Clinical commentary

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A novel mutation in *KCNQ3*-related benign familial neonatal epilepsy: electroclinical features and neurodevelopmental outcome

Ettore Piro [1], Rosaria Nardello [1], Elena Gennaro [2], Antonina Fontana [1], Maurizio Taglialatela [3], Giuseppe Donato Mangano [1], Giovanni Corsello [1], Salvatore Mangano [1]

[1] Department of Sciences for Health Promotion and Mother and Child Care "G. D'Alessandro," University of Palermo, Palermo
[2] Laboratory of Human Genetics, Galliera Hospital, Genoa
[3] Unit of Pharmacology, Department of Neuroscience, Reproductive and Odontostomatological Sciences, University of Naples Federico II, Naples, Italy

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ABSTRACT – Benign familial neonatal epilepsy (BFNE) is caused, in about 5% of families, by mutations in the *KCNQ3* gene encoding voltage-gated potassium channel subunits. Usually, newborns with BFNE show a normal neurological outcome, but recently, refractory seizures and/or developmental disability have been reported suggesting phenotype variability associated with *KCNQ3*-related BFNE. Here, we describe a proband from a BFNE family carrying a novel variant in the *KCNQ3* gene. Regarding the paucity of data in the literature, we describe the presented case with a view to further establishing: (1) a genotype/phenotype correlation in order to define a BFNE phenotype associated with favourable outcome; (2) an electroclinical pattern associated with BFNE based on video-EEG recording; (3) appropriate first-line AEDs; and (4) the duration of AED treatment. The presented case from Day 3 exhibited a cluster of ictal events, identified as epileptic seizures on Day 10 based on continuous video-EEG polygraphy. The seizures were characterized by asymmetric tonic posturing, associated with a generalized decrease in EEG amplitude, and followed by bilateral asynchronous clonic movements associated with bicentral sharp-wave discharges. The seizures were refractory to intravenous pyridoxine, whereas levetiracetam resulted in rapid total seizure control which has remained to date. This study demonstrates that the novel heterozygous *KCNQ3* (c. 914A>T; p.Asp305Val) variant, affecting residues in the pore region, is associated with a specific electroclinical pattern and favourable neurodevelopmental outcome. [*Published with video sequence on www.epilepticdisorders.com*]

Key words: benign familial neonatal epilepsy, *KCNQ*, voltage-gated potassium channels, genotype-phenotype correlations, electroclinical features

VIDEO ONLINE

Correspondence:
Salvatore Mangano
Department of Sciences for Health Promotion and Mother and Child Care "G.D'Alessandro",
University of Palermo,
Palermo, Italy
<salvatore.mangano@unipa.it>

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Benign familial neonatal epilepsy (BFNE) is an autosomal dominant epilepsy syndrome characterized by frequent unprovoked focal or generalized tonic seizures, followed by apnoea and clonic movements with oculofacial features often associated with autonomic signs, starting around the second/third day of life and occurring during wakefulness and sleep, up to 30 times a day. The seizures often remit spontaneously within weeks or months, but some patients become seizure-free only after trials with different antiepileptic drugs (AEDs) (Ryan *et al*., 1991; Ronen *et al*., 1993). BFNE is caused in >80% of families by mutations in the *KCNQ2* and *KCNQ3* genes encoding for voltage-gated potassium channel subunits, which underlie a slowly activating, non-inactivating potassium current called M-current (Biervert *et al*., 1998; Charlier *et al*., 1998; Singh *et al*., 1998; Wang *et al*., 1998).

