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Successful reversal of neuropathic eye pain by treatment of occult ocular surface disease: Case series and implications

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ABSTRACT

Purpose: To report the successful approach to managing neuropathic dry eye-like pain (NP) in three consecutive patients described as severe: 1) "burning fire," "burning acid," and "horrible burning pain" with hyperalgesia and allodynia, 2) refractory to topical anesthetic (TA), and 3) without surface hyperemia nor vital staining.

Observations: Two of three patients' pain was reversed with significant symptom relief within 48 hours by identification of occult obstructive Meibomian gland dysfunction (o-MGD) and treatment using Meibomian gland probing (MGP) with intraductal steroid lavage ($MGP_{(s)}$) and aqueous tear deficiency (ATD) treated with punctal thermocautery (PO). The third patient's pain was reversed within one week after treatment of superior conjunctivochalasis (CCh) using amniotic membrane surface reconstruction and ATD using PO with subsequent MGP and $MGP_{(s)}$ for o-MGD.

Conclusions and importance: It has been generally thought that central (NP) is strongly suggested by triad of 1) severe chronic burning pain with hyperalgesia and allodynia, 2) refractory to TA with 3) minimal signs. In this three-case series, treatment of *occult* surface disease consistently led to symptom reversal. Results may represent salutary effect of successful treatment to suppress nociceptive inflammation leading to reversal of central NP. Alternatively, the current triad of diagnostic criteria may be unable to differentiate centralized NP from peripheral sensitization alone, thereby requiring rigorous examination to uncover occult, yet treatable, surface disease to restore eye comfort and reverse psychosocial sequelae when possible. Furthermore, rigorous targeting of surface disease in patients with this pain triad may obviate unnecessary systemic treatments with associated risks of serious side effects.

1. Introduction

The current conventional thinking is that ocular surface disease may present with both nociceptive and neuropathic symptoms.[1–10] Nociceptive symptoms, which are a normal physiologic response to a noxious stimulus, may arise from microtrauma between the lid wiper and ocular surface during movements of the upper lid in the setting of inadequate lubrication.[11] This mechanical stress would then initiate the inflammatory cascade through the triple response of Lewis,[12] leading to inflamed lid and superior bulbar surfaces.[13,14] The TFOS DEWS II Pain and Sensation Report states that in this setting, the mechanical stress generated by blinking on superficial epithelial cells injures and inflames terminal nerve branches.[14] Inflammation of ocular surface nerves may also lead to an increased sensitivity of these nerves (neuropathic peripheral sensitization).[1–8,13,14] With chronicity, this can result in central sensitization (CS) with central neurons demonstrating a heightened level of pain awareness and responsiveness.[15] CS presents to the physician as pain disconnected to peripheral signs such as vital staining or hyperemia. CS may be characterized by allodynia (pain from non-noxious stimuli) or hyperalgesia (enhanced pain response to subthreshold noxious stimuli) and can lead to constant pain.[16] CS with neuropathic pain is thought to *not* respond to topical anesthetics (TA), which do relieve peripheral sensitization.[1,7,10,15] The ability of TA to differentiate peripheral from CS was emphasized by Dieckmann et al.[13] who wrote that patients not responding to proparacaine suffer, at least in part from central NP (although they were referring to cornea rather than conjunctiva, the concept is the same for all ocular surface somatosensory nerves). Causes or factors leading to CS and central NP, as seen in patients of this case series, include dry eye disease, recurrent erosion syndrome (RES), LASIK, and long term contact lens wear (CLW).[15] Such unrelenting pain contributes to psychosocial problems such as anxiety, stress, depression and even suicidal ideation leading to increasing use of systemic medications with potent addictive properties and other side effects.

