

## Deep Brain Stimulation for Obsessive-Compulsive Disorder

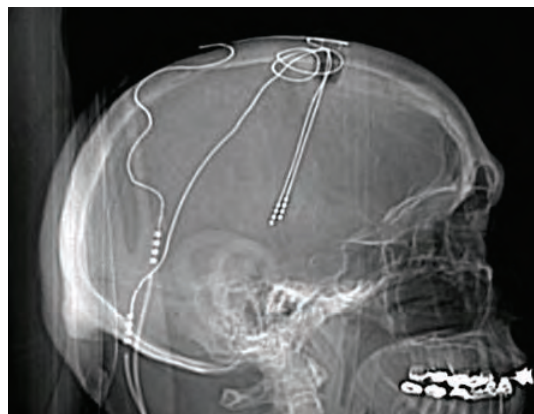
Adam Mamelak, MD

Obsessive-compulsive disorder (OCD) is a relatively poorly understood mental illness characterized by intrusive thoughts, rumination and compulsive behaviors. A characteristic aspect of the illness is an insistent repetition of set behaviors such as hand washing, running through checklists, opening and closing a door a set number of times, counting to a set number or repeatedly checking if a door is locked. OCD is generally thought to be a form of an anxiety disorder in which the person adopts certain ritual behaviors or compulsions as a means to reduce anxiety and prevent intrusive thoughts. Ironically, the compulsion to perform these acts often induces more anxiety. These behaviors can become both time-consuming and socially alienating, often leading to further isolation, economic loss and failure to function well in society. Even though patients with OCD may recognize their behaviors as irrational, they are often unable to suppress them, as failure to carry them out induces more anxiety. Patients with OCD also suffer from obsessive thinking, often focusing on set sexual, violent or religious ideas that can progress to frank psychosis.

OCD is the fourth most common mental disorder diagnosed in the United States. It is estimated that one in 50 people in this country suffer from OCD, making it as common as asthma or diabetes. A clear pathological explanation for the basis of OCD remains elusive and is the subject of much investigation. There is some evidence suggesting a genetic or inheritable aspect to the disease. Several studies have suggested abnormally high levels of dopamine in the prefrontal cortex and low levels of serotonin in the basal ganglia. Anatomic studies suggest reduced size of anterior cingulate and medial frontal regions of the brain in patients with OCD compared with normal controls or patients with other anxiety disorders.

Treatment of OCD is an evolving field. Cognitive therapy aimed at teaching patients to live with anxiety rather than perform compulsive behaviors is a mainstay of modern management. This form of aversive therapy is perhaps the most effective behavioral strategy. The use of selective serotonin

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Front and side view skull X-rays of DBS electrodes in an OCD patient.

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# HIV/AIDS: Reflections on 30 Years of the Epidemic

Howard Aaron Aronow, MD

## Neuro-HIV rounds

**2011:** It is past midnight on a typical day of rounds. I have seen several complicated AIDS cases in my academic neurological practice, including a 43-year-old gay white man with severe pain due to longstanding sensory neuropathy and multiple herniated discs in his cervical and lumbo-sacral spine. This patient also has end-stage liver disease from hepatitis C and hepato-biliary carcinoma that was resected one year ago with clean margins and no recurrence. He is on the waiting list for a liver transplant and has only mild cognitive complaints, mostly due to his liver disease. His pain is controlled and his quality of life is improving.

My day also included:

- A 51-year-old Latina with such severe polymyositis that she requires monthly infusions of immune globulin. She was in a wheelchair a year ago and now walks independently.
- A 39-year-old African-American woman with severe migraines with aura. Her husband likely transmitted the virus to her. My headache patients with AIDS are generally no more difficult to treat than the HIV negative population, but headache is twice as common in HIV patients.
- A 29-year-old bisexual African-American man who is celebrating his fourth year of being cancer-free after a diagnosis of primary brain lymphoma. He still suffers from headaches and uses medical marijuana to relieve the pain. He contracted HIV at age 16. His head MRI scans have remained without evidence of lymphoma recurrence as recently as one month ago.
- A 36-year-old Latina who is relatively stable with a diagnosis of cerebral toxoplasmosis. She is finishing a course of full therapy and hopefully will be able to go on lower maintenance doses of medications as long as her next MRI scan shows stability and she continues to improve. She is lucky to have only mild left-sided weakness, and the anti-retroviral medications have restored her immune system.
- A wheelchair- and bed-bound Latino former injection drug user who has both HIV-associated dementia and a brain infection with JC virus, which causes a disease known as progressive multifocal leukoencephalopathy (PML). The dementia made the PML more difficult to recognize, but I've finally got him on a multi-drug regimen with at least two



agents that penetrate into the brain. He's now able to transfer himself to the toilet, and his speech and memory are slowly improving. His complex partial seizures are less frequent and he is ready for more intensive inpatient cognitive and motor/gait rehabilitation.

