

Is benign familial neonatal *KCNQ2*-related epilepsy always familiarly benign?

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Abstract

A 1-year-old infant was referred for a diagnostic work-up, due to a past history of generalized clonic seizures migrating from one side of the body to the other side, of short duration, and presenting in cluster, occurred in the first days of life. He is a component a large family in whom several members were diagnosed and described in a previous report as affected by benign familial neonatal epilepsy (BFNE). This family has been followed-up for three generations and examined by report carried out in a single center and a personal interview. In a recent revision of the family, some members do not share the classical features of BFNE: one had the seizures onset at 3 months, another presented complex febrile seizures with EEG anomalies, and one suffered from partial seizures lasting until the age of 10 years. Looking at the data drawn from this family, and those from the literature, the term “BFNE” should be used with caution.

Keywords

Neonatal seizures, familial epilepsy, benign seizures, neonatal convulsions, *KCNQ2* mutation, *KCNQ3* mutation.

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Introduction

Benign familial neonatal epilepsy (BFNE) is a not uncommon clinical manifestation known for more than 50 years. The clinical features of BFNE are quite characteristic and consist of onset of seizures appearing in the first days of life in a well-being subject, with a family history of convulsive neonatal episodes that disappear within the first months of life and with a normal cognitive development [1-3].

The condition is inherited as an autosomal-dominant trait with no gender prevalence. BFNE has been recently associated with mutations in the *KCNQ2* gene, located on chromosome 20q13.33 [4-8]. Mutations causing BFNE are often inherited from affected parents [8].

In general, as per the definition, the course of intra-familial BFNE is not complicated by later epileptic manifestations and/or cognitive delay. As examples, neonatal seizures observed in 3 generations were reported by Rose and Lombroso [9] and in 8 members from 3 generations by Goutieres [10]: in all the cases, the convulsive episodes disappeared in the first months of life. Similar observations were published by Carton [11] in 8 family members plus a case report, and by Quattlebaum [12] in 15 members from 4 generations who suffered seizures in the neonatal period or early infancy and had a benign course. Furthermore, a previous publication by Pavone et al. [13] and a report by Wakai et al. [14] in 7 and 5 members, respectively, also showed similar results. In all of these individuals, the seizures were recorded in the neonatal period or in early infancy and in all cases the course was benign.

Conversely, among those experiencing BFNE, there are reports of patients being affected by epileptic disorders and/or cognitive delay as described since the first publications in this field. Rett and Teubel [15] are credited with having described some of the first family cases: they published an article on 8 members from 3 generations with neonatal convulsions starting on the 3rd day of life: the seizures disappeared in a few weeks and the child showed good cognitive

development. However, within this family, in some male newborns the seizures persisted until the adolescence. Subsequently, Bjerre and Corelius [16] published the article entitled *Benign familial neonatal convulsions* with 14 members belonging to 5 generations who presented frequent seizures starting in the 1st week of life and presenting a favorable outcome, both concerning the convulsive crises and the cognitive development. However, in this family some members continued having sporadic seizures until the age of 10 years.

Looking at the data drawn from the literature and from both the old and new observations, the latter based on molecular analysis, in the group of BFNE interfamilial and intrafamilial clinical heterogeneity exists with family members manifesting epileptic disorders and/or cognitive delay [8-17].

In this BFNE-*KCNQ2* report carried out in a single center and a personal interview, most of the members of the family presented with the classical characteristics of the disorders, with the exception of one who had the seizures onset not in the first days but at 3 months (**Tab. 1**). Moreover one member had complex febrile seizures at the age of 5 years and 6 months, with EEG epileptiform anomalies, and one with partial seizures lasting until the age of 10 years. Looking at the data drawn from this family, and those from the literature, the term “BFNE” should be used with caution.

Case report

A 1-year-old male infant was referred to the Unit of Pediatrics and Pediatric Emergency of the University Hospital, Catania, Italy, for a diagnostic work-up. He was born at term following an uneventful labor and delivery. The infant has 2 older brothers (aged 7 and 4, respectively), healthy. The mother was 37 years old and the father 40 years old at the time of gestation. The mother claimed having felt normal fetal movements and denied having had infectious diseases, hypertension, gestosis, or consuming alcohol or drugs during her pregnancy.