A reduction in M-current emerged as the common factor underlying neonatal seizures and haploinsufficiency, as the primary pathogenetic mechanism for BFNE (Soldovieri *et al*., 2007). Usually, newborns with BFNE show normal neurological and physical examination and unremarkable laboratory and neuroradiological investigations. Follow-up studies reveal that about 10-15% of patients develop a form of benign focal or generalized epilepsy later in life within a context of normal neurocognitive development (Ronen *et al*., 1993; Singh *et al*., 2003). Given the recent emergence of phenotype variability concerning the clinical course, the sensitivity to AEDs, and the treatment duration, in the present study, we describe the clinical course, electroclinical pattern revealed by video-EEG monitoring, response to AEDs, and the apparently favourable outcome of a proband from a BFNE family carrying a novel variant in the *KCNQ3* gene.

Case study

The proband was a 13-month-old male; the second born to non-consanguineous and apparently healthy parents at 38 + 6 weeks of gestation by elective Caesarean section following an uncomplicated pregnancy. The study was approved by the Ethics Committee "Palermo 1" of the University Hospital. Written informed consent for publication was obtained from the parents.

Apgar score at birth was 9 and 10 at one minute and five minutes, respectively. His weight was 3,240 g (36th centile), length 50 cm (44th centile), and head circumference 35 cm (63th centile).

From Day 3, he exhibited recurrent postprandial episodes of jerking involving the upper limbs, perioral cyanosis, and crying; symptoms considered to be associated with gastroesophageal reflux disease. As paroxysmal events recurred, on Day 9, the patient was referred to our NICU. On admission, the new-born showed mild axial hypotonia and reduced spontaneous motility. Complete blood count, procalcitonin, CRP, blood cultures, glucose, serum electrolytes, neonatal metabolic screening, and a head ultrasound were normal.

On Day 10, during a conventional EEG polygraphy (*see video*), the new-born showed, in active sleep, a cluster of three similar ictal events characterized by generalized or focal tonic (asymmetric tonic posturing) seizures with shallow breathing, mild desaturation, eye blinking, and tachycardia associated with a generalized decrease in EEG amplitude. The tonic component of the seizure progressed during a vibratory phase, gradually evolving into unilateral or bilateral asynchronous clonic movements, lasting for about a minute and associated with bicentral sharp-wave discharges. The focal seizures involved both sides, varying from one seizure to another one. The seizures ended without focal clinical and EEG signs or postictal EEG depression (*figure 1*).

After careful clinical and EEG evaluation suggesting the epileptic nature of paroxysmal events, we administered pyridoxine (100 mg; intravenous). Another similar seizure occurred three hours later. Therefore, after parental informed consent, we shifted to levetiracetam (LEV) (20 mg/kg; intravenous), repeated 12 hours later. A third brief seizure occurred 13 hours later; treatment with pyridoxine was interrupted and LEV was increased to 60 mg/Kg/day in two doses, resulting, after the first dose, in full seizure control. By Day 14, axial tone and spontaneous motility were normalised.

On Day 18, the infant was discharged, seizure-free, with oral LEV (200 mg/day). At one month of age, brain MRI and EEG were normal. At eight months of age, the baby showed normal global development and social contact. Oral LEV dosage (22 mg/Kg/day, equivalent to 200 mg/day) was then gradually withdrawn.

At clinical evaluation performed at 13 months and seven days of age, the child was alert, perceptive, and sensitive. He demonstrated a healthy interest in the testing materials with an appropriate level of activity, attention, adaptation to changes, and task persistence. He was socially engaged with the examiner, showing good communicative intent and reciprocity. He could stand without support. He vocalized in response to the examiner and to express attitude. His developmental functioning, assessed using the Bayley Scales of Infant and Toddler Development (Bayley III), showed scores in the average/upper average range (cognitive: 125; language: 94; motor: 91; social-emotional: 95; adaptive behaviour: 90). He walked without support at 13 months and 15 days of age.

