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Rapid diagnosis of *KCNQ2* associated early infantile epileptic encephalopathy improved outcome

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Introduction:

Early infantile epileptic encephalopathies (EIEEs) are a group of disorders with seizures presenting early in life. EIEE is associated with significant mortality and morbidity. Approximately 50 percent of the affected patients die in infancy. Those who survive develop therapy-resistant epilepsy and significant developmental delays¹. Structural brain lesions, metabolic disorders and genetic mutations, including *KCNQ2*, have been linked to EIEE^{1, 23}. Here, we report two neonates with EIEE due to *KCNQ2* mutations, one with a novel mutation diagnosed through the rapid genomic sequencing program at Rady Children's Institute for Genomic Medicine (RCIGM) and one diagnosed classically, and demonstrate how rapid diagnosis positively impacted care.

Case presentation:

Table 1 summarizes the genetic mutation, EEG and MRI findings, clinical presentation, and anti-epileptic drugs (AEDs) for the patients.

Patient 1 and 2 presented shortly after birth for seizures. Initial evaluations were unrevealing. Video EEG was consistent with EIEE. In both patients, seizures were controlled by combination of phenobarbital, levetiracetam, topiramate and/or fosphenytoin. Fosphenytoin was tried for patient 1 but not continued due to difficulty achieving therapeutic levels. Their clinical course was complicated by the sedating effects of the AEDs, reemergence of seizure activity upon attempt to wean AED, and difficulty with oral feeding. For patient 1, a commercial genetic epilepsy panel was sent at Day of Life (DOL) 21, after other diagnostic

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workups did not illuminate an etiology. The results returned seven weeks later, after the patient had been discharged on phenobarbital, levetiracetam and topiramate, and showed a heterozygous pathogenic missense mutation in the *KCNQ2* gene (c.811C>T p.Ala294Val)⁴. For patient 2, the establishment of RCIGM allowed for rapid sequencing not available to patient 1. By the RCIGM nomination process at the time, RCIGM enrolled neonates, with parental consent, at the Rady Children's Hospital who were thought by the treating team to have a condition potentially attributable to a genetic disorder. Thus, patient 2 and parents underwent RCIGM rapid whole genome sequencing at patient's DOL 2, and a *de novo* missense *KCNQ2* variant (c.875T>C p.Leu292Pro) was reported at DOL 6. This variant had not been previously characterized but was deemed pathogenic based on the American College of Medical Genetics variant classification criteria⁵. Per the RCIGM protocol, a commercial epilepsy panel was also sent and confirmed the pathogenic variant. Carbamazepine was added given previous reports on sodium-channel-targeting AEDs and their improved efficacy on *KCNQ2* associated EIEE⁶. Phenobarbital and topiramate were successfully weaned. Patient 2 was discharged on carbamazepine and levetiracetam at DOL 19. In contrast, patient 1 was discharged at DOL 60 due to difficulty balancing seizure control with sedation and feeding. Patient 2's significantly shorter hospital stay resulted in an 11-fold less hospital-related cost (8.6% of patient 1). At the 9-month clinic visit, patient 2 was meeting developmental milestones and remained seizure-free with carbamazepine and levetiracetam therapy. Unfortunately, patient 1 relocated after discharge and no follow-up information was available.

Discussion

EIEE is among the most severe epileptic syndromes. Clinical studies on patients with *KCNQ2*-associated epileptic encephalopathy have demonstrated improved seizure control with AEDs that target sodium channels⁶. Here, we report a new EIEE-related *KCNQ2* variant. We demonstrate that a rapid genetic diagnosis of the *KCNQ2* mutation allowed for a targeted medication regimen that rapidly controlled the seizures, shortened the hospital stay, improved prognosis, and improved health-care system efficiency. Thus, when indicated, a rapid genetic diagnosis may significantly change clinical practice and outcome. The emergence of targeted therapy for challenging neurological conditions should make genetic testing an early part of the diagnostic algorithm, especially if the initial infectious, metabolic and neuro-imaging evaluations returned unrevealing.

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Table 1:

Summary of patients' *KCNQ2* mutations, imaging findings, medications tried and clinical courses. PHB: Phenobarbital, LVT: Levetiracetam, B6: Vitamin B6, TPM: Topiramate, PHT: Phenytoin, CBZ: Carbamazepine.

Table 1	Patient 1	Patient 2
<i>KCNQ2</i> mutation	c.811C>T p.Ala294Val	c.875T>C p.Leu292Pro
Gestational age (wk)	41 2/7	37 3/7
Seizure onset	Day of life 1	Day of life 1
Initial EEG characteristics	EEG began at Day of life 1. In both sleep and awake states, there was discontinuity with epochs of asymmetric low voltage suppression. There were frequent to abundant interictal epileptiform discharges in either hemisphere or midline.	EEG began at Day of life 1. In both sleep and awake states, there was discontinuity with cerebral bursts between 1–10 seconds. In between the bursts were epochs of complete suppression in either or both hemisphere. There were abundant epileptiform discharges in either hemisphere or midline.
Inter-ictal background	Poorly organized background with frequent to abundant epileptiform discharges intermixed with asynchronous attenuations	Poorly organized background with near continuous epileptiform discharges intermixed with mostly synchronous attenuations
Ictal	Electrographical seizures started with diffuse or unilateral attenuation of the background with low voltage fast rhythm then evolved into a 2–3Hz spike and wave pattern in either or bilateral hemisphere or at the midline.	Electrographical seizures began with diffuse medium amplitude fast activity that abruptly attenuated. This was followed by diffuse 1–2Hz spike and wave activity that alternated with 3–5 second episodes of profound suppression. The suppression became complete at the cessation of the seizure.
MRI findings	MRI obtained at day of life 3, a small focus of reduced diffusion was seen in the left posterior parietal white matter. Repeat MRI on day of life 10 no longer showed the reduced diffusion and was otherwise unremarkable.	MRI obtained at day of life 2 and no abnormalities were noted.
Medications tried	PHB, LVT, B6, TPM, PHT,	PHB, LVT, TPM, CBZ
Days of life at discharge	60	19