Disputes & Debates: Editors' Choice

Steven Galetta, MD, FAAN, Section Editor

Editors' note: Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window

In their recent meta-analysis of 4 randomized-controlled trials (RCTs) evaluating the safety and efficacy of IV alteplase for patients treated beyond 4.5 hours after last known well, Dr. Tsivgoulis et al. confirm each trial's reported advantage of treatment over placebo. Although the risk-to-benefit ratio of IV alteplase undoubtedly dwindles with time—as prior trials and meta-analyses have demonstrated—there is a population of slow—or perhaps, slower—progressors who may yet benefit from treatment in the extended treatment window. Important to note is the 4 included RCTs from this meta-analysis restricted patient inclusion based on the presence of a reversible ischemic lesion, as identified via perfusion CT or diffusion-weighted MRI. Among patients who meet these imaging and other clinical criteria, the risk of symptomatic hemorrhage following thrombolysis is considerable (adjusted odds ratio 6.22, 95% confidence interval 1.37–28.26), and yet the long-term outcomes demonstrate a clear functional benefit without a higher probability of mortality. In response, Dr. Ishida cautions readers that these data do not indicate a shift in the paradigm of acute treatment for all-comers. Instead, they should be used to extend treatment opportunities for historically ineligible patients. What's more is that we should not use these data to justify treatment delays or to curtail stroke education emphasizing rapid evaluation and triage for stroke-like symptoms. Time is still tissue, although it may be more or less tissue on the individual patient level.

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Reader response: Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window

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The timely meta-analysis by Tsivgoulis et al.[1] is an illustration of the transformative shift in hyperacute stroke management that has characterized the last several years. Focus has appropriately expanded beyond the classic mantra, "time is brain," to view time as a necessary, but no longer sufficient, surrogate for predicting functional outcome and to recognize that, perhaps, now "penumbra is key." Ultimately, this is an extraordinary advance for the more than 13 million people having new stroke each year[2] and the first-line health care professionals who help treat them. The summation of these studies prompted the American Heart Association to update recommendations about thrombolysis in an extended time window. 2019 Guidelines now provide a Class IIa recommendation, supporting IV alteplase administration in select patients with unclear time of onset and MRI diffusion-positive FLAIR-negative lesions who have symptom recognition within 4.5 hours.[3]

However, a word of caution amidst the enthusiasm: it is vital to recognize this as not strictly a shift, but rather a refinement of our treatment paradigm. Although we can fortunately consider thrombolytic treatment for many more people now, time is still absolutely essential on the

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individual patient level. Efforts to educate patients and communities about the emergent nature of stroke, regional systems of care optimizing prehospital triage, and emergent protocols to decrease time to treatment after ER arrival remain, as ever, the cornerstone of acute stroke management.

Penumbra may have changed paradigm, but let's not forget the importance of time.

1. Tsivgoulis G, Katsanos AH, Malhotra K, et al. Thrombolysis for acute ischemic stroke in the unwitnessed or extended therapeutic time window. Neurology 2019;94:e1241–e1248.
2. GBD 2016 Stroke Collaborators. Global, regional, and national burden of neurological disorders, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016. Lancet Neurol 2019;18:439–480.
3. Powers WJ, Rabinstein AA, Ackerson T, et al. Guidelines for the early management of patients with acute ischemic stroke: 2019 update to the 2018 guidelines for the early management of acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2019;50:e344–e418.

Editors' note: Cerebrospinal fluid dynamics disorders: Relationship to Alzheimer biomarkers and cognition

