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LETTER TO THE EDITOR

Late seizures following cerebral venous thrombosis—may be a maladaptive attempt to release gravitational ischemia in the brain

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Dear Editor-in-Chief,

Recently, a group of cerebral venous thrombosis (CVT) Late Seizure Investigators systematically reviewed the literature to identify risk factors for late seizures due to CVT. Their meta-analysis, reported in the *Journal* [1], identified five leading clinical factors, beginning with the occurrence of symptomatic (early) seizures, which predict a greater likelihood for the occurrence of late seizures—seizures which occur more than one week after CVT [1].

The CVT Late Seizure Investigators concluded, in part, that further high-quality studies are warranted to develop predictive models for individualized risk stratification and prediction of CVT late seizures [1]. However, the overall literature about CVT suggests that important resources in that regard may include autopsy studies [2], combined with studies of systemic biological markers [3], and observations about gravity in the brain [4, 5].

A potential primary cellular etiological risk factor—cerebral venous intra-mural endothelial inflammatory infiltrates—was recently reported by CVT Autopsy Investigators [2]. In their autopsy case study [2], a thrombotic adhesion was revealed to be joining a thrombus to an area of endothelium including the superior sagittal sinus and left transverse sinus. In one sinus, they discovered a vascular endothelial inflammatory infiltration of lymphocytes and plasma cells.

Specifically, a 66-year-old woman with fever, dizziness, and malaise was convalescing two weeks after the onset of symptoms, having received no medical attention and living alone—but discussing her symptoms with her son by phone. Three days later, he found her dead. Although her death was unwitnessed, circumstances suggested that it may have been sudden, or seizure-related. A forensic autopsy revealed only a CVT and one very small hemorrhagic infarction in the left cerebral cortex [2].

The CVT Autopsy Investigators [2] suggested that intramural venous inflammation may potentially persist to cause endothelitis, with endothelial dysfunction. Others [4, 5] have observed that this may result in difficulty with transmural venous fluid movement and with release of gravitational ischemia in the brain. CVT may therefore cause both immediate and long-term difficulty with release of gravitational ischemia in the brain.

Gravitational ischemia in the brain results from the mass effect of one part of the brain upon another in a gravitational field [4, 5]. In any given head position, the top half of the brain (farthest from the center of the earth) is sitting on the bottom half as a weight-burden. In healthy individuals, head and body positions are roughly vertical for 16 h a day, and then roughly horizontal for 8 h at night during sleep. Horizontally pancaking layers of progressively increasing weight from the over-lying brain tissue compress blood vessels and reduce blood flow in the bottom layers, potentially resulting in regional gravitational ischemia on the bottom side of the brain.

Ischemia, which may form on the bottom layers, is reversible in its early stages. Gravitational ischemia in the brain may potentially be largely preventable by frequently changing the head tilt—just as ischemic skin breakdown, bed sores, and decubitus ulcers are currently prevented by frequent changes in general body positioning, focused on the effects of gravity [4, 5].

And although the CVT Autopsy Investigators [2] suggested that the cause of death in their case may have been acute intracranial hypertension (AIH), the information they provided suggested that AIH together with seizure

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activity may have been part of a constellation of physiological events occurring around the time of death. Like many real-world cases, this autopsy case includes a mix of knowns and unknowns, regarding exactly what happened and when.

The potential relevance of late seizures following CVT to gravitational ischemia in the brain may be this. Seizure activity in this setting might allow three physiological events to occur.

1. Release of adenosine in the brain, which promotes vasodilation and increases blood flow.
2. Transition to horizontal position, which helps to resolve positional ischemia.
3. Increased pCO_2 levels in the brain, causing cerebrovasodilation and increasing blood flow.

These three physiological events might potentially all contribute to the release or resolution of gravitational ischemia in the brain.

Significantly, the group of Neuro-inflammation Investigators [3] looked at systemic inflammation markers in both serum and cerebral spinal fluid (CSF).

In total, 95 suitable patients with CVT and 41 controls were compared. The inflammatory factors studied included hypersensitive C-reactive protein (Hs-CRP), interleukin-6 (IL-6), and neutrophil-to-lymphocyte ratio (NLR) in the peripheral blood and immunoglobulin A (IgA), immunoglobulin M (IgM), and immunoglobulin G (IgG) in the cerebrospinal fluid (CSF).

The Neuro-inflammation Investigators [3] found a positive correlation between the degree of inflammation and the severity if clinical outcomes. Inferred by the data is the concept that acute, subacute, and chronic stages of inflammation may play a role in long-term outcome following CVT. Inflammatory cellular organization may be occurring on, and within, the blood vessel walls, aside from whether it forms in the meninges or brain parenchymal tissue.

Cerebral veins near the original site of the CVT may become damaged as a result of inflammatory processes or other processes. This damage may result in the partial inability of these vessels to mediate the brain fluid shifts necessary to clear and release gravitational ischemia in the brain. An increase or worsening of gravitational ischemia in the brain is potentially caused by a blockage of its clearance or release. Seizures in this setting may represent a maladaptive attempt to release gravitational ischemia in the brain.

In conclusion, the CVT Late Seizure Investigators [1] reported important findings from their systematic review, which were potentially consistent with the findings of other recent papers [2–5] to the extent of supporting further research into a possible relationship between late seizures following CVT, cerebro-vascular inflammatory mechanisms, AQ3 and gravity in the brain. AQ4

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