Benign familial neonatal epilepsy (BFNE)

Jelena Radic

Ronit Pressler

J Helen Cross

UCL-Great Ormond Street Institute of Child Health, Guilford Street, London WC1N 3JH

1. The causal disease

Seizures occurring in the neonatal period most commonly arise the result of acute brain injury, related to hypoxic ischaemic injury ante or perinatally. In a small number however, seizures may spontaneously arise as part of an epilepsy syndrome or alternative cause. Two autosomal dominant inherited epilepsy syndromes may present in the neonatal period - benign familial neonatal epilepsy (BFNE, OMIM #121200) and benign familial neonatal-infantile epilepsy (BFNIE, OMIM #607745).

Benign familial neonatal epilepsy is a rare but significant epilepsy syndrome recognised within the International League Against Epilepsy (ILAE) classification[1]. BFNE is defined by a familial history, favourable outcome (for seizure control and psychomotor development) and the absence of subsequent epilepsy. The diagnosis of BFNE can be considered as a diagnosis by exclusion, that is if all other possible aetiologies have been excluded and importantly if there is a family history of neonatal seizures without any on-going sequelae in family members. The first BFNE family was reported in 1964 by Rett and Teubel[2]. Since this time close to four hundred cases have been reported, and family kinships demonstrate the autosomal dominant pattern of inheritance, with estimate penetration of 85%, which implies that about 15% of those who carry a mutated gene may fail to show seizures[3]. So far best estimate for BFNE population rate comes from a Canadian population-based study which involved 34 615 live births, among whom there were five cases of BFNE giving an incidence of 14.4 per 100 000 live births[4].

2. Epilepsy in the disease

In 80% of cases, seizures start on the second or third day of life, in a full term newborn, with the exception of very premature babies in whom seizures may appear to arise 2-3 days post term; an important point given the strict age-dependence of the syndrome[5]. There is always a seizure-free interval between birth and occurrence of seizures, in contrast to seizures the result of HIE. The sex ratio shows an equal distribution between boys and girls. The babies remains neurologically normal in most cases, feeding normally between seizures; mild transitory hypotonia can be noticed in some cases the likely result of antiseizure medicaiton[6]. No babies have been reported to require intensive care in the treatment of seizures.

In this syndrome, genetic susceptibility during the first week of life in full-term neonates is responsible for the appearance of seizures; it is a specific channelopathy which is the cause of this epilepsy syndrome but the precise mechanism still remains unknown[7]. Seizures occur in premature newborns when they reach 39 to 41 weeks of gestational age meaning that a step in maturation has to be reached for the channelopathy to be expressed.

In 1989, Leppert et al. established linkage of the gene for BFNE to the long arm of chromosome 20, the first linkage to be reported for an epilepsy syndrome[3]. The BFNE syndrome that maps to chromosome 20q has been designated as EBN1. Linkage to chromosome 20 markers D20S19 and D20S20 was excluded, however, in a three-generation Mexican–American family, suggesting locus heterogeneity[8]. Further study by Lewis et al. of that family demonstrated tight linkage to a locus on 8q, thus indicating heterogeneity (the BFNE syndrome on 8q is designated as EBN2)[9]. The sequencing of the genes mutated in EBN1 and EBN2 was reported in three papers early in 1998: *KCNQ2* located on 20q13.3 and *KCNQ3* on 8q24.[10-12].The genes *KCNQ2* and *KCNQ3* code for the potassium channels Kv7.2 and Kv7.3 respectively. Most detected mutations in BFNE are localized in the *KCNQ2* gene (~95%), with about 55% residing in the carboxy-terminal domain of the Kv7.2 channel protein[13], and exert their effect by haplo-insuffuciency. There is no explanation as yet for the very small number of KCNQ3 mutations in BFNE. In families with BFNE, sequence analysis in *KCNQ2* and *KCNQ3* will detect

mutations in 60-70% of cases. When this is negative, genomic microdeletions and rarely also microduplications (which are undetectable by classic sequence anaysis) may be revealed[14]. In some patients these microdeletions also include the neighbouring *CHRNA4* gene (known to be associated with autosomal dominant frontal lobe epilepsy in some families). This does not seem to change the phenotype[15,16].

Some BFNE families not associated with defects in *KCNQ2* and *KCNQ3* are also on record[17]. In one family with dominantly inherited neonatal seizures with intellectual disability *KCNQ2* and *KCNQ3* mutations were excluded, but a microduplication on chromosome 2q24.3 including several sodium channel genes (*SCN1A*, *SCN2A*, *SCN3A*) was detected[18] . Mutations in the sodium channel subunit gene *SCN2A* are associated with neonatal – infantile seizures, which are also a feature of BFNIE, also known as Watanabe - Vigevano Syndrome. The key clinical feature of BFNIE is that family members vary in their age at seizure onset from the neonatal to the infantile period, with the mean age being 11 weeks and seizure offset by 12 months in most cases[19].

