Central nervous system mechanisms in Sjögren's syndrome

O P van Bijsterveld, A A Kruize, R L A W Bleys

A theory

The origin of the dry eye in Sjögren's syndrome has hardly been a subject of discussion as it is assumed that lymphoplasmocytic cell infiltration of the tear gland deteriorates its function to such a degree that it causes dry eye. Several observations, however, may not support this concept that tear gland degeneration is the only causative factor in ocular dryness in Sjögren's syndrome.

Sjögren's syndrome is thought to be the consequence of a generalised autoimmune induced exocrinopathy resulting in localised symptoms including dry eyes and mouth, and generalised symptoms including fatigue, myalgia, and arthralgia. Rarely available epidemiological data suggest a prevalence varying between 1.5–4%, a phenomenon probably at least partly the result of the various classification criteria used. Important components in the pathogenesis are the emergence of autoreactive T cells and a subsequent failure of apoptosis of these activated cells, which might result in a persistent stimulation of B cells. Extensive lymphoplasmocytic infiltration of tear and salivary glands is thought to interfere with their secretory function, resulting in dry eyes and mouth.

Even in idiopathic keratoconjunctivitis sicca, usually not thought to be based on generalised autoimmune disease, a local immune driven inflammatory reaction in the tear gland is also thought to interfere with the functional unit comprising the ocular surface, tear gland, and interconnecting reflex arc. A critical decrease in androgen level leads to atrophy of the lacrimal glands. Resulting apoptotic fragments of the interstitial and acinar cells might act as a source of potential autoantigens that subsequently might be presented either by interstitial antigen presenting cells or acinar cells to CD4 cell antigen receptors and start an immune response. Several experimental and clinical observations cast doubt on the notion that tear gland degeneration is the only factor in deterioration of the tear flow in Sjögren's syndrome.

THE MURINE MODEL

Although in a murine model of Sjögren's syndrome, extensive lymphoplasmocytic cell infiltration of the lacrimal glands was observed, these glands contained a large number of apparently unaffected acinar and ductal cells. Despite this, lacrimal function was impaired to such a degree that aqueous tear deficient keratoconjunctivitis developed. Immunohistochemical analysis using specific antibodies to markers of parasympathetic, sympathetic, and sensory nerves demonstrated that the density and pattern of visceromotor and sensory innervation of the non-infiltrated parts of the lacrimal glands were indistinguishable from that of age matched healthy control lacrimal glands. Although not all parasympathetic markers available were investigated, this implies that the loss of the secretory function in Sjögren's syndrome is probably not due to impaired peripheral autonomic innervation. However, in another experiment using the murine model of Sjögren's syndrome, activation of nerves of lacrimal glands in fibres with plasmolymphocytic cells, did not increase the release of acetylcholine, thus contributing to an impaired secretion of the glands.

CLINICAL OBSERVATIONS

In a long term follow up study, 10 years after an initial diagnosis of Sjögren's syndrome was made, the average tear function returned to normal values, but not in all patients. Thus, a reversible component in tear function was suggested.

In a recent study (Kruize, personal communication) 25 patients were classified as suffering from (primary) Sjögren's syndrome, according to the EC criteria. Fourteen patients with relatively mild ocular signs and symptoms and 11 patients with rather severe ocular surface disease were compared with regard to severity of disease as indicated by serum immunoglobulin G. No differences in serum IgG between both patient groups were found (Table 1). Thus, the degree of dryness seems not to be linked directly to the severity of disease.

PARADOXICAL TEAR FLOW IN CHRONIC CONJUNCTIVITIS

Some patients with serious chronic inflammatory disease of the conjunctiva may bitterly complain of dry eyes. Clinical assessments may reveal repeatedly low or very low Schirmer-I test values without any clinical evidence of trigeminal neuropathy. Paradoxically, these patients may show copious tearing after an emotional event, indicating that the central and limbic efferent transmission of impulses to the superior salivatory nucleus are intact, as well as the parasympathetic route from this nucleus to the lacrimal gland.

All these clinical and experimental data consequently suggest a concomitant responsible component of the mechanisms responsible for perpetuation of tear function in Sjögren's syndrome. According to our theory, the central nervous system may be involved in reduction of lacrimation and in altered pain sensations, as will be suggested in the following paragraphs.

A-Delta and C fibre systems

In the trigeminal nerve two distinguishable afferent fibres carry nociceptive impulses from the peripheral nerve endings—one phylogenetically old system consists of non-myelinated small diameter fibres, slow in conducting which do not adapt easily: the C fibre system; the other, phylogenetically new system of myelinated, large diameter fibres, fast in conducting, which do adapt rather easily: the A-delta fibre system.

