FULL-LENGTH ORIGINAL RESEARCH

Rapid and safe response to low-dose carbamazepine in neonatal epilepsy

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Summary

Objective: **To evaluate treatment responses in benign familial neonatal epilepsy (BFNE).**

Methods: **We recruited patients with BFNE through a multicenter international collaboration and reviewed electroclinical and genetic details, and treatment response. All patients were tested at minimum for mutations/deletions in the *KCNQ2, KCNQ3,* and *SCN2A* genes.**

Results: **Nineteen patients were included in this study. A family history of neonatal seizures was positive in 16 patients, and one additional patient had a family history of infantile seizures. Mutations or deletions of *KCNQ2* were found in 14, and of *KCNQ3* in 2, of the 19 patients. In all patients, seizures began at 2–5 days of life and occurred multiple times per day. Four patients developed status epilepticus. Seizures were focal, alternating between hemispheres, and characterized by asymmetric tonic posturing associated with apnea and desaturation, followed by unilateral or bilateral asynchronous clonic jerking. Twelve of 19 patients were treated with multiple medications prior to seizure cessation. Seventeen of (88%) 19 patients were seizure-free within hours of receiving oral carbamazepine (CBZ) or oxcarbazepine (OXC). Earlier initiation of CBZ was associated with shorter hospitalization ($p < 0.01$). No side effects of CBZ were reported. All patients had normal development and remain seizure-free at a mean follow-up period of 7.8 years (6 months–16 years).**

Significance: **This study provides evidence that CBZ is safe and rapidly effective in neonates with BFNE, even in status epilepticus. We propose that CBZ should be the drug of choice in benign familial neonatal seizures.**

KEY WORDS: **Benign familial neonatal epilepsy, Neonatal seizures, KCNQ2, KCNQ3, Carbamazepine, Oxcarbazepine.**

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Key Points

- BFNE presents with recurrent clusters of seizures or status epilepticus in the first days of life leading to prolonged hospitalization
- Seizures are focal and characterized by asymmetric tonic component alternating laterality, associated with apnea, and sometimes followed by asynchronous clonic jerking
- Seizures promptly respond to low-dose oral carbamazepine even in the setting of status epilepticus
- Early diagnosis and treatment with oral carbamazepine is associated with dramatically shortened hospitalization

Benign familial neonatal epilepsy (BFNE) is a rare autosomal-dominant condition with incomplete penetrance, characterized by brief recurrent seizures beginning in the first days of life. BFNE is associated in >80% of patients with mutation in *KCNQ2* or *KCNQ3*, which encode heteromers of a voltage-gated ion channel responsible for a subthreshold potassium current important in limiting neuronal excitability.[1] BFNE is termed "benign" to reflect that, in most affected individuals, seizures are limited to the first year of life and neurologic development is normal. Nevertheless, seizures may be difficult to control in the neonatal period, and patients are often treated with loading doses of intravenous antiepileptic drugs (AEDs), such as phenobarbital and benzodiazepines, which may necessitate cardiorespiratory support and lead to prolonged, un-necessary hospitalizations.[2] In addition, up to 25% of patients with BFNE develop epilepsy later in life, and this risk has been shown to correlate with the number of seizures in the neonatal period, potentially elevating the importance of early seizure control for outcome.[3]

Herein we present retrospective data on the response to AEDs in the neonatal period in a multicenter international cohort of patients with BFNE.

Methods

Patients diagnosed with BFNE were identified through an international collaboration involving four centers. Clinical information was obtained directly from the referring physicians. Electroclinical data were obtained from original video–electroencephalography (EEG) recordings. Status epilepticus (SE) was defined as recurrent seizures for >50% of 1–3 h of recording time.[4]

A pair of sisters, patients 10 and 11, have been reported previously.[5] Mutations and deletions were identified using GeneDx commercial arrays and Sanger sequencing as described previously.[5,6] Variants were queried against ExAC and 1000 Genome databases, and sorts intolerant from tolerant (SIFT) and Polyphen-2 software were used to determine in silico likelihood of pathogenicity.[7,8] The study was approved by the human research ethics committee of the University of California San Francisco (UCSF) Benioff Children's Hospital, and the Bambino Gesu Children's Hospital and Research Institute.

Results

Genetic findings

Sixteen patients had a family history of seizures in the neonatal period (Fig. 1). Patient 8 had a family history of seizures in the first months of life. Patient 15 had, in addition, a family history of idiopathic focal epilepsy in childhood. Three patients had *KCNQ2* deletions and one patient had a deletion in *KCNQ3*. The *KCNQ2* deletion in patient 8 included the adjacent *CHRNA4* gene, and this patient had a typical BFNE phenotype, as reported by others.[9] Two patients had nonsense mutations, and two patients had frameshift mutations predicted to lead to early truncation. Seven patients had *KCNQ2* missense mutations, including three previously reported alleles. Patient 17 was without a family history of epilepsy and was found to have a de novo novel *KCNQ2* mutation. Patient 12 had a novel missense mutation in the pore region of *KCNQ3*. Both novel mutations were predicted to be pathogenic with a high degree of confidence.

