The New England Journal of Medicine recently published a case report about a teenage boy with an abnormal immune system who became ill with recurrent headaches, fever and light sensitivity. When a brain MRI and cerebrospinal fluid examination revealed meningoencephalitis – and a brain biopsy showed only inflammation without a specific organism – treating physicians at a hospital in the Midwest ultimately used empiric steroids, because they suspected that the patient was suffering from occult autoimmune encephalitis. Unfortunately, the patient continued to decline and became critically ill.

(continued on page 4)
Meeting Previously Unmet Clinical Needs

One of the most important roles of academic medicine is to work with our community partners to find new and better solutions for unmet clinical needs.

Sometimes those clinical needs have to do with conditions for which, to date, either the diagnostic or treatment options have been less than optimal. This issue of *Neuroscience at UCSF Medical Center* contains the example of using high-throughput gene sequencing to decipher a rare and mysterious case of encephalitis that was baffling physicians and endangering a young man’s life. Similarly, another piece in this issue highlights how clinicians and scientists at the UCSF Memory and Aging Center are helping to diagnose and better address the cognitive concerns of former NFL players. In doing so, we are sometimes deploying new positron emission tomography (PET) techniques that can more accurately reveal whether amyloid plaques are present; studies to image tau with PET scans are also under way.

Other times, our goal is to refine and disseminate existing best practices. In this issue, for example, we discuss the ways in which we at UCSF are garnering improved results and finding ways to be more responsive to patients with adult spinal deformities, multiple sclerosis flares and complex headaches, including migraines. Too often, patients suffering from these disorders don’t receive the best possible care, despite the fact that we possess the knowledge and capacity to deliver that care.

Remaining focused on meeting unmet clinical needs – from the most common to the most rare – can sometimes be a challenge in today’s hectic health care environment. It becomes easier when we remember that doing so – in partnership with you, our community partners – can translate into helping hundreds and often thousands of people lead healthier, more productive lives.

Mitchel S. Berger, MD
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Creating a California Institute for Spinal Deformities at UCSF

Among America’s aging population, the prevalence of adult spinal deformity has been reported to be as high as 60 percent, says neurosurgeon Christopher Ames, MD. Ames is the neurosurgical director of the planned California Institute for Spinal Deformities at UCSF, a joint project between the UCSF Departments of Neurological Surgery and Orthopaedic Surgery.

Adult degenerative deformity typically develops and becomes symptomatic between ages 45 and 80 due to disk degeneration, spinal arthritis or a prior surgery that failed to properly align the spine. All of these conditions can lead to scoliosis, kyphosis or global sagittal deformity – though disability in adult deformity tends to be most correlated to the sagittal plane, says Ames.

“What’s not widely known is that spinal deformity is on the level of lower-extremity amputation, cancer and COPD [chronic obstructive pulmonary disease] in terms of its effect on general health status, which is especially frustrating for a generation expecting high levels of activity into their later years,” says Ames.

A Challenging Population, a Complex Clinical Challenge

Treatment of adult spinal deformity presents unique challenges due to what are often multiple comorbidities and the high risk of complications. Moreover, the indications for surgery are different than those for adolescent idiopathic scoliosis.
“Instead of relying purely on spinal curvature and appearance, we quantify these adult deformity patients’ level of spine-specific disability, including pain levels and limitations on the activities of daily living,” says Ames.

**An Integrated Approach**

Ideal treatment for these disorders requires an expert center that uses a team-based, multiple-specialty approach from the time of original diagnosis through preoperative evaluation, surgery, postoperative care and rehabilitation. Key steps include:

- **Specialized Imaging:** Any patient who on clinical examination has evidence of spinal imbalance — or who has had multiple surgeries but never improved — should be screened with 3-foot X-rays that capture the entire spine on one X-ray.

- **Multidisciplinary Screening:** Determining fitness for surgery should include input from medicine, psychology, anesthesia, spine surgery and pain management.

- **Short- and Long-Term Planning:** Create an operative plan and postoperative treatment plan, including long-term rehabilitation that is individualized based on deformity type, age and other patient-specific factors and activity goals.

**Expert Surgical Care:** “We’ve already shown a two-surgeon approach that nearly halves operating room time has demonstrated superior outcomes versus single-surgeon approaches,” says Ames, who along with his orthopaedic surgeon colleague Vedat Deviren, MD, pioneered these techniques in 2007. Since that time, many other institutions have followed suit.

Based on patients tracked two to three years post-surgery, Ames and his colleagues have modeled the sustained health improvement over 10 years for adult deformity patients and found it to be cost-effective. The key, however, to sustained cost-effectiveness is preventing complications and avoiding reoperation. Bringing together the experts in one location for the planned institute will further ensure the efficiencies necessary in an era of health care reform, says Ames.

“The institute integrates UCSF’s historic leadership in spinal deformity care with the increased prevalence of these problems in adults and the need for specialized care,” he adds.

