Therapeutic Hypothermia for Refractory Status Epilepticus in a Child with Malignant Migrating Partial Seizures of Infancy and *SCN1A* Mutation: A Case Report

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Status epilepticus (SE) is a common indication for neurocritical care and can be refractory to standard measures. Refractory SE (RSE) is associated with high morbidity and mortality. Unconventional therapies may be utilized in certain cases, including therapeutic hypothermia (TH), bumetanide, and the ketogenic diet. However, the literature describing the use of such therapies in RSE is limited. Details of a case of TH for RSE in an infant with malignant migrating partial seizures of infancy were obtained from the medical record. A 4-month-old child developed SE that was refractory to treatment with concurrent midazolam, phenobarbital, fosphenytoin, topiramate, levetiracetam, folinic acid, and pyridoxal-5-phosphate. This led to progressive implementation of three unconventional therapies: TH, bumetanide, and the ketogentic diet. Electrographic seizures ceased for the entirety of a 43-hour period of TH with a target rectal temperature of 33.0°C–34.0°C. No adverse effects of hypothermia were noted other than a single episode of asymptomatic hypokalemia. Seizures recurred 10 hours after rewarming was begun and did not abate with reinstitution of hypothermia. No effect was seen with administration of bumetanide. Seizures were controlled long-term within 48 hours of institution of the ketogenic diet. TH and the ketogenic diet may be effective for treating RSE in children.

Introduction

STATUS EPILEPTICUS (SE) is defined as a seizure greater than 5–30 minutes or multiple sequential seizures without full recovery of consciousness (Riviello *et al.*, 2006; Brophy *et al.*, 2012). SE has an incidence between 135.2 and 156 per 100,000 infants (DeLorenzo *et al.*, 1996; Hesdorffer *et al.*, 1998) and is refractory to usual care in 37%–70% of cases (Brevoord *et al.*, 2005; Lewena and Young, 2006). Children with refractory SE (RSE) have a reported mortality rate of 16%–32% (Gilbert *et al.*, 1999; Sahin *et al.*, 2001). The youngest children have the greatest morbidity and mortality (Maytal *et al.*, 1989; Sahin *et al.*, 2001).

Recently published expert guidelines for the treatment of SE recommend stepwise administration of benzodiazepines and individual antiepileptic drugs (AEDs), culminating in continuous infusion of midazolam, propofol, or barbiturates for RSE (Brophy *et al.*, 2012). In cases where these extraordinary measures to control RSE are ineffective, more innovative therapies have been used. Therapeutic hypothermia (TH) has been described as a successful treatment for RSE in a small number of case reports (Vastola *et al.*, 1969; Orlowski *et al.*,

1984; Corry *et al.*, 2008; Elting *et al.*, 2010), as have bumetanide (Kahle *et al.*, 2009) and the ketogenic diet (Abend and Dlugos, 2008).

We describe the use of TH, bumetanide, and the ketogenic diet for RSE in an infant ultimately diagnosed with malignant migrating partial seizures of infancy (MMPSI), a recently described epilepsy syndrome often associated with a poor outcome (Coppola, 2009).

Case Report

A 4-month-old boy was admitted to our institution for convulsive RSE. He presented to a local Emergency Room with 2 days of rhinorrhea, cough, vomiting, and diarrhea, and 30 minutes of continuous generalized tonic–clonic seizure activity. There, he was afebrile (35.6°C), tachycardic (163 beats/min), and hypertensive (113/64 mmHg). Resuscitation was begun with administration of oxygen via a facemask (SaO2 < 70% with FiO2 = 0.21 upon arrival). Laboratory assessments demonstrated serum sodium = 134 mM and serum glucose = 125 mg/dL. In a stepwise manner, the patient was given diazepam (0.25 mg/kg rectally), lorazepam (0.2 mg/kg

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intravenously), fosphenytoin (30 mg/kg phenytoin equivalents intravenously), and midazolam (0.2 mg/kg intravenously). He was endotracheally intubated due to a decreased level of consciousness. During transport to our hospital, continued clinical seizures were treated with phenobarbital (40 mg/kg intravenously) and levetiracetam (40 mg/kg intravenously).

