Ketogenic diet therapy is effective in encephalitis with refractory seizures

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Objective and importance: Although ketogenic diet therapy is effective in refractory seizures in childhood, its effect on adult encephalitis with similar refractory seizures and prolonged encephalopathy has not been well reported.
Clinical presentation: We report here a case of a 22-year-old man with acute encephalitis with refractory repetitive partial seizures (AERRPS).
Intervention: Partial seizures of the face developed to repeated generalized convulsions, which were refractory against anti-epileptic drugs and a high dose of propofol. After struggling for 9 months, he dramatically recovered after ketogenic diet therapy.
Conclusion: Ketogenic diet therapy may be an important tool to help cure AERRPS.

Keywords: AERRPS, Encephalitis, SPECT with ^{123}I-iomazenil, Ketogenic diet therapy, Refractory seizures

Introduction

Some types of encephalitis and encephalopathy cause refractory seizures. Several different names for this condition have been proposed in case reports and series of children and adults, but cases were introduced as new entities, despite their similarities. These names include de novo cryptogenic refractory multifocal febrile status epilepticus, idiopathic catastrophic epileptic encephalopathy, new-onset refractory status epilepticus, severe refractory status epileptics owing to presumed encephalitis, devastating epilepsy in school-age children, acute non-herpetic encephalitis with refractory repetitive partial seizures, acute encephalitis with refractory repetitive partial seizures (AERRPS), fever-induced refractory epileptic encephalopathy syndrome, and fever-induced refractory epileptic encephalopathy.[1–9] Differential diagnosis between different types of encephalitis started by fever and refractory epilepsy is still controversial. The mechanism of encephalitis and encephalopathy is still unknown, and most of the prognoses are poor.[10–12] In all cases, status epilepticus was refractory to all attempted anticonvulsants. A ketogenic diet was attempted in a few cases, including ours, as a last resort. Nabbout *et al.* investigated the effect of a ketogenic diet (4 : 1 fat/protein and carbohydrate ratio) in nine patients in whom seven responded within 2–4 days.[9] Earlier attempts to use a ketogenic diet were reported in two patients with devastating epilepsy in school-age children, with one becoming seizure-free within 2 days.[5] We report here an adult case who dramatically recovered by ketogenic diet therapy after a long refractory course.

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Methods

We initiated ketogenic diet therapy to a man with AERRPS who suffered from refractory seizures against high dose of anti-epileptic drug combination therapy.

Results

A 22-year-old healthy man had a fever at 38.0°C and a headache. Two days later, he received loxoprofen sodium hydrate for the symptoms, which reduced his fever on the next day. However, he became euphoric and developed generalized convulsions 5 days after the onset. He was admitted to a local hospital and anti-epileptic drugs, such as sodium valproate (1200 mg/day orally), phenytoin (500 mg/day intravenously), and phenobarbital sodium (500 mg/day intravenously) were initiated. However, generalized convulsions became frequent. Therefore, he was transferred to our hospital 7 days after the onset of symptoms. He had no previous history of seizures, and a family history was not contributory.

A physical examination 7 days after the onset of symptoms showed bilateral superficial cervical and inguinal lymphadenopathy, which was soft, smooth,

