Internal Medicine
The Japanese Society of Internal Medicine
doi: 10.2169/internalmedicine.3510-19
Intern Med 59: 267-270, 2020
http://internmed.jp

【 CASE REPORT 】

New-onset Refractory Status Epilepticus Involving the Limbic System, Spinal Cord, and Peripheral Nerves

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Abstract:
A healthy 28-year-old woman presented suddenly with intractable status epilepticus: a focal seizure evolved into a generalized seizure preceded by a high fever. Brain magnetic resonance imaging indicated bilateral hyperintensities in the hippocampus on T2-weighted imaging. Electroencephalograms continuously demonstrated diffuse sharp waves and poly-spikes. Comprehensive immunomodulation therapies and antiepileptic drugs did not lead to any improvements. We therefore diagnosed her with cryptogenic limbic encephalitis and new-onset refractory status epilepticus (NORSE). We detected positive anti-ganglioside antibodies, IgG-GQ1b, GD1a, and GT1b, which were negative at six months after the onset. We emphasize the heterogeneous pathogenesis and intractable conditions of NORSE.

Key words: new-onset refractory status epilepticus, limbic encephalitis, anti-ganglioside antibodies, myelitis, polyneuropathy, pathology

(Intern Med 59: 267-270, 2020)
(DOI: 10.2169/internalmedicine.3510-19)

Introduction

New-onset refractory status epilepticus (NORSE) is defined as a clinical presentation where a febrile illness of unknown etiology leads to long-lasting status epilepticus with neurological deterioration, without a clear acute or active structural, toxic, or metabolic cause (1). NORSE is a challenging clinical diagnosis, not specific. The pathogenesis and mechanisms require identification due to the high incidence of death. Twenty-two percent of affected patients die in the hospital, and 62% have a poor outcome on discharge (2). Approximately half of patients have had an undetermined etiology. Thus, it is important to expand our knowledge to elucidate the pathomechanisms underlying NORSE.

We herein report an autopsy of a patient diagnosed with NORSE who presented with long-lasting status epilepticus over a six-month period despite several types of treatments and eventually died due to septic shock. The pathology revealed significant, widespread lesions throughout the limbic system, lateral funiculus of the spinal cord, and peripheral neurons. The biochemical data indicated an alteration in anti-ganglioside antibodies at six months. Our findings further elucidate the concepts behind NORSE.

Case Report

A healthy 28-year-old woman presented to our department. Eight days before admission, she had developed a persistent high-grade fever, disturbance of consciousness, automatisms, oral dyskinesia, upward-directed gaze palsy, and tonic-clonic seizure. On admission, her body temperature was 39.4℃.

A neurological examination found oral dyskinesia and clonic seizure without meningeal signs. Tests for autoimmune antibodies, including anti-nuclear antibodies, anti-TPO antibodies, and anti-thyroid globulin, were all negative. A cyto-biochemical examination of the cerebrospinal fluid (CSF) revealed a high protein level (53 mg/dL; normal, ≤45 mg/dL), and a high cell count (10/μL; normal, ≤5/μL). The IgG index was 0.82. The oligoclonal band was negative.