Past medical history was notable for a normal gestation and full-term delivery. Family history was unremarkable. At 1 month of life, he developed abnormal movements of the extremities; an magnetic resonance imaging (MRI) and electroencephalogram (EEG) at another facility at that time were reportedly normal. Further episodes led to an admission to our institution at 3 months of age during which our work-up
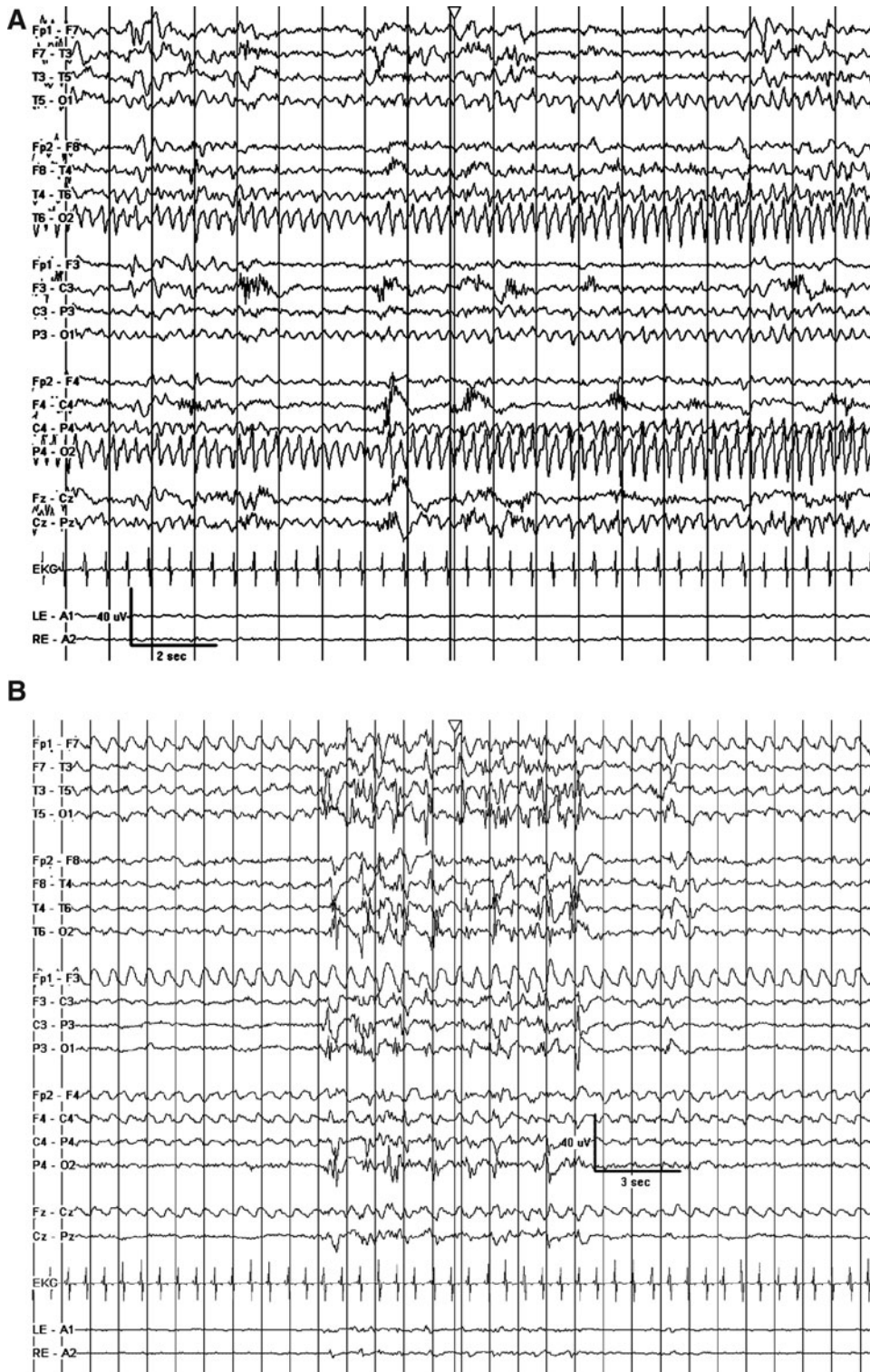

