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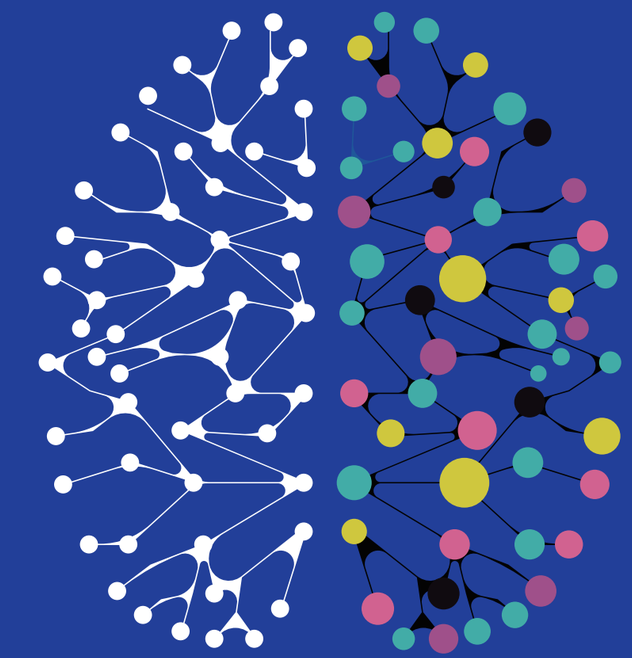

Symptomatic treatments of *N*-methyl-D-aspartate receptor encephalitis

Soon-Tae Lee

Initial cerebrospinal fluid-restricted oligoclonal bands associate with anti-*N*-methyl-D-aspartate receptor encephalitis severity: a pilot study

Sang Bin Hong, Yong-Won Shin, Jangsup Moon, Woo-Jin Lee, Kon Chu, Sang Kun Lee

Korean Encephalitis and Neuroinflammation Society

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Aims and Scope

Encephalitis is a peer-reviewed, Open Access journal that publishes original research articles, review/mini-review articles, and experimental or clinical studies/case reports on encephalitis and neuroinflammation. The journal was launched in January 2021 and is published quarterly on the 10th of every January, April, July, and October.

Encephalitis is a disease caused by the neuroinflammation in the brain. Neuroinflammation refers to inflammation that occurs in the nerves system. It can be triggered by a variety of causes or events, including infection, traumatic brain injury, seizure, toxic metabolites, and autoimmune responses. Acute inflammation is characterized by transient changes in inflammatory molecules, endothelial cell activation, and platelet deposition, but chronic inflammation is involved in the prolonged activation of glial cells and recruitment of other immune cells into the brain. The symptoms of encephalitis include severe headache, fever, confusion, seizures, trouble speaking, and memory problems. Although viral infections are considered the most common cause of encephalitis, in many cases the cause remains unknown, although it can be life-threatening. It is important to get a timely diagnosis and treatment.

Priority of *Encephalitis* is given to work that provides translational and/or fundamental insight into the workings of encephalitis and neuro-immune interactions in the brain. covers a wide range of topics related to encephalitis/neuroinflammation including neuroscience, immunology, pathophysiology, pharmacology, microbiology, genomics, diagnosis, cure of infectious diseases, and related general experimental and clinical research on the nervous system. *Encephalitis* serves as the major conduit of top-quality information for neuroscientist or neurobiologist community, as well as the neurologist community.

Acceptance for publication of submitted manuscript is determined by the editors and peer reviewers, who are experts in their specific fields of each topic. Review processing is performed by the editorial board members of journal and outside experts. All published articles will be assigned DOI provided by CrossRef.

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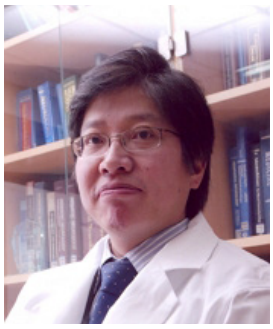

Congratulatory remarks on expanding the research field for encephalitis and neuroinflammation

Sang Kun Lee

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On behalf of all members of our society, it is my great pleasure and privilege to congratulate the publication of the first issue of *encephalitis*. The field of encephalitis and neuroinflammation is an extraordinary field of neuroscience that gives us a sense of awe. It includes various kinds of encephalitis and altered neuroimmunology diseases with remarkable clinical characteristics, which gives us very important insights into neuroscience regardless of the basic and clinical aspects.

Recently, many new categories of encephalitis have been found and the efforts to discover novel forms of this disease are also ongoing. With these discoveries and their associated efforts, we can begin to grasp the secrets of neuroimmunology and the functions and the connections between various neural systems macroscopically and microscopically. We, therefore, are able to refine the diagnosis and treatment of various encephalitis and neuroinflammation diseases and step forward to save the lives of patients and nervous system function.

Many more studies should provide us with a greater understanding of the mechanisms of these diseases and aid in further treatment strategy developments at the state of the art level. Korea is one of the leading countries doing cutting edge research to develop diagnosis and treatment guidelines for encephalitis diseases. As a result, we need a more suitable vehicle such as *encephalitis* to reach these various goals. *encephalitis* is dedicated to original research that encompasses basic and clinical fields that investigate encephalitis, neuroinflammation, and neuroimmunology. Case reports are also welcome. All the members of the Editorial Board and publication staff are looking forward to receiving a wide range of submissions and contributions from all international researchers and clinicians. Thank you very much.

Warm regards,

Sang Kun Lee

Honorary President,
Korean Encephalitis and Neuroinflammation Society

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New era exploring the brain

Manho Kim

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encephalitis is the first official journal of the Korean Encephalitis and Neuroinflammation Society (KENS) which was established in September, 2013.

With delight and deep appreciation, I extend special thanks to all the staff who have spent time and effort to launch the journal, expecting it will be a leader in advanced neurology research.

Even a decade ago, as is the case for most neurologists, patients with encephalitis were regarded as a part of the infection, thus, many of them were managed according to a standard protocol, such as anti-viral agents with seizure or intracranial pressure controls. However, even with rigorous treatment, some patients did not survive or were left with severe neurological deficits. Even the causative agents were not known.

Since the discovery of autoimmune encephalitis, starting with anti-*N*-methyl-D-aspartate receptor encephalitis, experts at this institution developed and began to provide diagnosis guidelines all across the country, along with consultations for clinical practitioners. Several thousand patients' lives were saved. Accumulating experiences have been communicated via lectures at seminars or conferences as well as among the members of KENS.

The discoveries so far are big steps in the exploration of the brain. Expanding datasets are expected and will need to be organized, from case reports to clinical trials, from basic and translational neuroscience to clinical practice, and then systemic reviews to update the new advances.

Now, as the second president of KENS, it is my great honor to celebrate launching the journal, *encephalitis*.

With my best regards,

Manho Kim

President, Korean Encephalitis and Neuroinflammation Society

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With a new journal "*encephalitis,*" hope to feel inspired

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Dear colleagues,

It is our great pleasure to announce a new journal, "*encephalitis*", and to share this news with all neurologists and neuroscientists. Moreover, my opportunity to serve as the founding editor-in-chief for this journal is a great honor and I appreciate the Korean Encephalitis and Neuroinflammation Society for appointing me to this position.

This journal is born from two continuing streams of academic study. The first one is neuroinflammation and the other is encephalitis. For a few decades, central nervous system (CNS) immunology was regarded as one of the common mechanisms of neurological diseases including acute as well as chronic degenerative diseases. Since researchers' long-held belief was that inflammatory responses could be controlled easily, they focused on neuroinflammation in nearly all kinds of neurologic diseases. However, excluding a few diseases such as multiple sclerosis and other some immunologic CNS diseases, we have recognized that neuroinflammation is only a part of disease, and inflammatory reactions are complex and thus, carefully targeted treatment is warranted. Encephalitis is a challenging disease for all neurologists. The first decision is whether the disease is infectious or noninfectious, which though it looks like an easy distinction, is definitely not that easy. The potential hope has been that the diagnostic yields for infectious organisms have been improved by novel technologies. However, in cases when noninfectious etiologies are suspected, diagnosis is a bumpy ride. Recent discovery of numerous autoantibodies and methods to detect these could help classify diseases more clearly and improve clinical outcomes, which deepen our knowledge of neuroimmunology.

Since the birth of the Korean Encephalitis and Neuroinflammation Society in 2013, core members in this society have put a lot of effort into uncovering the evidence for encephalitis and neuroinflammation that is relevant to diagnosis and treatment. Personally, I hope both basic researchers and clinicians who investigate encephalitis and neuroinflammation will actively submit articles and serve in the peer-review process. Novel basic or translational trials are welcomed, even if negative results are obtained. According to our aims and scope, this journal does not restrict articles on encephalitis but, can accept a broad range of all neuroinflammatory studies, which reveal the roles of inflammation in general neurological diseases. I look forward to meeting you as authors, reviewers, and readers in this journal soon.

With best regards,

Kyung-Il Park

Editor-in-chief, *encephalitis*

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Symptomatic treatments of *N*-methyl-D-aspartate receptor encephalitis

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N-methyl-D-aspartate receptor (NMDAR) encephalitis presents with multiple symptoms including memory loss, seizure, psychosis, aphasia, altered mentality, dyskinesia, autonomic dysfunction, and central hypoventilation. While immunotherapy protocols are improving, morbidity and mortality in the disease largely depend on supportive care to control intractable symptoms. However, no prospective or controlled trials have been conducted on immunotherapy or supportive care principles in the disease. Thus, this study discusses and shares experience and ideas for symptomatic care of NMDAR encephalitis.

Keywords: *N*-methyl-D-aspartate receptor, Encephalitis, Symptomatic, Treatment

Introduction

N-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common and serious form of autoimmune encephalitis. It is caused by autoantibody against NR1 subunit of the NMDAR receptor. Key symptoms include memory loss, psychosis, seizure, aphasia, altered mentality, dyskinesia, autonomic dysfunction, and central hypoventilation [1]. Immunotherapy is the main treatment and includes steroid, immunoglobulin, rituximab, tocilizumab, and/or cyclophosphamide, which are frequently combined to enhance outcomes. Although the final outcome has been improved after the application of novel immunotherapies, there still exist a lot of mortality and permanent morbidity by the disease. When treated for up to 24 months, 25% of patients remained disabled in 3 to 6 categories of the modified Rankin Score [1]. Hence, long-term integrated supportive care is essential until the full effect of immunotherapy can ameliorate disease symptoms.

This paper summarizes the details of supportive care for disabling symptoms of NMDAR encephalitis based on reported evidences and personal experience.

Memory Loss

Because NMDAR mediates long-term potentiation of memory [2], memory loss is the early and key symptom in NMDAR encephalitis. However, currently no symptomatic treatment is available to enhance memory function in this disease. EphB2 receptors form a complex with NMDAR, and anti-NMDAR antibodies disrupt the cross-talk between NMDAR and EphB2 receptors [3]. Moreover, ephrin-B2 (the ligand of the EphB2 receptor) prevents intracellular internalization of NMDAR by disease antibodies [4]. Accordingly, some chemicals modulating the EphB2 receptor could affect NMDAR encephalitis symptoms; however, no clinically usable drugs have been approved for this purpose. Because memory loss is largely reversible after remission of the disease, education regarding the disease course and psychological support for family members are necessary.

