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Mandl, Thomas

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PO Box 117
221 00 Lund
+46 46-222 00 00

From the Department of Rheumatology, Malmö University Hospital
Lund University, Sweden

Autonomic Dysfunction in Primary Sjögren's Syndrome

Thomas Mandl

Doctoral Thesis

By permission of the Faculty of Medicine, Lund University, Sweden;
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Supervisor:
Professor Lennart Jacobsson

Assistant supervisor:
Dr Rolf Manthorpe

Faculty opponent:
Professor Yrjö Konttinen
Department of Medicine, Helsinki University Central Hospital
Helsinki, Finland

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Abstract

The aims of this work were to evaluate objective and subjective signs of autonomic dysfunction (AD) in patients with primary Sjögren's syndrome (pSS) and to evaluate its clinical associations.

In study I, 46 pSS patients and 56/80/238 autonomic nervous function test (ANT) controls participated. Objective signs of AD were evaluated using three different cardiovascular ANTs and exocrine function in pSS patients by the Schirmer I test, rose bengal staining, and unstimulated whole sialometry. pSS patients showed objective signs of a parasympathetic and sympathetic dysfunction and also an abnormal orthostatic blood pressure reaction. However, there was a poor association between cardiovascular autonomic and exocrine function tests.

Study II comprised 31 patients with type I diabetes and 200 population-based controls. The Autonomic Symptom Profile (ASP), a questionnaire assessing autonomic symptoms, was translated into Swedish. The various scores were age-, sex-, height-, and weight-standardized and the reliability and validity of the ASP were assessed and considered acceptable or good.

In study III, 38 pSS patients and 200 population-based controls participated. Subjective signs of AD were evaluated using the ASP. The pSS patients were found to have symptoms of both parasympathetic and sympathetic dysfunction. AD symptoms were, however, poorly associated with objective signs of AD and other clinical features of the disease.

Study IV involved 20 consecutive pSS patients and 30 age- and sex-matched population-based controls. All study subjects were evaluated with a questionnaire on pharyngeal and esophageal symptoms and video-radiography and, in addition, pSS patients with two ANTs.

Dysphagia and pharyngeal and esophageal symptoms were more common in pSS patients than in controls while objective signs of pharyngeal and esophageal dysmotility were not. Dysphagia in pSS patients was not related to video-radiographical signs of dysmotility but it was associated with objective signs of parasympathetic dysfunction.

Key words: Sjögren's syndrome, autonomic dysfunction, neuropathy, dysphagia

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From the Department of Rheumatology, Malmö University Hospital
Lund University, Sweden

Autonomic Dysfunction in Primary Sjögren's Syndrome

Thomas Mandl

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Doctoral thesis, 2008

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Thomas Mandl,
Department of Rheumatology,
Malmö University Hospital,
SE-205 02 Malmö,
Sweden.
E-mail: thomas.mandl@med.lu.se

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Man muss einfach reden,
aber kompliziert denken –
nicht umgekehrt.

Franz Josef Strauß

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List of publications

This thesis is based on the following papers, which will be referred to in the text by their Roman numerals. The papers have been reprinted by permission of the publishers.

I. Autonomic and orthostatic dysfunction in patients with primary Sjögren's syndrome.
Mandl T, Wollmer P, Manthorpe R, Jacobsson L.
Journal of Rheumatology 2007;34:1869–74.

II. Assessment of autonomic symptoms in diabetics.
The Swedish version of the Autonomic Symptom Profile (ASP).
Mandl T, Granberg V, Apelqvist J, Wollmer P, Manthorpe R, Jacobsson L.
Manuscript, submitted to Clinical Physiology and Functional Imaging.

III. Autonomic symptoms in primary Sjögren's syndrome.
Mandl T, Granberg V, Apelqvist J, Wollmer P, Manthorpe R, Jacobsson L.
Rheumatology 2008, in press.

IV. Dysphagia and dysmotility of the pharynx and esophagus in patients with primary Sjögren's syndrome.
Mandl T, Ekberg O, Wollmer P, Manthorpe R, Jacobsson L.
Scandinavian Journal of Rheumatology 2007;36:394–401.

Abbreviations

ACE	Angiotensin converting enzyme
ACh	Acetyl choline
ACTH	Adrenocorticotropin
AD	Autonomic dysfunction
AECC	American-European Consensus Criteria
AI	Acceleration index
ANS	Autonomic nervous system
APC	Antigen presenting cell
AQP	Aquaporin
ANT	Autonomic nervous function test
ART	Autonomic reflex test
ASP	Autonomic Symptom Profile
BAFF	B-cell activating factor
BPV	Blood pressure variability
BRS	Baroreceptor sensitivity
BSED	Bolus-specific esophageal dysfunction
CD	Cluster of differentiation
CNS	Central nervous system
csSMR	Cause-specific standardized mortality ratio
CTD	Connective tissue disease
DHEA	Dehydroepiandrosterone
EC	European Community
EC93	Preliminary EC criteria for Sjögren's syndrome from 1993
EC96	EC criteria for Sjögren's syndrome from 1996
ECG	Electrocardiogram
EGF	Epidermal growth factor
E/I ratio	Expiration/inspiration ratio
ELISA	Enzyme-linked immunosorbent assay
GERD	Gastro-esophageal reflux disease
GI	Gastrointestinal
HPA	Hypothalamic-pituitary-adrenal
HRV	Heart rate variability
IBS	Irritable bowel disease
ICC	Intraclass correlation coefficient
IFNα	Interferon alpha
IgA	Immunoglobulin A
IgG	Immunoglobulin G

IL-1	Interleukin-1
IL-6	Interleukin-6
IP3	Inositol 1,4,5 trisphosphate
KCS	Keratoconjunctivitis sicca
lDBP ratio	Lowest diastolic blood pressure ratio
LES	Lower esophageal sphincter
lSBP ratio	Lowest systolic blood pressure ratio
M3R	Muscarine 3 receptor
MRI	Magnetic resonance imaging
MSSR	Malmö Sjögren's Syndrome Register
NA	Noradrenaline
NHL	Non-Hodgkin lymphoma
NO	Nitric oxide
NPY	Neuropepide Y
NSAID	Non-steroidal anti-inflammatory drugs
oCRH	Ovine corticotropin releasing hormone
PESD	Pharyngoesophageal segment dysfunction
PNS	Peripheral nervous system
pSS	Primary Sjögren's syndrome
QSART	Quantative sudomotor axon reflex test
RA	Rheumatoid arthritis
SIR	Standardized incidence ratio
SLE	Systemic lupus erythematosus
SS	Sjögren's syndrome
SS-A	Sjögren's syndrome A antigen
SS-B	Sjögren's syndrome B antigen
sSS	Secondary Sjögren's syndrome
S1t	Schirmer I test
TLR	Toll-like receptor
TNFα	Tumor necrosis factor alpha
VAC index	Vasoconstrictory index
vBS	van Bijsterveld score
VIP	Vasointestinal peptide

Introduction

Background

Sjögren's syndrome (SS), described in detail by the Swedish ophthalmologist Henrik Sjögren in his thesis from 1933 (1), is an autoimmune rheumatic disease characterized by lymphocytic infiltration and hypofunction of the exocrine glands, in particular the salivary and lacrimal glands, resulting in dryness of the mouth and of the eyes. Although exocrine gland involvement is a hallmark of SS, several non-exocrine organ systems may also be involved in the disease, including the locomotor system. SS is usually divided into primary Sjögren's syndrome (pSS), if it evolves without co-existing connective tissue disease (CTD), and secondary Sjögren's syndrome (sSS), if it is associated with another CTD—usually rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE) or scleroderma (2). Various sets of criteria have been used for the classification of SS. The Copenhagen criteria from 1984 (3), the Preliminary European Community criteria from 1993 (EC93) (4) and the European Community criteria from 1996 (EC96) (5) were used at our unit before the nowadays internationally widely accepted American-European Consensus Criteria (AECC) were published and implemented in 2002 (6) (Table 1). In comparison to the above-mentioned older sets of criteria, in which evidence of autoimmunity was not a prerequisite for diagnosis, the AECC requires signs of autoimmunity, i.e. autoimmune sialoadenitis in a lower-lip biopsy or the presence in of anti-SS-A/anti-SS-B antibodies in serum. Consequently, the AECC therefore cover a more homogenous and immunologically affected population of SS patients than the older sets of criteria.

Primary Sjögren's syndrome may occur in both sexes and in all ages, although there is a distinct preponderance of female cases (female:male ratio 9:1), the highest incidence being in women in the post-menopausal period (2). Due to the use of different classification criteria over time and in different parts of the world, epidemiological reports on the prevalence and incidence of the disease vary and are difficult to compare. However, two studies using the AECC have estimated the prevalence of pSS to be 0.1–0.6 % (7) and 0.15 % (8). The prevalence of sSS appears to vary between different CTDs with prevalences of 9–19 % having been reported in SLE patients, 4–31 % in RA patients, and 14–20% in scleroderma patients (9–12).