Had these patients received their diagnoses prior to 1995, they would not be alive today. There are many others in the community who have recently become infected but do not seek health care for diagnosis and treatment, either because they do not realize they are at risk or because they lack health insurance. Many are still dying when they come to our emergency rooms too late.

## Flashback to the 1980s

**1981:** The first cases of pneumocystis pneumonia and Kaposi's sarcoma are reported simultaneously on the East and West coasts. I am about to start my internship in internal medicine. I already know that I've matched for a neurology residency at Albert Einstein College of Medicine. Everyone is terrified of this new disease, originally called "GRID" for gay-related immunodeficiency disease.

**1982:** Now I know why so many gay men that I'd seen as a medical student had persistent generalized lymphadenopathy. I diagnose and treat a 31-year-old African-American bisexual, married postal worker with pneumocystis pneumonia (PCP) and HIV-associated dementia. The staff won't even bring in his meal trays; they are left outside his hospital room door. I am one of a few staff members willing to bring him his meals and help feed him. When it comes time to speak with his wife, he has a psychiatric break, and it takes three security guards to hold him down so I can give him an injection of Haldol® to tranquilize him.

Once destined to be a movement disorders specialist, I discover my calling to care for AIDS patients with neurological diseases.

## The AZT years

**1985:** AZT is in experimental use for dementia at doses much larger than standard, and patients show some improvement if they can tolerate the side effects of headaches, nausea and anemia. Their reprieve is short-lived, however. If fortunate, they have six months before failure and regression back to being mute and bed-bound before death.

**1988:** I've completed my fellowship in neurology at Memorial Sloan-Kettering Medical Center and I'm on my way to Los Angeles to take up an academic and clinical practice closer to my aging parents. I obtain privileges at virtually all of the dedicated AIDS units in hospitals across Los Angeles and the two AIDS hospices. (In 2011, all HIV-dedicated hospices will be gone, as well as most inpatient AIDS units.) Meanwhile, the American Academy of Neurology (AAN) issues its first set of diagnostic criteria for AIDS dementia complex, a constellation of cognitive, motor and psychiatric symptoms. This nomenclature encompasses both AIDS dementia and AIDS vacuolar myelopathy, the spinal cord component of severe AIDS-related neurological disease.

By the end of the decade, I have watched so many patients die that I no longer keep count.

## The HAART breakthrough

**1994:** I knew long before now that monotherapy, or two-drug therapy with anti-retrovirals, didn't work. The handful of my patients with overwhelming diagnoses like PML, whom I place on as many antivirals as are available, seem to improve. We are now at the beginning of "highly active anti-retroviral therapy," or HAART, consisting of at least three active medications. Some patients have made it long enough to benefit from HAART, but for many others it was too little, too late.

## HIV in the new millennium

**2000:** I'm seeing far fewer neurological opportunistic infections and tumors and a significant decrease in the severity of HIV-associated cognitive disorders, including dementia, in patients who are responding to HAART and whose immune systems have reconstituted. My research using the brains of AIDS patients who donated their brains at death shows only a small number of cases of the HIV-associated encephalitis that was so rampant during my fellowship. Instead, I am seeing brain changes associated with liver disease and large fatty livers. Something is changing, and perhaps it is not just

HIV that is causing losses in cognitive and motor function. Perhaps the increase in lipodystrophy and toxicity from long-term use of antiretrovirals is playing a key role.

Many patients feel disfigured by central obesity, facial wasting and abnormal hard fat collections, such as buffalo humps and bullfrog necks. Too many of my patients are co-infected with chronic hepatitis C virus, and they are faring worse as a result of peripheral neuropathy and cognitive-motor disorders than those with HIV alone.

Increasingly, teenagers and young adults think that HIV is just a disease for which one can take pills and continue to live normally. Once infected, they turn to crystal methamphetamine or crack cocaine in an attempt to ease their psychic pain and fears, which only makes them progress more rapidly when drug abuse interferes with their medication adherence.

### More nomenclature

**2007:** The American Academy of Neurology issues its third set of diagnostic criteria and nomenclature for HIV-associated neurological disorder (HAND) diagnoses.<sup>1</sup> At the least bothersome end of the scale, we now use the term asymptomatic neuro-cognitive impairment (ANI). It means that the patient has no major complaints, but has minor abnormalities on formal neuropsychological testing, which consists of a battery of multiple memory and movement tests designed to help diagnose all cognitive disorders.

