Original article

Effect of topiramate, in combination with lidocaine, and phenobarbital, in acute encephalitis with refractory repetitive partial seizures

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Abstract

Objective: Acute encephalitis with refractory repetitive partial seizure (AERRPS) is a peculiar type of post-encephalitic/encephalopathic epilepsy. Here we report an analysis of AERRPS in a series of children and propose an effective treatment option for seizure control in these children. Methods: We retrospectively reviewed cases of AERRPS treated in a pediatric intensive care unit, between February 2002 and June 2006. Clinical characteristics were systematically assessed. Burst suppression coma was induced by high-dose suppressive therapy; 24-h electroencephalogram (EEG) monitoring was performed on each patient. The goal of treatment was to achieve complete clinical seizure control or burst-suppression pattern on EEG, aiming for an interburst interval of >5 s. Brain imaging was done for each patient. Results: There were nine patients (seven boys), aged 5–15 years. Clinical symptoms included fever (100%), upper respiratory symptoms (66.7%) and altered consciousness (66.7%). All patients received multiple high-dose suppressive drugs and were intubated with/without inotropic agents. Seizures in three patients were stopped after high-dose lidocaine infusion (6–8 mg/kg/h) in the acute stage and three patients were stopped after high dose phenobarbital (serum level 60–80 ug/mL) combined with high-dose oral topiramate (15–20 mg/kg/day). Follow-up for this study was 16–61 months. Two subjects died while seven developed epilepsy and/or neurologic deficits; none returned to baseline. All survivors were discharged and continued multiple antiepileptic medications. Conclusions: Our data indicates that children with AERRPS have high mortality and morbidity rates. High-dose topiramate combined with high-dose lidocaine infusion or high-dose phenobarbital in the acute stage might be an effective treatment option for children with AERRPS.

Keywords: Acute encephalitis with refractory; Repetitive partial seizures

1. Introduction

Acute encephalitis with refractory, repetitive, partial seizures (AERRPS) was first reported by Awaya in 1986 as a peculiar type of post-encephalitic epilepsy [1]. It is a rare condition wherein acute encephalitis is accompanied by prolonged and refractory status epilepticus from the onset of the disease, and intractable partial seizures persist even after recovery from the acute illness. The incidence of AERRPS is unknown. Approximately 40 similar Japanese cases have been reported. Sakuma et al. proposed the term AERRPS to describe this epilep-
tic syndrome, with the following diagnostic criteria: (1) acute phase lasting for two or more weeks, (2) persistent partial seizures of a similar nature occurring from the acute phase through to the recovery phase, (3) frequent seizures often evolving into recurrent status epilepticus, (4) marked intractability of the seizures, and (5) exclusion of a specific etiology such as viral encephalitis and metabolic disorders [2]. However, many children with “viral encephalitis” stemming from undetected viral agents tend to have similar clinical courses with refractory repetitive seizures. AERRPS may be a heterogeneous entity, where infective or autoimmune factors may be involved in the pathogenesis. This condition is diagnosed by the listed criteria, and we identified nine Taiwanese patients presenting with clinical symptoms and courses which met the criteria for AERRPS. We also found that additional treatment options were effective for the management of acute-phase seizures in these patients, apart from the barbiturate therapy that has been recommended in preceding reports [3].

2. Subjects and methods

From February 2002 to August 2006, nine children with AERRPS, treated in the pediatric intensive care unit of Chang Gung Children’s Hospital, were enrolled. Approval for this study was obtained from the institutional review board. Information was collected by retrospective chart review regarding age, sex, clinical symptoms, initial seizure type, initial EEG patterns, neuroimaging, cerebrospinal fluid (CSF) analysis, metabolic survey, acute-stage suppressive drugs, hospital days and outcomes.

AERRPS was diagnosed according to the diagnostic criteria proposed by Sakuma. All children were previously healthy and none had prior seizures, including febrile seizures. Any children with a prior neurological insult, progressive neurological disorder, electrolytic imbalance, hypoglycemia and a family history of epilepsy or febrile seizures were excluded. The acute phase was defined as a period of appearance of diffuse, periodic bursts of high voltage spikes on EEG [2]. The goal of treatment was to achieve complete clinical seizure control or burst-suppression pattern on electroencephalogram (EEG), aiming for an interburst interval of >5 s [4]. Burst suppression coma was induced by high-dose suppressive therapy consisting of midazolam, lidocaine, propofol and thiopental. The duration of first-cycle burst suppression was 2–4 days. Weaning of high-dose suppressive therapy was guided by EEG monitoring [5]. The weaning process was aborted if there was return of status epilepticus or frequent clinical or electrographic seizures. All children were cared for in the pediatric intensive care unit. Round-the-clock EEG monitoring was performed on each patient. All EEGs were interpreted by pediatric neurologists.

