Early Diagnosis and Treatment of Dementia Presenting as Transient Global Amnesia in a 76-Year-Old Man

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This article reports the case of a high-functioning patient who had an "event" diagnosed as probable transient global amnesia (TGA) 1 year before being diagnosed with evolving cognitive impairment. Formal psychometric testing was necessary to make this diagnosis owing to the insensitivity of simple tests in this high-functioning individual. Neuropsychological evaluation showed impairment of short-term verbal memory, compounded by observed fluctuations in attention. In light of its reported benefits for cognitive function and attention, galantamine was administered starting at 4 mg b.i.d., then increasing to 8 mg b.i.d. and finally to 12 mg b.i.d. During galantamine dose escalation, the patient experienced transient vomiting on the first day of taking 12 mg b.i.d. With reassurance, he returned to the same dose and tolerated it during long-term treatment without problems. His cognitive function has remained at an improved level for 18 months on galantamine administration.

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Amnesia, or memory loss, often is an early hallmark of mild cognitive impairment or dementia. Because the memory problems evolve gradually, initial symptoms may be subtle, and the patient and family often attribute such memory problems to simple aging. As the memory loss worsens, sometimes a particular upsetting event "unmasks" the problem. In high-functioning persons who can compensate well for mild memory losses, it is possible to attribute the onset of memory loss to a perceived precipitating event, such as an episode of transient global amnesia (TGA); however, the event simply may represent the first time that the gradually evolving problem comes to attention.

TGA was first defined in 1958 as a disturbance characterized by a sudden inability to acquire new information (deficit of anterograde memory).[1] Epidemiologic data are scanty, and incidence rates vary among studies from different countries, but the reported annual incidences range from 3 to 32 per 100,000 persons.[1] After the first event, the annual risk of TGA recurrence is estimated to be 2.5%, according to a review of published literature.[1] Diagnostic criteria for TGA were developed in the 1980s, then modified and validated by Hodges and Warlow in 1990.[2]

Several theories have been proposed regarding the etiology of TGA, but the underlying causes remain obscure. Proposed risk factors include vascular risk factors, patent foramen ovale, and retrograde jugular venous flow.[3] A recent study found the role of these factors to be minimal and implicated cerebral venous hypertension caused by incompetence of the internal jugular valve.[3] Metabolic studies of the brain (cerebral positron emission tomography [PET] imaging with ^{18}F-labeled fluorodeoxyglucose) showed that some patients had low metabolism in local areas related to memory.[4]

Based on a study of 14 patients examined 3 or 4 days after the end of an episode of TGA, Kessler and colleagues[5] proposed a major role for stress in the etiology of TGA and in the continuation of cognitive impairment. Hodges and Warlow[2] identified a putative precipitating event in 13% of their 63 patients with prospectively ascertained TGA or an emotionally stressful event of at least moderate severity during the 24 hours leading up to the attack in 14%; in an additional 17%, the attacks occurred in association with moderate to severe physical exertion. These authors also distinguished a group of patients with probable epileptic amnesia, characterized by attacks lasting for less than an hour or recurring rapidly, who had a high likelihood for subsequent manifestation of epilepsy.

Pantoni and colleagues[1] noted that in spite of its typically benign prognosis, TGA is a frightening experience for patients and usually leads to extensive examinations in search of organic causes.

The following case report highlights the question of whether a TGA episode presages the development of

dementia or whether increased concern about cognitive function generated by a TGA episode may result in an earlier diagnosis of developing dementia than would occur otherwise.

CASE REPORT

Mr. A, born in 1926, is a married, retired engineer. His physician knows him as a bright and dynamic individual. Mr. A was admitted to the hospital in 2000 at age 74 years, his chief complaint being that he could not remember what had happened earlier on the day of admission. That morning he felt well and went to pick up a car that he had left at his dealership for repair. The last thing he recalled that day was having a significant verbal battle with staff at the dealership about repeatedly inadequate repairs. Other stressful events also were occurring in his life at that time. When he arrived home from the auto dealership, he complained that he could not recall anything that had happened earlier in the day subsequent to the discussion at the dealership; he also had diminished ability to recall events of the previous day. He had a mild headache but no other symptoms. His family became concerned about this memory loss and took him to the hospital, where he experienced some return of memory for the day's events.