FIG. 1. (A) Prolonged seizures arising out of the right occipital lobe despite maximal conventional antiepileptic drug (AED) therapy. (B) Marked attenuation and quasi-burst suppression pattern achieved with hypothermia (TH1). (C) Ongoing left temporal seizures after rewarming despite addition of bumetanide and ongoing maximal conventional AED therapy. (D) Control of seizures and improvement in background after initiation of the ketogenic diet.
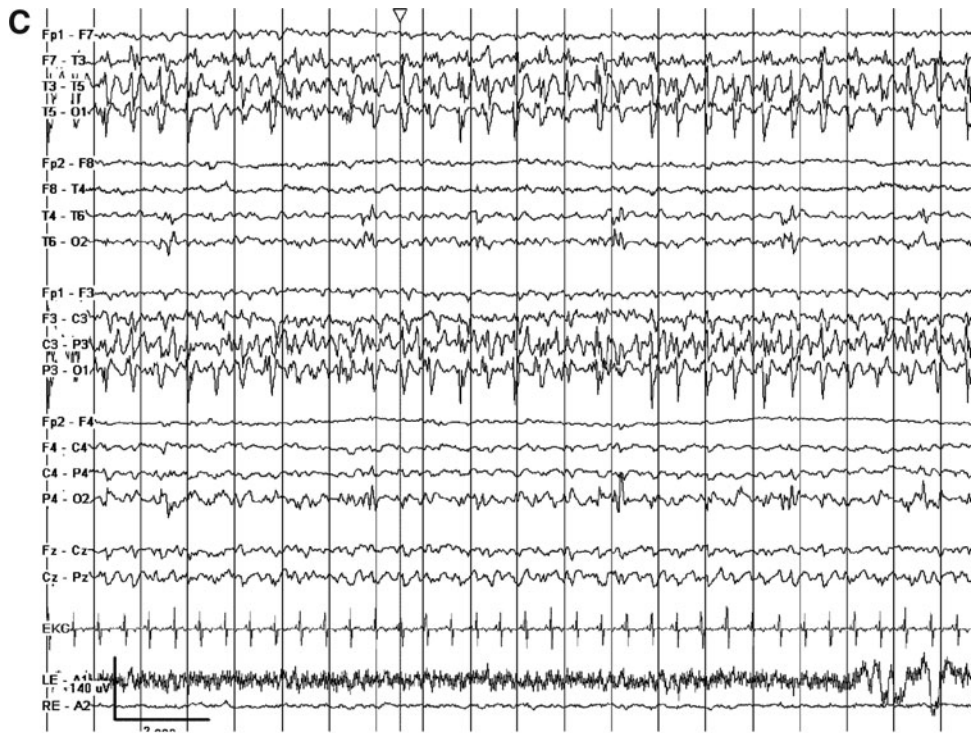
FIG. 1. (Continued).

was nondiagnostic, including a complete blood count (CBC), electrolytes (basic metabolic panel (BMP)), lactate, ammonia, serum amino acids (SAA), urine organic acids (UOA), and cerebral spinal fluid (CSF) studies (cell count, protein, glucose, Herpes Simplex Virus polymerase chain reaction [HSV PCR], and culture). At that time, an EEG showed frequent independent posterior multifocal sharp waves and bicentral sharp and slow waves. He was started on levetiracetam, had no seizures during hospitalization, and was discharged to home. Approximately 2 weeks later, he developed RSE.

