

Corneal Microscopy, Early Neuropathy Diagnosis

BY JEFF EVANS
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WASHINGTON — Corneal confocal microscopy can be used to noninvasively diagnose neuropathy early on in diabetic patients and to follow the course of the disease during treatment, several speakers said at the annual scientific sessions of the American Diabetes Association.

By comparison, the clinical neurologic exam may be easier than corneal confocal microscopy but it lacks sensitivity, said Mitra Tavakoli, a doctoral student at the University of Manchester (England).

Nerve conduction studies are time-consuming and are reliable only in measuring the function of large nerve fibers. Quantitative sensory testing also is easier to do, but relies on the patient's response to take measurements.

Skin nerve biopsies can provide much information, but are "highly invasive," she said.

Using a first-generation corneal confocal microscope, the ConfoScan P4 (Tomey Corp.), Ms. Tavakoli and her colleagues are able to obtain in vivo, real-time micrographs of the cornea at up to 680 times magnification without directly contacting the eye.

Patients who undergo the procedure are given an anesthetic drop on the cornea to make it easier to then place a gel on the cornea to reduce excessive reflections between the cornea and the instrument.

She and her coinvestigators studied 183 people including control patients without diabetes, diabetic patients without neuropathy, and diabetic patients with mild, moderate, or severe neuropathy.

They found that diabetic neuropathy was associated with progressive, significant reductions in corneal sensitivity (as measured by noncontact corneal aesthesiometry), nerve fiber density, nerve branch density, and nerve fiber length. Nerve fiber tortuosity also became progressively worse as the severity of neuropathy worsened.

Significant reductions in these measures were found even among diabetic patients without neuropathy, Ms. Tavakoli said.

The measurements of corneal nerve morphology obtained with confocal microscopy correlated well with assessments of corneal sensitivity and neuropathy severity, as measured by the Neuropathy Disability Score.

Corneal confocal microscopy "may act as a good surrogate marker to diagnose and follow the progression" of neuropathy during interventions and follow-up, she said.

In a poster presented at the meeting, Ms. Tavakoli and her colleagues used corneal confocal microscopy to show the effectiveness of pancreatic transplantation in improving neuropathy in 20 patients with type 1 diabetes who had an average age of 41 years.

Before transplantation, the diabetic patients had significantly reduced corneal sensitivity as well as significantly lower nerve fiber density, nerve branch density, and nerve fiber length on corneal confocal micrographs, compared with 18 indi-

viduals without neuropathy who had an average age of 55 years.

At 6 months after transplantation, repeat scans performed in 11 of the patients who had neuropathy showed that nerve fiber density and length had improved significantly.

Other posttransplantation studies that have employed electrophysiology and quantitative sensory testing have been able to detect improvements in large fiber function after 3-4 years, unlike the early de-

tection of small fiber repair at 6 months in this study, Ms. Tavakoli reported.

In the laboratory of Nathan Efron, Ph.D.—one of Ms. Tavakoli's collaborators—the microscopy technique has proved to have sensitivity (71%) and specificity (77%) comparable with the histopathologic examination of skin punch biopsy specimens (59% and 90%, respectively) when both are compared with the "gold standard" Neuropathic Disability Score.

Dr. Efron has used confocal microscopy to monitor longitudinal changes in corneal morphology among patients who have received myopic laser in situ keratomileusis (LASIK), which involves cutting a flap of the cornea, irradiating the corneal stroma with a laser, and replacing the flap.

The LASIK procedure severs corneal nerves in the subbasal nerve plexus where most of the corneal nerves reside.

Several weeks after the surgery, confo-



Important Safety Information:

- Antidepressants increased the risk of suicidal thinking and behavior (suicidality) in short-term studies in children and adolescents with major depressive disorder (MDD) and other psychiatric disorders.
- Patients started on therapy should be observed closely for clinical worsening, suicidality, or unusual changes in behavior.
- Cymbalta is not approved for use in pediatric patients.

Cymbalta should not be used concomitantly with monoamine oxidase inhibitors (MAOIs) or thioridazine and not in patients with a known hypersensitivity or with uncontrolled narrow-angle glaucoma.

