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Infantile Spasms in Tuberous Sclerosis Complex: Lesion or Network?

Tuber Locations Associated with Infantile Spasms Map to a Common Brain Network

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Objective: Approximately 50% of patients with tuberous sclerosis complex develop infantile spasms, a sudden onset epilepsy syndrome associated with poor neurological outcomes. An increased burden of tubers confers an elevated risk of infantile spasms, but it remains unknown whether some tuber locations confer higher risk than others. Here, we test whether tuber location and connectivity are associated with infantile spasms. Methods: We segmented tubers from 123 children with (n = 74) and without (n = 49) infantile spasms from a prospective observational cohort. We used voxelwise lesion symptom mapping to test for an association between spasms and tuber location. We then used lesion network mapping to test for an association between spasms and connectivity with tuber locations. Finally, we tested the discriminability of identified associations with logistic regression and cross-validation as well as statistical mediation. Results: Tuber locations associated with infantile spasms were heterogenous, and no single location was significantly associated with spasms. However, >95% of tuber locations associated with spasms were functionally connected to the globi pallidi and cerebellar vermis. These connections were specific compared to tubers in patients without spasms. Logistic regression found that globus pallidus connectivity was a stronger predictor of spasms (odds ratio [OR] = 1.96, 95% confidence interval [CI] = 1.10-3.50, *P* = .02) than tuber burden (OR = 1.65, 95% CI = .90-3.04, *P* = .11), with a mean receiver operating characteristic area under the curve of .73 (±.1) during repeated cross-validation. Interpretation: Connectivity between tuber locations and the bilateral globi pallidi is associated with infantile spasms. Our findings lend insight into spasm pathophysiology and may identify patients at risk.

Commentary

West Syndrome is a devastating infantile and childhood epileptic encephalopathy characterized by the development of epileptic spasms (ES).[1] The pathophysiology of ES is not well understood.[2] Untreated ES are associated with poor developmental outcome.[3] Chipaux et al suggest that spasms of focal onset have similar surgical outcomes to those in other medically intractable focal epilepsies that undergo surgical treatment.[4] However, as all of us know, finding a "lesion" is not the same as identifying the *epileptogenic zone*—especially if the lesion is extensive or multiple lesions are present, as is common in tuberous sclerosis complex (TSC).

ES as a Network Disease

In traditional functional neuroanatomy, we are taught that a given lesion leads to predictable symptoms based on established functions of the affected brain region. Despite an association between tuber burden in TSC and ES, no single location in the cortex predicts the development of ES.[5] Network science, which has seen a rapid growth in epilepsy research, might provide some answers. Could it be that the disruption of an identifiable cerebral network can predict ES where lesion-based functional neuroanatomy falls short?

In the recent work by Cohen et al,[6] the authors applied a novel and exciting method of "lesion mapping" to a large cohort of children with and without ES to identify the networks underlying the development of ES. Cohen's work extends the functional connectivity-based lesion mapping technique described by Boes et al.[7] Specifically, Boes et al found that particular functional deficits can be better predicted by an individual lesion's functional connectivity than by its specific location in the brain. Functional connectivity can be measured using low frequency fluctuations in blood oxygenation level dependent signals. The lesion network mapping technique of Boes et al involves a few logical steps. First, the three-dimensional volume of the lesion is transferred onto a reference brain. Then the intrinsic connectivity of this lesion with the rest of the brain is mapped using normative fMRI connectome data to determine a lesion associated network. Finally, lesion-associated networks from several such lesions are superimposed to look for common patterns of connectivity in patients with the symptom complex of interest.

Cohen et al.[6] have applied this concept of lesion network mapping to TSC using neuroimaging data gathered for the TSC Autism Centre of Excellence Network (TACERN). TACERN is

a multicentre prospective study in which patients were enrolled in the first year of life and followed longitudinally through 36 months. The authors studied 123 children with (n = 74) and without (n = 49) ES. Overall, a higher tuber burden was associated with ES. Using an automated tuber segmentation algorithm and voxelwise tuber-symptom (ES) mapping they did not find any significant association between specific tuber location and ES (highest predictive value of any tuber location for ES = 24%). Using the lesion network mapping technique, however, Cohen et al found that >95% of the children with ES had tubers that were functionally connected to the internal segments of the globus pallidi and lobule 8A of the cerebellar vermis. After correcting for other confounders including tuber burden, genetic etiology, and medication exposure, these functional connections remained a significant predictor of ES with a high sensitivity that persisted across split brain replications.

While the relationship between ES and the regions identified by Cohen et al—the globus pallidi and cerebellar vermis—is not immediately clear, prior research supports the involvement of subcortical structures in the generation of ES.[5,8,9] In their MRI study, Harini et al[5] did find that >70% of patients with ES with structural acquired etiology (hypoxic ischemic injury, for example) had evidence of involvement of the corpus callosum, cortical and subcortical (basal ganglia, thalamus) structures. Greater than 50% of patients with a structural developmental etiology for ES (eg malformations of cortical development) had MRI evidence of abnormalities in the corpus callosum and cortical structures. Previous studies by Moshe and Chugani's group have also indicated interactions between cortical and subcortical structures in the development of ES.[8,9]

Implications and Next Steps

Cohen et al.'s findings are yet more data points suggesting an interplay between cortical and subcortical structures in the pathophysiology of ES. Their study demonstrated that tuber distributions associated with ES map to consistent brain networks independent of medication choice, mutation type, and tuber burden. We do not yet know whether these data are specific only to TSC or can be extrapolated to other focal causes of ES such as malformations of cortical development. The next place to look might be focal cortical dysplasias type IIb, which are pathologically similar to tubers. Why brain regions with *negative* connectivity to the globi pallidi and cerebellar vermis seem to be the most predictive of ES also raises more questions than it answers. It is important to remember that the negative connectivity is seen in *healthy* individuals, and Cohen et al.'s study did not measure connectivity between the tubers in these deep structures in TSC. Thus, how the presence of tubers in connected regions influences the relationship with the globi pallidi and cerebellar vermis remains to be determined. We do not know if Cohen et al.'s findings represent causation, compensation, or downstream connectivity changes. The authors speculate that spiking activity at tubers could *further* suppress activity in the globi pallidi, thus disrupting the GABAergic outflow from the globi pallidi. If true, then could destructive lesions in the same areas lead to an *increase* in outflow from the globi pallidi? And if so, what are the consequences? Can knowledge of this negative functional relationship be harnessed to guide lesionectomies and/or targets for deep brain stimulation, such as specifically targeting the centromedian nuclei of the globus pallidus in TSC?

A limitation of functional connectivity in children in general, and young children in particular, is the lack of a robust functional connectome in these age groups. Boes et al.'s original work and the present study by Cohen et al both make use of a large functional connectivity dataset from young adults. Notably, however, Cohen et al were able to replicate their findings using data from the Adolescent Brain Cognitive Development 9-year-old group connectome with strikingly similar findings. Still, we do not know how congenital abnormalities of cortical development affect the connectome. Studies of early childhood epilepsies would benefit from a robust connectome of the very young.

All in all, the authors should be congratulated for thinking outside the proverbial box in their ability to extend lesion network mapping previously used in stroke patients to a group of highly vulnerable patients with a devastating epileptic encephalopathy like ES.

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