and an augmented intrathecal IL-6 level that was not suppressed by tocilizumab treatment (11). On the other hand, the serum IL-6 levels increase in RA patients following the administration of tocilizumab for at least two weeks, while RA symptoms continue to be ameliorated (10). Therefore, the temporarily augmented serum IL-6 levels induced by tocilizumab may allow IL-6 to spread into the brain parenchyma via a disrupted BBB, which may subsequently induce the secondary production of intrathecal anti-GluRε2 antibodies and limbic encephalitis.

Among several subtypes of GluRs, NMDA-type GluRs play key roles in synaptic plasticity related to learning and memory. These molecules exhibit a heterotetramer complex structure composed of NR1 and NR2/3 subunits. Antibodies against the glutamate NR1 and NR2A/NR2B subunits of NMDAR, known as anti-NMDAR antibodies, were originally reported in cases of ovarian teratoma-associated limbic encephalitis (12). Because antibodies against GluRε2 (NR2B) are detected in several diseases, including reversible autoimmune limbic encephalitis and other forms of encephalitis/encephalopathy, the presence of GluRε2 antibodies is thought to be less specific than that of NMDAR (13). Furthermore, cases involving the development of anti-NMDAR encephalitis following TdaP-IPV booster vaccination (14) or Guillain-Barré syndrome (15) have been reported. These examples imply that the production of either anti-NMDAR or anti-GluR antibodies can be induced via host immunomodulatory reactions and by drugs, such as tocilizumab.

To date, biological agents, including tocilizumab, have been increasingly used for the treatment of several inflammatory autoimmune disorders. However, strong suppression of specific cytokine receptors, such as IL-6R, may perturb the balance of the immune system under a disrupted BBB, thus resulting in the development of autoimmune encephalitis/encephalopathy. Therefore, careful attention should be paid to monitoring the development of encephalopathy under treatment with these biological agents due to their possible adverse effects.

The authors state that they have no Conflict of Interest (COI).

Acknowledgement

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LETTER TO THE EDITOR

Another case of respiratory syncytial virus-related limbic encephalitis

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Dear Sir,

We read the article entitled "Respiratory syncytial virus-related encephalitis: magnetic resonance imaging findings with diffusion-weighted study" in your journal with great interest [1]. In the article, Park et al. reviewed the medical records of 3,856 patients, diagnosed with respiratory syncytial (RS) virus bronchiolitis and identified three cases of RS virus-related encephalitis, including the first reported case of RS virus-related limbic encephalitis. This was the case of a 3-year-old boy in whom the RS virus was detected in the cerebrospinal fluid (CSF) by polymerase chain reaction (PCR). In that case, limbic encephalitis could have been caused by a direct invasion of the RS virus. Brain magnetic resonance imaging (MRI) revealed subtle bilateral hippocampal enlargement with increased signal intensity on fluid-attenuated inversion recovery (FLAIR) images; however, there was no diffusion abnormality on diffusion-weighted imaging (DWI).

We would like to report another case of respiratory syncytial virus-related limbic encephalitis, where anti-*N*-methyl-D-aspartate receptor (NMDAR) antibodies were detected. A 3-year-old girl developed fever, 10 days before admission, which persisted for 4 days. Thereafter, she developed convulsions for 1 h, after which, she was admitted to our hospital. The day of admission was designated as day of illness (DOI) 0. RS virus infection was found to be prevalent in our area for a few weeks prior to this presentation. The patient did not have any history of neurological disorders, overt RS virus infection, or any other contributory family history. The findings of CSF examination were unremarkable, except for the presence of mild pleocytosis: white blood cell count 8/μL and total protein level 24 mg/dL. The patient's nasopharyngeal aspirate was examined using a rapid RS virus antigen detection test; the test results were positive. Subsequently, the results of PCR were positive for RS virus, whereas those of PCR using CSF were negative [2]. Electroencephalography showed a generalized high-voltage slow wave. The patient showed bizarre behaviors and complex partial seizures. On DOI 1, brain MRI did not show any apparent abnormality. On DOI 6, follow-up brain MRI revealed amygdalar and hippocampal lesions consistent with a diagnosis of limbic encephalitis (Fig. 1). Signal abnormalities were evident not only on FLAIR images but also on DWI. There were no signs of neoplasms such as ovarian tumor on imaging studies. Enzyme-linked immunosorbent assay indicated significantly elevated levels of antibodies for the peptides NR2B and NR1, which are basic NMDAR components, in CSF on DOI 0 and in serum specimens on DOI 1 [3]. CSF titers of NR2B and NR1 on DOI 0 were higher than serum titers on DOI 1; however, by DOI 20, CSF and serum titers of these peptides normalized. The patient's condition almost normalized, with alleviation of hyperactivity, and she was discharged on DOI 29. On DOI 44, her developmental quotient was 83. On DOI 57, brain MRI revealed that the amygdalar and hippocampal lesions had reduced in size and did not have restricted diffusion. Nine months after symptom onset, she still experienced monthly seizures.

