Synapse
a clinical resource
FALL 2016, VOL. 7, ISSUE 3

MRI of the Brain: With or Without Gadolinium?

John Winn, MD

Since its first clinical use in 1998, gadolinium-based contrast agents (GBCA) have provided clinicians a powerful tool for diagnosing and treating a broad spectrum of clinical entities ranging from neurological and musculoskeletal to gastrointestinal and genitourinary derangements. To date, more than 300 million contrast-enhanced MRIs have been performed worldwide and over 30 million examinations performed annually.

Gadolinium (Gd3+) is a rare earth metal that demonstrates an enhancing or brightening property when used in conjunction with MRI imaging. Due to the toxic effects of free Gd ions, it is bonded to a carrier molecule known as a chelating agent that prevents the direct toxic effects of the ion while maintaining its diagnostic qualities.

Clinicians will need to carefully assess the appropriateness of enhanced MRI examinations but not deprive patients of its inherent benefits.

As a drug class, gadolinium agents are very safe with a low prevalence of allergic reactions (compared to other drug classes such as pain killers and antibiotics) with a frequency of .004% to 0.7%. Severe life threatening reactions are extremely rare (0.001% to 0.01%). They also have few adverse reactions compared to iodinated contrast agents used for computed tomography (CT) imaging.

However, a link between GBCA and a rare disorder known as nephrogenic systemic fibrosis (NSF) was made in early 2006. NSF is a potentially fatal disorder characterized by fibrosis of skin and subcutaneous tissues resulting in pruritic, erythematous plaques and commonly leading to contractures from muscle and tendon fibrotic shortening. The fibrosis can also involve multiple other organs leading to multisystem organ failure, including respiratory failure from diaphragmatic involvement.

NSF was found to occur in patients who had undergone MRI imaging with gadolinium in the setting of acute renal injury or chronic renal failure with or without hemodialysis, especially in those with concomitant liver disease. The exact pathophysiology is still not completely understood. The most commonly held hypothesis suggests that the gadolinium ion becomes disassociated from its chelating ligand resulting in accumulation within various tissues throughout the body including bone, skin, kidney, liver, and brain tissue. Normally, the vast majority of the GBCA dose is renally excreted. In those with impaired renal function, the reduced excretion allows more time for ion disassociation in vivo.

The dissociation rate of Gd+ ions is also believed to be related to the stability of the complexes among the various gadolinium agents. The two categories of agents are macrocyclics in which the gadolinium is enclosed in a rigid, cage-like structure and linear agents in which a backbone-like structure wraps around the gadolinium but does not fully enclose it. Linear agents

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A Practical Approach to the Diagnosis of Dementia

Peter T. Skaff, MD

Our population is aging. The first baby boomers are entering their 70s and age-related medical conditions are being diagnosed in primary care offices more than ever. One in nine individuals over age 65 has Alzheimer Disease, the most common form of dementia. Thus, a practical approach to the recognition and management of dementia is a necessary component of any primary care practice. In this brief article, the focus will be on the initial work-up of suspected dementia.

Dementia is defined most simply as a progressive decline in cognitive function involving multiple domains of cognition that interferes with activities of daily living. Alzheimer Disease causes over half of all dementias with other causes including vascular dementia, fronto-temporal dementia, and Lewy body disease. Vascular dementia may coexist with the neurodegenerative forms resulting in mixed dementia. A pre-dementia state in which cognition has declined but functional independence is maintained is referred to as mild cognitive impairment.

With our aging population, primary care physicians will be called upon with increasing frequency to assess patients presenting with cognitive decline.

The initial diagnostic focus is on the history. Although direct patient interview is necessary, concurrent history from the spouse, family members, or a close acquaintance is essential. Early symptoms of Alzheimer Disease reflect deficits in episodic memory and present as unusual forgetfulness, difficulty learning, and repetitive questioning. The "head turning sign" in which the patient turns frequently to a companion for answers to questions is a sensitive marker for early dementia. Other early onset symptoms include disorientation, impaired judgment, difficulty with communication, and changes in mood, personality, behavior, or perception. Difficulty performing complex tasks such as driving and financial management are also concerning. The medication list should be reviewed for anti-cholinergic, analgesic, psychotropic, and sedative/hypnotic agents—and a careful sleep history should be obtained.