The diagnosis of seizure patterns and seizure types in the acute phase were based upon clinical impressions of the attending neurologists. Frequencies of emergence in the acute stage were categorized as less than 10 min, every 10–20 min and more than 20 min. The seizure patterns, seizure types and the maximum frequency of emergence in the chronic phase (defined as last visit) were described by family. EEGs were categorized as having either a high voltage slow wave, or a focal, multifocal or generalized epileptiform discharge. Metabolic survey included analysis of blood samples by tandem mass, urine organic acid, serum total and free carnitine concentrations. Patient outcomes, including mortality, new neurological deficits and return to baseline, were determined from the last clinical visit, which was a minimum of 6 months after the episode of status epilepticus. The follow-up for the study group was 16–61 months.

3. Results

Ages at presentation for the nine children (two girls) ranged from 5–15 years. Prodromal symptoms included fever (9/9, 100%), upper respiratory symptoms (6/9, 66.7%), altered consciousness (6/9, 66.7%), vomiting (4/9, 44.4%) and headache (4/9, 44.4%). Acute phase duration ranged from 20 to 52 days. The seizure patterns of emergence, in the acute stage of hospitalization, were categorized as simple/complex partial (1/9, 11.1%), complex partial (4/9, 44.4%), primary complex partial and secondary generalized (4/9, 44.4%). The most common partial seizure types in the acute phase were eye deviation (9/9, 100%), hemifacial twitching (9/9, 100%) and hemi-clonic (6/9, 66.7%) and apneic seizures (9/9, 100%). Frequencies of emergence in the acute phase were divided into three groups: less than 10 min (3/9, 33.3%), every 10–20 min (4/9, 44.5%) and greater than 20 min (2/9, 22.2%). The initial EEG patterns of admission revealed high voltage slow wave in 4 (44.4%), focal epileptiform discharge in 1 (11.1%), multifocal in 2 (22.2%) and primary multifocal with secondary generalized in 2 (22.2%) subjects. EEG patterns during the acute stage revealed high-voltage slow-wave with multifocal epileptiform discharge in 4 (44.4%), and high-voltage slow-wave with primary multifocal and secondary generalized in 5 (55.6%) subjects. Clinical characteristics, duration of acute phase and EEG patterns of all nine children are summarized in Table 1. Seizure types, patterns of emergence and frequencies in the acute and chronic phases are listed in Table 2.

All patients underwent a thorough investigation during their hospitalization, including serological tests for viruses, polymerase chain reaction (PCR) in CSF for Herpes Simplex Virus (HSV) DNA (n = 5) and viral cultures of throat (n = 8), CSF (n = 9), and rectal (n = 8) specimens. Most children underwent serological tests for influenza A and B (n = 9), HSV (n = 8), Epstein-
Barr virus (EBV) \((n = 7)\), Mycoplasma pneumoniae \((n = 9)\), and Human herpes virus 6 (HHV-6) \((n = 2)\). In all cases, no organisms were identified by CSF bacterial and viral culture. Metabolic surveys were performed in all patients and all were negative. Lumbar punctures were performed in nine patients. White blood cell (WBC) count in the CSF studies ranged from 0 to 31 cells/μL; there was a predominance of monocytes (60–100%). CSF glucose levels ranged from 48 to 104 mg/dL and protein levels were 12.1–179.5 mg/dL. Table 3 summarizes serum and CSF data.

Neuroimaging studies [computed tomography (CT) or magnetic resonance imaging (MRI)] were divided into an initial phase (<1 week after disease onset), hospitalization phase (1 week to 3 months after disease onset) and follow-up (>3 months after disease onset). Cranial CT \((n = 6)\) performed during the initial phase was non-specific and included leptomeningeal enhancement or brain swelling with sulcal effacement, whereas hospitalization-phase MRI \((n = 9)\) revealed mild atrophy in one patient. Two patients had unilateral or bilateral hippocampal hyperintensities in T2, suggesting focal edema. Two others had global hypoxic ischemic encephalopathy; four had no specific findings. Follow-up phase cranial CT \((n = 4)\) or MRI \((n = 3)\) revealed brain atrophy in six patients and hippocampal atrophy in one patient. Table 4 shows the brain imaging from the nine AERRPS children.