Upon arrival in the Pediatric Intensive Care Unit, his physical examination was notable for tachycardia, hypertension, normoxia, and intermittent stiffening of his left upper extremity without generalized tonic–clonic movements. Admission work-up included a normal CT scan and normal/ nondiagnostic CBC, BMP, liver function tests, ammonia,

lactate, coagulation profile, urinalysis, urine drug screen, influenza by RNA, and respiratory syncytial virus. EEG upon admission revealed abundant multifocal spike waves and many prolonged seizures arising out of the right occipital lobe (Fig. 1A).

Intensive care included mechanical ventilation, broad-spectrum antimicrobials, maintenance of normal electrolyte levels, parenteral and enteral nutrition, and maintenance of euvolemia (requiring diuresis with furosemide). Further work-up revealed normal SAA, uric acid, thyrotropin, UOA, urine sulfite screen, chromosomes, oligoarray, very long chain fatty acids, *POLG1* genetic testing, and CSF studies (cell count, protein, glucose, lactate, pyruvate, amino acids, and HSV PCR). Brain MRI revealed only slightly prominent subarachnoid space. Cultures of blood, urine, CSF, and tracheal secretions grew no pathogenic organisms.

The patient continued to have clinical and electrographic seizures for several days despite escalating antiepileptic therapy. On hospital day #6, electrographic seizures arising out of both the right and left occipital lobes were nearly continuous despite treatment with midazolam [1.4 mg/(kg.h)], phenobarbital (serum level of 62.3 mcg/mL), fosphenytoin (free serum level of 2.0 mcg/mL), topiramate [10 mg/(kg.day)], levetiracetam [70 mg/(kg.day)], folinic acid [30 mg/(kg.day)], and pyridoxal-5-phosphate [30 mg/(kg.day)]. At this point, the clinical team began treatment with TH (first TH period, *TH1*). The patient was cooled with a servo-regulated cooling blanket and temperature regulation of the inhaled gas in the ventilator circuit to a target rectal temperature of 33.0°C–34.0°C. Goal temperature was reached within 90 minutes. Electrographic and clinical seizures were absent after the goal temperature was reached and remained absent for the 43 hours of *TH1* despite no adjustments in AED dosing. The EEG was markedly attenuated and consisted of a quasi-burst suppression pattern (Fig. 1B). The temperature was maintained within the target range for 35 of 43 hourly readings (6 were between 34.1°C–34.5°C and 2 were between 34.5°C–34.9°C). During *TH1*, there were no bleeding episodes, no new positive cultures, no electrolyte disturbances requiring treatment, and no hypotension requiring vasoactive medication. The only documented arrhythmia was sinus bradycardia, which had also been documented before initiation of TH.

Slow rewarming (by 0.5° every 2–4 hours) was begun from a rectal temperature of 34.0°C. After 10 hours, at a rectal temperature of 35.6°C, electrographic seizures were observed in both the right occipital lobe and the left temporal lobe. TH was reinstituted (*TH2*) by lowering the rectal temperature to 33°C–34°C and additional fosphenytoin was given with only a mild improvement in the seizure frequency. Bumetanide [0.1 mg/(kg.dose) every 8 hours intravenously] was administered with no significant change in the seizure pattern (Fig. 1C). Pentobarbital [2 mg/(kg.h)] stopped the seizure activity, though volume resuscitation and a norepinepherine infusion were required. During *TH2*, the patient required treatment with a single bolus of potassium chloride for a whole-blood potassium level of 2.3 mM; no other adverse events related to TH were noted. Seizures were absent for 24 hours at 34°C with burst-suppression of up to several minutes duration. The target temperature was raised by 1°C each day for 2 days, while the pentobarbital infusion was simultaneously weaned off; there were no breakthrough seizures requiring therapy.

