Small-Fiber Dysfunction May Underlie Pain

BY CHRISTINE KILGORE
Contributing Writer

BETHESDA, MD. — A growing body of research suggests that 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) has been "one of the most mysterious of the pain disorders"—one with no known cause, leaving few physicians willing to treat it and many others believing the disorder to be psychosomatic, said Dr. Oaklander, a neurologist at Harvard Medical School and director of the nerve injury unit at Massachusetts General Hospital, Boston.

However, "we now 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.

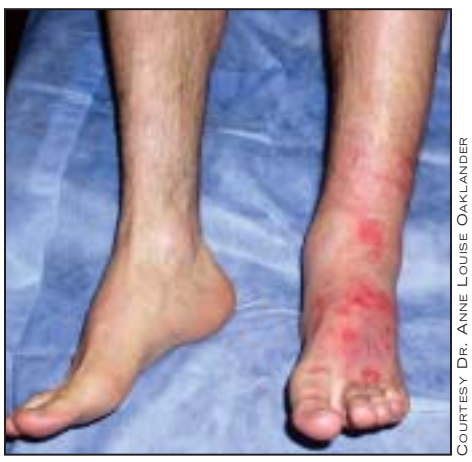
Most patients are classified as having CRPS-I (defined as having no known nerve injury); fewer than 10% receive a diagnosis of CRPS-II (having a known nerve injury). However, "seeing them in the clinic with the same presentation, it doesn't take a great leap of faith to believe these guys [with CRPS-I] have a nerve injury that wasn't discovered," she said.

CRPS is "what I call a focal 'pain-plus' syndrome. These 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."

Epidemiologic studies show that most patients diagnosed with CRPS are young (an average age of 39) and female (a 4:1 ratio), and that most patients recover spontaneously.

Skin biopsies done in Dr. Oaklander's lab of 18 CRPS-I patients show 30% fewer small-fiber nerve endings in painful CRPS-affected areas.

Results of ipsilateral and contralateral control biopsies discount a hypothesized effect of swelling on the number of nerve endings, and the fact that a control group of seven osteoarthritis patients with severe leg pain, edema, and disuse had no loss of nerve endings discounts the hypothesis that pain "burns out" nerve endings, Dr. Oaklander said. The identification of posttraumatic small-fiber loss in patients with CRPS has been validated by several other research groups, she noted.



COURTESY DR. ANNE LOUISE OAKLANDER

This patient's swollen ankle and shallow ulcers were caused by neurogenic edema, which may be triggered by the loss of small-fiber nerve endings.

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," Dr. Oaklander said.

New animal models developed to prove causality, including her own laboratory's mouse model of distal nerve injury, have reproduced the symptoms of CRPS—from allodynia and dysautonomia to bone loss, dystonia, and a regional and mirror-like spread of symptoms—and have shown that long-lasting pain behaviors usually remit and that the prevalence of allodynia is independent of lesion size.

"We really can't assume that it takes a severe injury to leave someone with chronic pain—in fact, the opposite may be true," Dr. Oaklander said. "Most of those who have small-fiber damage, however, may be able to regenerate their axons, and those whose axons do not regenerate may have either mild or no degeneration of their vasa nervorum," she said. ■

Most Neuropathic Pain Patients on Combo See Improved VAS Scores

BY MARY ELLEN SCHNEIDER
New York Bureau

NEW ORLEANS — Antidepressants and antiepileptics are both effective in treating neuropathic pain, but a combination performs best, according to Dr. Damon Robinson.

