Clinical commentary

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Pointed rhythmic theta waves: a unique EEG pattern in KCNQ2-related neonatal epileptic encephalopathy

Sarah Grace Buttle [1], Erick Sell [2], David Dyment [3], Srinivas Bulusu [4], Daniela Pohl [5]

[1] Faculty of Medicine, University of Ottawa, Ontario
[2] Division of Neurology, Children's Hospital of Eastern Ontario; University of Ottawa, Ontario
[3] Department of Genetics, Children's Hospital of Eastern Ontario; University of Ottawa, Ontario
[4] Neurophysiology Laboratory, Children's Hospital of Eastern Ontario, Ottawa, Ontario
[5] Division of Neurology, Children's Hospital of Eastern Ontario; University of Ottawa, Ontario, Canada

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ABSTRACT – We report the case of an infant with KCNQ2-related neonatal epileptic encephalopathy presenting with intractable seizures beginning on the second day of life, which were resistant to multiple antiepileptic drugs. Continuous EEG recordings starting on the sixth day of life demonstrated a unique pattern of inter-and postictal focal rhythmic pointed theta waves of lambdoid morphology in the immediate postictal period, localizing to the side of the antecedent seizure. Interictal EEG exhibited discontinuous background, including patterns of burst suppression and multifocal discharges, predominantly in the centrotemporal regions, which were aggravated during sleep. MRI demonstrated T1 signal abnormalities in the basal ganglia, bilaterally. Genetic testing revealed a *de novo* missense mutation in *KCNQ2* at position c.545 T>G, encoding a previously unreported substitution (p.Val182Gly). Seizure control was achieved immediately after starting a lidocaine infusion at age 4 weeks. The patient remained largely seizure-free following add-on oral carbamazepine for maintenance therapy and weaning off lidocaine. This is the first report of a patient with KCNQ2-related neonatal epileptic encephalopathy and therapy-refractory seizures aborted by lidocaine, demonstrating a unique EEG pattern of inter- and postictal focal rhythmic pointed theta waves. Whether this pattern could be an early EEG marker for this disorder remains to be confirmed. [*Published with video sequences on www.epilepticdisorders.com*]

Key words: *KCNQ2* mutation, neonatal seizure, epileptic encephalopathy, lidocaine, EEG marker

VIDEOS ONLINE

Correspondence:
Daniela Pohl
Children's Hospital of Eastern Ontario,
401 Smyth Road, Ottawa, ON,
K1H 8L1, Canada
<dpohl@cheo.on.ca>

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Mutations in *KCNQ2*, a voltage-gated potassium channel that functions to repolarize neuronal membranes after activation of excitatory neurotransmitter ion channels, were first described in association with neonatal seizures in 1998 (Singh *et al.,* 1998). Since then, various autosomal dominantly inherited *KCNQ2* mutations have been reported in approximately 100 families with benign familial neonatal seizures (BFNS). In BFNS, seizures appear in healthy infants within two to eight days after birth and are self-limiting, spontaneously resolving within the first year of life, and generally associated with normal neurodevelopment (Miceli *et al.,* 2010).

Recently, Weckhuysen *et al*. (2012) described novel *KCNQ2* mutations in patients with neonatal epileptic encephalopathy (NEE), thereby expanding the spectrum of KCNQ2-related disorders. Further work demonstrated that mutations in *KCNQ2* are found in 13% of patients with unexplained NEE; screening for *KCNQ2* mutations in these infants has been recommended (Weckhuysen *et al.,* 2013). KCNQ2-related NEE (KCNQ2-NEE) is affiliated with *de novo* missense mutations in *KCNQ2* that may result in loss or gain of function (Devaux *et al*., 2016), and represents a more severe phenotype than BFNS. Patients experience multiple treatment-resistant seizures with onset in the first week of life, decreasing seizure frequency in early childhood, and moderate-to-severe subsequent neurodevelopmental impairment (Weckhuysen *et al.,* 2012, 2013; Serino *et al.,* 2013; Millichap *et al*., 2016). Traditional antiepileptic drugs (AEDs) used in the neonatal period, including phenobarbital, demonstrate poor efficacy in neonates with KCNQ2-NEE (Serino *et al.,* 2013; Millichap *et al.,* 2016).

We report a case of multiple-AED-resistant KCNQ2-NEE affiliated with a novel mutation and a unique interictal and postictal high-voltage recurrent focal pointed theta pattern on continuous video-EEG monitoring, with prompt and sustained seizure control following lidocaine infusion and subsequent treatment with carbamazepine.

