

## Images Predicted Outcome

Diffuse Trauma from page 1

fusivity (velocity of water molecule diffusion within the fibers), and fiber length, volume, and density.

The researchers found significant differences in all parameters except mean diffusivity between patients and controls in the corpus callosum and perforant pathway.

The corpus callosum was the most sensitive site of injury, and fractional anisotropy was the most sensitive measure. No significant differences were found in the cingulum bundle.

The researchers then focused on whether the radiologic findings were indicative of clinical outcome by assessing patients 6 months after injury with the Glasgow Outcome Scale—Extended (GOSE).

Significant correlations with the GOSE were found with fractional anisotropy ( $r = .843$ ,  $P$  less than .001), fiber density ( $r = .729$ ,  $P = .007$ ), and number of fibers ( $r = .700$ ,  $P = .011$ ) in the corpus callosum with similar trends noted in the perforant path.

“Based on this pilot study, DTI tractography may be a useful biomarker for DAI and may provide insight into subsequent outcome,” she said. ■

*A processing program running under Windows—Dtristudio, available free from Johns Hopkins Medical Institutions (<http://lbam.med.jhmi.edu/DTIuser/DTIuser.asp>)—produced the maps and data for quantitative analysis.*

## Small-Fiber Dysfunction May Be the Key to Pain Syndrome

BY CHRISTINE KILGORE  
Contributing Writer

BETHESDA, MD. — A growing body of research suggests dysfunction of the small-fiber axons that mediate pain sensation and autonomic function underlies complex regional pain syndrome, Dr. Anne Louise Oaklander said at a meeting sponsored by the National Institutes of Health's Pain Consortium.

Complex regional pain syndrome (CRPS) is “one of the most mysterious of the pain disorders,” said Dr. Oaklander, a neurologist at Harvard Medical School and director of the nerve injury unit at Massachusetts General Hospital, Boston. With no known cause, few physicians are willing to treat it. Others believe it to be psychosomatic. However, “we are beginning to understand the disease biology,” she said. “It’s time to abandon the dichotomy between CRPS I and CRPS II [and to] consider changing the name to ‘posttraumatic neuralgia.’”

“Small-fiber axonopathy is what causes this,” Dr. Oaklander said.

Current diagnostic criteria for CRPS include the occurrence of a noxious event or other cause of immobilization; continuing or disproportionate pain, allodynia, or hyperalgesia; and edema, changes in skin blood flow, or abnormal sweating in the region of pain.

Most patients are classified as CRPS-I (no known nerve injury); fewer than 10% receive a diagnosis of CRPS-II (a known nerve injury). However, “a physician trained to diagnose nerve injuries can identify minor nerve injuries in most CRPS-I patients as well,” she said.

CRPS is “what I call a focal ‘pain-plus’ syndrome. Patients have chronic pain but also vascular dysregulation and sometimes dystonia, contralesional ‘mirror’ pain ... osteopenia,

[and focal changes in other innervated tissues],” Dr. Oaklander said. “[The disease] reflects pathological processes, not normal pain mechanisms.”

Most patients with CRPS are young (average age 39) and female (a 4:1 ratio). Most recover spontaneously.

Skin biopsies done in Dr. Oaklander’s lab of 18 CRPS-I patients show



**A swollen ankle and shallow ulcers are caused by neurogenic edema.**

30% fewer small-fiber nerve endings in painful CRPS-affected areas.

The identification of posttraumatic small-fiber loss in patients with CRPS was first described in 1996 and has been validated by other researchers, she noted. There is good evidence that trauma disproportionately damages small fibers, probably because they lack protective myelin and saltatory conduction. Pain results when undamaged axons within the same nerve, as well as regenerating axon spouts, malfunction, firing without cause, for instance, triggering neurogenic edema and tissue ischemia. “The problem isn’t so much with the nociceptive fibers that are degenerated—it’s with their neighbors, and the effects on the central nervous system,” Dr. Oaklander said. “We really can’t assume that it takes a severe injury to leave someone with chronic pain—in fact, the opposite may be true.” ■

## Biomarker May Help Predict The Severity of Brain Trauma

BY BRUCE K. DIXON  
Chicago Bureau

CHICAGO — An enzyme found in brain cells may become the first bedside biomarker for assessing the severity of traumatic brain injury, according to Dr. Linda Papa.

In a multicenter trial, levels of the enzyme ubiquitin C-terminal hydrolase (UCH-L1) rose significantly in severely injured brains, an increase that paralleled the rise in cerebral spinal fluid and correlated with the Glasgow Coma Scale (GCS) score, Dr. Papa told the annual meeting of the Society for Academic Emergency Medicine.