The next stage is named minor neuro-cognitive disorder, or MND (previous nomenclature referred to this as minor cognitive motor disorder, or MCMD). These analogous diagnoses remain the most common HIV-

associated neuro-cognitive disorders. The more current diagnosis of MND requires that at least two specific neuro-psych tests fall more than one standard deviation below the mean.

Finally, there is full blown HIV-associated dementia (HAD), which now requires that at least two tests fall more than two standard deviations below the mean. In lay terms, this describes a patient whose test performance is markedly abnormal. The problem with yet another set of nomenclature is that it makes sense scientifically, but is not very practical in a system where care providers can't access formal neuro-psych testing for patients who are poor and uninsured. Additionally, the tests are meaningful only if you have received education in the United States above third grade, rendering them useless for recent immigrants even when translated into Spanish. So much for naming diseases. Half of my patients have a severe pain syndrome and major psychiatric illnesses that may obscure the diagnosis of HAND.

### Back to 2011

Today, there remains no clear evidence as to which anti-viral medications best penetrate the central nervous system (CNS). I have to rely on whatever pharmacokinetic and limited population cognitive studies illustrate penetration into the CNS and efficacy against HAND. Statistical retrospective studies of viral loads have yielded some useful ranking scales for HIV medications, but we're still far short of a definitive treatment for initial CNS infection with HIV.

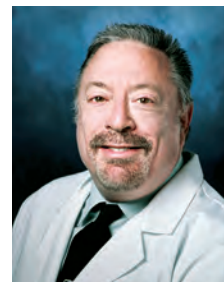
Complicating my task, I see many patients who have already started antiviral medications on the advice of their primary care

providers. Most such patients are started on protease inhibitor-based regimens, which involve very large molecules that don't penetrate the blood-brain barrier. Smaller molecule non-nucleoside reverse transcriptase inhibitors (NNRTIs) are often overlooked. These include nevirapine as well as etravirine, a newer generation drug that (for now) rarely encounters resistant strains of HIV.

Prior to 1980, it used to be said that if a doctor knew everything about syphilis, then that doctor was likely to be a good neurologist. Now the same is said for HIV and AIDS. I'm glad I made the choice to do this work, to teach and conduct research so that patients might receive better care. I can only hope that everyone with whom I have connected, be they patient, student or colleague, continues to make a difference. HIV patients need all the help they can get in a system that tragically continues to treat them differently based upon their ability to pay, an especially heartbreaking situation for people who still face an incurable disease.

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## Investigating Thrombin Toxicity During Stroke

Bo Chen, PhD

In a normal physiological context, thrombin activation is triggered by blood vessel damage, and thrombin is a key player in coagulation cascade by activating platelets, converting fibrinogen to fibrin, and promoting several positive feedback loops that amplify the coagulation signal. Thrombin has been shown to be toxic to neuronal cells and neural tissues *in vitro*. With this in mind, my neurology research team set out to test whether endogenous thrombin would similarly attack brain cells during a stroke *in vivo*.

About 85 percent of stroke cases result from ischemia, the occlusion of a major artery supplying the brain. To elucidate the mechanisms of stroke, we induced ischemic stroke in rodents by blocking the middle cerebral artery and used a large fluorescent

molecule, 2MDa FITC-dextran, to label severely damaged blood vessels.<sup>1</sup> We observed that severe vascular disruption could occur as early as one hour after stroke onset, suggesting that vascular damage might indeed contribute to stroke pathology in the acute stage.

When brain vessels are injured in this fashion, parenchymal tissue swells and plasma components that are normally excluded from the brain are allowed to enter. We hypothesized that thrombin could act as a powerful toxin in stroke when it comes in contact with brain cells.

In our rodent model, we found that intra-arterial infusion of thrombin significantly increased the vascular damage and neuronal

cell death; intravenous infusion of argatroban, a direct thrombin inhibitor, reduced such ischemic damage.<sup>2</sup> Using an antibody that detects thrombin, we also discovered the accumulation of thrombin antigen in the ischemic brain region. Are these thrombins actively involved in cellular toxicity and not quenched by the endogenous thrombin inhibitor?

To image the endogenous thrombin activity, we collaborated with Professor Roger Tsien from UC San Diego, whose lab has developed a group of imaging probes called the activated cell penetrating peptides (ACPP) for detecting protease activity *in vivo*.<sup>3</sup> They engineered an ACPP that is highly specific

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## OCD: continued from page 1

reuptake inhibitors (SSRIs) such as paroxetine, sertraline, fluoxetine, escitalopram and fluvoxamine are the mainstay of pharmacological therapy. Atypical antipsychotics, such as olanzapine and risperidone, have also been used in treatment-resistant OCD, but their significant side effects limit their use.