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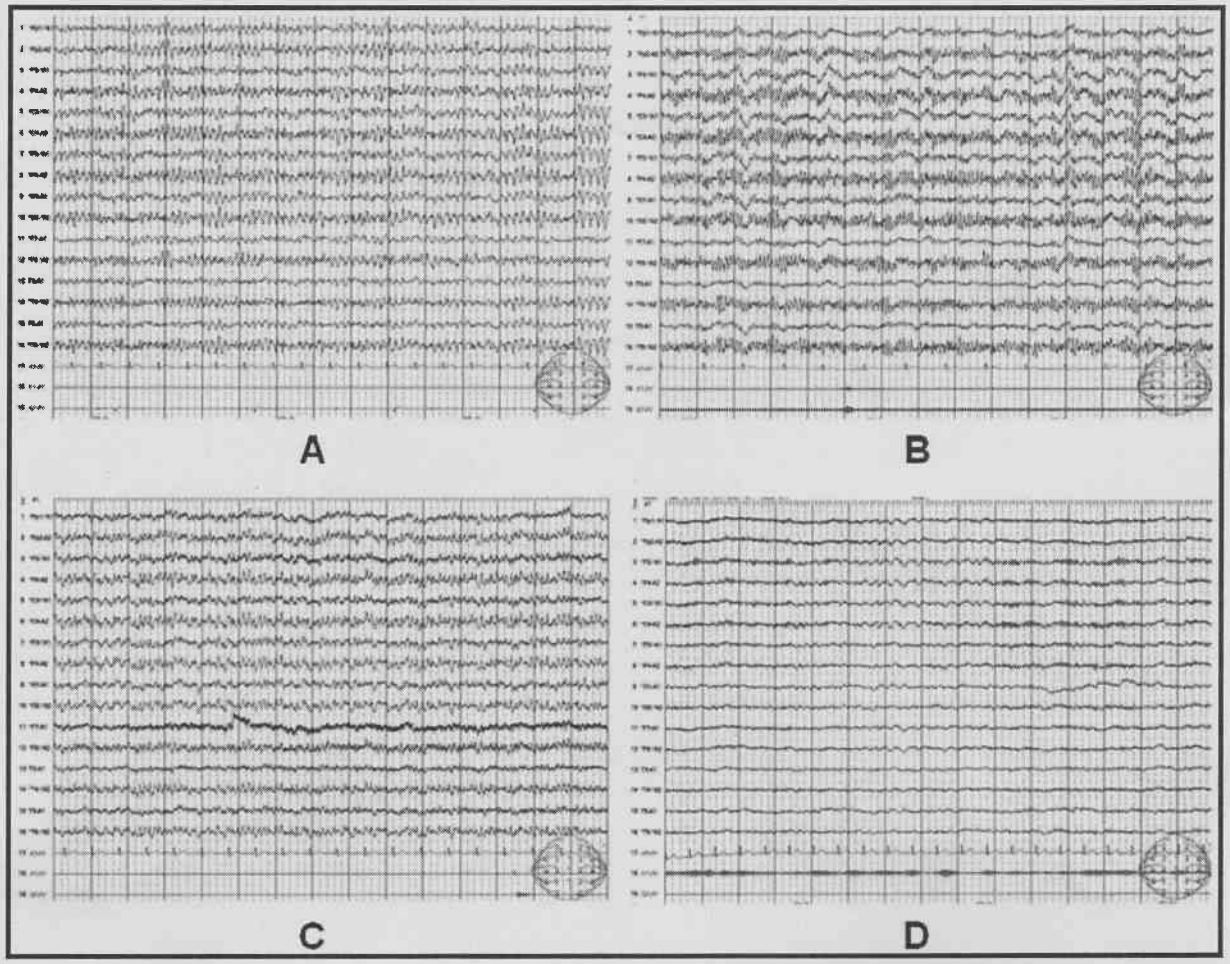

Figure 1 (A) EEG on day 12 showing bursts of epileptic discharges with a slow delta wave with ictal remissions, under anti-epileptic drugs of sodium valproate (1200 mg/day) and levetiracetam (2000 mg/day). (B) Non-convulsive status epilepticus continued under propofol (5 mg/kg/h) and mechanical ventilation on day 16. (C) Non-convulsive status epilepticus continued on day 148 before ketogenic diet therapy. (D) Epileptic discharge disappeared 25 days after ketogenic diet therapy on day 180.

and the size of a soy bean. His consciousness was stupor with a Glasgow coma scale score of 10 (E3V2M5). His extremities were flaccid and he had hyporeflexia without a pathological reflex. Nuchal rigidity or Kernig sign was not apparent. Laboratory examination showed elevated levels of C-reactive protein (1.61 mg/dl), creatine kinase (24,650 IU/ml), myoglobin (4290 ng/ml), and L-aspartate aminotransferase (200 IU/l). Bilateral superficial cervical and inguinal lymph nodes became normal in size and the levels of creatine kinase, myoglobin, and L-aspartate aminotransferase returned to the normal range after 16 days. Kidney function, blood sugar, vitamins, soluble interleukin-2 receptor, and plasma ammonia levels were otherwise normal. Serum antibodies against herpes simplex virus, cytomegalovirus, Epstein–Barr virus, *M. pneumoniae*, and Japanese encephalitis virus were negative. Autoantibodies, such as antinuclear antibodies, rheumatoid factor, anti-Sm, anti-SS-A, anti-SS-B, and anti-cardiolipin, were also negative. Free triiodothyronine and thyroxine levels were decreased to 0.58 pg/ml and 0.31 ng/dl, respectively, 129 days after the onset of symptoms, even though he received 175 μg/day dried thyroid. Thyroid-stimulating hormone was increased to 89.32 μU/ml, although antibodies to the thyroid, such as antithyroglobulin antibody, were normal. Blood gas analysis showed normal values at the awake supine position. A chest X-ray and electrocardiogram were normal. An electroencephalogram (EEG) showed bursts of epileptiform discharges replaced by a slow delta wave with ictal remissions (Fig. 1A). Magnetic resonance imaging (MRI) of the early clinical phase (day 9) was unremarkable (Fig. 2A and D). Single photon emission computed tomography (SPECT) with ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) showed a decrease in right anterior cerebrocortical and left cerebellocortical blood flow (Fig. 2G). SPECT with ^{123}I-iomazenil showed a decrease in ^{123}I-iomazenil uptake in the right temporal and parietal lobe on day 12 (Fig. 2H).