Electroclinical features

Table 1 details the findings in the 19 patients diagnosed with BFNE. Seizure onset was between 2 and 5 days (mean 2.9 days). Seizures were focal in onset in all patients consisting of asymmetric tonic posturing accompanied in most patients by apnea and desaturation, evolving in most patients to unilateral or asynchronous bilateral clonic movements (Fig. 2). Seizures lasted between 30 and 120 s, occurred multiple times per day in all patients, and four patients developed status epilepticus. Neuroimaging and EEG background was normal in all patients. Focal interictal EEG epileptiform abnormalities were recorded frequently recorded (12 of 17 patients) over the central regions in 7 infants, over the centrotemporal or frontotemporal region in 4 infants, and from the right temporal and left occipital regions in one other. The supplementary video shows a typical seizure recorded in patient 12 harboring a novel *KCNQ3* mutation, before CBZ was administered.

Antiepileptic drug response

Twelve (63%) of 19 patients were trialed on multiple AEDs prior to seizure cessation (Fig. 3). Fourteen patients were trialed with intravenous loads of phenobarbital (PB) and two responded; one was continued on oral PB and one was switched to oral carbamazepine (CBZ) maintenance therapy and remained seizure-free. The rest of these patients did not respond, despite documented PB levels of ≥40 μg/

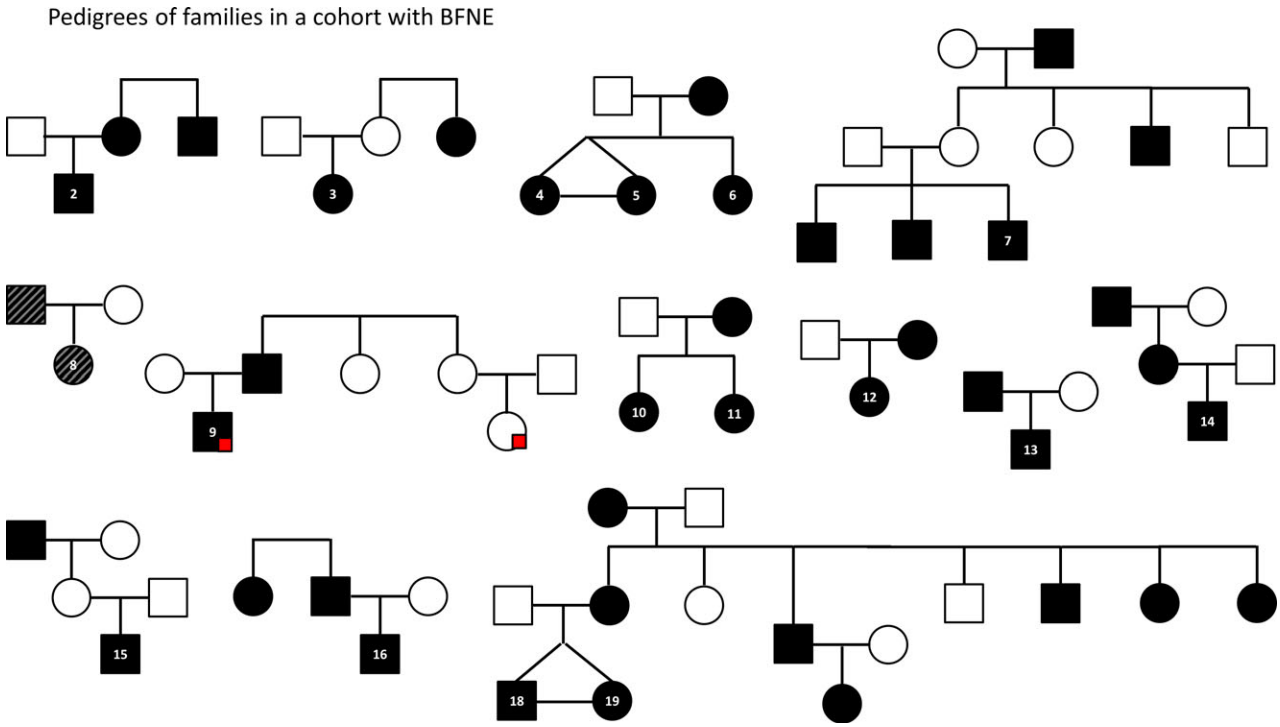

Figure 1.
Family trees in a cohort of with BFNE. Black: neonatal seizures. Red squares denote family members with febrile seizures. Striped: affected family members of proband 15 developed idiopathic focal epilepsy in childhood as well as neonatal seizures. See Table 1 for details.

mL. Additional treatments without response included intravenous pyridoxine in three infants, intravenous levetiracetam in three infants, high-dose intravenous benzodiazepines (diazepam or midazolam) in four infants, and oral benzodiazepines (clonazepam) in two infants. One patient responded to intravenous thiopental. Patient 9 responded to a loading dose of intravenous phenytoin (PHT), but seizures recurred at the first attempt to wean and the patient subsequently responded to oral CBZ. After an initial response to levetiracetam (patient 1) and PB (patient 14), seizures recurred and were not controlled with escalating doses until seizure freedom was achieved with initiation of CBZ at 3 months of age. Seventeen (89%) of 19 patients were seizure-free within hours of administration of low-dose oral CBZ (10 mg/kg/day) or oxcarbazepine (OXC), including four in whom CBZ was used as the sole first-line therapy. Earlier initiation of CBZ was associated with shorter duration of hospitalization (Fig. 4). Figure 4A excludes patients 1 and 14, who were hospitalized multiple times over the first 3 months for recurrent bouts of seizures and whose cumulative hospitalizations lasted approximately 1 month each. When CBZ was started within 3 days of seizure onset, hospitalization lasted under a week (Fig. 4B).