Table 1 – The American-European Consensus Criteria (AECC)

1. Ocular symptoms of dryness – a positive response to at least one of the following questions:
   a. Have you had daily, persistent, troublesome dry eyes for more than 3 months?
   b. Do you have a recurrent sensation of sand or gravel in the eyes?
   c. Do you use tear substitutes more than 3 times a day?
2. Oral symptoms of dryness – a positive response to at least one of the following questions:
   a. Have you had a daily feeling of dry mouth for more than 3 months?
   b. Have you had recurrently or persistently swollen salivary glands as an adult?
   c. Do you frequently drink liquids to aid in swallowing dry food?
3. Ocular signs – objective evidence of ocular involvement determined on the basis of a positive result in at least one of the following tests:
   a. Schirmer I test (abnormal if ≤5mm/5min)
   b. Van Bijsterveld score (abnormal if ≥ 4 points on a 0–9-point scale)
4. Histopathology – a focus score ≥ 1 in a minor salivary gland biopsy, with a focus defined as a conglomerate of more than 50 lymphocytes and a focus score defined as the number of foci per 4 mm^2 of glandular tissue.
5. Salivary gland involvement – objective evidence of salivary gland involvement determined on the basis of a positive result in at least one of the following three tests:
   a. Unstimulated whole sialometry
   b. Salivary gland scintigraphy
   c. Parotid sialography
6. Autoantibodies – presence in serum of the following antibodies:
   Antibodies to Ro (SS-A) or La (SS-B) antigens or both

Classification rules:

1. For primary SS (pSS) – in patients without any potentially associated disease, pSS can be defined as follows:
   a. The presence of any 4 of the 6 items is indicative of pSS as long as item 4 or 6 is positive.
   b. The presence of any 3 of the 4 objective criteria items (3, 4, 5, 6).
2. For secondary SS (sSS) – in patients with a potentially associated disease (for instance, another well defined connective tissue disease), the presence of item 1 or item 2 plus any one from among items 3, 4, and 5 may be considered as indicative of sSS.
3. Exclusion criteria
   a. Past head and neck radiation treatment
   b. Hepatitis C infection
   c. Acquired immunodeficiency disease (AIDS)
   d. Pre-existing lymphoma
   e. Sarcoidosis
   f. Graft versus host disease
   g. Use of anticholinergic drugs (since a time shorter than 4-fold the half-life of the drug).

Primary Sjögren's syndrome

Exocrine disease

Primary SS is a systemic autoimmune disease mainly affecting the exocrine glands, which become infiltrated with lymphocytes and hypofunctional, resulting in reduced secretory capacity and an altered secretory composition (13, 14). Although virtually all exocrine glands of the body may be affected, the involvement of the salivary and lacrimal glands, with resulting dry mouth and dry eyes, is often the most obvious. The sensation of dry and irritated eyes often leads to regular use of tear substitutes to alleviate the ocular symptoms. Besides the handicapping effects of the oral sicca symptoms with need of increased liquid intake to alleviate the oral dryness and to ameliorate swallowing when eating, it also results in an increased prevalence of caries and oral candidosis (15). In addition to affecting the external exocrine glands e.g. the salivary and lacrimal glands, pSS may also result in exocrine disease of internal organs and affect the parenchymal tissues of the lungs, the kidneys, the gastrointestinal tract, the pancreas, and the hepatobiliary system (16).

To evaluate the presence and degree of autoimmune inflammation in exocrine glands, accessory salivary glands are obtained via a lower lip biopsy for histopathological evaluation. The presence of focal sialoadenitis, represented by a focus of lymphocytes (i.e. ≥50) aggregated around a salivary gland duct, is characteristic of the autoimmune inflammation in the exocrine glands (17, 18). According to how many foci can be found in a cross section of 4 mm^2 of glandular tissue, it is possible to arrive at a focus score—with a score of ≥1 being characteristic of pSS (6). Although some studies have demonstrated an association between the degree of focal lymphocytic infiltration, i.e. the focus score, and salivary flow (18, 19), there is often a discrepancy between the degree of inflammation and the salivary flow (19, 20). Since the major proportion of saliva is produced in the major salivary glands and not in the accessory salivary glands, those studied for the presence of focal sialoadenitis, a difference in lymphocytic infiltration and exocrine gland destruction between the major and accessory salivary glands may explain such discrepancies. Due to the risk of complications when performing parotid gland biopsies (e.g. salivary gland fistula) rather than lower lip biopsies, the latter are usually preferred. In two studies, however, lower lip biopsy and major salivary gland biopsies were compared and they showed an association between the histopathological findings in major and accessory salivary glands, although with discordant findings in some subjects (21, 22).

As with many other organ functions, exocrine function becomes reduced with advancing age, resulting in diminished and altered exocrine secretion. However, the exocrine glands have substantial residual capacity, which is why age-related reduc-

tion in secretion *per se* does not appear to cause significant oral or ocular dryness if these are not aggravated by other factors such as anticholinergic drugs or SS (23). Due to the discrepancy between morphology and function, the reduced exocrine output cannot be explained solely by autoimmune inflammation and destruction; other mechanisms may also be at play. Since nervous signaling to the exocrine glands is a prerequisite for the start of exocrine secretion, a disturbance in different nervous transmission pathways could be a plausible explanantion for the exocrine insufficiency seen in SS patients who have rather intact glands morphologically (19).

Non-exocrine disease

Several non-exocrine organs may also be affected in pSS, resulting in various symptoms. Probably the most common and debilitating non-exocrine symptom is fatigue (24–26), the pathogenesis of which is still poorly understood. Factors that have been proposed to contribute to the fatigue are neuroendocrine disturbances (24, 27), sleep disturbances due to the disease itself (28), lower urinary tract symptoms (29), inflammation (30), co-existing hypothyreosis (31), depression (25, 32), and poor physical fitness (25, 26). The lack of one single pathogenetic factor that would explain fatigue in pSS thus implies a probably multifactorial etiology, with different factors contributing to fatigue in individual patients.

Apart from fatigue, other common non-exocrine symptoms in pSS include symptoms from the locomotor system such as myalgia, arthralgia, or objectively verified synovitis (16, 33). Other organ systems may also be involved in the disease, resulting in Raynaud's phenomenon (16) or gastrointestinal (34), neurological (35), or dermatological (36) symptoms, and also hematological and lymphoproliferative disease (Figure 1) (37–41). Finally, psychiatric symptoms, including depression and anxiety, also seem to be overrepresented in pSS patients, although their pathogenesis in these patients is obscure (32, 42).

Involvement of the nervous system in Sjögren's syndrome

Virtually all parts of the nervous system may be involved in pSS (35). Central nervous system (CNS) disease appears to be uncommon in pSS in comparison to SLE, but cases of focal cerebral deficit, seizure, aseptic meningoencephalitis, myelopathy, and transverse myelitis have been reported in SS patients without evidence of other CTD (43–45). Moreover, MRI detected white matter lesions (46) and neuropsychiatric abnormalities (42) have also been reported in pSS patients.

If CNS involvement in pSS seems rare, involvement of the peripheral nervous

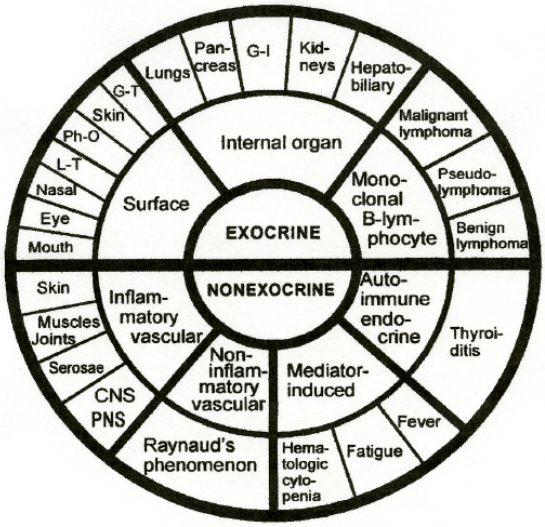


Figure 1. The Copenhagen classification wheel of primary Sjögren's syndrome, reproduced with permission from Dr Karsten Asmussen.
L-T: laryngotracheal; Ph-O: pharyngo-oesophageal; G-T: genital tract;
G-I: gastrointestinal; CNS: central nervous system;
PNS: peripheral nervous system

system (PNS) is more frequent and has been reported to give rise to symptoms of polyneuropathy in 21 % of pSS patients who were followed at a rheumatological unit, and neurophysiological abnormal findings in 23 % (47). In addition, a recent Norwegian cross-sectional study reported a 27 % prevalence of neuropathy in patients with pSS (48). The patterns of neuropathy observed in pSS patients have been reported to encompass sensory, motor, mixed, and cranial neuropathies as well as multiple mononeuritis (49–54). The pathogenesis behind neuropathy in pSS seems to be multifactorial, with some cases related to a vasculitic process affecting the vasa nervorum (49, 51, 53). In most cases of neuropathy the pathogenesis is more obscure, however, with histopathological findings of nerve fiber loss and lymphocytic infiltrates around peripheral nerves (49–54) and in dorsal root and sympathetic ganglia (49, 54). Due to the different neuropathological findings, the clinical picture of pSS related neuropathy varies (49). In a large study involving 92 pSS patients with neuropathic symptoms, some major patterns of neuropathy were described, namely: sensory ataxic neuropathy, painful sensory neuropathy without sensory ataxia, multiple mononeuropathy, multiple cranial neuropathy, trigeminal neuropathy, autonomic neuropathy, and radiculoneuropathy—of which the first was the most common pattern, affecting 39 % of the patients. It was concluded that the sensory ataxic

neuropathy, the painful sensory neuropathy and probably the trigeminal neuropathy were associated with a ganglio-neuropathic process whereas the multiple mononeuropathy and multiple cranial neuropathy were more closely related to a vasculitic process (49). Moreover, presence of antibodies to the dorsal root ganglion has been demonstrated in SS-related neuropathy, which may indicate a gangliopathic process (55).