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During a 4 month period, this author has managed three patients with the diagnostic triad of (1) severe global burning pain (2) refractory to TA,[5] (3) with no redness and no staining on examination. With typical characteristics of centralized NP and minimal signs of surface disease, these patients had been diagnosed and placed on NP treatment elsewhere. The diagnosis of CS and NP was confirmed in this office based on history, functional somatosensory testing to TA and initial clinical examination.[15] Subsequent treatment of occult surface disease[17] led to reversal of neuropathic symptoms. Specifically, within one week after treatment, each patient's severe pain showed complete resolution with TA. This suggests reversal of CS with residual symptoms of peripheral disease successfully anesthetized with TA. Within three weeks follow-up, these patients enjoyed significant reduction in symptoms without needing TA for relief. The detailed representative case study of one of these patients, with additional abbreviated description of two other cases, describe the successful identification of the location of the occult source of inciting nociceptive inflammation using concepts of 1) evoked signs and 2) altered presenting symptoms, followed by targeted treatment.[18] It is theorized that suppression of nociceptive activity through targeted treatment of occult ocular surface disease (OSD) led to reversal of neuropathic changes, a phenomenon described by Galor.[6,10,18] Interestingly, a literature search showed experimental NP in animal models can be reversed, without opioid use, in less than one week.[19–22]

2. Findings

2.1. Case 1

A middle aged woman presented to this author with a 2 year history of chronic dry eye symptoms including sandy, gritty, heavy and tired eyes with dryness on top of eyes, as well as a severe global burning acid sensation like cut onions with constant sensation of a fan blowing into her eyes (hyperalgesia) with light sensitivity (photo allodynia). The eyes were equally affected. She had a history of RES of the right cornea, nocturnal lagophthalmus and meibomian gland dysfunction. She had been treated with bedtime lubrication ointment and sleep goggles, omega 3 fatty acids, lid hygiene with warm compresses and Meibomian gland (MG) expression, artificial tears, steroid drops, muro 128 ointment, vitamin A ointment, tetracycline, doxycycline, ikervis (cyclosporin A preservative free emulsion), blepharo-exfoliation, and Blephasteam® goggles. She denied prior use of Accutane, history of contact lens use or eye surgery. She had previously seen 7 eye doctors and had symptom severity of 10 at times, on a scale of 0–10 (10 is worst pain imaginable inconsistent with life) that kept her home several days every week. During her recent exam two months prior to presentation to this author, *her doctor noted that topical anesthetic had no effect on her burning pain.* The patient did note this topical anesthetic numbed her throat.

Additional history obtained from her husband revealed the patient frequently manipulated the upper lids as though to raise them off her globes. She would also subconsciously move her eyes into different gaze positions while talking with people as if trying to find a comfortable position.

Surgical, family and social history were unremarkable. There were no known allergies. Her review of symptoms was remarkable for low serum thyroid hormone levels for the past 9 years for which she was being supplemented. She had a history of being treated with antidepressants more than 10 years earlier. She had a recent elevated prolactin level and stated that she had hair on her chin for the past 6 years. Her menses were normal and she was not overweight, nor pregnant.

The patient appropriately appeared somewhat anxious related to her chronic refractory pain. Examination of both eyes by this author was remarkable for good vision, no tarsal nor bulbar hyperemia, and no fluorescein staining on her ocular surfaces nor lid wipers. She did have bilateral decreased tear meniscus with trace mucus and conjunctivochalasis inferior-temporally and superior-temporally. The right cornea showed focal anterior basement membrane dystrophy with superficial fibroses at the presumed site of prior recurrent erosion. Tear break up times were immediate in the right eye over the focal basement membrane change and 5 seconds in the left eye. Gentle anterior to posterior manipulation of the upper lids with the globes in downgaze was able to evoke a rapidly appearing occult 3+ superior bulbar hyperemia with irritation. The lids were not tender. Further evaluation showed no improvement of burning symptoms to topical antihistamine or lipid emulsion drops. Importantly, as noted by one of her previous eye doctors, *topical anesthesia did not reduce her burning pain in either eye.*

Microbiologic studies were negative for Demodex. Fluorescein clearance test showed bilateral aqueous tear deficiency without reflex tear of the right eye.[23] There was no delayed tear clearance. There were 12 and 9 expressible glands (EG) in right upper (RU) and lower (RL) lids respectively, and 17 and 16 EG in left upper (LU) and lower (LL) lids respectively. Infrared meibography showed Grade 2 atrophy for right upper and lower lids and Grade 3 atrophy for left upper and lower lids[24] with whole gland (RU) and proximal gland dropout (atrophy) in all four lids. Confocal microscopy of upper lid showed findings consistent with varying degrees of periductal fibroses and rete ridge inflammation.[17,18,25] (Fig. 1).

