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Case Report

Perampanel Treatment for Patient with Refractory Status Epilepticus in Primary Angiitis of the Central Nervous System

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Abstract

Primary angiitis of the central nervous system (PACNS) is an uncommon and poorly understood inflammatory disease involving cerebrovascular and parenchyma. Refractory status epilepticus (RSE) as a manifestation of PACNS has rarely reported before. A 46-year-old woman was presented with recurrent facial twitching, which continued resulting in RSE. RSE was treated with a combination therapy of several antiepileptic drugs (AEDs). Among AEDs, administration of Perampanel has terminated RSE. PACNS was diagnosed by MRI, MR angiography and CSF analysis. Subsequent steroid and cyclophosphamide achieved favorable course. We present a case of RSE in PACNS.

Keywords: *Primary Angiitis of the Central Nervous System; Refractory Status Epilepticus; Perampanel*

Introduction

Primary angiitis of the central nervous system (PACNS) is a vasculitis confined to the CNS that affects all age groups, with all the vessels of CNS invaded exclusively, and it seems most common in medium- to small-sized vessels. It is an extremely rare with an annual incidence of 2.4 cases per 1,000,000. Clinical manifestations at diagnosis are non-specific, and many symptoms are usually present. Headache, cognitive impairment and focal neurologic manifestations are common. Seizure in PACNS is less frequent and status epilepticus (SE) related to PACNS is rare. Here, we present a refractory status epilepticus (RSE) case which was treated by perampanel in combination with immunotherapy successfully.

Method

RSE was diagnosed clinically and treated by staged treatment protocol.

PACNS was diagnosed according to the diagnostic criteria in 1988 and treated with immunotherapy.

We reviewed of literatures published between 1980 and 2015. Literatures were searched on PubMed, MEDLINE by terms such as "Primary angiitis of the central nervous system", "central nervous system vasculitis", "seizure", "status epilepticus", and "perampanel" through September 2017.

Case Report

A 46-year-old, right-handed woman was admitted for sudden developed right facial twitching and dysarthria 3 days ago. Past medical history including obstetrical and social history did not revealed any specific disease. On examination, she showed recurrent right facial twitching. Bain MRI showed acute atherosclerotic infarction of the left post-central and anterior parietal cortex. MRI angiography demonstrated focal stenosis of left middle cerebral artery (Figure 1).

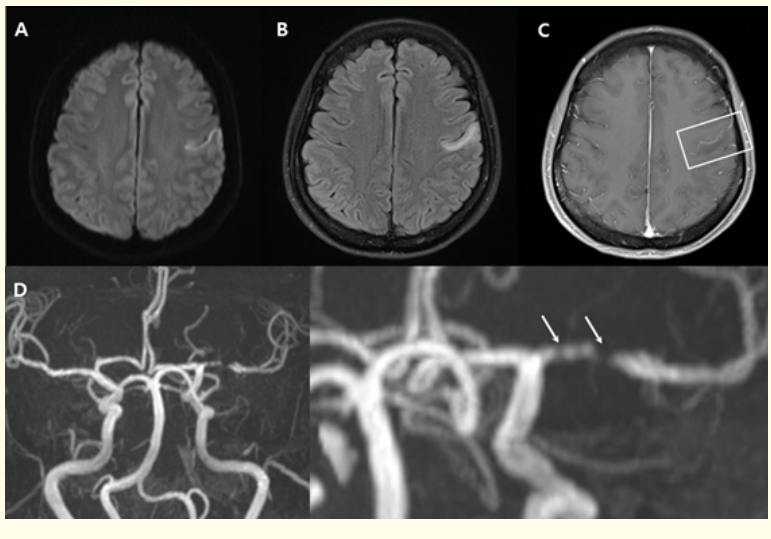

Figure 1: Initial MRI and MRA of primary angiitis of the central nervous system (PACNS). A. Diffusion-weighted imaging (DWI) shows diffusion restriction in the left post-central gyrus. B. Fluid-attenuated inversion recovery (FLAIR) image reveals corresponding hyperintensity signal at the same areas. C. Post-contrast gadolinium demonstrates leptomeningeal enhancement (box). D. Three-dimensional Time of Flight MR angiography demonstrates multiple focal stenoses (white arrows) of left middle cerebral artery.