A lumbar puncture on the first hospital day showed a slightly elevated cell count (9/μl; monocytes: 100%), protein (42 mg/dl), sugar (79 mg/dl), lactic acid (14.6 mg/dl), and pyruvic acid (1.0 mg/dl).

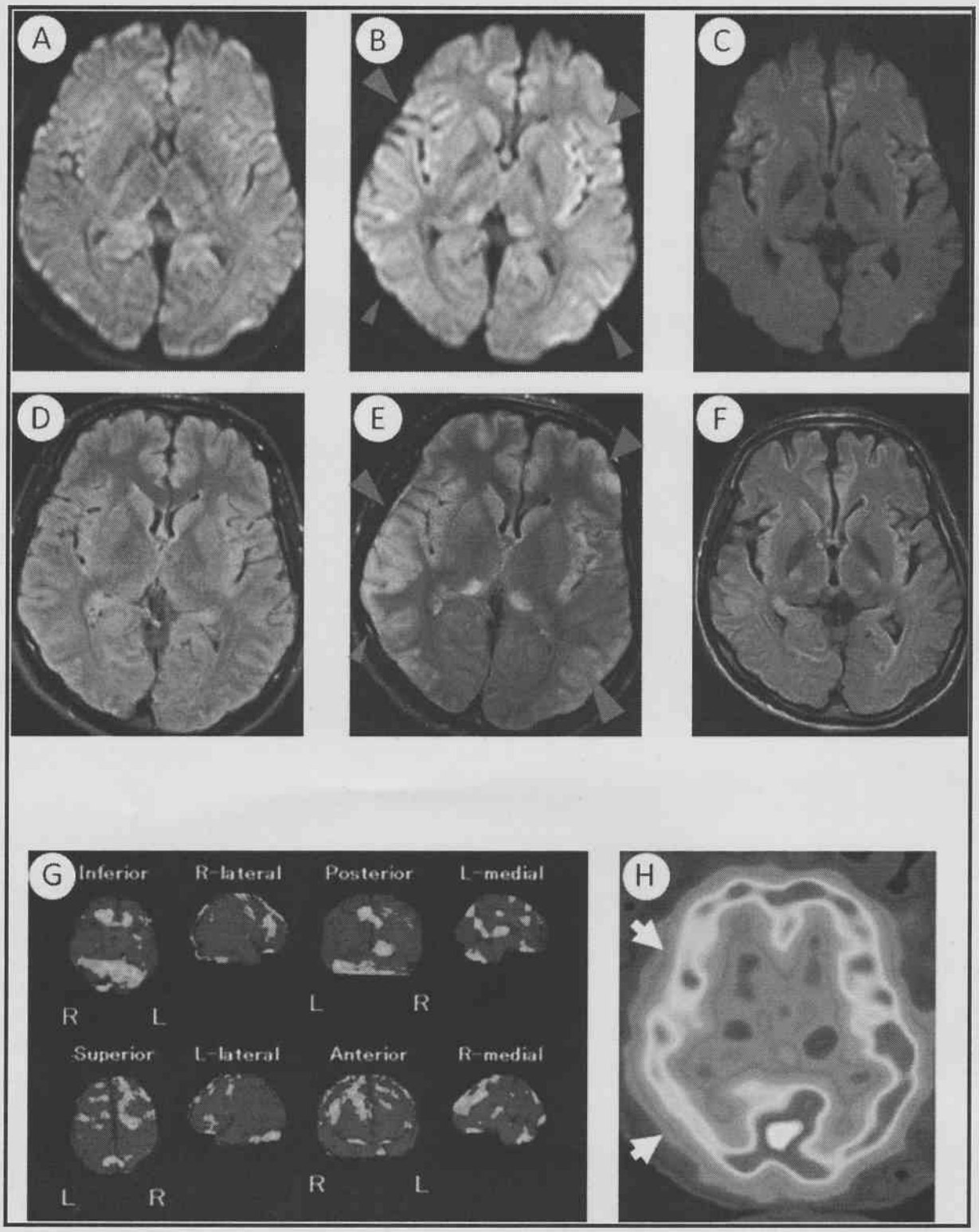

Figure 2 Axial diffusion-weighted (DW) images at 9 (A), 72 (B), and 271 (C) days of onset. Axial fluid attenuated inversion recovery (FLAIR) MR images at 9 (D), 72 (E), and 271 (F) days of onset. Note that there are no remarkable findings in (A) and (D), but high signal intensity is present in the cortex of bilateral anterior, temporal, and parietal lobes in DW (B) and FLAIR (E) images at 72 days (arrowheads). MRI abnormalities disappeared at 271 days of onset (C, F) 116 days after initiating ketogenic therapy. (G) ^{99m}Tc-ECD SPECT showing a decrease in right anterior cerebrocortical and left cerebellocortical blood flow in eZIS analysis at 10 days of onset. (H) SPECT with ^{123}I-iomazenil showing a decrease in ^{123}I-iomazenil uptake in the right temporal and parietal lobes at 12 days of onset (arrows).

