

Alterations in corneal nerves following crack cocaine use mimic diabetes-induced nerve damage

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Summary

The use of *in vivo* confocal microscopy (IVCM) is rapidly emerging as an important clinical tool to evaluate changes in corneal sensory nerves as a surrogate measure for diabetic peripheral neuropathy. Commonly used metrics to document and grade the severity of diabetes and risk for diabetic peripheral neuropathy include nerve fiber length, density, branching and tortuosity. In addition to corneal nerves, thinning of the retinal fiber layer has been shown to correlate with the severity of diabetic disease. Here, we present a case report on a pre-diabetic 60-year-old native American woman with abnormal corneal nerve morphology and retinal nerve fiber layer thinning. Her past medical history was positive for illicit substance abuse. IVCM showed a decrease in nerve fiber density and length, in addition to abnormally high levels of tortuosity. OCT revealed focal areas of reduced retinal nerve fiber layer thickness that were asymmetric between eyes. This is the first report of abnormally high levels of tortuosity in the corneal sub-basal nerve plexus in a patient with a past history of cocaine abuse. It also demonstrates, for the first time, that illicit substance abuse can have long-term adverse effects on ocular nerves for years following discontinued use of the drug. Studies using IVCM to evaluate changes in corneal nerve morphology in patients with diabetes need to consider a past history of illicit drug use as an exclusionary measure.

Learning points:

- Multiple ocular and systemic factors can impede accurate assessment of the corneal sub-basal nerve plexus by IVCM in diabetes.
- Although current history was negative for illicit substance abuse, past history can have longstanding effects on corneal nerves and the retinal nerve fiber layer.
- Illicit drug use must be considered an exclusionary measure when evaluating diabetes-induced changes in corneal nerve morphology and the retinal nerve fiber layer.

Background

Corneal confocal microscopy is rapidly emerging as an important clinical tool for the evaluation of corneal nerve morphology. Studies worldwide have repeatedly shown correlations between loss of the sub-basal nerve plexus and the development of diabetic peripheral neuropathy (1). These findings have been further validated in animal

models. Common metrics that have been used to quantify diabetes-related changes in the corneal sub-basal nerve plexus include corneal nerve fiber length, density, branch points and tortuosity (1). Similar to changes in the sub-basal nerve plexus, alterations or thinning of the retinal nerve fiber layer have also been reported in patients with



diabetes (2). Importantly, in both the cornea and retina, alterations in nerve morphology and thickness have been shown to correlate with disease severity (2).

It is well known that abuse of topical cocaine-derived anesthetics that are routinely used in clinical practice can result in corneal sensory nerve impairment, severe epithelial defects and in some cases, neurotrophic keratopathy (3). Similar to topical use, systemic administration of cocaine has been found to be associated with adverse ocular damage when used recreationally (4, 5). Today, nearly 5 million Americans use cocaine regularly, making it one of the most trafficked illicit drugs in the United States, second only to cannabis. Currently known manifestations of systemic use of cocaine in the eye include corneal epithelial defects that range from mild superficial punctate keratitis to more severe corneal epithelial defects and ulceration (4, 5, 6). The corresponding impairment of corneal sensitivity leads to reduced tear production and dry eye (5).

Prior studies have also shown that patients who use crack cocaine have an increased likelihood of optic neuropathy, retinopathy, retinal artery occlusion, intraretinal hemorrhages and transient monocular blindness (5, 7). It has also been suggested that patients who use crack cocaine have an increased likelihood for glaucoma-like retinal nerve fiber defects (8). A recent study reported on the effects of cocaine snorting on ocular surface damage (5). In their study, the authors investigated the effects of cocaine in habitual addicts and reported reduced corneal sensitivity and a decrease in corneal sub-basal nerve plexus fiber length using IVCN. In the current case, we report on highly abnormal corneal nerve morphological changes in a patient with a past medical history for crack cocaine use who also demonstrated changes in the retinal nerve fiber layer. These findings suggest that the ocular effects of systemic cocaine mimic those of diabetes and are long term and irreversible.

