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Letter to the Editor

Combination of ketogenic diet and stiripentol for super-refractory status epilepticus: A case report

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Dear Editor,

Super-refractory status epilepticus (SRSE) is defined as status epilepticus (SE) that continues for at least 24 h after initiation of general anaesthetic medications, including cases in which SE recurs on reduction or withdrawal of anaesthesia [1]. Given the severity of SRSE, there is a critical need for new therapies to halt ongoing seizure activity. Because neuronal excitation is regulated by energy metabolism, SRSE can be suppressed by inhibiting metabolic pathways. A ketogenic diet (KD) has been proven to be effective in critically ill adults with SRSE [2]; however, the mechanisms by which KD prevents seizures remain unknown. It has recently been found that one of the mechanisms that KD works on is a metabolic pathway via lactate dehydrogenase (LDH) and that LDH may be inhibited by stiripentol (STP) [3]. Here, we report that a combination of KD and STP appeared to constitute effective treatment of a patient with SRSE underlying anti-*N*-methyl-D-aspartate receptor (NMDAR) encephalitis.

A 20-year-old Japanese woman presented with a week of headaches followed by impaired consciousness. On admission, she exhibited abnormal behaviours, including altered manner of speaking and shouting loudly. She was unable to follow commands and became unresponsive to external stimuli. An electroencephalogram (EEG) showed generalized rhythmic delta frequency activity at 1 Hz with superimposed, frontally predominant bursts of rhythmic beta frequency activity (extreme delta brushes) (Fig. 1(A-1)). Her cerebrospinal fluid demonstrated mild pleocytosis (74 cells per mm^3) with a slightly elevated IgG index (1.01). Glucose and protein concentrations were normal. She was diagnosed as having NMDAR encephalitis (positive anti-NMDAR antibody result) with bilateral ovarian teratomas (pelvic CT findings) (Fig. 1(B)). Her symptoms were not alleviated by bilateral ovariectomy and immunotherapy (plasma exchange, intravenous immunoglobulin at 400 mg/kg over 5 days and intravenous methylprednisolone at 1000 mg over 3 days). Additionally, her seizures were unresponsive to conventional antiepileptic drugs (AEDs) such as valproate, carbamazepine, phenytoin, clonazepam, phenobarbital, and levetiracetam. Further, these treatments repeatedly resulted in a generalized rash accompanied by fever, leukopenia, and acute hepatitis and they were accordingly ceased. Two cycles of temporal administration of general anaesthetic medications such as midazolam, propofol, and thiamylal were simultaneously initiated to suppress her epileptic activities. After approved multiple drugs for SRSE treatment had failed to control her seizures, she was treated with a KD to avoid the adverse effects of the AEDs. Although she tolerated the KD, her SE continued to occur. After commencing the KD, we additionally administered STP as an off-label treatment (Approval number: 41-16-0004, Institutional review board of Nagoya City University) to support the KD. Because of a concern about adverse effects, we started with a low dose of STP (500 mg/day) and increased it gradually, taking two months to reach a maintenance dose (2500 mg/day) and stop the SE; her EEG showed attenuation of status activity followed by resolution (Fig. 1(A-2)).

Epileptic seizures result from excessive and abnormal neuronal activity in the brain. AEDs are thought to act on ion channels that generate action potentials, or neurotransmitter receptors that control synaptic transmission. Nevertheless, clinically available AEDs are ineffective in one-third of patients with epilepsy [4]. A KD, a high-fat, low-carbohydrate diet that can also be administered intravenously [5], is well-known as an effective treatment for adult patients with SRSE [2]. However, the mechanisms by which KD achieves suppression of seizures remain unclear. The following mechanisms have been proposed [6]: (1) increased gamma aminobutyric acid synthesis; (2) increased adenosine-mediated neuronal inhibition; (3) reduced synaptic glutamate release; and (4) inhibition of a metabolic pathway via LDH, a component of the astrocyte-neuron lactate shuttle (Fig. 1(C)) [7]. It has recently been reported that LDH inhibition suppresses seizures in vivo in a mouse model of epilepsy and that STP, a previously unknown LDH inhibitor, could potentially have an antiepileptic action, inhibition of LDH being a key aspect of KD [3].

In our patient, the adverse effects of repeated rashes necessitated cessation of treatment with conventional AEDs. We therefore instituted a KD to treat our patient's SE. To promote cessation of SE, we also administered STP because it is reportedly safe [8] and efficacious in controlling seizure activity in patients with SRSE [9] or Dravet syndrome [10]. In patients with SRSE who cannot tolerate conventional AEDs because of severe adverse effects, a combination therapy of KD and STP may be effective. It is possible that a key anti-seizure mechanism responsible for the clinical response may be inhibition of LDH, something that both KD and STP have been shown to exert [3].

The major limitations of this paper are that it is a retrospective case report of treatment administered after adjunctive surgical, immunotherapeutic and multiple AEDs treatment. We therefore cannot exclude the possibility that delayed effects of these previous interventions led to the observed clinical improvement and seizure cessation. Further, the cessation of SE may have partially reflected the natural history of NMDAR encephalitis.