Birth weight was 2,900 grams, length 50 cm, and head circumference 35 cm. The Apgar score was 8 and 9 at 1 and 5 minutes, respectively. The first 2 days of his life were uneventful. Then the newborn showed multifocal clonic seizures migrating from one side of the body to the other side, of short duration, and presenting in cluster. In such occasions, cyanosis, eye deviation, and vomiting were present. The seizures were prevalent

Table 1. Clinical characteristics of the affected members.

Number	Sex	Birth weight	Perinatal asphyxia	Age of onset	Number of crises	Last crisis	Therapy	Last visit	Persistence of seizures	CNS	EEG
1	M	3,000 g	No	3-5 d	5	60 d	-	64 y	No	Normal	Normal
2	F	3,200 g	Mild	3 d	5	15 d	PB	37 y	No	Normal	Normal
3	F	4,100 g	No	3 d	3	5 d	PB	42 y	No	Normal	Normal
4	M	3,500 g	Mild	3 d	3	60 d	PB	39 y	No	Normal	Normal
5	M	3,300 g	No	3-5 d	4	15 d	PB	42 y	No	Normal	Normal
6	M	3,400 g	No	3-4 d	2-3/y	10 y	PB	12 y	Yes	Normal	Normal
7	M	3,500 g	No	5.5 y	1-2/y	-	-	5.5 y	Yes (complex febrile seizures)	Normal	Frontal spike waves
8	M	2,900 g	No	3-5 d	10-12	7 d	PB	3 y	No	Normal	Normal
9	F	3,100 g	No	3 m	5	8 m	PB	6 y	No	Normal	Normal

Proband is no. 8. All the patients have been personally observed by the Authors.
M: male; F: female; d: days; m: months; y: years; PB: phenobarbital.

in the right side. The ictal EEG, performed on the 3rd day of life, showed the presence of a chaotic background (Fig. 1). Post-ictal EEG at the age of 7 days was normal (Fig. 2).

On the basis of the familial history [13] diagnosis of BFNE was made, treatment with phenobarbital (5 mg/kg/day intra muscle [i.m.]) was started, and the crises persisted during the night and the

following day. Seizures reappeared on the 5th and 7th day, and were always of short duration.

Since then, no other convulsive episodes were reported. Treatment with phenobarbital was stopped at 4 months. At the physical examination the infant presented with good general conditions: weight was 9.600 kg, height 76 cm, and head circumference 45 cm (all within the normal ranges).