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Cognitive testing performed in the office should be reasonably brief, accurate, and reproducible, administered in the patient's preferred language, and normalized to education level. The Mini-Mental Status Exam (MMSE) is a widely studied, proprietary, 30-point test that is approximately 90% accurate for correct classification of dementia. The Montreal Cognitive Assessment (MoCA) is a freely available 30-point screening tool that has shown superiority to the MMSE for detection of mild cognitive impairment. The Mini-Cog is a clock drawing task along with a three-item delayed recall task, and has accuracy similar to the MMSE.

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Mercy Medical Group Memory Clinic

Ashkan Javaheri, MD

Major Neurocognitive Disorder (NCD) is a new term for "dementia" and encompasses a group of disorders which can affect memory, attention, learning, language, perception, and social cognition. Alzheimer's disease is the most common form of major NCD with the projected prevalence of 5.2 million Americans over 65. Other common forms of major NCD are vascular dementia, Lewy body dementia, frontotemporal dementia, and Parkinson's disease dementia. Mild NCD can affect different domains of cognition but is not severe enough to affect day-to-day function. Because there is high likelihood that patients with mild NCD will go on to develop major NCD, close monitoring, educating patients and families, and setting expectations are important.

Addressing caregiver stress and offering pharmacological and non-pharmacological recommendations for behavioral and psychological symptoms of dementia might allow patients to stay at their place of residence longer.

The majority of these diseases are progressive and have no cure. Proper diagnosis and timely treatment may ease the burden of disease progression. Addressing caregiver stress and offering pharmacological and non-pharmacological recommendations for behavioral and psychological symptoms of dementia might allow patients to stay at their place of residence longer.

Caregivers of patients with NCD are considered "invisible patients." Fifteen million Americans provide unpaid care for patients with dementia. Sixty percent of caregivers have a "high" or "very high" self-reported level of emotional stress. Addressing these issues in a busy primary care clinic is very challenging and requires expertise and additional resources.

Mercy Medical Group's Geriatric Division and Dignity Health Neurological Institute of Northern California are collaborating to bring a number of professionals together to establish an interdisciplinary "Memory Clinic" at Mercy Medical Group. Geriatric physicians, case managers, and pharmacists will be the core team and will work with neurologists, neuropsychologists, behavioral health specialists, the Alzheimer's Association, and home health agencies to provide a comprehensive approach to caring for patients with NCD. When appropriate, patients will be referred for imaging studies, including MRI and PET scanning with other imaging technologies expected in the future. The Memory Clinic's goal is not only to establish an accurate diagnosis and offer treatment options, but also to provide support to families and caregivers through support groups offered by the Alzheimer's Association, advance care planning, and care coordination. The Memory Clinic will also evaluate patients' abilities to drive and to make complex medical or financial decisions. Different team members will work closely with patients and families to assure safety and offer assistance when transition to a higher level of care is needed. Clinical trials will be offered as new treatments are developed.

Mercy Medical Group's Memory Clinic will soon open its doors to patients and families at the Midtown location at 3000 Q Street and will accept patients on a referral basis. Referrals can be made for a second opinion or for ongoing care. To refer a patient, call 916.733.3460. Providing medical records and MRI images, when available, will greatly facilitate the evaluations. ■

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The neurological exam should include assessment of gait, testing of gross motor function including limb tone, and observation for involuntary movements such as tremor. Abnormal findings may be clues to vascular dementia or dementia related to extrapyramidal disorders. Signs of systemic vascular disease should be sought and the presence of significant hearing impairment noted. Blood tests should be limited to general chemistry profile, TSH, and vitamin B12 level. Routine testing for syphilis is not recommended. Cerebral imaging with non-contrast CT or MRI is indicated when cognitive impairment is detected, though the latter has higher sensitivity for structural abnormalities. Lumbar puncture and electroencephalography are reserved for specific circumstances.