She was diagnosed as partial seizure related to acute infarction. She took oral clonazepam 1 mg per day and then severity of facial twitching and dysarthria decreased. To prevent ischemic stroke, aspirin 300 mg/day was added to the regimen. 4 days later, she suddenly began to suffer from recurrent clonic jerks in right face and right upper arm with maintenance of consciousness. After 4 mg of intravenous lorazepam injection, the frequency and amplitude of clonic jerks diminished and discontinued. After 2 hours, 2nd clonic jerks of the right face and arm reoccurred and regressed within 3minutes by intravenous lorazepam.

After cessation of 2nd seizure, she was prescribed levetiracetam 750 mg twice a day adding to clonazepam. But 3rd seizure reoccurred and persisted over 10 minutes with somewhat impaired mental state. Despite intravenous lorazepam seizure continued resulting eventually in established partial status epilepticus (PSE). We gave 1500 mg of intravenous fosphenytoin. After loading of fosphenytoin, seizures stopped. On ICU admission, EEG monitoring began, EEG performed 1 hour after the 3rd seizure onset showed periodic lateralized epileptiform discharges (PLEDs) in the left fronto-temporal region and electrical seizures in same area recurring at an irregular repetition rate, which findings were compatible with RSE (Figure 2). Lamotrigine 100 mg/day and topiramate 200 mg/day added to levetiracetam 1500 mg/day. On ICU admission day 2, intermittent jerky seizure lasted and recovery of consciousness was not fully achieved. The treatment regime scheduled was levetiracetam 2000 mg, lamotrigine 200 mg, topiramate 300 mg. another 4 mg perampanel was given and clonazepam was stopped to avoid sedation. On ICU admission day 3, myoclonic jerks of the right face and the right arm decreased but did not disappeared completely in the morning. Another 4 mg perampanel was given and the daily dose of perampanel was increased to 8 mg/day. After this, the patient's seizures disappeared and were not seen in the afternoon. Her mental status became gradually improved, but she complained of severe throbbing headache around left temporal area. Fluid attenuated inversion recovery (FLAIR) MR image, performed 2 days after the seizure onset, demonstrated newly developed extensive high signal in left temporal cortex and right postcentral gyrus. DWI showed fluid restriction in left postcentral gyrus and left temporal subcortex. On ADC map, relatively increased intensity in both postcentral gyrus and left temporal subcortex was shown (Figure 3). These MRI features suggested acute vasculitis rather than atherosclerotic infarction. Blood tests including ESR, CRP, antinuclear antibody (Ab), antineutrophil Ab, anticardiolipin Ab, lupus anticoagulant Ab, paraneoplastic Ab, rheumatoid factor were unremarkable. Cerebrospinal fluid revealed elevated protein at 62 mg/dL (normal range, 15 - 45 mg/dL), glucose of 59 mg/dL, red blood cell count of 4/μL, and white blood cell count of 43/μL (normal range, 0 - 5 leukocytes/μL); opening pressure was 16 cmH_2O, with normal cytology.

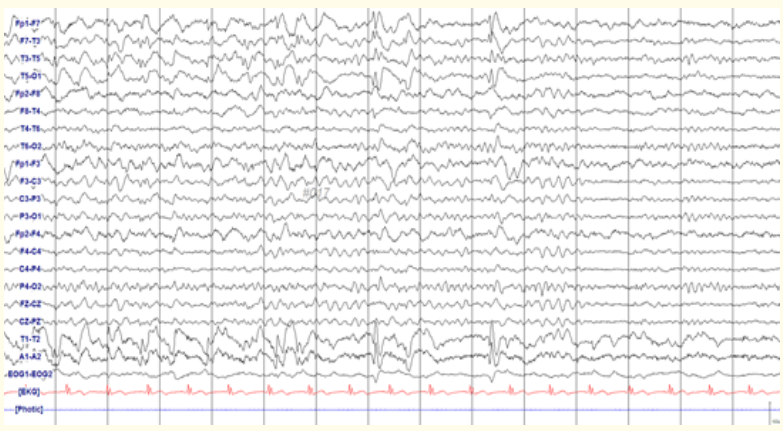

Figure 2: Electroencephalography (EEG) shows periodic spikes in left fronto-temporal lobe.

