

To Conquer Neurofibromatosis

Neurofibromatosis badly needs a PR campaign. Ask most people to name a disease that's passed from parent to child and their response is likely to be cystic fibrosis, muscular dystrophy, sickle-cell anemia, Tay-Sachs disease—any or all of these pop to the front of the mind.

But not neurofibromatosis. Yet NF, as it's also known, is among the most common inherited disorders, affecting more kids than cystic fibrosis. One in 3,500 children, roughly half of all people who develop NF, get it from their parents.

NF is an extraordinarily challenging disorder for neurologists to treat, partially because it's so unpredictable. NF wreaks havoc on nerve tissue, and NF-1, which accounts for 90 percent of NF cases, can be involved with everything from bone deformities to brain tumors. It's also a capricious disorder: Parents with NF who have nothing more than a few light “café-au-lait” brown spots on their skin can bear children who have exactly their mild symptomology or an exacerbated version of NF that may cause scoliosis, learning disorders, early or delayed puberty, blindness, disfigurement. The list is staggering.

This wide range of potential outcomes makes comprehensive and continuous care a must, which is where Johns Hopkins' Comprehensive Neurofibromatosis Center comes into play. Directed by neurologist **Jaishri Blakeley** and staffed by neurologist **Lori Jordan**, neurosurgeon **Allan Belzberg** and genetic counselor **Amanda Bergner**, the monthly clinic is a



In many cases, say Jaishri Blakeley and Lori Jordan, regular exams can allay worry.

ALTHOUGH TWO-THIRDS OF NF-1 CASES ARE MILD, MANY PARENTS COME IN FEARING THE WORST.

one-stop shop for NF care.

“Sometimes we see an affected parent and multiple children,” says Jordan, who usually treats pediatric patients and transfers them to Blakeley when they reach adulthood. “These families have all their records in one place, and in one half-day, the entire family can be seen. Coming to the center allows families to streamline their health care.”

Jordan says their work is equal parts education and medical management. Although two-thirds of NF-1 cases are mild, many parents, especially after a trip around the Internet, come in fearing the worst for

their child. “A lot of what we do is examine the child and talk about what we find,” Jordan says. Most of the time, the child is doing well.”

While there's currently no cure for NF, regular visits can limit the impact of emerging physical and mental issues, and Jordan impresses upon parents that continued vigilance is important, even in mild cases.

By catching scoliosis early, for example, “you can intervene surgically before it causes major complications,” she says.

For more severe cases where tumors grow along nerves, Blakeley, who specializes in neuro-oncology, works with Allan Belzberg to perform microsurgeries that can reduce pain and functional impairment. Blakeley's medical management of a patient's tumors are critical. Although most NF tumors are benign—and there can be hundreds of such tiny tumors in severe cases—there's still a 5 percent to 10 percent risk

that some may turn malignant.

Blakeley is also researching drugs to combat NF-2, the rarer form of the disease that mainly attacks the central nervous system and currently can only be treated surgically. The work has other potential applications as well. NF, she says, is “a very predictable model for studying nerve structure and changes in structure that happen during neuropathic pain,” especially pain that occurs after nerve resection. That work has the backing of a Department of Defense grant, which Blakeley says isn't surprising, because “it matters hugely to soldiers who have so-called phantom pain after amputation.”

Controlling amputation pain by studying NF? Now there's something worthy of a press release. ■

To refer a patient:
410-614-3853.

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The following clinical trials are actively recruiting patients.

Ataxia Telangiectasia

A trial of the effectiveness of baclofen to improve certain measures of ataxia in teens and adults with ataxia telangiectasia. *Info: Thomas Crawford, tcrawfo@jhmi.edu; Karen Rosquist, krosqui1@jhmi.edu, 1-800-610-5691*

HIV-Associated Cognitive Impairment

- A multicenter trial evaluating the safety and efficacy of an investigational medication for HIV-associated cognitive impairment that leads to disabling cognitive, behavioral and motor dysfunction in 43 percent of HIV-positive individuals with advanced infection. *Info: Ned Sacktor, P.I., sacktor@jhmi.edu; Kathryn Carter, coordinator, kcarter@jhmi.edu; 410-955-1895*
- A multicenter randomized trial evaluating central nervous system-targeted HAART (highly active antiretroviral therapy) in HIV-positive people with cognitive impairment in the United States. *Info: Ned Sacktor, P.I., sacktor@jhmi.edu; Vincent Rogalski, coordinator, vroglas1@jhmi.edu, 443-799-7257*