Case study

A term (39+4) female neonate, the product of a non-consanguineous conception assisted by infertility treatment, was born to a healthy 33-year-old G1 mother following an uneventful pregnancy. Emergency Caesarean section was performed three hours after spontaneous rupture of membranes for non-reassuring foetal heart rate. APGAR scores were 1 and 9 at 1 and 5 minutes, respectively. On the second day of life, the infant was noted to become red, rigid and apnoeic for a period of 20 to 30 seconds while breast-feeding. Respiratory rate increased following the episode, and the patient appeared jittery and irritable with a high-pitched cry when stimulated or examined. The infant was subsequently transferred to the Children's Hospital of Eastern Ontario in Ottawa, Canada, for admission to a tertiary level Neonatal Intensive Care Unit (NICU).

The family history was negative for neonatal seizures. Comprehensive septic and metabolic workups, including plasma amino acids and CSF cell count, protein, glucose, lactate, and amino acids, did not reveal an underlying infectious or metabolic aetiology. Placental pathology was unremarkable. Head ultrasound conducted upon admission to the NICU showed a subtle region of increased echogenicity within the right caudothalamic grove and questionable cystic change, suspected to represent a resolving type 1 germinal matrix haemorrhage. MRI on the third day of life showed bilateral basal ganglia signal abnormalities on T1 imaging in the globi pallidi, extending into the cerebral peduncles (*figure 1*), interpreted to represent a metabolic disturbance. In the light of the negative metabolic investigations, genetic testing, including epilepsy panel screening for 18 genes involved in neonatal epilepsy syndromes, screening for mitochondrial disorders, and aCGH, was ordered on Day 10.

Following admission, bedside amplitude-integrated EEG (aEEG) and continuous video-EEG (cEEG) monitoring were initiated on the sixth day of life. Interictal EEG was notable for an encephalopathic pattern characterized by excessive discontinuity, with bursts of high-amplitude sharp waves alternating with episodes of amplitude suppression (*figure 2A*). From Day 2 to 25, the neonate was observed to have minimally two and maximally 21 electrographic seizures daily, clinically characterized by eye and/or head deviation, often accompanied by tachycardia, and followed by tonic posturing, as well as mouthing movements. Ictal EEGs showed diffuse muscle artefact for several seconds, followed by fast activity over C3 or C4 (*figure 2B and video sequences 1-3*). Most seizures lasted for less than three minutes, although the infant did experience one seizure with a duration of 12 minutes. Seizures had the same electrographic signature but alternated in origin from the right or left temporal region. EEGs were most remarkable for a unique pattern of runs of focal pointed theta waves of lambdoid morphology, observed either interictally or in the immediate postictal period and lasting, on and off, for up to five minutes following each seizure, localizing to the region of the antecedent seizure (*figure 2C and video sequences 1-3*). This unique pattern of pointed theta waves was observed on the first cEEG recording on the sixth day of life, and on all subsequent recordings until seizures were controlled on Day 26.

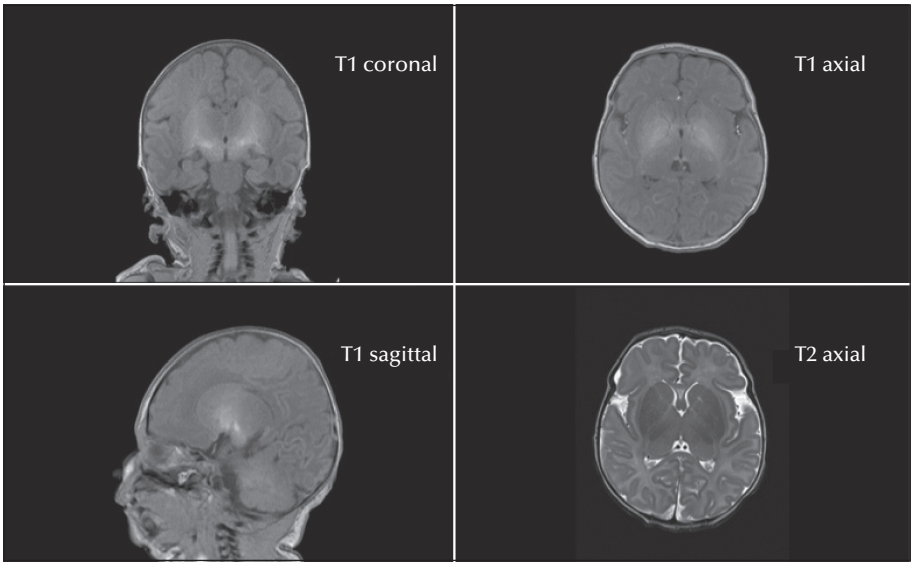

Figure 1. MRI on the third day of life demonstrating bilateral signal abnormality on T1-weighted imaging sequences in the basal ganglia, mainly in the globi pallidi and extending into the cerebral peduncles. There was no signal abnormality on T2-weighted imaging and no restricted diffusion.