Psychosis

Psychosis and behavioral problems not only increase caregiver burden but also can result in self-injury. To control psychosis, antipsychotics such as dopaminergic blockers and anxiolytics

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such as benzodiazepine can be prescribed. Because the pattern of psychosis is variable [5], control of symptoms depends on individual phenotypes. While psychiatric symptoms that emerge in the early disease phase can be partially controlled by antipsychotics, close monitoring is necessary because antipsychotics can aggravate rhabdomyolysis or induce neuroleptic malignant syndrome, especially in patients with dyskinesia [6]. Atypical antipsychotics can reduce extrapyramidal side effects, although further studies are needed. Similar to other symptoms of the disease, immunotherapy is the main tool to control psychosis. Meanwhile, psychosis is often re-aggravated during the later stages of the disease, and re-introduction of antipsychotics is sometimes necessary. Hyperactive forms of psychosis can re-emerge, such as anxiety, anger, or disinhibition, usually accompanied by improvements in memory function.

Dyskinesia

Dyskinesia is one of the most troublesome symptoms of the disease. Down-regulated NMDAR expression causes dopaminergic overactivation in the globus pallidus and might cause hyperkinetic movement disorders [7]. Severe dyskinesia causes self-injury, rhabdomyolysis, and renal failure [6]. In intensive care units, anesthetics or neuromuscular blockers are necessary in severe cases. However, when dyskinesia continues for several months, prolonged use of these agents is not clinically feasible due to other systemic complications.

Recently, I have shown that mega-dose enteral diazepam (ranging from 6 to 180 mg) can control dyskinesia effectively [8]. Previously, diazepam has demonstrated muscle-relaxant properties in neuroleptic malignant syndrome and tetanus [9,10]. In the severe form of dyskinesia resulting from NMDAR encephalitis, mega-dose diazepam decreased the severity of dyskinesia to tolerable levels and no patients had serious adverse events except mild sedation [8]. By using mega-dose diazepam, I could stop anesthetics or neuromuscular blockers in many patients and the effect was durable for the remaining immunotherapy period. I usually start diazepam at a medium dose (3–5 mg, three or four times daily) and then double the dose every several days depending on response, up to a maximum of 180 mg daily. Mega-dose enteral diazepam could be an effective treatment option for controlling dyskinesia in NMDAR encephalitis.

Seizure

The management of epilepsy in NMDAR encephalitis is in line with the management of autoimmune epilepsy, the clinical approach of which is described in a previous consensus [11]. In terms of antiepileptic drug (AED) selection, selection depends on clinician preference, seizure semiology, related medical conditions, and side effect profiles. Drugs with fewer side effects, no drug-drug interactions and that are fast loading are preferred, and next-generation AEDs such as levetiracetam, lacosamide, perampanel, zonisamide, topiramate, and pregabalin are good candidates for first-line use. However, because levetiracetam and perampanel can aggravate psychosis, they are frequently replaced with other AEDs when used in NMDAR encephalitis with psychiatric symptoms. Topiramate can cause language problems and memory decline, and its use is sometimes terminated early in NMDAR patients with language dysfunction and memory loss. Patients with aggressive immunotherapy often show neutropenia, which could be a side effect of immunotherapy or a hematologic side effect of AED. In patients being treated with steroid or cyclophosphamide, enzyme-inducing AEDs, such as phenytoin, phenobarbital, and carbamazepine, increase the hepatic degradation of the immunotherapy drugs, dampening the pharmacokinetics. Accordingly, non-enzyme-inducing AEDs are recommended for use in combination with immunotherapeutic agents with hepatic metabolism.

Hypersalivation

Hypersalivation is one of the symptoms caused by autonomic dysfunction in NMDAR encephalitis with a prevalence of 4% to 18% [12]. Hypersalivation is associated with profound drooling, constant suction, pneumonia, and sometimes volume depletion. While anticholinergics are often tried in other diseases, they can aggravate autonomic dysfunction and paralytic ileus in NMDAR encephalitis. Accordingly, effective treatments without systemic side effects are needed.

My team has shown that botulinum toxin injection into the salivary glands can control hypersalivation in NMDAR encephalitis [13]. The effects of one injection last for 12 to 16 weeks and sufficient mitigate the need for other anticholinergics. The injection can be repeated if needed after 12 weeks. Botulinum toxin is a better choice than anticholinergics for management of hypersalivation in NMDAR encephalitis.

Autonomic dysfunction

Autonomic dysfunction causes fluctuation in blood pressure and heart rate in NMDAR encephalitis. In severe cases, hypotension can cause ischemic organ damage such as ischemic hepatitis. Some patients show sinus arrest, the mechanism for

which is not fully understood, and need temporary pacemakers. To minimize complications of autonomic dysfunction, anticholinergic drugs should be prescribed with caution. Cholinergic drugs such as pyridostigmine can be helpful, and I frequently prescribe them in patients with paralytic ileus. However, they can increase salivation, and the overall clinical efficacy should be determined in further controlled trials. Midodrine can help to correct hypotension. Blood pressure and heart rate are very sensitive to beta-blockers, and these drugs should be used with caution because they can cause hypotension or bradycardia even at low doses.

Hypoventilation

Central hypoventilation in NMDAR encephalitis is the main cause of mortality and morbidity via hypoxic brain damage in general wards. If a patient shows rapid progression of the disease, especially altered mentality and dyskinesia, monitoring of oxygen saturation and heart rhythm might be helpful to detect central hypoventilation. Once it occurs, hypoventilation means that the disease course is severe and that 1-year outcomes will be poor, as indicated by the anti-NMDAR Encephalitis One-Year Functional Status (NEOS) score [14]. Intubation, tracheostomy, and ventilator care are inevitable in most patients with central hypoventilation.

Conclusion

Immunotherapy is the main treatment of NMDAR encephalitis and improves symptoms of the disease. Nevertheless, supportive care is needed to decrease mortality and morbidity. While the protocol for immunotherapy improves every year and several controlled trials on NMDAR encephalitis are being initiated, prospective research is also needed on supportive care topics. Because the final immunologic prognosis of NMDAR encephalitis is usually excellent, the management of organ damage and complications during the disease course is important to prevent permanent physical sequelae of this disease.

Conflicts of Interest

Soon-Tae Lee has been editorial board of *encephalitis* since October 2020. He was not involved in the review process of this review article.

Soon-Tae Lee have an advisory role for Genentech, UCB, and Ono Pharmaceuticals outside of the current work, and received research grants from GC Pharma outside of the current work.

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Initial cerebrospinal fluid-restricted oligoclonal bands associate with anti-*N*-methyl-D-aspartate receptor encephalitis severity: a pilot study

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Purpose
Intrathecal antibody production is thought to underly the pathogenesis and symptomatology of *N*-methyl-D-aspartate receptor encephalitis (NMDARE). In the present study, the clinical correlation of cerebrospinal fluid (CSF) restricted oligoclonal bands (OCBs), as a measure of intrathecal antibody synthesis, was examined in confirmed NMDARE cases.

Methods
The present study included patients with a confirmed diagnosis of NMDARE who underwent initial CSF evaluation and were followed up for a minimum of 12 months. Disease severity was assessed at baseline and 1, 3, 6, 9, and 12 months. Data regarding duration of hospitalization and intensive care unit (ICU) stay, the presence of uncontrolled seizures, and antiepileptic drug requirement were obtained for each patient.

Results
Among the 14 confirmed NMDARE patients, seven had CSF-OCBs. The presence of CSF-OCBs was associated with a more severe disease at baseline ($p = 0.004$), worse final outcome ($p = 0.005$), and longer hospitalization (median, 19 vs. 173 days; $p < 0.001$) and ICU stay (median, 0 vs. 29 days; $p = 0.006$). CSF-OCB positivity was closely associated with treatment refractoriness within 4 weeks ($p = 0.029$).

Conclusion
The presence of CSF-OCBs at the onset of disease in NMDARE patients was associated with initial treatment refractoriness and a more severe disease course leading to longer hospitalization, ICU admission, intractable seizures, and a poorer outcome. The results indicate that CSF-OCBs may be useful for prognostication. Furthermore, severe disease in NMDARE may be accompanied by oligoclonal expansion antibody-producing B cells.

Keywords: Autoimmune limbic encephalitis, Oligoclonal bands, Anti-*N*-methyl-D-aspartate receptor encephalitis

Introduction
With the increasing availability of antibody assays and clinical awareness of autoimmune encephalitides as a diagnosis of encephalitis, a growing literature exists on the diverse range of clinical manifestations of autoimmune encephalitides. One of the most commonly identified autoimmune encephalitis is anti-*N*-methyl-D-aspartate receptor encephalitis (NMDARE). NMDARE symptoms can range from seemingly benign to life-threatening [1-4]. Reliable biomarkers predictive of disease course at symptom onset would facilitate the administration of

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timely immunotherapy and adequate medical management of complications.

Previous prognostication scores, such as the anti-NMDA Receptor Encephalitis One-Year Functional Status (NEOS) score [5], have utilized various indices of disease severity to predict functional outcome. The prognostic potential of various baseline variables, symptoms, and clinical assessments in NMDARE have been evaluated in other studies [6,7]. However, despite many efforts to determine factors associated with prognosis in NMDARE, a more reliable biomarker with fewer practical limitations is currently needed [8].

Prior research indicates the pathology in NMDARE is directly mediated by the intrathecal presence of anti-NMDA receptor (NMDAR) antibodies, leading to the possibility that patient cerebrospinal fluid (CSF) may provide relevant information for predicting disease severity. However, commonly tested CSF parameters such as leukocyte count or protein level inconsistently correlate with prognosis [9,10]. Other CSF tests such as anti-NMDAR antibody titers [11] have a more limited applicability in the clinical setting.

CSF-restricted oligoclonal bands (CSF-OCBs) are present in various immune-mediated neurologic disorders, such as multiple sclerosis (MS), and central nervous system (CNS) infections. In MS in particular, diagnostic and prognostic use of CSF-OCBs has long been established [12], with more than two or three CSF-OCBs signifying dissemination in time and portending a severe disease course with more frequent relapses. In the NMDARE setting, CSF-OCB, as a sensitive and standard measure of intrathecal antibody synthesis, may also reflect disease activity and prognosis associated with expansion of clonal intrathecal antibody production.

In the present study, the clinical correlation of the presence of CSF-OCBs was examined and its potential value as a prognostic biomarker in NMDARE evaluated.

Methods

Subjects

The present study included patients with a definite diagnosis of NMDARE according to the criteria previously published [13], and subjects who underwent initial CSF evaluation, including CSF-OCB testing at our hospital. The patients were followed up for a minimum of 12 months. Informed written consent was obtained from each patient or patient guardian, and the study was approved by the Institutional Review Board at Seoul National University Hospital (No. 1204-078-406).

Diagnosis of anti-NMDARE

NMDARE was diagnosed based on clinical features, brain magnetic resonance imaging (MRI), CSF analysis, electroencephalography, and presence of anti-NMDAR antibodies in the CSF or serum. A commercial cell-based immunochemistry method and indirect fluorescence assay using human embryonic kidney 293 cells (Euroimmun AG, Lübeck, Germany) was used to screen for antibodies to NMDAR as previously described in the literature [14].