Diagnosis included CS with NP in the setting of bilateral aqueous tear deficiency, o-MGD, superior CCh with elicitable occult hyperemia,[13,23] nocturnal lagophthalmus, history of RES with focal cornea basement membrane dystrophy and fibroses right eye and hirsutism of chin with elevated serum prolactin in the setting of hypothyroid status on thyroid supplements.

Treatment focused on increasing tear volume with PO, and treating meibomian gland dysfunction with MGP with adjunctive $MGP_{(s)}$.[18,24,26–28] Probing revealed occult intraductal fixed, firm, focal unyielding (FFFUR)[17] obstruction in over 92% of glands in RU, LU and LL with 65.5% of glands in RL. (Average frequency of intraductal obstruction noted during initial probing for patients with clinical o-MGD ranges from 75% of glands in the upper lids to 55% of glands in the lower lids).[27] Bedtime lubricant ointment and sleep goggles were continued. Two days later the patient returned with relief of sandy and gritty symptoms, however some burning pain persisted. Numbers of expressible glands increased to 25, 19, 27 and 24 for RU, RL, LU and LL respectively. However, on this exam, *topical anesthetic drops reduced the bilateral global "burning acid" pain significantly to 2 out of 10. Raising the upper lids off the globes completely eliminated all burning pain.* The patient returned the next day with the same result—the "burning acid" pain was completely relieved with TA and raising the upper lids off the globes. Interestingly, there was a spatial and chronological relationship of the numbing effect of the TA. First, the feeling of dryness and burning on top of the eye was resolved, followed by resolution of burning nasally, then elsewhere. Once the anesthetic wore off, this was further investigated by employing an in-office diagnostic evaluation with a 20mm Kontur soft contact lens which significantly reduced burning by about 35%. A normal diameter bandage contact lens did not reduce burning. Follow up 10 days later revealed a 50–60% reduction in pain. Three weeks after her initial visit revealed a further reduction in pain to an overall reduction in pain by 50–80% (Fig. 2, Table 1).

2.2. Abbreviated case 2

A middle-aged woman with 5 month history of global "horrible burning pain" OD > OS plus hyperalgesia and photoallodynia post LASIK OD presented to this author after numerous failed treatments including artificial tears and steroid drops (and Medrol dose pak), doxycycline, omega 3 fatty acids, restasis, xiidra, azasite, inferior punctal plugs and Prokera x 5. She had been diagnosed elsewhere as a case of central NP and put on autologous serum (AS), Gabapentin, Lexapro and Lorazepam. There was no prior history of mental illness. Exam by this author was remarkable for minimal inferior perilimbal

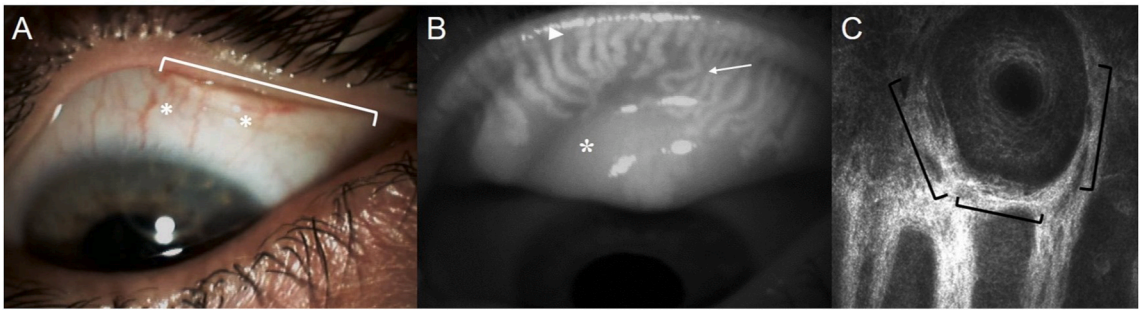

Fig. 1. Case 1 Exam Findings.
(A) Superotemporal CCh (bracket) left eye with upper lid mobilization and secondary irritation plus 1+ superior bulbar hyperemia (asterisk) which rapidly increased to 3+ severity (not shown). (B) Infrared-Meibography showing advanced MG atrophy with proximal (asterisk), whole gland (arrow head) and discontinuous (arrow) atrophy. (C) CFM of left upper lid MG orifice showing periductal fibrosis with flattening of external duct wall (brackets).

