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Case Report

Acute encephalitis with refractory, repetitive partial seizures: Pathological findings and a new therapeutic approach using tacrolimus

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Abstract

Acute encephalitis with refractory, repetitive partial seizures (AERRPS) is characterized by prolonged severe seizures and a high-grade fever. We experienced a boy with severe AERRPS with frequent partial seizures that exhibited right-side predominance. The patient required the continuous intravenous administration of many antiepileptic drugs and respirator management for several months. Methylprednisolone pulse therapy and intravenous immunoglobulin administration were only temporarily effective. The MRI and EEG showed the abnormality in the left occipital lobe. Although occipital lobectomy was performed, his seizures continued. His cerebrospinal fluid exhibited elevated protein and proinflammatory cytokine levels, and was positive for anti-glutamate receptor ε2 antibodies. Pathological examination showed infiltration of many neutrophilic leukocytes, T cells, and microglia in the area exhibiting severe spongiosis. We thought that the exaggerated microglia and T-cell responses were related to the pathogenesis of the patient's seizures, and we therefore initiated treatment with tacrolimus. As a result, many of the daily seizure clusters were ameliorated, and the patient was discharged. We attempted to discontinue the tacrolimus twice, but the patient's seizure clusters recurred each time. This is the first case report of the pathological findings of AERRPS and showing an effective therapeutic approach using tacrolimus. Tacrolimus may be an effective immunosuppressant, especially for patients with severe AERRPS.

Keywords: Acute encephalitis with refractory; Repetitive partial seizures (AERRPS); Tacrolimus; Surgery; Pathological findings

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1. Introduction

Patients with acute encephalitis associated with refractory, repetitive partial seizures (AERRPS) can develop severe seizures, and most require high-dose barbiturate therapy under ventilation for several weeks [1]. Sakuma et al. [2] proposed the clinical entity of AERRPS as (1) a prolonged acute phase of more than 2 weeks; (2) partial seizures of the same seminology persisting from the acute phase to convalescence; (3) seizures frequently evolving into convulsive status, particularly during the acute phase; (4) marked intractableness of the seizures; and (5) exclusion of related disorders such as known viral encephalitis or metabolic disorders. Most patients with AERRPS show self-limit seizures those decrease within two months of acute phase. The pathogenesis of AERRPS is poorly understood. AERRPS is currently suspected to be an inflammatory disorder of the central nervous system [2]. Saito et al. [3] showed that a prolonged inflammatory process is associated with the pathogenesis of AERRPS and may be pivotal in the epileptogenesis. Methylprednisolone pulse therapy and intravenous immunoglobulin have been used as treatments, but their effectiveness varies [2,3]. Tacrolimus was reported to be effective when used to treat Rasmussen's encephalitis, which is an autoimmune-related condition [4]. We herein present the clinical details and immunological and pathological findings of AERRPS and describe the effect of tacrolimus on AERRPS.

2. Case report

2.1. Clinical course

A previously healthy 11-year-old male with a 4-day history of fever was hospitalized because of recurrent seizures. The patient underwent hypothermia treatment and was administered thiopental and lidocaine to maintain a burst suppression electroencephalogram (EEG) pattern under respirator management. His clinical features met the criteria for AERRPS [2]. We continued intravenous midazolam and thiopental and tried several antiepileptic drugs. The patient's seizures were slightly reduced after the administration of intravenous immunoglobulin (400 mg/kg/day × 4 days) and methylprednisolone pulse therapy (30 mg/kg/day × 3 days). A few weeks later, however, the patient's seizures increased again and he developed a high fever. After 2 months of illness, the patient underwent left occipital lobectomy (Fig. 1). His seizures were reduced after the surgery, but he developed clusters of seizures occurring every 2–4 weeks. A ketogenic diet was not effective. After 5 month of illness, we administered PSL (2 mg/kg/day) and the patient's seizures were reduced in frequency; however, when we reduced the PSL dose, seizure relapse occurred.

After 15 month of illness, we attempted treatment with tacrolimus under the approval of the Tohoku University School ethical review board. When the trough blood concentration of tacrolimus reached about 4 ng/ml, the patient's seizures decreased to several times per day. He was discharged from the hospital after 20 months. We tried twice to discontinue the tacrolimus, but each time the epilepticus recurred (Fig. 1). After 5 years, the epilepticus became suppressed, but he continued to experience intermittent partial seizures and disturbances of consciousness.

2.2. Neuroimaging and EEG

A brain computed tomography scan on the first day was normal. Enhanced T1-weighted brain magnetic resonance imaging on day 21 revealed an enhanced area in the left occipital lobe (Fig. 2A).

The patient's seizures presented as focal clonic convulsions that started in the right leg or right angle of the mouth and spread across the entire right side of the body or sometimes over the whole body. An ictal EEG showed that small spikes started in the left parietal to occipital area with spike bursts that gradually spread to the left hemisphere and sometimes became secondarily generalized (Fig. 2B(1–3)). During the interictal state, periodic lateralized epileptiform discharges were observed over the left posterior hemisphere.

2.3. Laboratory data

Laboratory examinations showed that the patient's C-reactive protein level was 1.6 mg/dl, but the blood cell count, liver and kidney function, blood electrolytes, glucose level, and plasma ammonia level were all normal. The cell count in the cerebrospinal fluid (CSF) was elevated to 34 cells/μl (mononuclear cells, 32; polynuclear cells, 2), and the protein level was elevated to 233 mg/dl (Fig. 1). CSF was positive for anti-glutamate receptor (GluR) ε2 IgG antibodies on day 13 (Fig. 1). Four years later, high protein and GluRε2-IgG levels were still detected in the patient's CSF. No oligoclonal banding was evident. An assessment of the patient's CSF cytokine levels revealed increases in tumor necrosis factor-α (TNF-α), interleukin (IL)-6, IL-10, and interferon-γ on day 39.

2.4. Pathological findings

Pathological examination showed that both the cerebral cortex and white matter were affected. A severely affected area (Fig. 3A and B) and a relatively normal area (Fig. 3A and C) were admixed in one field of view (Fig. 3A). The severely affected areas exhibited spongiosis (Fig. 3B) and infiltration of the capillaries by large numbers of neutrophilic leukocytes, which were visible