The neurological signs of the proband observed in the neonatal period, the family history with three previous miscarriages, and the occurrence of uncertain paternal neonatal clinical events suggested that genetic testing

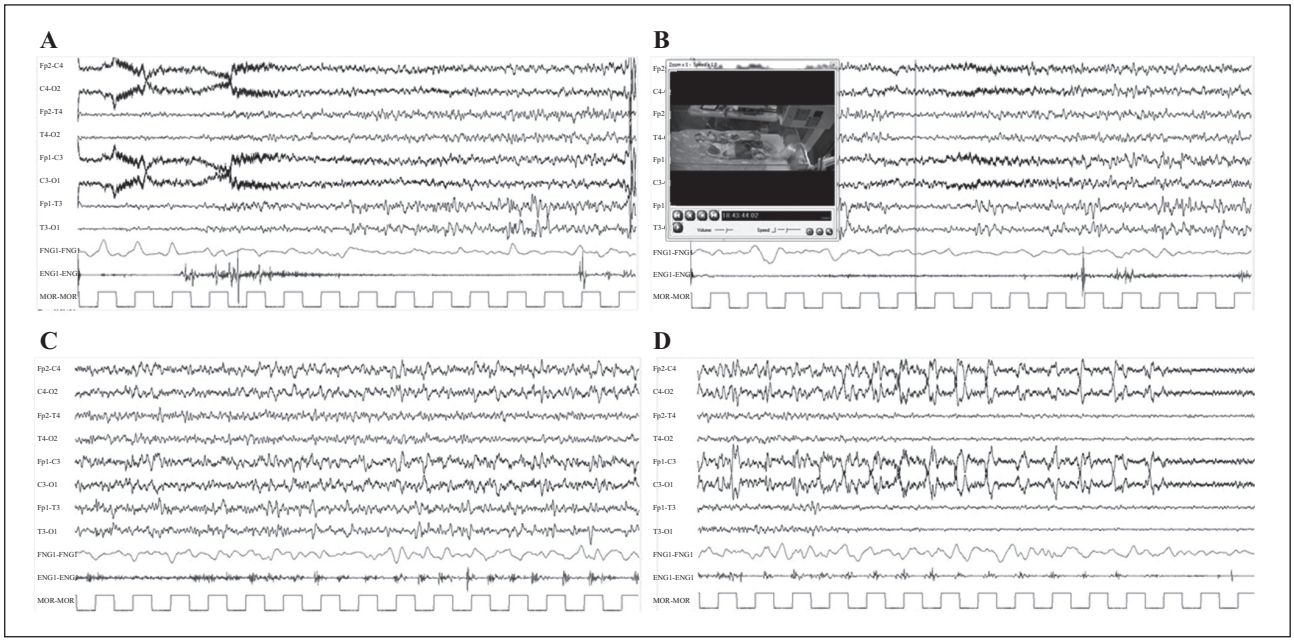

Figure 1. Electroclinical phenotype of the presented patient with BFNE. The seizure, following active sleep and arousal (A), is characterized by tonic extension and adduction of the upper limbs, flexion of the lower limbs, left trunk and head rotation associated with shallow breathing, tachycardia, and generalized decrease in EEG amplitude (B).
The tonic seizure evolves into a vibratory phase (C), and then gradually into bilateral asynchronous clonic movements of the limbs and ocular-facial regions associated with bicentral sharp-wave discharges (D).

should be performed. Based on a next-generation sequencing panel, not including the *KCNQ3* gene, no pathogenetically-relevant gene variants were detected. In close analogy to *KCNQ2* variants, phenotypic heterogeneity during the clinical course has also been reported in families carrying variants in *KCNQ3* (Miceli *et al*., 2017), therefore direct sequencing of the *KCNQ3* gene (NM_004519.3) was also performed, revealing the occurrence of a c.914A>T heterozygous variant. This nucleotide substitution, inherited by the symptomatic father, is responsible for the missense mutation, p.Asp305Val. The variant, affecting a highly conserved residue located in the S5-S6 pore region of the protein, is predicted to be "pathogenic" based on PolyPhen2 and Mutation Taster with a very high confidence score (>0.999). Multiplex ligation-dependent probe amplification of *KCNQ2* and *KCNQ3* did not disclose indels (*for more details, see the supplementary material*). The same variant was found in the father who likely suffered from neonatal epileptic seizures and in an asymptomatic sister. In addition, his paternal uncle, whose genetic data were not available, had neonatal seizures and an isolated seizure at 13 years old (*figure 2*).

