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Case report

A case of acute encephalitis with refractory, repetitive partial seizures, presenting autoantibody to glutamate receptor Gluε2

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Abstract

An 11-year-old male was admitted to our hospital because of high-grade fever, repetitive seizures, and prolonged impairment of consciousness (Glasgow coma scale E1, M5, V1). His seizures were repetitive complex partial seizures that expanded from the unilateral face to the corresponding side of the body. He sometimes developed secondary generalized seizures. While most seizures lasted 1 or 2 min, intractable seizures also frequently (about 5 times/h) occurred. We diagnosed him as encephalitis/encephalopathy, and treated him with artificial respiration, thiamylal sodium, mild hypothermia therapy, steroid pulse therapy, massive γ-globulin therapy, etc. Afterwards, he had sequelae, such as post-encephalitic epilepsy (same seizures continued to recur), hyperkinesia, impairment of immediate memory, change in character (he became sunny and obstinate), dysgraphia, and mild atrophy of the hippocampus, amygdala, and cerebrum. However, he could still attend a general junior high school. He was diagnosed as acute encephalitis with refractory, repetitive partial seizures (AERRPS). In this case, he was positive for autoantibody to glutamate receptor Gluε2 IgG or IgM in an examination of blood and spinal fluid, and we presumed that this may have influenced his sequelae. In this case, a combination of mild hypothermia therapy, steroid pulse therapy, and massive γ-globulin therapy was effective.

Keywords: Autoantibody to glutamate receptor Gluε2; Acute encephalitis with refractory, repetitive partial seizures (AERRPS); A peculiar type of post-encephalitic/encephalopathic epilepsy; Mild hypothermia therapy; Massive γ-globulin therapy; Steroid pulse therapy

1. Introduction

A peculiar type of post-encephalitic/encephalopathic epilepsy was first reported by Awaya et al. [1]. It is characterized by epilepsy with the same repetitive intractable partial seizures from the acute phase to the convalescence phase. However, it is not known when epileptogeneity is acquired. Soon thereafter, Shiomi et al. reported a similar case of encephalitis accompanied by frequent seizures in Japan. Sakuma et al. proposed the terminology acute encephalitis with refractory, repetitive partial seizures (AERRPS), which satisfied the following five criteria: (1) a prolonged acute phase of more than 2 weeks, (2) partial seizures with the same symptoms persisting from the acute phase to the convalescence phase, (3) seizures frequently evolving into status convulsivus, especially during the acute phase, (4) marked intractability of seizures, and (5) exclusion of related disorders such as known viral encephalitis or metabolic disorders [2], based on these two previous reports. On the other hand, it was reported that autoantibody to glutamate receptor Gluε2 was often positive in Rasmussen's encephalitis [3] and in acute encephalitis/encephalopathy. It is possible that autoantibody to glutamate receptor Gluε2 may cause persistent excitation of glutamate receptor Gluε2 and may be associated with seizures and impairment of the central nervous system. We report here a case of AERRPS, presenting autoantibody to glutamate receptor Gluε2. To the best of our knowledge,

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this is the first report of AERRPS presenting autoantibody to glutamate receptor Gluε2. It is possible that autoantibody to glutamate receptor Gluε2 may be associated with the pathophysiology of AERRPS.