For more information, contact the UCSF Spine Center at (866) 817-7463 ([866] 81-SPINE).
That’s when treating physicians at another hospital in the Midwest called in a team from a newly created encephalitis and meningitis clinic — a program within the UCSF Multiple Sclerosis and Neuroinflammation Center — to conduct gene sequencing on the boy’s cerebrospinal fluid. Using a UCSF-developed approach that deploys advanced computer algorithms to rapidly identify the source of nearly any foreign sequence in the tissue, the team uncovered a rare bacterium – *Leptospira santarosai* – as the cause of the illness.

“They stopped the steroids, started him on penicillin, and he made a remarkable recovery over the next three to four weeks,” says neurologist Michael Wilson, MD, of the UCSF center.

**Expertise, Advanced Technology Improve Diagnosis and Treatment**

Of the approximately 20,000 new cases of encephalitis annually in the US, about half never receive a firm diagnosis of the underlying cause, says Wilson. Often, it remains unclear whether the cause is infectious or autoimmune, making it a fraught decision to use empiric steroids or antibiotics when the initial workup and treatments have not been successful.

To address these types of concerns, the UCSF encephalitis and meningitis clinic is part of a comprehensive neuroinflammatory service that deploys experts in neuroimmunology, behavioral neurology, neuroinfectious disease, neuropsychology and electrophysiology. Teams provide rapid triage and evaluation of:

- *Encephalitis*
  - Infectious
  - Autoimmune and antibody-mediated
  - Paraneoplastic
- *Chronic meningitis*
  - Autoimmune/primary inflammatory
  - Infectious
  - Malignant
- *Suspected paraneoplastic neurological syndromes*

For acute problems that require urgent hospitalization, the team partners with the UCSF Neurohospitalist service.

To complement this clinical expertise, the clinic’s research program uses unbiased, next-generation sequencing to search for pathogens of meningitis and encephalitis, as well as innovative methods to screen for novel antibody-mediated causes of these conditions.

**Move Quickly**

“Each individual cause can be quite rare, so having the technology and an extremely experienced group of clinicians can make an enormous difference,” says Wilson.

That’s why, he adds, it’s important to refer or send cerebrospinal fluid to UCSF sooner rather than later. “Sequencing is more sensitive early on, so if you have an encephalitis case, freeze 1-2 milliliters of cerebrospinal fluid in case nothing definitive turns up with traditional laboratory diagnostics.”

*For more information, contact the UCSF Multiple Sclerosis and Neuroinflammation Center at (415) 353-2069.*
When someone with multiple sclerosis (MS) experiences a flare – or if a previously undiagnosed patient exhibits symptoms – rapid response can make a difference.

Especially if there is any question about etiology, it’s best to have these patients seen at a specialty clinic soon after symptom onset for a thorough diagnostic evaluation and management, says Carolyn Bevan, MD, who directs a new weekly urgent care clinic at the UCSF Multiple Sclerosis Center.

Responding to Urgent Needs
“A relapse in MS is defined as new or worsening neurologic symptoms corresponding with an exam change and lasting more than 24 hours,” says Bevan. “The severity of a relapse can vary greatly, and symptoms can be in many different domains – vision, brain stem, motor, sensory, cerebellar, bowel/bladder or cerebral dysfunction.”

The first response, says Bevan, is to make sure the flare is MS-related. She does the following:

• Conducts a physical exam and patient history.
• Orders imaging at or above the suspected lesion, especially in first-attack cases. “Before ordering a brain MRI, remember that lesions also occur in the spinal cord, so use the exam and history to narrow down the likely location,” says Bevan.
• Orders a complete blood count (CBC), urinalysis and culture.

She adds, “If a patient is having first demyelinating attack, we have a clinical trial that is studying disease triggers and would enable patients – even those without insurance – to be seen and evaluated quickly by a specialist.”

Treatment Options
If the relapse is, in fact, MS-related and is interfering significantly with a patient’s ability to live daily life, steroids are the first-line treatment.

“Steroids don’t help someone recover more than he or she would without steroids, but they do speed recovery,” says Bevan. “For a relapse with clear disability, they are an important first step, and the sooner patients get treatment, the better.”

Typically, patients receive a three- to five-day course of Solu-Medrol at 1 gram per day, with the number of days depending on the severity of symptoms. Yet because infusion centers are not always readily available, Bevan says oral steroids are an alternative, at equivalent doses for three to five days, along with medications for gastrointestinal protection and, possibly, a sleeping aid.

When patients do not respond to steroid treatment and their disability is significant, the next step is typically plasma exchange.

“Historically, plasma exchange for MS has required inpatient admission with seven exchanges, every other day, but many centers have adjusted this to five exchanges, once daily, with careful monitoring for coagulopathy and other complications,” says Bevan.

She adds that if the plasma exchange fails and severe disability remains, induction chemotherapy or other aggressive strategies become possible treatment options.

Finally, for patients who have confirmed MS and are already on modifying therapy, after the new symptoms recede, it’s important to discuss adjusting the therapeutic options to prevent future relapses.