However, 3 days after rewarming, clinical and electrographic seizures recurred (rectal temperature = 36.6°C). At this time, a ketogenic diet was initiated due to concerns that additional TH would have an adverse risk/benefit profile given its lack of obvious efficacy during *TH2*. Clinical and electrographic seizures were absent 48 hours later (Fig. 1D) and did not recur. Ultimately, *SCN1A* genetic testing revealed a mutation often associated with the Dravet syndrome. Nine months after hospital discharge, his therapeutic plan includes a ketogenic diet, levetiracetam, topiramate, and phenobarbital. He has had one episode of breakthrough seizures associated with a subtherapeutic serum topiramate level. His neurologic development is markedly delayed, with infrequent visual fixation, axial hypotonia, and absence of both rolling over and vocalization. The Institutional Review Board of the University of Pittsburgh exempts case reports from IRB review.

Discussion

We report the case of a child with SE due to MMPSI that was remarkably refractory to several conventional anticonvulsants. In this case, some efficacy was observed with two unconventional therapies, TH and a ketogenic diet. In contrast, no effect was seen with a third unconventional therapy, bumetanide.

Therapeutic hypothermia

TH has been shown in animal models of SE to treat seizures (Maeda *et al.*, 1999; Schmitt *et al.*, 2006) and attenuate epileptic neuronal damage (Liu *et al.*, 1993; Lundgren *et al.*, 1994; Takei *et al.*, 2004). Four published case series of systemic TH as a treatment for clinical RSE include a total of 13 patients, 12 of whom had improvement in their seizure frequency. Vastola *et al.* (1969) treated five adults with TH of 31°C–36.5°C for 11 hours–3 days (one treatment failure) and Corry *et al.* (2008) reported four adults treated with TH of 31°C–35°C for 20–61 hours. Elting *et al.* (2010) reported an infant treated with very mild TH of 36°C for 4 days. Three older children have been treated with TH of 30°C–31°C and concurrent barbiturate coma for 2–5 days (Orlowski *et al.*, 1984). Additionally, a case series of 25 patients with chronic intractable epilepsy treated with TH at 27°C–30°C (Sourek and Travnicek, 1970) reported moderate success and techniques to locally cool the brain have shown efficacy (Karkar *et al.*, 2002; Bagic *et al.*, 2008).

In our case, TH led to a total, although temporary, resolution of seizures. Before *TH1*, our patient was having near continuous electrographic seizures for at least 6 days. During *TH1*, he had zero clinical or electrographic seizures for the 43 hours when the target temperature was 33.0°C–34.0°C. At this level of TH, the risk of adverse events is lower than at the temperatures used in some previous series, and no adverse events related to TH were seen in our patient other than a single episode of asymptomatic hypokalemia during *TH2*. In comparison, all three children treated with TH of 30°C–31°C by Orlowski had hypotension requiring vasopressor administration. Similarly, significant adverse events (electrolyte abnormalities, increased coagulation times, thromboses, and urinary tract infections) occurred during TH in the only two patients reported by Corry with target temperatures of less than 33°C.

Given its dramatic effects during *TH1*, the absence of clear efficacy of TH during *TH2* was surprising. Metabolism of

AEDs may be altered by hypothermia. Serum levels of phenobarbital were similar during *TH1* (53.4–67.3 mcg/mL) and *TH2* (52.5–56.6 mcg/mL). Free phenytoin levels were within therapeutic range during *TH1* (1.4–2.2 mcg/mL), but were supra-therapeutic during *TH2* (2.6–3.3 mcg/mL). Phenytoin toxicity is a rare cause of seizures and may have contributed to the lack of efficacy of *TH2* (Osorio *et al.*, 1989). Additionally, previous studies report longer durations of TH before rewarming was initiated. It is possible that our patient may have had a better outcome if TH was continued longer, if rewarming was achieved more slowly, or if the ketogenic diet had been initiated during TH, and these options should be considered in future cases.