Treatment with CBZ was initiated based on the electroclinical presentation suggesting BFNE. No laboratory abnormalities or side effects were reported during treatment with CBZ. Three patients experienced seizure recurrence with attempt to wean treatment in the first year of life: patient 10 experienced recurrence with attempt to wean PB at 2 months of age, and patients 8 and 11, following an attempt to discontinue CBZ at 8 months. In all three of these patients, reintroduction of the maintenance therapy promptly led to seizure remission. The patient who responded initially to OXC at 20 mg/kg/day (patient 17) had seizure recurrence at 1.5 months of age, with a blood level of 4 μg/mL, and responded to an increase in the dose to 35 mg/kg/day. Doses were not otherwise weight adjusted over the course of treatment, and all patients were seizure-free after discontinuation of drugs between 12 and 18 months of life.

Mean follow-up was 7.8 years (6 months to 16 years). All patients had normal development and none had evolution to encephalopathy or severe epilepsy (Table 1). Patient 15 developed epilepsy with centrotemporal spikes at 3 years of age, which did not respond to clobazam but did respond to CBZ. One patient developed uncomplicated febrile seizures.

Discussion

We report the first study to evaluate AED treatment in neonates with BFNE. We aimed to review the response to AEDs, including timing, impact on duration of hospitalization in the neonatal intensive care unit (NICU), and

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Table 1. Genetic, clinical, and EEG characterizations of a cohort with BFNE

(a)

	Case 1 (U.S.A.)	Case 2 (U.S.A.)	Case 3 (U.S.A.)	Cases 4/5 fraternal twins (U.S.A.)	Case 6 sibling of cases 4/5 (U.S.A.)
Mutation	*KCNQ2* c.333_334delGT p.Ser113HisfsX6	*KCNQ2* c.1888delG p.Val630SerfsX12	*KCNQ2* c.619 C>T p.Arg207Trp	*KCNQ2* c.1057 C>G p.Arg353Gly	*KCNQ2* c.1057 C>G p.Arg353Gly
Clinical characteristics					
Sex	F	M	F	F & F	F
Gestation	39 weeks	39 weeks	38 weeks	34 weeks	39 weeks
Seizure onset	Third day of life	Fourth day of life	Second day of life	Second and fifth days of life, respectively	Second day of life
EEG characteristics					
Interictal EEG	Normal background Occasional interictal spikes at C4	Normal background Rare bilateral independent spikes centrally	Normal background Interictal spikes at Cz	Normal background	No EEG
Recorded seizures	Status epilepticus Left tonic arm/leg posturing => left arm/leg clonic jerking with apnea/ desaturation; 1–3 Hz spike and wave discharges originating at Fp2/F4/F8	Asymmetric tonic limb posturing with apnea and desaturation, and then unilateral clonic jerking; shifting laterality; ictal discharges originating independently from bilateral central leads; approximately 1 min duration	Asymmetric tonic posturing with apnea/desaturation, and then asynchronous clonic jerking of all four extremities; rhythmic delta evolving into spike and wave discharges originating bilateral independently (C3/ T3/O1 and T4) with shifting laterality;	Focal asymmetric tonic posturing, associated with apnea and desaturation; mainly upper limbs with shifting laterality; initial electrical decrement, evolving to rhythmic theta;	No EEG
Neuroimaging	MRI normal	MRI normal	MRI normal	MRI normal	No imaging
Family history	Negative for neonatal seizures	Positive for neonatal seizures (mother, maternal uncle)	Positive for neonatal seizures (maternal aunt)	Positive for neonatal seizures (mother, twin, sister)	Positive for neonatal seizures (mother, twin sisters)
Medications trialed	LZP × 4 doses, PB i.v. 40 mg/kg, LEV p.o. 60 mg/kg/day, MDZ drip, CBZ p.o. 10 mg/kg/day (effective)	PB iv 20 mg/kg + CBZ p.o. 10 mg/kg/day (effective)	PB iv 30 mg/kg, LEV i.v. 30 mg/kg, CBZ p.o. 10 mg/kg/day (effective)	PB iv 40 mg/kg, Pyridoxine iv 100 mg, CLN p.o., DZP i.v., CBZ p.o. 10 mg/kg/day (effective)	CBZ 10 mg/kg/day (effective)

Continued

Table 1. Continued.

(a)

	Case 1 (U.S.A.)	Case 2 (U.S.A.)	Case 3 (U.S.A.)	Cases 4/5 fraternal twins (U.S.A.)	Case 6 sibling of cases 4/5 (U.S.A.)
Hospitalization	Multiple hospitalizations for seizure recurrence over the first 3 months (approximately 25 days)	4 days	14 days	15 days	0 days
Follow-up	2 years, seizure-free off meds, normal development	2 years, seizure-free off meds, normal development	16 months, seizure-free off meds, normal development	16 years, both seizure-free off meds, normal development	13 years, off meds seizure-free, normal development

(b)

