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REVIEW

The potential role of neuropathic mechanisms in dry eye syndromes

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Abstract Dry eye syndromes can involve both nociceptive and neuropathic symptoms. Nociceptive symptoms are the normal physiological responses to noxious stimuli. Neuropathic symptoms are caused by a lesion or disease of the somatosensory nervous system and can be the result of hypersensitisation of peripheral or central corneal and conjunctival somatosensory nerves. For example, inflammation could induce neuroplastic peripheral sensitisation of the ocular surface or lid wiper and exacerbate nociceptive symptoms. Neuropathic symptoms may explain the incommensurate relation between signs and symptoms in some dry eye syndromes although absence of signs of a dry eye syndrome may also be a consequence of inappropriate methods used when examining for them. Involvement of neuropathic mechanisms may also help explain dry eye symptoms which occur in association with reduced corneal sensitivity. This review includes a discussion of the potential for ocular symptoms involving neuropathic mechanisms to contribute to psychosocial problems such as depression, stress, anxiety and sleep disorders as well as for these types of psychosocial problems to contribute to neuropathic mechanisms and dry eye syndromes. Failure to consider the possibility that neuropathic mechanisms can contribute to dry eye syndromes may reduce accuracy of diagnosis and the suitability of treatment provided. Dry eye symptoms in the absence of commensurate evidence of tear dysfunction, and unsatisfactory response to tear dysfunction therapies should prompt consideration of neuropathic mechanisms being involved. Symptoms which persist after local anaesthetic instillation are more likely to be neuropathic in origin. Reducing inflammation may help limit any associated neuroplastic hypersensitivity.

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PALABRAS CLAVE
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Papel potencial de los mecanismos neuropáticos en el síndrome del ojo seco

Resumen Los síndromes de ojo seco pueden implicar síntomas tanto nociceptivos como neuropáticos. Los síntomas nociceptivos son las respuestas fisiológicas normales a los estímulos nocivos. Los síntomas neuropáticos son causados por una lesión o enfermedad del sistema somatosensorial, y pueden ser resultado de una hipersensibilización de los nervios sensoriales periférico o central de la córnea, o de la conjuntiva. Por ejemplo, la inflamación podría inducir una sensibilización periférica neuroplástica de la superficie ocular, o una epilopatía del párpado en limpiaparabrisas, o exacerbar los síntomas nociceptivos. Los síntomas neuropáticos pueden explicar la enorme relación entre los signos y síntomas en algunos síndromes del ojo seco, aunque la ausencia de signos en dichos síndromes puede ser también consecuencia de los métodos inapropiados utilizados al examinar dichos ojos. La implicación de mecanismos neuropáticos puede ayudar también a explicar los síntomas del ojo seco que se producen junto con la reducción de la sensibilidad corneal. Esta revisión incluye una discusión sobre el potencial de que los síntomas oculares que implican mecanismos neuropáticos contribuyan a los problemas psicosociales tales como depresión, estrés, ansiedad y trastornos del sueño, así como que dichos tipos de problemas psicosociales puedan contribuir a los mecanismos neuropáticos y los síndromes del ojo seco. La ausencia de consideración de la posibilidad de que los mecanismos neuropáticos puedan contribuir a los síndromes del ojo seco puede reducir la precisión del diagnóstico y la idoneidad del tratamiento suministrado. Los síntomas del ojo seco, en ausencia de evidencia conmensurable de disfunción lagrimal, y respuesta insatisfactoria a las terapias de disfunción lagrimal, deberían impulsar la consideración de una implicación de los mecanismos neuropáticos. Es probable que la persistencia de los síntomas tras la instilación de anestésicos locales tenga un origen neuropático. Reducir la inflamación puede ayudar a limitar cualquier hipersensibilidad neuroplástica asociada.

Based on the definition adopted by the 2007 International Dry Eye Workshop[1] dry eye syndromes (DES) are multifactorial diseases of the tears, lids and ocular surface which can result in symptoms of discomfort and/or visual disturbance and/or tear film instability with the potential for damage to the ocular surface. They are usually accompanied by Meibomian gland dysfunction, increased osmolarity of the tear film and inflammation of the ocular surface[1] and for example, may be exacerbated by infrequent and/or incomplete blinking.[2] DES may be predominantly symptomatic but without obvious signs of ocular surface disease as well as presenting with evidence of ocular surface disease without significant symptoms.[1,3] Dry eye symptoms represent non-specific pain[4] with the most consistent clinical feature of dry eye disease being chronic dry eye-like pain.[5] Chronic pain syndromes are common in dry eye disease patients and are associated with increased severity of dry eye disease symptoms even though objective ocular surface signs are no worse[6] or even non-existent. It may be assumed that ocular irritation is a painful stimulus[7] so that many people with mild to moderate dry eye disease describe their symptoms as irritating rather than painful. However, many patients with a DES describe features of neuropathic pain,[8] sometimes presenting without signs of epitheliopathy (pain without stain).[9] Patients with more moderate symptoms arising from neuropathic mechanisms may present with symptoms of irritation without corresponding signs (irritation without desiccation for example).

However, a clinical finding of absence of signs of tear dysfunction may need to be qualified by the method of examination used. For example, a single instillation of fluorescein dye may not be sufficient to elicit evidence of ocular surface or lid wiper epitheliopathy associated with desiccation[10] Sequential instillations of appropriate concentrations of more than one dye may, over time, elicit staining of the ocular surface or lid wiper which was not previously evident.[11] The volume and concentration of stains instilled are additional variables and, for example, the type and manufacturer of dye impregnated strips could be important.[12] Further scope for qualifying observations is obtained by the use of barrier filters which improve the ability to detect staining.[13] A finding of 'no corneal stain' after a single instillation of one type of staining agent may be more correctly phrased as 'no corneal stain detected'. Multiple instillations may compromise the epithelium but a second instillation could be sufficient to manifest staining which indicates a deficient epithelial barrier function not detected with an initial instillation. Emphasis on corneal changes and failure to examine for conjunctival[14] and lid wiper epitheliopathy[11] may also contribute to under-assessment of signs of dry eye. Failure to detect evidence of tear hyperosmolarity, deficient aqueous tear production or Meibomian gland dysfunction for example, could be other reasons why signs and other evidence of a DES are underestimated or missed.

Lack of correlation between signs and symptoms in DES may also be due to the symptoms not being a result

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