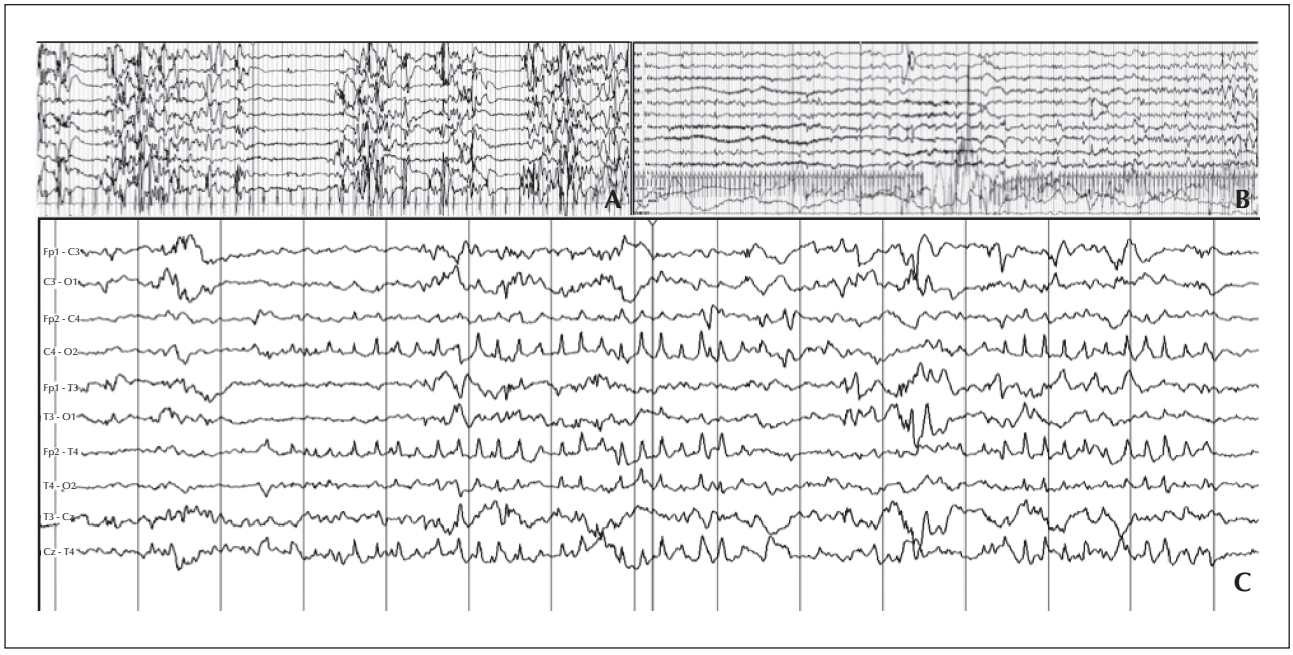

Figure 2. Composite of representative EEG tracings. (A) Background EEG abnormalities on the fifth day of life. EEG trace demonstrates a burst-suppression pattern, at times with polyspikes and sharp waves for bursts of five seconds and interburst intervals of one to three seconds (speed: 1.0 mm/s). (B) Ictal EEG displaying seizure onset with fast low-amplitude spikes arising from right centro-temporal areas on Day 26. Lidocaine infusion was started on the same day, following increased seizure burden over the preceding 24 hours (speed: 10 mm/s). (C) Postictal EEG demonstrating 4 to 5-Hz rhythmic theta waves of lambdoid morphology over the right posterior quadrant immediately after cessation of electrographic seizure activity on the sixth day of life (speed: 30 mm/s).

