

# Cortical Spreading Depolarizations: Under-Recognized Pathophysiology in Brain Disorders

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In this issue, Levesque et al. provide a comprehensive review on the topic of nonepileptical stereotyped intermittent symptoms (NESIS) in various forms of brain injury and the transient neurologic symptoms (TNS) observed in chronic subdural hematoma (cSDH) patients<sup>1</sup>. For those who manage cSDH patients, this is a vexing clinical problem which is often refractory to typical anticonvulsants and electroencephalogram (EEG) often fails to show evidence of epileptiform activity, just slowing and electrical attenuation. In cSDH, neuroimaging may not show structural changes to warrant surgical intervention, yet symptoms are often recurrent and stereotyped despite one or more anticonvulsant drugs. Symptoms are often distressing to patients, nurses, and clinicians since they remain of unknown etiology. The term NESIS is an important, potentially unifying terminology that has diagnostic and prognostic implications<sup>2</sup>. In a cohort of 84 patients hospitalized for treatment of cSDH, 26% experienced TNS. Of these, 59% scored positive for NESIS. Remarkably, mortality rate was 0% in the NESIS group compared to 33% in the nonNESIS group, the latter mainly considered to have seizures. Hence in the context of cSDHs, seizures are a bad prognostic sign.

The key point of this paper is that underlying cortical spreading depolarizations (CSDs) might explain mysterious nonepileptic cSDH symptoms. Further, CSDs also may cause secondary neuronal injury and outcomes in various forms of brain injury such as traumatic brain injury (TBI), cSDH, subarachnoid hemorrhage (SAH), and malignant cerebral infarction. The incidence of CSDs in cSDH is about 26%, 60% in TBI, 80% in SAH, and 90% in large hemispheric stroke. CSD's energy demand is estimated to be 4–8 times that of a focal seizure. While normal brain, such as in the case of migraine, may recover metabolically from depolarization-induced hyperemia and subsequent oligemia, injured brain appears to be more susceptible to the damaging effects of CSD, which paradoxically may be associated with prolonged vasoconstriction and secondary ischemia and propagation of neuronal injury. Another important finding is that CSD events are inversely proportional to systolic blood pressure and cerebral perfusion pressure. This observation is especially important in SAH and other brain-injured patients in which CSD leads to raised intracellular calcium and sodium influx and increased extracellular excitatory neurotransmitters. It is no surprise then that the best therapeutic candidates that reduce CSDs and are helpful in NESIS were either calcium channel blocking drugs like nimodipine, a cerebroselective L-type

calcium channel blocking drug on CSD, NMDA antagonists such as ketamine, as well as lamotrigine and topiramate, which block voltage-dependent sodium and calcium channels<sup>3</sup>. In fact, a recent SAH trial showed that ketamine reduced CSD<sup>4</sup>. NESIS phenomena may also be clinically observed in cerebral amyloid angiopathy (CAA) “spells” as well as cortical superficial siderosis from CAA or other causes of superficial blood products such as in cSDH. Migraine genetics also often colocalizes to mutations in sodium, calcium, or potassium channels.

The NESIS score was constructed based on prior work with scores of 4+ or higher being felt to be diagnostic of the condition, and prognostically NESIS patients responded 100% of the time to topiramate or lamotrigine, which reduce CSD, compared to levetiracetam, phenytoin, or lacosamide. The semiology of CSD appears linked to the location and type of brain injury. For example, positive migrational signs and symptoms typically occur in CSD migraine with aura as originally described by Aristeades Leão and in cortical SAH/superficial siderosis. In contrast, cSDH, stroke, and aneurysmal SAH tend to have negative neurological signs and symptoms. Having a name to describe this neurological phenomenon in cSDH is key to future clinical recognition, since it can become measurable, which is the first step to understanding the future prevalence and measuring treatment effects. However, several challenges lie ahead and further prospective validation is still needed. Also, prospective detection of CSD requires invasive brain monitoring (electrocorticography, ECoG), which not all patients will have per standard of care. To address these limitations, the authors mention an upcoming GENESIS (Generating Evidence for NESIS) trial being planned as a prospective study to investigate a population of cSDH patients presenting with TNS and a positive NESIS score. GENESIS eligible patients will be randomized to receive either levetiracetam (anticonvulsant without CSD suppression) or topiramate (anticonvulsant with CSD suppression benefits). Furthermore, refinements in neuromonitoring need to occur in parallel since Dreier et al.<sup>5</sup> detailed the recording, analysis, and interpretation of spreading depolarizations in patients in neurointensive care with intracranial ECoG. There are also advances in EEG signal processing including machine learning and combinatorial use of other technologies such as near-infrared spectroscopy, noninvasive brain monitoring with wireless and convenient scalp-based EEG systems, which could be used to further study the incidence and characteristics of CSDs

in large cohorts of patients with brain disorders of interest including TBI, cerebrovascular diseases, migraine, and seizures.

Coining the term NESIS was an important first step to help describe a clinical phenomenon seen in practice, and one that appears responsive to certain classes of CSD-suppressing antiseizure drugs, but which lacked a unifying name until now. This should help with greater recognition going forward. However, the term NESIS should be prospectively validated and refined in GENESIS and randomized therapeutic interventions studied to see which may reduce stereotyped spells, lessen CSD, and improve outcomes. Discovery of NESIS will also hopefully generate a new age for neuromonitoring in brain-injured patient research, around a familiar friend of CSD events and underlying brain physiology.

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