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For some people, stress can cause psoriasis symptoms to flare up.

PSYCHODERMATOLOGY

An emotional response

As the link between stress and psoriasis flare-ups becomes clearer, it seems the most vulnerable patients require a new type of treatment.

BY SARAH DEWEERDT

Most people have not-so-fond memories of having their skin break out in pimples during times of teenage stress, such as the night before an exam or their first dance. For many people with psoriasis, stress is written on the skin for their whole lives, and in a much more painful way than a few zits.

Emotional stress is the most frequently cited trigger for psoriasis symptoms, ahead of infections, diet, medication and the weather[1]. Not all psoriasis patients have stress-responsive disease, although as many as three-quarters, depending on the particular study population, say that psychological stress causes their disease to flare up.

Dermatologists and psoriasis patients have known about the link with stress for decades. Until recently, however, there was little research to support it. But this is changing. More researchers are probing the connection between stress and psoriasis, and several groups are investigating the cells and molecules involved in the skin's response to stress.

The results are not only illuminating the underlying mechanisms of psoriasis and other inflammatory disorders, but also pointing to the need for a multidisciplinary approach to psoriasis treatment. "Treating a patient with psoriasis is not just treating the skin, it's treating the individual," says Christopher Griffiths, a dermatologist at the University of Manchester, UK, who has conducted multiple studies of the interplay between stress and psoriasis.

In 2009 a group of researchers from Radboud University in Nijmegen, the Netherlands, published[2] a study that charted day-to-day stresses (such as losing something important, or making a social blunder) and psoriasis symptoms among 62 patients over the course of six months. This was the first large study to follow these relationships as they unfolded over time, as opposed to having patients recall past stresses and psoriasis flare-ups. The study revealed that stressful periods are linked to increased psoriasis symptoms four weeks later. However, this relationship only holds true for patients who worry or scratch a lot; for patients without these characteristics, there was no relationship between stress and the timing of psoriasis symptoms. This has implications for treatment, says clinical psychologist Andrea Evers, a member of the study team. "We have to look at the specific patient profiles that are most vulnerable to stress."

COMMON PROBLEM

Flare-ups of other skin problems, ranging from acne to much rarer disorders such as lichen planus (characterized by an itchy rash on the skin or in the mouth), have also been linked to stress. What do all these conditions have in common?

"Inflammation," says John Koo, director of the Psoriasis, Phototherapy and Skin Treatment Clinic at the University of California, San Francisco. "Inflammation seems to be upregulated by emotional stress." In fact, chronic inflammatory diseases that affect other body tissues, such as rheumatoid arthritis and inflammatory bowel disease, can also be worsened by stress.

One important inhibitor of inflammation is cortisol, a hormone produced by the adrenal gland that is normally released in response to both physical and emotional stress. Research suggests that the regulation of cortisol is dysfunctional in psoriasis, particularly in the large proportion of patients with stress-responsive disease.

One such study[3], led by Griffiths, asked psoriasis patients to prepare and deliver a short talk to a panel of strangers — this is the Trier test, a standard technique for inducing social stress. Before the test, some psoriasis subjects reported that stress induces flare-ups, while others said stress had no effect on their disease. After taking the test, patients who reported stress-responsive disease had lower cortisol levels than patients whose disease is not induced by stress.

These findings are not limited to the laboratory. In a six-month study[4] of stress and psoriasis symptoms, Evers's team also tracked patients' cortisol levels, and found that those with persistently high levels of daily stress had lower average cortisol levels. "These results are in line with the literature that people with, for example, post-traumatic stress disorder or other stress-related disorders also have

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lowered basal cortisol levels," Evers says.

Although the cortisol response is a good clue to what might be going on, it's not very specific — cortisol levels fluctuate for many reasons. So researchers are investigating how stress affects some cells and molecules thought to play a specific role in plaque formation in psoriasis. Griffiths's team has focused on immune cells called Langerhans cells, which are found near nerve fibres in the upper layers of the skin (see 'Psoriasis uncovered', page S50). "Where the nervous system and the immune system connect is the Langerhans cells," Griffiths says. "There's direct signalling between the two."

As psoriatic plaques form, Langerhans cells migrate out of the upper layers of the skin. When the lesions resolve, these cells return. Griffiths has found evidence[5] that, irrespective of cortisol levels, stress can spur Langerhans cells to move. Among healthy volunteers, the number of Langerhans cells in the upper layers dropped sharply following a Trier test.

Another type of immune cell under investigation is the mast cell. Like Langerhans cells, mast cells are found in large numbers in the upper layers of the skin, near nerve fibres. But whereas the population of Langerhans cells decreases in psoriatic lesions, mast cell numbers increase.