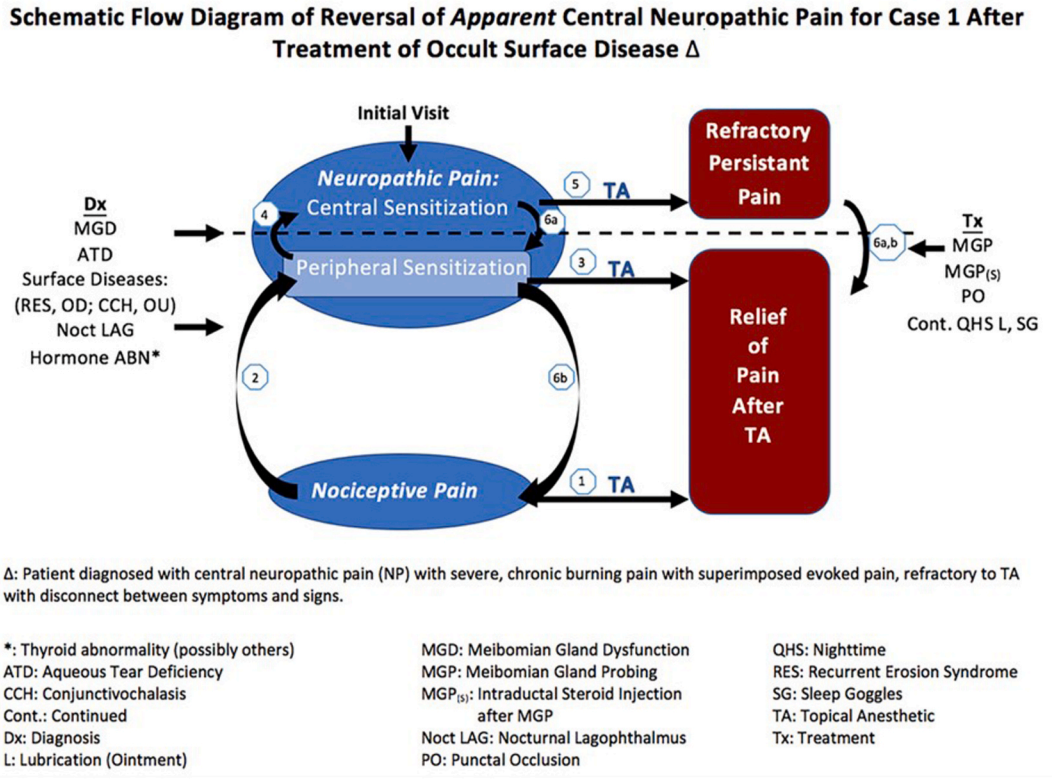

Fig. 2. Schematic Flow Diagram of Reversal of *Apparent* Central Neuropathic Pain for Case 1 After Treatment of Occult Surface Disease
These cases suggest a reversibility of neuropathic pain refractory to topical anesthetic by uncovering and reversing persistent tear, surface and Meibomian gland abnormalities.
Persistent nociceptive (physiologic) inflammation and pain, which is relieved with topical anesthetic (TA) (1), may lead to (2) neuropathic pain (NP). NP can be thought of as peripheral sensitization with hypersensitive peripheral nerves that do respond to TA with resolution of pain (3). With chronicity, peripheral sensitization progresses to central sensitization (4) which is considered refractory to TA with resultant persistent pain (5).
This case series shows that treatment of occult surface disease can lead to reversal of apparent centralized NP (6a,b), perhaps by suppressing long standing occult nociceptive inflammation. Alternatively, the functional somatosensory test of persistent pain after TA, as well as a disconnect between symptoms and signs, are not sufficiently specific to differentiate central from peripheral sensitization.

erosion post Prokera OD, o-MGD and superior CCh. There was no bulbar or tarsal hyperemia nor fluorescein staining elsewhere including lid wiper OU. Her pain was refractory to TA and the diagnoses of central NP was confirmed. Further testing showed ATD without reflex tear, presence of lid tenderness, meibomian gland cystic changes with proximal atrophy on IR-video meibography, rete ridge inflammation with periductal fibroses on confocal microscopy and greater than 92% of Meibomian glands demonstrated occult FFFUR found during MGP in three of four lids. Importantly, on exam, gentle anterior to posterior manipulation of the upper lids with the globes in downgaze was able to evoke a rapidly appearing occult 3+ superior bulbar hyperemia.[18] Treatment of occult OSD with MGP plus adjunctive MGP(s) and PO x four led to relief of global burning pain without TA by 24 hours post procedure. By one month patient had discontinued AS, Gabapentin and Lexapro and was tapering off Lorazepam (Table 1). She remained pain free at 9 weeks follow up.

