



Dendritic and Spine Loss in Epilepsy: What Seizures Got to Do With It?

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Dendritic Pathology, Spine Loss and Synaptic Reorganization in Human Cortex From Epilepsy Patients

Rossini L, De Santis D, Mauceri RR, Tesoriero C, Bentivoglio M, Maderna E, Maiorana A, Deleo F, de Curtis M, Tringali G, Cossu M, Tumminelli G, Bramerio M, Spreafico R, Tassi L, Garbelli R. *Brain*. 2021;144(1):251-265. doi:10.1093/brain/awaa387

Neuronal dendritic arborizations and dendritic spines are crucial for a normal synaptic transmission and may be critically involved in the pathophysiology of epilepsy. Alterations in dendritic morphology and spine loss mainly in hippocampal neurons have been reported both in epilepsy animal models and in human brain tissues from patients with epilepsy. However, it is still unclear whether these dendritic abnormalities relate to the cause of epilepsy or are generated by seizure recurrence. We investigated fine neuronal structures at the level of dendritic and spine organization using Golgi impregnation, and analyzed synaptic networks with immunohistochemical markers of glutamatergic (vGLUT1) and GABAergic (vGAT) axon terminals in human cerebral cortices derived from epilepsy surgery. Specimens were obtained from 28 patients with different neuropathologically defined etiologies: type Ia and type II focal cortical dysplasia, cryptogenic (no lesion) and temporal lobe epilepsy with hippocampal sclerosis. Autoptic tissues were used for comparison. Three-dimensional reconstructions of Golgi-impregnated neurons revealed severe dendritic reshaping and spine alteration in the core of the type II focal cortical dysplasia. Dysmorphic neurons showed increased dendritic complexity, reduction of dendritic spines, and occasional filopodia-like protrusions emerging from the soma. Surprisingly, the intermingled normal-looking pyramidal neurons also showed severe spine loss and simplified dendritic arborization. No changes were observed outside the dysplasia (perilesional tissue) or in neocortical postsurgical tissue obtained in the other patient groups. Immunoreactivities of vGLUT1 and vGAT showed synaptic reorganization in the core of type II dysplasia characterized by the presence of abnormal perisomatic baskets around dysmorphic neurons, in particular those with filopodia-like protrusions, and changes in vGLUT1/vGAT expression. Ultrastructural data in type II dysplasia highlighted the presence of altered neuropil engulfed by glial processes. Our data indicate that the fine morphological aspect of neurons and dendritic spines are normal in epileptogenic neocortex, with the exception of type II dysplastic lesions. The findings suggest that the mechanisms leading to this severe form of cortical malformation interfere with the normal dendritic arborization and synaptic network organization. The data argue against the concept that long-lasting epilepsy and seizure recurrence per se unavoidably produce a dendritic pathology.

Commentary

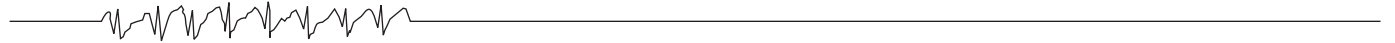
Medically uncontrolled seizures occur in 30% to 40% of the population with epilepsy.^{1,2} According to the International League Against Epilepsy, drug-resistant epilepsy happens when seizure freedom is not achieved following an adequate treatment with at least 2 anti-seizure drugs that were specifically selected to treat a person's seizure type.³ In cases where the seizure focus is identified, surgical resection can control the seizure burden. Some types of drug-resistant epilepsies that typically benefit from this procedure include mesial temporal lobe epilepsy (mTLE) with hippocampal sclerosis (HS) and focal cortical dysplasia (FCD), with 80% and 33% to 75% of patients, respectively, becoming seizure-free post-surgery.^{1,2} Even though mTLE and FCD involve different etiologies such

as brain injuries and cortical malformations, respectively, histological and biochemical characterizations of surgically resected tissues have shown some similar pathological alterations. These include reactive gliosis, neuroinflammation, and neuronal death as well as loss of synaptodendritic structures.⁴⁻⁶ While these pathological profiles are often associated with epileptogenic circuit remodeling, it is not definitively known whether they are a cause or a result of the seizures.

In trying to elucidate the role of seizures in the dendritic pathology in human epilepsy, the study by Rossini et al recently published in *Brain*, evaluated dendritic architecture, spine density, and synaptic proteins in different types of drug-resistant epilepsies where the seizure burden and brain lesions were variable, and compared them to nonepileptic autopsy



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tissues.⁷ Specifically, the authors investigated 3 types of drug-resistant epilepsies, FCD (Ia, IIa, and IIb), TLE-HS, and cryptogenic epilepsy. FCD is a neurodevelopmental disorder characterized by abnormal cortical lamination with neuronal loss and displacement, enlarged dysmorphic cells, and focal seizures that may be a result of the aberrant cytoarchitecture (8). FCD is characterized into 3 main types, type I (a, b, c), type II (a, b), and type III (a, b, c, d) based on their histopathological profiles.⁸ For instance, FCD types Ia, IIa, and IIb, which were investigated by Rossini et al⁷ are distinguished as follows: FCD type Ia has abnormal radial microcolumnar organization, FCD type IIa is associated with the presence of dysmorphic neurons (DN), and FCD type IIb is identified by the presence of both DN as well as balloon cells. TLE-HS is the occurrence of focal seizures that develop in the temporal lobe affecting brain areas such as the hippocampus, amygdala, and cortex, and is often associated with pathological changes and neuronal death in the hippocampus (hippocampal sclerosis or HS). Cryptogenic epilepsy is associated with seizures of an unknown cause and an absence of a clearly identifiable lesion.