	Case 7 (Italy)	Case 8 (Italy)	Case 9 (Italy)	Case 10 (Italy)	Case 11 (Italy)	Case 12 (U.S.A.)
Mutation	*KCNQ2* DEL ex 12–17	*KCNQ2* DEL ex 12–17+ *CHRNA4*	*KCNQ2* DEL ex 13–17	*KCNQ2* c.587 A>T p.Ala196Val	*KCNQ2* c.587 A>T p.Ala196Val	*KCNQ3* c.923 G>C p.Trp308Ser novel
Clinical characteristics						
Sex	M	F	M	F	F	M
Gestation	40 weeks	38 weeks	38 weeks	39 weeks	40 weeks	39 weeks
Seizure onset	Third day of life	Fourth day of life	Second day of life	Second day of life	Second day of life	Fourth day of life
EEG characteristic						
Interictal EEG	Normal background	Normal background Left centrotemporal spikes	Normal background	Normal background Central spikes/sharp waves	Normal background	Normal background Spikes in the bilateral independent central regions and at the vertex
Recorded seizures	Focal tonic with apnea, followed by clonic phase, alternating laterality	Status epilepticus Focal tonic with apnea and alternating laterality	Focal seizures	Tonic with apnea	Focal seizures	Focal tonic, then bilateral asynchronous clonic with apnea/desaturation; shifting laterality
Neuroimaging	MRI normal	MRI normal	MRI normal	Head ultrasound normal	Head ultrasound normal	Head ultrasound normal
Family history	Positive for neonatal seizures (maternal grandfather, maternal aunt, two brothers)	Positive for infantile seizures (father)	Positive for neonatal seizures (father) and for FS (first degree paternal cousin)	Positive for neonatal seizures (mother, sister)	Positive for neonatal seizures (mother, sister)	Positive neonatal seizures and febrile seizures (mother)
Medications trialed	PB i.v. 40 mg/kg, CBZ p.o. 10 mg/kg/day (effective)	CBZ p.o. 10 mg/kg/day (effective) Attempt to wean off CBZ	PB i.v. 20 mg/kg, PHT i.v. 18 mg/kg (effective) CBZ p.o. 10 mg/kg/day	PB i.v. 20 mg/kg then p.o. 5 mg/kg/day (effective) Attempt to wean off PB at	CBZ p.o. 10 mg/kg/day (effective) Attempt to wean off CBZ	CBZ p.o. 10 mg/kg/day (effective)

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Table 1. Continued.

(b)

	Case 7 (Italy)	Case 8 (Italy)	Case 9 (Italy)	Case 10 (Italy)	Case 11 (Italy)	Case 12 (U.S.A.)
		at 8 months led to recurrence	[for recurrence after weaning PHT at 10 days of life] (effective)	2 months led to recurrence	at 8 months led to recurrence	
Hospitalization	6 days	5 days	12 days	20 days	1 day	2 days
Follow-up	11 years, seizure-free off meds, normal development	10 years, seizure-free off meds, normal development	6 years, FS from 8 months to 4 years, otherwise seizure-free off meds, normal development	14 years seizure-free off meds, normal development	9 years, seizure-free off meds, normal development	3 months, seizure-free on CBZ, normal development

(c)

	Case 13 (Italy)	Case 14 (Italy)	Case 15 (Italy)	Case 16 (U.S.A.)	Case 17 (U.S.A.)	Cases 18 & 19 fraternal twins (U.S.A.)
Mutation	No mutations or deletions found in *KCNQ2*, *KCNQ3*, *SCN2A*	No mutations or deletions found in *KCNQ2*, *KCNQ3*, *SCN2A*	*KCNQ3* DEL ex 1-15	No mutations or deletions found in *KCNQ2*, *KCNQ3*, *SCN2A*	*KCNQ2* c.1700 T>A p.Val567Asp novel	*KCNQ2* c.807 G>A p.Trp269Ter
Clinical characteristics						
Sex	M	M	M	M	F	M & F
Gestation	40 weeks	39 weeks	39 weeks	40 weeks	39 weeks	38 weeks
Seizure onset	Third day of life	Second day of life	Fourth day of life	Fourth day of life	Second day of life	Third day of life
EEG characteristics						
Interictal EEG	Normal background Interictal bilateral independent central spikes	Normal background Focal frontotemporal spikes	Normal background Focal spikes (temporal right, occipital left)	Normal background Infrequent bilateral independent frontocentral spikes	Normal background	Normal background L > R centrotemporal sharp waves
Recorded seizures	Status epilepticus Focal tonic with apnea and subsequent clonic phase alternating	Focal, eyes and head tonic deviation, followed by unilateral or bilateral clonic phase	Status epilepticus Focal	Focal, head turn then arm and leg tonic->clonic phases	Focal and becomes bilateral asynchronous with initial tonic phase and apnea	Focal, initial tonic phase involving upper and lower limbs followed by unilateral or bilateral asynchronous clonic phase
Neuroimaging	MRI normal	MRI normal	MRI normal	MRI normal	MRI normal	Head ultrasound normal
Family history	Positive for neonatal seizures (father)	Positive for neonatal seizures (mother, maternal grandfather)	Positive for neonatal seizures and idiopathic focal epilepsy in childhood (maternal grandfather)	Positive for neonatal seizures (father, paternal aunt)	Negative (mutation demonstrated to be de novo)	Positive for neonatal seizures (mother, maternal grandmother, 2 maternal aunts and 2 maternal uncles)

Continued

Table 1. Continued.