With our aging population, primary care physicians will be called upon with increasing frequency to assess patients presenting with cognitive decline. By focusing on careful history-taking and use of proven, cognitive screening tools, effective diagnostic assessment of early dementia can be achieved. Management of dementia can be challenging, and the new Mercy Memory Clinic will provide that much needed support. ■

Surgical Management of Parkinson's Disease

Ehsan Hadi, MD

Parkinson's disease (PD) is the 2nd most common neurodegenerative disorder. The peak age at onset is approximately 60 years. PD risk increases with age, with a lifetime risk being 2%. Prevalence of PD is 1.8% at age 65, which increases to 2.6% at age 85 to 89. Positive family history increases the risk by 4%. It shows a slight preponderance of men with a male-to-female ratio of 3:2.

Etiology of PD remains unclear but is likely multifactorial. The current thinking is that in most cases, non-genetic factors play a part, probably in interaction with susceptibility genes. The pathological changes identified in Parkinson's disease include Lewy Bodies—clumps of sticky proteins called alpha-synuclein in the brains of PD patients. They are thought to be toxic and key contributors of neuronal death and disease propagation. The eventual manifestation of motor symptoms is due to inadequate levels of the neurochemical dopamine. PD remains a clinical diagnosis with both motor and non-motor symptoms. Cardinal motor features include bradykinesia (slowness of movement) with additional features of tremor (typically a resting tremor), rigidity, and postural instability, which causes impaired balance and coordination.

Management of Parkinson's disease is quite broad based and includes pharmacological (primarily dopaminergic), non-pharmacological, and surgical modes. Deep brain stimulation (DBS) is considered the cornerstone of surgical treatment for various movement disorders. DBS was introduced in 1987 by Dr. Alim Benabid, who discovered that high frequency stimulation of the thalamus mimics the therapeutic effects of older techniques of deconstructive lesioning. DBS hardware includes a surgically implanted DBS lead with four electrodes in the desired target (subthalamic versus globus pallidus interna), an extension wire that passes from the scalp area under the skin to the chest and an implantable pulse generator over the chest wall. The exact mechanism of benefits of DBS simulation is not clear, however DBS is thought to be a brain pacemaker that delivers electrical current, modulating specific targets in the brain, resulting in symptomatic improvement. DBS is preferred over past techniques of lesioning due to its reversibility, adjustability and good safety profile. DBS received its FDA approval for PD in 1992.

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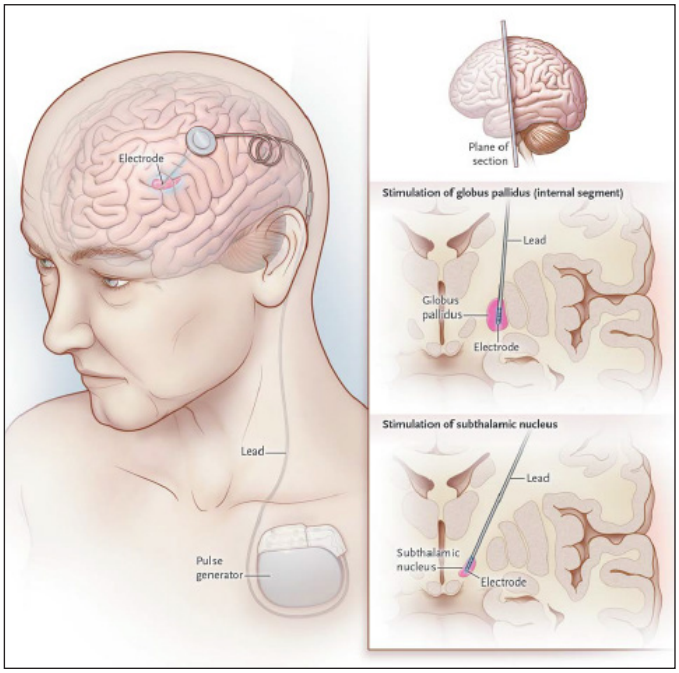

Electrode Implantation for Deep-Brain Stimulation. The lead for deep-brain stimulation is implanted in either the subthalamic nucleus or the internal segment of the globus pallidus. The lead passes through a burr hole in the skull. Attached to the lead is a connecting wire, which is tunneled under the skin of the scalp and neck to the anterior chest wall, where it is connected to an impulse generator.