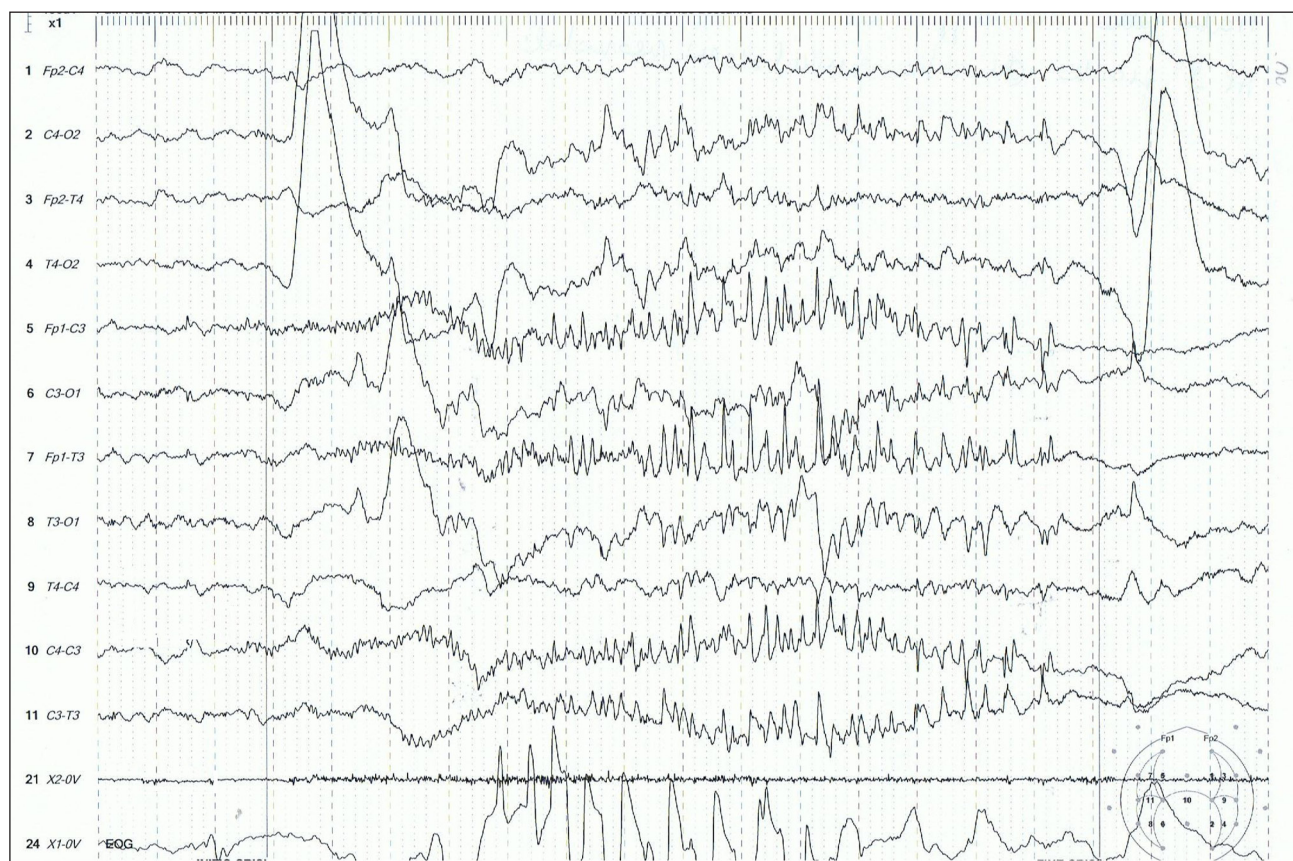


Figure 1. Ictal EEG of the proband, at the 3rd day of life during one of the daily crises, showing a severe background, with chaotic pattern.