OCB testing

The presence of CSF-OCBs was tested at initial presentation with CSF and paired serum sampling using gel electrophoresis and isoelectric focusing with immunofixation. Positive results included an oligoclonal response of more than two bands in the CSF with the paired serum showing a normal polyclonal response, and a CSF oligoclonal pattern of different isoelectric points compared with the serum. Negative results included a polyclonal response in both CSF and sera, a mirror type response with similar OCBs in CSF and sera, or a monoclonal response typical for paraproteins.

Clinical outcomes

Modified Rankin Scale (mRS) and clinical assessment scale in autoimmune encephalitis (CASE), as previously detailed [15], were used to assess each patient at baseline, and 1, 3, 6, 9, and 12 months, and last follow-up time points. Information on the length of intensive care unit (ICU) stay and hospitalization was also collected. To estimate the severity of seizures, information on antiepileptic drug (AED) prescription and seizure control was obtained based on retrospective review of medical records.

For each patient, the NEOS score [5], a 5-point maximum score comprising ICU admission, treatment delay of > 4 weeks, lack of clinical response to treatment within 4 weeks, MRI abnormality, and elevated CSF leukocyte count > 20 cells, was calculated based on retrospective review of medical records. The relationship between NEOS score and OCB components was examined. The performance of the NEOS score and OCB predicting 12-month outcomes (mRS 0–1: no impairment, mRS 2–5: impairment) was compared.

Statistical analyses

Statistical analyses were performed using R 3.6.1 (R Foundation for Statistical Computing, Vienna, Austria). Wilcoxon rank-sum test, Fisher exact test, and Spearman correlation test were used as appropriate. A p-value of < 0.05 was considered statistically significant.

Table 1 Baseline characteristics of the study population

Characteristic	CSF-OCB-negative (n = 7)	CSF-OCB-positive (n = 7)	p-value
Age (yr)	24 (19–45)	27 (22–44)	0.95
Female sex	5 (71.4)	5 (71.4)	> 0.999
CSF sampling after IVIg treatment[a]	4 (57.1)	5 (71.4)	> 0.999
IgG index[b]	0.51 (0.29–3.69)	0.83 (0.22–2.20)	0.95
CSF leukocytes (cells/μL)	36 (2–221)	26 (0–150)	0.84
Symptom duration at CSF sampling (day)	16 (6–49)	35 (12–65)	0.08
Follow-up duration (mo)	16 (10–28)	21 (19–77)	0.17
Treatment delay > 4 wk	2 (28.6)	3 (42.9)	> 0.999
Teratoma	2 (28.6)	3 (42.9)	> 0.999

Values are presented as median (range) or number (%).
CSF, cerebrospinal fluid; CSF-OCB, CSF-restricted oligoclonal band; IV, intravenous; Ig, immunoglobulin.
[a]Number of patients. [b]Calculated using (CSF IgG/serum IgG)/(CSF albumin/serum albumin).

Results

Clinical characteristics

Fourteen confirmed NMDARE patients received initial CSF-OCB testing. Differences in age, sex, and symptom duration at CSF-OCB testing were not observed (Table 1). Nine patients (four CSF-OCB-negative patients and five CSF-OCB-positive patients) underwent CSF testing after intravenous immunoglobulins had been started.

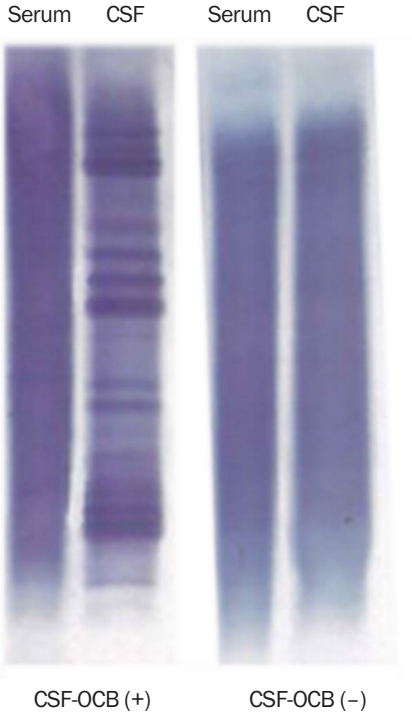
Among the patients, seven were positive for CSF-OCBs (Figure 1) and seven were negative. Significant differences in the initial CSF findings between CSF-OCB-negative and CSF-OCB-positive groups including CSF leukocyte count and immunoglobulin G (IgG) index were not observed (Table 1). IgG index (baseline: mRS [p = 0.61], CASE [p = 0.54]; 12 months: mRS [p = 0.37], CASE [p = 0.77]) or the CSF leukocyte count (baseline: mRS [p = 0.95], CASE [p = 0.92]; 12 months: mRS [p = 0.80], CASE [p = 0.89]) correlated with initial and follow-up clinical severity.

The follow-up duration after testing between CSF-OCB-negative and CSF-OCB-positive groups did not differ significantly, and differences in the proportion of patients receiving delayed immunotherapy were not observed (Table 1). All patients received multiple courses of first-line, second-line, and other immunotherapies, and teratoma removal in case of teratoma discovery, as previously detailed [16].

CSF-OCB positivity at disease onset is associated with marked differences in the initial severity and overall disease course

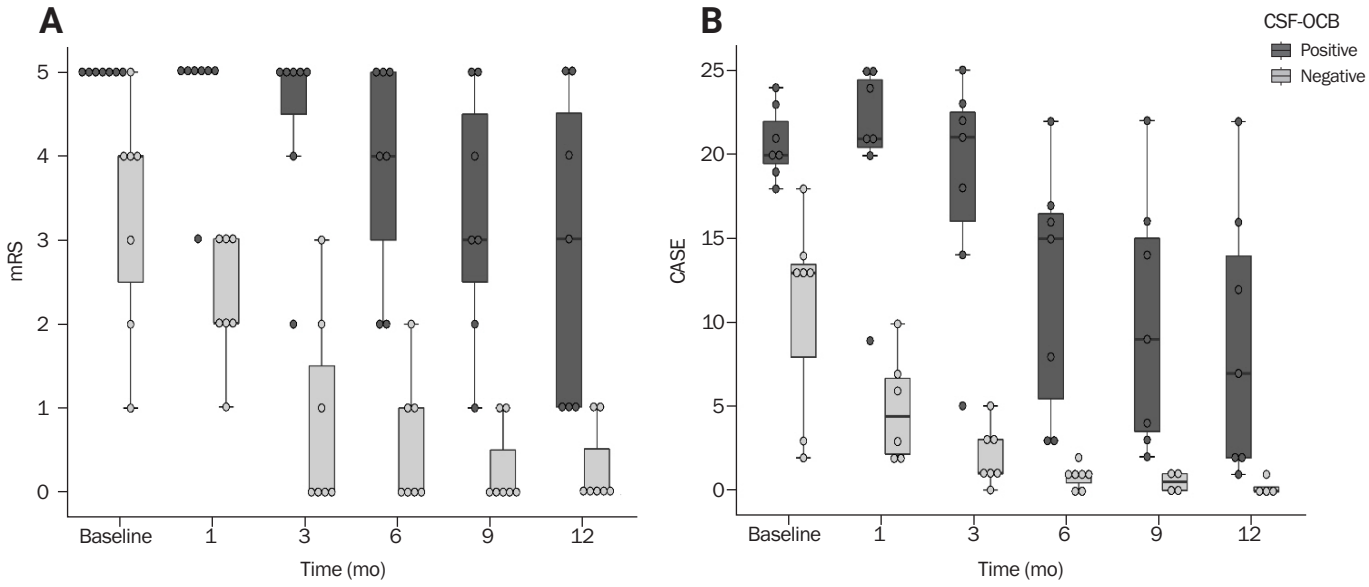
The mRS and CASE scores were significantly higher in CSF-OCB-positive patients than in CSF-OCB-negative patients at baseline, and 1, 3, 6, 9, and 12 months (Figure 2). Notably, an initial worsening of median CASE scores was observed in CSF-OCB-positive patients at 1 month after presentation, contrary to the rapid reduction in CASE scores in CSF-OCB-negative patients. In CSF-OCB-negative patients, the disease course was favorable and no patient had remaining sequela impairing daily life.

Figure 1 Patterns of multiple CSF, CSF-OCBs in anti-*N*-methyl-D-aspartate receptor antibody encephalitis patients



Gel electrophoresis, isoelectric focusing with immunofixation results of paired sera and CSF samples.
CSF, cerebrospinal fluid; CSF-OCB, CSF-restricted oligoclonal band.

Figure 2 One-year clinical trajectories in CSF-OCB-positive and CSF-OCB-negative patients



(A) Modified Rankin Scale (mRS). **(B)** Clinical assessment scale in autoimmune encephalitis (CASE).
CSF-OCB, cerebrospinal fluid-restricted oligoclonal band.

Table 2 Comparison of outcome variables between CSF-OCB-negative and CSF-OCB-positive groups

Variable	CSF-OCB-negative (n = 7)	CSF-OCB-positive (n = 7)	p-value
Total hospital stay (day)	19 (12–34)	173 (44–421)	< 0.001
Total ICU stay (day)	0 (0–2)	29 (0–54)	0.006
NEOS score	2 (0–3)	3 (2–4)	0.008
Lack of treatment response in first 4 wk	1 (14.3)	6 (85.7)	0.029
ICU admission	1 (14.3)	6 (85.7)	0.029
MRI abnormality	3 (42.9)	4 (57.1)	> 0.999
CSF leukocytes > 20/μL	3 (42.9)	4 (57.1)	> 0.999
Modified Rankin Scale			0.004
At baseline	4 (1–5)	5 (5–5)	
At 12 mo	0 (0–1)	3 (1–5)	0.005
CASE			
At baseline	13 (2–18)	20 (18–24)	0.002
At 12 mo	0 (0–1)	7 (1–22)	0.013
Seizure severity[a]	1 (0–2)	3 (2–3)	0.002
Maximum number of AEDs	3 (0–5)	6 (3–7)	0.028

Values are presented as median (range) or number (%).
CSF, cerebrospinal fluid; CSF-OCB, CSF-restricted oligoclonal band; ICU, intensive care unit; NEOS, anti-NMDA Receptor Encephalitis One-Year Functional Status; MRI, magnetic resonance imaging; CASE, clinical assessment scale in autoimmune encephalitis; AED, antiepileptic drug.
[a]Seizure severity: 0, no seizure; 1, controlled seizures; 2, uncontrolled seizures; 3, status epilepticus.

CSF-OCB positivity predicts prolonged hospital stay and ICU admission

CSF-OCB positivity was associated with a longer duration of hospitalization ($p < 0.001$) and ICU stay ($p = 0.006$, Table 2). Only one CSF-OCB-negative patient was admitted to the ICU and five of seven CSF-OCB-positive patients stayed in the ICU longer than 2 weeks.

CSF-OCB positivity indicates an increased risk of seizures

CSF-OCB-positive patients had more severe seizures and required administration of multiple AEDs (Table 2). No CSF-OCB-negative patient experienced status epilepticus; however, five CSF-OCB-positive patients experienced convulsive or non-convulsive status epilepticus with four requiring a trial of six or more concomitant administrations of AEDs. After 1 year of follow-up, four of seven CSF-OCB-positive patients remained dependent on multiple AEDs and only one CSF-OCB-negative patient was on a single AED.