Source: Okun, 2012

About 10–20% of individuals with idiopathic Parkinson's disease are candidates for DBS therapy. Tremor that improves with L-DOPA between dose fluctuations and dyskinesia is the most likely symptom to improve with DBS. Axial symptoms, including speech, swallowing and gait impairment, typically don't respond well and in some cases may get worse.

Pre-surgical evaluation plays an important role in appropriate patient selection, and in turn, successful surgical outcome. It requires a multidisciplinary team, typically comprising a movement disorder neurologist, a neurosurgeon and a neuropsychologist. The evaluation includes assessment of motor symptoms, ruling out atypical features, on/off testing to determine adequate L-DOPA responsiveness,

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Deep Brain Stimulation in Treatment of Parkinson's Disease

Cully A. Cobb, MD, FAANS

The brain has complicated systems to control its activity, and neuroscientists are gradually learning how they function. Many of these systems have specific locations, including the pathways controlling smooth movement, which are the ones affected by Parkinson's disease. Techniques have evolved which allow modulation of activity in localized areas of the brain. Electrical stimulation through electrodes placed in the appropriate locations can adjust the brain's own control pathways and improve brain function.

Parkinson's disease has been managed with medications with great benefit. One of the drawbacks is that although medications may improve movement, they have a global effect on the entire brain, and some of these effects may be unwanted. If the desired effect can be achieved from stimulation of a specific area, the unwanted effects can be reduced.

Deep Brain Stimulation (DBS) involves the precise placement of an electrode in a localized portion of the brain. The target is chosen based on current understanding of neurophysiology provided by the pioneering experience of centers throughout the world. The location of the target in the patient's head can be determined using an atlas which is based on measurements in cadaver brains. Measurements from normal structures in the brain seen on MRI, such as the anterior and posterior commissures, allow localization in the patient's brain.

Parkinson's disease has been managed with medications with great benefit. One of the drawbacks is that although medications may improve movement, they have a global effect on the entire brain.

MRI also allows a trajectory to be planned leading from a burr hole to the planned target and avoiding critical structures. Localization can be confirmed by passing a microelectrode to the target and recording the specific firing pattern of the cells in the target. When confirmation of target localization has been achieved by microelectrode recording, the microelectrode can be replaced with a larger permanent electrode. Stimulation of the permanent electrode during surgery is used to confirm its effect and make sure side effects of stimulation are tolerable. Electrodes can be routinely placed within 1-2 mm of the intended target chosen by MRI.

A recent randomized prospective trial of 255 patients with Parkinson's disease has documented the benefit of DBS. Patients were randomized to DBS or to best medical therapy, determined by neurologists with movement disorders specialization. Assessment was performed at 6 months by neurologists who were blinded to the patient's treatment.

Deep brain stimulation is complicated and requires specialized equipment and a team with specialized training.

Patients had control of movement without dyskinesias for 6.4 hours a day in the best medical therapy group and 10.9 hours per day in the DBS group. Time with troublesome dyskinesias decreased from 3.9 hours per day in the best medical therapy group to 1.8 hours per day in the DBS group. The time asleep was slightly longer in the DBS group and the time with bradykinesia was slightly shorter in the DBS group.

Deep brain stimulation is complicated and requires specialized equipment and a team with specialized training. Mercy Medical Group (MMG) Movement Disorder specialist, Ehsan Hadi, MD provides medical treatment and screening for DBS to patients with Parkinson's disease; but until recently, has had to send his patients to other centers for the surgical component. Dignity Health Neurological Institute has been able to acquire funding for the sophisticated neurosurgical equipment through Mercy Foundation thanks to the generosity of grateful donors and philanthropy. Dr. Cobb and Dignity Health are now able to provide this treatment for Parkinson's disease, as well as essential tremor and dystonia. Targets to treat obsessive compulsive disorder (OCD) have been approved by the FDA and there is active exploration in research centers to find targets to treat other problems. DBS is expected to revolutionize the management of many brain problems as it has already done for Parkinson's disease, tremor and dystonia. ■

