Benign familial neonatal seizures

Author: Doctor Maria Roberta Cilio[1]
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[1]Division of Neurology, Children's Hospital "Bambino Gesù", Piazza S. Onofrio 4, 00165 Rome, Italy. mailto:cilio@opbg.net

Abstract
Benign familial neonatal seizures (BFNS) is a rare condition of autosomal dominantly inherited idiopathic epilepsy of the newborn characterized by partial or generalized seizures, which occur during wakefulness and/or sleep. Seizures typically start in the first days of life and remit spontaneously by approximately 4 months of age. However, about 10 to 15% of patients have febrile or afebrile seizures later in childhood. Seizures observed in these newborns are brief and of a mixed type, starting with tonic posture, apnea, and often progressing to clonic movements and motor automatisms. The neonates are neurologically normal and neurocognitive development is usually normal. Electroclinical events are not specific and BNFS remains a diagnosis of exclusion. Prevalence of the syndrome is currently unknown. Genetic linkage studies have mapped two disease loci for BFNS, EBN1 on chromosome 20q13.3 and EBN2 on chromosome 8q24, indicating a genetically heterogeneous disorder. The causative genes, KCNQ2 on 20q and KCNQ3 on 8q, were identified as voltage-gated potassium channel genes. A form of idiopathic generalized epilepsy (EGI) with autosomal dominant inheritance and mapping to 8q24 may be allelic to EBN2. The role of anticonvulsant therapy in promoting seizures remission in the neonatal period is not yet clear, but the outlook has been consistently favorable.

Key words
Neonatal epilepsy, benign familial neonatal seizures, voltage-gated potassium channel, channelopathies

Disease name and synonyms
Benign familial neonatal seizures (BFNS); Benign familial neonatal convulsions (BFNC)

Excluded diseases
Benign neonatal seizures, familial or not, remain a diagnosis of exclusion, and all possible causes of epilepsies, including pyridoxine dependency should first be ruled out.

Definition
BFNS is a rare autosomal dominantly inherited idiopathic epilepsy of the newborn characterized by partial or generalized seizures, which occur during wakefulness and sleep.

Differential diagnosis
BNFS can be distinguished from benign idiopathic neonatal seizures (BINS) on the basis

of the occurrence of similar events in relatives, consistent with its autosomal dominant transmission.
BNFS must also be differentiated from Benign familial infantile seizures (BFIS) or Benign familial infantile convulsions (BFIC) which occur between 4 and 8 months of age with clusters of similar seizures over a few days in a previously well, developmentally normal infant. In 5 families affected with BFIC, Guipponi *et al*. (1997) mapped the *BFIC* gene to chromosome 19 by linkage analysis. The identification of a common haplotype in these Italian 19q-linked BFIC families suggested a founder effect. A second BFIC locus, BFIC2 maps to 16p12-q12 (Caraballo *et al*., 2001). It is possible, however, that BFIC2 is allelic with the gene that is mutant in a related autosomal dominant phenotype showing benign infantile convulsions associated with paroxysmal choreoathetosis (ICCA) [Lee *et al*., 1998), Finally, a third BFIC locus, BFIC3, maps to 2q24 (Malacarne *et al*., 2001).
Benign familial neonatal-infantile seizures is a recently described autosomal dominant syndrome (Heron *et al*., 2002). In members of affected families, the intermediate age of onset is between 2 days and 3.5 months (predominantly after 1 month) with a mean offset of 3.8 months. Thirteen individuals from two families have recently been reported: all of them showed normal development and intellect in a long-term follow-up, and none of them had seizures after nine months. Benign familial neonatal-infantile convulsions has been recently associated with mutations in the sodium-channel subunit gene *SCN2A* (Heron *et al*., 2002).