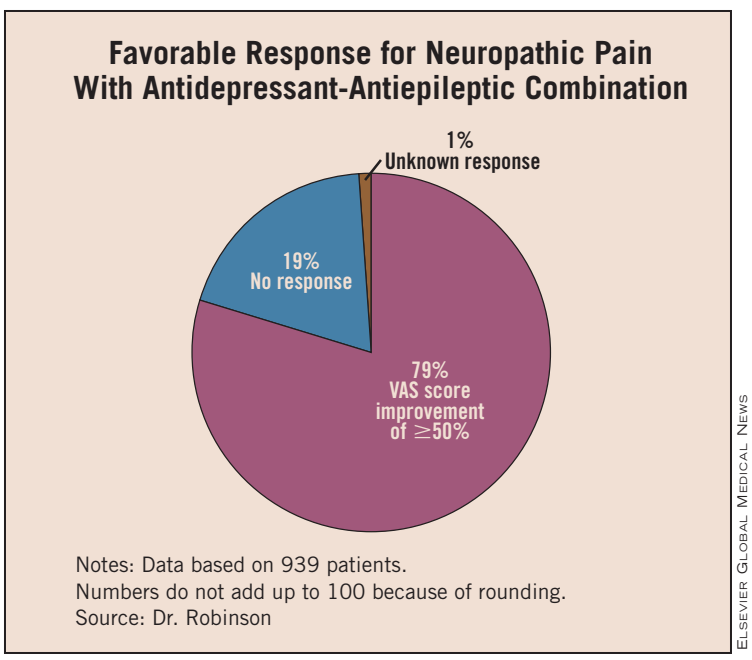
Dr. Robinson and colleagues found that nearly 80% of patients who took a combination of antiepileptics and antidepressant medications had a greater than 50% visual analogue scale (VAS) improvement, a statistically significant finding. The results were presented as a poster at the annual meeting of the American Academy of Pain Medicine.

Whereas clinical trials have shown clear evidence in favor of using antidepressants and antiepileptic medications alone in treating chronic pain, no studies have been designed to focus on the effect of combining antidepressants and antiepileptics for the treatment of neuropathic pain, wrote Dr. Robinson of Beth Israel Deaconess Medical Center and Harvard Medical School, Boston, and his colleagues.

Over a 2-year period, the researchers reviewed 6,129 charts with an initial encounter and a diagnosis of neuropathic pain. They also analyzed VAS, medical procedures, and antidepressant and antiepileptic use and dosage at each visit. Patients who had a 50% or greater improvement in their VAS score were considered to have a favorable response.

Of the charts reviewed, 3,370 patients had at least one antidepressant or antiepileptic prescribed. All of the antidepressant and antiepileptic drugs analyzed had favorable responses in more than 70% of patients. There was a statistically significant level of improvement among patients prescribed tertiary amines and among those prescribed a combination of antiepileptics and antidepressants. A total of 939 patients received the combination, with 79.4% reporting a VAS score improvement of 50% or greater. About 19.4% of patients who received combination therapy had no response, and 1.2% had an unknown response.

While retrospective studies have limits, the results are encouraging and indicate the need for prospective studies, Dr. Robinson said in an interview. ■



ELSEVIER GLOBAL MEDICAL NEWS

Chronic Headache Linked to Depression, Not Obesity

BOSTON— Chronic daily headache was not associated with obesity but was significantly associated with depression in a study of more than 300 neurology patients in Brazil.

The lack of an association between obesity and headache in the Brazilian sample contradicts findings from a recent population-based study in the United States showing that obese individuals in the community were at significantly increased risk for developing chronic daily headache, Dr. Luiz Queiroz said at the annual meeting of the American Academy of Neurology.

Dr. Queiroz of the Universidade Federal de Santa Catarina in Florianópolis, Brazil, and colleagues interviewed 336 patients at two neurology clinics from May to November 2005 regardless of whether or not their main complaint was for headache-related symptoms. The interview covered questions about sociodemographic data, the Beck Depression Inventory (BDI), and headache characteristics.

The prevalence of depression in the full sample, indicated by a score of 21 or higher on the BDI scale, was 31%, and the prevalence of obesity was 17%, Dr. Queiroz reported in a poster presentation. Depression and obesity were not significantly associated, but both obesity and depression were significantly more prevalent among women than men, Dr. Queiroz said.

Of the 336 patients (237 women), 291 reported experiencing headaches within the past 12 months, and 73% of those with headache met the International Headache Society criteria for either migraine or probable migraine, and 46% met the criteria for chronic daily headache (15 or more headaches in the previous month).

Women were twice as likely as men to have chronic daily headache (CDH). Age also had an effect, with people aged 30-59 years being twice as likely to have CDH as those 60-84 years of age. People 13-29 years of age were slightly less likely than those 30-59 years old to have CDH. Participants with Beck Depression Inventory scores of 21 or higher were twice as likely to have CDH as those scoring below 21.

Assessment of body mass index (BMI) of patients with chronic daily headache failed to show any correlation between BMI of 30 or higher and chronic daily headache. Among patients with CDH, no statistically significant association was found between headache and obesity.

—Diana Mahoney