Sjögren's syndrome

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 the 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.[1] 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.[2–4] Important components in the pathogenesis are the emergence[5] and persistence of autoimmune T cells[6] and a subsequent failure of apoptosis of these activated cells,[7] which might result in a persistent stimulation of B cells. Extensive lymphoplasmocytic infiltration of tear and salivary glands is thought to intervene with its 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.[8 9] A critical decrease in androgen level leads to atrophy of the lacrimal glands.[10] 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.[11] 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.[12] 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.[12] However, in another experiment using the murine model of Sjögren's syndrome, activation of nerves of lacrimal glands infiltrated with plasmolymphocytic cells, did not increase the release of acetylcholine, thus contributing to an impaired secretion of the glands.[13]

Table 1 No statistical differences were found between two groups of Sjögren patients, classified according to the EC criteria, one group with severe and another with mild ocular signs and symptoms, with regard to severity of the generalised autoimmune disease as expressed by mean concentrations of serum IgG (g/l)

Ocular disease	Number	Mean concentration of serum IgG (g/l)	SD
Mild	14	17.0	6.7
Severe	11	18.9	7.8

Normality of distribution of serum IgG levels was confirmed in both patient groups, subsequently equal variance *t* test analysis was performed.

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.[14] 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.[4] 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 cortical 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 perpetual deterioration 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 somaesthetic fibre systems 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

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."[15]

SUBSTANTIA 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.[16]

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[17] and called "wind-up."[18] 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.[18 19] 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 trigeminoreticulothalamic 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 nucleus, 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 cornea 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 important even: we hypothesise 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.[20] 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,[19] we hypothesise 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/or parasympathetic dysfunction,[21–27] 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, long term, low dose treatment of chronic inflammatory disease of the conjunctiva, consisting of twice a day a drop of 0.025–0.1% dexamethasone, markedly improved subjective and objective conditions in Sjögren patients. This treatment allowed a number of patients to discontinue any local medication, including tear substitutes. In case of the complication of a herpes simplex infection of the eye, a maximal oral dose of antiviral agents during 3 weeks, in addition to tapering down the local steroid treatment, not lower than an equivalent of a once a day drop of 0.1% dexamethasone, may be necessary.

Furthermore, in our long term follow up study, many, but not all, Sjögren patients had subjective rather than objective improvement of tear function. The most important contribution to the understanding of the alleviation of discomfort and pain, without an objective improvement under these conditions, is the emphasis on central neural mechanisms, as will be explained now.

CENTRAL CONTROL OF PAIN

In a previous section it was pointed out that afferent fibres in the medulla oblongata and spinal cord, transporting nociceptive information, activate many brain centres, among them peri-aqueductal grey and brainstem raphe nuclei. Descending systems originating in these centres modulate the sensitivity of the substantia gelatinosa, the primary processing centre of nociceptive impulses. Limbic brain structures influence the peri-aqueductal grey, which explains altered pain sensations during stressful events. For example, some soldiers severely wounded at the Anzio beachhead in the second world war experienced no pain, probably because they realised they had escaped from the ordeal of the battlefield alive.[28] Central nervous system activities subserving emotion, attention, and memories of previous experience are thus able to exert control over the sensory input through modulating the synaptic transmission.[29] In our view this mechanism underlies subjective improvement of discomfort as a result of 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.

Br J Ophthalmol 2003;**87**:128–130

Authors' affiliations
O P van Bijsterveld, Oogcentrum Houten, Achterom 16b, 3995 EB Houten, The Netherlands
A A Kruize, Department of Rheumatology and Clinical Immunology, University Medical Centre Utrecht, F02-127, PO Box 85500, 3508 GA Utrecht, The Netherlands
R L A W Bleys, Rudolf Magnus Institute of Neuroscience, Department of Pharmacology and Anatomy, University Medical Centre Utrecht, STR02-208, PO Box 80039, 3508 TA Utrecht, The Netherlands

