Benign familial infantile convulsions: report of a UK family and confirmation of genetic heterogeneity

EDITOR—Benign familial infantile convulsions (BFIC) (OMIM 601764) is a recently recognised idiopathic epilepsy syndrome originally described in families of Japanese ancestry and more recently in Italian families.1–3 It has since been reported in France, Singapore, Sweden, Germany, USA, and Argentina.4–7 but to our knowledge never in the United Kingdom. The onset of seizures in BFIC is between 3 and 12 months old, and they are mostly of a partial type, some with secondary generalisation. These seizures tend to occur in clusters over several days and remit spontaneously at about 18 months. Ictal electroencephalograms (EEG) show diffuse discharge from the centro-occipital region, although the interictal EEG is normal. The course of the disease is benign with ultimately normal psychomotor development.

There is considerable evidence that genetic factors are involved in the human epilepsies, although these genetic factors are complex and incompletely understood. One approach to understanding the molecular pathological basis of seizure disorders is to identify the genes involved in defined familial epilepsy syndromes. To date, genes for four autosomal dominant epileptic diseases have been mapped or cloned: benign familial neonatal convulsions at chromosomes 20q13 (EBN1) and 8q24 (EBN2), partial epilepsy with auditory symptoms at chromosome 10q (EPT), autosomal dominant nocturnal frontal lobe epilepsy at chromosome 20q13 (CHRNA4), and BFIC at chromosome 19q in five Italian families.6–8 Haplotype mapping suggests that the BFIC locus at 19q is likely to lie in an approximately 6 cM region between D19S49 and D19S251.4 This locus has been excluded in a single large Italian BFIC family, strongly suggesting that the condition is genetically heterogeneous.9

We present a family of United Kingdom origin with BFIC. In total, five family members were affected by a seizure disorder.

The proband (case III.1, fig 1) was a male child, aged 3 years 6 months at last follow up, who presented at the age of 4 months with a cluster of seizures. In total, there were five seizures in this cluster over two days. The seizures were clinically partial and involved one arm twitching, eyes rolling, and mouth trembling. They lasted less than five minutes and never became generalised. Intercital neurological examination was normal. Skin examination including Woods lamp detected no skin stigmata of any neurocutaneous syndrome. At the age of 9 months, he experienced one further seizure similar in character to the previous seizures. Treatment with phenobarbitone was started and he has been seizure free since this episode. There was no past medical history of significance and development has been entirely normal. An ictal EEG was not carried out, although the interictal EEG was normal. An ultrasound scan of the head showed one small echogenic focus on the wall of the lateral ventricle of uncertain significance. There was a strong family history of a seizure disorder.

Case II.1, the proband’s father, had experienced similar seizure clusters, starting at 6 months of age, with a total of three episodes and controlled by phenobarbitone. There were no more seizures after weaning off medication and psychomotor development was normal.

Case II.4, the proband’s paternal aunt, also had similar patterns of seizures, remitting after the first year, again with normal psychomotor development.

Case III.3, a first cousin of the proband, first presented at 5 months of age with a two day cluster of eight seizures which was treated with phenobarbitone and intravenous diazepam. The seizures were initially clinically partial, with

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[Figure 1: Pedigree of family with benign familial infantile convulsions, showing genotyping results for markers D19S226, D19S414, and D19S220. Filled symbols: affected with benign familial infantile convulsions, part filled symbol: adult onset absence type seizures, + =DNA available.]
twitching of the left side, becoming generalised and typically lasting a few minutes, although the initial seizure lasted for over an hour. An interictal EEG was normal. Biochemical and haematological investigations including full blood count, urea and electrolytes, glucose, magnesium, calcium, and ammonia were normal. A septic screen including a lumbar puncture and virology was negative. A cranial ultrasound scan showed no gross abnormality. A second episode of a single seizure occurred at 7 months and a final seizure occurred at 14 months of age. When phenobarbitone was stopped at 16 months there were no more seizures. Psychomotor development has been normal.

Case I.2, the proband’s paternal grandmother, had no known history of infantile seizures, but had absence type seizures that developed during pregnancy, lasting a few seconds, several times a day.

None of the cases had a history of febrile convulsions and no other family member had a known history of infantile convulsions or any other seizure disorder.

