GIVE PEAF A CHANCE

Idiopathic Partial Epilepsy with Auditory Features (IPEAF): A Clinical and Genetic Study of 53 Sporadic Cases

Bisulli F, Tinuper P, Avoni P, Striano P, Striano S, d'Orsi G, Vignatelli L, Bagattin A, Scudellaro E, Florindo I, Nobile C, Tassinari CA, Baruzzi A, Michelucci R

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The purpose of our study was to describe the clinical characteristics of sporadic (S) cases of partial epilepsy with auditory features (PEAF) and to pinpoint clinical, prognostic, and genetic differences with respect to previously reported familial (F) cases of autosomal dominant partial epilepsy with auditory features (ADPEAF). We analyzed 53 patients (24 females and 29 males) with PEAF diagnosed according to the following criteria: partial epilepsy with auditory symptoms, no family history of epilepsy, and absence of cerebral lesions on nuclear magnetic resonance imaging (NMR) study. All patients underwent a full clinical, neuroradiologic and neurophysiologic examination. Forty patients were screened for mutations in *LGI1*/epitempin, which is involved in ADPEAF. Age at onset ranged from 6 to 39 years (average, 19 years). Secondarily generalized seizures were the most common type of seizures at onset (79%). Auditory auras occurred either in isolation (53%) or associated with visual, psychic, or aphasic symptoms. Low seizure frequency at onset and good drug responsiveness were common, with 51% of patients seizure free. Seizures tended to recur after drug discontinuation. Clinically, no major differences were found between S and F patients with respect to age at onset, seizure frequency, and response to therapy. Analysis of *LGI1*/epitempin exons failed to disclose mutations. Our data support the existence of a peculiar form of nonlesional temporal lobe epilepsy closely related to ADPEAF but without a family history. This syndrome, here named IPEAF, has a benign course in the majority of patients and could be diagnosed by the presence of auditory aura. Although *LGI1* mutations have been excluded, genetic factors may play an etiopathogenetic role in at least some of these S cases.

COMMENTARY

As the interplay between epilepsy and genetics is more broadly defined, the information regarding how specific molecular events lead to individual epilepsy syndromes becomes more complicated. Whereas numerous monogenic disorders that are associated with epilepsy are now identified, many syndromes, which likely result from molecular events, are still without an identified gene defect. Most puzzling are syndromes that share either clinical or histologic features with known genetic disorders yet do not exhibit mutations in these genes.

A particularly interesting group of disorders are those that appear sporadically, without family pedigree, yet exhibit highly consistent and reproducible phenotypes. For example, despite histologic similarities between focal cortical dysplasia (FCD) and tubers in the tuberous sclerosis complex (TSC), the molecular pathogenesis of these two cortical malformations is quite distinct. FCD appears as a sporadic malformation, whereas TSC is passed in an autosomal dominant fashion. Gene mutations in *TSC1* and *TSC2* are not identified in FCD, even though the cellular constituents of FCD appear quite similar to those in tubers. These findings raise the interesting hypothesis, either that multiple gene mutations can be responsible for a variety of similar brain disorders, such as generalized epilepsy with febrile seizures plus (GEFS+), or that mutations in genes, which serve similar functions or lie along similar cellular cascades, can lead to common pathway disorders. Simply stated, the already intricate genotype–phenotype relation identified for many epilepsy syndromes is likely to become more complex.

The article by Bisulli and colleagues examines an interesting epilepsy phenotype known as partial epilepsy with auditory features (PEAF) and compares it with an autosomal dominant form (ADPEAF). None of the sporadic PEAF patients in the study had a family history of seizures, and none had significant morphologic abnormalities on brain imaging. The authors use both clinical phenotype and genotype approaches to define the features of 53 adults with sporadic PEAF. With the exception of a statistically nonsignificant increase in the incidence of febrile seizures and paroxysmal EEG features in sporadic PEAF, the clinical features of sporadic PEAF were similar to those of ADPEAF. Interestingly, mutational analysis of the leucine-rich, glioma-inactivated *LGI1*/epitempin gene, known to be responsible for ADPEAF, did not reveal mutations in patients with sporadic PEAF. In addition, sequence variations and

polymorphisms in the *LGI1*/epitempin exons were not identified. Intronic sequence was not assessed.

Without question, the most fascinating aspects of these data are the nearly identical clinical appearance between ADPEAF and idiopathic PEAF (IPEAF) and the absence of *LGI1*/epitempin exon mutations in IPEAF. What does this mean for the broad understanding of sporadic epilepsy syndromes? Several possible and tenable hypotheses may explain these results. First, IPEAF may be a syndrome coincidentally identical to ADPEAF. Alternatively, PEAF may result from a gene mutation that is within a similar gene family; within a gene related to *LGI1*/epitempin; or within a gene in a pathway related to *LGI1*/epitempin.

In a recent study, mutations were detected in many, but not all, analyzed ADPEAF families (1), suggesting that even ADPEAF is genetically heterogeneous. In this cohort, ADPEAF pedigrees that failed to reveal an *LGI1* mutation did not exhibit mutations in the related genes *LGI2*, *LGI3*, or *LGI4*. Thus screening of related or *LGI1*/epitempin family genes may provide useful candidates for sporadic PEAF. Alternatively, identifying mutations or genes that are upstream or downstream of *LGI1*/epitempin (i.e., genes that control or are modulated by *LGI1*/epitempin) may be pivotal. A recent study demonstrated that *LGI1* may play a role in suppressing the production of matrix metalloproteinases through the phosphatidylinositol 3-kinase/ERK pathway (2). The *LGI1* gene was originally identified because it was inactivated by a reciprocal chromosome translocation in the T98G glioma cell line.

Loss of *LGI1* expression in high-grade astrocytic brain tumors is associated with loss of chromosome 10 during glioma progression. Thus genes or proteins whose expression is modulated by *LGI1*/epitempin may be ideal candidates for gene-mutation analysis. One compelling notion is whether a causative gene mutation responsible for sporadic PEAF occurs as a germline or somatic event. That is, does an IPEAF-related gene mutation occur in the earliest stages of zygote formation, or rather, does it occur in neural progenitor cells? If the latter scenario is accurate, then the mutation can be detected only in brain tissue and not in a blood screen, as has been shown for numerous sporadic cancers.

Perhaps the most compelling feature of the PEAF syndromes is the final genotype–phenotype relation between an IPEAF-related gene mutation and the clinical semiology of epilepsy with auditory features. Why *LGI1* mutations lead to an epilepsy syndrome defined by auditory symptoms is truly a fascinating question. Does the encoded protein somehow modulate normal auditory processing? Does a loss-of-function mutation in *LGI1* impair auditory memory retrieval? The message from these data is that much can be learned about sporadic syndromes from genetic disorders but that defining the etiology and pathogenesis of sporadic syndromes remains a challenging and creative process.

by Peter B. Crino, M.D., Ph.D.

References

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