Table 1
Case series data.

Case	#1	#2	#3
Demographics	Middle aged woman	Middle aged woman	Middle aged woman
Duration	2 years (chronic)	5 months (chronic)	2 years (chronic)
Worse Sx	Global "Burning Acid" Photoallodynia Hyperalgesia	Global "Horrible Burning Pain" Photoallodynia Hyperalgesia	Global "Burning Fire" Allodynia Hyperalgesia
Effect of TA*	Refractory with no effect and 10/10 severity	Refractory with no effect and 6/10 severity	Reduced but persistent 4/10 severity
History	•DED •RES[13] (OD) •NL •MGD	•s/p LASIK[13] (OD) •Hx Accutane (remote)	•DED •SDWCTL[13] (31 yrs)
Failed Treatments	•AT •Steroid •Muro 128 ung •VitA ung •Tetracycline •Doxycycline •LH with WC and MGE •Ω-3-FA •qhs ung/goggles •Ikervis •Blepharo-exfoliation •Blephasteam® goggles	•AT •Steroid (topical and oral) •Doxycycline •Ω-3-FA •Restasis •Inferior PP •Xiidra •Azasite	•AT •Steroid •Doxycycline •Ω-3-FA •Restasis •Inferior PP •Xiidra •Bromsite •Bepreve •Cliradex •PF Systane ung •Moved from dry to humid climate
Past Neuropathic Pain Treatment	None	•AS •Lorazepam •Gabapentin •Lexapro •Prokera x 5	•AS •Lorazepam •Clonazepam •Prokera
Pertinent Exam Findings	•No FL staining •No hyperemia •Reduced TM •CCH S/I •TBUT immediate (OD), 5 (OS)	•Perilimbal PEE from 3 to > 9 o'clock (OD), 2° to Prokera? •No hyperemia •CCH S/I •TBUT immediate (OD)	•No FL staining •No hyperemia •Reduced TM •CCH S/I •TBUT 2 (OD), 3 (OS)
Tests			
EVOKED SIGN[Δ]	Superior Bulbar HyP with irritation	Superior Bulbar HyP with irritation	Superior Bulbar HyP with irritation
FCT	ATD with no reflex	ATD with no reflex	ATD with no reflex
LT	None	Present	Present
EG	12/9 (OD) 17/6 (OS)	14/15 (OD) 16/20 (OS)	14/12 (OD) 12/16 (OS)
IR-M	•Cystic (OU) •Atrophy grade: 2 (RU), 3 (LU) •Atrophy: proximal (OU), whole gland (RU)	•Cystic (OU) •Atrophy grade: 2 (RU), 1 (LU) •Proximal Atrophy (OU)	•Cystic (OU) •Atrophy grade: 1 (OU) •Proximal Atrophy (OU)
CFM	•Severe rete ridge inflammation •Periglandular fibrosis	•Severe rete ridge inflammation •Periglandular fibrosis	•Severe rete ridge inflammation •Periglandular fibrosis
MGP Findings[+]	≥92% RU, LU, LL 65% RL	>92% RU, RL, LL 84% LU	>92% RU, RL, LL 85% LU
Treatment	•PO x 4 •MGP •$MGP_{(s)}$	•PO x 4 •MGP •$MGP_{(s)}$ •OSR with AMT for CCH	•PO x 4 •OSR with AMT for CCH •MGP •$MGP_{(s)}$ •Pazeo
Result after Treatment	•Elimination of centralized sensitization of global burning pain, hyperalgesia, and photo allodynia by 48 hrs	•Central sensitization symptoms and peripheral symptoms relieved without TA by 24 hrs post MGP,	•Central sensitization symptoms and peripheral symptoms relieved without TA by 1 wk post treatment
	•TA reduced peripheral symptoms to 2/10 and with LR reduced to 0/10 by 48 hrs post treatment •50–80% peripheral symptom relief without TA by 3 wks	$MGP_{(s)}$, and PO •D/C AS, gabapentin, and Lexapro and decreased Lorazepam by 1 month •Remained pain free at 9 weeks follow up	•D/C AS •Lorazepam prn •Clonazepam daily •Remained pain free at 11 weeks follow up