Seizures persisted despite treatment with phenobarbital, levetiracetam, lorazepam, clonazepam, pyridoxine, and folinic acid. Fosphenytoin provided some decrease in seizure frequency. A lidocaine infusion of 2 mg/kg/hr, titrated up to 4 mg/kg/hr, was initiated on Day 26 with immediate cessation of clinical and electrographic seizures. Results of the genetic sequencing were reported on Day 28, revealing a novel point mutation in *KCNQ2* at position c.545, involving a G to T substitution [NM_172107.2],

leading to p.Val182Gly. The patient was then weaned off lidocaine infusion and 40 mg carbamazepine, PO BID (20 mg/kg/day), was introduced. Planned discharge was complicated by viral pneumonia requiring intubation and ventilation, extending the patient's stay in the NICU. No other seizures were noted during this period. The patient was discharged on Day 54 and has since been followed closely by the neurology department. She is now 13 months old and has remained largely seizure-free on carbamazepine, having only experienced two questionable seizure-like events at seven to 8 months of age with no further epileptic activity. Repeat EEGs have demonstrated normalization of background activity and seizure resolution, with no further instances of electrographic seizures or pointed theta wave patterns observed. However, follow-up neurological examinations continue to demonstrate abnormalities, including diffusely increased tone in limbs bilaterally, brisk reflexes, and exaggerated response to stimuli. Comprehensive developmental assessment at one year of life revealed global developmental delay with a corresponding developmental age of 3-4 months. At 12 months, our patient demonstrated gross motor skills equivalent to 4-5 months, language skills equivalent to a 3-4-month stage of development, and fine motor/problem solving abilities equivalent to 3-4 months. She is receiving ongoing occupational, speech/language, and physical therapy for these concerns along with community infant development support.

Discussion

We report a child with neonatal epileptic encephalopathy secondary to a novel mutation in *KCNQ2*; c.545 T>G (p.Val182Gly). This variant was absent in the child's parents, consistent with a *de novo* mutation. It was not found in the Exome Aggregation Consortium Browser (Exome Aggregation Consortium 2015), ClinVar (Landrum *et al.,* 2014), or the Human Gene Mutation (Stenson *et al.,* 2014). The variant has been predicted to be deleterious using the SIFT tool (Kumar *et al.,* 2009), PolyPhen-2 (Adzhubei *et al.,* 2010), and Mutation Taster (Schwarz *et al.,* 2014). Missense mutations in *KCNQ2* have previously been described as the underlying cause of neonatal seizures and epileptic encephalopathy (Singh *et al.,* 1998; Weckhuysen *et al.,* 2012). Given this evidence, the detected mutation is the likely explanation for the extreme seizure burden observed in our patient during the neonatal period.

Our patient's favourable response to lidocaine and carbamazepine, both sodium channel blockers, further supports class IV evidence suggesting that AEDs with this mechanism of action are effective in reducing seizure burden in newborns with KCNQ2-NEE (Numis *et al.,* 2014; Pisano *et al.,* 2015). The positive response to lidocaine observed in our case highlights the utility of lidocaine infusions to control intractable seizures in the neonatal period. Lidocaine is an under-utilized AED, possibly due to concerns regarding increased risk of adverse cardiac events. However, apprehensions regarding the safety profile of this medication are largely unfounded, and retrospective analyses have suggested response rates of up to 70% in term infants when lidocaine infusions are initiated for intractable seizures as a second- or third-line medication (Weeke *et al.,* 2016). This case provides further evidence that lidocaine can be safely and effectively used in neonates after first-line AEDs fail to eliminate seizure activity.

Seizure control was achieved more rapidly in our case than in other reported cases of KCNQ2-NEE. Previous reports have suggested that early recognition and treatment of KCNQ2-NEE may improve neurodevelopmental outcomes (Serino *et al.,* 2013; Weckhuysen *et al.,* 2013), yet it is still unclear to what extent early treatment may affect prognosis. Our patient continues to have neurodevelopmental delays, despite seizure control within the first month of life. Further studies will be necessary to assess the impact of early treatment on subsequent neurodevelopment in KCNQ2-NEE.

Our patient demonstrated an inter- and postictal EEG pattern of repeated pointed theta waves, previously unreported in KCNQ2-NEE. In KCNQ2-NEE, ictal EEG findings have been characterized by focal, low-voltage fast activity, followed by recruiting theta rhythms. Interictal EEG patterns have been commonly reported as a burst-suppression pattern and discontinuous background (Millichap *et al.*, 2016). While these patterns are consistent with our case, we are not aware of any reports of recurrent pointed theta waves of lambdoid morphology in KCNQ2-NEE. Of note, a pattern called "theta pointu alternant" has previously been described in benign familial neonatal seizures (Dehan *et al.,* 1977), a disorder now known to be associated with KCNQ2 mutations. However, the theta pointu alternant pattern has in the past been considered to predict a favourable neurological prognosis (Plouin and Anderson, 2005), which is not the case for patients with KCNQ2-NEE.

