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Case Report

A case of succinic semialdehyde dehydrogenase deficiency with status epilepticus and rapid regression

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Abstract

Background: Clinical phenotypic expression of SSADH deficiency is highly heterogeneous, and some infants may develop refractory secondary generalized seizures.

Patient: A 9-month-old boy manifested partial seizures, developing severe status epilepticus, and conventional antiepileptic drugs were ineffective. Use of ketamine contributed to the control of status epilepticus, achieving a reduction in frequency of partial seizures, and improving EEG findings without apparent complications. Diffusion-weighted images showed hyperintensities in the bilateral basal ganglia and fornix, and multiple T2 hyperintensity lesions were detected. ^{123}I-iomazenil (IMZ) SPECT revealed a decrease in binding of ^{123}I-iomazenil predominantly in the left temporal region by the 18th day of hospitalization. However, repeated IMZ-SPECT on the 46th day of hospitalization demonstrated almost no accumulation across a broad region, sparing the left temporal region. The patient showed rapid regression, refractory myoclonus, and severe progressive brain atrophy.

Conclusion: IMZ-SPECT findings demonstrated reduced benzodiazepine receptor binding and its dynamic changes in an SSADH-deficient patient. Considering the down regulation of the $GABA_A$ receptor, ketamine should be included in pharmacotherapeutic strategies for treatment of refractory status epilepticus in SSADH-deficient patients.

Keywords: SSADH deficiency; Refractory status epilepticus; Ketamine; ^{123}4-Hydroxybutyric aciduria; Gamma-hydroxybutyric aciduria

1. Introduction

Succinic semialdehyde dehydrogenase (SSADH) deficiency is an autosomal recessive disorder of the γ-aminobutyric acid (GABA) metabolic pathway, having considerable phenotypic heterogeneity. The SSADH gene (*ALDH5A1*) has been mapped on chromosome 6p22. Both GABA and 4-hydroxybutyrate (GHB) accumulate in the absence of SSADH. Major clinical manifestations include developmental delay, hypotonia, ataxia, and seizures, and are typically non-progressive. Approximately 10% of patients have a progressive course featuring developmental regression and substantial extrapyramidal manifestations, including dystonia, choreoathetosis, and myoclonus [1–3]. $GABA_A$ receptor down regulation was previously demonstrated as one pathophysiological mechanism

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underlying this disorder by using (11C) flumazenil positron emission tomography (FMZ-PET) [4].

Here, we describe a patient with a severe SSADH deficiency who showed status epilepticus (SE) and rapid regression. We also present atypical MRI and ^{123}I-iomazenil (IMZ) SPECT findings observed in this patient.

2. Patient report

The patient was a 9-month-old boy who had no family history of epilepsy, developmental delay, or sudden death. At 2 months of age, it had been noticed that the patient showed paroxysmal elevation in both upper limbs, concomitant ocular deviation, and facial flushing for about 2–3 min. At 9 months of age, his head control was insufficient and he displayed mild hypotonia. In the same month, the patient was admitted twice in one week due to status epilepticus related to fever. Both seizures were secondary generalized tonic–clonic seizures (sGTCs) that spread from the right upper limb, lasted 35–45 min, and ceased by intravenous administration of midazolam. Routine assays of blood and cerebrospinal fluid and head CT were unremarkable. Virus surveillance including human herpes virus 6 in serum was negative. However, on the seventh day of hospitalization, the patient showed irritability and a tonic posture of the left upper limbs. On the tenth day of hospitalization, the patient developed twitching on the right side of his face, and clonic convulsion of the right upper limb with tachycardia. Clusters of partial seizures with occasional generalization were observed 13 days after admission. Ictal electroencephalography (EEG) revealed that the seizure activity originated from the left temporal region, and spread into the left hemisphere. The basic rhythm was disorganized with frequent slow waves of high voltage, sharp waves, and spikes, predominantly in the left hemisphere. Treatment with continuous intravenous administration of midazolam, bolus infusion of fos-phenytoin, steroid pulse therapy of 30 mg/kg/day methylprednisolone for 3 days, and initiation of levetiracetam were not effective, and the seizures recurred every 20–30 min, lasting 5–10 min. On the 14th day of hospitalization, the patient showed SE (Fig. 2). Intravenous ketamine therapy was initiated after informed consent was obtained from his family. The seizures discontinued after 1 mg/kg/dose bolus infusion of ketamine, and EEG showed a burst-suppression pattern. Continuous intravenous administration of ketamine at 2 mg/kg/dose showed significant efficacy. Brief, partial