Volleys of impulses generated after high intensity stimulation of the outer eye are carried by A-delta fibres to the central transmission cells. The stimulus exceeding a critical firing level of these cells will activate neural mechanisms responsible for perception of acute pain, resulting in behavioural patterns aimed

---

**Table 1**

<table>
<thead>
<tr>
<th>Ocular disease</th>
<th>Number</th>
<th>Mean concentration of serum IgG (g/l)</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>14</td>
<td>17.0</td>
<td>6.7</td>
</tr>
<tr>
<td>Severe</td>
<td>11</td>
<td>18.9</td>
<td>7.8</td>
</tr>
</tbody>
</table>

Normality of distribution of serum IgG levels was confirmed in both patient groups, subsequently equal variance t test analysis was performed.
at avoiding sensory and affective sensations. It will also activate the parasympathetic system resulting in tearing.

If the stimulus continues, however, volleys of impulses are also carried by the C fibre system. These fibre impulses are transmitted to the substantia gelatinosa of the spinal trigeminal nucleus especially and will be transmitted to higher centres to be perceived as “slow pain.”

**SUBSTANZIA GELATINOSA, A TRANSMISSION MODULATING SYSTEM**

The substantia gelatinosa is the region in the spinal cord and the spinal trigeminal nucleus where many nociceptive impulses are processed after entering the central nervous system. This region contains densely packed small interneurons which interconnect by short fibres and are also connected with longer fibres of the spinal trigeminal tract. It is believed that the substantia gelatinosa acts as a synaptic transmission modulating system of nerve impulses from the peripheral trigeminal fibres to the central transmission cells. Summation through continuous stimulation of these cells by A-delta fibres is prevented by a negative feedback mechanism. However, under conditions of prolonged stimulation, the A-delta fibre system begins to adapt and gives way by transmission through the C fibre system. Volleys in small diameter fibres activate a positive feedback mechanism, which enhances the effect of the incoming impulses.

Because of the positive feedback mechanism in the substantia gelatinosa there is a temporal summation of the incoming signals to the central transmission cells, a mechanism first suggested by Livingstone and called “wind-up.” The wind-up response is thought to underlie central sensitisation, an adaptation of afferent neurons to prolonged nociceptive stimuli as occurs in tissue damage and inflammation, which contributes to hyperalgesia and persistence of pain. When the output of the central transmission cells exceeds a certain level, a number of responses may be triggered through ascending systems. Nociceptive information uses the trigeminothalamic and trigemino-reticulothalamic tracts, as well as direct pathways to limbic structures such as the hypothalamus and amygdala. Subsequent activation of, particularly, the thalamus, the amygdala, the hypothalamus, the parabrachial nuclei, the brain stem reticular formation, as well as the parietal and frontal cortex, may occur.

**C FIBRE TRANSMISSION**

In Sjögren’s syndrome, the amount of tear flow is initially decreased through infiltration of the tear gland with subsequent loss of function, which causes increased friction between the outer ocular tissues. Dryness of the cornea may cause exfoliation of the superficial corneal epithelium leaving corneal erosions, resulting in considerable ocular discomfort, which is chronic in nature, because of the character of Sjögren’s syndrome. Because of the continuous stimulation caused by the chronic inflammatory reaction of the conjunctiva and the exfoliative changes of the corneal epithelium in Sjögren’s syndrome, repeated constant C fibre stimuli result in “slow pain,” a diffuse, burning sensation of the conjunctiva, so characteristic of the dry eye in Sjögren’s syndrome. This relatively unchecked C fibre input can also easily lead to summation (wind-up), which can augment responses of spinal trigeminal nucleus neurons and lead to central sensitisation. More importantly, we hypothesize that this C fibre input can induce a frequency conditioned reversal of the expected response by inhibiting the parasympathetic system. Frequency conditioned reversal of responses of the autonomic nervous system have been described for the cardiovascular system. It is uncertain which circuitry is responsible for this inhibition. Considering the connections between ascending pathways and limbic structures (hypothalamus and amygdala) on one hand, and between limbic structures and the peri-aqueductal grey on the other hand, we hypothesize that the inhibition process takes place in this circuitry, the hypothalamus being important to coordinate autonomic functions. As a consequence there is reduction of tearing and this we believe is the reversible and additional factor in Sjögren’s dry eye.

**ADEQUACY OF THE THEORY**

In chronic inflammatory conditions of Sjögren’s dry eye, summation of peripheral input may occur since C fibre activity starts to dominate the A-delta fibre activity resulting in an active inhibition of the parasympathetic system at the central level in the peri-aqueductal grey area of the limbic system. There have been reports of peripheral sympathetic and parasympathetic dysfunction, but none of these reports are incompatible with the concept of C fibre induced inhibition of tear flow in Sjögren’s syndrome. Also, in clinical practice, including persistent and consequent care of a supportive ophthalmologist, the central control is complex and may be very selective, however, which may explain individual differences.

