

## Transient Ischemic Attack—Not So Transient After All!

Eric E. Smith, MD, MPH; Babak B. Navi, MD, MS

**According to conventional thinking**, transient ischemic attacks (TIAs) are supposed to resolve without permanent injury to the brain. However, this conventional view may be too rosy. A study<sup>1</sup> in this issue of *JAMA Neurology* suggests that TIAs are far from benign and should instead be considered potential harbingers of progressive cognitive decline.

**+**  
Related article

Some prior studies have associated TIA with cognitive impairment and decline.<sup>2</sup> However, findings have been mixed, potentially due to variation in sample sizes, patient characteristics, cognitive assessment protocols, and duration of follow-up. Additionally, most relevant studies have been limited by a lack of prospective information before the TIA and, therefore, have struggled to determine whether cognitive impairment was triggered by the TIA or instead existed before the TIA, potentially related to vascular risk factors such as hypertension. Many of these prior limitations are addressed by a new study<sup>1</sup> in this issue of the journal, which nests a study of incident TIA and neuroimaging-confirmed stroke within a large, prospective ongoing epidemiological study.

Between 2003 and 2007, the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study enrolled 30 239 Black and White community-dwelling persons, 45 years or older, living in the US. These participants have been followed up over time with the primary aim of investigating regional and racial differences in stroke risk. Since 2006, a cognitive sub-study has been included with a brief neuropsychological test battery administered by telephone every other year.<sup>3</sup> This battery consists of 4 tests: Consortium to Establish a Registry for Alzheimer Disease (CERAD) Word List Learning, CERAD Word List Delayed Recall, letter *F* verbal fluency, and animal naming verbal fluency.

After applying several eligibility criteria, the current analysis included 16 203 REGARDS participants without a history of stroke or TIA at enrollment whose cognitive abilities were followed up through 2022, with a median follow-up time of 14 years. Incident cerebrovascular events were adjudicated by a vascular neurologist, and TIA was defined as an acute ischemic cerebrovascular event resolving within 24 hours and with no acute infarction on diffusion-weighted magnetic resonance imaging. Because of the large sample size, a substantial number of study participants had a TIA ( $n = 356$ ) or stroke ( $n = 965$ ) during their follow-up. This gave the investigators the opportunity to compare pre-TIA and post-TIA trajectories of cognitive change within the same participant, controlling for demographics, education, and vascular risk factors. For participants without TIA or stroke, an arbitrary time point was chosen to match the index event date for TIA/stroke.

Trajectories of cognitive decline in the 3 groups were nicely illustrated in Figure 2 of the article. Before the TIA, the investigators found that the rate of cognitive decline was the same as stroke- and TIA-free participants. On the visit after the TIA, cognition was unchanged. However, after the TIA, the rate of cognitive decline accelerated and was not statistically different than in patients with a stroke. The accelerated cognitive decline in patients with TIA was largely driven by worsened performance in immediate and delayed memory recall, rather than a decline in verbal fluency.

The strengths of this analysis include the prospective design, large sample size, population-based cohort, long follow-up period, restriction to TIAs without acute infarctions on imaging, validation of cerebrovascular events by a vascular neurologist, and the rigorous statistical analyses and adjustments to control for confounding. The inclusion of a large sample of Black participants was another strength, although the lack of racial and ethnic diversity beyond Black and White participants was a relative limitation. Another limitation was the restriction to 4 simple cognitive tests that may not reflect global cognitive function.

This study's findings suggest that something happened around the time of the TIA that accelerated cognitive decline so that the trajectory of these participants' long-term cognitive function was no different than what participants with stroke experienced. What could have occurred to cause this? The answer is not clear. It is probably not due to vascular risk factors, because trajectories were compared within the same participants, and vascular risk factors were adjusted for in multivariable models. The authors speculate that  $\beta$  amyloid and tau pathology could be present, that  $\gamma$ -aminobutyric acid transmission could have been disrupted<sup>4</sup> or that blood brain barrier opening could have promoted neuroinflammation. Another possibility is that TIAs may cause permanent injury that is not readily visible on routine clinical imaging.<sup>5</sup> A more prosaic possibility is that neurodegenerative symptoms, such as forgetfulness or confusion, may have been mistakenly diagnosed as TIA.