2. Case report

An 11-year-old male was admitted to our hospital because of high-grade fever, repetitive seizures, and prolonged impairment of consciousness (Glasgow coma scale E1, M5, V1). His seizures were repetitive complex partial seizures that expanded from the unilateral face to the corresponding side of the body. He sometimes developed secondary generalized seizures. While most seizures lasted 1 or 2 min, intractable seizures also frequently (about 5 times/h) occurred. The family history and past history were not marked. On admission, he showed no abnormal neurological findings except for impairment of consciousness and intractable seizures. On blood examination, he showed no abnormality except for FDP and ALT (16 μg/ml (1–12 μg/ml), 53 U/l (5–40 U/l), respectively). On spinal fluid examination, leukocyte count was 25 mm^3. Brain computed tomography (CT) and magnetic resonance imaging (MRI) with T2-weighted imaging (T2-WI) showed no abnormality (Fig. 1(A)). There was no significant increase in any virus antibody titer. His clinical course after admission is described in Fig. 2. On day 1 of admission, he was administered glycerol (5 ml/kg × 4 times/day), acyclovir (5 mg/kg × 3 times/day), γ-globulin (250 mg/kg/day for 3 days), steroid pulse therapy (methylprednisolone 25 mg/kg/day for 3 days), and midazolam (0.1 mg/kg/h) for his encephalitis and seizures. On day 2, since he had repetitive seizures, the dose of midazolam was increased and he was administered lidocaine hydrochloride. On day 3, artificial respiration was begun along with thiamylal sodium at 3 mg/kg/h because of intractable seizures. Afterwards, we treated him with thiamylal sodium at 8 mg/kg/h because of intractable seizures and mild hypothermia therapy. He was given an intravenous injection of phenytoin (5 mg/kg × 2 times/day) during treatment with thiamylal sodium, but this was not effective. Interictal electroencephalogram (EEG) on day 8 showed slow spike and wave predominantly in the frontal and central region (Fig. 3(A)). Ictal EEG on day 8 showed rhythmic spikes in the left frontal–central–temporal region with antecedent spikes (Fig. 3(B)). At this time, he was treated with thiamylal sodium at 6 mg/kg/h because of repetitive seizures. Interictal EEG on day 10 showed a burst-suppression pattern and spikes were present during the burst phase (Fig. 3(C)). He was then treated with mild hypothermia therapy and thiamylal sodium at 8 mg/kg/h, and the seizures stopped. On day 10, the leukocyte count was 3 mm^3 and IgG was 10.2 mg/dl (reference value, 0.2–0.6 mg/dl) on spinal fluid examination. Since we thought that a mechanism of abnormal immunity may be involved in his encephalitis because of the increase in IgG on spinal fluid examination, massive γ-globulin therapy (400 mg/kg/day over 5 days) was performed again on day 12. On day 12, we discontinued treatment with thiamylal sodium and began treatment with massive phenobarbital suppository therapy (20 mg/kg/day) because of an impairment of liver function on blood examination. In association with a decrease in thiamylal sodium, his EEG findings worsened. However, EEG spikes almost disappeared following treatment with

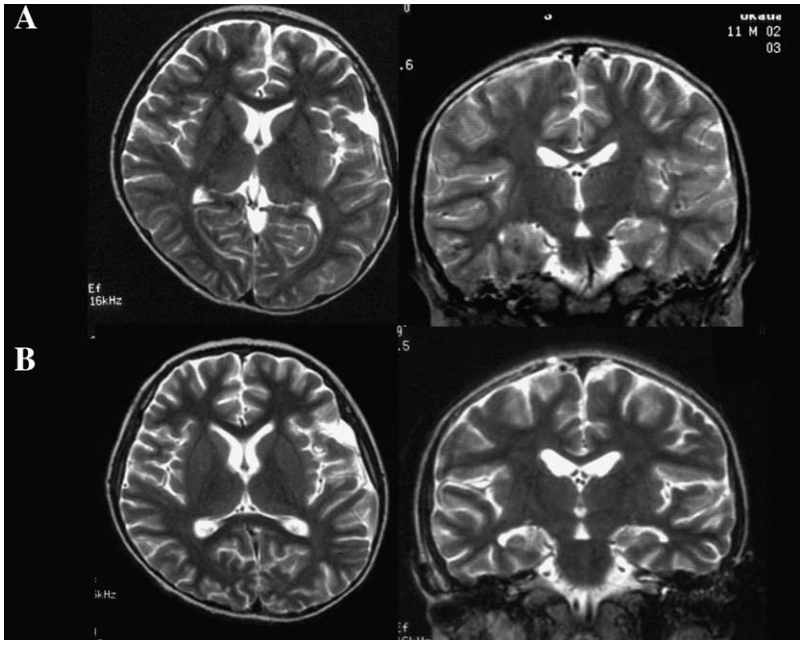

Fig. 1. (A) Brain MRI T2-WI on admission showed no abnormality. (B) Brain MRI on day 36 showed mild atrophy of the hippocampus, amygdala, and cerebrum.