Following consultation with international experts and a detailed review of the current literature, we feel that the observed pointed theta EEG pattern may be a unique EEG trait of patients with seizures secondary to *KCNQ2* mutations. This pattern could therefore potentially serve as an early EEG marker for this disorder, facilitating appropriate anticonvulsant treatment even prior to diagnostic confirmation by genetic testing. Further reports of this finding, potentially in patients carrying the same mutation as in our patient, are necessary to confirm whether this EEG pattern is

affiliated with a specific mutation, the syndrome of KCNQ2-NEE, or more broadly with seizures secondary to *KCNQ2* mutation, including benign familial neonatal seizures. □

Supplementary data.
Summary didactic slides are available on the www.epilepticdisorders.com website.

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The authors have no conflict of interest to disclose.

Legends for video sequences

Video sequence 1

At the beginning of the video, the neonate appears awake, demonstrating random movements. At 17 seconds, an episode of behavioural arrest starts, followed by arching, head version to the right, brief flexion of both legs, mouthing/chewing, and staring, lasting for 80 seconds. Electrographically, multifocal spikes and sharp waves are recorded in the first 20 seconds of the recording, followed by sudden generalized amplitude attenuation, then, at 30 seconds, right hemispheric low-amplitude rhythmic beta activity. At 55 seconds, a semi-rhythmic higher-amplitude, sharply configured theta-delta activity with phase reversal over T4 is recorded, lasting for 30 seconds, again turning into rhythmic low-amplitude right hemispheric beta activity, lasting for another 20 seconds, followed by right hemispheric, slowly resolving, amplitude depression. Starting at 3:03 minutes, two runs of rhythmic, 4-Hz lambdoid pointed theta waves are seen, the first one lasting for seven seconds and the second one, starting at 3:23 minutes, lasting for six seconds.

Video sequence 2

The video starts with a brief interictal sequence and the neonate is apparently sleeping. Ten seconds after the beginning of the video, the seizure starts electrographically with low-voltage fast rhythmic beta activity originating from the left temporal region, subsequently spreading to involve the whole left hemisphere. Five seconds later, the clinical seizure starts with head deviation to the left, flexion of the left arm, followed by flexion of both legs, tonic extension of the right arm, eye opening, and mouthing movements. There is tachycardia, as well as an increased respiratory frequency accompanying the seizure event. Clinical seizure manifestations stop after one minute, and the EEG demonstrates left hemispheric amplitude depression, lasting for two minutes, followed by focal left hemispheric high-amplitude, rhythmic 4-Hz lambdoid pointed theta waves at 2:55 minutes, lasting for five seconds.

Video sequence 3

The video starts with interictal EEG, demonstrating a brief three-second run of focal right hemispheric rhythmic, 4-Hz lambdoid pointed theta waves, maximum over the right temporal area. The neonate appears to be asleep, with eyes closed, but is being handled by nurses. Three seconds after the end of the theta pattern, the clinical seizure starts with head deviation to the left, extension of the left arm, flexion of both legs, eye opening, and mouthing movements, as well as tachycardia. Electrographically, the seizure starts with first generalized, then left hemispheric amplitude depression, followed by left hemispheric low-voltage fast rhythmic beta activity. The electroclinical seizure lasts for one minute, and is electrographically followed by left hemispheric amplitude depression lasting for two minutes, followed by left hemispheric high-amplitude, rhythmic 4-Hz lambdoid pointed theta waves at 3:13 minutes, lasting for six seconds. Another episode of left hemispheric high-amplitude, semi-rhythmic 4-Hz lambdoid pointed theta waves occurs at 4:38 minutes, lasting for five seconds. At 4:58 minutes, high-amplitude, rhythmic 4-Hz lambdoid pointed theta waves are recorded over the right hemisphere, lasting for four seconds.

Key words for video research on www.epilepticdisorders.com

Phenomenology: head deviation, eye deviation, oral automatisms, tonic posturing, tachycardia
Localisation: temporal
Syndrome: neonatal seizures
Aetiology: *KCNQ2* mutation

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TEST YOURSELF

(1) What disorders can be caused by *KCNQ2* mutations?

(2) What is the treatment for KCNQ2-related neonatal epileptic encephalopathy?

(3) What are the common EEG findings in neonates with KCNQ2-related neonatal epileptic encephalopathy?

Note: Reading the manuscript provides an answer to all questions. Correct answers may be accessed on the website, www.epilepticdisorders.com, under the section "The EpiCentre".