Clinical worsening and suicide risk: All adult and pediatric patients being treated with an antidepressant for any indication should be observed closely for clinical worsening, suicidality, and unusual changes in behavior, especially when initiating drug therapy and when increasing or decreasing the dose. A health professional should be immediately notified if the depression is persistently worse or there are symptoms that

*Cymbalta vs placebo ($P \leq .001$) by MMRM on 24-hr average pain severity score
Cymbalta vs placebo ($P \leq .009$) by MMRM on 24-hr night pain severity score

Reference: 1. Data on file, Lilly Research Laboratories: CYM20050314A, B&D.

cal microscopy shows a “hazy image” devoid of any nerve fibers. At 3 months, a few nerve fragments can be seen, and at 6 months a few continuous nerves begin to appear (Optom. Vis. Sci. 2003;80:690-7).

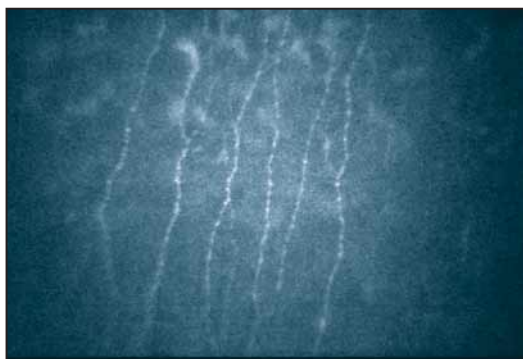
Other researchers have reported that it takes 5 years for corneal nerves to completely recover after LASIK (Am. J. Ophthalmol. 2005;140:1059-64).

“Certainly, this has implications with respect to diabetic patients who are having this LASIK procedure,” said Dr. Efron, research professor at Queensland University of

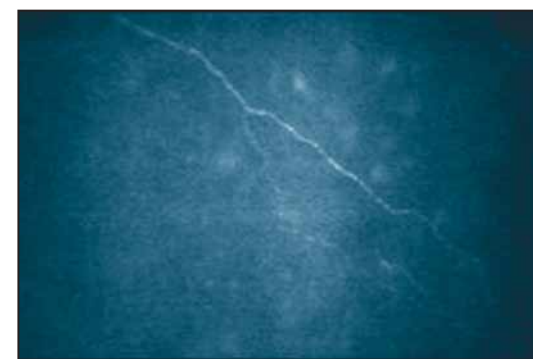
Technology, Brisbane, Australia.

Two second-generation corneal confocal microscopes are available, the \$80,000 ConfoScan4 (Nidek Co.) and the \$60,000 confocal laser microscope (Heidelberg Engineering GmbH), said Dr. Efron, who has no commercial interest in either device.

The Nidek microscope uses a white light source whereas the Heidelberg uses a laser light source, which provides “much better contrast” and is recommended by Dr. Efron, although it is a “little less user friendly.” ■



Corneal confocal microscopy offers a noninvasive alternative to many traditional diagnostics. This micrograph demonstrates nerves in a control patient without neuropathy.



Diabetic neuropathy was associated with progressive, significant reductions in corneal sensitivity, nerve fiber density (above), nerve branch density, and nerve fiber length.

PHOTOS COURTESY MITRA TAVAKOLI

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are severe, sudden, or were not part of the patient's presentation. If discontinuing treatment, taper the medication.

Cymbalta should not be administered to patients with any hepatic insufficiency or patients with end-stage renal disease (requiring dialysis) or severe renal impairment (CrCl <30 mL/min).

Postmarketing, severe elevations of liver enzymes or liver injury with a hepatocellular, cholestatic, or mixed pattern have been reported.

Cymbalta should generally not be prescribed to patients with substantial alcohol use or evidence of chronic liver disease.

Most common adverse events (≥5% and at least twice placebo) in MDD premarketing clinical trials were: nausea, dry mouth, constipation, fatigue, decreased appetite, somnolence, and increased sweating. Most common adverse events in diabetic peripheral neuropathic pain (DPNP) premarketing clinical trials were: nausea, somnolence, dizziness, constipation, dry mouth, increased sweating, decreased appetite, and asthenia.

See Brief Summary of full Prescribing Information, including Boxed Warning, on adjacent page.