FIBRO-DRY EYE-GIA?

Fibromyalgia may have lessons for dry eye disease. What to do when the mind and body connect but the signs and symptoms do not.

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"They have a chronic illness, chronic pain, and I see them when something new or unmanageable is going on. There's no point. There's nothing more I can offer them."

To what medical condition is this physician referring? It could be many things. As it turns out, this statement of resignation appeared in a 2010 study that examined the attitudes of physicians toward fibromyalgia.[1] It could well have appeared in a study examining physicians' attitudes toward dry eye disease (DED). Many ophthalmologists have, in fact, opined that DED is the fibromyalgia of eye care. Could they be right? What exactly does that statement mean?

For eye care providers, the DED patient carries the stereotype of being time-consuming. Many physicians express frustration over a sense of futility: their patients with DED seem to present with either symptoms out of proportion to signs or with signs unresponsive to treatment. Both patient types seem relentlessly dissatisfied. Needless to say, this stereotype overlooks an equally important but often forgotten group of DED patients who present with the opposite characteristics: the patients who fail even to disclose their DED symptoms, dismiss the condition as a mere nuisance, and are more than happy to return in a year after doing nothing about their disease.

For the purposes of this article, however, the former stereotype will be examined using fibromyalgia as a model. Specifically, this article will use physicians' extensive history of managing fibromyalgia to better understand both the psychosomatic and pathophysiologic basis behind the sign-symptom disconnect that characterizes DED. It is precisely this discordance between the slit-lamp examination and the patient's subjective experience that often hampers progress in the office and in new DED drug development.

FEATURES OF DED, FIBROMYALGIA

Ever since Hippocrates predicted that a person's temperament could be determined by the interaction of the body's four vital fluids, the mind-body connection has been well established. Even the rudimentary example of the fight-or-flight response demonstrates the importance of perceptions to physiology. Furthermore, the ability of a placebo treatment to elicit the same physiologic response as an authentic treatment adds further validity to the interconnectedness of mind and body.

AT A GLANCE

- Physicians' extensive history of managing fibromyalgia may help increase the understanding of both the psychosomatic and pathophysiologic basis behind the sign-symptom disconnect that characterizes DED.
- One important factor that can easily influence the reporting of patients' DED symptoms is their level of anxiety.
- Ophthalmology must continue to re-evaluate the complexity of DED and to unhitch DED's traditional pathogenic equations.

That perception of disease influences experience of disease should come as no surprise. Is there anything about DED and fibromyalgia, however, that makes these conditions uniquely sensitive to the mind-body connection?

Both diseases can present with protean symptoms without corresponding physical signs (See Definition of Fibromyalgia). Furthermore, both conditions lack gold-standard laboratory or radiographic diagnostic tests, and in many cases, both conditions seem unresponsive to traditional therapies. Both states can have highly variable presentations: consider the variability between aqueous-deficient DED and evaporative DED. Often, both diseases lack a clear beginning and a clear end.

It is these inherently amorphous qualities that can allow psychosomatic processes to flourish. Compounding this are the similar resultant attitudes of physicians toward DED and fibromyalgia; many physicians harbor doubts about the authenticity of the pathogenesis of these diseases and, in many cases, question the validity of the patient's subjective experience.

PSYCHOSOMATIC BASIS FOR SIGN-SYMPTOM DISCONNECT

As evidenced by the paucity of new DED drugs receiving regulatory approval, the pharmaceutical industry faces unique challenges in the researching and development of new DED

DEFINITION OF FIBROMYALGIA

I. Disorder of unknown etiology characterized by widespread pain, abnormal pain processing, sleep disturbance, fatigue and often psychological distress
II. Symptoms present for at least 3 months
III. Absence of other condition to explain pain
IV. Concomitant symptoms include
  a. morning stiffness
  b. tingling or numbness in hands or feet
  c. headaches, including migraines
  d. irritable bowel syndrome
  e. sleep disturbances
  f. cognitive problems with thinking and memory
  g. painful menstrual periods and other pain syndromes

Source: Centers for Disease Control and Prevention, January 2015.

medications. One such challenge has been to reach primary clinical endpoints for both symptoms and signs; this reflects the exceptional variability of the pathogenesis of the disease. Compare this to the relative ease of demonstrating concomitant improvement of signs and symptoms in postoperative inflammation, where the signs and symptoms pair much more predictably.

