

Transient global amnesia and stroke: not that benign?

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After more than 50 years since Fisher and Adams' original description in 1964,¹ transient global amnesia (TGA) is still a puzzling syndrome. Over time, several mechanisms have been proposed for TGA pathogenesis, including venous congestion, cortical spreading depression, seizures and arterial ischaemia.^{2–4} A sufficient amount of studies in favour and against each of these mechanisms has emerged, fostering uncertainty regarding aetiology as well as prognosis. To this extent, most of the controversy stands on whether TGA represents a risk factor for stroke, or whether this is just as benign as originally thought.⁵

In this volume of *Stroke and Vascular Neurology*, Lee and colleagues add a further episode to the saga, building on data from a large propensity-matched cohort study.⁶ Using records from the Korean National Health Insurance Service, they selected 10 447 patients with TGA and 20 493 controls through greedy nearest neighbour method, following both cohorts for up to 11 years to assess the occurrence of stroke. After adjusting for enrolment year—a strategy to mitigate differences in follow-up duration—TGA was associated with a higher risk of stroke compared with control population. Hypertension, diabetes and atrial fibrillation substantially increased the risk of stroke among TGA cohort, suggesting potential preventive measures to be implemented under specific circumstances.⁶

The results from this Korean study raise up the debate around the benign nature of TGA. To reach such definition, TGA has been under the lens for decades, mainly through single centre observational studies.^{2,7–10} While original reports showed prevalence of stroke as high as 46% in TGA cohorts,^{11,12} recent evidence supported rates comparable to that of migraineurs, people with epilepsy⁹ or general population.⁸ TGA benign nature was also corroborated by the substantially lower risk of stroke compared with transient ischaemic attack in longitudinal investigations.^{5,10} However, most of the studies were limited by

their sample size (well below a thousand people with TGA) as well as by their observational design.

Estimating prognosis in real-world setting becomes increasingly important in neurovascular diseases, as prevention strategies are gaining high impact hand-in-hand with high complexity.¹³ Drawing on large database represents a practical approach to identify features less susceptible to local bias, including long-term prognosis in real-world environment.

In this study, patients with TGA were selected from a database with internally tested coding accuracy, and propensity score matching also involved cardiovascular risk factors, psychiatric disorders, migraine and epilepsy, reinforcing the genuine nature of the trends identified.⁶ At the same time, the findings critically diverge from those of a similar investigation applying propensity score-matching on the Nationwide Readmission Database.¹⁴ In this American cohort, 21 202 TGA cases were matched with 21 293 controls, and no difference in the risk of stroke was found. As for the previous study, matching was not limited to cardiovascular risk factors but also involved alcohol use, migraine, income and education, again giving strength to the results.¹⁴

How can we interpret these differences between such large-scale studies? Despite using different International Classification of Diseases (ICD) editions, both reports relied on standardised coding for TGA and outcomes, so that little influence could be attributed to adjudication or selection bias. To this extent, TGA coding inaccuracies are reasonably similar in these studies, and the volume of data prevented from investigating adjusted rates of events depending on the diagnostic workup, which could reinforce the diagnosis.¹⁵ Therefore, a look at the underlying population might help us in putting the findings into context. First, the overall distribution of cardiovascular risk factors in the population differed, with hypertension, hyperlipidaemia and atrial fibrillation being more frequent in the American population¹⁴

compared with the South Korean one,⁶ in line with recent global estimates.^{16 17} Second, the control cohort selected with matching had specific features. In the American study, controls derived from inpatient setting and, compared with TGA, had a marginally higher Charlson comorbidity index¹⁴ that correlates to the risk of stroke.¹⁸ On the other side, the Korean study had prevalent female composition, and the increase in risk of stroke among TGA emerged over a consistently longer follow-up (up to 11 years⁶) compared with that of the American report (1 year).¹⁴ May people with TGA have a marginally higher risk of stroke, detectable only over a very long-term period? May then other factors, common among people with TGA such as hypertension and diabetes, be involved in building the relative increase in risk over time?

Differences across these well-conducted large-sample studies seem to reinforce the elusive nature of TGA. It seems that, even with vast cohorts, the issue regarding its very nature remains. We still miss the pathogenesis, we are again uncertain on its benign prognosis, and yet we have to manage it reasonably, avoiding overdiagnosis and overtreatment. At the same time, on the basis of this report from Lee and colleagues,⁶ one might wonder if a specific subgroup of people with TGA—namely those with several cardiovascular risk factors—might benefit from stringent primary prevention measures, a topic definitely worth exploring, as we may rise with the occasion of TGA to reduce the risk of stroke in a large population.

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