Mr. A was seen by his primary care geriatrician and a neurology consultant. The workup was largely negative; magnetic resonance imaging results showed minimal periventricular white-matter changes and an occluded or hypoplastic vertebral artery. Carotid duplex sonography showed multiple small plaques without stenosis and the occluded right vertebral artery seen on MRI. Results of laboratory testing, including complete blood count, sedimentation rate, standard blood chemistry panel, thyroid-stimulating hormone level, prostate-specific antigen level, and fecal occult blood examination as well as electrocardiographic results were normal. The patient was discharged from the hospital with a tentative diagnosis of probable TGA, made by the neurology specialist.

After discharge from the hospital, Mr. A felt "unnerved" by this event and would gasp for breath on occasion. During the next few months, he felt that he was suffering from anxiety and continued to be concerned about his memory loss. His primary care physician considered the possibility of an early cognitive disorder and recommended that he be monitored closely.

In March 2002, Mr. A noted that in addition to poor memory, he would frequently transpose numbers; he also noted new-onset difficulty in visualizing items in 3 dimensions when doing repairs around the home. Because of increasing concern about evolving cognitive impairment, the patient underwent formal neuropsychological testing using the Wechsler Adult Intelligence Scale-Revised (WAIS-R),[6] the Rey Auditory-Verbal Learning Test (RAVLT),[7] and the Logical Memory I and II and subtests of the Wechsler Memory Scale-Revised (WMS-R).[8] He was found to have short-term verbal memory impairment out of proportion to the rest of his cognitive function. The Mini-Mental State Examination (MMSE)[9] score recorded at this time was 28. Although his scores on many cognitive tests were high for his age group, they were deemed to show a reduction relative to the patient's historical level of functioning. The consulting psychologist who performed the evaluation hypothesized that problems with attention at times reduced his performance on the short-term memory tests.

Given Mr. A's documented memory impairment coupled with self-reported visuospatial deficits and calculation deficits, early dementia with attention deficits was suspected, rather than mild cognitive impairment. The patient was started on galantamine at 4 mg b.i.d. Administration of this dose was continued for 1 month, and then the dose was escalated monthly according to the recommended schedule. He tolerated the 4-mg and 8-mg b.i.d. doses well, but he vomited on the first day of the 12-mg b.i.d. dose. His physician reassured him that nausea and vomiting were likely transient and advised him to take his medicines with food; the patient returned to the 12-mg b.i.d. dose and had no further difficulty tolerating the medication at the highest recommended dose. He and his family noted improvement in his cognitive function, and an MMSE score of 28 was recorded.

Because of this relatively high MMSE score, in the fall of 2002, Mr. A's insurance company questioned the need for medication and recommended a repeat neurologic consultation. The consultation confirmed the suspected cognitive deficit disorder, and a recommendation was made to continue galantamine. The patient was advised to minimize alcohol intake and continue meticulous control of hypertension and hyperlipidemia. At the time of the most recent evaluation, approximately 18 months after the amnesia event, his level of functioning was unchanged from the initial improvement seen after initiation of galantamine therapy.

Medical History

Mr. A's medical history was remarkable only for radical prostatectomy for prostate cancer 15 years earlier, a 10-year history of hypertension and hyperlipidemia well managed with medications, and an approximately 10-year history of glaucoma treated with timolol eyedrops. He also had acne rosacea, treated with erythromycin and topical clindamycin. At age 69, he had been hit on the head with a golf ball but reported no loss of consciousness or other sequelae. He usually drank 16 oz of red wine per day, but results of all liver tests were normal, and his blood tests did not show elevated mean corpuscular volume. The patient had a history of occasional ocular migraine (predating the golf ball injury), lumbar disk disease treated with epidural injections, and Dupuytren's

Table 1. Additional Past Medical Disorders

Scintillating scotomata
Impingement syndrome, shoulders
Diverticulosis with history of diverticulitis
Colonic polyps treated with colonoscopic polypectomy
Recurrent herpes simplex labialis
Episode of herpes zoster
Hearing loss
Gastroesophageal reflux disease with history of gastrointestinal bleeding

Table 2. Current Medications

Verapamil
Hydrochlorothiazide
Atorvastatin
Rabeprazole sodium
Aspirin (daily low dose)
Erythromycin
Vitamin C
Vitamin E
Lutein
Timolol eyedrops
Glucosamine and chondroitin
Clindamycin skin ointment

contractures. The contractures and an inguinal hernia were repaired in 2002. He stopped smoking in 1969 after having smoked for approximately 20 years. Otherwise, Mr. A was a healthy, physically and mentally active individual. Table 1 provides additional details of his medical history; Table 2 lists medications being taken at the time of the event.