Taken together, the different clinical and histopathological appearances of pSS-related neuropathies suggest a multifactorial pathogenesis. This would also explain the different levels of success obtained after treatment of different patients with various anti-inflammatory medications, e.g. intravenous immunoglobulins and steroids (49, 53).

Gastrointestinal involvement in Sjögren's syndrome

Xerostomia is the most common gastrointestinal (GI) symptom in pSS patients, although other gastrointestinal complaints are common as well (34). For example, dysphagia (i.e. subjective difficulty in swallowing) is very frequent in pSS (34) and has been reported to affect 33–92 % of pSS patients (56–62). It has been attributed to either lack of saliva (57, 58, 62), esophageal dysmotility (59, 62, 63) or esophageal webs (58, 64). Although the lack of saliva makes swallowing difficult by interfering with pharyngeal contraction (57) and bolus passage over dry mucosal surfaces of the esophagus in pSS (64), only one study has found correlations between lack of saliva, dysphagia, and esophageal dysmotility (62). However, this lack of association does not exclude diminished saliva production as a possible pathogenetic factor in causing dysphagia since salivary flow results usually vary little in SS patients, with many patients showing sialometry measurements close to 0 mL/min. It is possible that an association between dysphagia and low salivary flow would be found if studies were to include not only pSS patients but also patients with a more moderate degree of reduced salivary flow, such as patients with sicca symptoms without obvious etiology. In most previous studies on esophageal dysmotility in pSS, esophageal manometry has been used. According to these studies, one-third of pSS patients show varying degrees of esophageal dysmotility—including increased prevalence of aperistalsis, low contractions, and tertiary contractions as well as differences in peristaltic velocity, duration, and lower esophagus sphincter (LES) pressures relative to to controls (56, 59, 61, 63, 65). Although some previous studies have reported some correlation between dysphagia and esophageal dysmotility (59, 62), most others have not (56, 58, 60, 61). In two studies, esophageal webs have been suggested as one possible reason for dysphagia; they were found in about 10 % (58, 64) of pSS patients. In

another study in pSS patients, a correlation between GERD symptoms, increased reflux time, and tertiary contractions was found, indicating that diminished saliva formation may result in reduced esophageal acid clearance capability, morphological changes in the esophagus and esophageal dysmotility, possibly causing dysphagia (56). A summary of previous studies on dysphagia and esophageal dysmotility is presented in Table 2.

Stomach involvement in pSS includes an increased prevalence of atrophic gastritis, which is partly explained by the increased co-morbidity in pSS patients with autoimmune gastritis and also the lack of secretion of epidermal growth factor (EGF) from the salivary glands in SS, both of which cause mucosal atrophy and an increased sensitivity to acid exposure (34). Disturbances of the LES with reduced pressure (56) as well as a decreased gastric emptying, which have been found in 70% of pSS patients studied by gastric emptying scintigraphy (66), may also result in an increased prevalence of various dyspeptic complaints.

Since the major part of the pancreas is an exocrine organ, it may be involved in SS. However, SS-related pancreatitis is usually characterized by a rather benign and subclinical form of chronic pancreatitis (34, 67). Finally, coeliac disease (68) and hepatobiliary disease entailing primary biliary cirrhosis and autoimmune hepatitis (69) are also part of the clinical spectrum of SS-associated gastrointestinal disease.

The autonomic nervous system

The autonomic nervous system (ANS) is the part of the nervous system that cannot be influenced by will. It governs or modulates important functions of the body, e.g. heart rate, blood pressure, sexual function, gastrointestinal motility, and exocrine secretion. The activity is modulated by the hypothalamus, which is the most central part of the ANS, controlling and modulating autonomic nervous outflow from the CNS (70).

Classically, the ANS has been divided into the parasympathetic and the sympathetic nervous systems. The former exerts its action via efferent nerve fibers in the III, VII, IX and Xth cranial nerves and also via sacral nerves (70), and signals mainly with the neurotransmitter acetylcholine (ACh)—but also with vasointestinal peptide (VIP) and nitric oxide (NO), for example. The latter exerts its action via efferent nerve fibers, leaving the spinal cord at the Th1–L2 level, and signals mainly with adrenaline and noradrenaline (NA)—but also with neuropeptide Y (NPY), for example (70). The two parts of the ANS often seem to antagonize each other—for example, in the heart and the blood vessels where the parasympathetic nervous system reduces heart rate and blood vessel tonus and the sympathetic nervous system increases them. In

Table 2 – Studies on dysphagia and esophageal dysmotility in pSS

All studies were performed as case-control studies apart from one (64) which was a case-series.

Year	Authors	Ref	Number of patients	Methods	Findings in pSS patients (vs. controls)
1967	Hradsky et al	(64)	30	X-ray Endoscopy	Esophageal webs in 10 % Mucosal atrophy in 100 %
1985	Tsianos et al.	(65)	22	Manometry	36 % had esophageal dysmotility Aperistalsis, tertiary and low contractions No association between dysmotility and salivary flow
1986	Kjellen et al.	(58)	11 pSS and 11 sSS	Questionnaire X-ray Manometry	73 %/36 % had dysphagia for solids/liquids, respectively Esophageal webs in 10% Shorter persitaltic contraction time in SS Peristaltic velocity increased No association between dysphagia and dysmotility
1993	Grande et al.	(60)	20	Questionnaire Manometry	75 % had dysphagia Increased LES pressure No differences in esophageal motility vs. controls No association between dysphagia and dysmotility No association between dysphagia and salivary flow
1994	Palma et al.	(61)	21	Questionnaire Manometry	81 % had dysphagia 33 % had esophageal motor abnormalities 10 % had aperistalsis and 5% had tertiary contractions 19 % had an increased LES pressure No association between dysphagia and dysmotility

1997	Anselmino et al.	(59)	27	Questionnaire Manometry	74 % had dysphagia (7/26/41 % mild/moderate/severe) No difference in contraction velocity and amplitude Simultaneous contractions in 22 % distally and 11 % proximally No association between dysmotility and salivary flow Patients with simultaneous contractions had severe dysphagia
2001	Rostóczy et al.	(62)	25	Questionnaire Manometry	92 % had dysphagia Reduced peristaltic velocity and increased contraction time Increased simultaneous contractions Patients with reduced peristaltic velocity had: – a reduced salivary flow – a higher liquid requirement when eating – a higher rate of simultaneous contractions on dry swallows
2004	Volter et al.	(56)	21	Questionnaire Manometry 24h pH	33% had dysphagia and 62% had heartburn Reduced LES pressure No association between dysphagia and dysmotility Tertiary contractions in 29% - those patients had: – an increased reflux time and GERD symptoms
2005	Türk et al.	(57)	40	Questionnaire Manometry	65 % dysphagia 35 % dysmotility Increased LES pressure Lower peristaltic velocity & longer peristaltic contraction time No association between dysphagia and dysmotility
2007	Mandl et al.	(235)	20	Questionnaire X-ray	Dysphagia in 65 % (vs. 3 % in controls) Dysmotility in 40 % (vs. 30 % in controls) Prevalence of dysphagia but not dysmotility increased Dysphagia associated with AD

24h pH: 24 hour pH measurement; AD: autonomic dysfunction;
GERD: gastroesophageal reflux disease; LES: lower esophageal sphincter;
pSS: primary Sjögren's syndrome; sSS: secondary Sjögren's syndrome

some organs, one of the two systems may have by far the most pronounced effects e.g. the parasympathetic nervous system in the GI tract, where it influences motility as well as secretion. On the other hand, in the male reproductive system they co-operate in sexual function to produce parasympathetically mediated erection and sympathetically mediated ejaculation (71). In the exocrine glands, the two parts also work synergistically to produce mainly parasympathetically modulated secretion of liquid and mainly sympathetically modulated secretion of protein (72, 73).

Autonomic nervous function tests

The activity in the ANS can be measured using different techniques. Commonly, autonomic reflex tests (ARTs) are used to measure various cardiovascular autonomic reflexes, which are modulated differently by the parasympathetic and sympathetic nervous systems. Examples of the ARTs are the *deep-breathing test*, which measures the degree of sinus arrythmia to deep breathing (parasympathetic); the *orthostatic test*, which measures the heart rate (mainly parasympathetic but partly also sympathetic) and blood pressure reaction (sympathetic) to orthostatic challenge; the *cold pressor test*, *which* measures the vasoconstrictory response to cooling (sympathetic); the *Valsalva test*, which measures the heart rate reaction to the Valsalva maneuvre (parasympathetic) and the *sustained hand grip test*, which measures the diastolic blood pressure reaction to sustained hand grip (sympathetic) (74, 75). In addition to the cardiovascular autonomic nervous function tests, additional tests exist for evaluation of other parts of the autonomic nervous system, e.g. the quantitative sudomotor axon reflex test (QSART) and sympathetic skin response, which measure sudomotor function (74, 76, 77) and pupillometry, which measures pupillomotor function (70).