Presence of CSF-OCBs is predictive of important NEOS score components

CSF-OCB-positive patients were more likely to be admitted to the ICU ($p = 0.029$) and have a lack of response to treatment in the first 4 weeks ($p = 0.029$) than CSF-OCB-negative patients. Significant relationship was not observed between the presence of CSF-OCBs and MRI abnormality or CSF leukocyte count. Both NEOS score and CSF-OCB positivity predicted outcome at 12 months equally well (sensitivity, 100%; specificity, 64%; area under the receiver operating characteristic curve, 0.82).

Discussion

In our NMDARE cohort, half of the patients were CSF-OCB-positive, somewhat comparable with previously reported prevalence ranging from 50% to 67% [17,18]. When the clinical correlation of CSF-OCB positivity was examined, the results showed a close association with early treatment refractoriness and ICU admission, greater clinical severity, and an initially deteriorating clinical course leading to prolonged hospital stays, uncontrolled seizures, and poorer outcome.

Other candidate prognostic markers have also been proposed. Anti-NMDAR antibody titers in the CSF were shown partially associated with clinical outcome [11] as well as other measurable factors such as cell-free CSF mitochondrial DNA [19], NLRP3 inflammasome levels [20], Th17 cells [21], and cytokines [22]; however, routinely tested CSF parameters were shown to not correlate with disease trajectory [9,10], as was the case in our cohort. CSF-OCB testing is advantageous because the test can be performed while a diagnosis of NMDARE is only suspected, and is widely available with an established method useful in many neurologic conditions.

Among the items of the NEOS score, treatment refractoriness in the first 4 weeks and ICU admission were the two strongest predictors of outcome [5]. Both factors closely paralleled CSF-OCB positivity, and CSF-OCB positivity alone performed equally well as the NEOS score in predicting 1-year outcomes in our cohort.

The pathomechanistic implications of our results may be notable for two reasons. First, although in previous literature the focus was on a single antibody targeting the GluN1 subunit of the NMDAR as being pathogenic [23-25] and responsible for most symptoms [26-29] in NMDARE, the concomitant presence of oligoclonal antibodies appear to have clinical relevance. In MS, CSF-OCBs are thought to be produced by clonally expanded B cells within the intrathecal space [30] as a result of somatic hypermutation of B cells upon continued antigen presentation [31]. Therefore, CSF-OCBs in NMDARE could be a result of continued and prolonged exposure to antigens in the CNS triggering persistent immune response. This also may be the reason early removal of teratoma improves prognosis in NMDARE [32] and indicates multiple related antigenic targets that intensify disease pathology may exist in a portion of NMDARE patients. Another possibility is that CSF-OCBs reflect direct damage to the CNS and release various types of neural and glial antigens due to severe disease activity, and are not the cause.

Second, intrathecal humoral immune response appears closely associated with clinical severity in NMDARE. Among CSF-OCB-negative patients, the majority had a normal polyclonal pattern in both serum and CSF (five of seven; two had single bands in the CSF), and among CSF-OCB-positive patients, six of seven showed a normal polyclonal response in the serum. Thus, a distinct immune profile within the CNS was correlated with severe symptomatology, indicating intrathecal humoral immune response is primarily responsible for determining the clinical trajectory of NMDARE.

Lastly, a few issues should be considered when interpreting these results. Initial symptom severity in our cohort delineated patients with severe disease course from patients with milder disease course. Because clinical evaluations were made at similar time points as the lumbar puncture, any additional prognostic value beyond the initial clinical evaluation may be disputable. However, the CSF-OCBs have a practical advantage because they are a single diagnostic and prognostic biomarker, requiring no additional expert interpretation.

Further limitations of this study include the small sample size and the tertiary care setting with limited generalizability. However, the drastically contrasting clinical course of CSF-OCB-negative and CSF-OCB-positive patients that was clearly demonstrated in our small cohort, warrants further studies in which the relationship between CSF-OCB and clinical severity is investi-

gated.

In conclusion, the present study results indicate initial CSF-OCB testing in NMDARE may aid in identifying patients with unfavorable disease course and clearly stratifying patients into a severe and a benign group. Larger prospectively designed studies will help determine the clinical utility of initial OCB testing in NMDARE.

Conflicts of Interest

Jangsup Moon, Kon Chu, Sang Kun Lee have been editorial board of *encephalitis* since October 2020. They were not involved in the review process of this original article. No other potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: SB Hong, YW Shin, K Chu, SK Lee; Data curation, Formal analysis, Project administration, Investigation: SB Hong; Methodology: SB Hong, YW Shin; Resources: K Chu, SK Lee; Supervision: YW Shin, J Moon, WJ Lee, K Chu, SK Lee; Writing–original draft: SB Hong; Writing–review and editing: SB Hong, YW Shin, J Moon.

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Respiratory virus-related meningoencephalitis in adults

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Purpose

Respiratory viruses (RVs) are pathogens that can cause central nervous system (CNS) infection, but previous research has been limited to a pediatric population. In recent years, several cases of adult RV meningoencephalitis have begun to be reported. We decided to research the CNS infection of RV in the entire neuroinfection registry.

Methods

We retrospectively reviewed the neurologic infection registry of Seoul National University (Seoul, Korea). Among a total of 661 patients in the registry, 10 adult patients were diagnosed with RV-related meningoencephalitis on RV multiplex polymerase chain reaction (PCR) screening test. We analyzed the clinical presentation, laboratory findings, and clinical course of the 10 patients.

Results

Three patients were definite RV meningoencephalitis who had positive PCR results from cerebrospinal fluid. The other seven patients were diagnosed with probable RV meningoencephalitis if they had positive PCR results in the sputum and negative results in other extensive workup.

Conclusion

RV-related meningoencephalitis should be considered a possible etiology in adult meningoencephalitis patients. To diagnose these viruses, screening test of RV PCR is recommended even in patients without upper respiratory infection symptoms.

Keywords: Central nervous system viral infections, Meningitis, Encephalitis, Polymerase chain reaction

Introduction

The respiratory virus (RV) group consists of viruses such as adenovirus; respiratory syncytial virus (RSV) A and B; rhinovirus A and B; coronavirus, influenza A and B; parainfluenza 1, 2, 3; and metapneumovirus. RVs mainly cause upper or lower respiratory tract infections, but they can also cause central nervous system (CNS) infection, mostly in children [1]. Adult cases of RV-related meningoencephalitis have been reported in a limited number of patients, predominantly those with influenza virus [2]. How-

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ever, up to 66% of adult encephalitis cases fail to have a causative pathogen identified despite extensive diagnostic laboratory tests [3]. Therefore, further research is needed to identify unusual but detectable pathogens such as RV. We retrospectively reviewed the neurological infection registry, and analyzed the pathogenic etiology of the CNS infections, including the RVs.

Methods

From March 2012 to December 2015, patients visiting Seoul National University Hospital (Seoul, Korea) with a clinical suspicion of CNS infection were enrolled in the neurological infection registry of Seoul National University Hospital (Seoul, Korea). The inclusion criteria were as follows; (1) clinical suspicion of CNS infection, (2) ≥18 years of age, and (3) cerebrospinal fluid (CSF) pleocytosis. The exclusion criteria were as follows; (1) CNS infection related to a recent surgical intervention, or (2) the presence of an additional etiology, such as autoimmune encephalitis or metabolic encephalopathy.

All patients in this registry underwent RV multiplex polymerase chain reaction (PCR) (Anyplex II RV 16 Detection; Seegene Inc., Seoul, Korea) analysis of CSF and sputum. This test provides qualitative analysis for 16 species of RV (adenovirus, influenza A and B, parainfluenza virus 1/2/3/4, rhinovirus A/B/C, RSV A and B, bocavirus 1/2/3/4, metapneumovirus, coronavirus 229E, coronavirus NL63, coronavirus OC43, and enterovirus). Other extensive diagnostic tests were performed, which included CSF culture, CSF PCR, and serum antibody tests for bacteria and viruses. Work-ups for rare pathogens such as tuberculosis, fungus, and parasites were also performed. A clinical diagnosis of meningitis or encephalitis was made based on the initial manifestation of symptoms. Meningitis was characterized by fever and headache without any neurological symptoms. Encephalitis was characterized by headache, altered level of consciousness, and symptoms and signs of cerebral dysfunction such as cognitive impairment, behavioral changes, focal neurologic abnormalities, and seizures [4]. Individual patients were treated according to clinical decisions made by an expert physician from the neurological infection department. Because of its retrospective nature, this study was exempted from the approval of the Institutional Review Board and the written informed consent of the subject.

Results

A total of 661 patients were diagnosed with CNS infection and enrolled in the registry. Among these 661 CNS infection patients, 351 had meningitis, 275 encephalitis, and 35 brain abscess. Etiological pathogens were confirmed in 421 patients (63.7%). Viral infection (253, 60.1%) was the major etiology in pathogen-confirmed CNS infection, followed by bacterial infection (105, 24.9%), mycobacterial infection (25, 5.9%) and fungal infection (21, 5.0%). In pathogen-confirmed viral infection, EBV was the leading etiology (73, 28.9%) followed by herpes simplex virus (HSV; 62, 24.5%), varicella-zoster virus (VZV; 53, 20.9%), and enterovirus (51, 20.2%).

A total of 10 patients were diagnosed with RV-related meningoencephalitis. RV PCR of CSF or sputum yielded positive results, with no other findings on extensive workup. The median age of the patients was 38 years (range, 21–72 years). Four patients were clinically diagnosed with encephalitis and the others were diagnosed with meningitis. Six patients (60.0%) had prior upper respiratory infection (URI) symptoms before manifestation of CNS infection. Leptomeningeal enhancement was the most frequent finding (70.0%) observed on brain magnetic resonance imaging (MRI). Antiviral therapy was administered in 3 of 4 encephalitis patients and 2 of 7 meningitis patients. All of the patients recovered fully without any neurological sequelae, except for one patient (patient 3) who deteriorated despite antiviral treatment (Table 1).

We classified these patients into two different groups according to PCR results. The first was the “definite” group, in which RV presence was confirmed by CSF PCR, and the second was the “probable” group, in which RV presence could be confirmed only by sputum PCR.

Definite respiratory virus meningoencephalitis

Three patients were classified into the “definite” group. Two patients had positive PCR results for influenza A in CSF. The other patient had positive results for human parainfluenza 3 virus in CSF.