AMT: Amniotic membrane transplant
AS: Autologous serum
AT: Artificial tear drops
ATD: Aqueous tear deficiency
CCH: Conjunctival Chalasis
CFM: Confocal microscopy
EG: Expressible glands (upper/lower)
D/C: Discontinued
DED: Dry Eye Disease (Chronic)
FA: Fatty acid
FCT: Fluorescein clearance test
FL: Fluorescein
HyP: Hyperemia
IR-M: Infrared-meibography
LL: Left lower lid
LR: Lid retraction
LT: Lid tenderness
LU: Left upper lid
MGE: Meibomian gland expression
MGP: Meibomian gland probing
$MGP_{(s)}$: Meibomian gland probing with intraductal steroid injection
NL: Nocturnal lagophthalmous
OD: Right eye
OS: Left eye
OSR:Ocular surface reconstruction
OU: Both eyes
PEE: Punctate epithelial erosions reconstruction
PF: Preservative free
PO: Punctal occlusion with thermocautery PP: Punctal plugs
prn: as needed
qhs: bedtime
RES: Recurrent erosion syndrome
RU: Right upper lid
RL: Right lower lid
S/I: Superior/Inferior
s/p: Status post
SDWCTL: Soft daily wear contact lens
Sx: Symptoms
TA: Topical anesthetic
TBUT: Tear break-up time
TM: Tear meniscus
ung: ointment
WC: Warm compress

* Severity out of possible 10. 10/10 is worse pain imaginable where patient does not want to live.
[Δ] Clinical sign elicited with gentle anterior to posterior manipulation of upper lids with globe in down gaze.
[+] % of glands with fixed intraductal obstruction.

2.3. Abbreviated case 3

A middle-aged woman with chronic dry eye and a 2 year history of "burning fire" OS > OD plus hyperalgesia and allodynia with a 30 year history of soft daily wear contact lenses, presented to this author after numerous failed treatments including artificial tears, topical steroid, doxycycline, omega 3 fatty acids, Restasis, Xiidra, inferior punctal plugs, Bromsite, Prokera, Bepreve, Cliradex, and PF Systane ointment. She had been diagnosed with central NP and put on AS, Lorazepam and Clonazepam. There was no prior history of mental illness. With no symptom improvement, she and her husband then moved from a dry to a more humid environment, again without improvement. Initial exam by this author was remarkable for a lack of bulbar and tarsal hyperemia with presence of superior CCh and o-MGD. There was no fluorescein staining of either cornea or conjunctiva including lid wipers OU. With TA, she had persistent although reduced severe burning and the diagnosis of combined central and peripheral NP was confirmed. Subsequent tests showed ATD without reflex tear, presence of lid tenderness, meibomian gland cystic changes with proximal atrophy on IR-video meibography, rete ridge inflammation with periductal fibroses on confocal microscopy and greater than 92% of glands demonstrating occult FFFUR found in three of four lids during MGP. Importantly, on exam, gentle anterior to posterior manipulation of the upper lids with the globes in downgaze was able to evoke a rapidly appearing occult 3+ superior bulbar hyperemia.[18] She was treated for her OSD with ocular surface reconstruction (OSR) using amniotic membrane, PO times four, Pazeo, and

subsequent MGP with adjunctive MGP(s). Symptoms were relieved without need for TA by 1 week post treatment (OSR) and she was able to discontinue autologous serum and Lorazepam (Table 1). She remained pain free at the 11 week follow up.

