Clinical commentary

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KCNQ2 mutation in an infant with encephalopathy of infancy with migrating focal seizures*

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ABSTRACT – A male neonate presented with seizures at 18 hours of life, characterized by tonic posturing with eye deviation to the right, apnoea, bradycardia, and oxygen desaturation. Initial structural, metabolic, and infectious work-up was unremarkable. He continued to have seizures refractory to a variety of antiepileptic medications. A phenobarbital coma was trialled, leading to cessation of clinical seizures but continuation of electrographic status epilepticus. On EEG, ictal discharges originated from both the right and left hemispheres, migrating to the opposite hemisphere, consistent with encephalopathy of infancy with migrating focal seizures. At this time, he developed septic shock and was trialled on a ketamine infusion and ketogenic diet. Due to his poor prognosis, a goals of care discussion was carried out with the family, leading to withdrawal of care and his subsequent death at one month and seven days. A posthumous genetic panel revealed a *de novo KCNQ2* p.Ser247Leu variant, considered likely to be pathogenic. This is the third reported case of a *KCNQ2* mutation associated with an encephalopathy of infancy with migrating focal seizures phenotype. We discuss potential cellular mechanisms underlying this unique *KCNQ2* phenotype, as well as future therapeutic considerations.

Key words: epileptic encephalopathy, *KCNQ2*, migrating focal seizures, potassium channels, neonatal seizures

KCNQ2 is a gene that encodes for the Kv7.2 channel subunit of the Kv7 voltage-gated potassium channel. Neuronal Kv7 consists of homomeric or heteromeric combinations of four subunits encoded by a combination of *KCNQ2* (Kv7.2) and *KCNQ3* (Kv7.3) (Cooper *et al.,* 2000). Functionally, this current is a non-inactivating sub-threshold current that is important in stabilization of neuronal excitability (Niday *et al.,* 2017). Kv7 channels are thought to be localized at the axonal initial segments (AIS) and at nodes of Ranvier (Devaux *et al.,* 2004).

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Clinically, *KCNQ2* variant phenotypes vary in their severity, from the relatively benign self-limited neonatal familial epilepsy and myokymia, to the more severe *KCNQ2* encephalopathy and early myoclonic encephalopathy (Weckhuysen *et al.,* 2012; Kojima *et al.,* 2018).

Our patient, despite having a *KCNQ2* variant, presented with an electroclinical phenotype of encephalopathy of infancy with migrating focal seizures (EIMFS). EIMFS is a rare epilepsy syndrome characterized by seizure onset in the first six months of life, almost continuous migrating polymorphous focal seizures, multifocal ictal EEG discharges, and progressive deterioration of psychomotor development (Coppola, 2013). The aetiology of EIMFS is variable, with 39% of cases found to be due to variants in the sodium-gated potassium channel subunit KCNT1, as well as causative variants found in *SCN1A* and *SCN2A* (Coppola, 2013; Howell *et al.,* 2015; Lim *et al.,* 2016). This case demonstrates the third known case of EIMFS due to a *KCNQ2* variant (Duan *et al.,* 2018; Spagnoli *et al.,* 2018).

Case study

This male patient was the second child born to non-consanguineous parents at 38 weeks gestation via a planned Caesarean section. Pregnancy was uncomplicated with normal ultrasounds and regular antenatal care. His birth was complicated by meconium stained liqueur, and APGARs of 8, 4 and 6. He subsequently became apnoeic and required positive pressure ventilation and continuous positive airway pressure support. His birth weight, length, and head circumference were between the 50th-90th percentiles. At 18 hours of life, the patient exhibited abnormal tonic posturing in his upper extremities, associated with apnoea, oxygen desaturation, and bradycardia. This episode lasted 10-15 seconds and reoccurred four times over the next 12 hours with no clear antecedent. He was treated with a phenobarbital load and started on ampicillin and tobramycin. Initial blood workup was normal. Initial examination was unremarkable other than hyperreflexia noted on the left hemibody. Subsequently, a complete workup was undertaken to rule out structural, metabolic, and infectious causes. Results returned normal other than non-specific patchy areas of hyperintense T2 signal in the deep white matter on brain MRI.