Other more modern ways of assessing cardiovascular autonomic function include studies on heart rate variability (HRV), where fast HRV changes are considered to be parasympathetically and slower changes are considered to be sympathetically mediated (74, 75). HRV can be studied in short-term electrocardiograms (ECGs) but it is better studied in 24-h ECGs (78). In addition, baroreceptor sensitivity (BRS) can also be studied. This involves measurement of the sensitivity of the baroreflex by assessing the relation between increase in blood pressure and decrease in heart rate either by performing concomitant blood pressure and heart rate measurements during the day or during orthostatic challenge, but ideally during phenylephrine infusion (74). ARTs are thought to measure ANS activity when the ANS is under stress while the HRV and BRS are thought to measure ANS function under basal conditions i.e. the tonic activity. The advantage of ARTs is the ease of performing these, in contrast with those involving HRV and BRS. All depend upon the co-operation of the subject

under study, however, but this is less critical in the case of HRV. Another proposed advantage of HRV & BRS investigations in comparison with ARTs is the higher sensitivity and reproducibility of the former (78–80), although claims of superiority of these modern techniques over ARTs are not always justified (81). Since many factors affect the ART variables, it is of great importance that the autonomic nervous function tests should be performed under standardized conditions, i.e. with uniform temperatures, during the same time of the day, without prior eating, drinking or smoking—and finally, without medication affecting the autonomic nervous function indices (e.g. various vasoactivive drugs) (74). Moreover, since autonomic function deteriorates with advancing age (80, 82, 83) and since certain autonomic nervous function parameters (83, 84)—although not all (80, 82, 85)—appear to differ between sexes, studies should take this into account and match subjects accordingly. Ideally, several different autonomic nervous function tests should be combined when evaluating ANS function, since this facilitates determination of the extent as well as the degree of autonomic involvement (86).

Physiology of exocrine glands

In pSS, the cardinal symptoms are related to exocrine gland dysfunction, commonly noticed as dry mouth and dry eyes due to hypofunction of the salivary and lacrimal glands.

Saliva is produced in the parotid, submandibular, sublingual, and accessory salivary glands, moisturizing and protecting the surfaces of the oral cavity and teeth against noxious microbial and chemical agents and also ameliorating bolus production, swallowing, and digestion of food (34). The saliva is produced by the acinar cells and modified with regard to, for example electrolyte composition by the ductal cells on its passage to the oral cavity (13). The surrounding myoepithelial cells, with their contractile properties, also play an important part in facilitating secretion and expulsion of the saliva (73). Although much of the secretion consists of liquid, there are many other constituents in saliva, e.g. IgA, lysozyme, amylase, and lactoferrin (72, 73). Tears are produced in a similar way in the lacrimal glands but other constituents such as mucins, produced by goblet cells, and lipids, produced by the Meibomian glands, have an important role in tear function by increasing tear film stability and reducing evaporation of tears from the surfaces of the eye (87–89).

To start secretion, the exocrine glands are dependent on autonomic nervous signaling. The liquid part of secretion appears mainly to be parasympathetically modulated and the protein secretion to be sympathetically modulated, although the two parts

of the autonomic nervous system work synergistically in the exocrine glands (72, 73, 90). Also, sex hormones appear to have some influence—on the lipid secretion in the lacrimal glands in particular, where androgens stimulate secretion from the Meibomian glands (89). The control of salivary gland secretion has been thoroughly studied, and involves a series of events. As the liquid in saliva is derived from blood, sufficient blood flow to the exocrine glands is a prerequisite for secretion. Before secretion, the salivary gland blood flow is increased due to release of NO and vasointestinal peptide (VIP) from parasympathetic nerve endings (72). Otherwise, the main signal for secretion is ACh, which is also released by parasympathetic nerve endings. ACh binds to the G-protein coupled muscarine 3 receptors (M3R) on the acinar cells in the exocrine glands. The activated G-protein stimulates phospholipase C to generate inositol 1, 4, 5-trisphosphate (IP3). IP3 binds to IP3 receptors on intracellular Ca^{2+} stores, causing a release of Ca^{2+} ions. The increment of intracellular Ca^{2+} both stimulates further release of Ca^{2+} via the IP3 and ryanodine receptors and activates apical membrane Cl^{-} channels and basolateral K^{+} channels, causing an efflux of Cl^{-} and K^{+} ions. The efflux of Cl^{-} ions to the apical lumen also causes a similar movement of Na^{+} ions in order to maintain electrochemical neutrality, resulting in an osmotic effect that brings water into the lumen (91)—a process further facilitated by the presence of aquaporins (AQPs), protein water channels, in the acinar and myoepithelial cells (Figure 2) (91, 92). Apart from the parasympathetic pathways, sympathetic pathways also affect the glandular cells through nerve-mediated signaling. These act via NA and adrenaline (activating mainly the adenylate cyclase pathway) and also NPY. The sympathetic pathways play a role in modulating protein secretion in particular, but also liquid secretion to some extent (72, 73). In addition to the secretory effects of autonomic nerve signals there are also trophic effects, as illustrated by the atrophy seen in a salivary gland deprived of parasympathetic signals (73). Following the production of primary saliva, its composition is modulated by the salivary ductal cells during its passage through the salivary gland ducts, which secrete IgA and EGF for example and also modulate the electrolyte composition of the saliva—e.g. by secreting K^{+} in exchange against Na^{+} ions, although not in equivalent amounts (73).

Pathogenesis in primary Sjögren's syndrome

Genetic factors are thought to increase the risk of developing pSS, as reflected by an increased prevalence in pSS patients of certain HLA class II genes, namely HLA-DR2 and -DR3. Several non-HLA-genes may also be involved (93–95), examples of the latter being various polymorphisms in genes coding for cytokines e.g. interleukin 10 (IL-10), IL-6, IL-1 receptor antagonist (IL-1ra), and tumour necrosis factor-alpha (TNFα), and also polymorphisms in other genes, e.g. those encoding Ro52, man-

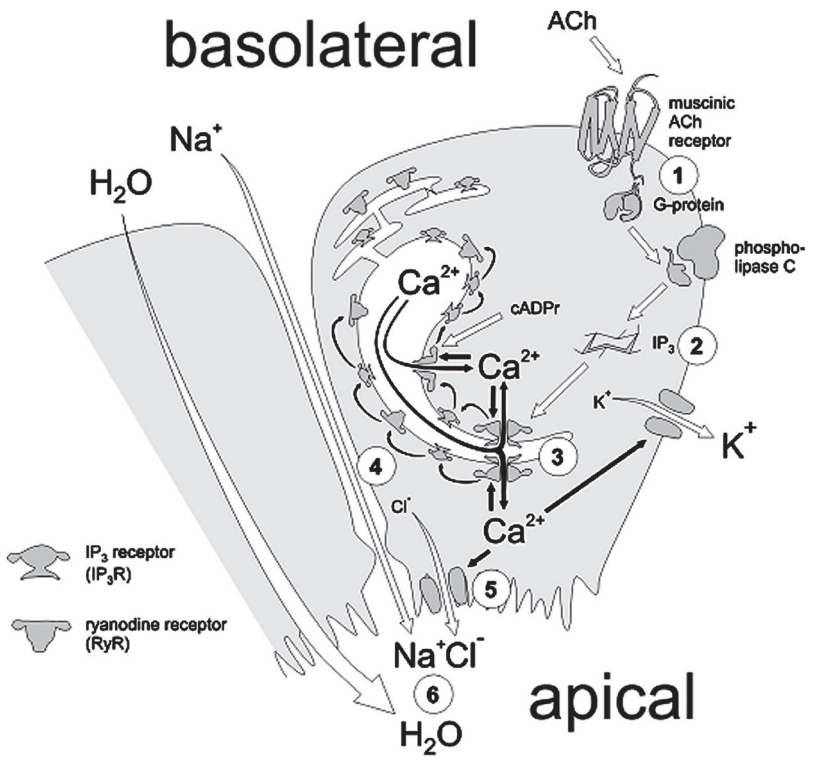


Figure 2. Control of fluid secretion in salivary acinar cells, reproduced with permission from Dr Luke Dawson.

nose binding lectin (MBL), Fas, and Fas-L (93–95). The predisposition to produce anti-SS-A antibodies is especially associated with the presence of certain HLA class II genes (95).

Due to the higher proportion of women with pSS, hormonal factors have also been considered as possible predisposing factors for the disease. Sex hormones are known to affect autoimmune disease (96), which explains the increase in disease activity in SLE patients during pregnancy and in RA patients post partum. Since estrogens and androgens have a somewhat antagonistic effect on different parts of the immune system, the balance between the two may influence several autoimmune processes (96–98). In pSS patients, a disturbance of the androgen–estrogen balance has been suspected to account for the gender differences in the prevalence of the disease, but studies on the effects of sex hormones (including the androgen dehydroepiandrosterone (DHEA)) have yielded conflicting results with one study reporting reduced serum concentrations of DHEA sulfate in pSS patients (97) and another study finding serum levels of various sex hormones including DHEA to be within the normal

range in pSS patients (98). It has, however, been speculated that lack of androgens and increasing age may increase the susceptibility of the exocrine glands to various noxious stimuli that can trigger exocrine autoimmune inflammation (99). Another hormone with immunomodulatory effects is prolactin. In accordance with the divergent results when studying estrogens and androgens in pSS patients, studies on prolactin levels in pSS have also been contradictory (97, 100), and the role of prolactin, if any, in pSS is still unclear. Finally, a hypofunction of the hypothalamic-pituitary-adrenal (HPA) axis has been reported with reduced levels of adrenocorticotropin (ACTH) and cortisol as well as a blunted response to stimulation with ovine corticotropin releasing hormone (oCRH) of unclear etiology and with unclear clinical implications (27). This could possibly be the effect of chronic stimulation of the HPA axis due to various stress factors in pSS, resulting in a fatigue in the former.

