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KCNQ2 encephalopathy

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Clinical/Scientific Notes

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KCNQ2 ENCEPHALOPATHY: DELINEATION OF THE ELECTROCLINICAL PHENOTYPE AND TREATMENT RESPONSE

Neonatal-onset epilepsies are rare conditions, mostly genetically determined, that can have a benign or severe phenotype.[1,2] There is recent recognition of de novo *KCNQ2* mutations in patients with severe neonatal-onset epilepsy with intractable seizures and severe psychomotor impairment, termed *KCNQ2* encephalopathy.[3,4] This is a rare condition and all patients reported so far were diagnosed well after the neonatal period.[3,4] We report on 3 new cases of *KCNQ2* encephalopathy diagnosed in the neonatal period and studied with continuous video-EEG recording. We describe a distinct electroclinical phenotype and report on efficacy of antiepileptic drug (AED) therapies.

Classification of evidence. This study provides Class IV evidence that oxcarbazepine/carbamazepine is effective in reducing seizures in newborns with neonatal epileptic encephalopathy associated with heterozygous de novo missense mutations in the *KCNQ2* gene.

Methods. We reviewed the clinical details and video-EEG monitoring of patients with neonatal epileptic encephalopathy who, on genetic testing, demonstrated disease-causing mutations in *KCNQ2*. Details of genetic testing are found in appendix e-1 on the *Neurology*® Web site at www.neurology.org.

Standard protocol approvals, registrations, and patient consents. Parents gave informed consent to this study, which was approved by the local human research committee.

Results. We identified 3 newborns with neonatal epileptic encephalopathy associated with novel heterozygous de novo missense mutations in the *KCNQ2* gene (appendix e-1). Family histories were all negative for epilepsy or mental retardation. We describe in detail the clinical characteristics; genetic, EEG, and MRI findings; and trialed AEDs (table).

In all infants, neurologic examination was abnormal from the very first days of life, even prior to seizure onset, and demonstrated lack of visual fixation, decreased spontaneous movements, and axial hypotonia. Seizures began in the first week of life in all cases. Semiology was characterized by tonic head, conjugate eye, and mouth deviation, associated with unilateral tonic abduction of the limbs, apnea, and desaturation requiring oxygen administration (videos 1 and 2, video legend). Ictal and interictal EEGs are shown in figures e-1 and e-2.

After several treatments had failed, oxcarbazepine/carbamazepine was initiated at 3 months, 13 months, and 4 months of life in cases 1, 2, and 3, respectively. Patients 1 and 2 experienced a dramatic reduction of seizure frequency, with seizure freedom within 2 weeks of treatment. Patient 3 was treated with carbamazepine for 10 days with no clear improvement and died shortly after of respiratory failure in the setting of infection. Patients 1 and 2 remained seizure-free on follow-up at 12 and 30 months of age, respectively. However, both infants showed severe psychomotor delay, quadriplegia, axial hypotonia with appendicular hypertonia, and a tendency to opisthotonic posturing.

Discussion. Prolonged video-EEG monitoring is a useful tool in the diagnosis of neonatal-onset epileptic encephalopathies, allowing for accurate recognition of electroclinical syndromes. A precise diagnosis often has implications for management and prognosis. We observed a similar electroclinical pattern in 3 newborns with *KCNQ2* encephalopathy characterized by focal tonic seizures affecting alternatively both sides of the body and ictal discharges involving the left or right hemisphere, with a severely abnormal background characterized by multifocal epileptiform abnormalities and random attenuations. A similar seizure type is reported in benign familial neonatal seizures (BFNS), which also can be associated with *KCNQ2* mutations. However, in comparison to BFNS, these infants were severely neurologically impaired from birth with axial hypotonia and lack of visual tracking, and their EEG was severely abnormal from onset.[5] Differently from Ohtahara syndrome and early myoclonic encephalopathy, we did not observe myoclonic jerks or tonic spasms at presentation or during several months of follow-up. Moreover, while EEG demonstrated transient periods of discontinuity after phenobarbital loading, it lacked the invariable and regular periodicity of the suppression-burst pattern of Ohtahara syndrome.[6] MRI abnormalities similar to those observed in our