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Received: June 14, 2019; Accepted: July 25, 2019; Advance Publication by J-STAGE: September 11, 2019
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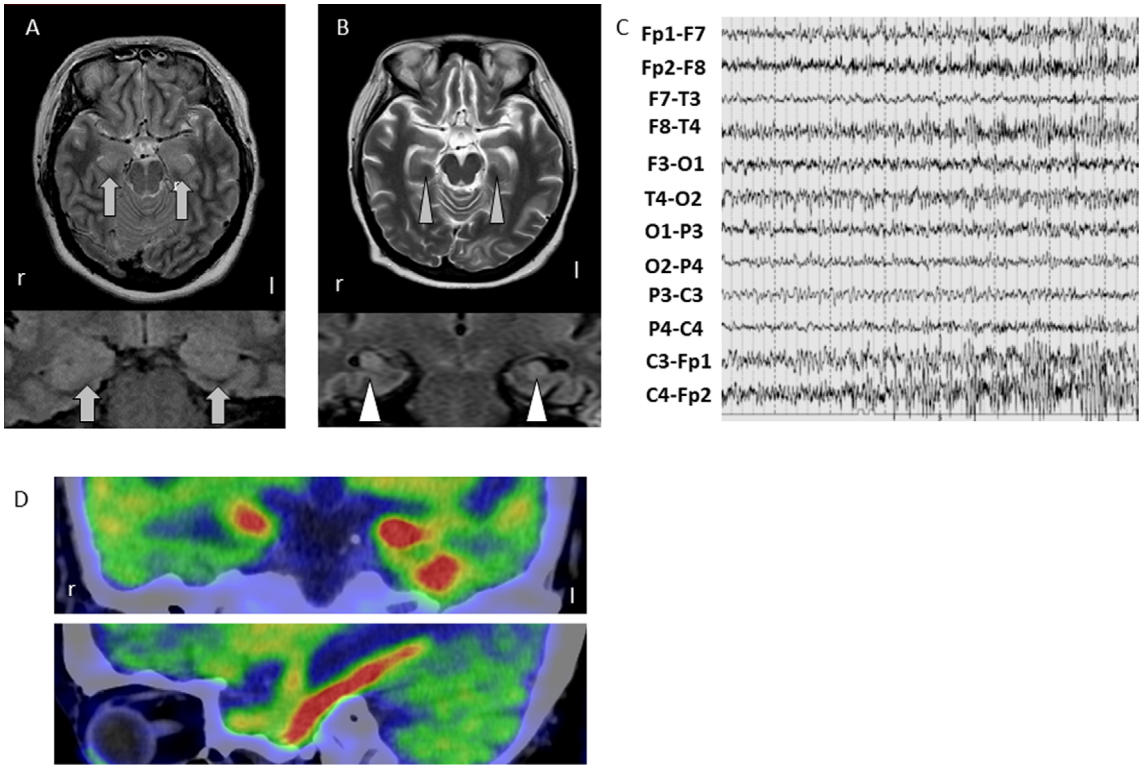

Figure 1. Findings of brain MRI, electroencephalogram and positron emission tomography. Axial T2-weighted brain MRI (A and B). (A) Brain MRI on admission revealed hyperintensities and swelling bilaterally in the hippocampi (white arrows) and cortices. (B) Brain MRI three months after admission showed bilateral progressive severe atrophic changes in the hippocampi (white triangles) and cortices, especially in the temporal lobes. (C) An electroencephalogram indicated diffuse high sharp waves and poly-spikes under thiopental sedation five months after admission. (D) Brain positron emission tomography with [^{18}F] fluorodeoxyglucose depicted hyper-metabolism in the bilateral hippocampi (above) and a widespread lesion in the temporal lobe, predominantly on the left side (below).

Tests for antibodies to herpes simplex virus type 1 and 2 were negative in the CSF. Brain magnetic resonance imaging (MRI) revealed bilateral hyperintensities in the hippocampi and cortices, along with swelling on T2-weighted imaging (Fig. 1A). Electroencephalography showed diffuse sharp waves and poly-spikes (Fig. 1C). Positron emission tomography with [^{18}F]-fluorodeoxyglucose indicated hypermetabolism in the bilateral hippocampi (Fig. 1D). Thus, our first diagnosis was non-herpetic acute limbic encephalitis.

Her seizure activity prolonged and evolved into status epilepticus. On antibody tests, positive results were obtained for anti-ganglioside Ab, IgG-GQ1b +, GD1a +++, and GT1b +++ at the onset of the disease (optical density: <0.1, negative; 0.1-0.3, +; 0.3-0.5, ++; 0.5-1.0, +++; >1.0; ++++). We examined anti-ganglioside antibodies due to prior symptoms related to infection and the complication of peripheral neuropathy. Negative results were obtained for antibodies related to paraneoplastic syndromes, such as anti-Titin, SOX1, Rec, Hu, Yo, Ri, Ma2/Ta, crossveinless-2, and Amp antibodies (EUROLineScan, EUROIMMUN, Luebeck, Germany); and antibodies related to paraneoplastic limbic encephalitis, such as anti-N-methyl-D-aspartate receptor (NMDA), anti-glutamate receptor 1 (mGluR1), anti-gamma-aminobutyric acid (GABA) (A) and (B), anti-metabotropic glutamate receptor 1 (mGluR1), GluR5, leucine-rich glioma-inactivated 1 (LGI1), contactin-associated protein 2 (Caspr2), dipeptidyl-peptidase-like protein 6 (DPPX), Neurexin3-α, and Iglon5 antibodies (courtesy of Dr. J. Dalmau) (3). Other antibodies, such as glutamic acid decarboxylase antibody, myelin oligodendrocyte glycoprotein antibody, and anti-Aquaporin 4, were negative.