Other factors that have been proposed to predispose individuals to pSS are prenatal factors that may possibly affect the maturation of the immune system. For example, increased birthweight has been found to be associated with an increased risk of development of pSS (101). Apart from the above-mentioned factors that may predispose an individual to pSS, age-related decline in exocrine function and xerogenic medications may contribute to and aggravate sicca symptoms experienced by pSS patients (23).

Hypothetically, some triggering event might start the inflammation in the individual who is predisposed to pSS. Various viruses have been proposed to be triggering factors (102), including the hepatitis C virus (103), Epstein-Barr virus (104), and—most recently—the coxsackie viruses (105). Since many pSS patients do not show evidence of any known sicca related viral infection, other environmental factors have also been suggested as possible triggers of pSS, e.g. oxidative stress (106). In a susceptible subject this triggering event results in damage to the epithelial cells and generation of danger signals (106). These are perceived by various cells, resulting in activation of both the innate and adaptive immune system responses. The innate immune system is the first line of defense in the body and it includes different phagocytotic cells, Toll-like receptors (TLRs), and the complement system. Although the complement system has been more thoroughly studied in SLE (107), it is probably involved in severe manifestations in pSS also. It has, for example, been demonstrated that low levels of complement are associated with severe disease manifestations (108) and development of lymphoma (37, 39). In addition, expression of TLR2, TLR3, and TLR4 has been reported to be upregulated in the salivary glands of pSS patients, which also suggests that the innate immune system is involved in the pathogenesis of pSS (109).

Furthermore, it is hypothesized that the exposed location of the exocrine glands (at the host-environment interface), makes the exocrine gland cells easily susceptible various noxious stimuli, e.g. infectious agents, and the exocrine glands may therefore play a part in the host defense as a *locus minoris resistentiae* (99) to various microbes and other harmful factors.

Consequently, the exocrine gland cells not only have exocrine functions but may also play an important role in immune-inflammatory defense, e.g. against various microbes (99). This is seen especially in the exocrine gland inflammation in pSS, where exocrine cells are not only victims of—but also inducers of—inflammation, since salivary gland cells in pSS patients have been demonstrated to act as non-professional APCs expressing HLA class II molecules (110), co-stimulatory molecules (111), and TLRs (109) on their surface. During inflammation, several intracellular molecules become presented on the cell surface (112), resulting in further danger signaling as well as activation of CD4+ T-lymphocytes, i.e. helper T-cells. Being in the center of the adaptive immune system, the second line of defence of the body, the CD4+ T-lymphocytes activate CD8+ T-lymphocytes, i.e. cytotoxic T-lymphocytes, as well as antibody-producing B-cells. During these processes, several cytokines e.g. IFNα (113, 114), BAFF (114–116), TNFα (117), and chemokines (118) are produced, resulting in recruitment, activation and proliferation of T- and B-lymphocytes as well as induction of transcription of various genes.

Consequently, T-cells of both the CD4+ and CD8+ subsets and also B-cells infiltrate the glandular tissues and may cause tissue damage. In addition, an imbalance of various pro- and anti-apoptotic factors may cause infiltrating lymphocytes of both the B- and T-cell subsets to become less prone to undergo apoptosis, while the opposite is true in exocrine gland cells. Thus, the disturbed apoptosis may result in exocrine gland demise and an exaggerated immune response due to prolonged survival of autoreactive lymphocytes (119). During the autoimmune inflammation, the CD8+ T-cells cause cell-mediated tissue damage whilst the B-cells produce antibodies; the latter may be innocent bystanders, but they may also play a part in inflammation (120). Further antibodies in pSS may also have functional properties by blocking cholinergic neurotransmission to the exocrine glands—e.g. the anti-M3-receptor (M3R) antibodies (91), which may deprive the exocrine gland cells of nerve-mediated signals required for secretion. Such antibodies may also affect the intracellular distribution of AQPs, the water channels facilitating water transport in the exocrine gland (92, 121–122), thereby resulting in exocrine hypofunction. In addition, after some time inflammation in pSS may become self-sustaining and may continue even after the initial trigger has disappeared, resulting in further successive destruction of glandular tissue (123).

As previously mentioned, however, tissue destruction in pSS is often much less pronounced than the functional impairment, suggesting that there may be other mechanisms behind the exocrine dysfunction (19). Since autonomic nervous signaling is a prerequisite for exocrine secretion and some pSS patients have been found to express antibodies blocking cholinergic transmission, impaired autonomic nervous transmission might possibly explain the discrepancy between morphology and function seen in exocrine glands in pSS.

Autonomic dysfunction

Involvement of the ANS is a complication of many chronic diseases, including type I and II diabetes mellitus (124, 125), rheumatoid arthritis (126, 127), systemic lupus erythematosus (128, 129), scleroderma (129, 130), and inflammatory bowel disease (131, 132), and may be related to both troubling symptoms (133) and increased mortality due to ventricular arrhythmias and sudden death (133–135). Also, pSS patients have an increased frequency of various AD symptoms, e.g. orthostatic intolerance (136–138), urinary symptoms (29, 138), Adie's syndrome (139), and constipation (49), which may be due to ANS involvement. When studying autonomic nerve function in pSS by objective ARTs, signs of both parasympathetic and sympathetic dysfunction have been demonstrated (140–145) whilst studies on HRV and BRS have yielded contradictory results (145–149). These discrepancies may, however, reflect differences between these studies with regard to the use of classification criteria for pSS, standardization of autonomic nerve tests, and exclusion of patients on medications affecting autonomic nerve parameters—as well as differences between the autonomic nerve tests and control subjects used in different studies. An overview of the studies on autonomic function in pSS is given in Table 3.

Autonomic function is easiest to assess in the cardiovascular system, where various cardiovascular autonomic nerve tests, e.g. ARTs, HRV, and BRS exist. The function in other parts of the ANS, e.g. in the secretomotor, gastrointestinal, and urinary systems, are more difficult to assess due to a lack of methods assessing autonomic function in these. Since these other parts of the ANS seem to be more affected in pSS than the cardiovascular ANS, studies on exocrine autonomic nerve function, for example, would be of great interest but this has seldom been studied in pSS patients (150).

In pSS, AD has been ascribed to various immunological mechanisms—namely anti-M3R antibodies (151–153), cytokines interfering with nervous signaling (154–156) and inflammation of autonomic nerves, nerve vessels, and ganglia (49, 52). Al-

though many chronic AD symptoms may be explained by the anti-M3R antibodies (e.g. secretomotor dysfunction, urinary symptoms, and gastroparesis), a more subacute occurrence of AD symptoms, e.g. orthostatic intolerance (136–138), would fit better with a vasculitic process affecting autonomic nerves. Moreover, the Adie's syndrome that affects some pSS patients (139) is best explained by an inflammation affecting the ciliary ganglion, although the anti-M3-receptor antibodies could also be causative. Due to the differences in clinical manifestations and temporal development of various AD symptoms in pSS, with some symptoms developing over months/years and some symptoms occasionally developing over days/weeks, AD is probably due to different mechanisms in different patients. The clinical consequences of AD in pSS of course include several AD symptoms, but in contrast to what is found in patients with diabetes, AD in pSS does not seem to be associated with excessive cardiovascular mortality (157), which suggests that there may be different types of ANS involvement in patients with diabetes and pSS. Since it has been shown that parasympathetic nerve signaling may have an attenuating effect on macrophage-induced inflammation and production of various cytokines (158), a parasympathetic dysfunction may also affect the autoimmune inflammatory process in pSS and possibly result in an exaggerated inflammatory response. The parasympathetic nervous system appears to exert its anti-inflammatory effects on macrophages mainly through ACh and the nicotine receptor (158). Thus, the reduced focus scores and reduced prevalence of anti-SS-A antibodies reported in tobacco smoking pSS patients could fit with an immunomodulatory effect of nicotine in addition to that of the parasympathetic nervous system (159). Also, it has been reported that anti-muscarinic antibodies might cause an increased inflammatory response in pSS by increasing cycloxygenase-2 expression and prostaglandin E2 production (120).

Disturbed cholinergic transmission and the anti-M3-receptor antibodies

The fact that pSS patients often have large amounts of acinar tissue in the exocrine glands that is morphologically intact but which functions at a subnormal level in vivo (160) has heightened the interest in the mechanisms governing exocrine secretion and in possible mechanisms interfering with the normal signal transduction to and within acinar cells. The main parasympathetic receptor in exocrine glands is the M3R, which is also found elsewhere, e.g. in the gastrointestinal system and the bladder. In contrast, other muscarinic receptor subtypes, namely the M1- and M2-receptors, are more important in the brain and the heart, respectively. In healthy subjects, exocrine secretion starts when ACh stimulates the M3R. However, several factors could result in reduced stimulation of the M3R with resulting exocrine dysfunction, namely:

Table 3 – Studies on autonomic nervous function in patients with pSS
All studies were performed as case-control studies. In one study (144), however, some ART variables were considered abnormal if being below certain predefined values.

