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Expert Opinion

Transient Global Amnesia and Migraine

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CLINICAL HISTORY

A 31-year-old woman presented with a history of transient memory problems. The day before, upon awakening at her normal time, she had trouble with her memory such as remembering events of the day before, the day of a dinner engagement the week before, and a movie she saw a week ago. The memory problem lasted all day and resolved by the next morning. Her father stated that her speech was normal but she just seemed confused. She had no associated headache or other neurologic or systemic symptoms or signs. There is a history of migraine without aura from childhood until 10 years ago and migraine aura without headache occurring once every couple of months for the past several years. Past medical history was otherwise negative. Neurological examination was normal. A MRI scan of the brain, complete blood count, chemistry profile, TSH, and vitamin B12 level were all normal.

Question.—Is there a relationship between transient global amnesia and migraine?

EXPERT COMMENTARY

This patient presented with an acute episode of memory disturbance, suggestive of the memory disturbance seen in transient global amnesia (TGA). Patients with TGA have an acute inability to form new memories. This anterograde amnesia is typically evident by the patient's repetitive questions and comments that continue despite being answered. Patients often have insight into the memory disturbance and can appear distraught. The repetitive questions and comments often reflect this insight and can include comments such as "What day is it," "What's going on with me," or "There's something wrong." Although not described in this patient's case history, the confusion reported by the patient's father most likely included repetitive questions and comments related to her memory loss.

In addition to anterograde amnesia, during the attack, patients have the inability to access memories for events that occurred days, weeks, or even months ago. This retrograde amnesia is often evident by the patient's inability to answer many of the memory questions that witnesses invariably ask the patient during the attack, as reported here. Access to more distant memories remains intact during TGA.

By definition, TGA lasts less than 24 hours, but most attacks last about 4 to 6 hours. As the attack resolves, the retrograde amnesia resolves so that preevent memories close to the moment of onset are again able to be recalled. Because TGA causes total loss of ability to form new memories, however, the patient will always remain amnesic for the entirety of the event itself. TGA also typically affects patients in their 50s to 70s, unlike the age of this patient.

To me, the most interesting feature of TGA relates to the activities that the patients (or witnesses) so often report as having occurred immediately prior to the onset of the event. Typical TGA-precipitating activities include sexual intercourse, vigorous exercise,

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immersion in cold water, severe pain, and acute emotional stress.[1] No typical triggering event is reported in this patient's clinical history. However, she was described as amnesic upon awakening, so if there were no witnesses to the onset it may be impossible to know. Mild head trauma can also occasionally cause a memory disturbance indistinguishable from typical TGA, so in the absence of a witness, this cannot be excluded as the cause of this young patient's memory disturbance.[2]

What is the cause of TGA? The presumption that TGA occurs due to transient dysfunction of the bilateral hippocampi is not controversial—the hippocampi are involved in forming new episodic memories, and in retrieving recently acquired episodic memories. What remains uncertain is the cause of this transient hippocampal dysfunction. The two main hypothesized etiologic mechanisms are migraine and ischemia. It is generally agreed that an epileptic pathogenesis is unlikely for TGA; however, some patients with temporal lobe seizures can have amnesic episodes that are typically shorter in duration and more often recurrent than typical TGA.

The migraine hypothesis for TGA, as formally proposed by Olesen and Jorgensen, suggests that the events that trigger TGA cause the release of glutamate in the hippocampi, triggering migrainous spreading depression and transient hippocampal dysfunction.[3] Evidence for the migraine hypothesis is based primarily on several epidemiologic studies which show an excess of migraine in TGA patients.[4] In addition, a number of case series have described associations between the two entities, including migrainous accompaniments and headache during TGA in some reported patients.[5] In my opinion though, the migrainous hypothesis has never adequately explained the older-age-group predilection for TGA, nor its common precipitating activities, which are not typical triggers for migraine.