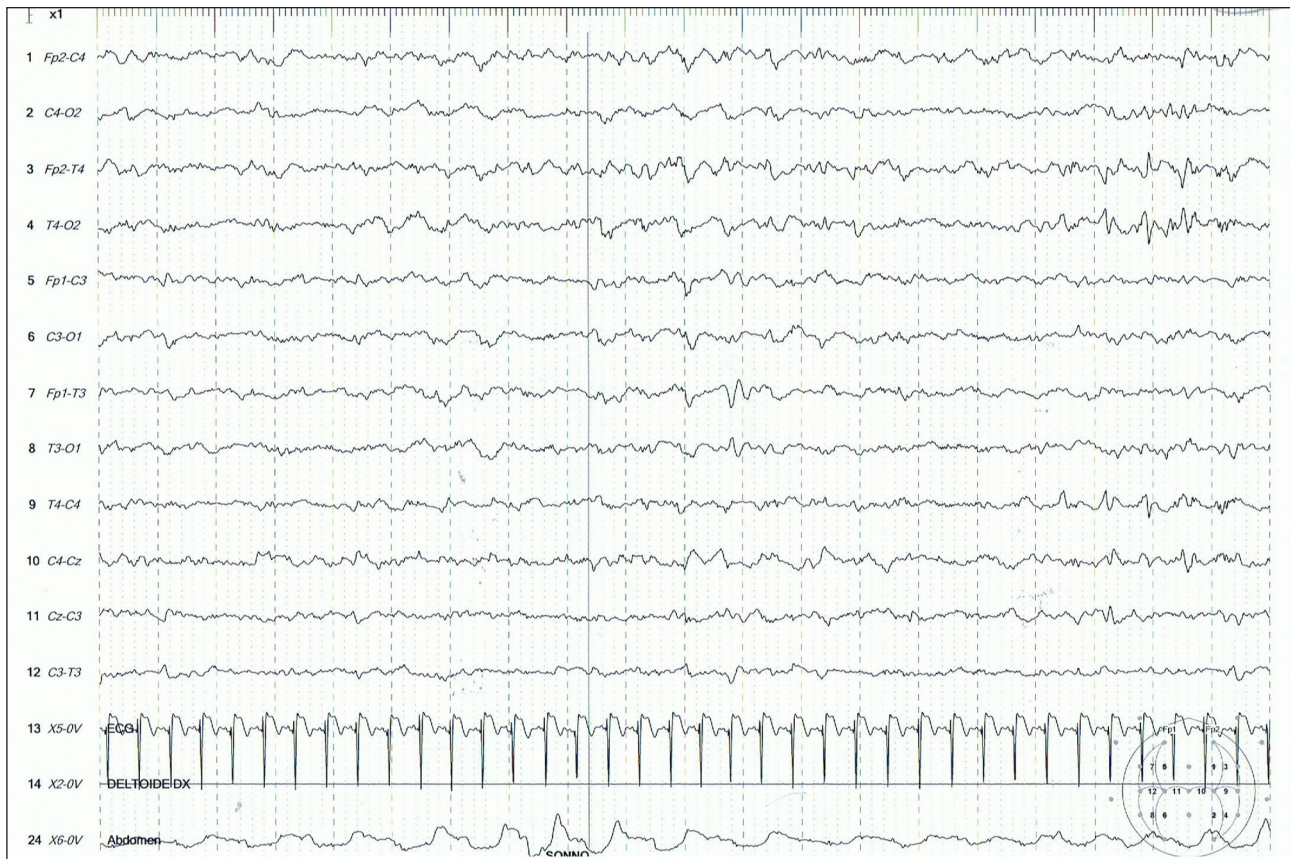


Figure 2. Post-ictal EEG of the proband at the 7th day of life, with a normal pattern.

Neither cutaneous or malformation anomalies were noticed. Heart, lungs, and hypochondriac organs were normal; developmental milestones were normally reached.

Laboratory investigations including a complete blood count, electrolytes, coagulation testing, blood lactate, pyruvate, glucose, ketones, total cholesterol, CK, plasmatic purines and pyrimidines, plasma and urine aminoacids, urinary organic acids were normal.

ECG, heart and brain ultrasounds were normal, as was the interictal EEG.

During the admission, the molecular analysis disclosed a pattern of C.1508 C>G in heterozygosis in *KCNQ2* gene. CGH array was negative.

At a follow-up at 3 years of age, the child is in good health, neurodevelopment is normal and no seizures have been reported. The pedigree of the family and a clinical summary of the affected members of the family are reported in **Fig. 3**. Most of the family members displayed a benign and typical course of BFNE; but in one member the seizures' onset was at the age of 3 months (rather than in the neonatal period), another member presented with epileptic seizures lasting to the age of 10 years, and lastly a 5.5-year-old boy presented

an episode of complex febrile seizures lasting more than 5 minutes, with hemi-lateralization and onset of seizures on the 3rd day of fever. The EEG in this boy, performed in another institution, showed the presence of spike and slow spikes bilaterally in the left temporal and right fronto-temporal regions; during the sleep such paroxystic anomalies increased (**Fig. 4**).

Genetic testing

A panel of codifying exons of 36 genes related to epilepsy and epileptic encephalopathy, using a re-sequencing with GS FLX Titanium 454 Roche platform was performed. Benign variants or variant present in more than 1% of the referral population (ESP6500_ALL and/or 1000g2012feb_ALL) were not reported.

A pathogenic variant c.1508 C>G in heterozygosis in the gene *KCNQ2* causing frameshift and precocious interruption of the protein was found.