In the design of DED drug studies, the baseline characteristics of the treatment and control groups are often carefully matched for demographics, medical history, and age as well as for clinical markers such as visual acuity, conjunctival hyperemia, corneal stain, and Schirmer scores. However, there is one characteristic that influences the reporting of symptoms that is not controlled for: anxiety.

A participant's baseline anxiety level could easily influence the reporting of his or her DED symptoms. We see this in the office all the time, as we note that some DED patients are consumed by the symptoms of their disease while others cannot even be convinced that the symptoms are part of a disease worth treating.

In a recent study of more than 460,000 patients seen between 2008 and 2013 in the University of North Carolina outpatient system, investigators discovered a statistically significant association between DED and anxiety.[2] Furthermore, several recent articles have revealed an association between posttraumatic stress disorder (PTSD) and DED.[3,4] Although many will be quick to note that the association may simply reflect the desiccating anticholinergic effects of anxiety medications, the association proves to be far more complex. For example, in the study by Fernandez et al, which compared the reporting of DED symptoms in a group of DED subjects with PTSD to a group of DED subjects without PTSD, investigators discovered that the symptoms were associated with level of PTSD, not with tear parameters.[3] In other words, subjects with PTSD reported greater symptoms than those without PTSD, but both groups had similar Schirmer scores, tear osmolarity, corneal staining, tear breakup time, and meibomium gland quality. If the association was one solely based upon desiccating anticholinergic effects, one would expect those effects to be reflected in the groups' tear parameters; this was not seen.

A similar association between fibromyalgia and anxiety has been documented. One large multicenter study found that between 44% and 51% of fibromyalgia patients experience anxiety.[5] Another study reported that patients with a diagnosis of fibromyalgia were four times more likely to have a concomitant diagnosis of anxiety than a control group without fibromyalgia.[6] Furthermore, like DED, an association between fibromyalgia and PTSD has been identified as well.[7]

The principles of behavioral medicine have long held that psychological stress can exacerbate or cause physical distress. As such, psychological stress may explain why some patients fail to respond to traditional therapies and why some patients appear more incapacitated than would be predicted by their clinical exams.

NEUROPATHIC BASIS FOR SIGN-SYMPTOM DISCONNECT

As we have seen, anxiety can influence patients' perceptions of their symptoms and, in the case of PTSD, can affect how patients report their DED symptoms independent of tear parameters. Alone, this would seem to nicely explain the sign-symptom disconnect; however, there is potentially a pathophysiologic, in addition to a psychological, explanation as well. Once again, fibromyalgia provides a useful framework to explore this possibility.

Neuropathic pain represents a dysfunction of the nervous system that may result from peripheral or central sensitization, typically without any obvious sign of tissue damage. Ophthalmologists may be most familiar with neu-

ropathic pain in the setting of postherpetic neuralgia where, despite complete resolution of the signs of viral infection, patients report chronic pain in an area of previous involvement. However, neuropathic pain may in fact be far more common and may underlie DED symptoms as well.

Neuropathic pain often differs in quality from typical nociceptive pain, and it is characterized by dysesthesia (spontaneous pain), hyperalgesia (amplification of pain), and allodynia (pain in response to typically nonpainful stimuli). For example, patients reporting extreme sensitivity to light (photoallodynia) or patients describing unique sensitivity to cold and wind (hyperalgesia) may be experiencing neuropathic pain.

Unfortunately, commonly used DED surveys, such as the Ocular Surface Disease Index survey, do not distinguish between nociceptive and neuropathic pain. Furthermore, slit-lamp examination typically reveals no corneal signs in neuropathic pain states.

The pain of fibromyalgia has long been suspected to be neuropathic in origin. Characteristically, this diffuse and widespread pain presents in the absence of any anatomic damage. Neuropathic pain can be divided into peripheral and central categories. Peripheral neuropathy results from the hyperexcitability of peripheral nerve endings due to increased activity of nerve terminal sodium channels. Interestingly, investigators have documented the presence of peripheral nerve disease in fibromyalgia by examining the altered morphology of corneal nerves.[8]

As it turns out, similarly to fibromyalgia, peripheral neuropathic pain may also underlie the pathogenesis of DED pain. The cornea is unique. No other tissue in the human body contains more densely packed nerve endings. Furthermore, the nerve endings in the cornea, interwoven among epithelial cells, remain directly exposed to the environment, allowing the exquisite sensitivity of the tissue. From an evolutionary perspective, this sensitivity may offer an obvious protective advantage; however, the evolutionary story likely proves a bit more complex.