Etiology
Familial epilepsy syndromes generally refer to epilepsies with identifiable inheritance. Due to their inheritance with high penetrance, some familial epilepsies have been recently associated with genetic defects. Although most forms of idiopathic epilepsies have a genetic component, only few specific syndromes are single-gene disorders (Berkovic and Scheffer, 1997).
BFNS is a monogenic epilepsy inherited via an autosomal dominant trait with high penetrance. Among monogenic epilepsies, BFNS represent so far one of the best recognized disease models of idiopathic epilepsies; therefore, investigation of the molecular mechanism(s) underlying BFNS is of fundamental relevance also for the treatment of idiopathic epilepsy in the adult population. Genetic linkage studies have mapped two disease loci for BFNS, EBN1 on chromosome 20q13.3 (Leppert *et al*., 1989) and EBN2 on chromosome 8q24 (Lewis *et al*., 1993), indicating a genetically heterogeneous disorder. Most families in which the disorder occurs are linked to chromosome 20. Seizures are characterized by paroxysmal neuronal excitability. Ion channels that regulate neuronal excitability have been proposed as possible epilepsy genes (Ptacek, 1997). Characterization of an interstitial deletion on chromosome 20q in one family led to clone the novel *KCNQ2* potassium channel gene (Singh *et al*., 1998) and identify five additional mutations in family with BFNS. Using sequence database and cDNA amplification, a homologous gene, *KCNQ3*, has been cloned, and a single mutation has been discovered in the only known family that shows genetic linkage to chromosome 8q (Charlier *et al*., 1998). Potassium channels are important for repolarizing action potentials. *KCNQ2* and *KCNQ3* are expressed in the brain and belong to a subfamily of potassium channel genes that have been implicated in other diseases. Mutation in *KCNA1* potassium channel gene cause episodic ataxia, a non-epileptic disorder with paroxysmal cerebellar symptoms. Because BFNS is associated with the loss of function of a potassium channel, the pathological neuronal hyperexcitability in this epilepsy syndrome is likely to be caused by impaired repolarization. The identification of mutation in the homologous *KCNQ2* and *KCNQ3* potassium channel genes in a single disorder support the hypothesis that these two potassium channel genes may make a up a single functional entity. Importantly, it has been recently demonstrated (Wang *et al*., 1998) that the M-current, a tonic inhibitory potassium current, is made up of the KCNQ2 and KCNQ3 proteins (Brown and Adams, 1980). The M-current has a major role in controlling excitability because it regulates the ability of a neuron to fire an action potential (Marrion, 1997; McKinnon, 2000). Pharmacological reduction of the M-current results in the excessive firing of action potentials typical of an epileptic seizure (Brown and Adams, 1980). A recent study (Singh *et al*, 2003) has expanded the naturally occurring mutation spectrum of *KCNQ2* and supported the previous findings that the C-terminus is the region that contains the most mutations. Moreover, it has been observed that *KCNQ2* mutations occurred in both neonatal-onset seizures and infantile-onset seizures (beyond 4 months) in a single family (Singh *et al*., 1998), and that three families with *KCNQ2* mutations have a subset of cases with infantile-onset seizures (Singh *et al*., 2003). However, a linkage analysis between BFIS and chromosome 20 markers performed in affected families (Malafosse *et al*., 1994) demonstrated that the *BFNS* gene is not responsible for BFIS.
Finally, we cannot exclude that a form of idiopathic generalized epilepsy (EGI) with

autosomal dominant inheritance and mapping to 8q24 may be allelic to EBN2 (Zara *et al*., 1995).

