The importance of matrix metalloproteinase 9 (MMP-9) in identifying ocular surface dryness has been recognized for years. Until recently, however, an understanding of this cytokine’s full implications with regard to the corneal surface and in ocular surgery has been hampered by the expensive laboratory equipment and time required to detect it. Now, a new in-office test for detecting elevated levels of MMP-9 is enabling surgeons to obtain an accurate evaluation within 10 minutes.

**MMP-9 AND DRY EYE**

Dry eye syndrome (DES) is a multifactorial disease that destabilizes the tear film. The condition is accompanied by increased osmolarity of the tear film and inflammation of the ocular surface. Hyperosmolarity of tears contributes to the inflammatory cascade, which causes distressed epithelial cells to produce elevated levels of the cytokine MMP-9. In turn, this cytokine exacerbates the inflammatory cycle.

Chotikavanich showed that the activity of MMP-9 increases proportionally with the heightened severity of a patient’s dysfunctional tear syndrome or ocular dryness. Elevated levels of MMP-9 correlate with dry eye symptoms found during clinical examination and may be a more sensitive marker than these clinical signs. Abnormal levels of MMP-9 (> 40 ng/mL) have been shown to correspond with moderate-to-severe dry eye disease, as defined by the Dry Eye Workshop (DEWS) Report. Increased MMP-9 activity in dry eyes may contribute to deranged corneal epithelial barrier function, increased corneal epithelial desquamation, and corneal surface irregularity.

**DIAGNOSIS OF DES**

It is common for patients to complain of dry eyes, and DES accounts for a significant percentage of visits to eye care professionals. The clinical signs of this condition, however, do not always correlate with patients’ complaints, which makes DES difficult to diagnose. Ocular surface disorders are regularly underdiagnosed,
particularly in patients who have reduced corneal sensitivity and therefore do not report symptoms. The diagnosis is made even more challenging after corneal surgery. For example, punctate epithelial keratopathy was detected using rose bengal or fluorescein staining in 2% to 6% of eyes that had undergone LASIK. Yet, symptoms of ocular dryness and irritation were found in 48% to 59% of these patients.

In addition, Wilson showed that eyes that developed signs of DES 1 to 6 months after undergoing LASIK had no significant difference in tear production compared with asymptomatic eyes as detected by a Schirmer test with anesthesia. The altered function of the corneal epithelial barrier causes ocular irritation and visual morbidity in patients with DES.

Increased MMP-9 activity has been observed in the tears of patients with DES. Eye care professionals now have a rapid, in-office test to detect elevated levels of MMP-9 and facilitate an accurate diagnosis of DES.

**DETECTION OF DES**

InflammaDry (Rapid Pathogen Screening, Inc., Sarasota, FL; not available in the United States) uses nanogold technology and is built on a platform that involves the direct sampling of a microfiltration immunoassay. A small Dacron (Invista, Wichita, KS) pad on the test’s sample collector automatically draws up a small (10 µL) sample of tear fluid to detect MMP-9. This test is simple enough that it can be performed by a technician on any patient who presents with signs of DES or as part of preoperative screening. The figure shows how the examiner collects a small sample of tears from the palpebral conjunctiva and places it directly onto the test strip. Then, he or she activates the test by dipping it into a provided vial of buffer solution for 20 seconds. The test’s results are available in 10 minutes.

In clinical trials, the sensitivity and specificity of InflammaDry was compared to clinical truth, which included the following commonly used measures of DES: an Ocular Surface Disease Index score of 13 or more, Schirmer tear test results of less than 10 mm, reduced tear breakup time of less than 10 seconds, and the presence of keratoconjunctival staining. These findings have recently been corroborated (Sambursky R, Davitt W, Latkany R, et al, unpublished data, 2011). The test’s sensitivity was also compared to normal, healthy controls, including an Ocular Surface Disease Index score of 7 or less; a Schirmer tear test result of 10 mm or more, a tear breakup time of 10 seconds or more, and the absence of keratoconjunctival staining. A small, prospective, two-center phase 1 clinical trial enrolled 42 patients and demonstrated a sensitivity of 87% and a specificity of 92%. A larger prospective, multicenter, sequential phase 2 clinical trial enrolled 206 patients and demonstrated a sensitivity of 85% and a specificity of 94% (Sambursky R, Davitt W, Latkany R, et al, unpublished data, 2011). Other tests commonly used in the diagnosis of DES detect other markers and do not account for the presence of inflammation among additional factors. Some tests have demonstrated low sensitivity and/or specificity. For example, in its 510(k) submission, the TearLab Osmolarity System (TearLab Corporation, San Diego, CA) demonstrated a sensitivity of 64% and specificity of 71%.

**SURGICAL COMPLICATIONS AND MMP**

Studies have shown an important link between elevated levels of MMP-9 after ocular surgery. DES is one of the most common complications of PRK and LASIK, affecting approximately 50% of post-LASIK patients 1 week after surgery, 40% at 1 month, and 20% to 40% of patients at 6 months. Other complications such as fluctuating vision, decreased BCVA, and severe discomfort occur in approximately 10% of post-LASIK patients.

MMP-9 has also been implicated in poor epithelial healing, epithelial ingrowth, and corneal ulceration after refractive surgery. It has been demonstrated that corneal wound healing may not finish by 3 months after LASIK, and this may lead to an insufficient attachment between the corneal flap and the corneal bed. The dislocation of corneal flaps as well as ectasia consisting of a progressive deformation and thinning of the cornea after LASIK have been shown to be related to corneal wound healing.

Existing ocular surface disease can be made worse after LASIK, PRK, or corneal transplantation. The successful identification and treatment of patients with ocular surface disease can help improve the health of the ocular surface, ensure more accurate presurgical measurements, and enhance outcomes.

**TREATMENT**

Patients with LASIK-induced neurotrophic epitheliopathy often respond to topical cyclosporine (Restasis;
Allergan Inc.), which treats the underlying inflammation and may benefit nerve regeneration. Thus, the treatment of dry eyes prior to refractive surgery reduces the risk and severity of postoperative DES. 13 Studies have also shown that elevated levels of MMP-9 respond to anti-inflammatory therapies such as cyclosporine, 16 corticosteroids, doxycycline, 17 and azithromycin (Azasite; Merck & Co., Inc.). 18 Monitoring levels of MMP-9 during treatment may provide an objective measure of therapeutic effectiveness.

CONCLUSION

MMP-9 detection may be the single best test available to diagnose DES and ocular surface disease, to predict the value of anti-inflammatory treatment, and to use preoperatively to reduce postsurgical complications. InflammaDry is currently available outside the United States, and data have been submitted to the FDA for 510(k) review.

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10. TearLab performance testing summary. 510(k) summary; section VI. 2009.