(c)	Case 13 (Italy)	Case 14 (Italy)	Case 15 (Italy)	Case 16 (U.S.A.)	Case 17 (U.S.A.)	Cases 18 & 19 fraternal twins (U.S.A.)
Medications trialed	Pyridoxine i.v. 100 mg, PB i.v. 40 mg/kg, MDZ drip, CBZ p.o. 10 mg/kg/day (effective)	PB i.v. 20 mg/kg (multiple loads), CBZ p.o. 10 mg/kg/day (effective)	PB i.v. (multiple loads), MDZ drip, Thiopental drip (effective)	PB i.v. 20 mg/kg, CBZ p.o. 10 mg/kg/day (effective)	PB i.v. (multiple loads), LEV i.v. 40 mg/kg × 2, OXC p.o. 20 mg/kg/day (effective) Dose increased to 35 mg/kg/day for 1 recurrence at 1.5 months	CBZ p.o. 10 mg/kg/day
Hospitalization	20 days	Multiple hospitalizations for seizure recurrence over the first 3 months (approximately 38 days)	14 days	5 days	20 days	1 day
Follow-up	13 years, seizure-free off meds, normal development	5 years, seizure-free off meds normal development	12 years; BECTS at 3 years, responsive to p.o. CBZ; now seizure-free off meds, normal development	2 years, seizure-free off meds, normal development	6 months, seizure-free on OXC, normal development	4 months, seizure-free on CBZ

Patients 4 and 5 and patients 18 and 19, two sets of fraternal twins, are listed together.
LZP, lorazepam; PB, phenobarbital; LEV, levetiracetam; MDZ, midazolam; CBZ, carbamazepine; CLZ, clonazepam; DZP, diazepam; PHT, phenytoin; OXC, oxcarbazepine; FS, febrile seizures; BECTS, benign epilepsy with central temporal spikes.

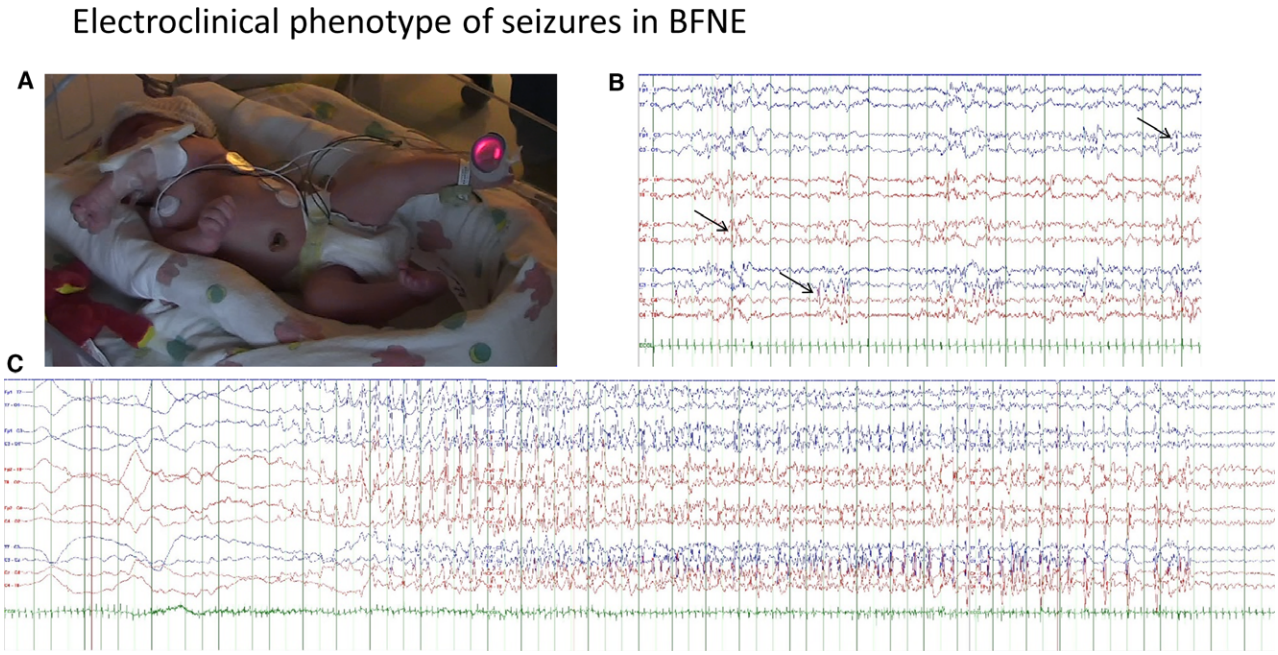

Figure 2.
Electroclinical phenotype of seizures in BFNE. (**A**) Asymmetric tonic posturing with apnea and desaturation during a benign neonatal seizure (patient 12). Subsequently, the seizure evolved to asynchronous bilateral clonic movements. (**B**) Interictal EEG of the same patient, showing focal epileptiform discharges in the bilateral central regions and at the vertex (arrows) in the setting of an otherwise normal background. (**C**) Electrographic seizure from this patient, showing onset of rhythmic sharpened delta over the left hemisphere.

long-term outcome. Our findings demonstrate that oral CBZ is a safe and effective therapy for seizures in neonates with BFNE, and moreover suggest that recognition of the electroclinical phenotype early in the clinical course can prompt timely initiation of CBZ and avoid sedation and hypotonia associated with loading doses of intravenous PB, which delays establishment of oral feeding and consequently prolongs the NICU stay of these otherwise healthy babies.

The 19 patients reported here shared the hallmark features of benign neonatal seizures: onset of seizures within the first days of life in otherwise healthy neonates with normal interictal EEG findings and neuroimaging, who often have a family history of seizures in the neonatal period. The electroclinical phenotype was defined by prolonged video-EEG monitoring and found to be stereotyped across our cohort: clusters of focal seizures with alternating laterality, characterized by initial asymmetric tonic posturing, often with apnea and desaturation, followed by a clonic component (Video S1). Electrographically, focal seizures arose alternately from each hemisphere, out of a continuous EEG background with or without epileptiform discharges but without focal slowing or attenuation to suggest an underlying lesion.

