What causes transient global amnesia?

New insights from DWI

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Transient global amnesia (TGA) is a dramatic event. Without warning, the patient suddenly experiences antegrade memory loss.1,2 As quickly as the amnesic syndrome appears, it resolves, usually within 24 hours. There are no apparent long-term sequelae, and recurrence is uncommon.

What causes TGA? For years this question has been debated. Various proponents have advocated ischemic, migrainous, and epileptic causes.3 Even a neuropsychological cause has been proposed. Unfortunately, definitive evidence supporting any of these mechanisms has been lacking.

More recently, Lewis hypothesized that TGA was related to venous congestion due to retrograde venous cerebral blood flow, because of the commonly reported association between TGA and situations that result in reduced venous return and retrograde venous blood flow (e.g., sexual activity, stress, Valsalva maneuver).4 Interestingly, there is some support for this hypothesis. The same group has reported that a significantly higher percentage of TGA patients possess jugular venous backflow with Valsalva compared with controls.5,6

Can MRI help provide answers? The profound nature of the memory deficit has encouraged speculation that memory-related structures such as the hippocampus are involved. Until recently, this has been difficult to prove since TGA has not been associated with any findings on CT or MRI. More recently, diffusion-weighted imaging (DWI) has detected high signal abnormalities in the medial temporal lobe and possibly other structures implicated in memory functioning.7-9 However, these reports have been conflicting, with some investigators reporting no detectable DWI abnormalities, while others report these findings in a high percentage of cases.7,10-11 Until now, the reason for this marked discrepancy has been unknown.

In this issue of Neurology, an explanation for this discrepancy is presented.12 Sedlaczek et al. report a high frequency of DWI positivity in TGA patients, but primarily (>90%) in individuals who were scanned more than 24 hours after symptom onset. Overall, DWI abnormalities were detected in 36/59 (61%) TGA patients. The lesions were small and located in the hippocampal and thalamic regions—a finding consistent with previous works using SPECT and PET that showed hypoperfusion in these same areas.3

Is TGA really a TIA? Both recover within 24 hours, and now both have been associated with DWI abnormalities. However, there are differences. The apparent time course of TGA-detected DWI findings is unusual for conventional arterial ischemia. Although rare reports describe ischemic DWI lesions after a significant time delay, these lesions typically appear very soon after ischemia onset. In contrast, according to the authors, DWI changes associated with TGA regularly occur following a 24-hour delay. TIA-associated DWI lesions also tend to be larger than TGA (although still small), and have lower apparent diffusion coefficient (ADC) values than TGA-associated lesions. Moreover, the correlation between vascular risk factors and TGA is weak, making the relationship of TGA to an ischemic cause even more suspect.

Status epilepticus, hypercellular tumors, bacterial abscesses, hemiplegic migraine, and acute multiple sclerosis lesions also may result in DWI positivity, although these causes are quite uncommon.13,14 Focusing on the significantly higher ADC values that they observed in TGA, the authors speculate that this condition may be explained by venous congestion, consistent with Lewis’ venous backflow hypothesis.4 A lower ADC is associated with a more severe degree of tissue injury, they argue, and this would have suggested more pronounced ischemic insult such as is seen in arterial disease. While this is a possible explanation, less severe reductions in ADC have been reported with small lesions, such as those identified in TIA patients. A venous explanation also would not explain why TGA does not recur more

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frequently in a previously affected patient, since presumably anatomic factors predisposing to retrograde flow do not diminish over time. Moreover, given the high frequency of situations that result in diminished venous return such as sexual activity, stress, and Valsalva maneuvers, TGA should be more frequent in the population if this were the explanation.

Should the presence of these new DWI findings change patient management? This depends on whether there is a plausible reason to believe that the patient should be considered for antithrombotic therapy. The individuals described in the present study had many risk factors, in contrast to other studies that reported a low incidence of vascular risk factors in TGA. Therefore, in individuals with vascular risk factors, antiplatelet therapy should be considered. One approach would be to add antiplatelet therapy to patients with DWI abnormalities particularly if they possess conventional cerebrovascular risk factors. Further studies evaluating stroke occurrence in TGA patients who are DWI positive vs negative might be useful in clarifying this question. The relative rarity of TGA makes such studies problematic, and it is unlikely we will have a definitive answer in the near future.

The study by Sedlaczek et al may point the way for better understanding TGA. Using this work as a stepping stone, perhaps we can further clarify the mechanism of this condition by combining these findings with perfusion weighted MRI, functional neuroimaging such as PET or SPECT, and possibly venography using MR and Doppler techniques. The current study provides tantalizing new information regarding the nature of TGA. We can only hope that further studies can more definitively clarify the etiology of this enigmatic process.

References