Multiple Sclerosis

- Relapsing Remitting Multiple Sclerosis (RRMS): A Combination Trial of Copaxone Plus Estriol in Relapsing Remitting Multiple Sclerosis (RRMS) (Estriol in MS). A multicenter trial evaluating whether oral treatment with estriol, the major estrogen of pregnancy, decreases relapses in relapsing remitting multiple sclerosis subjects when used in combination with injectable Copaxone. *Info: Peter Calabresi, P.I., Stephanie Syc, coordinator, ssyc1@jhmi.edu, 410-502-2488*
- A study of the immunology of natalizumab (Tysabri). Enrollment criteria: patients starting Tysabri infusion. *Info: Girish Hiremath telephone: 410-502-2937; pager 410-283-7032, Kristie Albright, telephone 410-502-6867; pager 410-434-2134*
- A study of fingolimod (FTY720) in PPMS patients with one attack in the last year or two attacks in the last two years. *Info: John Ratchford, P.I., jratchf1@jhmi.edu, telephone 410-502-8670, pager 410-434-3657; Kristie Albright, senior research nurse, telephone 410-502-6867, pager 410-434-2134*
- Acute Optic Neuritis: A Randomized, Double-Blind, Placebo-Controlled, Multicenter Study of the Effects of Glatiramer Acetate (GA) on the Retinal Nerve Fiber Layer (RNFL) and Visual Function in Patients With a First Episode of Acute Optic Neuritis (AON) (Octagon) A multicenter trial to determine whether glatiramer acetate is neuroprotective in acute optic neuritis. Participants must be randomized within nine days of visual disturbance. *Info: Peter Calabresi, P.I., Stephanie Syc, coordinator, ssyc1@jhmi.edu, 410-502-2488*

Parkinson Disease

A study to evaluate the effects of coenzyme Q 10 in patients diagnosed with Parkinson disease within the last five years who are not currently being treated for it. *Info: Ted Dawson, P.I., Becky Dunlop, 410-955-8795 or rdunlop@jhmi.edu*

Spine

Randomized, controlled, multicenter trial to evaluate the safety and effectiveness of DuraGen Plus adhesion barrier matrix in the prevention of epidural fibrosis following lumbar disc surgery. *Info: Timothy Witham, P.I., twitham2@jhmi.edu; Barbara Levit, coordinator, 443-287-7486*

Werdnig-Hoffmann Disease

A phase I/II, multicenter trial to determine the safety of valproic acid and L-carnitine for children with severe infantile spinal muscular atrophy type 1 (Werdnig-Hoffmann disease), to develop new outcome measures for future trial design, and to ascertain potential benefit from treatment. *Info: Thomas Crawford, tcrawfo@jhmi.edu; Study coordinator Opal Lin-Tsai, otsaiz2@jhmi.edu, 443-287-6294*



Gregory Riggins

Clues to a Cure May Reside in Glioblastoma's Genome

Gregory Riggins believes it may already be out there—a drug that can extend the survival time of patients with a glioblastoma. There's a good possibility, he says, that a drug approved for another purpose or one sitting on a shelf in a laboratory somewhere can destroy the cells that cause this most lethal of brain tumors. Riggins is committed to finding it.

"The idea," says the director of Johns Hopkins' Brain Cancer Biology and Therapy Research Laboratory, "is to make sure there's not already something that we can use in humans before going to design a new drug, which can take 10 to 15 years and perhaps millions of dollars."

Basically, Riggins is using what he calls a "brute force" approach. "We try to gather up all the drugs that are safe to use in people, in particular those with evidence that they may target altered pathways in glioblastoma. And we try to see, using our culture model of glioblastoma, which ones kill cells by arresting growth."

Riggins' approach recently got a huge boost. This past fall, a large research team that included Riggins and was led by Johns Hopkins oncologist **Bert Vogelstein** completed sequencing the 20,661 genes that make up the glioblastoma genome. The scientists, who reported their results in the September 4, 2008 *Science*, also analyzed the genetic mutations found in the 22 tumor samples used for the study. "What was interesting about the analysis," says Riggins, "was the sheer complexity of the mutations." On average, each patient had about 40 different mutations.

Even though the array of mutations is incred-

ably complex, and no two patients seem to have the same pattern, many glioblastomas appear to have alterations in the same molecular pathways of growth. So alterations in different genes might set off the same molecular cascade that, in the end, leads to uncontrolled growth. "So we may not be able to get a drug for every mutation," notes Riggins, "but we might be able to target a pathway."