Discussion

BFNE is a disorder with distinctive features consisting in: brief seizures starting on the 2nd-3rd day of life, spontaneous disappearance of seizures

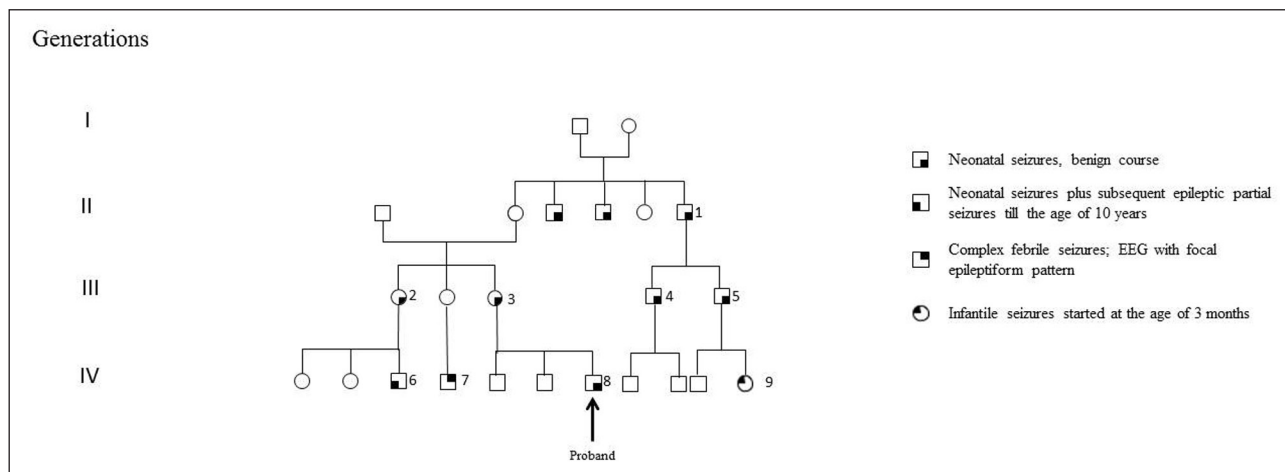


Figure 3. Genealogic tree of the family, spanning 4 generations.