Year	Authors	Ref	Inclusion criteria	Number of patients	Methods	Main findings in pSS patients
1997	Mandl et al.	(141)	Cph / EC93	19	ARTs	Parasympathetic dysfunction
1998	Andonopoulos et al.	(143)	EC93	32	ARTs	AD
1999	Barendregt et al.	(144)	EC93	41	ARTs Pupillography	Parasympathetic dysfunction
2000	Niemelä et al.	(147)	EC96	28	24h HRV	No AD
2000	Tumiati et al.	(149)	EC93	16	HRV	Increased parasympathetic tone
2000	Kovacs et al.	(171)	EC93	22	CCh induced vasodilatation in the skin	Impaired vasodilation to CCh
2001	Mandl et al.	(142)	Cph / EC96	30	ARTs	Parasympathetic dysfunction Sympathetic dysfunction
2002	Barendregt et al.	(146)	EC93	43	ARTs, BRS, HRV	Minor abnormalities
2003	Niemelä et al.	(148)	AECC	30	ARTs, BRS, 24h HRV	No AD

Table 3 – Studies on autonomic nervous function in patients with pSS (Cont.)

Year	Authors	Ref	Inclusion criteria	Number of patients	Methods	Main findings in pSS patients
2004	Kovacs et al.	(145)	AECC	51	ARTs, BRS, BPV, HRV	Abnormal ARTs Reduced HRV & BRS Reduced BP variability
2007	Mandl et al.	(140)	AECC	46	ARTs	Parasympathetic dysfunction Sympathetic dysfunction Abnormal orthostatic BP reaction

24hHRV: 24-hour heart rate variability; AD: autonomic dysfunction; ARTs: autonomic reflex tests; BP: blood pressure; BPV: blood pressure variability; BRS: baroreceptor sensitivity; CCh: Carbachol; Cph: Copenhagen criteria; EC: European Community; HRV: heart rate variability; pSS: primary Sjögren's syndrome

1. Reduced innervation of the exocrine glands. Although it is plausible that inflammation and neural degeneration could result in a reduced innervation of acinar, myoepithelial and ductal cells in the exocrine glands, this is not supported by previous studies (160, 161).
2. Reduced ACh release. *In vitro* experiments using exocrine glands from MRL/lpr mice have indicated that certain cytokines (i.e. TNFα, IL-1α, and IL-1β) may impair neuronal release of ACh but this has not been confirmed in humans (160, 162). In addition, cytokines have also been proposed to affect the transcription and thus also the surface expression of neurotransmittor receptors, thereby interfering with signal transduction (155).
3. An increased degradation of ACh by cholinesterases. SS patients have been shown to have increased levels of cholinesterases, the enzymes that degrade ACh, in saliva. However, the implication of this finding is uncertain. Of note is that hydrochloroquine, which is sometimes used as an immunomodulatory drug in pSS, is a cholinesterase inhibitor, which is why treatment with this drug could possibly affect ACh degradation in exocrine glands—and thereby exocrine gland function (160, 163).
4. Antibodies directed against and blocking the M3R. The presence of such antibodies in pSS patients has been reported by various authors using different techniques. These include:
    a. Radioligand binding studies where sera from SS patients were found to bind noncompetitively to the M3R of rat parotid gland and exorbital lacrimal gland membranes (164, 165).
    b. Various immunological approaches e.g. using M3R transfected Chinese hamster ovary cells as the basis of a flow cytometric assay (166) and ELISA using a 16-mer sequence of the second extracellular loop of the M3R (167). These have, however, either not been able to be reproduced or have had a low specificity (91).
    c. Bioassays studying the effect of SS sera on e.g. carbachol induced contractility of mouse colon or bladder strips, for example. Here, the SS sera were shown to attenuate carbachol-induced contractions (151, 168).
    d. Bioassays using human salivary gland cells where carbachol-induced, fluorometrically assessed intracellular increase in Ca^{2+} is blunted by antibodies in the IgG fraction of SS sera. Using this technique, the M3R was found to be blocked by the M3R-antibodies in a reversible manner (169).

Additional studies have shown that after a period of blockade of cholinergic trans-

mission, these antibodies may induce a cholinergic hyperresponsiveness with up-regulation of the M3R, which may explain bladder irritability—which is commonly encountered in pSS patients (29, 66, 170). These antibodies have also been suggested to cause gastrointestinal symptoms, e.g. gastroparesis (66), and disturbance of microvascular responses to cholinergic stimulation (171). Reports on abnormal distribution of AQP in acinar cells (92, 121, 122) and an abnormal expression of certain protein kinase C isoforms (172) in various exocrine gland cells also show a disturbed intracellular signaling downstream of the M3R, which could fit in with the presence of anti-M3R antibodies. Furthermore, the physiologically measurable effects of the anti-M3R antibodies and the symptoms probably associated with them have also been reported to be diminished by anti-idiotypic antibodies/intravenous immunoglobulins (168, 173).

In conclusion, there is substantial evidence that a serological factor exists in the IgG fraction of sera from pSS and sSS patients, which seems to interact with the response of the M3R to cholinergic stimuli. The exact target of these antibodies is still a matter of debate, but the second extracellular loop of the M3R has been implicated (174). Probably due to their low concentration and our lack of knowledge about their exact specificity, they are difficult to detect using conventional immunological methods such as ELISA. The best methods for their detection today seem to be various bioassays studying their effects on murine colon and bladder contractility (91) or on increase in intracellular Ca^{2+} in human salivary gland cells as a result of cholinergic stimulation (91).

Prognosis and outcome

The exocrine disease in pSS, with resulting dryness of the eyes and mouth, is usually a relatively stable process at the time when the diagnosis is made, with small changes of objective exocrine function over time (175–177). However, one has to keep in mind that many patients have a substantial loss of exocrine function already at diagnosis, which is why further deterioration—as measured by exocrine function tests—is not possible. Furthermore, the degree of subjective sicca symptoms and fatigue also seems to be stable over time (177).

While the exocrine disease causes constant discomfort for SS patients, it is the increased prevalence of non-Hodgkin lymphomas (NHL) in SS patients that is the most severe complication of pSS. The association between SS and NHL was first reported in an epidemiological study in 1978, where a 44-fold increased risk of NHL was reported in a group of SS patients at a tertiary referral center (178). More recent epidemiological studies have reported a standardized incidence ratio (SIR) of 13–15

(37, 38) for lymphomas in pSS patients and a cause-specific standardized mortality ratio (csSMR) of 8 for lymphoma-related mortality (157). Since incidence of lymphoma has been found to increase with increasing disease duration, the risk of NHL in pSS appears to be related to the cumulative inflammatory burden of the disease (37). Various predictors of NHL have been identified, namely: parotid swelling (39, 179) lymphadenopathy (39, 179), palpable purpura (39, 179), low-grade fever (39), and also peripheral neuropathy (39). In addition, several laboratory predictors have been reported, including: anemia (39), lymphopenia (39) including CD4+ T-lymphocytopenia (37), low levels of complement factor 3 (37, 180) and 4 (37, 179, 181) and cryoglobulinemia (182). Although no significant excess mortality has been reported for pSS patient as a whole (157, 179) and the increased incidence of NHL is confined to pSS patients diagnosed according to the AECC (37), the lifetime risk of developing NHL still has been estimated to be 1–10 % in SS patients (41).

Considering the prognosis for neurological involvement in pSS, the peripheral neurological involvements in pSS are usually rather stable or slowly progressive (183) and spontaneous improvement without medication has been described (52). However, peripheral neuropathy is a predictor of NHL development (39); thus, pSS patients with symptomatic peripheral neuropathy should be closely monitored with regard to lymphoproliferative disease.

Treatment

Treatment of pSS can be divided into local treatment, mainly aimed at alleviating symptoms of dryness at various locations, and systemic treatment, aimed both at ameliorating sicca symptoms and at affecting different non-exocrine manifestations of the disease.

1. Local treatment

The mainstay of dry eye treatment is the use of various tear substitutes that are available with different viscosities, the more fluid forms being preferable during the day and the more viscous forms (including ointments) in the evening and at night (184). In addition to the use of artificial tears, various non-pharmacological methods can be used for dry eyes—including the avoidance of extensive indoor ventilation, use of room-humidifiers, having a working position that does not encourage evaporation of tears from the surface of the eye (e.g. a low-placed computer screen) and also occasionally lacrimal duct plugs. All of these measures are aimed at conserving the tears that are still produced by the lacrimal glands (184). Studies on topical treatment with NSAIDs have shown beneficial effects on ocular symptoms (184) and topical treatment with cyclosporine in the eyes has been reported to improve ocular symptoms,

objective exocrine function in the eyes, and also inflammation (185). Their current use in clinical practice is, nevertheless, limited.