3. Discussion

It has been written that diagnosis and therapy of NP in the patient with dry eye is challenging and more easily dismissed than addressed.[1] As detailed above, in three consecutive cases of *apparent* centralized ocular surface NP refractory to TA and without redness or vital staining, occult OSD was identified, which when treated led to elimination of centralized neuropathic symptoms including severe burning pain. Sensitization appeared to have emanated from ocular surface nerves of the superior bulbar surface and lid wiper, and Meibomian glands rather than corneal nerves. In the detailed representative case presented, clues to help localize nociceptive disease included (1) the history of dryness on top of eyes, and (2) history provided by husband of the patient manipulating her upper lids and moving eyes in different gaze positions seemingly to find comfort. In addition to the history, there were key supplemental diagnostic examinations helpful in making and localizing this diagnosis because there were no initial signs to explain the severe pain. These supplemental examinations were able to *evoke* signs and *alter* presenting symptoms which confirmed the location of the sensitized surface nerves. Evoked pain over the initial site of injury is a common feature in patients with neuropathic pain. This pain can be evoked by light touch which normally would not cause pain (allodynia).[16] These exam findings included (1) evoked occult irritability and hyperemia of the superior bulbar surface *only* when gently moving the upper lid anterior to posterior over this area, (2) the two-day follow-up response to treatment using MGP, $MGP_{(s)}$, and PO where all symptoms were relieved by TA along with lifting the upper lid off her superior globe, (3) symptom reduction, without topical anesthetic, by using 20 mm Kontur contact lens on two-day follow-up exam after MGP, $MGP_{(s)}$, and PO, with no improvement using normal diameter contact lens. Importantly, Meibomian gland probing of case 1 demonstrated and relieved *occult fixed, unyielding proximal gland intraductal obstruction in over 92% of glands of each upper lid* despite no lid tenderness and presence of expressible glands.[17,24] Case 2 and 3 also showed *occult fixed unyielding proximal intraductal obstruction in over 92% of the MG's in the right upper and both lower lids with 84% and 85% respectively of the MG's of the left upper lid.* Confocal microscopy showed severe rete ridge inflammation in all cases with periductal fibroses. Obstructed and inflamed glands may cause lid congestion with blink induced mechanical stress to bulbar surface tissues particularly in the setting of co-morbid CCh and ATD.[11,24,26] Moreover, inadequate lubrication may lead to o-MGD creating a cycle of lid and surface inflammation. In this case series, the superior bulbar surface and lid wiper were sites of occult mechanical stress, without initial signs such as hyperemia, or staining on conjunctival or lid wiper surfaces.[14] Lack of clinical signs is a hallmark of centralized NP resulting from hypersensitization of somatosensory nerves, with superimposed chronic inflammation.[15] Additionally, it is generally thought that symptoms refractory to topical anesthetic represent CS.[1,7,15] The ability to differentiate peripheral from central sensitization using TA was recently emphasized by Dieckmann et al., who recently wrote that patients not responding to proparacaine suffer, at least in part from central NP.[15] Taken together, the findings of these cases strongly suggest pain from CS.

The other diagnostic possibility is that the generally accepted current criteria for centralized NP including the triad of (1) history of chronic severe burning eye pain with hyperalgesia and allodynia (2) refractory to TA with (3) minimal signs (disconnected with the severity of symptoms) is incorrect or, at least incomplete and should not be relied upon to identify true centralized NP. *Perhaps patients with these triad findings may not necessarily demonstrate true CS*. Perhaps these patients may have only peripheral sensitization. If so, why would these cases not respond to topical anesthetic? I have found peripheral sensitization primarily from two sources: (1) fixed obstruction Meibomian glands and (2) friction from microtrauma between superior bulbar CCh and lid wiper. It is important to know that commercially available topical anesthetic does not anesthetize pain emanating from the Meibomian glands. However, Meibomian gland pain from fixed obstructions does respond to gland probing with immediate and dramatic relief but relies on compounded 8% lidocaine in jojoba ointment to provide adequate anesthesia. In the more severe cases I may apply two rounds of topical anesthetic ointment with possible addition of a nerve block. For cases of peripheral sensitization from friction related CCh, the lack of anesthetic response to commercially available topical anesthetic simply suggests that the peripheral nerve sensitivity of the superior bulbar region and possible lid wiper exceeds the capacity of the topical anesthetic to provide pain relief. This may occur when nerves are hypersensitive and have a low threshold for pain perhaps analogous to burning one's finger on the cooktop whereby the hypersensitive nerves are easily aggravated by minor irritants (allodynia) such as lightly brushing against another surface. If indeed these cases are of peripheral and not CS, how can it be explained that within 48 hours of treatment these cases show an anesthetic response to commercially available topical anesthetic? For pain emanating from Meibomian glands, the gland probing procedure by releasing fixed obstruction from periductal fibrosis and restoring ductal integrity immediately allows equilibration of intraductal pressure with symptom relief. In the case of friction related sensitization of superior bulbar and possibly lid wiper nerves in the setting of CCh, ATD, and MGD, reducing friction induced pain with combined treatments such as PO, MGP, and ocular surface reconstruction using amniotic membrane for CCh leads to a restoration of healthier functioning nerves. Whereas the pre-treatment hypersensitive nerves were unable to be anesthetized by topical anesthetic, post treatment with significantly improved nerve function and no longer hypersensitive, these nerves now respond to routine topical anesthetic with elimination of residual symptoms. Therefore, if these cases that do not respond to TA do represent peripheral sensitization, then we should seek to identify new specific threshold criteria for CS. Furthermore, this clinical presentation should no longer be assumed refractory to current ophthalmic therapies while opting for prescribed treatments typically used for systemic neuropathic pain.[15] Perhaps most compelling, it would be imperative for patients presenting with the triad of chronic pain refractory to TA and with minimal signs, to undergo a rigorous history and examination to uncover occult ocular surface disease which can be successfully treated. With treatment, at least some patients can reverse this incapacitating, destructive and life altering eye pain. Moreover, this author believes caution should be used to not fall into the cognitive trap of concluding that any pain that cannot be explained must necessarily represent intractable neuropathic CS.