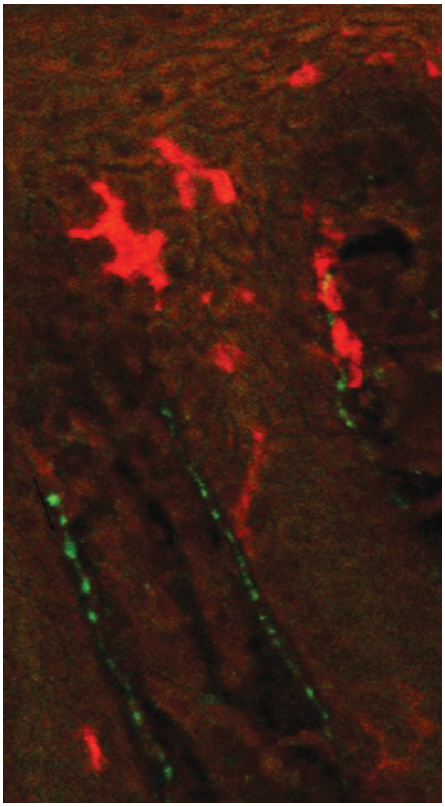
"One of the earliest morphological changes is endothelial swelling and mast-cell activation when a psoriatic lesion develops," says Ilkka Harvima, a mast-cell biologist and dermatologist at Kuopio University in Finland. "The mast cell participates in the early phases and may direct this entire system."

Mast cells can be activated by stress hormones such as corticotropin-releasing hormone. Animal studies designed to promote stress — for example, exposing mice to loud noise — show activation of mast cells in the skin. Equivalent studies in humans have not yet been conducted.

Activated mast cells release substances such as histamine that can stimulate the growth of sensory nerve fibres, which are more prevalent in psoriatic lesions. Harvima and other mast-cell biologists think this creates a cycle that helps skin inflammation and psoriasis symptoms persist: stressed nerves release substances that activate mast cells, and these cells encourage the growth of more nerve fibres, which in turn release more of the molecules that activate mast cells.

The effect of stress on psoriasis symptoms is complicated by the fact that psoriasis itself causes stress (see 'Under their skin', page S64). People who say their psoriasis is influenced by stress tend to rate their disease as more severe than those who don't, even though the body area covered by psoriasis (the main severity measure doctors use) is the same. Stress responders also tend to have more psoriasis on highly visible areas of the body, such as the face and hands.

There is no evidence that stress causes psoriasis to appear specifically in visible areas, but once these lesions exist "it's really a downward spiral", Koo says. "The more visible you have it, the more upset people get. The more upset you get, the more inflammatory your skin disease gets."



There is a close link between nerve fibres (green) and immune cells called Langerhans cells (red).

CROSS-TALK

The nerve cells, immune cells, skin cells and signalling molecules involved in the cross-talk between the nervous system and the skin are known as the brain–skin axis. The relationship has a deep biological basis, says Mohammad Jafferany, a Michigan-based dermatologist and psychiatrist. "The skin and brain have a common embryological origin," he points out. Both are derived from ectoderm, the outer layer of cells in an embryo. "This connection is from the very early stages of life."

Psoriasis is not the only disorder that involves the brain–skin axis, and a better understanding of this disease might point to ways to treat other skin ailments. "The mechanism is probably similar for many inflammatory skin conditions," says Koo. "Emotional stress exacerbates inflammation relatively non-specifically." Psoriasis is a particularly good model to use because it is relatively common, has a distinctive appearance, and its severity doesn't change much from day to day (unlike eczema, say).

Psoriasis studies might even yield insights into other chronic inflammatory conditions, such as inflammatory bowel disease. "What we find with psoriasis and stress is transferable to inflammation in organs that are less accessible," Griffiths says. "I suspect the mechanisms are very similar."

The role of stress in exacerbating psoriasis has implications for treatment too. A few studies have suggested that psoriasis patients benefit from interventions such as group therapy, relaxation techniques and stress management.

Cognitive behavioural therapy (CBT), a technique for changing troublesome thoughts and behaviours, has shown promise in relieving stress-responsive psoriasis. A study of 93 patients found that those who received standard psoriasis medications plus a six-week programme of CBT had greater improvements in their psoriasis symptoms than those who received medication alone[6]. What's more, this improvement remained in effect six months after completing the programme. "Once they have those techniques on board, they are more likely to get a prolonged response to therapy," says Griffiths, who led the work.

CBT "should be implemented more regularly, particularly for highly stress-vulnerable patients", Evers says. Such patients could be identified through questionnaires and standardized screening instruments soon after psoriasis is diagnosed, so that treatment strategies can then be tailored to their needs.

Such individualized treatment requires new types of collaboration among healthcare professionals. Jafferany, who runs one of a handful of psychodermatology practices in the United States, says that optimal treatment of patients with stress-responsive psoriasis might involve a psychiatrist, a psychotherapist and a social worker as well as a dermatologist.

This multidisciplinary approach is rare. In a survey carried out by a group that included Jafferany, dermatologists in Washington state admitted that although they commonly encounter patients with conditions such as psoriasis that have psychological ramifications, they rarely refer them to a psychiatrist. Furthermore, the survey found that nearly half of the respondents had no formal training in the psychological impacts of psoriasis.

For people with stress-responsive psoriasis, traditional dermatological treatments aren't enough. As Jafferany says: "If you are not looking at the stress element, then you are treating only half the problem." ■

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