High-convexity tight sulci (HCTS) has emerged in the last decade as a radiographic biomarker among cognitively impaired individuals with enlarged subarachnoid spaces, with most of the literature reporting an association with normal pressure hydrocephalus (NPH) and responsiveness to CSF shunting. Using their previously validated, automated imaging analysis of HCTS—which was further validated by a neuroradiologist in this investigation—Drs. Graff-Radford and colleagues explored the relationships between HCTS and various cognitive and radiographic parameters in a cohort of 684 patients aged ≥50 years. Patients with HCTS had more frequent cognitive impairment, subcortical microvascular ischemic disease with lower white matter and cortical volumes, and (most importantly) lower Tau burden. The investigators reported that the lower Tau burden in patients with HCTS indicated that subarachnoid space enlargement could not be related to Alzheimer pathology. Furthermore, the fact that HCTS correlated strongly with less cortical volume (which might otherwise suggest an underlying tauopathy) suggests that this imaging signature could be used to identify a subgroup of cognitively impaired patients without Alzheimer pathology and who may not respond to targeted Alzheimer therapeutics. Drs. Alali and Laticevschi recall their related observations from the Geneva NPH cohort, which further validate HCTS as a radiographic indicator of a nontauopathy condition. Together, these studies typify biomarkers like HCTS as indicators of a nontauopathy state, which could be useful in future clinical trials enrolling patients with neurodegenerative conditions.

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Reader response: Cerebrospinal fluid dynamics disorders: Relationship to Alzheimer biomarkers and cognition

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We read with great interest the article by Graff-Radford et al.,[1] which showed that patients with high-convexity tight sulci (HCTS) were associated with a lower tau PET standard uptake value ratio than patients without HCTS. In the Geneva normal pressure hydrocephalus (NPH)

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cohort,[2] we tested the hypothesis that patients with HCTS are associated with decreased CSF phosphorylated tau level. Eighty-three consecutive patients with suspicion of NPH (age: 76.5 ± 7.8 years; 32.5% female) who performed an analysis of CSF biomarkers were included. HCTS has been determined following the definition of the Radscale[3]: HCTS was considered positive when narrow parietal high-convexity sulci (assessed in the transverse plane in the most superior slices and in the coronal plane) = 2 (presence of vertex narrow sulci).

Patients with HCTS (67.5%) presented a lower level of phosphorylated tau in comparison to those without HCTS (39.9 ± 16.4 vs 49.7 ± 21.3 ng/L; p value = 0.042). This association between low phosphorylated tau and HCTS persisted when adjusting for age, sex, white matter burden, and Mini-Mental State (β:−11.8; 95% confidence interval [−20.7 to −3.0]; p = 0.010).

This result suggests that HCTS in NPH (like in normal aging[1]) is not a consequence of neurodegenerative processes, especially those related to tau pathologies.

1. Graff-Radford J, Gunter JL, Jones DT, et al. Cerebrospinal fluid dynamics disorders: relationship to Alzheimer biomarkers and cognition. Neurology 2019;93:e2237–e2246.
2. Allali G, Laidet M, Armand S, et al. A combined cognitive and gait quantification to identify normal pressure hydrocephalus from its mimics: the Geneva's protocol. Clin Neurol Neurosurg 2017;160:5–11.
3. Kockum K, Lilja-Lund O, Larsson EM, et al. The idiopathic normal-pressure hydrocephalus Radscale: a radiological scale for structured evaluation. Eur J Neurol 2018;25:569–576.

Author response: Cerebrospinal fluid dynamics disorders: Relationship to Alzheimer biomarkers and cognition

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We would like to thank Drs. Allali and Laticevschi for their comment on our recent publication.[1] They report previously unpublished findings from an NPH cohort in Geneva,[2] which showed that the presence of a high-convexity tight sulci (HCTS) was associated with a lower CSF phosphorylated tau level. Both their observations and ours show converging evidence of an association with lower tau burden and the presence of HCTS, which is an MRI indicator of a CSF dynamics disorder. In our study, we demonstrated the presence of HCTS was associated with lower tau signal on PET in a population-based study,[1] and the Geneva group showed low CSF phosphorylated tau levels in a cohort of patients with NPH. Similar findings in 2 different cohorts with 2 different ways of measuring tau provide additional evidence that the HCTS pattern is not secondary to Alzheimer disease tauopathy.

1. Graff-Radford J, Gunter JL, Jones DT, et al. Cerebrospinal fluid dynamics disorders: relationship to Alzheimer biomarkers and cognition. Neurology 2019;93:e2237–e2246.
2. Allali G, Laidet M, Armand S, et al. A combined cognitive and gait quantification to identify normal pressure hydrocephalus from its mimics: the Geneva's protocol. Clin Neurol Neurosurg 2017;160:5–11.

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