Beautifully reconstructed Golgi-stained dendritic architectures from cortices of the different types of epilepsy (TLE-HS, cryptogenic, FCD type Ia, and perilesional FCD types IIa and IIb) and nonepileptic autopsy cases revealed highly intricate neuronal arbors in the human tissues. From these, the authors quantified dendritic branching and spine densities, and found only significant decreases in dendritic branch points between the autopsy and TLE-HS groups. However, when specifically examining dendritic arbors from normal looking neurons (NN) and DN localized in the core of the lesions in FCD types IIa and IIb relative to neurons within perilesional FCD types IIa/b areas and autopsy tissues, architectural alterations were observed. The findings included decreased branching and spine density in NN as well as increased dendritic arborization in DN of both types of FCD, and decreased spine density in DN of FCD type IIb only. In parallel, the study shows a robust immunostaining for the glutamatergic and GABAergic presynaptic elements vGLUT1 and vGAT, respectively, surrounding DN in FCD types IIa/b. The authors quantified and compared these synaptic markers in lesional and perilesional areas of the FCD types IIa/b, and found significantly decreased vGLUT1 and increased vGAT immunoreactivity only in the FCD type IIb lesional area. While the article mentions that tissues from the other epilepsies and autopsy samples were immunostained, the results were not shown. Thus, whether there are comparable alterations in the levels of vGLUT1 and vGAT in TLE-HS, cryptogenic epilepsy or FCD type Ia relative to the autopsy samples is not known. It is also not clear why only presynaptic proteins were examined given the alterations seen in dendritic arbors and spines. Paralleled alterations in postsynaptic markers and dendritic/spine changes would have further supported dendritic pathological alterations in human epilepsy.

The novelty and strength of Rossini's study is the comprehensive reconstruction and quantification of dendritic architectures in different types of epilepsy, and the direct comparison of the dendritic morphological features between NN and DN in


lesional versus perilesional tissues from FCD types IIa and IIb. Given the known presence of somatic mutations in genes involving the mechanistic target of rapamycin (mTOR) pathway in many cases of FCD, the authors speculate that differences in the activation of mTOR within DN may result in the enhanced arborization of these cells, as has been shown by others.⁹ Due to the severe abnormalities observed in FCD type II that were not seen in the other epilepsies (TLE-HS, cryptogenic epilepsy, or FCD type Ia) the authors concluded that the underlying cause of the dendritic pathology in long-lasting epilepsy is unlikely to be seizure-related. However, the study also shows decreases in dendritic branch points of pyramidal cells within the temporal neocortex of the TLE-HS group, thereby suggesting that dendritic remodeling also occurs in the cortex of these TLE cases. Given that hippocampal dendrites are known to be injured in TLE-HS, a comparison between dendrites in the hippocampus (lesional) versus neocortex (perilesional) could have been useful to further understand the role that seizures, or the seizure focus, may play in the dendritic pathology of human epilepsy.

One important limitation to the interpretation of the findings by Rossini et al is the quantitative comparison to tissues from autopsy cases of only 2 individuals of ages 80 and 69 relative to cases with younger epileptic patients [FCD type Ia (13 years old, 1 case); FCD type IIa (6-9 years old, 2 cases); FCD type IIb (22-52 years old, 3 cases); TLE-HS (35-40 years old, 2 cases); and cryptogenic epilepsy (35-46 years old, 2 cases)]. Extensive evidence from both humans and rodents supports decreases in dendritic complexity with age^{10,11} and in association with seizures.⁵ Thus, it is possible that due to age-related loss of synaptodendritic structures in the autopsy samples, the impact of seizures and epilepsy in the dendritic pathology was underestimated. In this case, age-matched brain specimens from autopsy cases would be more appropriate. Furthermore, the type of tissue collection approach such as autopsy versus fresh biopsy from epilepsy resection surgeries, as well as gender, which is not described in this study, can influence the complexity of dendritic arbors. For instance, Alonso-Nanclares et al found a significant difference in synaptic density in the anterolateral temporal cortex when comparing surgically resected epileptic tissue between men and women who suffered from mTLE.¹²


In sum, Rossini et al provides further evidence that drastic dendritic architectural alterations are present in human drug-resistant epilepsy associated with FCD type II (more specifically with type IIb). Even though the authors indicate that the abnormal dendritic arbors are likely to be etiology-driven instead of seizure-dependent, extensive evidence from preclinical models support that seizures may directly contribute to the dendritic structural pathology in epilepsy. Studies using high resolution microscopy and live imaging of neuronal processes before, during, and after seizure activity in both *in vitro* preparations and in animal models have shown synaptodendritic changes.⁵ Thus, as corresponding advances in cutting-edge high resolution clinical imaging technologies along with surrogate markers for injured dendrites become available, we may



be able to determine with more precision whether seizures are a cause or a consequence of the synaptodendritic pathology in human drug-resistant epilepsies.

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