One that Riggins has explored is called the Akt pathway. He and Johns Hopkins neurosurgeon **Gary Gallia** have found that genetic mutations activating the Akt pathway are present in at least 85 percent of all glioblastomas. In recent studies, this team identified a small-molecule drug that effectively blocked the Akt pathway in glioblastoma cell lines. His group then tested the compound in a rat model of glioblastoma. The researchers implanted polymer wafers containing the drug near the site of the tumors. They found that animals that had received the drug implants survived for twice as long as a control group of animals.

The results are gratifying but there's still much more work to be done, says Riggins. An effective therapy against glioblastoma will most likely have to target more than one growth mechanism, which means identifying more than one effective drug. "It is not like trying to design a specific magic bullet," he says, "It's like trying to design a cocktail." ■

Information:

hopkinsmedicine.org/neuro
410-502-2905

Defending the Brain Against HIV

Formerly a successful finance professional, the man now couldn't balance his checkbook, much less keep track of the financial transactions he had supervised for 25 years. A long-term HIV infection, which antiretroviral drugs had kept in check for decades, was now taking its toll—on his brain. He began forgetting to take his medications. Even his judgment was impaired, leading him to have unprotected sex.

The man had HIV-associated neurocognitive disorder (HAND), and the number of cases like his is increasing substantially as patients with chronic HIV survive for longer periods of time, says Neurology Department Director **Justin McArthur**. He and biochemist **Joe Steiner** are leading a research effort to search for drugs that can protect the brain and central nervous system from the damage of HIV. Their studies are based at the Hopkins NIMH Center for Novel Therapeutics of HIV-Associated Cognitive Disorders.

"It's probably not HIV replication alone that causes the neurological damage," says Steiner. Instead, viral proteins appear to trigger inflammation in the brain, which in turn leads to oxidative stress and a host of other damaging effects.

As a starting point in the team's research, Steiner developed a model of oxidative stress in cultures containing neurons and glial cells. He then used the model to screen 2,000 FDA-approved drugs, searching for agents that could shield the cells from oxidative stress and thus enhance cell survival.

"We identified about 25 to 30 compounds that looked interesting," says Steiner. He then narrowed down that list, rejecting any that were of low potency, a detriment in a drug that must penetrate the blood-brain barrier. Resveratrol, for example, the red wine antioxidant, showed promising neuroprotective results, but only in extremely high concentrations. "You'd have to drink 10 bottles of wine to see an effect," Steiner says jokingly.

One set of compounds, however, proved both neuroprotective and highly potent—antidepressants, particularly the SSRIs. Just nanomolar concentrations of these drugs protected the cell cultures from oxidative stress.

Steiner has also tested various SSRIs in a mouse model; the results show that the compounds safeguard mice neural cells from the damaging effects of a key HIV protein. Eventually, the team may pursue a clinical study. However, if antidepressants do help shield the brain



Justin McArthur and Joe Steiner are seeking neuroprotective options.

from HIV's neurocognitive damage, then HIV patients who already happen to be taking SSRIs may be receiving this extra benefit. "We're going back through patient records to try to tease out whether we see some effect," says McArthur.

Among patients with chronic HIV, 20 percent to 25 percent will develop neurocognitive problems as a conse-

quence of their infection, notes McArthur. "Some degree of those problems might be reversible if treated with a neuroprotective agent. Our ultimate goal is to get people back to as normal function as possible." ■

Information:

hopkinsmedicine.org/neuro

DIAGNOSTIC PATHOLOGY



Michael Polydefkis and Andrea Corse

Two Labs Specialize in Muscle and Nerve Puzzles

The patient had progressive muscle weakness serious enough to require hospitalization. His symptoms pointed to an inflammatory myopathy. But which one? An autoimmune form of the disease? Inclusion-body myositis? Or another category of muscle disease?

Solving these mysteries is the business of Johns Hopkins Hospital's Neuromuscular Pathology Lab, which uses muscle and nerve biopsies to diagnose a wide variety of diseases. The comprehensive staining, which the lab provides for physicians at both Hopkins and other medical centers, is not offered at community hospitals, says lab co-director **Andrea Corse**.

For the biopsy, three cylindrical sections (1.5 x 0.5 cm) of muscle are removed from the patient under local anesthesia. The lab applies histochemical stains to highlight abnormalities. "We look for inflammatory cells, myofiber necrosis and architectural changes," says Corse. The results may reveal systemic diseases such as vasculitis or muscle disease such as myositis, toxic myopathy, muscular dystrophy or rarer metabolic diseases. (The lab also conducts biopsies on the sural or

other sensory nerves.)