Of the entire optical system of the eye, the majority of refraction occurs at the interface between the air and the cornea. Maintaining an adequate thickness of the tear film is, therefore, required for proper refraction of light and visual acuity. Through these highly dense, exposed peripheral nerve endings, evolution has created a real-time mechanism for regulating tear thickness. A recent study demonstrated a new class of thermosensitive corneal nerves designed to monitor temperature variances between blinks as a mechanism to maintain proper tear thickness.[9] The study demonstrated that, in states of DED, hyperosmolar changes result in sensitization of these thermosensitive nerves. As a result, whereas these nerve terminals typically require a 4° to 5°C drop for activation, in this study, a drop of only 1°C was enough for activation in hyperosmolar conditions. This

study, therefore, suggests an important mechanism for the peripheral neuropathic pain of DED that one might expect in the absence of clinical signs and, furthermore, probes the interesting possibility that DED pain may partly represent an evolutionary maladaptation.

The story of neuropathic pain gets more complex, however: neuropathic pain may originate not only within the peripheral nervous system but within the central nervous system as well. Descending inhibitory central pathways, originating from multiple areas of the somatosensory cortex and midbrain, synapse in peripheral ganglia. At this location, the descending central pathways typically dampen the pain response originating from peripheral nerves. Multiple studies have demonstrated that, in certain pathological states such as in anxiety, these descending inhibitory pathways are themselves inhibited, leading to subjectively increased pain awareness.[10,11] These results provide a compelling possibility of a central neuropathic connection between the anxiety associated with fibromyalgia and with DED.

These central influences on DED pain further emerged in a remarkable study from 2013, in which investigators confirmed a link between DED and pain sensitivity.[12] What made these results so remarkable, however, was that the pain sensitivity investigated was not in the eye but on the forearm. Specifically, individuals with and without DED were exposed to noxious thermal stimulation on their forearms. The DED group had a statistically significantly decreased threshold to pain compared with the control group without DED. This finding points decisively toward a unifying central mechanism for enhanced sensitivity to pain in DED patients. Furthermore, it provides yet another explanation for the disconnect between signs and symptoms in DED—this time from the central nervous system.

PARADIGM SHIFT IN UNDERSTANDING OF DED

Clearly, the complexity of DED pain transcends mere considerations of tear quantity. Over the past decade, ophthalmology has gained an improved awareness of the contributions of inflammation and osmolarity to the pathogenesis of DED. Perhaps now, the role of psychosomatic and neuropathic processes should be added to this paradigm shift.

Consider the case of glaucoma. For more than a century, ophthalmologists have focused treatment exclusively on lowering IOP; however, the role of alternative pathogenic factors such as vascular perfusion, neuroprotection, and corneoscleral hysteresis continue to attract attention. Similarly, with DED, ophthalmology may be beginning to refine the traditional emphasis on tears and the traditional formula that DED simply equals the ocular surface minus tears.

In this article, I have attempted to provide witness to this complexity by using fibromyalgia as a model to better understand the psychosomatic and neuropathic origins of the sign-symptom disconnect in DED. The intent was to examine these diseases in parallel, not necessarily at their intersection. Interestingly, however, in a 2013 article, a clear association between tear osmolarity and the severity of fibromyalgia symptoms was identified.[13] Furthermore, it is intriguing to consider that gamma-aminobutyric acid analogues, better known as GABA, the first class of drugs to receive an indication from the FDA for fibromyalgia, now have begun to be used as treatment for severe corneal neuropathic pain after laser refractive surgery.[14]

Nevertheless, one need not require a direct association to recognize a direct relevance. It is abundantly clear that ophthalmology must continue to re-evaluate the complexity of DED and to unhitch DED's traditional pathogenic equations. As ophthalmologists, we can continue to scratch our heads in puzzlement as to why the signs and symptoms fail to correlate, or we can dare to look beyond the slit lamp to consider the complexity of the corneal nerves, of the central nervous system, and of the mind. Only then will the old stereotypes finally give way to a new conception of DED. ■

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