Patient 1 was a 40-year-old female. She visited the emergency room for altered mentality and fever lasting 5 days. Before the onset of neurologic symptoms, she complained of cough, rhinorrhea, and mild fever. Initial CSF revealed pleocytosis with a white blood cell (WBC) count of 129/mm^3 (polymorphonucleocytes, 82%; lymphocytes, 4%; other cells, 14%), and elevated protein (153 mg/dL). Initial brain MRI showed leptomeningeal enhancement, but electroencephalography (EEG) did not demonstrate abnormal findings. On extensive diagnostic workup, CSF PCR was positive for influenza A virus. She was treated with oseltamivir and recovered fully after 2 weeks of antiviral therapy; she was discharged at a modified Rankin Scale (mRS)

Table 1 Characteristics of the respiratory virus-related meningoencephalitis patients

Case No.	Age (yr) /sex	Initial symptom	Clinical manifestation	PCR		Positive virus	CSF WBC count, /mm^3 (% of P/L/O)	MRI finding	EEG finding	Antiviral therapy	Onset to treat (day)	Outcome (mRS)
				CSF	Sputum							
1	40/F	URI, fever, altered mentality	Encephalitis	+	ND	Influenza A	129 (82/4/14)	LE	Normal	Oseltamivir	9	0
2	21/M	Fever, headache, seizure	Encephalitis	+	ND	Human parainfluenza 3	139 (34/48/18)	LE	Normal	Ribavirin	35	0
3	67/M	URI, irritability, confusion	Encephalitis	+	+	Influenza A (CSF)	25 (20/80/0)	SAH, LE	Slowing	Oseltamivir	40	5
						Metapneumovirus (sputum)				Peramivir		
4	69/M	Confusion, fever, gait disturbance	Encephalitis	ND	+	Human parainfluenza 2	13 (0/1/12)	Normal	Slowing	NA	NA	0
5	25/F	URI, fever, headache	Meningitis	ND	+	Human rhinovirus A/B	194 (5/90/5)	NA	Normal	NA	NA	0
6	45/F	URI, fever, headache	Meningitis	ND	+	Influenza A	50 (0/42/8)	LE	Normal	Oseltamivir	10	0
7	35/M	URI, headache	Meningitis	ND	+	Human rhinovirus A/B	385 (0/84/16)	Normal	Normal	NA	NA	0
8	33/M	URI, fever, headache	Meningitis	ND	+	Human RSV A	210 (2/95/3)	LE	NA	NA	NA	0
9	72/M	Headache	Meningitis	ND	+	Human coronavirus 229E/NL63	940 (66/20/14)	LE	NA	NA	NA	0
10	28/M	Fever, headache	Meningitis	ND	+	Influenza B	216 (4/72/24)	LE	Normal	Oseltamivir	7	0
						Human RSV A						

PCR, polymerase chain reaction; CSF, cerebrospinal fluid; WBC, white blood cell; P, polymorphonuclear leukocytes; L, lymphocytes; O, other cells; MRI, magnetic resonance imaging; EEG, electroencephalography; mRS, modified Rankin Scale; F, female; M, male; URI, upper respiratory infection; LE, leptomeningeal enhancement; SAH, subarachnoid hemorrhage; RSV, respiratory syncytial virus; ND, not detected; NA, not available.

score of 0.

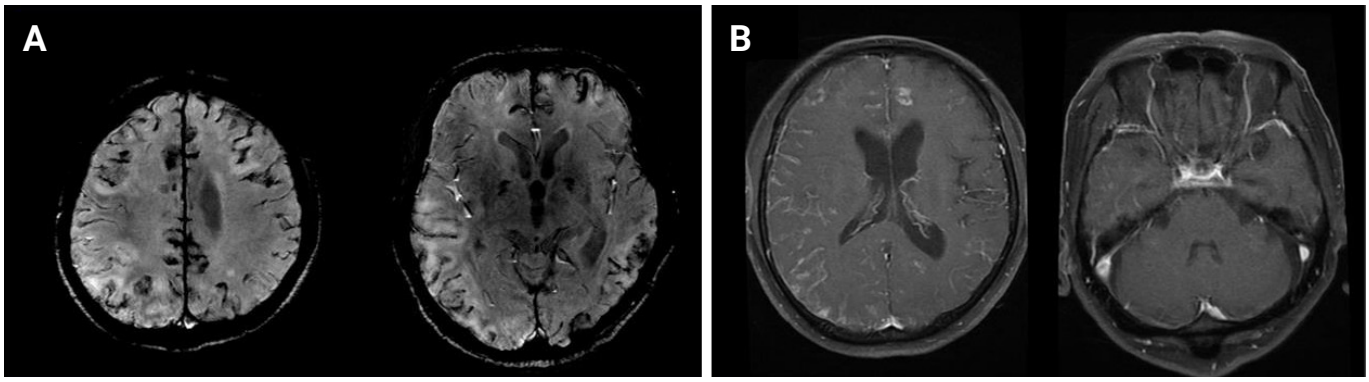
Patient 2 was a 21-year-old male who presented with first-onset seizure. He had a generalized tonic-clonic seizure after complaining of headache for 5 days. Initial CSF showed pleocytosis with red blood cells (RBC) of 12/mm^3, a WBC of 139/mm^3 (polymorphonucleocytes, 34%; lymphocytes, 48%; other cells, 18%), and elevated protein (52 mg/dL). RV PCR of CSF was positive for human parainfluenza virus 3; otherwise, there were no abnormal findings on extensive diagnostic workup. Brain MRI showed leptomeningeal enhancement and EEG demonstrated no focal epileptiform discharge but did reveal generalized intermittent rhythmic delta activity. He was treated with ribavirin for 1 week, after which he was clinically recovered and did not complain of any headache or seizure. Follow-up EEG was also normal after ribavirin treatment.

Patient 3 was a 67-year-old male who had been hospitalized previously for headache, right-side weakness, and transcortical motor aphasia. Prior to headache, he suffered from cough and rhinorrhea for 1 month. Brain computed tomography at a previous hospital showed cortical subarachnoid hemorrhage (SAH). He was treated with corticosteroids in order to reduce intracranial pressure. Initial CSF results revealed pleocytosis with RBC of 270/mm^3, WBC of 25/mm^3 (lymphocytes, 80%; polymorphonucleocytes, 20%), and elevated protein (214.7 mg/dL). He recovered partially and was discharged after 1 week of steroid treatment. However, before long, he started to show confused mentality again and was transferred to our hospital for a second opinion. Follow-up CSF analysis in our hospital revealed persistent pleocytosis with an RBC of 18/mm^3 and WBC of 16/mm^3 (lymphocytes, 13; other cells, 3), and elevated protein (137 mg/dL). On RV PCR, the CSF specimen was positive for influenza A and the sputum specimen was positive for human metapneumovirus. On brain MRI, cortical SAH (Figure 1A) was aggravated and leptomeningeal enhancement (Figure 1B) was observed. Initially, acyclovir was administered for 1 week but was changed to oseltamivir after CSF PCR results were obtained. Although we treated him with oseltamivir for 2 weeks and follow-up CSF PCR results were negative, his mental status worsened. Finally, we administered intravenous peramivir, but the patient entered a persistent vegetative state (mRS score 5) without clinical response.

Probable respiratory virus meningoencephalitis

We classified the other seven patients into the clinically "probable" group. Patients in this group were clinically diagnosed with meningoencephalitis and no pathogens were found on extensive workup other than positive RV PCR of sputum. There were

Figure 1 Brain MRI of a respiratory virus-related encephalitis patient with a poor outcome (patient 3)



(A) Diffuse cortical subarachnoid hemorrhage on susceptibility-weighted angiography MRI. **(B)** Leptomeningeal enhancement on T1-weighted contrast-enhanced MRI.
MRI, magnetic resonance imaging.

two human rhinovirus A/B infections, one of influenza A, one of human parainfluenza virus 2, one human coronavirus 229E/NL63, and one case with both influenza B and human RSV A. Four of these patients had URI symptoms prior to headache. Two patients whose PCR results were positive for influenza A were treated with oseltamivir, and the other patients underwent conservative management. Four patients exhibited leptomeningeal enhancement on MRI. Specific clinical information is presented in Table 1.

Discussion

Here, we demonstrated that, although rare, RVs can be a causative pathogen of meningoencephalitis in adults. According to our data from an adult population, 1.5% of total CNS infection patients were diagnosed with RV-related meningoencephalitis. This accounts for 4.0% of the total CNS viral infections.

Recently, neurologic manifestations of respiratory viral infection have come to the fore. RVs can invade the CNS through either a hematogenous route or a peripheral nerve route [5]. Many cases of RV-associated meningoencephalitis have been reported in adult patients with adenovirus [6], bocavirus [7], influenza A [8-10], influenza B [11,12], parainfluenza [13], and metapneumovirus [14-17]. Reports of meningoencephalitis caused by diverse types of RVs are more common in pediatric cases. RV-related encephalitis comprises approximately 20% of all encephalitis cases in children aged 1 month to 15 years [2]. However, even in adults, RVs remain an important pathogenic cause of meningoencephalitis around the world.

The diagnostic strategy for RV-related meningoencephalitis is similar to other infectious meningoencephalitis. PCR and real time-PCR assays of CSF for the detection of viruses are the most reliable diagnostic tools. A wide range of PCR tests should be carried out, including RV panel, HSV-1, HSV-2, VZV, CMV, and enterovirus, among others. Serologic tests, including serum and CSF specimens, are also helpful to specific etiological diagnosis. In the case of respiratory viral infection, we believe PCR testing of sputum will help establish a diagnosis [18].

Detailed history taking about prodromal symptoms, recent travel, geographic location, exposure history, and occupation provides important clinical clues regarding infectious pathogens. Nevertheless, clinical symptoms and neurologic examination findings are similar among CNS infections. In our study, it is remarkable that a considerable portion of RV-related meningoencephalitis patients (4 of 10) did not have URI symptoms. In 2009, a prospective longitudinal study showed that respiratory pathogens are frequently detected in samples not only from children with respiratory symptoms (56%) but also from those without respiratory symptoms (40%) [19]. Therefore, we believe that a respiratory PCR panel should be routinely conducted in patients with suspected CNS infections.

Most RV-related meningoencephalitis patients showed favorable outcomes. RV-related encephalitis is treatable with properly timed antiviral therapy. In particular, influenza A encephalitis can be treated with antiviral therapy [20,21]. Influenza A encephalitis can be fatal not only in children but also in adults [22-24]. Cortical SAH can develop from influenza A infection [25,26]. In our cases, patient 3 showed a poor clinical outcome despite

antiviral treatment. He already had a cortical SAH long before antiviral treatment began. The delay between onset and administration of the antiviral agent could be the reason why he was the only patient with clinical deterioration. This case showed the importance of fast and accurate diagnosis of RV-related meningoencephalitis [27]. Ribavirin, a broad-spectrum antiviral agent, is used to treat *Paramyxoviridae* pneumonia, such as human RSV, parainfluenza virus, and metapneumovirus [28]. Intravenous ribavirin was effective in Nipha-virus encephalitis [29], which is caused by another *Paramyxoviridae* disease. In our study, patient 2 was also successfully treated with ribavirin. Ribavirin is the treatment of choice when any patient is infected with RVs like those described above.

Our study has some limitations in the certainty of diagnosis. Because of the low detectability of viral nucleic acids in CSF, many cases of encephalitis were diagnosed based on the results of serological tests, antigen detection, viral culture, and nucleic acid detection from sputum, stool, urine, or blood [4]. Positive PCR results from sputum also can be indirect evidence of a diagnosis. Previous studies of RV-related meningoencephalitis and other studies of CNS infection etiology have used these indirect methods for specific etiological diagnosis [3]. Nevertheless, these indirect tools provide a lower level of confidence than PCR results from CSF and have the possibility of detecting asymptomatic coinfections limited to the upper respiratory system. This is an unavoidable limitation of our study. Therefore, we chose to divide the patients into two groups based on the certainty of diagnosis.

In conclusion, this is the first etiological study of adult RV-related meningoencephalitis in a large CNS infection registry. Clinicians should keep in mind that, although rare, RVs can cause acute meningoencephalitis in adult patients, even in those without URI symptoms.