Cully A. Cobb, MD, FAANS

Three W's of Speech Pathology Consults: Who, Why, and When

Dodie Newman, MA, CCC

Who: Speech-language pathologists within our Mercy outpatient centers are trained to work with a wide variety of neurological patients including those with stroke, tumor, traumatic brain injury, anoxia encephalopathy, Parkinson's Disease (PD), Multiple Sclerosis (MS), dementia, ALS, post-concussion syndrome, Mild Cognitive Impairment (MCI), or Huntington's Disease. Our LSVT LOUD (Lee Silverman Voice Training) certified therapists at the Mercy Outpatient Rehabilitation Center treat patients with reduced vocal volume due to PD. Patients experiencing swallowing problems and voice disorders can often be helped by speech therapy. Some of our Mercy facilities treat children with speech delays or articulation disorders. (Children suspected to be on the autistic spectrum would be better served at the UC Davis MIND Institute.) The speech pathologists at our outpatient centers work closely with physical therapists and occupational therapists to assist patients in achieving their goals. This multidisciplinary approach focuses on functional goals patients can use in their home and community. Treatment goals emphasize activities the patient needs or desires to resume, which result in increased functional activity and productivity.

Why refer to speech therapy? Our training helps the patient remediate deficits and/or incorporate strategies to compensate for their challenges. In addition to helping patients who are experiencing difficulty with their communication (speaking, word finding, reading, writing, and understanding what they see or hear), a speech pathologist assists those patients facing challenges with cognitive problems such as short-term memory, distractibility, poor initiation, impulsivity, impaired social skills, scattered thinking, impaired decision making, poor organization/planning and those who are easily overwhelmed. For patients facing progressive disorders such as MS, PD, MCI or dementia, speech therapy can assist the patient and their family in developing strategies and routines to maximize the patient's independence and safety as well as to educate the family for long-term adaptation planning. Beyond structured therapy drills and home programs, therapists can teach patients to use technology to compensate for their deficits. For example, smartphone applications can be used to remind the patient to take his/her medications, produce audible words typed by the patient, and set reminders for tasks with alerts to improve time management and productivity. Speech pathologists can help the patient overcome deficits in communication, cognition, voice and swallowing.

A speech pathologist assists those patients facing challenges with cognitive problems.

If treatment is delayed, the patient may develop secondary challenges such as anxiety, job loss, isolation or other conditions.

When should you refer your patient for outpatient speech therapy? Simply put, when you, the patient or family members observe speech, cognitive or swallowing problems. It is never too late to refer a patient for an assessment, but it is better to refer the patient early in their illness. Patients experiencing mild cognitive problems such as memory, attention and information processing following a concussion can sometimes be quickly assisted if seen early on. In contrast, if treatment is delayed, the patient may develop secondary challenges such as anxiety, job loss, isolation or other conditions. ■

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performing a detailed neuropsychological evaluation to assess cognitive/psychiatric status, and brain imaging to help rule out any secondary etiologies.

DBS should not be reserved as a last resort approach. Rather, it is used as an adjunctive therapy along with dopaminergic medications to improve motor function and is best suited for patients who develop motor complications such as dose fluctuations/wearing off, dyskinesia or inadequate control with dopaminergic medications. Clinical trials comparing DBS with best medical therapy have shown statistically significant improvement in not only motor scores and on time without dyskinesia but also in quality of life outcomes. Newer DBS techniques under consideration to improve efficacy and prolong battery life include identifying new nuclei, innovative stimulation techniques and closed loop DBS. ■

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are thought to be less stable and have been implicated in the majority of NSF cases.

The radiology community quickly reacted to the findings and adopted new standards of care with more stringent screening of renal function, modified dosing for renally impaired patients, and reclassifying GBCAs based on their stability. With the widespread change in practice protocols, the incidence of NSF diminished and there have been no new cases of NSF since 2009.

