Brain Scans Reveal Secrets of Itch-Scratch Cycle

BY PATRICE WENDLING
Chicago Bureau

CHICAGO — Neuroimaging of patients with atopic dermatitis has shown that different areas of the brain are activated in the itch versus scratch cycles.

The findings provide insight into the the role of peripheral and central neural sensitization of nerve fibers in contributing to atopic dermatitis itch. The findings also support the growing interest in drugs that act as antipruritics to reduce central sensitization, Dr. Gil Yosipovitch said.

Using arterial spin labeling–based functional MRI, Dr. Yosipovitch and colleagues at Wake Forest University, Winston-Salem, N.C., showed that the anterior cingulate cortex and dorsolateral prefrontal cortex are highly activated in patients with atopic dermatitis, but are not activated in healthy subjects when itch is induced. The activity in these cortices is also significantly correlated to itch intensity and disease severity scores in atopic dermatitis, according to unpublished data.

Curious about brain processing during scratching, the investigators, in another study, exposed 13 healthy subjects to a scratching stimulus. They found that repetitive scratching activates areas in the brain not activated in itch, most notably the secondary somatosensory cortex (J. Invest. Dermatol. 2008;128:1806-11). They also found significant activity in the cerebellum, which may be involved in coordinating the itch-scratch cycle.

What was more striking was a robust deactivation of the anterior cingulate cortex, which is involved in the unpleasant sensation of itch and thus may explain why scratching is so pleasurable, said Dr. Yosipovitch. Furthermore, there was a significant correlation between perceived scratching intensity and bilateral deactivation of the cingulate cortex.

"There is a hypersensitization of the nerve fibers in chronic itch; the nerve fibers are acting wacky," he said. "So when you give a painful stimulus instead of it being perceived as pain, it actually aggravates itch. It's very similar to patients with chronic pain, who when you induce an itchy state, it is perceived as pain.

A robust deactivation of the anterior cingulate cortex may explain why scratching is so pleasurable.

DR. YOSIPOVITCH

"Now you can understand why one of my treatments of itch is reduction of central sensitization," he said at the American Academy of Dermatology's Academy 2008 meeting

Drugs targeting this mechanism include selective noradrenergic reuptake inhibitors such as mirtazapine, neuroleptics, and kappa opioids.

Butorphanol is an approved kappa agonist and mu-receptor antagonist analgesic that is available in injectable and intranasal spray formulations, he said. Butorphanol nasal spray is very effective in treating patients with chronic, intractable itch that affects their sleep and quality of life.

"I don't want to send the wrong message that this is a first-line drug for itch, but I'm quite sure we all have these patients and sometimes it's worth a try," he said.

Dr. Yosipovitch also uses 15 mg of mirtazapine (Remeron) at bedtime for intractable itch in patients aged 10 years and older, almost half of whom report a significant improvement in sleep and quality of life. The antidepressant is not addictive, but weight gain can occur. He suggested that the immunosuppressant azathioprine (Imuran), which is used to prevent kidney transplant rejection and to treat severe rheumatoid arthritis, is underutilized in the United States for atopic dermatitis. He acknowledged concerns about the increased risk of lymphoma associated with azathioprine therapy, but said this is unlikely with short-term use of 1 year or less at a dosage of 1 mg/kg.

In a double-blind, randomized trial conducted in the United Kingdom in 63 patients who had moderate to severe atopic eczema despite having received optimum topical therapy, azathioprine dosed by thiopurine methyltransferase (TPMT) was well tolerated; however, two patients developed drug hypersensitivity (Lancet 2006;367:839-46). At week 12, there was a 37% improvement in mean disease activity with azathioprine, compared with a 20% improvement with placebo. Significant improvements in itch, area of involvement, and quality of life were also observed.

Although the psoriasis biologic therapies—efalizumab, alefacept, and rituximab—are being studied for atopic dermatitis, Dr. Yosipovitch said he is not convinced at this point of their efficacy.

Dr. Yosipovitch, known as "Dr. Itch" to his patients, is fond of the old-fashioned remedy of double-layer wet pajamas in which a moist wet-wrap dressing is covered by a layer of dry pajamas. A Korean study in 10 patients with severe atopic dermatitis confirmed that wet-wrap dressings were associated with clinical improvement and recovery of the epidermal barrier (J. Eur. Acad. Dermatol. Venereol. 2007;21:1360-8).