Conflicts of Interest

Jangsup Moon, Soon-Tae Lee, Kyung-Il Park, Keun-Hwa Jung, Sang Kun Lee, Kon Chu have been editorial board of *encephalitis* since October 2020. They were not involved in the review process of this original article. No other potential conflict of interest relevant to this article was reported.

Author Contributions

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Refractory neuro-Sweet disease successfully treated with tocilizumab and mycophenolate mofetil

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Sweet syndrome, or acute febrile neutrophilic dermatosis, is mainly a dermatologic condition presenting with erythematous plaques; however, neutrophils infiltrate multiple systems. Neuro-Sweet disease is a neurological manifestation of Sweet syndrome and a rare cause of recurrent aseptic meningoencephalitis, which needs to be distinguished from neuro-Behçet disease. Although neuro-Sweet disease generally responds well to corticosteroids, relapsing neuro-Sweet disease is not an exceptional case. Herein, we present a case of a 51-year-old male with recurrent encephalitis followed by erythematous plaques. The patient was confirmed as Sweet syndrome based on skin biopsy and showed partial response to corticosteroids. With intravenous immunoglobulin, rituximab, tocilizumab, and mycophenolate mofetil, his neurologic symptoms were fully recovered.

Keywords: Sweet syndrome, Tocilizumab, Mycophenolic acid

Introduction

Sweet syndrome (acute febrile neutrophilic dermatosis) was first described by Dr. Robert Douglas Sweet in 1964 [1]. The syndrome is characterized by fever, neutrophilic leukocytosis, and tender erythematous plaques. Biopsy of erythematous plaques shows a dense dermal infiltration with mature neutrophils. Response to corticosteroid treatment is generally rapid and favorable. Neurological manifestation of Sweet syndrome, termed neuro-Sweet disease, is a rare cause of aseptic meningoencephalitis. Neuro-Sweet disease also responds to corticosteroids, however, refractory cases with multiple relapses have occurred. Herein, we report a case of a patient with refractory neuro-Sweet disease, who was successfully treated with intravenous immunoglobulin (IVIG), rituximab, tocilizumab, and mycophenolate mofetil.

Case Report

A 51-year-old male with a history of recurrent episodes of unconsciousness (10, 7, 2 years, and 4 months before the current visit) presented with cognitive impairment. The patient was admitted to another hospital for altered mental state 10 and 7 years before the current visit. Although no definitive diagnosis was made, his consciousness was restored with supportive treatment. When visiting another hospital 2 years before his current visit (May 2016), the patient had erythematous plaques on the neck and legs accompanied by headache, myalgia, febrile sense, and unconsciousness. On admission to our hospital, a brain magnetic resonance imaging (MRI) scan showed T2 hyperintensities on bilateral basal ganglia, frontal, temporal, and insular subcortices (Figure 1A and B). Biopsy of the posterior neck skin lesion on admission revealed dermal neutrophilic infiltration

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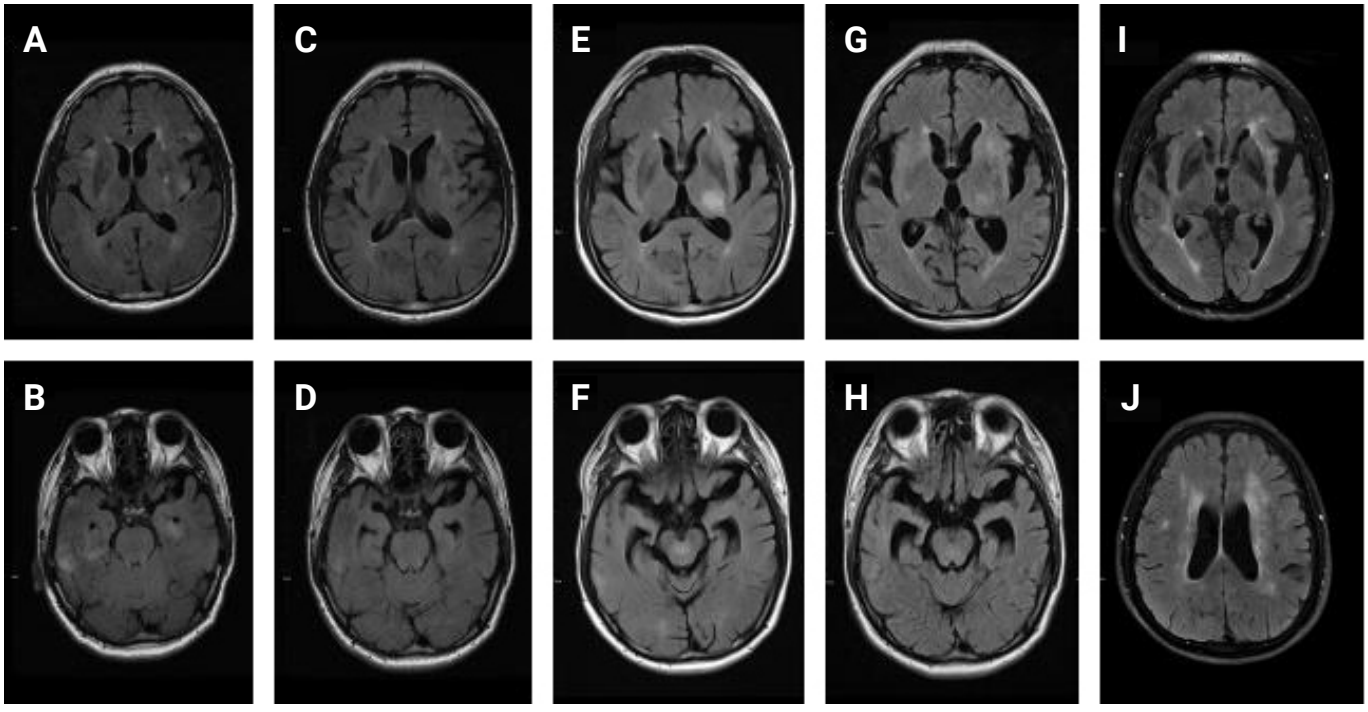
compatible with Sweet syndrome. The patient received symptomatic treatments and erythematous plaques were resolved without corticosteroid therapy. Brain MRI after 2 months showed resolution of bilateral basal ganglia and subcortical T2 hyperintense lesions (Figure 1C and D).

The patient presented 4 months earlier (January 2018) with sore throat, headache, myalgia, febrile sense, unconsciousness, and erythematous nodules on his face spreading to the whole body. T2 hyperintense lesions were observed in the left thalamus, midbrain, and pons on brain MRI scan (Figure 1E and F). After treatment with high-dose corticosteroids for 5 days, his symptoms improved and T2 hyperintensities on brain MRI scan disappeared (Figure 1G and H). However, he complained of persistent dysarthria and cognitive impairment for months.

The subject was admitted to our center for further treatment in May 2018. Neurologic examination revealed mild dysarthria without other cranial nerve dysfunction. Fever and erythematous plaques were absent on admission. Neutrophilia (leukocytes, 14,880/μL; neutrophils, 11,859/μL; 79.7% of neutrophils) and elevated C-reactive protein (CRP) level (1.17 mg/dL) were observed despite oral prednisolone maintenance (10 mg/day) for the preceding 4 months. Cerebrospinal fluid examination was unremarkable. Viral, fungal, tuberculous, or bacterial pathogens were not detected. Human leukocyte antigen (HLA) typing confirmed HLA-B52/B54. Mini-mental state examination score was 25 of 30 with impaired memory registration, recall, and calculation. Frontal assessment battery showed decreased word fluency. Clinical assessment scale for autoimmune encephalitis (CASE) score was 3 and modified Rankin scale (mRS) score was 2 [2].

IVIG treatment (400 mg/kg/day for 5 days) was initiated followed by weekly rituximab (375 mg/m^2 for 4 weeks). After the 2nd administration of rituximab, dysarthria and language fluency were slightly improved (CASE score, 2; mRS score, 2). After the 4th dose of rituximab, brain MRI scan showed new T2 hyperintensities on bilateral frontal, temporal, and insular subcortices (Figure 1I and J). However, neurologic deterioration was not observed and four cycles of monthly rituximab therapy were

Figure 1 Serial MRI scan images (fluid attenuated inversion recovery images)



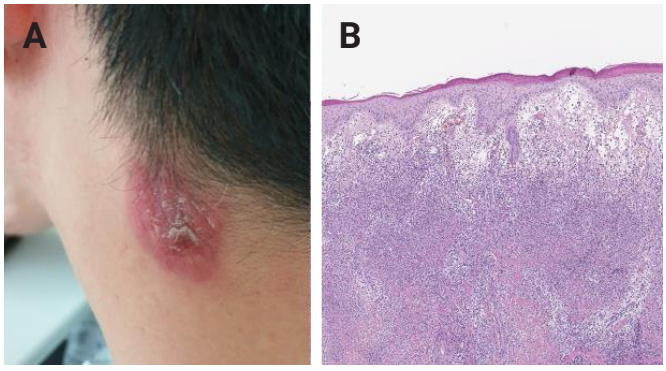
MRI scan in May 2016 **(A, B)** shows T2 hyperintense lesions in bilateral basal ganglia and subcortical frontal, temporal, and insular lobes, which were reduced on follow-up MRI scan in July 2016 **(C, D)**. **(E, F)** New T2 hyperintense lesions in left thalamus, midbrain, and pons were observed in February 2018. **(G, H)** Partial resolution of previous lesions was observed in March 2018. **(I, J)** In June 2018, MRI scan revealed bilateral subcortical T2 hyperintensities in bilateral frontal, temporal, insular, and parietal lobes. These lesions remained on follow-up MRIs in December 2018 and May 2019 (not shown).
MRI, magnetic resonance imaging.

maintained. Dysarthria or language dysfunction was not observed but mild memory dysfunction remained (CASE score, 1; mRS score, 1).

In November 2018, an erythematous rash developed without neurologic deterioration. Oral mycophenolate mofetil (500 mg/day) and high-dose corticosteroid were initiated resulting in resolution of erythematous plaques. Intravenous tocilizumab (6 mg/kg every month) was administered from December 2018 to June 2019. Erythematous plaques recurred in February and May 2019 (Figure 2A), which resolved with tocilizumab (and combined high-dose intravenous corticosteroid in February 2019). Skin biopsy from a plaque on the posterior neck in May 2019 (Figure 2B) revealed dermal neutrophilic infiltration suggestive of Sweet syndrome. After the 6th injection of tocilizumab, only mycophenolate mofetil was maintained without recurrence of rash and neurologic symptoms. Mycophenolate mofetil was discontinued in December 2019. Rash and neurologic symptoms did not relapse until the last visit in March 2020 (CASE score, 0; mRS score, 0). Time course of immunotherapies and clinical events are depicted in Figure 3.

Written informed consent was obtained for publication of this case report and accompanying images.