In the case of the man who was hospitalized, his biopsy indicated colchicine myopathy. He'd been taking colchicine for gout. After his diagnosis, he stopped the medication, and his myopathy improved.

Another Hopkins lab, the Cutaneous Nerve Laboratory, offers a different set of specialty diagnostic services. It uses skin biopsies to diagnose neuropathies that leave their signature in the small nerve fibers that interlace the epithelium. One of the first labs to specialize in this field, it handles several thousand biopsies a year from patients around the world and is one of only a handful of labs in the country to offer such services.

When a patient has numbness, pain or tingling in the feet, a physician might perform a standard nerve conduction test to assess for neuropathy, says lab co-director **Michael Polydefkis**. While those tests can identify neuropathies that affect the large myelinated nerve fibers, they can't detect small nerve fiber neuropathies. Another test, a biopsy of the sural nerve at the ankle, can be used to diagnose small fiber neuropathy. But it

is invasive and removes a relatively large segment of nerve.

Instead, the Cutaneous Nerve Lab uses a skin punch biopsy technique, which involves removing a 3-millimeter in diameter segment of skin from the patient's ankle, knee and thigh, and examining the density and morphology of the samples' epidermal nerve fibers. "Nerves might appear thick, have blebs or swelling, or their density could be depleted, and these changes could mark nerve degeneration," says Polydefkis. The test, he adds, can also reveal the progression of the disease, which generally begins in the feet and moves up.

A variety of different conditions, from vitamin deficiencies and inflammatory disorders to diabetes, can lead to small fiber neuropathy. "If we can catch somebody at the earliest stages of neuropathy," says Polydefkis, "we have a better chance of arresting the process." ■

Information:

Neuromuscular Lab, 410-614-4278
Cutaneous Nerve Lab, 410-614-6399

When Tumors Attack the Spine

Fifteen years ago, only about one out of 10 spinal tumor patients was a candidate for surgery, says **Ziya Gokaslan**. Today, he estimates, that figure is eight or nine times greater. The reason: innovations in surgery.

“We didn’t have the approaches needed to access the tumor,” says Gokaslan, director of the Johns Hopkins Spine Center. Moreover, surgeons were severely limited in their ability to reconstruct the spine.

Gokaslan and his colleagues treat both patients with extrinsic tumors, which arise from the bone or soft tissue of the spinal column; and those with the less common intrinsic, or intramedullary, tumors, those that originate from the spinal cord itself.

The surgical team begins by first removing any segment of the spine bone that blocks access to the tumor. They then use microsurgical techniques to remove the tumor. In some cases, the team uses a laser and ultrasonic aspirator to vaporize part or all of the tumor.

Throughout the procedure, the patient’s spinal cord function is constantly monitored through electromyography, motor evoked potentials or somatosensory evoked potentials. “If we see changes in these recordings, then we make a decision as to whether it’s safe to proceed,” says Gokaslan.

If a portion of spine has been removed, reconstruction is the next step. Spinal tumors can range from a few centimeters in length to the size of a watermelon, and in the latter case, the reconstruction can be highly complex. “Fifteen years ago,” notes Gokaslan, “outside of a few screws and a rod, we didn’t have anything to reconstruct the spine.” Today, they’re rebuilding spines with titanium cages, plates, spacers and other implants.

Among the particularly challenging forms of spinal tumor are those that grow on the spinal cord. Neurosurgeon **George Jallo** specializes in such cases. Many of his patients have been told by previous doctors that their case is inoperable. Last year, for example, he cared for a 17-year-old who had the extremely rare spinal tumor known as an ependymoma. Doctors at the boy’s local hospital had concluded that surgery to remove the tumor would be too risky. They adminis-



Ziya Gokaslan and George Jallo take on cases that others may deem inoperable.

tered radiation therapy instead. Still the tumor continued to grow. “He then had surgery here,” says Jallo, “and we were able to remove the entire tumor without any new deficits, and he is doing well.”

A surgeon’s reluctance to operate in this vulnerable region is understandable, says Jallo. “The margin of error is on the order of millimeters.” But with a practiced team of specialists, those risks are significantly reduced. The Johns Hopkins Spine Center is one of a handful of places that specializes in spine tumor surgery, says Jallo.

Still, even with a dedicated team of specialists, any

surgery on the spine involves a degree of risk. So both Gokaslan and Jallo in their research labs are searching for less invasive alternatives. Instead of a complete surgery, for example, one option is to make a small incision and apply a chemotherapeutic agent near the tumor site, an approach they are testing in animal models. “We haven’t found a cure yet,” says Jallo, “but we have promising results.”

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