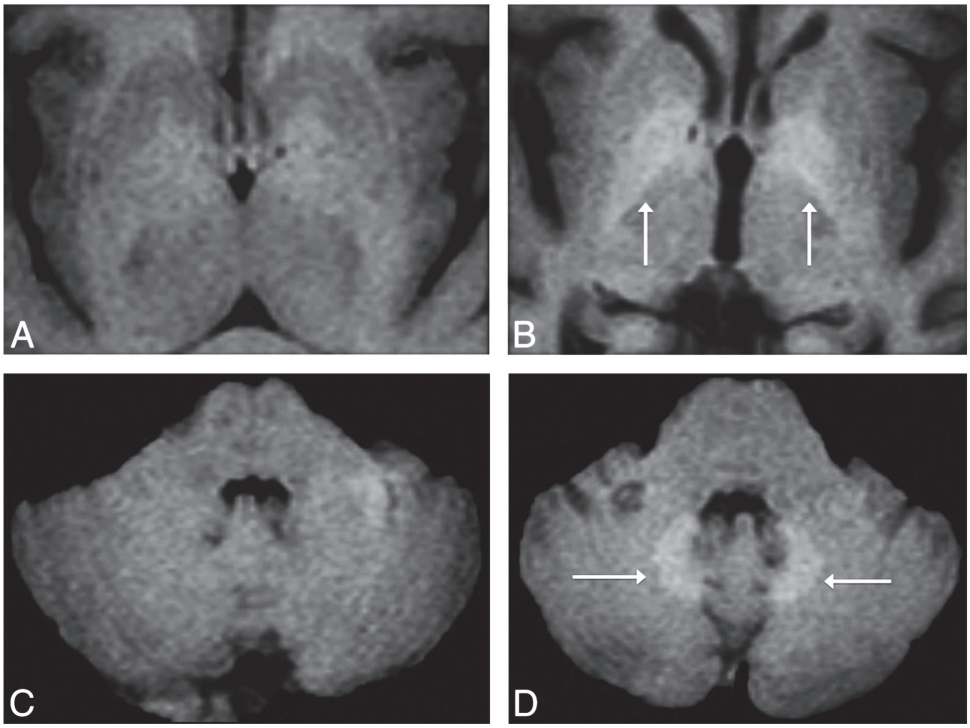
The most commonly held hypothesis suggests that the gadolinium ion becomes disassociated from its chelating ligand resulting in accumulation within various tissues throughout the body including bone, skin, kidney, liver, and brain tissue.

Then in 2014, an observation of increased signal intensity in areas of the brain, most notably within the basal ganglia (globus pallidus) and the dentate nuclei within the cerebellum, was associated with repeated exposure to GBCAs in patients with normal renal function. Post mortem studies of brain tissue that had prior GBCA exposure and normal renal function confirmed the presence of gadolinium in the same areas that demonstrated increased signal intensity on unenhanced MRI exams. The degree of signal intensity changes was also found to be greater with increasing number of doses. These findings suggest that gadolinium accumulates and is retained in tissue.

As with NSF, the linear agents have been found to result in a greater degree of signal abnormality changes in comparison to the more stable macrocyclic agents raising similar concerns of accumulated disassociated Gd+ ions. However, it is still unknown whether the accumulated gadolinium is in its free state or chelated state.

Currently, the clinical implications, if any, of the intracranial gadolinium accumulation is still unknown. Although there have been no reports of specific clinical symptoms in patients with the observed increased intracranial signal abnormality, there is a growing, ongoing body of research to evaluate its clinical relevance.

For the last 18 years, gadolinium-based contrast agents have become an essential adjunct tool in patient care and management. However, its ubiquitous use has revealed safety concerns with its association with NSF and more recently with gadolinium accumulation within tissues of the body, including areas within the brain, with repeated exposures. More clinical research will be necessary to elucidate the latter's true clinical ramifications. Going forward, clinicians will need to carefully assess the appropriateness of enhanced MRI examinations but not deprive patients of its inherent benefits. ■



Axial MR images in a 51-year-old woman with parkinsonism. Unenhanced T1-weighted MR imagings of the first (A and C) and fifth (3 years later; B and D) gadolinium-enhanced MR imagings performed with a nonionic linear GBCA (Omniscan) at the level of the basal ganglia (A and B) and the level of the dentate nuclei of the cerebellum (C and D). The images show progressively increased T1 signal of the globi pallidi and dentate nuclei (white arrows, B and D), undetectable on the first MR imaging.

Source: American Society of Neuroradiology, 2015

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