Correspondence to: A A Kruize; a.kruize@azu.nl

REFERENCES

1 **Fox RI**, Stern M, Michelson P. Update in Sjögren's syndrome. *Curr Opin Rheumatol* 2000;**12**:391–8.
2 **Fox RI**, Robinson CA, Curd JG, *et al.* Sjögren's syndrome. Proposed criteria for classification. *Arthritis Rheum* 1986;**29**:577–85.
3 **Daniels TE**, Talal N. Diagnosis and differential diagnosis of Sjögren's syndrome. In: Talal N, Moutsopoulos HM, Kassan SS, eds. *Sjögren's syndrome. Clinical and immunological aspects.* Berlin: Springer Verlag, 1987:193–9.
4 **Vitali C**, Bombardieri S, Moutsopoulos HM, *et al.* Preliminary criteria for the classification of Sjögren's syndrome, results of a prospective concerted action supported by the European Community. *Arthritis Rheum* 1993;**36**:340–7.
5 **Gatenby PA**, Irvine M. The bcl-2 proto oncogene is overexpressed in systemic lupus erythematosus. *J Autoimmun* 1994;**7**:623–31.
6 **Goodnow CC**, Adelstein S, Basten A. Peripheral tolerance and homing receptors on endothelial cells. *Science* 1990;**248**:1373–9.
7 **Hebbar M**, Lassalle P, Janin A, *et al.* E-selection expression in salivary endothelial cells and sera from patients with Sjögren's syndrome and systemic sclerosus. *Arthritis Rheum* 1996;**38**:406–12.
8 **Augustin AJ**, Spitznas M, Kaviani N, *et al.* Oxidative reactions in the tear fluid of patients suffering from dry eyes. *Graefes Arch Clin Exp Ophthalmol* 1995;**233**:694–8.
9 **Stern ME**, Beuerman RW, Fox RI, *et al.* The pathology of the dry eye: the interaction between the ocular surface and lacrimal glands. *Cornea* 1998;**17**:584–9.
10 **Mircheff AK**, Warren DW, Wood RL. Hormonal support of lacrimal function, primary lacrimal deficiency, autoimmunity, and peripheral tolerance in the lacrimal gland. *Ocul Immunol Inflamm* 1996;**4**:145–72.
11 **Azzarolo AM**, Wood RL, Mircheff AK, *et al.* Androgen influence on lacrimal gland apoptosis, necrosis, and lymphocytic infiltration. *Invest Ophthalmol Vis Sci* 1999;**40**:592–602.
12 **Zoukhri D**, Hodges RR, Dartt DA. Lacrimal gland innervation is not altered with the onset and progression of disease in a murine model of Sjögren's syndrome. *Clin Immunol Immunopathol* 1998;**89**:126–33.
13 **Zoukhri D**, Kublin CL. Impaired neurotransmitter release from lacrimal and salivary gland nerces of a murine model of Sjögren's syndrome. *Invest Ophthalm Vis Sci* 2001;**42**:925–32.
14 **Kruize AA**, Bijsterveld OP van, Hené RJ, *et al.* Long term course of tear gland function in patients with keratoconjunctivitis sicca and Sjögren's syndrome. *Br J Ophthalmol* 1997;**81**:435–8.
15 **Ochoa J**, Torebjörk E. Sensations evoked by intraneural microstimulation of C nociceptor fibres in human skin nerves. *J Physiol* 1989;**415**:583–99.
16 **Melzack R**, Wall PD. Pain mechanisms, a new theory. *Science* 1965;**150**:971–9.
17 **Livingston WK**. *Pain mechanisms.* New York: Macmillan, 1943.
18 **Dickensen AH**. Spinal cord pharmacology of pain. *Br J Anaesth* 1995;**75**:193–200.
19 **Willis WD**, Westlund KN. Neuroanatomy of the pain system and of the pathways that modulate pain. *J Clin Neurophysiol* 1997;**14**:2–31.
20 **Kaada BR**. Somato-motor, autonomic and electrocorticographic responses to electrical stimulation of "rhinencephalic" and other structures in primates, cat and dog. *Acta Physiol Scand* 1951;**24**:suppl 83.
21 **Barendregt PJ**, Heyde GL van de, Breedveld FC, *et al.* Parasympathetic dysfunction in rheumatoid arthritis patients with ocular dryness. *Ann Rheum Dis* 1996;**55**:612–15.
22 **Mandl T**, Jacobsson L, Lilja B, *et al.* Disturbances of autonomic nervous function in primary Sjögren's syndrome. *Scand J Rheumatol* 1997;**26**:401–6.
23 **Barendregt PJ**, Markusse HM, Man in 't Veld AJ, *et al.* Primary Sjögren's syndrome presenting as autonomic neuropathy, a case report. *Neth J Med* 1998;**53**:193–5.
24 **Wright RA**, Grant IA, Low PA. Autonomic neuropathy associated with sicca complex. *J Auton Nerv Syst* 1999;**75**:70–6.
25 **Barendregt PJ**, Meiracker AH van der, Markusse HM, *et al.* Parasympathetic failure does not contribute to ocular dryness in primary Sjögren's syndrome. *Ann Rheum Dis* 1999;**58**:746–50.
26 **Kovacs L**, Torok T, Bari F, *et al.* Impaired microvascular response to cholinergic stimuli in primary Sjögren's syndrome. *Ann Rheum Dis* 2000;**59**:48–53.
27 **Mandl T**, Bornmyr SV, Castenfors J, *et al.* Sympathetic dysfunction in patients with primary Sjögren's syndrome. *J Rheumatol* 2001;**28**:296–301.
28 **Beecher HK**. *Measurement of subjective responses.* New York: Oxford Univ Press, 1959.
29 **Melzack R**. From the gate to the neuromatrix. *Pain* 1999;**suppl 6**:121–6.