Similar to other studies of BFNE, the rate of mutation detection in this cohort was approximately 85%.[1,3,6] Our cohort included one novel de novo missense mutation of *KCNQ2*, a *KCNQ3* deletion, and one novel mutation in the *KCNQ3* gene. The novel *KCNQ2* missense mutation, V567D, is in a region of the C-terminus near other residues reported to be pathogenic. Although de novo mutations are generally associated with KCNQ2 encephalopathy; in this case, the allele appears to represent a founder mutation. *KCNQ2* deletion is a known cause of BFNE,[10] but to our knowledge *KCNQ3* deletion has not previously been reported as a cause of BFNE. We described a novel missense mutation in *KCNQ3*, W308S, in the channel pore predicted to be pathogenic with a high degree of confidence and adjacent to one of the only 10 other sites for reported missense mutations, W309R,[11] which has been confirmed in vitro to result in dramatically reduced potassium currents.[12,13]

It has been suggested that neonatal seizures should no longer be regarded as a separate entity and that seizure semiology should be approached in the same manner as with older patients.[14] Reviewing the video-EEG recordings of our series of newborns with BFNE, we noted that the seizure semiology has close similarities with seizures involving the supplementary sensorimotor area (SSMA) as described in older children and adults.[15,16] Of interest, focal epilepsies with SSMA and other frontal semiology appear to respond well to CBZ.[16–18] Attention to seizure semiology along with review of the EEG background and the neurologic examination early in the clinical course and, in particular, prior to the administration of large quantities of sedating

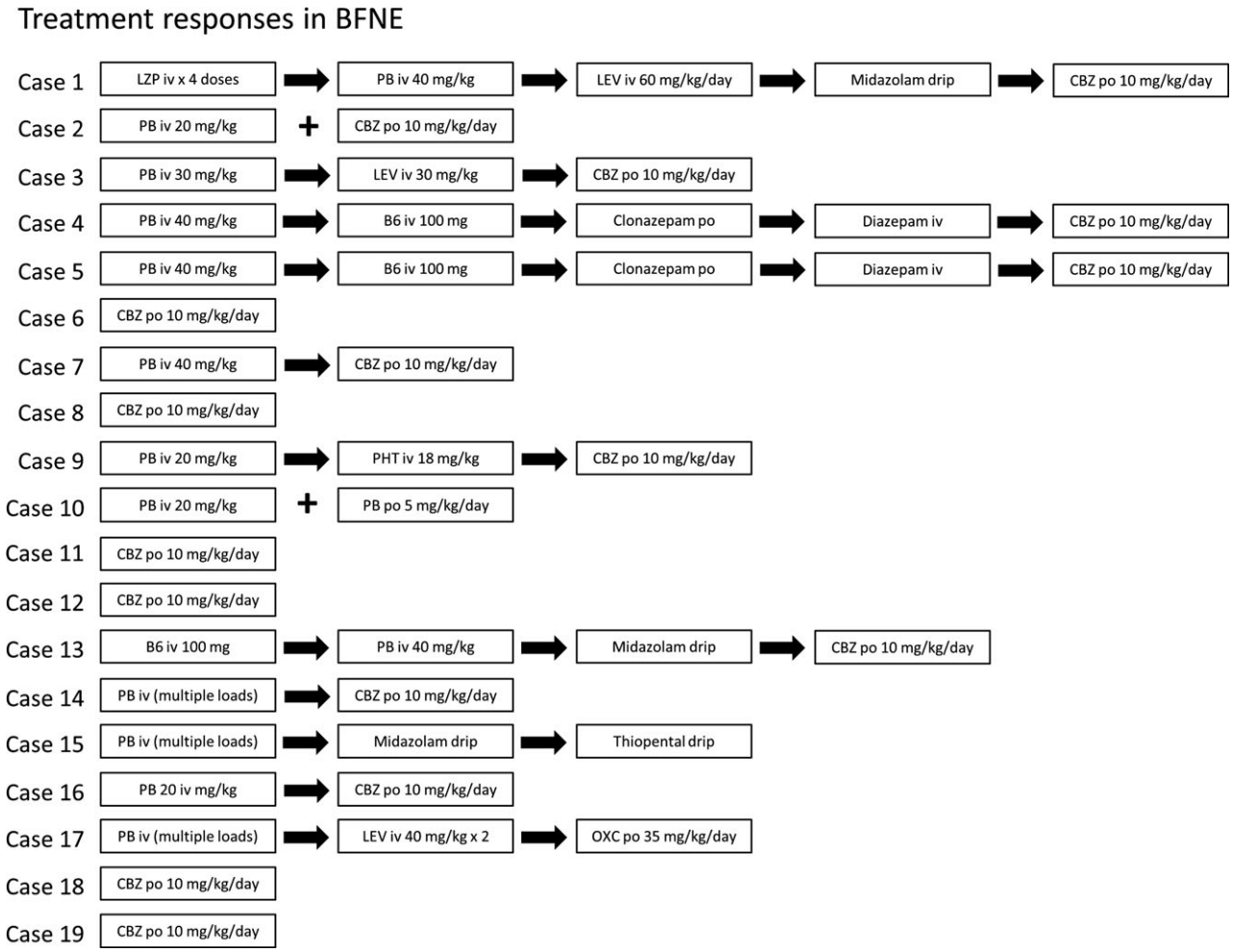

Figure 3.