Oligoclonal banding or myelin basic protein in the cerebrospinal fluid (CSF) was negative. Bacterial and viral cultures of the CSF were negative. Real-time polymerase chain reaction of the herpes simplex virus in the CSF was negative. The interleukin-6 level in the CSF was 80.4 pg/ml. Cytodiagnosis of CSF cells was

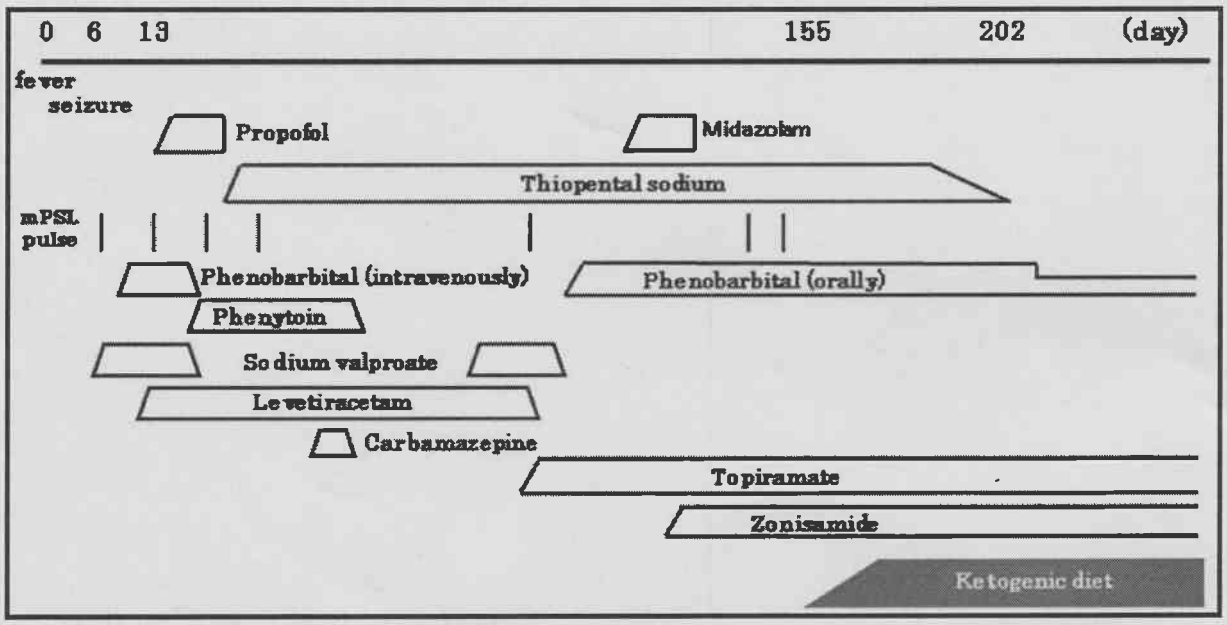

Figure 3 Summary of the clinical course of the case.

class II. The histocompatibility locus antigen haplotypes were A2, A11, B39, and B54. Anti-GluRepsilon2 and delta2 antibodies were negative in the serum and CSF. Serum anti-NH2 terminal of alpha-enolase antibody, anti-ganglioside antibodies, and voltage-gated potassium channel antibodies were negative. Enteroviral cultures from the throat and stool were negative. A muscle biopsy of the left vastus medialis was performed only to show disuse atrophy on day 115.