Figure 2 Posterior neck plaque in May 2019



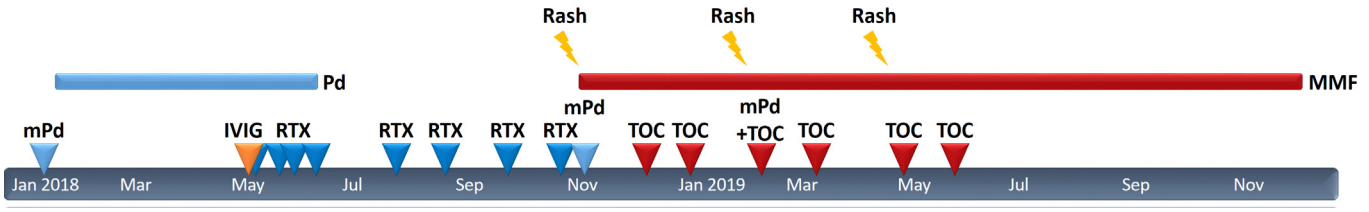
(A) Erythematous plaque on left posterior neck. **(B)** Skin biopsy of erythematous plaque on left posterior neck (H&E stain, ×40). Mixed lymphohistiocytic and numerous neutrophilic infiltrations in dermis.

Discussion

Sweet syndrome (acute febrile neutrophilic dermatosis) is characterized by fever, leukocytosis, and tender erythematous skin lesions [1]. Erythema typically involves head, neck, and limbs. Leukocytosis (neutrophilia) and elevated CRP and erythrocyte sedimentation rate are common laboratory findings. Skin biopsy shows dermal neutrophilic infiltration in the absence of vasculitis. Although skin is most commonly involved, other organs such as eyes, liver, kidneys, and lungs can be infiltrated with neutrophils [3]. Response to corticosteroid is favorable, resulting in complete remission without scarring in most cases [4].

Neurologic manifestation of Sweet syndrome, termed neuro-Sweet disease, has been reported since the 1990s [5]. Common presentation of neuro-Sweet disease is aseptic meningoencephalitis with or without erythematous plaques [3]. Various symptoms such as altered consciousness, headache, cognitive impairment, aphasia, or peripheral neuropathy can be observed. Typically, erythematous plaques precede neurologic symptoms; however, cases of encephalitis followed by skin involvement or cases without erythematous plaques have been reported [6]. Computed tomography or MRI scans reveal multiple central nervous system lesions [3]. Basal ganglia and brainstem are frequently involved similar to neuro-Behçet disease. Because skin is commonly involved in neuro-Sweet disease and neuro-Behçet disease, differentiating these two conditions is important. In neuro-Behçet disease, skin biopsy shows vasculi-

Figure 3 Time course of immunotherapies and clinical events



Arrows and bars on the timelines indicate the timing/duration of each immunotherapy. Yellow lightning indicates timing of relapsed erythematous plaques.
mPd, intravenous high-dose methylprednisolone; Pd, oral prednisolone; IVIG, intravenous immunoglobulin; RTX, rituximab; TOC, tocilizumab; MMF, mycophenolate mofetil.

tis in contrast to dermal neutrophilic infiltration in neuro-Sweet disease. Neuro-Sweet disease usually responds to corticosteroids, and in some cases supportive treatment can lead to spontaneous remission. HLA-B54 (63% in neuro-Sweet disease vs. 14% in Japanese population) and HLA-Cw (89% in neuro-Sweet disease vs. 28% in Japanese population) are frequently detected in patients with neuro-Sweet disease [3]. Although recurrence is common, there is no established preventive therapy to date. Conversely, response to corticosteroids is poor and HLA-B51 is frequently detected in patients with neuro-Behçet disease [7].

Treatment options other than corticosteroids include colchicine and potassium iodide as first-line treatment options for dermal involvement of Sweet syndrome [8]. Nonsteroidal anti-inflammatory drugs, dapsone, clofazimine, cyclosporine, and thalidomide are second-line therapies. There are reports of effective treatment of Sweet syndrome with methotrexate, interferon-α, IVIG, anakinra, or anti-tumor necrosis factor (TNF)-α [8,9]. Rituximab (anti-CD20 monoclonal antibody) and tocilizumab (anti-interleukin-6 monoclonal antibody) have shown efficacy in case reports of refractory Sweet syndrome [10,11]. However, possible anti-TNF-α- or tocilizumab-induced Sweet syndrome has been reported, and the effectiveness of these drugs remains controversial [12].

In the present case, the patient had a history of recurrent neuro-Sweet syndrome. Because skin was involved years after the initial neurologic manifestation, he experienced a diagnostic odyssey. He was undiagnosed until the erythematous plaques appeared 2 years before the current visit, which prompted skin biopsy confirming the diagnosis of neuro-Sweet disease. Despite spontaneous remission after supportive treatment 10, 7, and 2 years earlier, high-dose corticosteroid treatment induced partial remission 4 months before the current visit. Dysarthria and cognitive impairment remained even with long-term maintenance of oral corticosteroid. Additional immunotherapy with IVIG, rituximab, mycophenolate mofetil, and tocilizumab induced complete remission of neuro-Sweet disease without neurologic sequela.

The present case demonstrates efficacy of multiple immunotherapies in neuro-Sweet disease. Although numerous reports of dermal manifestation of Sweet syndrome treated with immunomodulatory drugs exist, reports on immunotherapy treatment in neuro-Sweet disease are limited. Reportedly, cyclosporine, dapsone, and infliximab (TNF-α inhibitor) have been used in cases of corticosteroid-resistant or corticosteroid-dependent neuro-Sweet disease [13,14]. To the best of our knowledge, this is the first case of neuro-Sweet disease treated with rituximab, tocilizumab, and mycophenolate mofetil. Tocilizumab, which is commonly used in rheumatoid arthritis, is reportedly associated with neutropenia in some cases [15]. Although the exact mechanism is not established, this anti-neutrophil effect may serve as a therapeutic target in Sweet syndrome [16]. A case of Sweet syndrome or neuro-Sweet disease treated with mycophenolate mofetil has not been reported to date. Although mycophenolate mofetil was initiated after cutaneous relapse in November 2018, the contribution of mycophenolate mofetil cannot be established due to concomitant administration of corticosteroids followed by tocilizumab. However, tentative therapeutic effects of mycophenolate mofetil should be further studied in refractory cases of neuro-Sweet disease. Reversibility of neurologic symptoms even after months from relapse highlights the importance of adequate immunotherapy in steroid-unresponsive neuro-Sweet disease. The mechanism by which each immune-modulating agent acts on neuro-Sweet disease, and priority of each immunotherapy, remain to be elucidated.

Conflicts of Interest

Jangsup Moon, Soon-Tae Lee, Kyung-Il Park, Sang Kun Lee, Kon Chu have been editorial board of *encephalitis* since October 2020. They were not involved in the review process of this case report. No other potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: S Hwang, K Chu; Data curation, Investigation: S Hwang, H Son; Formal analysis, Visualization: S Hwang; Methodology: S Hwang, J Moon, K Chu; Project administration, Resources, Supervision: K Chu; Writing–original draft: S Hwang; Writing–review and editing: all authors.

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Anti-*N*-methyl-D-aspartate receptor encephalitis 8 years after serial herpes simplex virus type 1 and human herpesvirus type 7 encephalitis

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Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is triggered by herpesvirus encephalitis. Human herpesvirus type 7 (HHV-7) is a recently described herpesvirus for which neuroinvasion has been reported rarely. We report a case of anti-NMDAR encephalitis detected 8 years after recurrent herpes encephalitis associated with herpes simplex virus type 1 and HHV-7 in an immunocompetent host. Our case suggests that anti-NMDAR encephalitis may be triggered by HHV-7 meningoencephalitis in immunocompetent adults, and patients with a history of herpesvirus encephalitis should be vigilantly monitored.

Keywords: Herpes simplex virus 1, Human herpesvirus 7, Encephalitis, Foscarnet, Anti-*N*-methyl-D-aspartate receptor encephalitis

Introduction

Anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis is the most common disease among autoimmune encephalitis. Most patients are female, and ovarian teratoma is a source of autoantibody among 40% of patients [1]. However, for male and female patients without teratoma, the mechanism of breakdown of immune tolerance to NMDAR is unclear. It has been suggested that direct damage to the central nervous system (CNS) through viral infection could be the origin of the autoantigen, and previous studies have shown that herpesvirus infection can precede anti-NMDAR encephalitis [2-4].

Herpesviruses are large, double-stranded DNA viruses, of which eight human herpesviruses have been identified [5]. They are mostly neurotrophic, sometimes causing serious neurological manifestations either by primary infection or secondary activation [5]. Human herpesvirus type 7 (HHV-7) is a recently described herpesvirus that is ubiquitous and mostly acquired in childhood [6]. Primary infection usually occurs in infants, and symptoms vary from a nonspecific high fever to exanthem subitum [6]. Very little is known of HHV-7 infection in the CNS of immunocompetent hosts, but there have been a few case reports describing HHV-7 neuroinvasion [7-9].

Here, we describe a 32-year-old man who developed anti-NMDAR encephalitis after recurrent herpesvirus meningoencephalitis. Written informed consent was obtained for publication of this case report and accompanying images.

Case Report

Event 1. Herpes simplex virus type 1 encephalitis

A 32-year-old man was admitted due to fever, headache, and al-

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tered mental status. He was previously healthy and had no recent history of travel. A cerebrospinal fluid (CSF) study revealed pleocytosis showing 68/mm^3 of white blood cells with lymphocyte dominance (75%) and mildly elevated protein (58 mg/dL) (Table 1). Brain magnetic resonance imaging (MRI) showed bilateral asymmetric hyperintense lesions on T2-weighted images, with a mass effect involving both insulas, the hippocampus, lingual gyrus, and left anterior temporal area. A polymerase chain reaction (PCR) study was performed for herpes simplex virus type 1 (HSV-1) and HSV-2 in the CSF specimen and revealed a positive result for HSV-1 DNA. No other viral gene studies were performed. The patient was diagnosed with HSV-1 encephalitis and received acyclovir at a dose of 500 mg intravenous (IV) every 8 hours. After 20 days of treatment, he was discharged without symptoms.

Event 2. HHV-7 encephalitis

One month after discharge, the patient complained of visual hallucination and agitation and showed aggressive behavior. He was readmitted to the hospital, and a CSF study disclosed 18/mm^3 of white blood cells (Table 1), with HSV-1 DNA detected by PCR. He received acyclovir 500 mg IV every 8 hours for 1 month, but his symptoms worsened to drowsy mental status with no response to verbal stimuli and intermittent oral automatism. Body temperature was high at 37.6°C. The follow-up CSF study showed 14/mm^3 of white blood cells, no red blood cells, 25 mg/dL of protein, and 77 mg/dL of glucose (serum glucose, 97 mg/dL) (Table 1). Video-electroencephalogram (EEG) monitoring detected intermittent semirhythmic delta waves in the right temporal area. Brain MRI showed increased extent of the T2 hyperintense lesion, which was more prominent at the left side, at the bilateral temporal lobes, and positron emission tomography revealed profound hypometabolism in the left temporal lobe (Figure 1A and C). Viral gene PCR was used to evaluate HSV-1, HSV-2, varicella-zoster virus, Epstein–Barr virus, cytomegalovirus, HHV-6, and HHV-7. All tests were negative except that for HHV-7 DNA, which was strongly positive in the CSF specimen. Thus, the patient received foscarnet of 2,000 mg IV every 8 hours for HHV-7 encephalitis. After 2 weeks of treatment, he recovered from the drowsy mental state and no longer showed oral automatism or aggressive behavior. Brain MRI showed clear improvement (Figure 1B), and follow-up EEG indicated resolution of the intermittent rhythmic delta slowing in the right temporal area. He was discharged with mild short-term memory decline with instruction to maintain oxcarbazepine of 1,200 mg/day and levetiracetam of 1,000 mg/day.