There are several possible mechanisms by which TH treats seizures. TH slows cerebral metabolism (Maeda *et al.*, 1999; Erecinska *et al.*, 2003), which may preserve energy stores. TH reduces neurotransmitter release (Volgushev *et al.*, 2004) and cerebral NO production (Takei *et al.*, 2004), and alters the function of cerebral ion channels (Volgushev *et al.*, 2000), effects which may explain the increased ictal latencies seen in animal models (Maeda *et al.*, 1999). TH may increase intracerebral concentration of AEDs by increasing blood–brain barrier permeability (Oztas and Kaya, 1994) and slowing AED metabolism (Hostler *et al.*, 2010). In a child with the Dravet syndrome, TH may be effective by preventing fevers, which can precipitate seizures in this disease. Further study is warranted to determine the mechanisms, efficacy, and safety profile of TH for RSE.

Bumetanide

Experimental and clinical evidence shows bumetanide, a loop diuretic, may augment GABAergic AEDs (i.e., barbiturates, benzodiazepines) in neonatal seizures. Mature neurons have a low intracellular Cl^- concentration, so opening of $GABA_A$-receptor-associated chloride channels causes membrane hyperpolarization via Cl^- influx. Immature neurons have increased intracellular chloride concentrations due to high levels of the Na-K-2Cl cotransporter (NKCC1). Therefore, opening of the $GABA_A$-receptor-associated chloride channels may depolarize membranes via Cl^- efflux, lowering the seizure threshold (Kahle *et al.*, 2009). Bumetanide, which inhibits NKCC1, has shown efficacy in an *in vitro* rat model of seizures (Dzhala *et al.*, 2008) and a case report of a neonate with bacterial meningitis (Kahle *et al.*, 2009). Possible reasons for lack of efficacy in our patient include a decreased concentration of neuronal NKCC1 by 4 months of age, the previous use of furosemide masking any effect of bumetanide, and seizures being more dependent on the sodium concentration than the chloride concentration in the presence of the abnormal *SCN1A*-encoded sodium channel.

Ketogenic diet

The ketogenic diet is a well-recognized treatment for chronic epilepsy that relies on the premise that conversion from glycolysis to ketosis allows for decreased glucose flux, increased cerebral energy reserves, and, ultimately, increased resistance to seizures in the ketotic brain. It is typically used to treat refractory generalized epilepsies and there are conflicting views as to its role in the treatment of partial epilepsies (Nordli and DeVivo, 2008). The ketogenic diet has efficacy in children with the Dravet syndrome (Caraballo, 2011; Nabbout

et al., 2011) and it appears to have been effective in this child with MMPSI and an *SCN1A* mutation, despite previous reports of limited efficacy in MMPSI (Coppola, 2009). Both the ketogenic diet and TH can increase cerebral energy stores and may work synergistically, though concurrent treatment was not used in our case. Interestingly, our patient had a clinical response to the ketogenic diet in 2 days, which is faster than the reported median time to first improvement of 5 days (Chin *et al.*, 2008).

Malignant migrating partial seizures of infancy

This report describes an infant with the clinical and electrophysiologic appearance of MMPSI, a recently described cryptogenic epilepsy syndrome that is now included in the International League against Epilepsy classification system (Engel, 2001). It was first reported in 1995 (Coppola *et al.*, 1995) and has now been reported in ~50 patients (Coppola, 2009). The typical natural history of this disorder is a period of sporadic partial seizures early in life that progresses to very frequent focal seizures during the first year of life. Seizures may remain localized, expand to contiguous regions, or secondarily generalize. Outcome and prognosis for these infants is generally quite poor, with severe mental retardation being the norm and many reports of deaths within the first year of life (Coppola, 2009). Seizures are often markedly resistant to treatment even with multiple concurrent AEDs (Coppola, 2009) and in our patient, unconventional neurocritical care therapies were required.

Conclusion

We describe the use of TH, bumetanide, and the ketogenic diet in a child with RSE from MMPSI and a sodium channelopathy. Though it is impossible to test therapeutic efficacy in a single clinical case, our patient's timeline suggests that TH may be effective acutely in treating RSE in children, including those with MMPSI and the Dravet syndrome, and the ketogenic diet may have sustained benefit. The potential interaction between the two therapies merits exploration.

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Disclosure Statement

The authors declare that no competing financial interests exist.

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