Dr. Yosipovitch disclosed that he has been on the advisory board of, been a consultant for, or received research grant support from, Acologix Inc., Cara Therapeutics, Taisho Pharmaceutical Co., Stiefel Laboratories Inc., UCB Pharma, Connetics Corp., and the National Eczema Association. ■

Psychoanalytic Theory of Eczema Shouldn't Be Discarded

BY BETSY BATES
Los Angeles Bureau

LAS VEGAS — Most experts in psychodermatology long ago abandoned the psychoanalytic theory of atopic eczema, characterized in 1940 by Dr. Franz Alexander as an outgrowth of a child's emotional angst at being unable to express anger and hostility arising from maternal rejection.

Still, increasing evidence points to a psychoneuroimmunologic "setup" for atopic dermatitis (AD), if not an eczema personality profile, asserts Dr. Torello M. Lotti, professor and chair of dermatology at the University of Florence, Italy.

Dr. Lotti and other researchers have hypothesized that an interconnection between genetic and environmental factors may predispose a patient to allergic inflammation, which may then cascade in a vulnerable individual into a long-lasting diminished capacity for appropriate protective reactivity within the hypothalamus-pituitary-adrenal (HPA) axis.

Certain responses to experimental conditions point to notable differences in the psycho-neuroendocrine-immune function of people with atopic dermatitis and other inflammatory allergic diseases, Dr. Lotti said during a seminar on dermatology sponsored by Skin Disease Education Foundation.

He cited numerous studies:

- Diurnal plasma cortisol (stress marker) variations in AD patients were found to rise and fall with atopy-relevant inflammatory parameters, with associated waxing and waning of allergic symptom severity (J. Clin. Invest. 1992;90:596-603).
- AD-like symptoms were actually precipitated in healthy volunteers after treatment with the glucocorticoid receptor antagonist RU 486 (J. Clin. Endocrinol. Metab 1990;71:1474-80).
- When exposed to experimental stressor conditions (asking volunteers to speak and do mental arithmetic tasks in front of an audience), eosinophil counts and IgE levels rose significantly in atopic eczema sufferers, but not in healthy volunteers (J. Neuroimmunol. 2002;129:161-7).
- Finally, epidemiologic evidence appears to bolster the argument that stress—either exerted by outside events or exquisitely experienced by a vulnerable personality—contributes to the cycle of events perpetuating atopic dermatitis, he said.

A severe shock or emotional event has been found to precede the onset or aggravation of AD in patients in early dermatologic studies, which also tracks with his clinical experience, he noted. An increasing prevalence of AD in children in the Western World may be symptomatic of the more highly-stressed, pressured environments in which they live.

In Dr. Lotti's view, a "biochemical setup" for atopic dermatitis activates not only stress (influencing the sympathetic nervous system and immune response), but also behavior and personality.

An appropriate approach, he said, is to utilize treatments that impact psychological symptoms of distress as well as physiologic symptoms such as pruritus.

He favors doxepin (10 mg at bedtime) or amitriptyline (starting at a dose of 50 mg/day) over antihistamines for "the itch of atopic dermatitis," which he said "is not a regular itch."

Direct acknowledgement of the psychological contributors to atopic dermatitis facilitates "liaison consultations," in which Dr. Lotti sees patients sometimes in the same room at the same time as do psychologists or psychiatrists.

Dr. Lotti disclosed receiving grant or research support or speakers bureau contributions from Merck-Serono, Wyeth, Abbott, and Schering-Plough.

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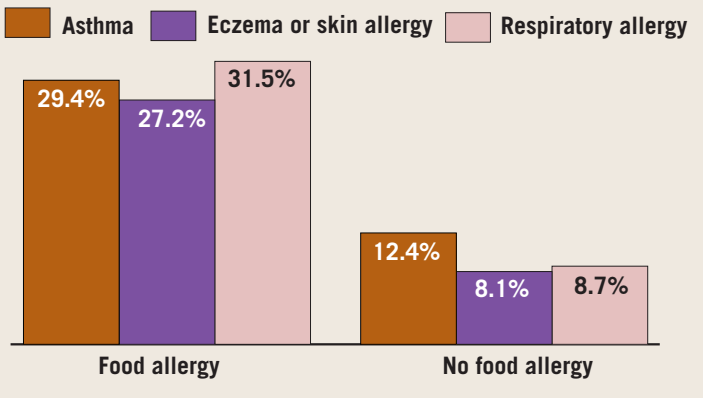
DATA WATCH

Children With Food Allergy Are More Likely to Report Asthma or Other Allergic Conditions



Note: Data are weighted estimates from the 2007 National Health Interview Survey.
Source: National Center for Health Statistics