For more information, contact the UCSF Multiple Sclerosis Center at (415) 353-2069.
Assessing Cognitive Loss in Retired NFL Players

UCSF’s Memory and Aging Center is one of six sites nationwide the National Football League is recommending as an assessment site for former players experiencing cognitive concerns, says Mitchel Berger, MD, chair of Neurological Surgery at UCSF Medical Center.

The need for testing emerged from concerns about the potential long-term effects on the brain of playing professional football. A member of the league’s Head, Neck and Spine Committee, Berger says the Memory and Aging Center was selected based on its internationally renowned expertise in diagnosing and treating cognitive deficits.

“It really is the place for anybody in the community concerned about concussion and the long-term effect on cognitive function,” says Berger.

Determining the Extent and Nature of the Problem
Evaluation at the UCSF Memory and Aging Center includes a comprehensive battery of cognitive tests that examine multiple domains, including:

- Memory
- Language
- Executive function
- Visual/spatial abilities
- Mood

“It’s important that these retired players receive a formal, detailed evaluation, because there are potentially addressable components of their cognitive deficits that need to be separated out,” says neurologist David Perry, MD, of the Memory and Aging Center. “We’re looking for whether a player has a degenerative brain disease like Alzheimer’s, Parkinson’s or chronic traumatic encephalopathy (CTE), but also other more treatable causes of the symptoms, such as medication effects on cognition or sleep disorders.”

Beyond its expertise in diagnosis and treatment of these disorders, the center’s nurses, social workers and counselors are available to help patients and families adjust to any necessary lifestyle changes.

Long-Term Observation Can Strengthen Diagnostic Insights
Interested former players can also participate in an observational research study at UCSF. The Alzheimer’s Disease Research Centers – a multi-center collaborative funded by the National Institute on Aging – oversees the study.

“Players that participate can benefit from periodic neurological evaluations and cognitive testing in a research setting,” says Perry.

One aspect of this study involves the use of new positron emission tomography (PET) techniques that can do a better job of revealing whether amyloid plaques are present; studies to image tau with PET scans are also under way. Both proteins can be found in various forms of dementia.

One of the many potential benefits of such imaging is that it could add to the paucity of quality longitudinal data about those living with CTE.

“We don’t know yet how to diagnose CTE in living players, but increasingly we think that some of these imaging biomarkers could be helpful for a person with the right background and clinical symptoms,” says Perry.

For more information, contact the UCSF Memory and Aging Center at (415) 353-2057.
“Getting the diagnosis right is as important in headache medicine as it is in other branches of neurology and medicine,” says Morris Levin, MD, the new director of the UCSF Headache Center. “Once we’ve achieved the right diagnosis, we can help most patients get relief.”

As an example, he cites the fact that most recurrent headaches accompanied by nausea tend to be migraines – and that treatment advances have rendered migraines much more manageable, making a once depressing diagnosis relatively good news.

Expert centers also can typically achieve treatment success for everything from cluster headaches to headaches due to trauma, tumor and strokes by drawing on clinical experience while deploying a team-based approach with other subspecialists.

Preventing and Treating Migraine

“What’s most important to patients, of course, is getting acute relief from particularly bad headaches,” says Levin, who has authored multiple books on headache medicine over the last 30 years and was formerly co-director of the Headache Center at Dartmouth-Hitchcock Medical Center. He notes, for example, that by effecting changes in blood vessels and inflammatory areas in the brain, triptan strategies have proven to be very effective in treating migraines.

“We’ve also found that if one triptan doesn’t work, it is worth trying another,” he says. “And combining a triptan with antinausea and anti-inflammatory medications can also be quite effective.”

In addition, Levin and his team are focused on decreasing the number and severity of migraines their patients experience. The list of effective therapies to prevent migraine includes:

- Antiepileptic medications, such as topiramate and valproate
- Tricyclic antidepressants, such as amitriptyline and nortriptyline
- Antihypertensives, such as beta-blockers and angiotensin II receptor blockers (ARBs)
- Herbal and other nonpharmaceutical agents
- Lifestyle and wellness strategies

“At the Headache Center, we tailor the preventive approach to each patient, and any of these treatments may serve as a first step,” says Levin. “Typically, we can reduce the number of headaches dramatically – say from two or three times a week to one or two a month. That reduces the level of stress on everyone – patients, families and physicians alike.”

Working with Refractory Headaches

When patients fail to respond to first-line treatment approaches and are still experiencing frequent severe migraines, the center will turn to more experimental though well-tested approaches including:

- Nerve blocks
- Trigger-point injections
- Manual therapies
- Botulinum toxin injections
- Electrical stimulation

“In some cases, inpatient treatment can also be very helpful in unlocking the key to reducing the headaches,” says Levin.

Finally, the center is conducting research into causes and treatment of all headaches, including migraines, cluster headaches, post-traumatic headaches and cervicogenic headaches. Many patients may be eligible for both inpatient and outpatient research-based protocols.  

For more information, contact Dr. Levin at (415) 353-8393.
Neuroscience
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