Phenobarbital maintenance was initially trialled, with EEG showing reduced amplitude of background activity, burst suppression during sleep, frequent abnormal waves from both hemispheres, and frequent bilateral sharp-wave transients from central temporal regions predominantly. Clinical seizures continued, so phenytoin maintenance therapy and a midazolam infusion was started. EEG at the time then revealed cessation of clinical seizures but a desynchronized background with multiple sharp waves from either hemisphere. Midazolam was then discontinued due to hypotension but phenytoin was continued for a week. Reassessment of continuous EEG monitoring subsequently demonstrated that on phenytoin, clinical seizures returned with eye deviation and tonic posturing, with the persistence of frequent polymorphous ictal episodes originating from one hemisphere, migrating and subsequently terminating in the opposite hemisphere, fitting the electroclinical criteria of EIMFS. A representative ictal event is shown in *figure 1*. A comprehensive genetic panel was then sent to investigate a genetic cause.

A phenobarbital and midazolam-induced coma was then initiated. Despite initial seizure reduction, after six days, the patient began experiencing frequent

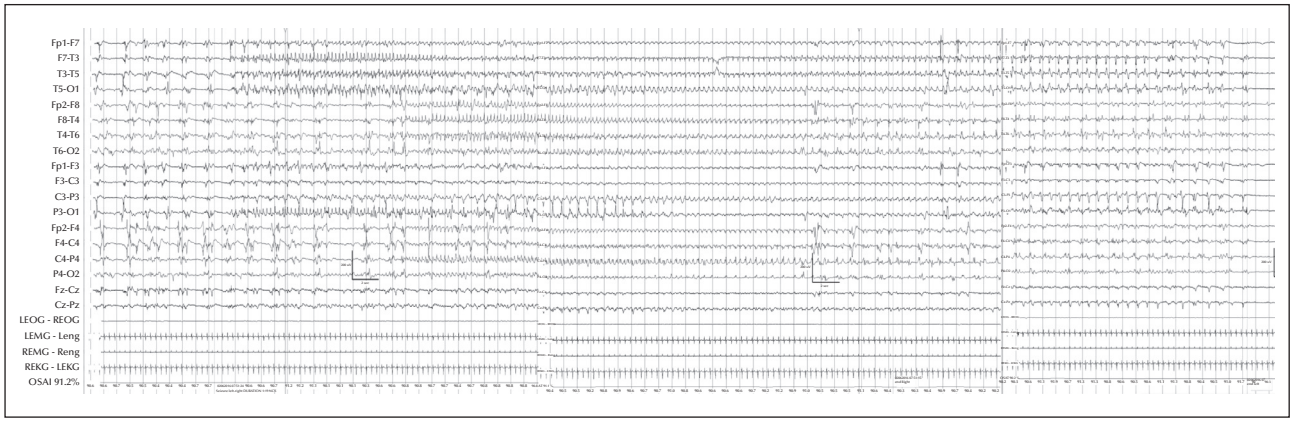

Figure 1. A representative ictal event of the patient.

electrographic multifocal seizures. After a week, he developed septic shock and was weaned off phenobarbital. Next, ketamine infusion and the ketogenic diet were trialled. Initially, there was seizure control, but his EEG background remained excessively discontinuous and asynchronous. A family meeting was held to discuss the patient's poor prognosis and his parents decided to withdraw care. He passed away aged one month and seven days old.

Posthumously, the genetic panel showed a *de novo KCNQ2* p. Ser247Leu pathogenic variant, as well as a second maternally inherited *KCNQ2* variant, at p.Ser374Pro, that is thought to be benign.

Discussion

The p.Ser247Leu mutation is a novel variant occurring within the pore of the Kv7.2 channel. Previously, one other case was reported with pathogenic variant due to missense mutation at this amino acid residue, p.Ser247Trp. The patient with this variant presented with neonatal seizure onset at Day 1, remitting with ACTH treatment at 13 weeks, but with moderate to severe developmental delay at two and a half years of age. On EEG, the patient had asynchronous background activity with burst-suppression pattern and multiple paroxysmal abnormalities, with ictal activity of different hemispheric origin (Dedek *et al.,* 2003).