Treatment responses in BFNE. Antiepileptic therapies used across the cohort in the order in which they were administered. The last therapy was associated with cessation of seizures. In case 9, phenytoin (PHT) led to seizure cessation, but seizures recurred with weaning and carbamazepine (CBZ) was initiated with no further recurrence. LZP, lorazepam; PB, phenobarbital; LEV, levetiracetam; OXC, oxcarbazepine.

medications, was critical in raising early suspicion for benign genetic epilepsy. In all patients, treatment was initiated based on the electroclinical diagnosis, well before the results of genetic testing were available. Early recognition of BFNE is a prerequisite for implementation of tailored therapy and appropriate prognostic counseling. CBZ could be given as first-line therapy for two neonates (patients 6 and 11) who were siblings of previously diagnosed patients in whom the genetic etiology had been confirmed and in four others (patients 8, 12, 18, and 19) based on phenotype alone.

The natural history of seizures in BFNE is unclear from the literature, as these seizures have often been noted to disappear after 6 months of age in many patients; details on effective therapies and treatment duration are scarce. We found oral CBZ to be effective in all treated patients, leading to seizure cessation within hours, regardless of at what point in the clinical course it was initiated, even in the setting of SE. Although benign in terms of developmental outcome, seizures in BFNE were frequent at presentation and associated with apnea and desaturation, leading to admission to the NICU. As a marker of its efficacy, we found that the timing of treatment with CBZ was related directly to the length of hospitalization. In the extreme, two infants were repeatedly hospitalized over the first 3 months of life, with approximately 1 month of hospitalization in each before cessation of seizures after starting CBZ. In contrast, in four cases in which CBZ was given as first-line therapy, the length of hospitalization was <24 h. Patient 6 was not even admitted and was treated as an outpatient.

There is little information to guide practitioners in the duration of AED treatment in BFNE, although anecdotal reports have suggested that seizures can recur if medications are weaned prior to 9 months.[19] Indeed, *KCNQ2* mutation

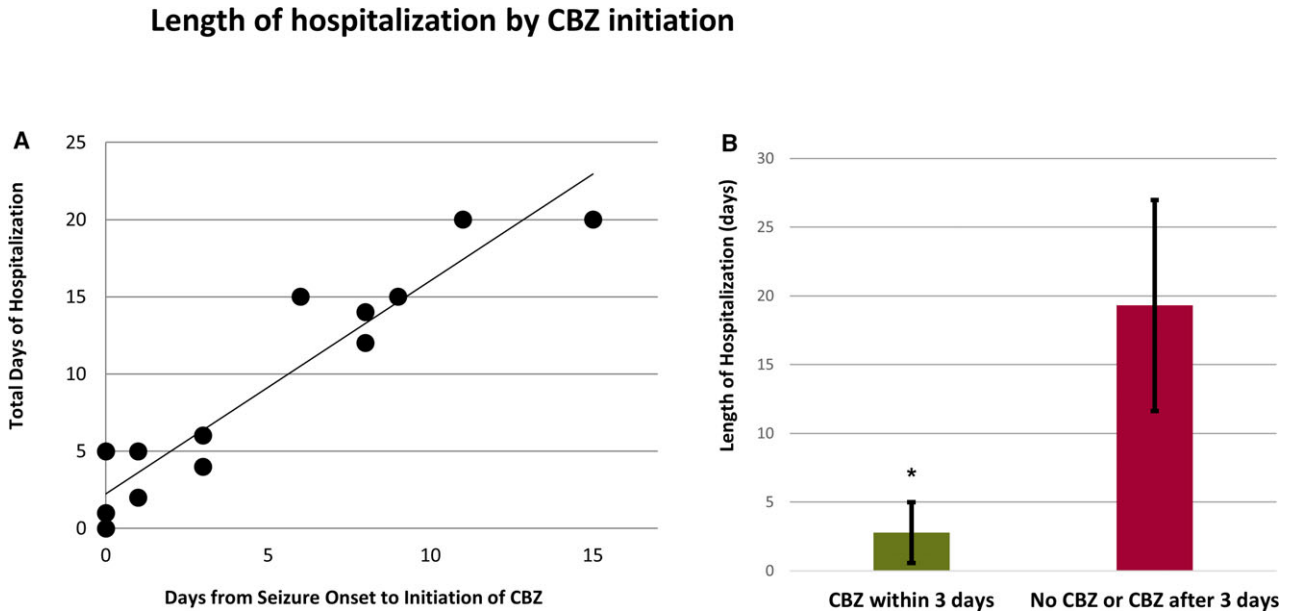

Figure 4.
(**A**) Length of hospitalization by time to CBZ. In patients treated with CBZ or OXC in the neonatal period, the length of hospitalization was directly correlated with when CBZ or OXC was initiated, $p < 0.01$. (**B**) Administration of CBZ within 3 days of seizure onset was associated with hospital stays of under 1 week, compared to longer hospitalization if CBZ was not administered or if initiated after 3 days, $p < 0.01$.

not infrequently presents with benign epilepsy during infancy outside of the neonatal period, arguing a window of particular susceptibility that extends throughout the first year of life.[1] Our cohort is notable for the recurrence of seizures in two patients at 8 months of age on attempt to discontinue therapy. In patients with follow-up beyond 2 years of age, except for one patient who developed benign epilepsy with centrotemporal spikes (BECTS), unprovoked seizures did not recur after discontinuation of treatment between 12 and 18 months, suggesting that this may be an appropriate duration of therapy.

Although, CBZ, a sodium-channel blocker, has been used in adults and children for >30 years with an excellent therapeutic and side effect profile, it is seldom used in newborns. Its use in this population has been reported previously only in two studies in term[20] and preterm neonates.[21] Consistent with these reports, none of the 17 patients in our cohort treated with CBZ as neonates and infants experienced any gastrointestinal, hepatic, hematologic, renal, or dermatologic side effects. We used a low dose of CBZ; however, since the dose was not subsequently adjusted for weight, it is possible that even lower doses may be effective.

