Response to Letter by Caplan

Response:
As commented in our editorial,\(^1\) increasing evidence links transient global amnesia (TGA) to different pathophysiological factors including venous flow abnormalities, spreading cortical depression, phobic personality trait, and vasoconstriction. However, none of these mechanisms considered alone seems to completely justify TGA clinical course and diagnostic findings.

How come so different pathological pathways were hypothesized to subend such a stereotyped clinical syndrome? A possible explanation is that, once triggered by precipitating events, these factors act as intermediate mechanisms inducing a metabolic and oxidative stress in the CA1 subfield of the hippocampal cornu ammonis and thus determining a neuronal dysfunction responsible for the TGA typical amnesic state. Symptoms would last until stunned hippocampal neurons are able to recover from the pathological cascade characterized by glutamate-mediated increase in calcium influx, metabolic stress, and anaerobic glycolysis.\(^2\)

In this scenario, a transient but sudden increase in venous pressure may lead to hippocampal venous congestion with subsequent ischemia. On the other hand, a less abrupt but sustained increase in venous pressure might be gradually compensated by cerebral hemodynamics, thus not leading to venous ischemia. Nevertheless, internal jugular valve insufficiency cannot be the only determinant of TGA because up to one quarter of patients with TGA presents with competent valves. It is possible that venous reflux triggers a regional arterial constriction as well as a cortical spreading depression. Similarly, one could argue that vasoconstriction is not the only culprit for the hippocampal dysfunction subtending TGA because the abuse of potent cerebral vasoconstrictors such as cocaine and/or caffeine has never been related to TGA onset. Additionally, it could be hypothesized that vasoconstriction would overcome autoregulation limits more easily in the posterior circulation, where autonomic innervation is less effective, leading to lesion sites less stereotyped than those observed in TGA.\(^2\) In fact, in acute posterior cerebral artery strokes, additional extrahippocampal lesions are highly likely.\(^3\) In line with this observation, radiological studies found in migraineurs an increased prevalence of silent infarct-like lesions scattered in the posterior circulation territory.\(^4\) Migraine represents a risk factor for TGA only in younger patients,\(^5\) where an increased susceptibility to cortical spreading depression could lead to neuronal dysfunction also in absence of other cofactors (eg, hippocampal neurons made more vulnerable by aging, less effective hemodynamics, venous valve insufficiency).

In summary, venous flow abnormalities, spreading cortical depression, phobic personality trait, and vasoconstriction could all play a role in TGA physiopathology, interacting differently depending on individual susceptibility. However, our impression is that we are still missing some pieces to assemble the TGA jigsaw puzzle.

Disclosures
None.

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