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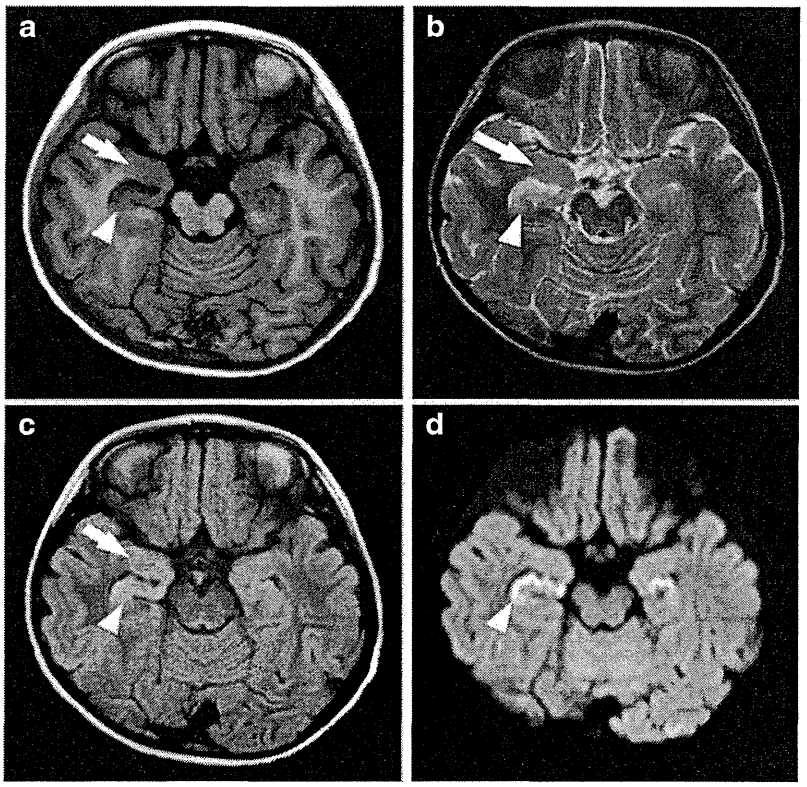

Fig. 1 Axial magnetic resonance imaging using a 1.5 T image showing the amygdalar (*arrow*) and hippocampal (*arrow head*) lesions on both sides, on day of illness 6. Low signals on (**a**) a T1-weighted image (repetition time[TR]/echo time[TE]/inversion time[TI] 2464/15/1,000 ms) and high signals on (**b**) a T2-weighted image (TR/TE 4383/120 ms), (**c**) a FLAIR image (TR/TE/TI 11000/140/2,800 ms), and (**d**) a diffusion-weighted image (TR/TE 2860/78 ms); the high intensity signals for the hippocampus are clearly visible on the diffusion-weighted image (**d**)

Unlike the report by Park et al., in our patient, the RS virus was not detected in CSF by PCR, and NMDAR antibodies were detected in CSF and serum. Therefore, the cause of limbic encephalitis in our patient was not direct invasion of the RS virus, but more likely, a parainfectious immune-mediated response. MRI signal abnormalities were evident not only on FLAIR but also on DWI. Park et al. speculated that diffusion abnormalities on DWI-related biological structures undergo irreversible structural changes. The MRI signal pattern may reflect the pathophysiological difference or disease severity itself. There have been only two reported cases of RS virus-related limbic encephalitis; therefore, we are far from a conclusion. Future studies on infectious pathogens and various auto-antibodies in limbic encephalitis may provide additional insights.

Conflict of interest We declare that we have no conflict of interest.

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Clinical commentary

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Chronic periodic lateralised epileptic discharges and anti-N-methyl-D-aspartate receptor antibodies

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ABSTRACT – Periodic lateralised epileptiform discharges (PLEDs) are uncommon transient electroencephalographic findings accompanied by acute brain lesions. A small proportion of PLEDs persist for more than three months and are called "chronic" PLEDs, the pathophysiology of which is still debated. Herein, we report a man with right hemispheric PLEDs which lasted for more than 14 months and mild left hemispatial neglect after he experienced status epilepticus. Although MRI was normal, positron emission tomography revealed right temporo-parieto-occipital hypometabolism, which coincided with the source area of PLEDs estimated by magnetoencephalography. In addition, levels of anti-*N*-methyl-D-aspartate (NMDA) receptor antibodies and granzyme B were found to be high in the cerebrospinal fluid. Following two courses of steroid pulse therapy, the patient's left spatial neglect improved and the PLEDs were partially resolved. These findings suggest that the chronic PLEDs present in this case were an interictal phenomenon and that their pathophysiology involved autoimmune processes.

Key words: status epilepticus, magnetoencephalography, steroid pulse therapy, left hemispatial neglect

Periodic lateralised epileptiform discharges (PLEDs) are uncommon electroencephalographic findings characterised by repetitive focal complexes that contain one or more sharp-wave components of approximately 0.5-3 Hz in frequency (Chatrian *et al.*, 1964).

Most PLEDs are relatively transient, appearing within 24 to 72 hours after the onset of acute brain lesions and resolving in a few days or weeks (Chatrian *et al.*, 1964; García-Morales *et al.*, 2002). However, a small portion of PLEDs persist for more than three months and are differentially termed "chronic" PLEDs, the underlying cause of which appears to differ (Westmoreland *et al.*, 1986; Fitzpatrick and Lowry, 2007). Although more than 80% of patients with PLEDs experience clinical

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