DNA was isolated from blood from all consenting family members. The family was genotyped using three microsatellite markers chosen from the ABI LMS2 fluorescent marker set (Perkin Elmer, Foster City), two of which, D19S226 and D19S220, flanked the BFIC locus on chromosome 19q, the other of which, D19S414, is at the same genetic distance as D19S114, the marker which has the highest reported lod score in previously described chromosome 19q linked BFIC families. Primer sequences for all of the markers are available from the Génethon microsatellite linkage map. PCR reactions were carried out for each marker in a 5 µl reaction volume, containing approximately 50 ng of DNA, 2.5 mmol/l MgCl₂, 10 mmol/l Tris-HCl, pH 8.3, 50 mmol/l KCl, 250 µmol/l dNTPs, 0.625 pmol of each primer, and 0.25 U of AmpliTaq Gold (Perkin Elmer, Foster City). Reactions were carried out on a Perkin Elmer 9600 thermal cycler. A standard thermocycling profile was used for all markers, and consisted of an initial denaturation of 12 minutes at 95°C, followed by 10 cycles with denaturation at 95°C for 15 seconds, annealing at 55°C for 15 seconds, and synthesis at 72°C for 30 seconds. This was followed by 20 cycles with denaturation at 89°C for 15 seconds, annealing at 55°C for 15 seconds, and synthesis at 72°C for 30 seconds. PCR products for the markers were ethanol precipitated and size fractionated on a 5% denaturing polyacrylamide gel (Amresco, Ohio) by electrophoresis on an ABI 377XL sequencer. PCR products were sized using the Genescan version 2.1 program and scored using the Genotyper version 2.0 program.

Pairwise linkage analysis was carried out using the MLINK program of the FASTLINK version 4.0 package, accessed via the Genetic Linkage User Environment interface (UK Medical Research Council Human Genome Mapping Project Resource Centre). Multipoint linkage analysis was carried out with the program Linkmap, using previously published genetic distances.
between markers. In view of the previously described incomplete penetrance of BFIC,3 we carried out both pairwise and multipoint linkage analysis using a conservative affected only strategy. Cases II.1, II.4, III.1, and III.3, where there was a definite diagnosis of BFIC, were defined as affected. Case I.2, where there was no history of infantile seizures, but a history of adult onset absence type seizures, was defined as unknown, as was II.6, who had no history of seizures. Spouses (I.1, II.2, II.3, and II.5) of family members affected by seizures were classified as unaffected. For linkage calculations, allele frequencies were assumed to be equal, the gene frequency for BFIC was assumed to be 10⁻⁵, and male and female recombination rates were assumed equal.

Genotyping results for markers D19S226, D19S414, and D19S220 are shown in fig 1. Pairwise lod scores for markers D19S226, D19S414, and D19S220 using the affecteds only linkage strategy described above are shown in table 1. Multipoint linkage analysis using the three markers and previously published genetic distances (Perkin Elmer, Foster City) generated a lod score of <-2 for an approximately 20 cM region, which contained the entire BFIC candidate region, excluding linkage at this locus (fig 2).

We have described a family which fulfils the clinical diagnostic criteria for BFIC: onset of partial type seizures between 3 and 12 months of age, occurring in clusters, remitting by the second year of life with normal neurodevelopmental status and no demonstrable underlying pathology. The inheritance pattern was consistent with autosomal dominant inheritance, as with all previously reported cases. This family is therefore, to our knowledge, the first reported in the United Kingdom with BFIC.

Clinical heterogeneity within the same pedigree has been described in many idiopathic generalised epilepsy syndromes, for example a parent with tonic-clonic seizures may have a child with juvenile myoclonic epilepsy. The epilepsy phenotype may also change over time in an individual patient.12 13 Thus, variable expression may be a feature seen in case 5, who had absence seizures in pregnancy, but no known infantile seizures.

Linkage analysis in our family confirms the previous report of genetic heterogeneity in BFIC, since we excluded linkage at the known BFIC locus on 19q. Several precedents for genetic heterogeneity occurring within epilepsy syndromes already exist, for example, there are loci for benign familial neonatal convulsions at chromosome 20q13 and at 8q24.14 15

Recognition of BFIC is important as reassurance can be given regarding the benign course of the disease and recurrence risks can be communicated to the family. If necessary, antiepileptic treatment can be used for the period of infancy, when seizure risk is highest. Our family emphasises documentation of family history as an important part of the management of patients presenting with a seizure disorder.

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1 Fukuyama Y. Borderland of epilepsy, with special references to febrile convulsions and so-called infantile convulsions. Seishin Igaku 1963;5:211-33.
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