In terms of management, all patients received multiple high-dose suppressive drugs and were intubated with/inotropic agents. Eight patients received intravenous immunoglobulin (IVIG). The seizures of three patients (Patient #4–6) were stopped after high-dose lidocaine infusion (6–8 mg/kg/h) in the acute stage, followed by high-dose oral topiramate (15–20 mg/kg/day) combined with multiple anticonvulsants. In the three patients (Patient #7–9), burst suppression was achieved by midazolam infusion and the midazolam infusion could terminate the seizures temporally, but the seizures were still present later. Finally, they were stopped after high-dose phenobarbital (serum level: 60–80 μg/mL) and combined with high-dose oral topiramate (15–20 mg/kg/day) in the acute stage, and the high dose phenobarbital and topiramate were effective to taper off the midazolam infusion. A cluster of seizures in Patient #1 was terminated after thiopental (10 mg/kg/h). Another (Patient #2) was stopped after thiopen-
Patient #3 had persistent seizures after a combination therapy of lidocaine (6 mg/kg/h) and propofol (6 mg/kg/h). All of these latter three patients had severe cardiopulmonary complications, including profound hypotension, despite inotropic agent use. Two of these three patients died. Patient #2 died from the adverse effects of thiopental-induced profound hypotension, despite inotropic agent use. Patient #3 died of sepsis. Total duration of high-dose suppressive therapy ranged from 20 to 41 days. Total durations of high-dose suppressive therapy are listed in Table 5.

As a representative example, patient #4, a 14-year-old female, experienced high fever, headache and fluctuations of consciousness on the second day of illness along with complex partial with/without secondary generalized tonic–clonic convulsions. On admission, she was comatose and on artificial ventilation. CSF cell count and brain CT were normal. Phenytoin, phenobarbital, and valproic acid could not suppress the recurrent seizures, and midazolam infusion was initiated on day 2 of admission. EEG on admission showed multifocal epileptiform discharges over the bilateral hemispheres (Fig. 1A). Due to repetitive generalized seizures, with eyelid twitching and smacking, on day 6 of admission, the midazolam infusion rate was increased to 1.2 mg/kg/h. When the midazolam infusion rate was increased up to 0.7 mg/kg/h, inotropic agents were required for hypotension management. Because of the emergence of frequent clinical/subclinical seizures, we administered high-dose lidocaine (6 mg/kg/h) on day 9. Subsequent EEG revealed a burst-suppression pattern (Fig. 1B). The propagation of the focal epileptiform discharges decreased markedly. Clinical seizures terminated within 24 h of high-dose lidocaine infusion. Topiramate (1 mg/kg/day) was started via nasogastric tube on day 9. Localized rhythmic epileptiform discharges persisted, and generalization increased after the dose of lidocaine was tapered (Fig. 1C). We then increased the dosage of topiramate (1 mg/kg/day) every 3 days, up to 15 mg/kg/day on day 51. After trials with various combinations of anticonvulsants, the complex partial seizures were controlled to less than 2–3 times/day by treatment with clonazepam, high dose phenobarbital (10 mg/kg/day), valproic acid, and high-dose topiramate (15 mg/kg/day). Lidocaine could be completely tapered off after 41 days of continuous infusion.
Table 5