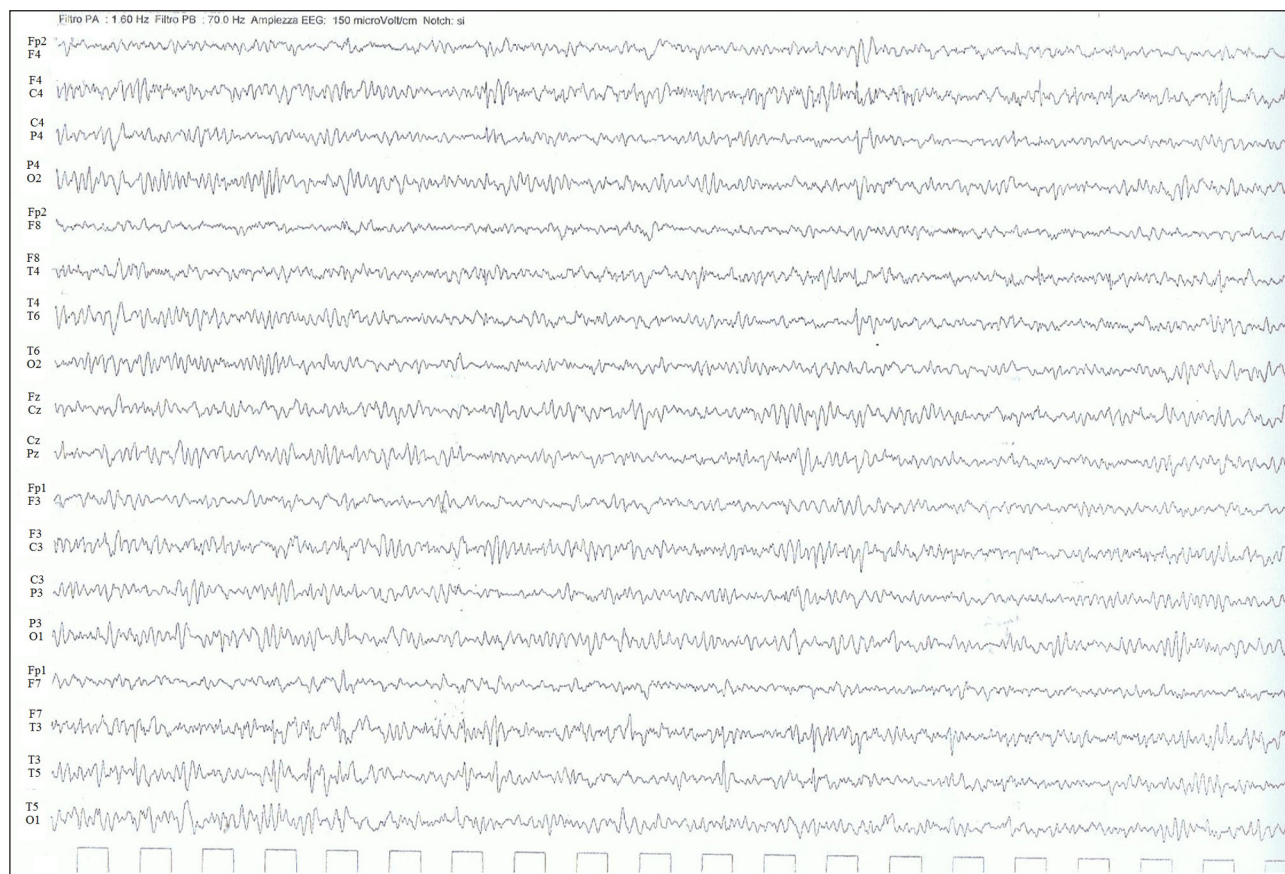


Figure 4. EEG of patient n. 7, showing paroxysmic anomalies. Asynchronous and synchronous spike and slow spikes can be observed in the left temporal and right fronto-temporal areas.

within a few months, positive family history of benign neonatal seizures, AD inheritance; absence of secondary causes of seizures, normal physical examination with no other epileptic episodes, and normal neurodevelopment [18].

The proband and his family history presented some of the characteristic clinical features of the BFNE. He had the first seizures on the 3rd day of

life (mainly clonic), migrating from one side to the other, all of short duration. Initially, treatment with i.m. phenobarbital was partially effective, as the seizures re-appeared in 5th and 7th days of life. After then, no other seizure was noted, and treatment was stopped at the end of 4th month. At a 3-year follow-up the child is neurologically normal; neither epileptic crises nor development delay

were reported. In the same family some members do not show the typical course of the disorder with onset starting in one member at the age of 3 months (rather than in neonatal period), a boy with epileptic seizures lasting to the age of 10 years, and a 5.5-year-old boy presented an episode of complex febrile seizures lasting more than 5 minutes, with hemi-lateralization and onset of seizures during the 3rd day of fever and EEG anomalies. In this family, male/female ratio was 8:3.

In the last decade, gene mutations and genetic variants have played a relevant role in the diagnosis of early-life and neonatal epilepsy. In the proband, molecular analysis disclosed a mutation in the *KCNQ2* gene, typical of this disease. BFNE is known to be associated with mutations in the *KCNQ2* gene, located on chromosome 20q13.33. This gene encodes for KV7.2, a subunit of a voltage-gated potassium channel and it is expressed in the central nervous system from the 22nd week of gestational age. The gene has a noticeable role in the inhibition of the neuronal excitability [4-7,19]. Mutations in *KCNQ2* are associated with several disorders, mainly with benign course and more rarely with severe brain involvement [19, 20]. Recently, diseases caused by *KCNQ2* mutations are reported under the term “*KCNQ2*-related disorders” and include the classical BFNE, which is the largest represented disorder but the Benign Familial Neonatal Infantile Seizures (BFNIS) and the Benign Familial Infantile Seizures (BFIS) are also included. The age of the clinical appearance of the seizures is distinctive for a diagnosis of each of these types of disorder. The *KCNQ2*-related disorders are also associated, even if rarely, with epileptic encephalopathy under the term “*KCNQ2*-encephalopathy”, in which affected members present with intractable (mainly tonic-clonic) seizures, presenting in the 1st week of life with an anomalous EEG pattern, showing burst-suppression or multifocal epileptiform pattern. In the affected patients, the brain MRI shows abnormalities located to the basal ganglia or thalamus [21]. The outcome for the affected patients is usually severe.