**CONCLUSION**

The central nervous system may have an important role in the cascade of events that occur in Sjögren’s syndrome. Our presented theory of repeated constant C fibre stimuli, in combination with frequency conditioned inhibition of the central autonomic centre for tear flow, has a striking power to explain clinical and experimental discrepancies of the concept of infiltration and destruction of the tear gland as a single cause in tear flow depression. In addition, central neural mechanisms may also explain those cases where patients have subjective rather than objective improvements of complaints.
Eye care in China

Ophthalmology in Hong Kong

D S C Lam, C C Y Tham

A catalyst for ophthalmic developments in China

Hong Kong is unique in China: she is where the virtues of the East meet the values of the West. Her sovereignty returned from the British to the Chinese Government in 1997, but Hong Kong has continued to flourish, under the “one country, two systems” model, and remains international, dynamic, innovative, and prosperous. Western style rule of law and freedom of speech and thought have persisted here. Against this unique historical and political background, ophthalmology has made important strides in Hong Kong over the past decade, both in academic research and in the provision of quality care of international standard to the local population. Hong Kong has also increasingly become a catalyst for ophthalmic developments in China.

One of our earliest projects to bring quality ophthalmic care to remote and poverty stricken regions of China was the “Lifeline Express.” (DSCL is a founding executive committee member and an ambassador of sight of the Lifeline Express, and the honorary director of the Shantou University/The Chinese University of Hong Kong Joint Shantou International Eye Center.) The Lifeline Express is a tailor built train to help eliminate cataract blindness in China (Fig 1). It is a charity project with most of its funding raised in Hong Kong. Ophthalmologists on the Lifeline Express not only provide totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for about 10 000 cataract operations per year.

Figure 1 The “Lifeline Express.” A modern ophthalmic centre, with diagnostic, therapeutic, and surgical units, all on a train that brings modern ophthalmic care and training to remote, poverty stricken regions of rural China.
The main problems are a shortage of well trained ophthalmologists and modern facilities, especially in poor and more remote regions of China.

Though the PRC fellowship programme has offered some excellent training opportunities for the fortunate few, its training capacity is still very limited. In order to help more mainland patients receive high quality ophthalmic care, and to allow more mainland doctors to acquire knowledge and skills of the highest international standard, the Joint Shantou International Eye Center (JSIEC, Fig 2),1 a collaborative effort between Shantou University and The Chinese University of Hong Kong, and fully funded by the Li Ka Shing Foundation, was founded in Shantou, PRC, in 2000. The vision of the JSIEC is to achieve international excellence in ophthalmology. It is a very modern and comprehensive ophthalmic centre. Apart from clinical services, a well equipped basic science research facility, with many laboratories and full animal house support, is also established. There are also wet laboratory facilities for training purposes. All medical and nursing staff working over there are given opportunities for training attachment in Hong Kong. Subspecialty experts from Hong Kong also regularly visit the JSIEC to share experience and expertise with the local doctors. The Fourth Hong Kong International Symposium of Ophthalmology was held in Shantou to commemorate the opening of the JSIEC in June 2002. It was well attended by leading national and international renowned experts, as well as PRC doctors from all over China. One very important mission of the JSIEC is to train young ophthalmologists from different regions of China. By setting up a training centre in China, the overall cost of training is much lower. There will be no communication difficulties arising from the speaking of different dialects, as Putonghua is more or less universally spoken within China. In future, it is hoped that many more such joint eye centres could be set up in other cities in China.

In addition to financial affordability of medical care to patients, the other main problems of eye care in China remain the shortage of well trained ophthalmologists and the shortage of modern facilities, especially in poor and more remote regions of China. Hong Kong will continue to have a catalyst role, sharing her expertise in ophthalmology, research, and management, with her mainland counterparts. Through continued training and exposure, PRC ophthalmologists will excel and be more able to provide high quality eye care to their local people. Such a mentoring model may also be applicable to other places when they have a neighbour that can offer such skill and technological sharing and transfer.

ACKNOWLEDGEMENTS

We thank Nellie K M Fong, chairman of the Executive Committee and founder of the Lifeline Express, Hong Kong, and Hui-ming Tang, director of the Shantou University: The Chinese University of Hong Kong Joint Shantou International Eye Centre, Shantou, PRC.

Financial support: Nil.


Authors’ affiliations

D S C Lam, C C Y Tham, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, Hong Kong Eye Hospital, Kowloon, Hong Kong, People’s Republic of China

Correspondence to: Professor Dennis S C Lam, Department of Ophthalmology and Visual Sciences, The Chinese University of Hong Kong, University Eye Center, Hong Kong Eye Hospital, 147 K Argyle Street, Kowloon, Hong Kong; dennislam@cuhk.edu.hk

Accepted for publication 4 November 2002

REFERENCES

1 “Lifeline Express”: http://www.lifelineexpress.org,hk
2 Joint Shantou International Eye Center: http://www.jsiec.com/
3 Li Ka Shing Foundation: http://www.lksf.org