Clinical description
BFNS is a rare familial condition characterized by clusters of generalized and partial seizures affecting exclusively neonates and remitting spontaneously. Seizures typically start around day 3 of life and most often disappear after several weeks or months. Seizures observed in these newborns are brief and of a mixed type, starting with tonic posture, and other symptoms such as apnea, and other autonomic features may occur. The seizures often progress to clonic movements and motor automatisms. The postictal state is brief, and the neonates look normal in the interictal period (Ronen *et al*. 1993). Seizures reoccur frequently up to 20 times per day. The ictal electroencephalogram (EEG) pattern with generalized suppression of amplitude at onset may be unique. Interictal EEG is either normal or shows minimal focal or multifocal abnormalities or a pattern of "theta pointu alternant". Although, this pattern is present in almost 60% of cases (De Weerd *et al*, 1999), it is not specific for this syndrome. It is characterized by a dominant theta activity, alternating or discontinuous, unreactive, with sharp waves. EEG patterns suggestive of poor prognosis, such as paroxysmal or inactive EEG, have never been reported. The neonates are neurologically normal. Neurocognitive development is usually normal. According to the international classification of epilepsies, the BFNS syndrome belongs to the idiopathic generalized epilepsies, but some authors (Mizrahi and Kellaway, 1987) consider that the electroclinical presentation suggests an age-dependent partial idiopathic epilepsy.

Disease course
The natural course of the seizures is self-limited. Seizures stop spontaneously within a few days or weeks. However, about 10 to 15% of patients have febrile or afebrile seizures later in childhood, often provoked by unexpected stress (Ronen *et al*.,1993; Berkovic *et al*., 1994). A single family (Maihara *et al*., 1999) with neonatal seizures, which remit at about 4 months and are followed, in two patients, by progression to rolandic seizures at around 4 years, has been recently reported. The rolandic seizures remit in adolescence and all the family members had normal psychomotor development, with neurological sequelae. Other families have febrile seizures, absence seizures, and generalized seizures beginning as early as 1 year of age and show considerable intrafamilial variability in age and type of seizures.

Diagnostic methods
BNFS rests entirely on the occurrence of similar events in relatives, consistent with an autosomal dominant transmission. However, clinician must be aware of the fact that the definition of the syndrome is rather loose and that BFNS remains a diagnosis of exclusion, and all possible causes, including pyridoxine dependency, should have been ruled out. Genetic confirmation of the diagnosis is not yet available in the current practice. In some families, linkage was neither found with chromosome 20 nor with chromosome 8, confirming genetic heterogeneity.

Treatment
Regarding the seizures in the neonatal period, the role of anticonvulsant therapy in promoting remission is not yet clear, but the outlook has been consistently favorable. Many anti-epileptic drugs (AEDS) have been used for BFNS, often in combination, to deal with the very frequent seizures and the diagnostic difficulties at the time of the first cluster. However, treatment has not had a consistent effect on the duration of seizures. Most often the seizures stopped without treatment, but occasionally the end seemed to be related to administration of diazepam or phenytoin.

Unresolved questions
Although monogenetic epileptic channelopathies are rare, they must be considered in the differential diagnosis of seizures in newborn babies and infants. The reports in the literature suggest that classification of disorders on the basis of clinical phenotypes is inadequate. The reports further confirm the principle of genetic heterogeneity: some function may be regulated by more than one gene (*i.e.*, different genetic mutations may result in the same disease phenotype). Thus benign neonatal-infantile convulsions may be caused either by potassium or sodium channelopathies (Celesia, 2003).
It has been suggested that expression of the mutated genes differs among family members, causing clinical heterogeneity.

Perspectives
Recognizing BFNS is a challenge, firstly because the syndrome has a benign outcome, which suggests that not all neonatal seizures have a poor prognosis, secondly for genetic studies. There is also some suggestion that ion channels are altered in some acquired epilepsies (Berkovic, 2001). Channel function in complex genetic and acquired epilepsies is much more difficult to study and much remains to be elucidated. The future of anticonvulsant therapy includes the identification of molecular targets

that will interfere with epileptogenesis. The elucidation of the molecular defect of monogenetic epilepsies, such as BFNS, shows how genetic research leads to better understanding of the pathophysiology of more common disorders (such as acquired epilepsies) and opens the possibility of new therapeutic approaches.

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