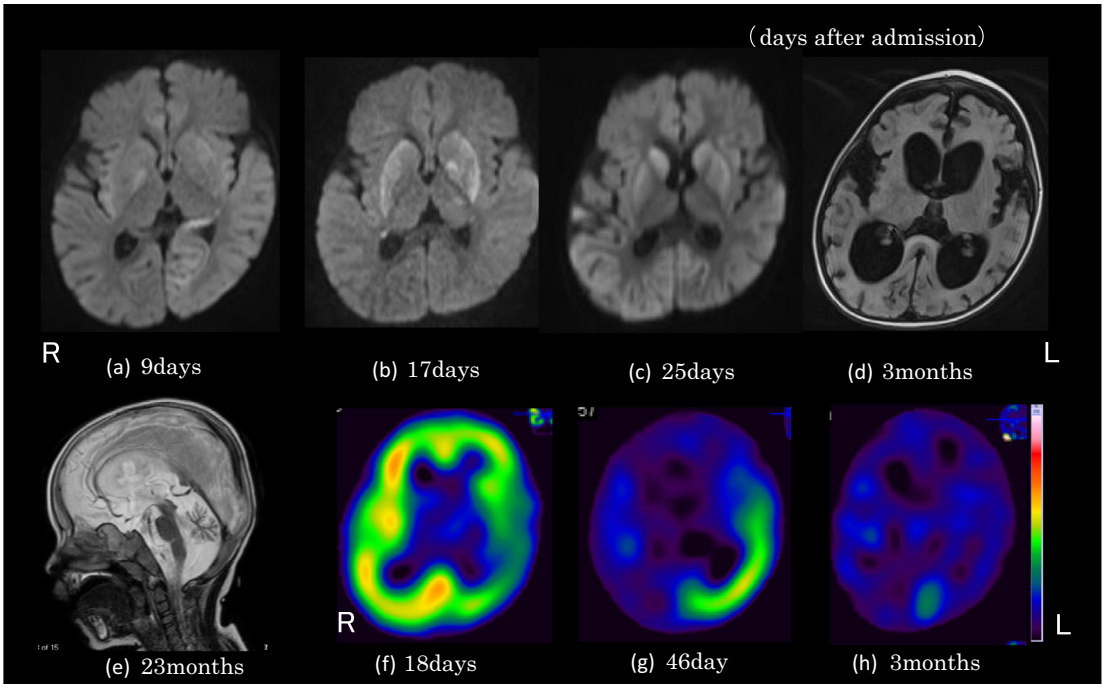

Fig. 1. (a) DWI image of head MRI on the 9th day after admission shows high intensities in the right insular cortex, right globus pallidus, a part of the bilateral hippocampus, bilateral fornix, left caudate nucleus, and left occipital gray matter. (b) DWI image on the 17th day after admission shows high intensity regions in the bilateral basal ganglia. (c) DWI image on the 25th day after admission. The high intensities previously observed in the basal ganglia are weaker, but are detected in broad regions throughout the cerebral cortex. (d) FLAIR image 3 months after admission. Severe cerebral atrophy is observed. (e) T2-weighed image. Cerebellar atrophy was manifested at 23 months of age. (f) IMZ-SPECT shows a decrease in binding of ^{123}I-iomazenil predominantly in the left temporal region on the 18th day of hospitalization. (g) Repeated IMZ-SPECT on the 46th day of hospitalization demonstrates almost no accumulation across a broad region, sparing the left temporal region. (h) Three months after admission, almost no reactivity is observed in the cerebrum.