Pelvic MRI and positron emission tomography of the whole body revealed no tumors. Nerve conduction studies indicated severe axonal polyneuropathy in the motor and sensory nerves. Only thiopental-barbiturate maintenance coma was effective in controlling her seizures. We initiated two courses of intravenous methylprednisolone, 1,000 mg per day for 3 days, plasmapheresis for 8 days, and intravenous immunoglobulin, 20 g per day for 5 days. Subsequently, she repeatedly presented with a high fever and infectious diseases, such as aspiratory pneumonia and urinary tract infection, which prevented us from administering second-line immunotherapies. All other anti-epileptic drugs, including perampanel (12 mg per day), topiramate (300 mg), levetirasetam (3,000 mg), carbamazepine (1,200 mg), gabapentin (2,400 mg), fosphenytoin (490 mg), lacosamide (300

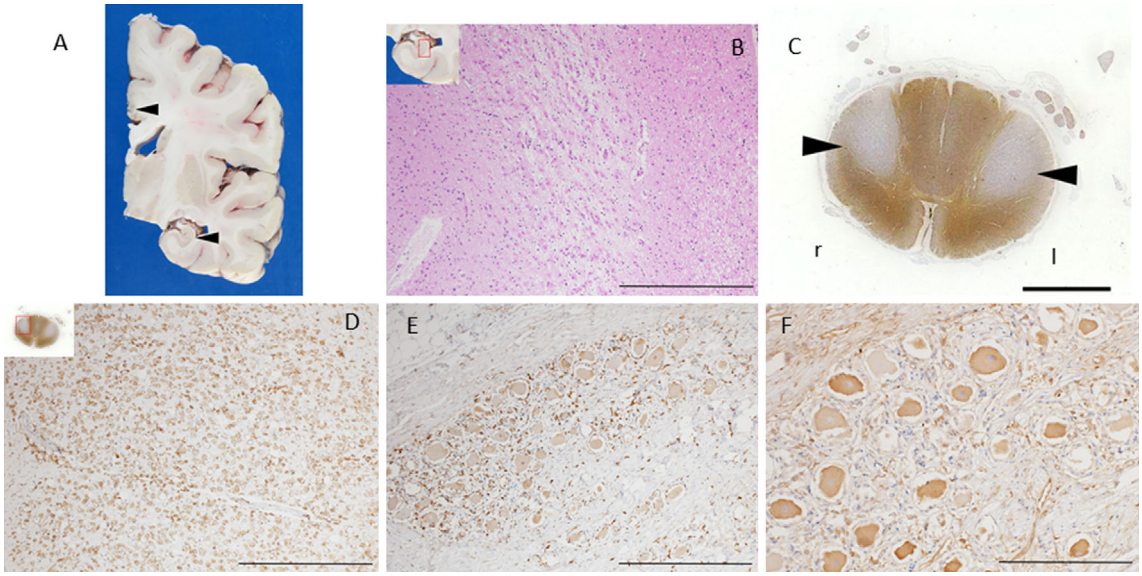

Figure 2. **Neuropathological findings of the autopsied brain, spinal cord, and nerve root. (A) Macroscopic coronal section of the left cerebral hemisphere, along with atrophic and necrotic changes in the cingulate cortex and hippocampus (black triangles). (B) Severe spongiform necrosis and gliosis in the hippocampus on Hematoxylin and Eosin staining (scale bar, 500 μm). (C) Coronal section of the lumbar spinal cord immunostained with anti-neurofilament phosphorylated antibody (SMI31). Discolored parts (black arrowheads) represent selective axonal loss in the bilateral lateral funiculi. (D) Numerous macrophages have infiltrated the lateral funiculus, showing staining for anti-Iba1, which is a marker of microglia and macrophages (scale bar, 500 μm). Dorsal root ganglion immunostained with anti-Iba1 antibody (scale bar 500 μm) (E) and anti-IgG antibody (scale bar 200 μm) (F). Macrophages have infiltrated the interstitial space of the ganglion. The neurons of the ganglion are positively stained with anti-IgG antibody. r: right, l: left**