Event 3. Anti-NMDAR encephalitis

The patient had no symptom recurrence, even after tapering of the antiepileptic drug oxcarbazepine to 900 mg/day. Eight years later, however, seizure recurred with severe headache and auditory hallucinations. Thorough evaluation was repeated, including viral gene PCR and autoantibody tests. All viral gene PCR evaluations were negative, but anti-NMDAR antibody was detected in serum (Table 1). Immunotherapy with IV immunoglobulin and rituximab was planned for the patient. After four cycles of rituximab treatment, his symptoms improved, and he has had no seizure during four years of follow-up.

Polymerase chain reaction

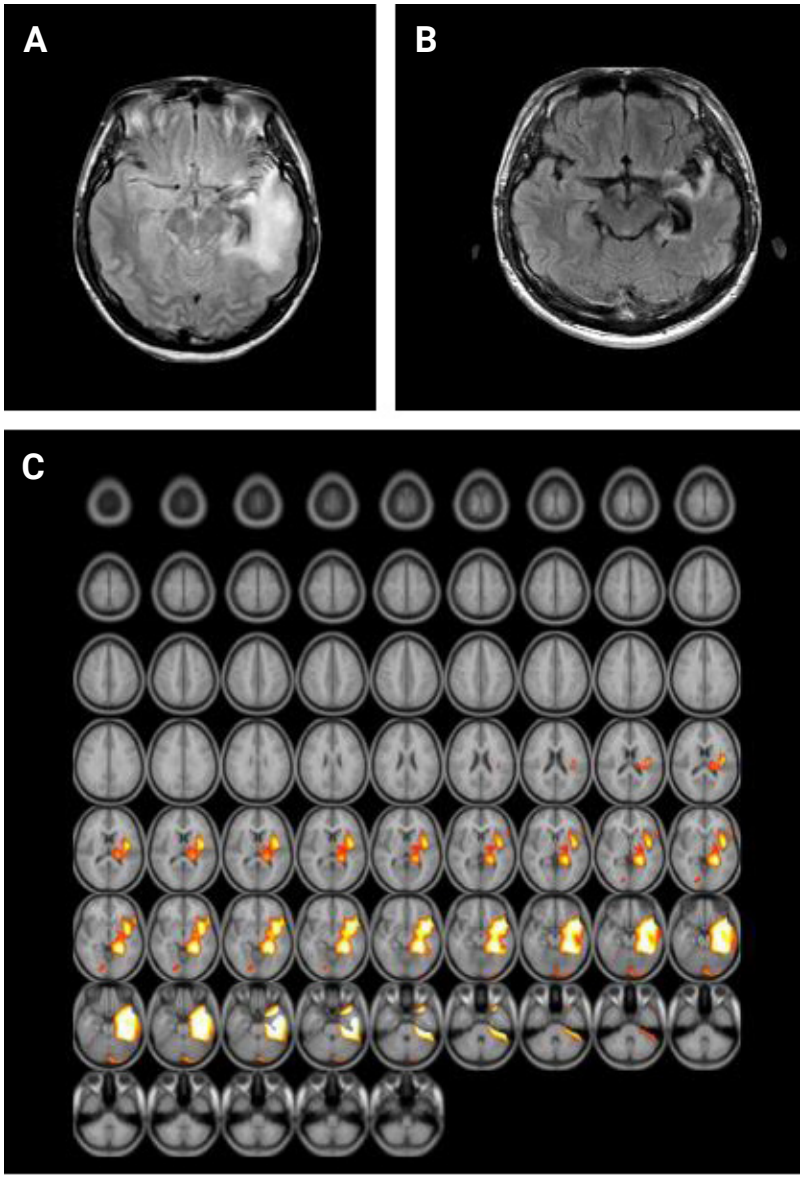
Nucleic acid was prepared from cell pellets of CSF or peripheral blood mononuclear cells using the QIAamp DNA Blood Mini Kit (Qiagen, Crawley, UK) following the manufacturer's instruc-

Table 1 Cerebrospinal fluid profiles

	Day 1	Day 44	Day 84	Eight years later
Status	Initial manifestation	Relapse	Aggravation	Relapse
Symptom	Headache, fever, drowsy mentality	Abnormal behavior, visual hallucination	Drowsy mentality	Seizure, headache, auditory hallucinations
CSF study				
RBC (/μL)	4	1,020[b]	0	NA
WBC (/μL)	68	18	14	NA
Protein (mg/dL)	58	52	25	NA
Glucose (mg/dL)	60	62	77	NA
PCR[a]	HSV-1(+)	HSV-1(+)	HSV-1(−), HHV-7(+)	HSV-1(−), HHV-7(−)
Autoantibody	NA	NA	NA	Anti-NMDAR antibody (+)
Treatment	Acyclovir 500 mg	Acyclovir 500 mg	Foscarnet	Rituximab
Response	Recovered	No response	Recovered	Recovered

CSF, cerebrospinal fluid; RBC, red blood cell; WBC, white blood cell; PCR, polymerase chain reaction; HSV-1, herpes simplex virus type 1; HHV-7, human herpesvirus type 7; NA, not available.
[a]Only HSV-1 and 2 DNA were examined in the first two lumbar puncture studies.
[b]Note that traumatic tap was performed in a lumbar puncture study performed on day 44.

Figure 1 Brain images of human herpesvirus type 7 encephalitis



(A) Fluid-attenuated inversion recovery shows high signal intensity, more prominent on the left side, at the bilateral temporal lobes. **(B)** The lesions regressed after foscarnet treatment. **(C)** Positron emission tomography with statistical parametric mapping analysis reveals profound hypometabolism in the left temporal lobe.

tions. We performed nested PCR using 15 L of nucleic acid from serum or CSF. The sequences of the outer pair of primers were TAT CCC AGC TGT TTT CAT ATA GTA AC and GCC TTG CGG TAG CAC TAG ATT TTT TG, and the sequences of the inner pair of primers were CAG AAA TGA TAG ACA GAT GTT GG and TAG ATT TTT TGA AAA AGA TTT AAT AAC. The PCR products were compared by electrophoresis on 2.5% agarose gels containing ethidium bromide. Positive results were confirmed by repeated tests.

Antibody determination

Anti-NMDAR antibody was confirmed with two methods, as described previously [10]. These methods were serum and CSF assays with immunostaining of rat brain sections and a cell-based immunochemistry kit (Euroimmun AG, Lübeck, Germany). Antibodies against the contactin-associated protein-like 2 (CASPR2), the leucine-rich glioma-inactivated 1 (CASPR2) receptor, anti-α-amino-3-hydroxy-5-methyl-4isoxazolepropionic acid 1 (AMPA1), AMPA2, and γ-aminobutyr-

ic-acid type B (GABA-B) receptors were negative, as were antibodies against Hu, Yo, Ri, Ma2, CV2, amphiphysin, recoverin, Sox1, and titin antibodies.

Discussion

Our case illustrates recurrent meningoencephalitis associated with HSV-1, HHV-7, and subsequent anti-NMDAR encephalitis in an immunocompetent adult host. After HHV-7 had been treated with foscarnet, the patient's drowsy mental state significantly improved, along with cessation of nonconvulsive seizures. Follow-up brain MRI and EEG showed findings consistent with resolution of encephalitis, including absence of active lesions and epileptic activity, respectively. The seizure relapse 8 years later led to detection of anti-NMDAR encephalitis, and the patient was treated with immunotherapy.

In the present case, HHV-7 could be associated with recurrent encephalitis after the first HSV-1 infection had been sufficiently treated by acyclovir. The causative agent for the initial event could have been HSV-1, considering the bilateral temporal lobar involvement demonstrated on brain MRI and detection of HSV-1 DNA by PCR. Recurrent encephalitis in HSV-1 infection is occasionally reported and is related with severity of the first infection [5]. Because the initial viral DNA studies examined only HSV-1 and HSV-2, it is unclear whether HHV-7 initially coinfected the patient or if he was infected later. Nonetheless, a later CSF study revealed a negative result for HSV-1 DNA and a positive result for HHV-7 DNA, suggesting involvement of HHV-7 infection in the second episode of encephalitis.

Furthermore, dramatic symptom relief after foscarnet treatment supports the idea that HHV-7 was related to the recurrent encephalitis in our case. Although there are no treatment guidelines or randomized clinical trials for HHV-7 infection, foscarnet or ganciclovir is recommended as a therapeutic option because HHV-7 is resistant to acyclovir [7]. On the other hand, acyclovir, which must be phosphorylated by virus-encoded kinases to retain antiviral activity, is an effective antiviral agent against HSV-1 and HSV-2 [11]. Foscarnet and its analogues achieve their antiviral effects via inhibition of viral polymerases, without activation or phosphorylation of the compounds by viral or cellular proteins [12]. Therefore, they have shown effective antiviral activity against acyclovir-resistant herpes simplex infection and herpesviruses such as HHV-7 [11,13].

In the present case, the autoimmune encephalitis was identified 8 years after serial herpesvirus encephalitis, and the symptoms might have been too mild to be detected before the infection was identified. Whether the NMDAR antibody was present at the time of HHV-7 infection is unclear; NMDAR-autoantibody detection was not available in 2007 when there was no concept of anti-NMDAR encephalitis [14]. Moreover, we do not know whether HSV-1 infection or HHV-7 infection resulted in breakdown of immune tolerance to NMDAR. According to the hypothesis that CNS damage triggers autoimmunity by exposure of NMDARs [4], either herpesviruses could be the cause of the patient's anti-NMDAR encephalitis. Our result implies that HHV-7 infection, which is ubiquitous and generally asymptomatic, can be the origin of autoimmunity for patients with anti-NMDAR encephalitis who have no teratoma. Thus, development of anti-NMDAR encephalitis should be vigilantly monitored in patients with a history of herpes virus encephalitis. Conversely, in patients with anti-NMDAR encephalitis who have no teratoma, herpes viral infection history should be carefully investigated.

In summary, we report a case of recurrent herpesvirus encephalitis followed by anti-NMDAR encephalitis in an immunocompetent young man. This report furthers our knowledge about the clinical manifestations of rare HHV-7 infection and suggests that anti-NMDAR encephalitis can be identified years after herpes virus infection.

Conflicts of Interest

Jangsup Moon, Kyung-Il Park, Soon-Tae Lee, Keun-Hwa Jung, Sang Kun Lee, Kon Chu have been editorial board of *encephalitis* since October 2020. They were not involved in the review process of this case report. No other potential conflict of interest relevant to this article was reported.

Author Contributions

Conceptualization: Chu K; Investigation: Kim JM, Moon J, Chu K; Data curation: Jang Y, Kim JM; Formal analysis: Lee ST; Resources, Funding acquisition: Park KI, Jung KH, Chu K, Lee SK; Supervision: Chu K; Writing–original draft: Jang Y, KimJM; Writing–review and editing: all authors.

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Review article	250	5,000	200	Not limited
Perspective	Not required	3,000	30	0
Case report	250	2,000	30	5
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