More recently, surgical procedures have been tested for the treatment of severe OCD. Lesioning of the anterior cingulate gyrus, the anterior limb of the internal capsule and the subcaudate region have been employed, all with variable but sometimes dramatic success. In an effort to avoid irreversible injury and allow for modification of the treatment zone, deep brain stimulation (DBS) has been tested. DBS electrodes provide chronic electrical stimulation of a select brain area, and result in suppression of activity in that region via over-excitation. DBS is widely used for the treatment of tremor and Parkinson's disease, as well as dystonia. The FDA granted a humanitarian device exemption (HDE) for DBS in severe, medication-resistant OCD. The target for this purpose is the anterior limb of the inter-

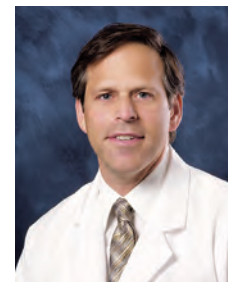
nal capsule, which primarily contains fibers projecting from the thalamus to the frontal cortex. Ablation of this pathway via chronic stimulation is presumed to mediate hyperactivity and reduce OCD symptoms, although the exact mechanisms of action remain uncertain. Clinical trials demonstrated a long-lasting reduction in OCD symptom severity following DBS, and seemed especially effective for patients with the "checklist" variant of OCD.<sup>1</sup> Symptoms were reduced by an average of 45 percent at one year, although responses were variable and several patients discontinued therapy altogether. Currently, only centers that have institutional review board (IRB) approval for the use of DBS, such as Cedars-Sinai, are able to perform this procedure. Determining surgical candidacy requires a careful evaluation by psychiatrists and neurosurgeons working closely together.

While OCD may be the first psychiatric disorder to receive an HDE for DBS, it is unlikely to be the last. As the biological basis of psychological disorders is better established, new brain targets for DBS are being identified. Clinical trials for the use of DBS in depression, obesity and post-

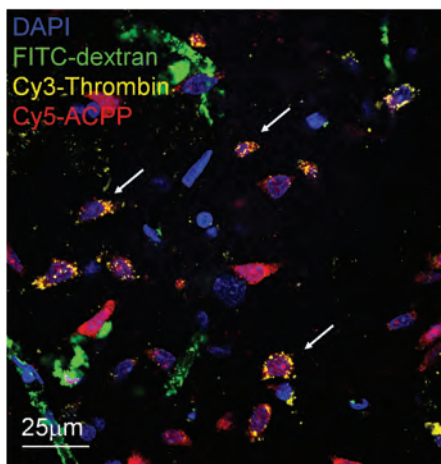
traumatic stress disorder are being carried out, and it is quite likely that DBS will play a greater role in the management of severe, medically refractory psychiatric disorders in the near future. Close interaction between psychiatrists, neurologists, neurosurgeons and behavioral neuroscientists will play an increasingly larger role in the development and testing of these strategies in the years to come.

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**Figure 1:** ACPP probe (red)-labeled thrombin activity in ischemic brain. Immunostaining with the thrombin antibody (yellow) co-localized ACPP-positive cells, confirming the specificity of the probe.

## Thrombin: continued from page 3

to thrombin activity (Fig. 1), which we applied in our stroke model. To our surprise, we found that most of the thrombin activities are associated with neurons but not with other types of brain cells. Furthermore,

these thrombin-associated neurons have a higher probability of cell death than other neurons during stroke. This cell-specific phenomenon suggested the possibility of a cellular signaling pathway, possibly mediated by a previously identified thrombin receptor known as protease-activated receptor 1 (PAR1).

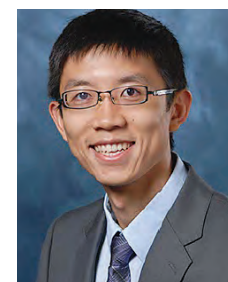
We continued to test the involvement of the PAR1 pathway in mediating thrombin toxicity. Immunostaining using a PAR1 antibody revealed that PAR1 was activated in the ischemic brain region. Infusion of a PAR1 agonist promoted both vascular and neuronal damage, just as thrombin did; in contrast, infusion of a PAR1 antagonist reduced ischemic damage. These results confirmed our conjecture that leaking thrombin caused neuronal toxicity through cellular pathways such as PAR1.

How do these findings impact our understanding of and treatment for stroke? First, thrombin has been the target of anti-thrombosis for decades, and we now see the potential of targeting thrombin for neuroprotection. Second, vascular damage during the acute stage of ischemia and the subsequent leakage of serum protease exacerbate the brain injury, so early treatment with drugs

that protect the vasculature could play a critical role in stroke outcomes. Finally, further study of the PAR1 pathway should shed light on the mechanisms of thrombin toxicity and suggest new targets for treating stroke patients.

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