Case presentation

A 60-year-old native American woman presented to an ophthalmology outpatient clinic at the James W. Aston Ambulatory Care Center of The University of Texas Southwestern Medical Center (Dallas, TX, USA). She presented to the clinic as a research participant. Written informed consent was acquired prior to her participation in the study. All procedures were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center (Dallas, TX, USA) and in accordance with the Declaration of Helsinki. Her past medical history was positive for

pre-diabetes, hypothyroidism, hyperlipidemia, diverticulitis, depression, restless leg syndrome and chronic back pain. Her past ocular history was unremarkable and negative for contact lens wear. She was currently taking levothyroxine (112 µg/day). Anthropometric measurements revealed neck, hip and waist circumferences of 15, 44.5 and 40 inches, respectively. Her body mass index (BMI) was 29.7, classifying her as borderline obese. She currently smokes ½–1 pack of cigarettes per day. She had a previous history of substance abuse that included a 7-year history of marijuana, acid and psilocybin use and a 4-year history of crack cocaine abuse that ceased ten years prior. She denies any history of intravenous drug use.

Investigation

Biomicroscopic examination of the cornea and eyelids revealed trace erythema in the lids and lashes, moderate lid margin telangiectasia and blepharitis, mild conjunctival hyperemia and moderate conjunctival chalasis. Her pinhole visual acuity with habitual correction was 20/25 –1 OD and 20/20 –1 OS. She had grade 2 inferior corneal staining in each eye, defined as macropunctate staining with some coalescent areas. Her tear fluorescein break-up time (less than 5 s OU) and Schirmer's test without anesthesia (average 6.5 mm OU) were indicative of mild-to-moderate dry eye. This diagnosis was supported by an ocular surface disease index score of 30.0. Corneal sensitivity testing using a Cochet–Bonnet Aesthesiometer (Luneau Ophthalmologie, Chartres, France) was 45 mm in the central cornea, which was slightly below normal for her age. She had no evidence of diabetic retinopathy. Laboratory examination revealed her C reactive protein was high (19.9 mg/L) and her hemoglobin A1c was slightly elevated at 6.3% at this visit, classifying her as pre-diabetic. Upon subsequent examination three months later, her hemoglobin A1c was 5.8%, supporting her diagnosis of pre-diabetes. Her laboratory findings were consistent for her diagnosis of high cholesterol. At the time of examination, her cholesterol/HDL ratio was 7.9 and her lipid panel showed a total cholesterol of 291 mg/dL, HDL 37 mg/dL, triglyceride 176, LDL cholesterol 219 mg/dL and non-HDL cholesterol 254 mg/dL. Her thyroid function testing at the approximate time of her visit showed a TSH level of 21.45 IU/L and a free T4 of 0.7 ng/dL. Normal reference values in our laboratory are 0.40–4.50 IU/L and 0.8–1.8 ng/dL for TSH and free T4 respectively, supporting her diagnosis of hypothyroidism.

IVCM was performed using a HRT II with Rostock Cornea Module (Heidelberg Instruments) modified

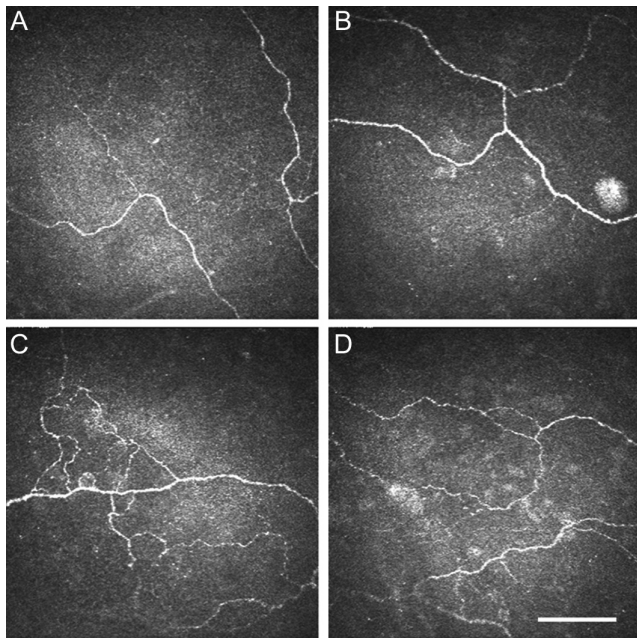


Figure 1
IVCM of the corneal sub-basal nerve plexus demonstrating tortuosity in a former crack cocaine addict. (A, B, C and D) Representative images from the paracentral cornea showing focal areas of thin nerve fibers that are highly tortuous. Scale bar: 100µm.