BFNE has also been reported, although more rarely, in subjects with mutations in *KCNQ3*, a gene coding for the KV7.3 voltage-gated potassium channel [22].

It is now quite clear that the *KCNQ2*- and *KCNQ3*-related disorders represent a continuum of clinically heterogeneous features ranging from benign seizure (BFNE) to severe epileptic

encephalopathies [6]. The *KCNQ2*-related epilepsy has been the object of some recent studies. In 17 patients/families with a diagnosis consistent with BFNE, Soldovieri et al. [23] found 16 different heterozygous mutations in *KCNQ2* including 10 substitutions, 3 insertions, and 3 large deletions. One substitution was found in *KCNQ3*. Allen et al. [21] report on 4 infants who presented with neonatal or infantile seizures: among these, 3 infants carried abnormalities in *KCNQ2* and 1 infant had a *KCNQ3* mutation. According to these authors, the difference in the *KCNQ2* mutation is cause of the variability of the phenotype: an intragenic c.419-430 duplication was found in the infant with BFNE while a 0.76-1Mb 20q13.3 contiguous gene deletion was present in an infant with seizures started at the age of 3 months, and a recurrent *de novo* missense mutation C.881 C>T in a neonate with *KCNQ2* encephalopathy. Mutations in *KCNQ3*, c.989 G>A were observed in an infant with BFNE.

In a study regarding familial neonatal seizures observed in subjects of 36 families, Grinton et al. [4] screened for *KCNQ2*, *KCNQ3*, *SCN2A*, and *PRRT2* mutations and found the following results: 33 families presented with the clinical features of the classic BFNE, and among these, 27 showed the *KCNQ2* mutations, 1 presented with *KCNQ3* mutation, and 2 presented with *SNC2A* mutations. In 31% of these subjects, the seizures persisted after the age of 6 months and the higher number of neonatal seizures was associated with higher frequency of later seizures.

KCNQ2 mutations are the most frequent anomaly reported in the cases of BFNE involving about the 60-70% [4-6] of cases. A novel mutation c.1126_1127 del A in exon 9 of *KCNQ2* was found in a large family from Emirates, with BFNE type 1 [24].

There is no agreement on the treatment of the seizures in newborn patients suspected to be affected by BFNE according to the clinical examination and the family history. Treatment of convulsing newborns is generally performed with intravenous boluses of phenobarbital at the dosage of 0.1-0.3 mg/kg or by i.m. injection of 5 mg/kg/day. Treatment is advised to be hold for 4 to 6 months. A recent re-evaluation of the use of phenobarbital in the treatment of neonatal seizure has been questioned as such treatment causes subsequent problems [25]. Moreover, a recent observation by Maeda et al. [26] claimed having used massive doses of phenobarbital and

midazolam to treat seizures in a patient with BFNE causing paradoxical neuronal excitation and severe epileptic encephalopathy. No response to the treatment with phenobarbital and phenytoin was reported in a convulsing newborn with BFNE, and the subsequent treatment with vigabatrin was successful [27].

BFNE is a not rare event in the neonatal age. In most of the cases, the outcome is favorable both in the affected newborn and in the components of the family with this disorder. In the present family, the outcome was favorable in most of the family members, but variability of the clinical expression of BFNE was observed at the age of presentation (infantile rather than neonatal) in 1 member, a complex febrile seizure was reported in another, and epileptic crises till the age of 10 years in another.

Conclusion

This report, carried out in a single center and a personal interview, and other similar cases in the literature highlight that the term “BFNE” could not always be suitable and such a diagnosis should be reconsidered and assigned with caution.

Declaration of interest

The Authors declare that there is no conflict of interest.

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