The possibility that TGA occurs due to ischemia has classically been based on the anatomical fact that the mesial temporal lobes are supplied by the posterior cerebral arteries. Ischemia in the territory of the single basilar artery can cause memory disturbances, and transient ischemia in this territory could conceivably be the cause of TGA. However, epidemiologic studies have generally shown a decreased incidence of vascular risk factors and subsequent vascular events in TGA patients compared to patients with TIA or stroke.[4]

In 1998 I proposed a new ischemic hypothesis for the cause of TGA, based primarily on two suppositions regarding the common TGA triggers—first, that these triggers would likely cause increases in venous return from the arms to the superior vena cava; second, common TGA triggers would likely cause a simultaneous Valsalva, transiently blocking drainage of the superior vena cava into the right heart. In short, the hypothesis states that increased venous return toward a blocked superior vena cava could cause transient retrograde venous congestion and venous ischemia to bilateral hippocampal or diencephalic structures, resulting in TGA.[6] Since incompetent jugular valves would make patients more susceptible to retrograde venous flow, I proposed that one test to support this hypothesis would be to look for an excess of incompetent jugular vein valves in TGA patients, although in an individual patient the presence of incompetent valves would neither be necessary nor sufficient to cause TGA. Several investigators have subsequently shown an increased prevalence of incompetent jugular valves in TGA patients compared to controls.[7-9]

MRI studies in TGA patients over the last couple of years have been especially enlightening, and seem to lead further away from the migraine theory. Recent studies using diffusion-weighted imaging (DWI) have shown punctate bilateral or unilateral hippocampal lesions in a significant proportion of TGA patients scanned 24 to 48 hours after TGA, with most of these lesions not evident when patients were scanned in the hyperacute phase.[10,11] Although the DWI lesions reported in TGA are most compatible with ischemia, the authors of these studies note that the delay in visualization of these punctate lesions is unusual for typical arterial ischemia. In addition, the apparent diffusion coefficient values of these lesions is higher than in typical TIA-associated DWI abnormalities. This suggests that if these lesions are due to ischemia, a mechanism other than arterial ischemia may be causative. Notably, DWI abnormalities have not been reported in migrainous spreading depression in humans. Finally, a recent study using high-resolution 3.0-Tesla T2 reversed MRI showed hippocampal cavitary lesions

in all patients (15/15) studied with a previous history of TGA. These lesions were significantly more prevalent, larger, and more frequently bilateral than in control patients, in whom none were bilateral.[12] The authors of this study noted that the presence of these lesions suggest ischemia to the CA1 region of the hippocampus. They conjectured that these findings might reflect delayed neuronal death due to venous congestion.

So, is there an association between TGA and migraine? Maybe, but in my opinion, probably only an epidemiologic one. Migraine might be a risk factor for TGA but is probably not directly related to the causation of typical TGA. The usual age distribution of TGA, the unusual precipitating activities that provoke it, and the recent MRI findings, all seem to argue against migrainous spreading depression as the cause of TGA. Moreover, the recent imaging studies are particularly supportive of an ischemic pathogenesis, whether venous or otherwise. This was anticipated by Bender in his initial description of TGA nearly 50 years ago, when he stated: "Of the various possibilities considered, a transient circulatory disturbance of the brain would seem to be the most acceptable."[13]

Finally, back to this patient: if migraine is becoming less plausible as the cause of TGA, can migraine nonetheless be related to this patient's presentation? There is no reason to exclude the possibility that migraine can occasionally present as a memory disturbance resembling TGA, just as migraine can cause other focal neurologic disturbances. This young woman, who at age 31 is significantly younger than the typical age group for TGA, and who has a strong personal history of migraine, might have had a memory disturbance due to migraine. In other words, her event may have been similar to TGA, but perhaps not TGA. I would also suggest the caveat that in a patient with a TGA-like syndrome but outside of the typical TGA age group and without a clear-cut precipitating event, the possibility of temporal lobe seizure should be more strongly entertained. However, the prolonged duration of this patient's episode would be atypical for either an ictal or post-ictal amnesic event.

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