for remote controlled scanning and real-time image streaming. Twenty live streamed volume files were acquired within her paracentral (>6mm) and central cornea (6mm). The cornea was scanned horizontally beginning superiorly and moving inferiorly with each subsequent passage. Her IVCM scans were analyzed for the following: nerve fiber length and density, tortuosity (short term and long term), basal epithelial cell density, and dendritic cell density using MetaMorph (Molecular Devices, Sunnyvale, CA, USA) and the online program ImageJ (National Institutes of Health). Analyses of her

IVCM images showed focal areas of abnormally increased tortuosity (Fig. 1A, B, C and D), whereas adjacent regions showed nerves that were long, straight and much fewer in number. In some regions, only one linear nerve fiber was present. OCT was performed using Spectralis Tracking Laser Tomography (Heidelberg Engineering, Heidelberg, Germany). Her OCT examination revealed asymmetric focal regions of borderline thinning of the retinal nerve fiber layer OD and OS (Fig. 2).

Treatment

No treatment was administered as this was a single visit, cross-sectional, non-interventional study.

Discussion

This is the first report showing abnormally high levels of tortuosity in the corneal sub-basal nerve plexus by IVCM in a patient with a long-term history of crack cocaine use. Interestingly, these anatomical changes in nerve morphology persisted 10 years after cessation of use. It is well documented from prior reports that the systemic use of crack cocaine can result in significant epithelial defects, the most well-known being the syndrome ‘crack eye’. In their cases series, Sachs *et al.* reported that crack cocaine use results in an impairment in corneal nerve function and a corresponding decrease in the integrity of the corneal epithelium (4). In addition to direct effects on trigeminal nerve function, other reports of ocular surface changes associated with crack cocaine use, including epithelial defects and infectious corneal ulceration, are thought to be caused by eye rubbing due to crack cocaine smoke or other side effects of drug use (4). More recently, Mantelli *et al.* evaluated a series of current cocaine and

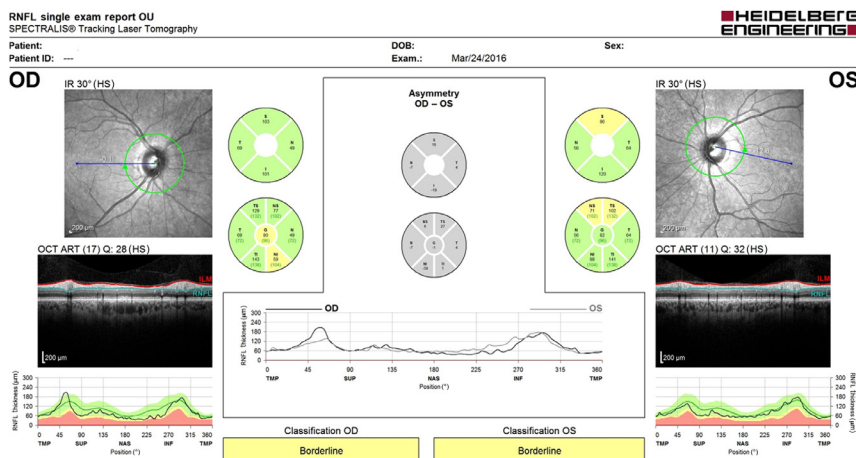


Figure 2
Optical coherence tomography showing thinning of the retinal nerve fiber layer. Focal asymmetries were noted between OD and OS.



heroin addicts for ocular surface disease (5). In this report, use of cocaine for a minimum of one year prior to the examination was considered an inclusion criterion for the study. They found that cocaine use had the greatest impact on loss of corneal sensitivity and reflex tear secretion when compared to heroin or the non-drug controls. In six of their cocaine addicts, IVCN was performed using a Confoscan confocal microscope to evaluate morphology of the sub-basal nerve plexus. In habitual cocaine addicts, they reported a decrease in nerve fiber length and branching that appeared to correspond to a reduction in corneal sensitivity.