DISCUSSION

This case study illustrates that, despite gradually developing symptoms, a patient and family may not notice an evolving cognitive deficit until it becomes the focus of attention as a result of a particular event. As is often the case, the patient may be aware of the cognitive deficit in the early stages of dementia, although the awareness may fade later. After a notable event occurs, the patient and the family may attribute the memory problems to a newly prescribed medication, a stroke, an illness, a food, or some other factor. Regardless of etiologic assumptions, it is important for the physician to take the patient's concern about cognitive problems seriously, follow up through formal or informal testing, and begin treatment if appropriate. Early cognitive decline, mild cognitive impairment, or dementia in a high-functioning patient may not be detected by standard tests, and if there is concern, performance of formal psychometric testing or referral to a specialist may be indicated.

The differential diagnosis of suspected TGA should include the possible initial presentation of early cognitive impairment or mild delirium. Attempts to rule out organic causes such as blood clot, stroke, or ischemic disease are an integral part of the workup for TGA.[2] However, the presence of any of these factors does not confirm it as the sole cause of the event. Meticulous management of coexisting medical problems in patients with suspected TGA is crucial, especially when cardiovascular factors may contribute to progressive cognitive impairment. Also crucial is elimination of possible aggravating factors such as excessive use of alcohol or unnecessary polypharmacy, especially with any of the strongly anticholinergic medicines used for sleep disturbances, bladder problems, and depression.

Specific therapy such as cholinesterase inhibitors and vitamin E may be indicated if the patient meets the criteria for Alzheimer's disease (AD) or other conditions for which cholinesterase inhibitors have been shown to be beneficial (vascular dementia, diffuse Lewy body disease, and probably mild cognitive impairment). In some instances, reliable observations about particular deficits in cognitive function by the patient or relatives (such as the visuospatial deficits or transposition of numbers reported in this case) may lead the physician to initiate dementia-specific therapy even if the criteria for diagnosis of AD on screening tests are not fully met.

In early stages of cognitive impairment, patients and families may be frightened by the thought of having AD or dementia and may dispute application of the label. The more descriptive diagnostic label of "cognitive deficit disorder of the . . . type" (e.g., Alzheimer's, multi-infarct, diffuse vascular, diffuse Lewy body, or Pick's), analogous to the diagnostic label of attention deficit disorder, should be considered for universal use as a more accurate and medically meaningful diagnosis, with fewer emotionally charged implications than the other currently used terms. Acceptance of a diagnosis may facilitate compliance with therapeutic recommendations.

AD is a progressive disorder, and abilities that are lost as the disease progresses may never be regained.[10] Galantamine has been shown to be beneficial in delaying cognitive decline in patients with mild-to-moderate AD.[11–14] Galantamine has a dual mode of action: it allosterically modulates acetylcholine receptors of the nicotinic type and inhibits acetylcholinesterase.[15,16] Findings from studies in animals, smokers, and patients with AD indicate that nicotinic receptor function is particularly important in maintaining attention[17] and that galantamine has an attention-enhancing effect.[18]

Adverse events associated with galantamine usually are mild and transient.[12] The most frequent adverse events are gastrointestinal in nature and include nausea, vomiting, and anorexia. These events most commonly occur at the start of galantamine treatment or when the dosage is increased, and they generally stop (without treatment) during continued administration of galantamine, as was seen in the present case.

In a placebo-controlled trial of galantamine with an open-label extension in which patients were started on

galantamine after a 6-month placebo phase, the patients who received galantamine in the open-label extension showed recovery or a slowing of decline in cognitive function, but their cognitive abilities remained behind those of patients who had received galantamine since the beginning of the trial.[19] Similarly, when galantamine treatment was stopped and then reinitiated in a randomized withdrawal study, patients' cognitive function did not return to the level achieved before withdrawal.[19] Therefore, the argument can be made that early, continuous acetylcholinesterase inhibitor treatment is optimal for preservation of cognitive function. An unpublished report indicates that galantamine may be beneficial in mild cognitive impairment.[20]

It should be noted that, in the absence of pathognomonic diagnostic testing, it is possible that Mr. A does not have AD but that he may have cognitive impairment due to a different etiology or several contributing factors. Furthermore, based on this single case report, there is no proof that the medication caused the observed improvement or stabilization in this patient.

Drug names: acetylcholine (Miochol), atorvastatin (Lipitor), clindamycin (Clindagel, Cleocin, and others), erythromycin (Eryc, E-Glades, and others), galantamine (Reminyl), hydrochlorothiazide (Microzide, Oretic, and others), rabeprazole sodium (Aciphex), timolol (Cosopt, Betimol, and others), verapamil (Verelan, Isoptin, and others).

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