mg), and potassium bromide (3,000 mg), showed limited effectiveness. Vagus nerve stimulation did not lead to any improvement. Brain MRI revealed severe atrophy and hyperintensities in the bilateral hippocampi and cortical atrophy three months after the admission (Fig. 1B). The second assessment of ganglioside antibodies turned out to be negative six months after the onset. She ultimately died of sepsis 232 days after admission.

Neuropathology

The brain weighed 1,280 g, which was within the normal range for an adult Japanese woman. Macroscopically, atrophic changes in the mesial temporal lobe and encephalomalacia in the limbic system were seen (Fig. 2A). Histologically, there was significant spongiform necrosis with severe neuronal loss and gliosis in the hippocampus, amygdala, cingulate cortex, and cerebellar cortex (Fig. 2B). In addition, there was marked gliosis, especially in the superior temporal cortex, with mild gliosis in other neocortical regions. A few microglia were found in the cortex by Iba1. In the spinal cord, there was severe axonal loss and infiltration of macrophages in the lateral funiculus from the cervical to sacral region, although macrophages were not seen in other pyramidal tracts (Fig. 2C and D). Peripherally, there was also axonal loss and increased numbers of macrophages in the dorsal root ganglion and nerve roots of the cauda equina (Fig. 2E). We performed IgG immunostaining to examine the reaction for ganglioside antibody. Positive immunoreactions were not observed in the central nervous regions but were seen in the dorsal root ganglion and nerve root (Fig. 2F).

Discussion

To our knowledge, the pathological findings of NORSE have only been described in two previous reports from three patients (4, 5). Two of those patients were described as lacing inflammatory processes, with diffuse patchy neuronal cell loss with reactive gliosis (4). Another report mentioned a patient having significant atrophy of the temporal lobes and severe neuronal loss and gliosis in the bilateral hippocampi, amygdala, thalamus, and cerebellum (5). Compared to those patients, the pathology of our case clearly showed more severe findings, with widespread lesions affecting the limbic system, spinal cord, and peripheral nerves. Lesions in the brain and spinal cord were not continuous. Both lesions appeared separately but shared a similar appearance with severe neuronal loss and gliosis. Inflammation was primarily observed in the spinal lesions and peripheral nerves, but quite a few changes were observed in the central nervous system. We were therefore concerned that the lesions in the brain and spinal cord might have been caused

by different processes during the course of the disease. Central chromatolysis and positive immunoreactions for IgG staining in the peripheral nerves were found. As for the differential diagnosis of polyneuropathy, we excluded critical illness polyneuropathy because it does not involve spinal cord lesions, mainly affects distal axonopathy, and has fewer findings of inflammatory changes.

Physiologically, the high expression of gangliosides in the normal human brain (95%), including GM1, GT1b, GD1a, and GD1b, has been reported (6). The positive ganglioside antibodies in our case turned out to be negative six months after the onset. Thus, GQ1b, GD1a, and GT1b might play a role in the onset of limbic encephalitis. The symptoms of our patient were quite different from those of typical ganglioside-related disorders of anti-GQ1b syndrome or Bickerstaff brain stem encephalitis, which are typically responsive to immune therapies and are associated with a recovery period of a few months (7). Our case report suggests that anti-ganglioside antibodies may be associated with the onset of NORSE and peripheral neuropathies. However, we cannot definitively state whether or not anti-ganglioside antibodies were directly related to the inflammatory processes in our patient. Further studies will therefore be needed to confirm our findings.

In conclusion, we demonstrated the heterogeneous characteristics and complex pathogenesis of NORSE.

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

Acknowledgement

We would like to thank Dr. Josep Dalmau (University of Barcelona, Spain) for measuring the titers of antibodies related to paraneoplastic limbic encephalitis and Dr. Toshiyuki Takahashi and Dr. Kazuo Fujihara (Department of Multiple Sclerosis Therapeutics, Tohoku University Graduate School of Medicine) for measuring anti-myelin oligodendrocyte glycoprotein antibody.

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