With both variants involving the replacement of the polar serine with non-polar amino acids within the pore of Kv7, it is possible that the functional impact of these mutations would be similar; a reduction in Kv7-associated current leading to increased neuronal excitability. *In vivo*, increase in Layer 2/3 pyramidal neuronal excitability has been shown in the mouse neocortex by conditionally ablating and introducing a loss of function *KCNQ2* variant (Niday *et al.,* 2017). The patient described by Spagnoli *et al*. (2018) with EIMFS due to a *KCNQ2* variant had a deletion of the non-polar phenylalanine within the pore of the channel (p.Phe305del), supporting the conclusion that variants affecting the pore of Kv7.2 can result in this phenotype. Although the reduction in Kv7-associated current could lead to this severe phenotype, the p.Ser247Leu variant may lead to the EIMFS phenotype via a different mechanism.

A recent study noted that differences in phenotype between the p.Ala294Val and p.Ala294Gly *KCNQ2* variants was unlikely to be due to reduction in current, but rather due to reduction in targeting of the Kv7 channels to the AIS (Abidi *et al*., 2015). The patient described by Duan *et al*. with the EIMFS phenotype also harboured this p.Ala294Val *KCNQ2* variant, suggesting that improper mobilization of Kv7 channels can also result in this severe syndrome (Duan *et al*., 2018). It is possible that in addition to causing a reduction in Kv7-associated current, the p.Ser247Leu variant causes improper channel localization. This is also possible due to the patient's maternally inherited variant, p. Ser374Pro. The p.Ser374Pro variant is located in the calmodulin binding site in the C-terminal tail of Kv7.2. *In vitro*, calmodulin binding to Kv7.2 has been shown to regulate the axonal surface expression and enrichment of channels at the neuronal axon (Cavaretta *et al.,* 2014). This variant may impair localization of these channels to the axon, and in synergy with the p.Ser247Leu variant result in the EIMFS phenotype. This hypothesis is less likely due to the mother being asymptomatic with this variant alone, although it is possible that she exhibits mosaicism. Future clarity concerning the physiological effects of these variants could be elicited through neurophysiological studies.

If a patient is found to have EIMFS secondary to a *KCNQ2* variant, an initial trial of carbamazepine should be considered, as complete seizure control was achieved with a patient with EIMFS with a *KCNQ2* variant (Spagnoli *et al.,* 2018). Carbamazepine should also be considered as it led to seizure cessation in six patients with *KCNQ2* encephalopathies. Phenytoin also led to seizure cessation in five patients in the same study, but unfortunately was ineffective in the patient described in this case study (Pisano *et al.,* 2015). Secondly, ACTH should be considered, as seizure control was previously achieved in a patient with a similar variant, p.Ser247Trp, and this may also be possible in patients with the p.Ser247Leu variant (Dedek *et al.,* 2003). Thirdly, in patients with *KCNQ2* encephalopathy with variants in the channel pore, potassium channel agonists, such as retigabine, were shown to have a qualitative positive effect on seizures (Millichap *et al.,* 2016). Although retigabine has since been removed from the market, a future potassium channel agonist could be a therapeutic option. Although we are presenting, in this case, the outlook that it is best to control neonatal seizures, the effect of controlling neonatal seizures with antiepileptic medication on long-term outcome is not known due to the complex interaction of underlying seizure aetiology and the seizures themselves.

This case highlights the third known case of EIMFS caused by a *KCNQ2* variant. Potential mechanisms for the EIMFS phenotype include decreased Kv7-associated current, impaired channel trafficking, and reduced receptor density due to either a primary *de novo* p.Ser247Leu variant or a synergy between the *de novo* p. Ser247Leu and maternally inherited p.Ser374Pro variant. Treatment options for future cases with EIMFS due to a *KCNQ2* variant include the consideration of carbamazepine and phenytoin, ACTH, and future potassium channel agonists similar to retigabine. □

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TEST YOURSELF

(1) What genes have been implicated in encephalopathy of infancy with migrating focal seizures?

(2) What phenotypes have been associated with *KCNQ2* variants?

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".