Local treatment of dry mouth includes an increased water intake to lubricate the dry mucosal surfaces of the oral cavity, both to alleviate oral discomfort and to ameliorate chewing and swallowing when eating. In addition, the use of various lozenges and chewing gums stimulates the residual secretory function of salivary glands (15). Daily use of fluoride in combination with meticulous dental hygiene is also very important since both measures help to prevent caries and subsequent tooth decay (184). The use of topical immunomodulation for the treatment of SS related dry mouth has been studied using lozenges containing IFNα, which have been shown to increase salivary flow in pSS patients (15, 186). However, possible concerns with this study were the high placebo response rates, possibly explained by salivary stimulation by the lozenges irrespective of whether or not they contained IFNα. Finally, acupuncture has also been shown to improve salivary flow in some studies (187, 188), but its place in the treatment of oral sicca symptoms is still not clear.

2. Systemic treatment

One of the most commonly used forms of systemic treatment in pSS is the use of the secretagogues pilocarpine and cevimeline. The latter is still not available in Europe at present. These drugs exert their effects by stimulating mainly the M3R, and they have been shown to increase salivary flow rates and ameliorate oral and ocular symptoms in placebo-controlled trials (184, 189, 190). However, the presence of the M3R elsewhere in the body makes some patients experience adverse effects of these drugs, e.g. sweating, abdominal distress, and aggravated irritable bladder symptoms (184).

Bromhexine has been used for a long time for stimulation of the exocrine glands and in one study it was shown to improve lacrimal flow, as measured by the Schirmer I test (S1t), in SS patients (191). However, currently there is a lack of confirmatory studies.

Classical immunosuppressive drugs have not given much success in the treatment of pSS (184), although hydroxychloroquine is used occasionally—mainly for concomitant dermatological or musculoskeletal symptoms. The exocrine disease does not appear to be affected by hydroxychloroquine (192), although as a cholinesterase inhibitor this drug could possibly have beneficial effects on the exocrine disease (163). However, measurable anti-inflammatory effects with reduced IgG and erythrocyte sedimentation rates have been reported (192).

IFNα has been tried as an immunomodulatory treatment, not only in the form of oral lozenges (186) but also by subcutaneous administration (193), with some effects

on inflammation (194) and possible effects on peripheral neuropathy (195), which however remain to be confirmed. Considering the increased activity of the type I interferon system in pSS, drugs targeting IFNα would seem more rational.

A study using the androgen DHEA—based on the hypothesis that there may be a relative lack of androgens in pSS patients showed limited effects, although it has to be acknowledged that the study was small (196).

Finally, studies on biological agents include studies on TNFα blockers, the anti-CD20 antibody rituximab and the anti-CD22 antibody epratuzumab (197). Although an open pilot study with the TNFα blocker infliximab showed beneficial effects on salivary flow, for example (198), two randomized controlled trials with infliximab and etanercept failed to confirm this positive effect (117, 199). In open studies, rituximab has shown effects not only in the treatment of SS-related lymphoma but also in the treatment of various non-exocrine manifestations, although its effect on the exocrine disease is still unclear (200–202). Again, these findings and the effects on the exocrine disease must be confirmed by larger randomized studies since the studies so far have been open and small. Furthermore, it is plausible that the best effect on exocrine symptoms is probably to be expected in patients with short disease duration, when exocrine hypofunction is still due to various reversible inflammatory mechanisms and not to destruction of exocrine glands.

For the treatment of pSS-associated CNS disease, a combination of cyclophosphamide and steroids is usually the regimen of choice (184) but one case report has also shown rituximab to be a treatment option in subjects who are refractory to common treatment (203).

In case reports, the more common peripheral and autonomic neuropathies associated with SS have been reported to respond to intravenous immunoglobulins (204, 205), corticosteroids (138), infliximab (206), IFNα (195), and recently also rituximab (207). However, there is a lack of larger studies on this topic. Moreover, since various pathogenetic mechanisms (e.g. vasculitis, ganglionitis, anti-M3-receptor antibodies) may underlie the various neurological complications of pSS, this also underscores the importance of individualization of treatment in different patients based on the clinical picture and the pathophysiological mechanisms.

Aims

The aims of the studies presented in this thesis were the following:

I. To assess the prevalence and degree of ANS involvement in a cohort of pSS patients according to the AECC, and to relate autonomic nervous function to variables of exocrine function tests performed when diagnosing pSS (Study I).

II. To translate the English Autonomic Symptoms Profile (ASP), a questionnaire for evaluation of autonomic symptoms, into Swedish, to calculate standardized values for the different ASP domains, and to evaluate its reliability and validity in patients with type I diabetes (Study II).

III. To evaluate autonomic symptoms in pSS patients using the Swedish version of the ASP and to study associations between symptoms of AD and clinical and serological features of pSS (Study III).

IV. To assess the prevalence of pharyngeal and esophageal symptoms and of dysmotility in patients with pSS by comparison with age- and sex-matched controls (Study IV).

V. To relate dysphagia and video-radiographically assessed dysmotility to autonomic nervous function in pSS patients (Study IV).

Material and methods

Subjects

Patients

The patients with pSS were followed regularly at the Department of Rheumatology, Malmö University Hospital, where SS patients have been systematically registered in the Malmö Sjögren's Syndrome Register (MSSR) and prospectively followed since 1984. Initially, patients included in this register were diagnosed according to the Copenhagen criteria (5) but since 1993 the European Community criteria (3, 4) have also been utilized in parallel. The MSSR also includes patients with isolated xerostomia and KCS, who were followed to monitor their possible development into definitive SS patients. The nowadays widespread and well-established AECC (6) for SS were published in 2002 and these are the set of criteria most frequently used today. They have been used in our department since 2002. All pSS patients included in the studies described in this thesis fulfilled the AECC. The patients with type I diabetes belonged to a cohort being followed at the Department of Endocrinology, Malmö University Hospital, with regard to ANS involvement.

Study I comprised a cohort of 46 pSS patients included in the MSSR (median age 54 years, range 24–60 years; 43 females), 4 of whom were 60 years of age. All patients in the MSSR who did not meet any exclusion criteria were asked to participate in the study. The patients recruited were followed regularly at the outpatient clinic of the Department of Rheumatology, Malmö University Hospital. Exclusion criteria were: age > 60 years, concomitant disease known to affect autonomic nervous function, namely diabetes mellitus, inflammatory bowel disease, or other inflammatory rheumatic disease besides pSS, and current treatment either with drugs affecting autonomic nervous function (anti-cholinergic drugs, beta-blockers, calcium channel blockers, ACE inhibitors, or angiotensin-2 receptor blockers) or with disease-modifying anti-rheumatic drugs. Two pSS patients were treated with pilocarpine (5 mg qid) and one with prednisolone (5 mg daily), in whom treatment was discontinued 1 week prior to testing of autonomic and exocrine function.

Study II involved 31 patients (median age 52 years, range 39–69 years; 12 females) with type I diabetes, 6 of whom were ≥60 years of age (range 61–69 years). The patients belonged to a cohort of type I diabetics followed at the Department of Endocrinology, Malmö University Hospital since 1984–1985 with regard to autonomic nervous function. The patients had been diagnosed with type I diabetes at 15–25 years of age and had a median disease duration of 33 years. Thirteen patients had

co-morbidities or medications possibly affecting autonomic function. Due to co-morbidities, it was not possible to stop the medications prior to the study.

Study III comprised 38 of the 46 pSS patients in **Study I** (median age 56 years, range 25–61 years; 35 females) of whom eight patients were ≥ 60 years old (range 60–61 years). All patients included in **Study I** were asked to participate in **Study III.** However, six patients had moved or declined participation and two patients were excluded due to the use of pilocarpine. None of the patients who were included had any co-morbidity or were currently on any medication known to affect autonomic nervous function (anti-cholinergic drugs, beta-blockers, calcium channel blockers, angiotensin converting enzyme-inhibitors, angiotensin-2 receptor blockers or pilocarpine).

Study IV included 20 patients with pSS (median age 47 years, range 19–60 years; 18 females), 2 of whom were 60 years of age. The patients were recruited consecutively at the outpatient clinic of the Department of Rheumatology, Malmö University Hospital. Exclusion criteria were: age >60 years, current treatment with any drugs affecting autonomic nervous function (anti-cholinergic drugs, beta-blockers, calcium channel blockers, ACE inhibitors, or angiotensin-2 receptor blockers) or with glucocorticosteroids or disease-modifying anti-rheumatic drugs, and prior gastroesophageal surgery. In addition, for purposes of radiation hygiene, pregnancy and prior multiple (≥5) chest X-ray examinations were also used as exclusion criteria.

Controls

The controls for the deep breathing test (**Studies I–IV)** and orthostatic heart rate tests (**Studies I–III)** consisted of 56 healthy individuals (median age 40 years, range 16–59 years; 22 females), all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders or diabetes mellitus. The controls for the orthostatic blood pressure reaction test (**Studies I–III)** consisted of 238 healthy non-diabetic individuals (median age 60 years, range 16–96 years; 106 females). Finally, the finger-skin blood flow test (**Studies I–IV)** involved 80 healthy subjects (median age 43 years, range 19–81 years; 37 females), all of whom were non smokers, had no history of vascular disease, and were not on any medication. The control materials had been studied with the autonomic nervous function tests several years earlier than the pSS patients and type I diabetes patients, and although population-based controls would have been preferable, the controls were mainly recruited from laboratory staff, their friends, and relatives. However, the protocols and equipment used when studying patients and controls were identical.