Although the reason for the seizures was uncertain, we induced propofol up to 5 mg/kg/h under mechanical ventilation to achieve complete control of seizure activity on days 13–18. However, non-convulsive status epilepticus continued and we could not control the seizures by propofol (Fig. 1B). Partial seizures from the face developed into repeated generalized convulsions and these were refractory against anti-epileptic drugs. Therefore, we diagnosed this patient with AERRPS, and thiopental sodium was initiated up to 5 mg/kg/h from day 19, which allowed burst suppression to appear from day 20. However, secession of thiopental sodium was difficult because the generalized convulsions appeared when the thiopental sodium was withdrawn. Anti-epileptic drugs, such as sodium valproate (1200 mg/day), phenytoin (300 mg/day), carbamazepine (200 mg/day), phenobarbital (240 mg/day), levetiracetam (2000 mg/day), and topiramate (600 mg/day) were used as combination therapy. We had to stop giving carbamazepine because of a rash as a side effect. Although blood levels of anti-epileptic drugs were sufficiently elevated (74.0 μg/ml of sodium valproate, 20.9 μg/ml of phenytoin, 26.9 μg/ml of phenobarbital, and 13.3 μg/ml of topiramate), they could not suppress the generalized convulsions. Methylprednisolone pulse therapy (1000 mg/day) was performed seven times at days 6, 13, 20, 27, 90, 136, and 143, but there was no effect. Moreover, signal abnormalities on diffusion weighted images of MRI became evident in cortices of bilateral anterior, temporal, and parietal lobes 72 days after the onset of symptoms (Fig. 2D and E). Bilateral femoral vein thrombosis as a side effect of chronic use of thiopental sodium was detected by contrast computed tomography on day 134. We did not perform intravenous immunoglobulin therapy because of thrombotic tendency and expected that it would be difficult to continue thiopental sodium because of side effects. We decided to initiate ketogenic diet therapy from 155 days after the onset of symptoms (Fig. 3). Epileptic discharge then disappeared on the EEG 180 days after the onset of symptoms (Fig. 1C and D), and generalized convulsions also disappeared without thiopental sodium 202 days after the onset of symptoms. With continuation of ketogenic diet therapy, the patient dramatically recovered and became able to speak his name 260 days after the onset of symptoms. His cognitive function continued to improve and a mini-mental state examination score was elevated to 17/30 and the frontal assessment battery value was elevated to 8/18 282 days after the onset of symptoms. Although several anti-epileptic drugs were gradually decreased, seizures did not recur. Signal abnormalities of MRI disappeared 271 days after the onset of symptoms (Fig. 2C and F). He was transferred to another hospital for rehabilitation 310 days after the onset of symptoms and planned to go home.

Discussion

We experienced a patient who suffered refractory seizures against anti-epileptic drugs without thiopen-

tal sodium, in whom this side effect was nearly fatal. Although several anti-epileptic drugs, including the maximum permissible dose of propofol and midazolam, could not suppress the convulsions, EEG improved 18 days after initiation of ketogenic digestion therapy. Ketogenic diet therapy has been reported to be effective in some cases of childhood epilepsy.[9,13,14] Although the mechanism of ketogenic diet therapy is not completely understood, there are some hypotheses. Ketogenic diet may control seizures by handling of glutamate. Ketonic acids change brain astrocyte metabolism and enhance conversion of glutamate to glutamine. As a result, there is more efficient conversion of glutamine to gamma-aminobutyric acid, which is the major inhibitory neurotransmitter produced.[15] Another hypothesis is that ketogenic diet therapy involves ATP-sensitive potassium channel modulation and increases gamma-aminobutyric acid.[16] In addition, a possible mechanism of ketogenic diet therapy is neuroprotection by changes in mitochondrial density or it has anticonvulsant effects by inhabitation of mammalian target of rapamycin pathway signaling.[17,18] Several mechanisms may overlap in ketogenic diet therapy.[19] We believe that the unique mechanisms of ketogenic diet therapy, which are different from anti-epileptic drugs, were effective for our patient. Although ketogenic diet therapy was induced 155 days after the onset of encephalitis and encephalopathy with refractory seizures, the present patient was rescued and his cognitive function is still recovering. Ketogenic diet therapy may be the most effective treatment in adult onset or the late phase of encephalitis and encephalopathy with refractory seizures.

Disclaimer Statements

Contributors Koji Abe is corresponding authour. Kosuke Matsuzono was contributing for researching the effect and analysis. Tomoko Kurata, Shoko Deguchi, Toru Yamashita, and Kentaro Deguchi were contributing for advising for paper and analysis.

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Conflicts of interest The authors report no conflicts of interest.

Ethics approval Our manuscript was Case Reports and we got informed consent belonging to the Declaration of Helsinki.

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