Management and outcomes of nine children with AERRPS

<table>
<thead>
<tr>
<th>MV</th>
<th>Inotropic agent</th>
<th>IVIG</th>
<th>AED in acute phase</th>
<th>Duration of HDST</th>
<th>Hospital days</th>
<th>Outcome</th>
<th>AED during follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Ineffective</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Y</td>
<td>D+E</td>
<td>Y</td>
<td>Thiorpeptal (10 mg/kg/h)</td>
<td>26</td>
<td>83</td>
<td>Epilepsy Vegetative status</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Thiopental (10 mg/kg/h)</td>
<td>20</td>
<td>27</td>
<td>Expired –</td>
</tr>
<tr>
<td>2</td>
<td>Y</td>
<td>D+E</td>
<td>Y</td>
<td>Lidocaine(6 mg/kg/h) + Propofol (6 mg/kg/h) → TPM(15 mg/kg/day)</td>
<td>41</td>
<td>102</td>
<td>Epilepsy Moderate PMR</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lidocaine(6 mg/kg/h) → TPM(15 mg/kg/day)</td>
<td>21</td>
<td>65</td>
<td>Epilepsy Mld PMR</td>
</tr>
<tr>
<td>3</td>
<td>Y</td>
<td>D</td>
<td>Y</td>
<td>Lidocaine(5 mg/kg/h) → TPM(20 mg/kg/day)</td>
<td>21</td>
<td>137</td>
<td>Epilepsy Vegetative status</td>
</tr>
<tr>
<td>4</td>
<td>Y</td>
<td>D</td>
<td>Y</td>
<td>Lidocaine(6 mg/kg/h) → TPM(20 mg/kg/day)</td>
<td>27</td>
<td>63</td>
<td>Epilepsy Severe PMR</td>
</tr>
<tr>
<td>5</td>
<td>Y</td>
<td>D</td>
<td>Y</td>
<td>Lidocaine(6 mg/kg/h) → TPM(15 mg/kg/day)</td>
<td>33</td>
<td>107</td>
<td>Epilepsy Severe PMR</td>
</tr>
<tr>
<td>6</td>
<td>Y</td>
<td>D</td>
<td>Y</td>
<td>Lidocaine(6 mg/kg/h) → TPM(20 mg/kg/day)</td>
<td>20</td>
<td>63</td>
<td>Epilepsy Mild PMR</td>
</tr>
<tr>
<td>7</td>
<td>Y</td>
<td>–</td>
<td>Y</td>
<td>HPB + TPM(15 mg/kg/day)</td>
<td>27</td>
<td>63</td>
<td>Epilepsy Severe PMR</td>
</tr>
<tr>
<td>8</td>
<td>Y</td>
<td>D</td>
<td>Y</td>
<td>HPB + TPM(15 mg/kg/day)</td>
<td>33</td>
<td>107</td>
<td>Epilepsy Severe PMR</td>
</tr>
<tr>
<td>9</td>
<td>Y</td>
<td>–</td>
<td>Y</td>
<td>HPB + TPM(20 mg/kg/day)</td>
<td>20</td>
<td>63</td>
<td>Epilepsy Mild PMR</td>
</tr>
</tbody>
</table>

MV, Mechanical ventilation; D, Dopamine; E, Epinephrine; AED, Anticonvulsant; HDST, High-dose suppressive therapy; PHT, Phenytoin; PB, Phenobarbital; HPB, High-dose phenobarbital; VPA, Valproic acid; MDL, Midazolam; TPM, Topiramate; LEV, Levetiracetam; OXC, Oxcarbazepine; PMR, Psychomotor retardation.

Fig. 1. Electroencephalographic findings in patient #4. (A) EEG, obtained on admission day 1, showing multiple focal epileptiform discharges over bilateral hemispheres. (B) Burst-suppression pattern can be seen on the EEG, who received high-dose lidocaine infusion (6 mg/kg/h) on day 9. (C) Localized rhythmic epileptiform discharges persisted and generalization increased after the dose of lidocaine was tapered to 5 mg/kg/h on day 14. (D) A diffuse sharp wave can be noted over bilateral hemispheres after the discontinuation of lidocaine on day 55.
wave was noted over the bilateral hemispheres after the discontinuation of lidocaine (Fig. 1D).

With regards to the outcome of the nine children, two died and seven survived. Hospital stays ranged from 63 to 137 days. All survivors were discharged on antiepileptic medications. Seven children were followed up with a minimum duration of 6 months. All seven developed epilepsy and/or neurological deficits, and none returned to baseline. Three showed mild to seven developed epilepsy and/or neurological deficits, and none returned to baseline. Three showed mild to moderate psychomotor retardation, two patients remained severely psychomotor retarded and two showed vegetative status. All survivors were discharged on multiple antiepileptic medications. Management and outcomes of the nine children with AERRPS are summarized in Table 5.

4. Discussion

Refractory epileptic seizures for AERRPS begin at the onset of encephalitis as status epilepticus or clusters of seizures. All of our cases had a history of acute febrile illness, and suddenly developed refractory status epilepticus. Based on these symptoms, along with mild pleocytosis or elevated CSF proteins, a diagnosis of encephalitis was made for these patients; however, no infective agents were identified.

A hypothesis concerning AERRPS etiology, including unknown viral infection or immunological disorders, has been proposed in Japan. When Awaya et al. reported AERRPS, cases of influenza encephalopathy were not well recognized or detected as much as now. Some patients with influenza encephalopathy may also have similar clinical presentations. Besides, children with genetic disorders such as with SCN1A mutation may have similar clinical presentations. In our cases, serology for influenza A and B were done on all nine children and all were negative. However, we did not check for the SCN1A mutation. Further study is necessary to establish the etiology.

