Autologous Serum Tears for Treatment of Photoallodynia in Patients with Corneal Neuropathy: Efficacy and Evaluation with In Vivo Confocal Microscopy

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ABSTRACT **Objective: Patients suffering from corneal neuropathy may present with photoallodynia; i.e., increased light sensitivity, frequently with a normal slit-lamp examination. This study aimed to evaluate the efficacy of autologous serum tears (AST) for treatment of severe photoallodynia in corneal neuropathy and to correlate clinical findings with corneal subbasal nerve alterations by in vivo confocal microscopy (IVCM). Methods: Retrospective case control study with 16 patients with neuropathy-induced severe photoallodynia compared to 16 normal controls. Symptom severity, clinical examination and bilateral corneal IVCM scans were recorded. Results: All patients suffered from extreme photoallodynia (8.8±1.1) with no concurrent ocular surface disease. Subbasal nerves were significantly decreased at baseline in patients compared to controls; total nerve length (9208±1264 vs 24714±1056 μm/mm^2; P<.0001) and total nerve number (9.6±1.4 vs 28.6±2.0; P<.0001), respectively. Morphologically, significantly increased reflectivity (2.9±0.2 vs 1.8±0.1; P<.0001), beading (in 93.7%), and neuromas (in 62.5%) were seen. AST (3.6±2.1 months) resulted in significantly decreased symptom severity (1.6±1.7; P=.02). IVCM demonstrated significantly improved nerve parameters (P<.005), total nerve length (15451±1595 μm/mm^2), number (13.9±2.1), and reflectivity (1.9±0.1). Beading and neuromas were seen in only 56.2% and 7.6% of patients. Conclusion: Patients with corneal neuropathy-induced photoallodynia show profound alterations in corneal nerves. AST restores nerve topography through nerve regeneration, and this correlated with improvement in patient-reported photoallodynia. The data support the notion that corneal nerve damage results in alterations in afferent trigeminal pathways to produce photoallodynia.**

KEY WORDS **autologous serum tears, corneal neuropathy, laser in vivo confocal microscopy, light sensitivity, nerve growth factor, photoallodynia, regeneration**

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I. INTRODUCTION

Corneal neuropathy, a recently described entity, is characterized by dysfunctional nerves following direct damage to the trigeminal nerve endings.[1] Chronic and persistent ectopic activity of injured corneal

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nerves causing pain in response to both innocuous stimulation (allodynia) and noxious stimuli (hyperalgesia) of the cornea is the hallmark feature of neuropathy, with patients typically reporting severe spontaneous corneal pain.[1-3] In addition, a large number of these patients may experience increased light sensitivity, which may serve as a proxy symptom to the pain. The severe ocular discomfort in response to light in these neuropathic patients is referred to as *photoallodynia*, which has a serious debilitating impact on the quality of life of the patients.[2,3] Patients may be unable to carry out activities of daily living, even when wearing dark glasses, resulting in loss of work hours, impaired social functioning, frustration, and increased anxiety and depression.[4]

Despite the severe impact on the quality of life, corneal neuropathy-induced photoallodynia is often overlooked by ophthalmologists and remains severely undertreated.[4] Because evidence of nerve injury is required for the diagnosis of neuropathy, routine slit-lamp biomicroscopy does not allow for diagnosis of this condition. The recent advent of laser in vivo confocal microscopy (**IVCM**), which is a noninvasive, high-resolution, real-time imaging device, has allowed visualization of the cornea at 800-times magnification with a lateral digital resolution of 1μm/pixel. Layer-by-layer analysis of the corneal ultrastructure in both ocular health and disease, including detailed visualization of corneal nerves and immune cells, is now possible. Both quantitative and qualitative assessments of the cellular and nerve properties can be performed and provide insight into the underlying disease pathogenesis, diagnosis, and efficacy of treatments.[5-14] Very recently, laser IVCM has demonstrated corneal nerve abnormalities in patients with severe symptoms of pain or photoallodynia, despite the lack of clinical signs on slit-lamp examination, thus prompting a diagnosis of corneal neuropathy.[3,15-17]

Given that the basis of the extreme corneal neuropathy-induced photoallodynia is associated with nerve injury, therapeutic strategies resulting in regeneration of damaged nerves may help alleviate patient symptoms. This rationale is based on reports on the use of neurotrophic factors, particularly nerve growth factor (**NGF**) to reduce allodynia in animal models with neuropathic pain.[18,19] By reducing reactive astrocytosis and reversing the glial morphomolecular modulation, NGF reduces both allodynia and hyperalgesia. Administration of neurotrophic factors results in post-injury repair of peripheral nerves and their functional recovery.[20] Successful corneal nerve regeneration following the use of autologous plasma in neurotrophic keratopathy,[21] as well as with autologous serum tears (**AST**) in dry eye patients,[22] prompted us to consider the possible application of AST in patients suffering from corneal neuropathy-induced photoallodynia.

We hypothesized that AST would result in corneal nerve regeneration and subsequent functional recovery of the damaged peripheral corneal nerves in patients suffering from corneal neuropathy, leading to symptomatic improvement in photoallodynia. The purpose of this pilot study is thus to assess corneal nerve changes in patients with corneal neuropathy associated with photoallodynia and to evaluate the clinical efficacy of AST therapy as correlated with IVCM.

II. METHODS

A. Study Design and Patients

All subjects were recruited from the Cornea Service of the Massachusetts Eye & Ear Infirmary, Department of Ophthalmology, Harvard Medical School, Boston, MA, between 2009 to 2012. The protocol was approved by the Institutional Review Board/Ethics Committee, complied with the Health Insurance Portability and Accountability Act (HIPAA), and adhered to the tenets of the Declaration of Helsinki.

This was a retrospective, single-center study. Sixteen patients (10 females and 6 males, mean age 61.8±4.4, range 27-88 years) with the diagnosis of corneal neuropathy were included in the study and were compared to 16 controls (10 females and 6 males, mean age 56.4±3.1, range 25-74 years; P=.6). Inclusion criteria included symptoms of severe photoallodynia, a presence of a normal slit-lamp examination, and the absence of clinical signs of ocular surface disease by slit-lamp examination at the time of baseline examination. Specific exclusion criteria included any anterior or posterior segment pathology that could independently cause the symptoms of light sensitivity, such as corneal abrasion, ulcer, ocular infections, uveitis, and iridocyclitis. All the patients had tried frequent lubrication for at least 3 months without any relief in symptoms of photoallodynia, and were currently being treated with 20% AST 8 times/day for the purpose of inducing corneal nerve regeneration, in order to address symptoms of photoallodynia. Both eyes of all patients were studied; however, only one eye was randomly selected for analysis.

B. Clinical Chart Review

The charts of all the patients were reviewed for symptoms, activities of daily life that were affected, and previous