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Widespread Effects of Clinically Unilateral Focal Nerve Injuries

Pedram Hamrah^{1,2,3,4}, Afsun Sahin^{2,3}, and Anne Louise Oaklander^{5,6}

¹Cornea Service, New England Eye Center

²Center for Translational Ocular Immunology, Department of Ophthalmology, Tufts Medical Center, Tufts University School of Medicine, Boston, MA

³Ocular Surface Imaging Center

⁴Cornea and Refractive Surgery Service, Massachusetts Eye and Ear Infirmary, Department of Ophthalmology, Harvard Medical School, Boston, MA

⁵Department of Neurology, Massachusetts General Hospital, Harvard Medical School, Boston, MA

⁶Department of Pathology (Neuropathology), Massachusetts General Hospital, Boston, MA

We admired the recent article by Younis et al.[29] in which they performed bilateral quantitative sensory testing (QST) on both sides of the face and one hand of patients with unilateral, presurgical, trigeminal neuralgia (TN). Their goal was to evaluate the long-standing impression that neurological deficits in TN are restricted to the classical receptive field of the damaged trigeminal division(s). They meticulously studied 36 patients with concealed endophenotype, and compared results between those with or without persistent pain between TN attacks. Comparing participants' QST data to external normative references revealed that they had mechanical and thermal sensory abnormalities not only in the TN-affected face but also in their contralesional mirror-image asymptomatic face and in their hands. These widespread subclinical abnormalities were attributed to undefined central nervous system abnormalities ("central sensitization").

Aside from one mention that "peripheral sensitization" could not be excluded, the authors did not reference the robust evidence that unilateral nerve injuries routinely cause functional and anatomical changes in contralesional sensory neurons, as reviewed in Koltzenburg et al. [13] The best evidence from the face comes from animal studies in the cornea and from cornea imaging studies of living patients with laser *in vivo* confocal microscopy (IVCM). Its rapid, objective, high-resolution, non-invasive optical sectioning provides a window into the morphology and pathology of the first trigeminal division (V₁) nociceptive C-fibers that comprise virtually all corneal innervation. [4-6; 8; 9; 28] Focal trigeminal lesions and systemic "small-fiber" polyneuropathies both cause clearly detectable damage.[7; 21; 24] For instance, we used IVCM to analyze corneal innervation in both eyes of 27 patients with unilateral V₁ herpes zoster ophthalmicus (HZO) and 31 with V₁ herpes simplex virus (HSV) and healthy controls.[8; 9] Both diseases caused reductions in the number and density of

corneal neurites (depicted in Fig. 1). These occurred not only in patients' infected corneas (controls – $2,258.4 \pm 989.0$ $\mu\text{m}/\text{frame}$, HSV – 595.8 ± 358.1 , HZO – 595.8 ± 358.1 ; both $p < 0.001$), but also in the contralesional clinically unaffected corneas of HSV (992.7 ± 465.0 ; $p < 0.01$) as well as HZO patients ($1,053.1 \pm 441.4$; $p < 0.01$).[8; 9] This pathology correlated with deficits in corneal nociceptive function. The contralesional losses were not merely due to spreading infection, because unilateral axotomy of the ciliary ophthalmic branches of V_1 in mice causes similar contralesional changes by day 1 post-surgery.[28] The anatomical pathway may involve the small number of fibers that each eye (and other trigeminally innervated tissues)[23] sends to the contralateral peripheral Gasserian ganglion.[11; 20] Plus, some central axons of peripheral trigeminal afferents project to the contralateral as well as ipsilateral central trigeminal nucleus.[3] This contralesional corneal denervation may involve the leukocyte infiltration we saw in the contralateral asymptomatic eyes of 28 patients with acute unilateral bacterial keratitis.[6] Others have reported similar findings.[26]

The contralesional effects of unilateral nerve injuries are not restricted to the face. PGP 9.5-immunolabeled skin biopsies from the torsos of 34 adults with or without postherpetic neuralgia (PHN) after one-sided thoracic shingles demonstrated that unilateral PHN is also associated with bilateral damage to epidermal nociceptors.[19] These findings were reproduced in a surgical-injury rat model, confirming they did not merely reflect infectious spread.[18] Unilateral nerve damage can cause mirror-image altered function of nociceptive terminals,[1] pain-related behaviors,[2] changes in peripheral sensory ganglia[16; 17] and in the dorsal horn,[15] presumably involving the dorsal commissure connecting the left and right dorsal horns.[22; 27]

And what of Younis' et al. finding of thermal and mechanical changes in their subjects' hands?[29] The contralesional changes above are generally restricted to the mirror-image receptive fields.[19] But one does not necessarily need to invoke the catch-all "central sensitization". Evidence going back to the increased prevalence of carpal tunnel syndrome in diabetics demonstrates that generalized peripheral nerve dysfunction (polyneuropathy) increases risk for persistent focal mononeuropathies.[12] Diseased axons are less likely to be able to compensate and regenerate from compression and other local traumas.

These peripheral findings do not exclude the brain's participation—in fact they implicate it. Advanced imaging increasingly demonstrates that peripheral neuropathies, and even non-neurologic painful conditions including routine menstrual pain, suffice to trigger radiologically detectable brain changes.[10; 25] "Central sensitization" refers to the brains' normal plasticity in response to altered peripheral signals, and it does not mean that the brain is the origin of the problem.[14] The peripheral nervous system should have been included in Younis et al.'s discussion.

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Figure 1.

Representative laser *in vivo* confocal microscopy images of corneal subbasal nerves (black arrows) in the normal healthy eye (A) and in a herpes zoster ophthalmicus (HZO) affected eye (B) and contralateral eye (C) of the same patient. Note the significant decrease of subbasal nerves in both affected and contralateral eye of HZO patient as well as an increase of dendritic-form immune cells in both eyes of HZO patient (black arrow head).