The characteristic of epilepsy in AERRPS is that an identical seizure pattern, consisting of complex partial seizures with or without secondary generalization. Apart from the secondary generalization during the early phase, (1) eye deviation, (2) hemifacial twitching, (3) hemiconic or (4) apneic seizures are the predominating seizure types in both acute and chronic phases in individual patients [3]. This suggests that the essential pathology underlying the long-term refractory seizures is initiated during the acute phase of illness, in contrast to the usual post-encephalitic epilepsy with a latent period. In our cases, the seizure type in the acute stage of hospitalization was categorized as simple/complex partial (1/9, 11.1%), complex partial (4/9, 44.4%), primary complex partial and secondary generalized (4/9, 44.4%). The clinical features and seizure pattern of our patients all met the criteria of AERRPS.

Neuroimaging in AERRPS patients usually shows non-specific, mild atrophy of the cerebrum [6]. In our series, the brain CT in the acute phase showed no specific findings, such as increased leptomeningeal enhancement or brain swelling, whereas the follow-up brain CT (n = 4) or MRI (n = 3) revealed brain atrophy in six patients and hippocampal atrophy in one patient. However, the presence of "hypoxic–ischemic encephalopathy" is quite unusual for AERRPS, and may be secondary.

In the acute stage, high-dose barbiturate anesthesia is the sole means to suppress such refractory, repetitive partial seizures. Sakuma et al. reviewed the efficacy of anticonvulsants in 21 AERRPS cases and found that barbiturate infusion was effective in 15 out of 17 cases, including five cases treated with pentobarbital sodium at a dose higher than 5 mg/kg/h [2]. Saito et al. studied three AERRPS patients who required high-dose pentobarbital therapy under artificial ventilation in the acute stage and proposed high-dose barbiturate anesthesia as a tentative therapeutic strategy for the acute stage of this catastrophic epileptic syndrome [3]. Since pentobarbital was not available in Taiwan, we tried different agents beyond the recommended dosage guidelines [7–15]. We used high-dose lidocaine continuous infusion (6–8 mg/kg/h) in three patients, which resulted in seizure termination within 24–36 h. In addition, we used high-dose phenobarbital (serum level: 60–80 ug/mL) combined with high dose topiramate (15–20 mg/kg/day) in three other patients and successfully controlled seizures in the acute stage. Topiramate is an anticonvulsant with multiple mechanisms of action, including modification of Na+ and/or Ca++-dependent action potentials, enhancement of GABA-mediated Cl− fluxes into neurons, and inhibition of kainate-mediated conductance at glutamate receptors of the AMPA/kainate type. In addition, topiramate has been shown to reduce neuronal injury after prolonged status epilepticus and may prevent delayed neuronal death [15]. Because of these multiple mechanisms of action and potential neuroprotective effects, topiramate was evaluated as an agent to treat refractory status epilepticus. In previous reports in children, topiramate administered via a nasogastric tube has been reported to be effective in terminating refractory status epilepticus. Two pediatric series have used low initial doses of topiramate (1–5 mg/kg/day), with titration to doses ranging from 5 to 25 mg/kg/d over several days [12–13]. Another pediatric study used 10 mg/kg/d, for two consecutive days, followed by maintenance doses of 5 mg/kg/day [14]. In each case, status epilepticus was aborted within 24–72 h after reaching the maximum dose. In our study, we used a lower initial dose of topiramate (1 mg/kg/day) and titrated to doses ranging about 15–20 mg/kg/day over several days. Seizures were aborted within 24–72 h after reaching the maximum dose. Topiramate was not enough to control the seizures alone; however, as above,
there appears to have been some beneficial effect of topiramate regarding mortality, as two out of three patients that did not receive topiramate died, while six out of seven who received topiramate survived. Therefore, we propose that high-dose lidocaine or high dose phenobarbital combined with high dose topiramate might play an important role for seizure control in the acute stage of AERRPS.

5. Conclusion

Because of the small number of patients, there are limitations to interpretation of the results; further studies may be needed to confirm such findings in a larger number of children with AERRPS. Nevertheless, in this report, we demonstrate a tentative therapeutically effective regimen for seizure control. High-dose topiramate combined with high-dose lidocaine infusion or high-dose phenobarbital in the acute stage might be an effective treatment option in children with AERRPS.

References