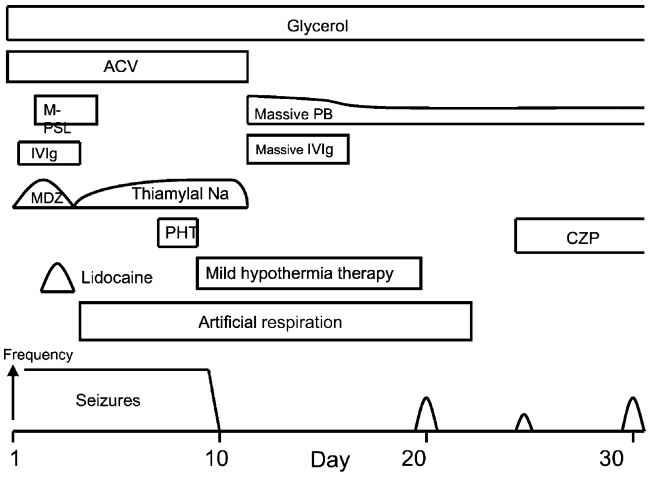

Fig. 2. Clinical course after admission. Abbreviations: ACV, acyclovir; M-PSL, methylprednisolone (steroid pulse therapy); IVIg, intravenous γ-globulin; PB, phenobarbital; MDZ, midazolam; PHT, phenytoin; CZP, clonazepam.

massive γ-globulin therapy and massive phenobarbital suppository therapy. On day 12, acyclovir was also stopped because polymerase chain reaction of herpes simplex virus DNA was negative on spinal fluid examination. On day 20, we stopped mild hypothermia therapy and on day 22 he was extubated. After extubation, his level of consciousness gradually improved. However, since the same seizures appeared several times per week, we started clonazepam (0.075 mg/kg/day) on day 24. The frequency of seizures then gradually decreased. Brain MRI on day 36 showed mild atrophy of the hippocampus, amygdala, and cerebrum (Fig. 1(B)). EEG on day 39 showed a disappearance of spikes. However, the same seizures continued to recur at about once per month under the oral administration of phenobarbital and clonazepam. Afterwards, he had sequelae, such as post-encephalitic epilepsy (same seizures continued to recur), hyperkinesia, impairment of immediate memory, change of character (he became sunny and obstinate), and dysgraphia. However, he could still attend a general junior high school. He was positive for autoantibody to glutamate receptor Gluε2 IgG or IgM in an examination of blood and spinal fluid on day 10, but negative on day 80.

3. Discussion

For the treatment of seizures in AERRPS, barbiturate and benzodiazepine are often effective in the acute phase, and phenytoin, zonisamide, and potassium bromide in addition to barbiturate and benzodiazepine are often effective in the convalescence phase [2]. In this case, midazolam, lidocaine hydrochloride, and phenytoin were not effective, and a complete suppression~burst suppression pattern on EEG and thiamylal sodium at 8 mg/kg/h were necessary to stop his seizures; thus, he showed inveterate epileptogeneity. Massive phenobarbital suppository therapy (20 mg/kg/day)