If, however, these cases do represent true centralized NP, then as Galor et al. observed, this process of CS may be reversible, at least initially.[6] Animal models of experimental neuropathic pain showed reversibility in less than one week without use of opioids.[19–22] Therefore, seeking out, identifying, and treating occult sources of surface inflammation may reduce, limit or reverse neuropathic sequelae.[1,6] It was likely that the initial approach of providing adequate lubrication by increasing tear volume using PO together with relieving diffuse MG obstruction (Fig. 2) through the use of MGP and $MGP_{(s)}$ as well as OSR (case 3) led to reduced mechanical stress to sensitized ocular surface and MG nerves. Reduced focal trauma with improved lubrication to sensitized surface nerves may have reduced local peripheral nociceptive inflammation with reversal of CS, allowing anesthetic to subsequently eliminate residual nociceptive pain at 48 hour follow-up with further symptom reduction of up to 80% within three weeks (case1) while cases 2 and 3 showed elimination of pain without TA within one week of treatment. These results were observed despite having symptoms for up to two years and CS for months as documented by the referring ophthalmologist (case 1). This result holds great implications for simpler

and safer therapy as one would prefer not to use anti-neuropathic pain medications such as tricyclic antidepressants, anticonvulsants, opioids and opioid like drugs with associated risks of addiction and other side effects.

Patients with severe dry eye symptoms exceeding signs, such as fluorescein staining and hyperemia, as well as "pain despite topical anesthetic", as in the patients of this case series, have typically experienced multiple treatment failures and prolonged dry eye treatment. They are often stressed, anxious, depressed and at times suicidal receiving various oral anti-neuropathic pain medications, on scleral lenses and autologous serum.[24] It seems imperative to the successful management of these cases to perform key, essential, supplemental diagnostic examinations to identify occult OSD by *evoked* signs and *altered* presenting symptoms to uncover and localize factors of their severe pain. These exams may be as simple as checking for lid tenderness, expressible glands, sensitivity of the ocular surface to lid excursion, effect of lifting lid off of globe, effect of different diameter bandage contact lenses as well as serial Schirmer tests with anesthesia, plus infrared meibography. Importantly, MG probing may be helpful diagnostically as well as therapeutically as it may uncover occult proximal (deep) fixed, unyielding gland obstruction.[9,10,17,18,28]

4. Conclusions

Neuropathic Dry Eye Pain is presently a diagnosis of exclusion considered in the setting of severe ocular surface pain refractory to topical anesthetic without corresponding signs of surface disease such as vital staining and hyperemia. This case series indicates treatment of occult and non-obvious disease such as deep proximal meibomian gland duct fixed obstruction and superior conjunctivochalasis may reverse symptoms avoiding the need to prescribe oral agents used for neuropathic pain elsewhere within the body.

Patient consent

The patients consented to chart review with publication.

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Authorship

All authors attest that they meet the current ICMJE criteria for Authorship.

Declaration of competing interest

Dr. Maskin is a >5% shareholder of MGDi which owns patents on the devices and methods of intraductal diagnoses and treatment of Meibomian Gland disease.

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