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Short Communication

Mapping "Time is Brain" from Stroke to Alzheimer's Disease

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Our team at the Medical University of South Carolina (MUSC) is developing alternatives to the current situation of long wait times and an absence of specialized programs for the diagnosis and treatment of Alzheimer's Disease and related dementias through the creation of a statewide network designed to innovate care at all phases. This endeavor is called the South Carolina Alzheimer's Network (SCAN). A program like SCAN has many parts, but treatment preparedness is one crucial component. Our team, in part, comes from a background of stroke. In this brief paper, we offer comparisons based on how stroke care evolved from an unorganized state of medical activity into a highly tuned system of care characterized by rapid diagnosis, pre-hospital protocols that are initiated en route to the hospital with specialized destinations or "Stroke Centers" offering graduated levels of expertise and capability enabled by telemedicine at all levels.

One can argue that the all-important "first treatment" drove the stroke system's design and the pace at which it was developed. The FDA approved the recombinant tissue plasminogen activator or rTPA in June of 1996. rTPA was very significant, but it took time to transform the field. What partially changed the thinking was the notion that there existed this very narrow window of time with which we had to work. This change in thinking was the concept of Time Is Brain, and more to the point, Time {Lost} is Brain {Lost} forever.

One of our team members was at the Medical College of Georgia in Augusta at the time of rTPA introduction. The experience was typical of many tertiary sites (later to become Joint Commission Certified "Stroke Centers") that had become comfortable with tPA usage. However, they needed more candidates to treat because subjects often arrived after their treatment window had expired. While we could reduce the "door to needle" time to some extent with training, the "onset to door" time was just too long. We often sat in Augusta, Georgia, ready to treat, as patients traveled to us in EMT trucks from Thomson, Georgia, and Allendale, South Carolina but by the time they arrived their treatment window had often expired. Our frustration with this dangerous delay led us to develop one of the United States' first web-based tele-stroke networks, partly addressing this problem. Several experiences from that time are being re-lived in the Alzheimer's world today, and this comparison can be instructive. For example:

A. Editorials and opinion pieces from thought leaders in the early 1990s, after a string of failed tPA studies but before the landmark NEJM 1995 report [1] began to speak the unspeakable—namely, that restoration of blood flow to the ischemic brain—very easily accomplished in the lab—was perhaps never going to work in clinical practice. This was particularly discouraging as the field had failed to find a 'brain saving" molecule (or "neuroprotectant") that could extend the treatment window. This all changed when Jim Grotta, as artfully recounted in his personalized history of Acute Ischemic Stroke Treatment [2] began a press conference on December 14, 1995, with the words: "Until today, stroke was an untreatable disease."

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B. By analogy to Alzheimer's Disease, fast forward 15 years and see that several large and expensive studies aimed at reducing the accumulation of amyloid failed to show positive results, leading to speculation that the "amyloid hypothesis" may not be the reliable foundational hypothesis, so hoped for [3].

C. Campbell et al. [4] summarized the stroke experience in 2015, and their observations are still pertinent:

"It has been now 20 years since the publication of the National Institute of Neurological Disorders and Stroke (NINDS) tissue-type plasminogen activator (tPA) trial1. This randomized controlled trial initiated a paradigm shift in managing ischemic stroke. Before 1995, it was standard for patients with stroke to languish in emergency departments with no need to perform urgent brain imaging because it was argued that even the fundamental differentiation of intracerebral hemorrhage and ischemic stroke would not change management. The subsequent licensing of tPA provided an impetus to redesign stroke services to allow rapid assessment and delivery of therapy…".

Today one can reason that without a tPA-like landmark "first treatment" galvanizing our response, it is the standard for patients with Alzheimer's disease to "languish" on our waiting lists and in our clinic waiting areas for months while their treatment windows melt away and amyloid accumulates to dangerous levels in their brains. We desperately need a "paradigm shift" like the one in stroke in 1995. Perhaps one of the two antibodies with conditional FDA approval but limited CMS payment support is that drug, and we have yet to realize it. Whether it is Aducanumab, Lecanemab, or a future agent yet to be approved, it is likely that soon we will have that treatment. Preparing now and learning how to mobilize, move quickly, and prevent our patients from losing their all-important treatment window makes excellent sense.

The comparison to stroke can progress another step when considering how long it took for mechanical thrombectomy to reach Class 1 recommendation status (2018). The year 2015 was particularly gloomy as researchers reported three negative trials, casting doubt on what seemed then, and proved later to be, an imminently logical and sensible idea, which was with all haste to "open the arteries." Now, after numerous successful trials since 2015, near miraculous results are routine with rapid, catheter-based thrombectomy.

For those of us treating Alzheimer's disease, we continue to embrace the mantra of preventing the accumulation of the toxin—amyloid—and removing what has already accumulated. It is simple, appealing, and very likely correct and will be demonstrated as such when the proper treatment meets up with the right clinical trial design in the hands of the right investigators. It is not the time to fold our hands but to double down and intensify our efforts.

In preparation for that moment, we should do all we can to ensure our patients are ready and have practical operational tools and procedures to determine the "last known normal" or the Alzheimer's equivalent and how much of the treatment window remains in a given patient. We have the opportunity to learn valuable lessons from the stroke experience. Now is the time to act on the "Time is Brain" concept to better treat our patients with Alzheimer's and related dementias in 2023 and beyond.

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