Focal epilepsy etiology

The etiology of focal seizures is usually identified in only about one third of cases.

Traumatic brain injury is an increasingly common etiology for focal seizures.

Penetrating head injuries have the highest risk for the development of epilepsy.

For a closed head injury to carry a significant seizure risk, there should be loss of consciousness or amnesia lasting longer than 30 minutes.

A slight elevation in risk may be present even with <30 minutes of amnesia.

CNS infection may result in focal seizures. The presumed mechanism is a CNS insult, which sets up an epileptogenic focus.The more complicated the CNS infection, the more likely that it will contribute to seizure development.

Brain tumors are another source of focal seizures: low-grade tumors seem more epileptogenic than high-grade tumors.

Although not completely assessed, case series have suggested that 28% of patients undergoing surgery for brain tumors suffer from seizures.

Focal seizures may also develop after a stroke. Risk for seizure activity is at least 3 times higher after stroke, but prophylactic antiepileptic drug therapy is typically not recommended.

Both Alzheimer disease (AD) and non-AD dementia have been associated with seizure development.

Genetic variants

Perinatal injuries seem to contribute to the development of epilepsy only when there is coexistent neurologic handicap (e.g., cerebral palsy). Family history is also related to the development of focal epilepsy, although this is not a simple relationship. Some syndromes are thought to be due to a single gene inheritance (familial temporal lobe epilepsy), while others have a complex inheritance (idiopathic partial epilepsies and cryptogenic/symptomatic partial epilepsies).

Benign focal epilepsies of childhood refers to a group of idiopathic syndromes known to cause focal seizures in developmentally and neurologically normal children. They include benign childhood epilepsy with centrotemporal spikes and childhood epilepsy with occipital paroxysms. These syndromes follow a benign course and usually remit prior to adulthood.

Neurocutaneous syndromes such as neurofibromatosis, Sturge-Weber syndrome, and tuberous sclerosis may result in focal or generalized seizures. Although some intracranial arteriovenous malformations are largely asymptomatic, others, including cavernous hemangiomas, do carry a risk of seizures.

Post-zygotically acquired genetic variants, or somatic variants, that arise during cortical development

have emerged as important causes of focal epilepsy, particularly those due to malformations of cortical development. Pathogenic somatic variants have been identified in many genes within the PI3K-AKT-mTOR-signaling pathway in individuals with hemimegalencephaly and focal cortical dysplasia (type II), and more recently in SLC35A2 in individuals with focal cortical dysplasia (type I) or non-dysplastic epileptic cortex. Given the expanding role of somatic variants across different brain malformations, Lai et al. sought to delineate the landscape of somatic variants in a large cohort of patients who underwent epilepsy surgery with hemimegalencephaly or focal cortical dysplasia. They evaluated samples from 123 children with hemimegalencephaly (n=16), focal cortical dysplasia type I and related phenotypes (n=48), focal cortical dysplasia type II (n=44), or focal cortical dysplasia type III (n=15). They performed high-depth exome sequencing in brain tissue-derived DNA from each case and identified somatic single nucleotide, indel, and large copy number variants. In 75% of individuals with hemimegalencephaly and 29% with focal cortical dysplasia type II, they identified pathogenic variants in PI3K-AKT-mTOR pathway genes. Four of 48 cases with focal cortical dysplasia type I (8%) had a likely pathogenic variant in SLC35A2. While no other gene had multiple disease-causing somatic variants across the focal cortical dysplasia type I cohort, four individuals in this group had a single pathogenic or likely pathogenic somatic variant in CASK, KRAS, NF1, and NIPBL, genes associated with neurodevelopmental disorders. No rare pathogenic or likely pathogenic somatic variants in any neurological disease genes like those identified in the focal cortical dysplasia type I cohort were found in 63 neurologically normal controls (P = 0.017), suggesting a role for these novel variants. They also identified a somatic loss-of-function variant in the known epilepsy gene, PCDH19, present in a small number of alleles in the dysplastic tissue from a female patient with focal cortical dysplasia IIIa with hippocampal sclerosis. In contrast to focal cortical dysplasia type II, neither focal cortical dysplasia type I nor III had somatic variants in genes that converge on a unifying biological pathway, suggesting greater genetic heterogeneity compared to type II. Importantly, they demonstrate that FCD types I, II, and III, are associated with somatic gene variants across a broad range of genes, many associated with epilepsy in clinical syndromes caused by germline variants, as well as including some not previously associated with radiographically evident cortical brain malformations [1)].

1)
Lai D, Gade M, Yang E, Koh HY, Lu J, Walley NM, Buckley AF, Sands TT, Akman CI, Mikati MA, McKhann GM, Goldman JE, Canoll P, Alexander AL, Park KL, Von Allmen GK, Rodziyevska O, Bhattacharjee MB, Lidov HGW, Vogel H, Grant GA, Porter BE, Poduri AH, Crino PB, Heinzen EL. Somatic variants in diverse genes leads to a spectrum of focal cortical malformations. Brain. 2022 Apr 20:awac117. doi: 10.1093/brain/awac117. Epub ahead of print. PMID: 35441233.