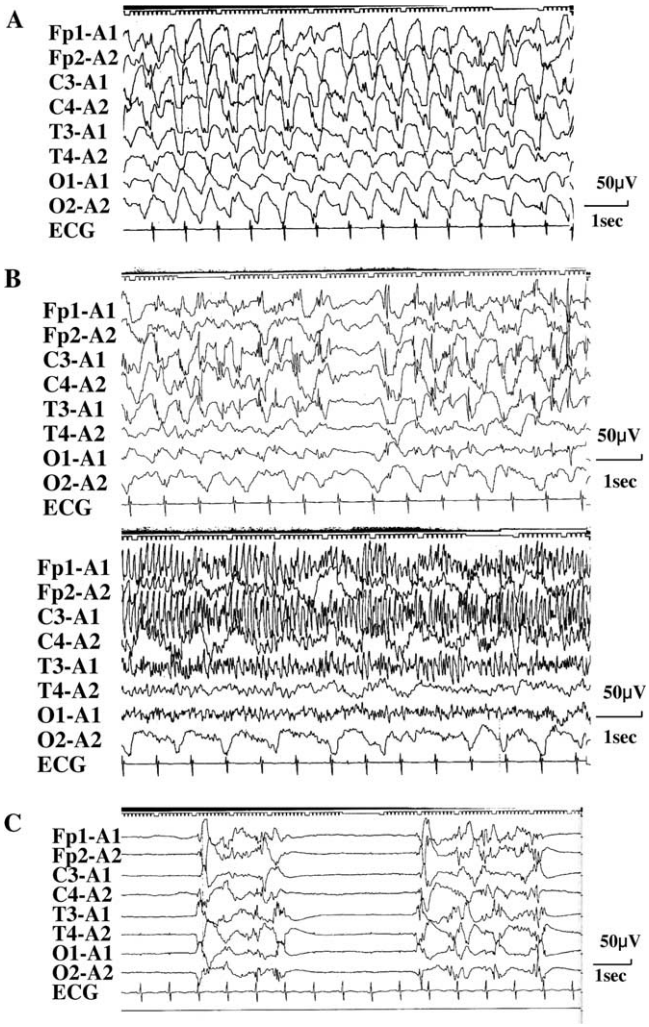

Fig. 3. (A) Interictal EEG on day 8 showed slow spike and wave predominantly in the frontal and central lobe. He was treated with thiamylal sodium at 6 mg/kg/h because of repetitive seizures. (B) Ictal EEG on day 8 showed rhythmic spikes in the left frontal–central–temporal region with antecedent spikes in the same region. (C) Interictal EEG on day 10 showed a burst-suppression pattern and spikes were present during the burst phase. He was treated with mild hypothermia therapy and thiamylal sodium at 8 mg/kg/h, and the seizures stopped.

was partly effective and made it possible to break away from thiamylal sodium. Sakuma et al. reported that massive phenobarbital therapy or phenytoin was useful for the discontinuation of barbiturate [2]. In our case, phenobarbital was most effective at stopping seizures after the early phase of treatment. Sakuma et al. reported that phenobarbital was effective in 2/15 cases in the acute phase, and in 4/12 cases in the convalescence phase [2]. Hamano et al. reported a case of AERRPS that showed the transient disappearance of seizures with the occurrence of choreo-ballistic involuntary movements [4]. That case showed secondary generalized seizures that originated in the face. It was thought that epileptic discharge from the lateral motor cortex was transmitted to basal ganglia or the brain stem, and resulted in secondary generalized seizures. Thus, it is possible that

impairment of the basal ganglia associated with involuntary movement may have blocked epileptic discharge from the motor cortex, and convulsions decreased accompanied by a worsening of involuntary movement [5]. It is possible that hyperexcitability in the subcortex may have blocked epileptic discharge from the cortex [4]. These results may be useful for the treatment of AERRPS.

For the treatment of encephalitis/encephalopathy in AERRPS, we used steroid pulse therapy, massive γ-globulin therapy, and mild hypothermia therapy. A combination of mild hypothermia therapy with steroid pulse therapy is recommended for encephalopathy [6,7]. In encephalitis, since cytokine [8] and neopterin [9] are both increased on spinal fluid examination, it is thought that inflammation and immunoreaction are present in the central nervous system. The aims of hypothermia therapy and steroid pulse therapy are (1) to suppress brain edema, (2) to suppress secondary impairment of nerve cells due to the transmission of excitatory amino acids and neurotoxic materials, and (3) to suppress an abnormal increase in cytokine [6]. In this case, the aims of massive γ-globulin therapy were (1) to immunize against contagions, (2) to suppress an abnormal increase in cytokine, and (3) to suppress abnormal immunity and the generation of antibody (autoantibody to glutamate receptor Gluε2, etc.) because of an increase in IgG on spinal fluid examination. Sandstedt et al. reported that γ-globulin therapy was more effective in cases with a high level of IgG on spinal fluid examination in intractable post-encephalitic epilepsy [10].