Our study parallels the recent report of rapidly effective treatment of the seizures in *KCNQ2* encephalopathy to CBZ.[22] Although the two conditions result from mutation of the same gene and the seizure semiology is similar, the differential diagnosis can be made clinically based on the neurologic examination and EEG background, both of which are severely abnormal prior to onset of seizures in *KCNQ2* encephalopathy.[23] It has been speculated that co-localization of voltage-gated potassium and sodium channels at regions of the neuronal membrane critical for action potential generation and propagation[24] may impart sensitivity to sodium channel blockade. It is notable that one patient who was treated with PHT did seem to respond, suggesting that either of these sodium-channel blockers may be effective treatment, although PHT may be less desirable for maintenance drug during the first year of life. Although PHT is known to potentially exacerbate *SCN1A*-related conditions, relative success has been reported in treating early epilepsy associated with mutations in *SCN2A*[25,26] or *SCN8A*.[27] In addition, benign familial infantile epilepsy BFIE, a benign autosomal-dominant epilepsy with a later age of presentation than BFNE and caused by mutation in the *PRRT2* gene in >70% of families,[1] has also been shown to be sensitive to low-dose CBZ.[28] Indeed, sodium channel blockers are emerging as old drugs with a new indication in treating early onset genetic epilepsies. Epilepsies caused by *PRRT2* and *KCNQ2* share in common focal seizures with a tonic component,[29] suggesting that seizure semiology is relevant for treatment choice.

PB is the most commonly prescribed first-line agent for neonatal seizures, regardless of etiology. However, intravenous loads of PB failed to stop seizures in the majority of our patients with BFNE, despite serum levels of ≥40 during bouts of recurring seizures. Indeed, only 2 of 13 patients treated with PB had an apparent clinical response, and in one CBZ was initiated simultaneously as maintenance

therapy, leaving open the possibility that the response was due to CBZ. Exacerbation of benign neonatal seizures with PB followed by midazolam infusion has been reported previously.[2] The particular combination of PB loading followed by midazolam infusion was used in one of our patients, whose seizures were ultimately aborted by thiopental. It is unclear whether this clinical course reflects exacerbation by the treatment protocol or the natural clinical course. Because PB was used early in 13 of 19 of our patients, it is unclear whether it could have led to more seizures than anticipated due to poor efficacy alone. Notably, CBZ was effective in babies who received a dose of PB as first line and, moreover, initiation of CBZ within 3 days of seizure onset was invariably associated with short duration of hospitalization regardless of prior exposure to PB. Intravenous administration of PB in our cohort likely contributed to prolonging the hospitalization due to sedation, hypotonia, and difficulty with feedings.

Recently, it was demonstrated that up to 25% of neonates with BFNE go on to have other forms of epilepsy later in childhood.[3] Only one patient in our cohort developed epilepsy later in life. It is intriguing that seizure burden in the neonatal period has been implicated in risk for epilepsy in both human and animal studies.[30–32] Although suggestive, our cohort size is too small to draw conclusions regarding whether prompt seizure control may have affected this risk. The one patient in our cohort who developed epilepsy had a *KCNQ3* deletion and developed BECTS. BFNE due to *KCNQ2* mutation and later development of BECTS has been well described.[3,33,34] BFNE due to *KCNQ3* and later BECTS has been noted in one patient previously,[34] and one other has been reported with benign infantile epilepsy who went on to develop BECTS.[35] Although CBZ was not used to treat this patient's seizures in the neonatal period, it was used successfully to treat his Rolandic seizures later in life, again suggesting a connection between *KCNQ2/3* mutations, seizures with frontal lobe semiology, and response to CBZ.

Our study has the inherent limitations of a retrospective study. Of particular concern would be that the apparent efficacy of CBZ in our cohort was due to the self-limited nature of the condition, seizures tending to abate over time in all patients. We feel that this possibility is belied by the fact that patients started on CBZ at any point in their course universally responded, including those started on CBZ as first line. Another potential concern is that our results might be derived from a bias, whereby less severely affected babies were selected for early treatment with oral CBZ, whereas more severely affected individuals were chosen for more aggressive treatments. Although this possibility cannot be ruled out, we note that all patients, regardless of treatments trialed, were affected by recurrent clusters of seizures, and in one patient CBZ was used as first line in the setting of status epilepticus with rapid cessation of seizures. Whether other AEDs that target the sodium channel would be equally effective and safe in BFNE was not answered here. Although OXC was effective and safe in one child, little can be gleaned from a single patient, and at this point the authors recommend treatment with CBZ as first line.

We have found CBZ to be a safe and rapidly effective treatment for the seizures in BFNE, even when used to treat SE. Prompt initiation of a trial of CBZ in neonates with BFNE may reduce unnecessary exposures to other AEDs, some of which (e.g., PB) have raised concerns for neurodevelopmental effects,[36] reduce the complications and costs associated with protracted hospitalization in these otherwise well neonates, and perhaps lower the risk of later epilepsy.

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Disclosure

None of the authors has any conflict of interest to disclose. We confirm that we have read *Epilepsia's* position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Video S1. Ictal video-EEG recorded in a neonate with a *KCNQ3* mutation (patient 12) during monitoring prior to treatment. Administration of CBZ led to rapid cessation of seizures.