In contrast to their findings, our patient denied any cocaine use within 10 years of the examination. Although few patchy areas with decreased nerve fiber length and branching were evident, large regions of the cornea both superiorly and inferiorly showed thin, highly tortuous nerves with intricate nerve branching patterns. We speculate that this abnormally tortuous nerve morphology may be due to attempted nerve regeneration after the cessation of drug use. Corneal sensitivity, measured by mechanical touch, was slightly low for her age and would be consistent with the reduced nerve fiber density noted in her scans. This could be due to her history of long-term drug use, but may also be confounded by her hypothyroid disease. The effects of hypothyroid disease on corneal sensitivity are unknown. Most ocular effects of thyroid eye disease are due to chronic exposure of the cornea due to lower lid retraction, increased vertical height of the palpebral fissure and lagophthalmos due to the presence of significant exophthalmos. This patient presented with none of those clinical findings. When evaluating her sensitivity, it is important to consider the limitations of use associated with the Cochet–Bonnet Aesthesiometer, including its low sensitivity and detection threshold. In addition, corneal sensitivity measures using touch thresholds do not always correspond clinically to measures of corneal nerve morphological parameters. Our studies using three-dimensional nerve modeling in the diabetic mouse cornea have shown that patchy loss of the corneal sub-basal nerve plexus occurs prior to loss of the branching terminal epithelial nerve fibers that run anteriorly toward the cornea (9). This finding, applied to the human, may explain why her decrease in corneal sensitivity was not more severe despite her highly abnormal nerve morphology.

Interestingly, in addition to corneal nerve abnormalities, the patient also presented with focal asymmetries in the retinal nerve fiber layer between eyes,

as measured by OCT. This finding is in concert with a study performed in the mid-nineties that analyzed 60 crack cocaine addicts and demonstrated significant retinopathy and retinal nerve fiber changes (8). Electron microscopic studies of the optic nerve in response to cocaine exposure in neonatal rats demonstrated that the number of axons was not altered (10). Instead, there was an increase in small-sized axons in cocaine-exposed rats with fewer large-sized axons compared to that in controls. An effect such as this may account for the borderline changes in nerve fiber layer thickness seen in our patient. Likewise, in the rat retina, visually apparent changes viewed by light microscopy were not evident, but electron microscopic studies revealed a greater frequency of degenerated ganglion cells in the cocaine-exposed animals compared to controls (10). Although visual field testing was not performed in our study, it would be interesting to see if the thinning of the retinal nerve fiber layer measured by OCT corresponded to any changes in the visual field.

In summary, the surprising and key finding in this report is that ten years after cessation of crack cocaine abuse, nerve abnormalities in both the cornea and retinal nerve fiber layer persisted and failed to return to age-normal levels; decreased corneal sensitivity also persisted. Given the patient's current and past medical history, her previous cocaine abuse is the most likely explanatory factor for the gross morphological changes that are present in the corneal sub-basal nerve plexus. However, the potential for her long-term history of marijuana, acid and psilocybin abuse to have adversely influenced her corneal nerves cannot be ruled out. Inarguably, IVCN is rapidly becoming a widely used non-invasive clinical tool to evaluate corneal nerve morphology in patients with diabetes. This case represents the importance of obtaining a thorough case history on any patient who is undergoing nerve evaluation by IVCN, including a history of current and past illicit drug use, which can mimic many of the adverse ocular changes reported in diabetes.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

This work was funded by the National Eye Institute (EY024546 (D M R), EY024333 (D M R)), National Eye Institute Core grant for Vision Research (EY020799) and an unrestricted grant from Research to Prevent Blindness, New York, NY, USA.



Patient consent

Written informed consent was acquired prior to her participation in the study. All procedures were approved by the Institutional Review Board at the University of Texas Southwestern Medical Center (Dallas, TX, USA) and in accordance with the Declaration of Helsinki.

Author contribution statement

D M R designed the study, conducted the clinical examinations and wrote the manuscript. W L S performed the nerve analysis and contributed to writing the manuscript. B K G coordinated the research study, assisted with clinical data acquisition and contributed to writing the manuscript.

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Received in final form 3 February 2017

Accepted 10 February 2017