In this case, autoantibody to glutamate receptor Gluε2 was positive on blood and spinal fluid examination. It has been reported that autoantibody to glutamate receptor is often positive in Rasmussen's encephalitis [3] and acute encephalitis/encephalopathy [11]. On the other hand, patients with West syndrome or Lennox–Gastaut syndrome, or control subjects are negative for autoantibody to glutamate receptor [11]. In acute encephalitis/encephalopathy, it has been speculated that severe cases tend to generate autoantibody to glutamate receptor Gluε2 [11]. Patients with status convulsivus in the acute phase generated autoantibody to glutamate receptor Gluε2 significantly more often than those without status convulsivus [11]. Furthermore, patients who were positive for autoantibody to glutamate receptor Gluε2 had sequelae such as developmental delay, motor paralysis, or epilepsy significantly more often than those who were negative for autoantibody to glutamate receptor Gluε2 [11]. It is possible that autoantibody to glutamate receptor may persistently adrenalize glutamate receptor, and this may be associated with the generation of seizures and impairment of the central nervous system. Also, since the glutamate receptor plays an important role in the genesis of memory and learning in the hippocampus, it has been speculated that autoantibody to glutamate receptor may be associated with atrophy of the hippocampus and impairment of memory. To the best of our knowledge, there has been no previous report in which autoantibody to glutamate receptor Gluε2 was positive in AERRPS. In general, AERRPS shows a neurologically poor prognosis, and the appearance of autoantibody to glutamate receptor also reflects a neurologically poor prognosis. If it can be demonstrated that an abnormal immune state is involved in AERRPS based on an examination of autoantibody to glutamate receptor Gluε2, it may be possible to reduce the incidence of sequelae through the use of immunotherapy. In this case, the patient could attend a general junior high school. These results suggest that active therapy such as with a combination of mild hypothermia therapy, steroid pulse therapy, and γ-globulin therapy may be effective in AERRPS.

References

[1] Awaya Y, Fukuyama Y. Epilepsy sequelae of acute encephalitis or encephalopathy (third report). Jpn J Psychiatry Neurol 1986;40:385–7.

[2] Sakuma H, Fukumizu M, Kohyama J. Efficacy of anticonvulsants on acute encephalitis with refractory, repetitive partial seizures (AERRPS) (in Japanese). No To Hattatsu (Tokyo) 2001;33:385–90.

[3] Rogers SW, Andrews PI, Gahring LC, Whisenand T, Cauley K, Crain B, et al. Autoantibodies to glutamate receptor GluR3 in Rasmussen's encephalitis. Science 1994;265:648–51.

[4] Hamano K, Watanabe A, Kohyama J. A case of acute encephalitis with refractory, repetitive partial seizures (AERRPS) showing transient disappearance of the seizure with occurrence of choreoballistic movement (in Japanese). No To Hattatsu (Tokyo) 2003;35:59–64.

[5] Chase TN, Oh JD. Striatal dopamine- and glutamate-mediated dysregulation in experimental parkinsonism. Trends Neurosci 2000;23(10 Suppl):586–91.

[6] Kimura S, Ohtsuki N, Adachi K, Nezu A, Aihara Y. Efficacy of methylprednisolone pulse and mild hypothermia therapies in patients with acute encephalopathy (in Japanese). No To Hattatsu (Tokyo) 2000;32:62–7.

[7] Munakata M, Kato R, Yokoyama H, Haginoya K, Tanaka Y, Kayaba J, et al. Combined therapy with hypothermia and anticytokine agents in influenza A encephalopathy. Brain Dev 2000;22:373–7.

[8] Ichiyama T, Nishikawa M, Yoshitomi T, Hayashi T, Furukawa S. Tumor necrosis factor-alpha, interleukin-1beta, and interleukin-6 in cerebrospinal fluid from children with prolonged febrile seizures. Comparison with acute encephalitis/encephalopathy. Neurology 1998;50:407–11.

[9] Kimura S, Ohtsuki N, Adachi K, Nezu A. Marked efficacy of steroid pulse therapy in an infant with acute encephalopathy having elevated cerebrospinal fluid level of neopterin (in Japanese). No To Hattatsu (Tokyo) 1999;31:282–3.

[10] Sandstedt P, Kostulas V, Larsson LE. Intravenous gammaglobulin for post-encephalitic epilepsy. Lancet 1984;2:1154–5.

[11] Takahashi Y, Sakaguchi N, Kondo N, Ariki M, Hattori S, Matsuo N, et al. Investigation about diagnosis and therapy of higher brain function disorders by autoantibodies against NMDA-GluRs. In: Kaga M, editor. (in Japanese) Development and Developmental Dysfunction of Higher Cortical Function, (Report of Research Grant (12B-2) for Nervous and Mental Disorders from the Ministry of Health, Labor and Welfare) (Ichikawa) 2003:93–9