Supplemental data at www.neurology.org

Table Genetic, clinical, and EEG characterization in KCNQ2 encephalopathy in the neonatal period

	Case 1: de novo c.1734 G>C; p.Met578Ile	Case 2: de novo c.973 A>C; p.His324Arg	Case 3: de novo c.629 G>A; p.Arg210His
Clinical characteristics			
Gestational age, wk	34	40	37
Seizure onset	Fourth day of life	First day of life	First day of life
EEG characteristics			
Interictal background	Lack of organization and physiologic features with almost-continuous multifocal epileptiform abnormalities intermixed with random asynchronous attenuations	Lack of organization and physiologic features with almost-continuous multifocal epileptiform abnormalities intermixed with random asynchronous attenuations	Lack of organization and physiologic features with almost-continuous multifocal epileptiform abnormalities intermixed with random asynchronous attenuations
Ictal	Low-voltage fast activity followed by recruiting spikes or theta rhythms arising mainly from the central regions of either hemisphere, followed by focal spike-wave complexes and prolonged focal or diffuse postictal attenuation	Focal low-voltage fast activity followed by rhythmic theta rhythm arising mainly from the frontocentral region of both hemispheres, alternatively followed by diffuse marked postictal attenuation lasting up to 8 minutes	Low-voltage fast activity followed by focal theta rhythms involving the right or left hemisphere
MRI findings	At 20 and 33 days of life (with spectroscopy): progressive diffuse hypomyelination with marked thinning of the corpus callosum; T1 signal prolongation in the lentiform nuclei that normalized on day 33 of life	At 1 and 12 months of age (with spectroscopy): progressive diffuse hypomyelination with marked thinning of the corpus callosum and volumetric reduction of the frontal lobes and the midbrain	At 2 months of age: diffuse hypomyelination with marked thinning of the corpus callosum
Medications trialed	PB, LVT, TPM, VGB, CLB, CZP, KD, CBZ (effective), pyridoxine, PLP, folinic acid	PB, LVT, TPM, VGB, PHT, NZP, LGIT, CBZ (effective)	PB, LVT, TPM, VGB, VPA, CBZ, CZP

Abbreviations: CBZ = carbamazepine; CLB = clobazam; CZP = clonazepam; KD = ketogenic diet; LGIT = low glycemic index treatment; LVT = levetiracetam; NZP = nitrazepam; PB = phenobarbital; PHT = phenytoin; PLP = pyridoxal 5-phosphate; TPM = topiramate; VPA = valproic acid; VGB = vigabatrin.

cases have been reported in *KCNQ2* encephalopathy, but also in subjects with *STXBP1* mutations and during treatment with vigabatrin.[1]

The electroclinical findings in this report help to recognize a distinct neonatal phenotype and may guide the diagnostic workup, which should include *KCNQ2* testing.

We found a dramatic response with seizure freedom to carbamazepine. This was unlikely attributable to evolution of the syndrome, as just 1 of 8 infants with *KCNQ2* encephalopathy had seizure freedom by 3 months of age.[4] Carbamazepine stabilizes the inactive state of voltage-gated sodium channels, while *KCNQ2* mutations decrease the inhibitory potassium current on membranes.[2] Seemingly disparate, voltage-gated sodium channels and KCNQ potassium channels colocalize and are bound at critical locations of the neuronal membrane[7]; modulation of one channel may significantly affect the function of the channel complex. Accordingly, retigabine, which increases potassium current through the KCNQ channels, may also be of benefit in *KCNQ2* encephalopathy. Therefore, these patients could benefit from a trial of carbamazepine, followed by consideration of retigabine. Studies investigating the efficacy of these agents in *KCNQ2* encephalopathy and whether their early use is potentially of benefit in improving neurodevelopmental outcomes are warranted.

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