However, we know that continuous neuronal hyperexcitability associated with seizures may exacerbate them and make them

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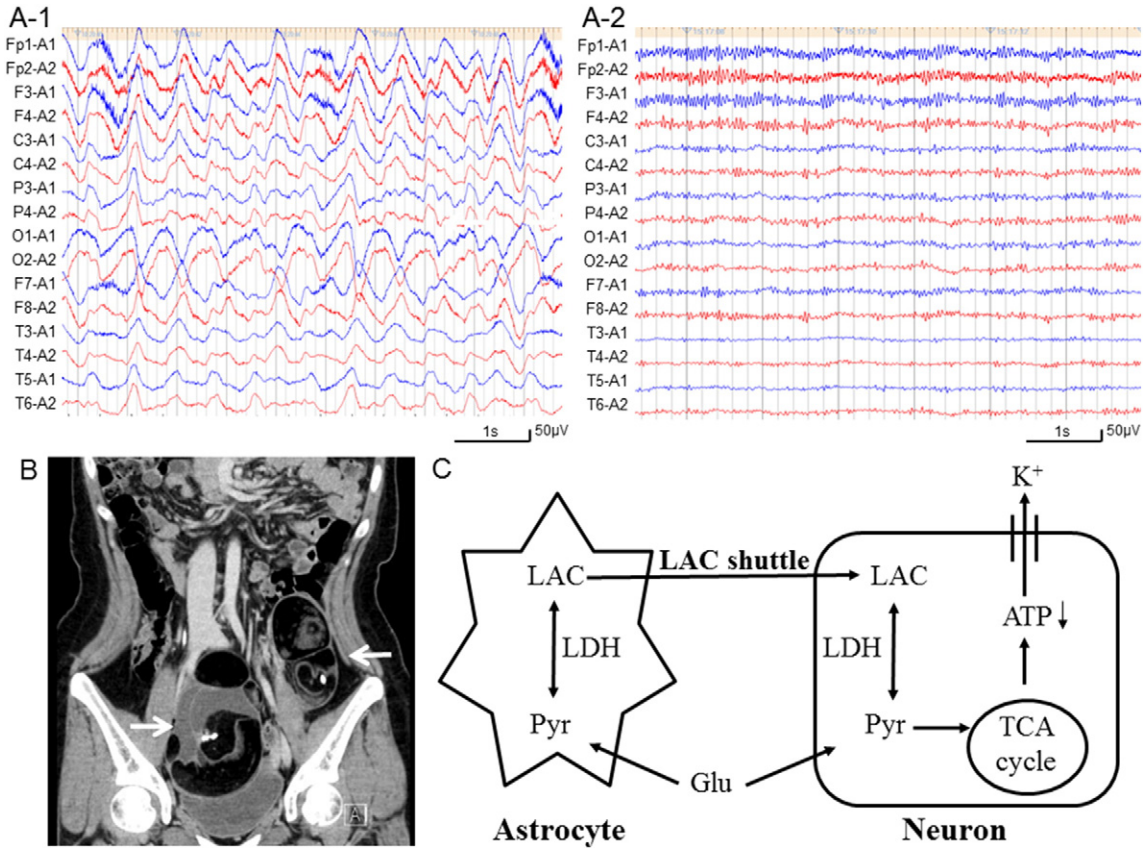

Fig. 1. Consecutive electroencephalogram and imaging finding in a 20-year-old woman with super-refractory status epilepticus caused by anti-*N*-methyl-D-aspartate receptor encephalitis and schema of the astrocyte-to-neuron lactate shuttle. (A-1) Initial EEG tracing showing generalized rhythmic delta frequency activity at 1 Hz with superimposed, frontally predominant bursts of rhythmic beta frequency activity (extreme delta brushes). (A-2) Two months after treatment with KD and STP, the extreme delta brush pattern has resolved and background EEG activity has largely normalized. (B) Coronal reconstruction, CT scan of the pelvis shows bilateral ovarian cysts with small calcifications (*arrows*). (C) Glucose is provided to astrocytes via glycogen breakdown. Pyruvate (Pyr), the end product of glycolysis, is then converted to lactate (LAC) by lactate dehydrogenase (LDH). LAC is shuttled from astrocytes to neurons. Once inside neurons, LAC is again converted by LDH to Pyr, which then enters mitochondria, to feed into the tricarboxylic acid (TCA) cycle. Adenosine triphosphate (ATP) is produced and released into the cytosolic compartment. High ATP levels inhibit ATP-sensitive potassium (KATP) channels on the plasma membrane, whereas low ATP concentrations activate these channels and lead to efflux of positively charged potassium ions, thereby hyperpolarizing the neuronal-cell membrane and inhibiting neuronal discharge. Within this pathway, LDH inhibition highly activates KATP channel by ultimately decreasing ATP production and rendering neurons less excitable.

more refractory. When there are no tolerable conventional AEDs for SRSE patients, a combination of KD and STP may, in part, play a role achieving a normal status. Prospective trials are warranted to confirm the efficacy and safety of this regimen for patients with SRSE.

Conflicts of interest

The authors declare that they have no conflicts of interest.

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