Discussion

About 5% of families with BFNE carry *KCNQ3* pathogenetic variants with incomplete (0.8-0.85) penetrance (Miceli *et al*., 2017). *KCNQ3* mutations have been for a long time considered to cause a typical phenotype characterized by neonatal seizures that remit spontaneously after a few months with normal neurocognitive development (Charlier *et al*., 1998; Singh *et al*., 2003). Instead, in close analogy to the wide phenotypic spectrum associated with *KCNQ2* mutations, some *KCNQ3* mutations were recently found to be associated with more severe phenotypes characterized by refractory seizures and variable motor and cognitive impairment (Soldovieri *et al*., 2014; Miceli *et al*., 2015). The rare occurrence of *KCNQ3*-related BFNE and the uncertainty about the electroclinical phenotype, outlined mainly by retrospective studies or, sometimes, by incomplete clinical observations, has hampered the identification of accurate genotype-phenotype correlations. Thus, we believe that video-EEG monitoring is the best method to define a specific BFNE electroclinical pattern. We present the electroclinical, genetic, and developmental data from a family with neonatal seizures and a novel *KCNQ3* mutation identified in three affected individuals over two generations (*figure 2*).

The ictal electroclinical features, documented by video-EEG monitoring, showed initial asymmetric tonic posturing, shallow breathing, inconstant desaturation, and tachycardia, associated with a generalized decrease in EEG amplitude. The tonic phase was followed by unilateral or asynchronous bilateral clonic

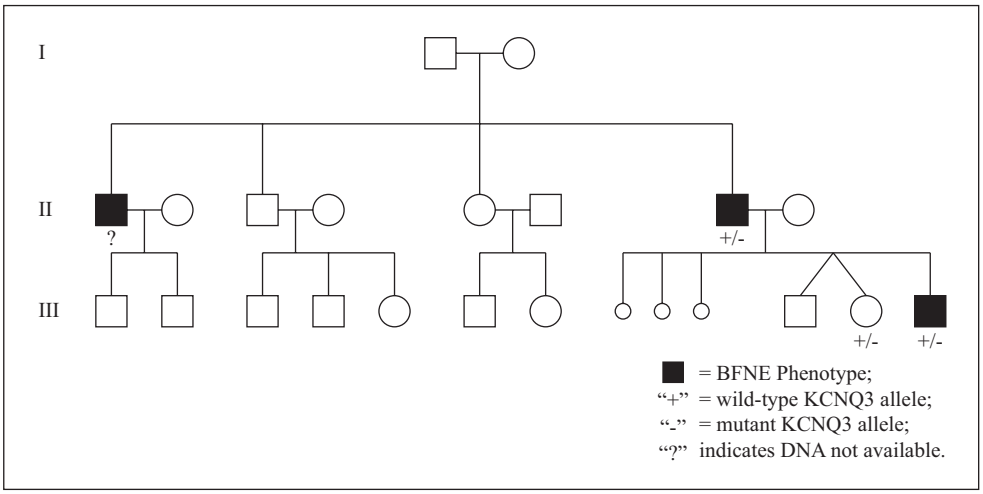

Figure 2. Pedigree of the family with BFNE.