If further study confirms the value of UCH-L1 as the first clinical biomarker in traumatic brain injury (TBI), physicians will be better able to identify targets for drug therapy and guide the timing of treatment with such agents as tissue plasminogen activator, explained Dr. Papa, director of academic clinical research at Orlando Regional Medical Center.

This prospective case-control study enrolled consecutive adult patients presenting to two tertiary care teaching hospitals following severe TBIs, defined by a GCS score of less than 8 and requiring invasive intracerebral monitoring. Fourteen patients with severe TBI were enrolled over 16 months. Their



mean age was 38 years, and four-fifths were men. Patients were excluded if they did not have ventriculostomy, which is necessary to obtain cerebrospinal fluid (CSF). Ventricular CSF was drained from each patient at 6, 12, 24, 48, 72, and 96 hours following TBI, and was measured by enzyme-linked immunosorbent assay for UCH-L1 levels.

Mean 12-hour UCH-L1 levels in the control group of uninjured patients with other indications for CSF drainage were 145 ng/mL for patients with GCS scores of 3-5, and 38.5 ng/mL in those with GCS scores of 6-8. Similarly, 24-hour levels were 76 and 36 ng/mL for those with GCS scores of 3-5 and 6-8, respectively. The largest increase in the experimental bio-

marker occurred during the first 48 hours after injury, Dr. Papa said, noting: “Then we found that patients with evolving lesions had significantly higher levels of the biomarker” than did patients with nonevolving lesions at both 48 and 72 hours.”

“There is a significant increase in CSF UCH-L1 following severe human TBI compared to uninjured controls, and there is a significant association with severity of injury as measured by GCS and the presence of evolving lesions on CT,” Dr. Papa concluded, adding that these data suggest that UCH-L1 is a potential TBI biomarker. ■

levels of the enzyme in the CSF corresponded to severity of injury and to CT evidence of evolving lesions.

## Botulinum Toxin Relaxes Muscles In Cerebral Upper Limb Spasticity

BY MICHELE G. SULLIVAN  
Mid-Atlantic Bureau

BOSTON — Botulinum toxin injections are significantly more effective than oral tizanidine in reducing muscle tone and normalizing the appearance of spastic upper limbs in patients who have experienced a stroke or traumatic brain injury.

In fact, Dr. David Simpson reported at the annual meeting of the American Academy of Neurology, tizanidine—a first-line therapy for cerebral spasticity—was significantly less effective than placebo, suggesting it’s time for physicians “to reconsider our first-line treatment for these patients,” said Dr. Simpson, professor of neurology at the Mount Sinai School of Medicine, New York.

Allergan Inc. sponsored the trial; Dr. Simpson and some of his coinvestigators have received research support and personal compensation from the company.

He presented the initial results of an 18-week three-way study of botulinum toxin, tizanidine, and placebo in 60 patients with increased upper limb tone secondary to stroke or traumatic brain injury.

Patients were randomized to either botulinum toxin injection plus oral placebo; tizanidine plus placebo injections; or oral placebo-placebo injections. All botulinum toxin patients received a mandatory injection of 50

units in the wrist flexors; providers could also inject additional toxin in other upper limb muscles, at doses deemed therapeutic. The maximum botulinum exposure was 500 units. Dilutions above the elbow were 2 cm<sup>3</sup>/100 U, and below the elbow, 5 cm<sup>3</sup>/100 U.

Tizanidine was titrated according to the label indications: 4 mg/day, escalating 4 mg every 3-4 days based on frequent consultation and patient reaction, to a maximum of 36 mg/day. If adverse events occurred, patients were permitted to slow their titration.

At baseline, all patients had a modified Ashworth score of at least 3 (0 indicates normal tone, whereas 5 indicates rigidity). By week 3, patients receiving the toxin showed significantly more wrist flexor relaxation than the other groups (–1.25 vs. –0.25 for tizanidine and –0.67 for placebo). The results were similar at week 6. By week 18, the toxin group was moving back toward its baseline scores.

Finger tone was also significantly more improved in patients in the toxin group than in those in the tizanidine or placebo groups (–1.32 vs. –0.22 and –0.69).

“In fact, the placebo group did significantly better than the tizanidine group in both categories,” he said.

Only limb posture cosmesis was significantly improved in the Disability Assessment Score, he said. The greatest improvement occurred in the botulinum toxin group. ■