Recently, Grinton et al. examined the clinical and molecular features of 33 familial neonatal seizure families and analyze the clinical overlap of syndromes caused by *KCNQ2*/*KCNQ3* and *SCN2A* mutations. The molecular cause was identified in 91% of BFNE families, with *KCNQ2* being the most common gene; one had a *KCNQ3* mutation, and two families had *SCN2A* mutations. Linkage studies in two families excluded known loci, suggesting that further genes are involved in BFNS[20].
KCNQ2 mutations may also lead to a more severe epileptic encephalopathy phenotype[21]. This recently confirmed phenotype, known as "*KCNQ2*-encephalopathy," also presents with seizures in the first week of life, but with an electroclinical pattern characterized by intractable, usually prominent, tonic seizures, burst-suppression or multifocal epileptiform abnormalities with attenuation on EEG, acute MRI abnormalities of the basal ganglia or thalamus in many cases, and adverse neurodevelopmental outcome in all children[22-24]. Although no *KCNQ2*-encephalopathy mutation has been seen in BFNS, mutations affecting the same amino acid residue have occurred in both *KCNQ2*-encephalopathy and BFNE, give the possibility of different degrees of potassium channel impairment[25]. More complex molecular mechanisms including mutations potentially leading to mislocalization of KCNQ channels and modifier gene effects may determine further differences in the phenotypes of KCNQ-related epilepsies.

No guideline has been proposed concerning the treatment of BFNS. The choice of the drug depends on the country, the continent and the year of publication of the study. Knowledge of the genetic mutation and the recent development of a specific antiepileptic drug know to be a potassium channel modulator, retagabine, has led to speculaiton about possible targetted treatment. Further, in children with KCNQ2 encephalopathy, sodium channel blockers have been demonstrated to be particularly effective against seizures[26]. Most babies with BNFS, as part of a neonatal seizure protocol, are reported as having been given phenobarbital for 2 – 6 months, rarely more. There is classically no need to use more than one antiepileptic drug. The question remains open however about the usefulness of an antiepileptic drug treatment: grandparents of these babies may not have been not treated and have done well. If a treatment is initiated at the time of the seizures, it seems reasonable to interrupt it by the third or sixth month. Seizures remit spontaneously at about 3-4 months of age. Although the spontaneous remission of seizures usually appears to be complete, with normal psychomotor development, about 16% of individuals with BFNS will experience one or more seizures later in life, often provoked by sudden unexpected stress[5,27] . Maihara et al. reported two siblings with BFNE who later developed epilepsy with centrotemporal spikes: both became seizure free with carbamazepine, and had normal psychomotor development[28]. According to recently reviewed 33 BFNE families by Grinton et al, forty (31%) of the 130 KCNQ2 mutation–positive individuals from BFNE families had later seizure types other than neonatal or infantile seizures. Thirteen individuals had focal-onset seizures, including four with a history suggestive of benign epilepsy with centrotemporal spikes (BECTS), and seven individuals had tonic–clonic seizures (TCS). Those with a greater number of

neonatal seizures had a higher likelihood of later seizures[20]. These data raise the question as to whether BFNE can indeed be described as a benign disorder, and which are the genetic and/or environmental factors that influence the outcome.

3. Diagnostic tests

An EEG of course would be the first line investigation in a neonate presenting with such seizures. Interictal EEG is normal or demonstrates only subtle minor changes (see figure Hirsch et al. recorded 14 seizures in three neonates with video-EEG monitoring; all seizures started with a diffuse tonic component, with a right or left maximum, varying from one seizure to the next in any given baby, always accompanied by tachycardia and short apnea. The clonic phase (focal or generalised) was introduced by vocalisation or chewing[29].

Genetic evaluation utilisng next generation sequencing may reveal a causative mutaiton, which will be helpful to confirm the diagnosis and future counselling. Nevertheless it is necessary to exclude other etiologies (not least as genetic results are not available immediately), metabolic or infectious, and for that purpose a clinical work-up, brain ultrasound and a lumbar puncture should be performed. It could be argued CT/MRI scan may not indicated if the diagnosis is suspected (with definitive family history) and the neurological state of the baby remains normal. However if doubt then it is likely an MRI would be desirable.

Summary and conclusion

Recognizing the phenotype of BFNE is important, first because of the prediction of a favorable neurological outcome, and second for the contribution to genetic studies which is great example how genetic dissection of an epilepsy can lead not only to a better understanding of disease mechanisms but also broaden our knowledge about the physiological function of the affected proteins and enable novel approaches in the antiepileptic therapy design.[7,30]

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