movements associated with generalized sharp-wave discharges without postictal depression. Both clinical and EEG data of our patient seem to be consistent with the electroclinical pattern previously reported (Hirsch *et al*., 1993; Ronen *et al*., 1993; Maljevic *et al*., 2016; Sands *et al*., 2016). The *KCNQ3* variant found in our family is the substitution c.914A>T, which leads to the p.Asp305Val missense mutation. This substitution affects a residue located in the S5-S6 pore region of the protein, likely altering the potassium channel structure at this functionally-critical region. A mutation at the same codon (c.914A>G), but resulting in a different amino acid substitution (p.Asp305Gly), was found in a patient described by Ryan *et al*. (1991) exhibiting a typical BFNE phenotype, characterized by onset of seizures at two days, positive response to phenobarbital, seizure freedom from the third week of life, and normal psychomotor development at 10 months of age. When expressed with *KCNQ2* subunits, incorporation of *KCNQ3* mutant subunits into heteromeric channels decreased the maximal M-current by ~40%. Notably, both Asp305Gly found in the family studied by Ryan *et al*. and the Asp305Val variant described in the present study cause the replacement of a negatively charged amino acid with a smaller, non-polar amino acid. Such structural similarities likely translate into a comparable degree of channel dysfunction and current decrease, although functional studies would be needed to confirm such a hypothesis.

Until now, seizures in BFNE patients have been treated with various conventional AEDs (Miceli *et al*., 2015), and only recently have first-line drugs emerged. In particular, evidence indicates that carbamazepine or oxcarbazepine are safe and more effective, providing a rapid response, seizure control, shorter hospitalisation, and favourable long-term outcome for BFNE patients (Sands *et al*., 2016).

Our patient showed a rapid and effective response to LEV and remained seizure-free from the third dose, similar to the patient of Maljevic *et al*. (2016). The duration of treatment reported in previous studies is unclear, ranging from a few weeks to 18 months. In our case, we are unable to state whether the child recovered from active epilepsy before eight months of age, as a gradual reduction in LEV was initiated with termination of treatment at 10 months following a lack of seizure relapse. The electroclinical outcome of our patient seems to be consistent with the typical course of the disorder. The composite scores of Bayley III were within normal range with cognitive performance being particularly strong.

Similar to a previous report (Ryan *et al*., 1991), the developmental follow-up of our patient was limited to the first 13 months of age, however, the lack of seizure relapse without evidence of significant developmental delay suggests that the novel variant, c.914A>T (p.Asp305Val), is likely to be associated with a favourable outcome.

In conclusion, we demonstrate a novel variant in the *KCNQ3* gene within a family with rather typical BFNE electroclinical features, consistent with the previously described benign outcome associated with heterozygous variants affecting residues in the pore region of this voltage-gated potassium channel subunit (Miceli *et al*., 2017). □

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

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Legend for video sequence

On Day 10, the newborn showed, in active sleep, a cluster of three similar ictal events characterized by generalized or focal tonic (asymmetric tonic posturing) seizures with shallow breathing, mild desaturation, eye blinking, and tachycardia associated with a generalized decrease in EEG amplitude. The tonic component of the seizure progressed into a vibratory phase, gradually evolving into unilateral or bilateral asynchronous clonic movements, lasting for about a minute, and associated with bicentral sharp-wave discharges. The focal seizures involved both sides, varying from one seizure to another one.

Key words for video research on www.epilepticdisorders.com

Phenomenology: neonatal seizure
Localisation: focal seizure not otherwise specified
Syndrome: benign familial neonatal epilepsy (bfne)
Aetiology: KCNQ3 mutation

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TEST YOURSELF

(1) Which of the following statements about families with BFNE carrying *KCNQ3* pathogenic variants is correct?
A. About 15% show complete penetrance
B. About 10% show incomplete penetrance
C. About 5% show incomplete penetrance

(2) Which of the following statements about BFNE associated with *KCNQ3* mutations is not correct?
A. BFNE associated with *KCNQ3* mutation is an autosomal dominant epilepsy syndrome
B. *KCNQ3* mutations are always associated with severe phenotypes
C. The phenotypic spectrum associated with *KCNQ3* and *KCNQ2* mutations is similar.

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".