Interestingly, a similar phenomenon of accelerated cognitive decline has been seen after systemic vascular events, such as myocardial infarction.<sup>6</sup> This raises the possibility of other mechanisms, including systemic inflammation<sup>7</sup> and postevent anxiety or depression.<sup>8</sup>

Regardless of the mechanism, clinicians should be aware that patients with TIA are at elevated risk for cognitive decline. Stroke-prevention specialists and primary care practitioners should question patients with TIAs, and ideally an informant such as a spouse, about the presence of cognitive symptoms and be prepared to do a cognitive screen

for impairment. This screening is even more important now that disease-modifying therapies for Alzheimer disease, which could cause subtle decline unmasked by a TIA, are

available. TIA should now be viewed as a risk marker for cognitive decline as well as a risk marker for adverse vascular events.

#### ARTICLE INFORMATION

**Author Affiliations:** Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, Calgary, Alberta, Canada (Smith); Clinical and Translational Neuroscience Unit, Feil Family Brain and Mind Research Institute and Department of Neurology, Weill Cornell Medicine, New York, New York (Navi); Editorial Board, *JAMA Neurology* (Navi).

**Corresponding Author:** Eric E. Smith, MD, MPH, Department of Clinical Neurosciences, Hotchkiss Brain Institute, University of Calgary, 3330 Hospital Dr NW, Health Sciences Centre, Room 2941, Calgary, AB T2N 4N1, Canada (eesmith@ucalgary.ca).

**Published Online:** February 10, 2025.  
doi:10.1001/jamaneurol.2024.5090

**Conflict of Interest Disclosures:** Dr Navi reported receiving personal fees from MindRhythm Inc outside the submitted work. No other disclosures were reported.

#### REFERENCES

1. Del Bene VA, Howard G, Gropen TI, et al. Cognitive decline after first-time transient ischemic attack. *JAMA Neurol*. Published online February 10, 2025. doi:10.1001/jamaneurol.2024.5082
2. van Rooij FG, Kessels RP, Richard E, De Leeuw FE, van Dijk EJ. Cognitive impairment in transient ischemic attack patients: a systematic review. *Cerebrovasc Dis*. 2016;42(1-2):1-9. doi:10.1159/000444282
3. Levine DA, Wadley VG, Langa KM, et al. Risk factors for poststroke cognitive decline: the REGARDS Study (Reasons for Geographic and Racial Differences in Stroke). *Stroke*. 2018;49(4):987-994. doi:10.1161/STROKEAHA.117.018529
4. Figlewski K, Andersen H, Stærmosé T, von Weitzel-Mudersbach P, Nielsen JF, Blicher JU. Decreased GABA levels in the symptomatic hemisphere in patients with transient ischemic attack. *Heliyon*. 2018;4(9):e00790. doi:10.1016/j.heliyon.2018.e00790
5. Easton JD, Johnston SC. Time to retire the concept of transient ischemic attack. *JAMA*. 2022;327(9):813-814. doi:10.1001/jama.2022.0300
6. Smith EE, Silbert LC. Myocardial infarction bends the curve of age-related cognitive decline, but how? *JAMA Neurol*. 2023;80(7):665-667. doi:10.1001/jamaneurol.2023.0466
7. Smith EE, Biessels GJ, Gao V, et al. Systemic determinants of brain health in ageing. *Nat Rev Neurol*. 2024;20(11):647-659. doi:10.1038/s41582-024-01016-z
8. Dollenberg A, Moeller S, Lücke C, et al. Prevalence and influencing factors of chronic posttraumatic stress disorder in patients with myocardial infarction, transient ischemic attack (TIA) and stroke: an exploratory, descriptive study. *BMC Psychiatry*. 2021;21(1):295. doi:10.1186/s12888-021-03303-1