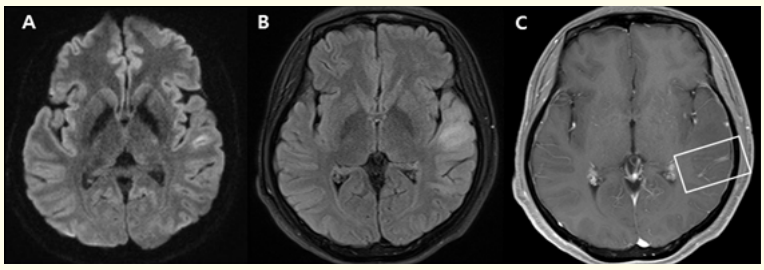

Figure 3: Followed MRI of primary angiitis of the central nervous system (PACNS). A. Diffusion-weighted imaging (DWI) shows newly developed diffusion restriction in the left temporal lobe. B. Fluid-attenuated inversion recovery (FLAIR) image reveals extensive hyperintensity signal over the diffusion restricted lesion. C. Post-contrast gadolinium demonstrates leptomeningeal enhancement (box).

She was diagnosed with PACNS and then treated by intravenous pulse methylprednisolone 1g for 3 days. Headache quickly disappeared and further seizure did not occur. Subsequent oral prednisolone 60 mg/day (1 mg/kg/day) in combination with cyclophosphamide 2 mg/kg/day was continued according to previous reports. The patient's condition was stable and seizure-free for 3 months after seizure onset. Levetiracetam 1000 mg/day and Perampanel 4 mg/day was maintained.

Discussion

CNS vasculitis can be classified as PACNS when it is confined to the CNS and secondary when associated with various other disorders. In 1988, the criteria for the diagnosis of PACNS were proposed. The presence of an acquired and otherwise unexplained neurologic deficit and with (a) the presence of either classic angiographic or histopathologic features of angiitis within the CNS, and (b) no evidence of systemic vasculitis or any condition that could elicit the angiographic or pathologic features [1]. The neurological manifestations are diverse, but generally consist of headache, altered cognition, focal weakness, stroke, or seizure. Serologic markers of inflammation are usually normal. Cerebrospinal fluid is abnormal in about 80 - 90% of patients [2]. Treatment for PACNS has been derived from anecdotal reports, and from cohort studies, which comprised of corticosteroids in combination with cyclophosphamide [3].

Seizures are less often a feature of PACNS. They occur in 20% to 44% of patients, which was developed by inflammatory mechanisms that create structural damage to blood vessels that may lead to ischemia or hemorrhage [4].

In 31 - 43% of SE patients, SE is not controlled with benzodiazepine and other AEDs (phenytoin, levetiracetam, or valproic acid). In this stage, called RSE, treatment recommendations depend on retrospective case series and uncontrolled studies. In animal model of RSE, subcellular maladaptive changes with internalization of postsynaptic GABAA receptors to the cytoplasm make GABAnergic drugs less efficacious or eventually ineffective. 'Spare' subunits of AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) and NMDA (N-methyl-D-aspartic acid) receptors move from subsynaptic sites to the synaptic membrane, causing further hyperexcitability and possibly explaining the preserved sensitivity to NMDA blockers late in the course of SE [5]. Perampanel, a novel noncompetitive AMPA receptor antagonist may be effective in this condition [6]. In a lithium–pilocarpine rat model of SE, the efficacy of diazepam and Perampanel in RSE was assessed. In this study, Perampanel terminated seizure activity when administered 10 minutes and 30 minutes after SE onset, whereas diazepam did not terminate seizure activity at 30 minutes. Hence, efficacy of perampanel in the termination of benzodiazepine resistant SE was suggested [7].

After oral administration, peak plasma concentrations of perampanel have been observed within 15 minutes to 2 hour. Perampanel distributes into the body tissue, and the remaining plasma fraction has a terminal half-life of about 105h, whereas the calculated effective half-life is 48h, reaching a steady state after 10 to 19 days [8]. With repetitive administrations, the plasma concentration will increase considerably. Therefore, the effectiveness of perampanel to terminate SE should increase from day to day, and it may have a considerable part in the termination of RSE even more than 72h after the first administration [9]. Data on the efficacy or perampanel in the treatment of RSE in humans are missing. Hence, controlled studies for efficacy and tolerability of higher doses of perampanel in the treating of RSE are warranted.

Limitation

When initial Brain MRI was performed, the pattern of linear hyperintensity was not according to vascular territory, and Focal stenosis of middle cerebral artery in MR angiography was not long segment. So we should consider the possibility of arteritis rather than atherosclerotic infarction and if early immunotherapy with AEDs had been done, the progress would have been more favorable. Brain biopsy was not done in this case, but neurologic symptoms, MR angiographic features and laboratory findings supported the diagnosis of PACNS sufficiently.

This is only case report and more randomized studies will be needed in the future.

Conclusion

We present a RSE case which was treated by perampanel in combination with immunotherapy successfully.

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