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."[1] (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 are either volunteer doctors from Hong Kong, or doctors from mainland China who have been trained in Hong Kong. Currently there are two trains, but the third will be in operation by the end of 2002, giving a capacity to perform about 10 000 cataract operations per year. The Lifeline Express not only provides totally free cataract surgery for poor and helpless people in remote regions of China, but also helps to train local doctors in modern microsurgical cataract extraction. It is the philosophy of its founders that the best way to help people is to teach them how to help themselves, and this has been the guiding principle for the Lifeline Express from the very beginning.

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.

Many ophthalmic centres in Hong Kong have achieved international

Figure 2 The Shantou University/The Chinese University of Hong Kong Joint Shantou International Eye Center: a state of the art ophthalmic service, research, and training centre in mainland China. This may be a role model for future ophthalmic centres in China.

excellence in their patient service, training programme, research work, and administrative infrastructure. The PRC (People's Republic of China) Fellowship Programme of The Chinese University of Hong Kong has made it possible for up to 20 ophthalmologists from the PRC to come to Hong Kong for attachment every year. Through these attachments, it is hoped that PRC ophthalmologists can enhance their clinical knowledge and surgical skills, get exposure and training in quality research, become accustomed to the western style of management that is often taken for granted in Hong Kong, and also become acquainted with the information technologies in the clinic and academic settings in Hong Kong.

Many PRC fellows have also made full use of this very much sought after opportunity to further polish their English. Duration of attachment varies from 3 months to 1 year. The shorter attachments are more geared towards allowing the fellow to learn a specific diagnostic, surgical, or research technique, while the longer attachments are designed for subspecialty or laboratory training. The molecular genetics laboratory of the department has become one of the most popular areas for our PRC fellows. During their stay in Hong Kong, many PRC fellows also have the opportunity to participate in international publication.

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),[2] a collaborative effort between Shantou University and The Chinese University of Hong Kong, and fully funded by the Li Ka Shing Foundation,[3] 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.

Proprietary interest: Nil.

Financial support: Nil.

Br J Ophthalmol 2003;**87**:128–131

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, 147K 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.stjec.com/
3 **Li Ka Shing Foundation:** http://www.lksf.org