Phenotype definition in the idiopathic generalized epilepsies

Winawer et al. show that examination of specific seizure types—myoclonic, absence, and generalized tonic-clonic—can divide the idiopathic generalized epilepsies into groups that share susceptibility genes. They suggest the use of seizure types as well as syndromes to define groups for genetic analysis.

The profusion of genotypes and phenotypes in “idiopathic” generalized epilepsies

Commentary by Robert A. Gross, MD, PhD

The myriad genetic associations with idiopathic (primary) generalized epilepsies (IGE) are challenging to both researchers and caregivers. There are numerous mutations, among them voltage-gated sodium, potassium, and calcium channels and ligand-gated GABA receptors. A variety of mutations may produce similar phenotypes, while, equally troublesome, single mutations may produce a range of phenotypes.1 What is the best approach to making clearer correlations of mutations with phenotypes? The task is daunting, if only because IGE syndromes overlap; seizure types may differ within families and vary in individuals over time. While this might seem an arcane area of greater interest for research geneticists, there are prognostic and therapeutic implications: are certain seizure patterns more likely to persist, requiring lifelong treatment? Might some genetic patterns be more responsive to treatment than others?

Winawer et al. approach this problem soundly, extending their earlier results.2 Their insight was to use seizure type, rather than the less defined epilepsy syndrome, to uncover subgroups within the IGEs. Utilizing a database of IGE families from Australia and Israel—for analysis of absence and myoclonic seizures—and combining their database with that at Columbia3 for analysis of generalized tonic-clonic seizures (GTCs), they found that absence, myoclonic, a combination of those seizures, or GTCs clustered in families to an extent greater than expected. Concordance for JME as a syndrome was greater than for the absence syndromes. They conclude that the genetic contributions for myoclonic seizures are distinct from absence and that there may be a distinct genetic contribution to GTC expression, regardless of the epilepsy syndrome within which it occurs. This supports their premise that seizure type is valuable in determining the genetic bases of IGE, and suggests that the interplay of genetic factors may determine the epilepsy syndrome and the particular manifestation—whether GTCs occur in the context of an absence syndrome, for example. This may guide future genetic investigation, and may also, to the extent pharmacogenetic associations can be made, ultimately inform therapy. It is not too far-fetched to imagine that gene chip technology may allow a genetic determination in the office, thus suggesting the medications more likely to be effective and tolerated.

References
August 23 Highlight and Commentary: The profusion of genotypes and phenotypes in "idiopathic" generalized epilepsies

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