The Autonomic Symptom Profile (ASP) controls in **Studies II–III** were randomly selected from the Swedish general population registry and were living in the City of

Malmö or its surroundings. Controls were asked by mail if they would like to participate in the study, if they had any disease (diabetes mellitus, rheumatoid arthritis, or Sjögren's syndrome) or were on any medication (anti-hypertensives, cardiovascular medication, or anti-depressants) possibly affecting autonomic function. If the subject was willing to participate and had no disease or medication that would affect autonomic function, the questionnaire was filled out once and sent back by post. If there were no answer after 4 weeks, a reminder letter was sent and if no answer was received, a new control of the same age and gender was selected. The response rate was 73%, but among the letters returned there were 43 from subjects who did not want to participate and 96 from subjects who had to be excluded due to the fact that they fulfilled one or more exclusion criteria (diabetes, n = 14; rheumatoid arthritis, n = 6; anti-hypertensive treatment, n = 59; cardiovascular medication, n = 8; and use of anti-depressants, n = 25). Two hundred controls (median age 45 years, range 20–69 years; 100 females) were thus included in the study.

In **Study IV,** the age- and sex-matched controls for the questionnaire on pharyngeal and esophageal symptoms and for the pharyngoesophageal video-radiography examination (median age 48 years, range 18–60 years; 27 females) were randomly selected from the Swedish general population registry. They lived in the city of Malmö or its surroundings. The exclusion criteria were the same as for the patients with pSS who were included in that study.

Experts

In **Study II,** two AD experts participated for the evaluation of the content validity of the Swedish ASP.

Autonomic nervous function tests

The patients with pSS in **Studies I**, **III**, and **IV** and the patients with type I diabetes in **Study II** were all studied by autonomic nervous function reflex tests (Figure 3), namely the deep breathing test (**Studies I–IV**), the orthostatic heart rate and blood pressure test (**Studies I–III**) and the finger-skin blood flow test (**Studies I–IV**). Since the autonomic nervous function variables are affected by various environmental factors, all autonomic nervous function tests were performed in the morning under standard conditions, i.e. the temperature conditions were kept stable and patients were not allowed to eat, drink coffee, or smoke later than 2 hours prior to testing.

1. The deep breathing test

This test measures the variability of heart rate from deep breathing, i.e. the degree of sinus arythmia, and it has previously been shown to be a specific test for para-sympathetic function since this reflex is diminished by atropine but not by propranolol (78). During the test, the subject was resting in the supine position for 15 minutes, while the heart rate was being monitored by ECG. When heart rate was constant, after 4 or more minutes of monitoring, six maximal expirations and inspirations were performed over a one-minute period. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R-R intervals during the expirations divided by the mean of the shortest R-R intervals during the inspirations (208).

2. The orthostatic heart rate and blood pressure test

During this test, the heart rate and blood pressure response to passive tilt is measured. According to previous studies, the reaction of heart rate to tilt is mediated mainly parasympathetically (133), but also sympathetically to some degree (209, 210), while the blood pressure response to tilt mainly seems to be sympathetically modulated (86).

While performing this test, the subject was strapped on a tilt table in the supine position for 10 minutes, and then, within 2 seconds, tilted to an erect position in which he/she remained for 8 minutes. The heart rate was constantly monitored by ECG during the entire procedure, starting 1 minute before tilt. Systolic and diastolic blood pressures were measured before and also every minute after tilt. A mean of the R-R intervals before tilt (A) was calculated and the shortest R-R interval during the first minute after tilting (B) was determined. From the values above, an acceleration index (AI), defined as [(A-B)/A×100] was calculated (211).

Moreover, the systolic and diastolic blood pressures before tilt (SBPrest and DBP–rest) and also the lowest systolic and diastolic blood pressures during the first 8 minutes after tilt (lSBP and lDBP) were determined. From these orthostatic systolic and diastolic blood pressure-ratios, lSBP ratio [= lSBP/SBPrest] and lDBP ratio [= lDBP/DBPrest] were calculated (212).

3. The finger-skin blood flow test

This test measures reflectory vasoconstriction to contralateral cooling and has been shown to be a sensitive test of sympathetic nervous function, since the reflex it measures is abolished in patients who have been sympathectomized due to excessive hand sweating (80).

The test was performed while the subject was sitting in a semi-recumbent position with the left hand on an aluminum holder, situated at heart level with the third finger placed in a groove of the holder, the temperature of which was kept stable at 40° C (Figure 3). The finger-skin blood flow was monitored by a laser doppler imaging (LDI) instrument, which scans an area of 2 × 2 cm of the distal phalanx of the third finger, every minute for 6 minutes, during rest at the 40° C heating (h) procedure. The subject then immersed the contralateral hand and forearm in a 15° C water bath and kept the forearm there for 3 minutes. A scan of the left middle finger was made every 30 seconds during immersion, and afterwards for a further 3 minutes. Hence, the finger-skin blood flow of the left hand was being monitored during this contralateral cooling (c) procedure. By dividing the lowest value of finger-skin blood flow during the first minute of contralateral cooling, LDI_c, by the mean of the two last measurements of finger-skin blood flow at rest before the cooling procedure, LDI_h, a vasoconstriction (VAC) index could be calculated: VAC index = LDI_c / LDI_h (80).

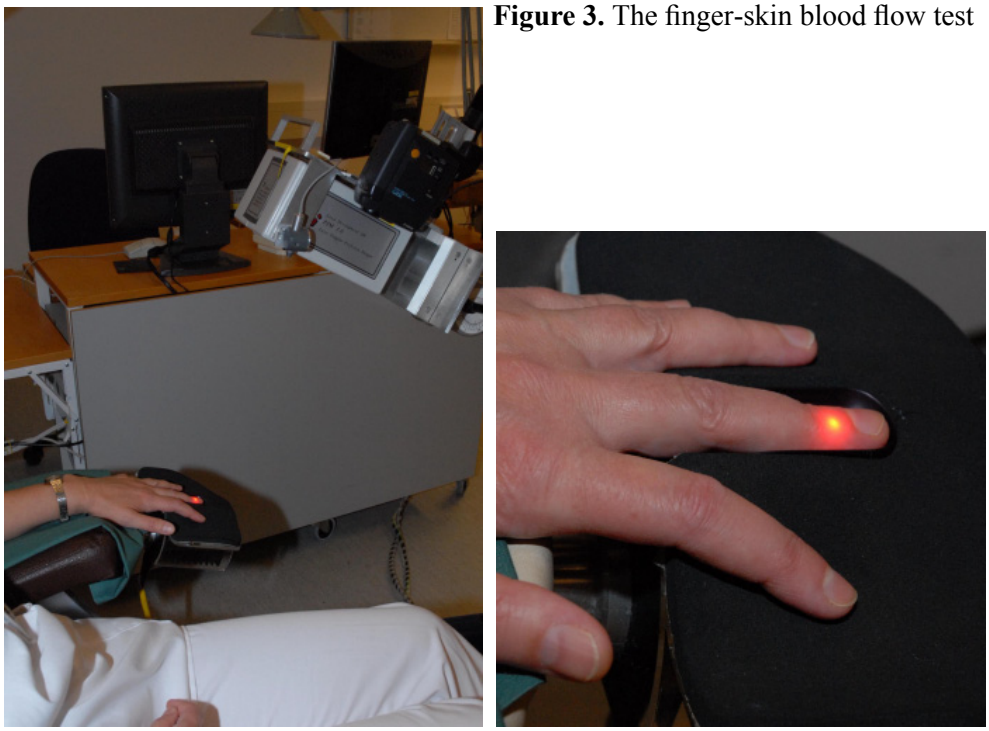
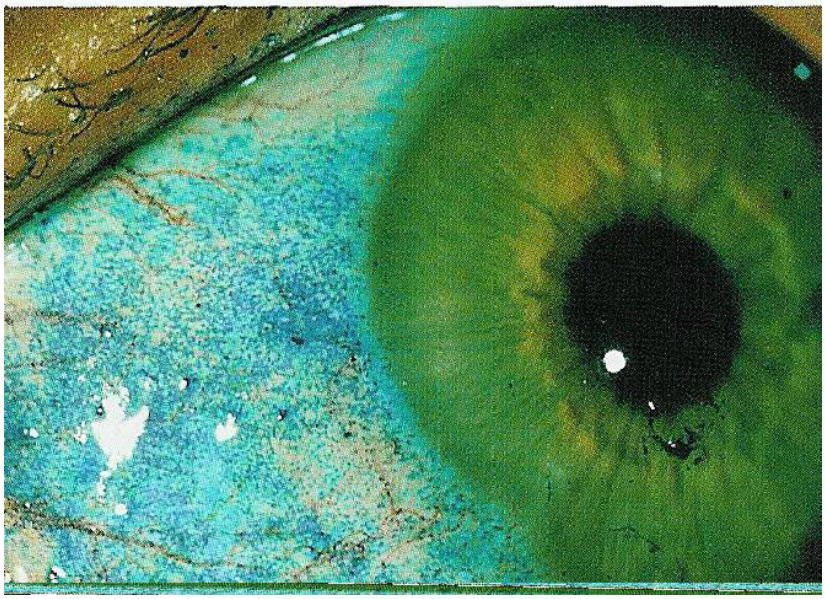


Figure 3. The finger-skin blood flow test



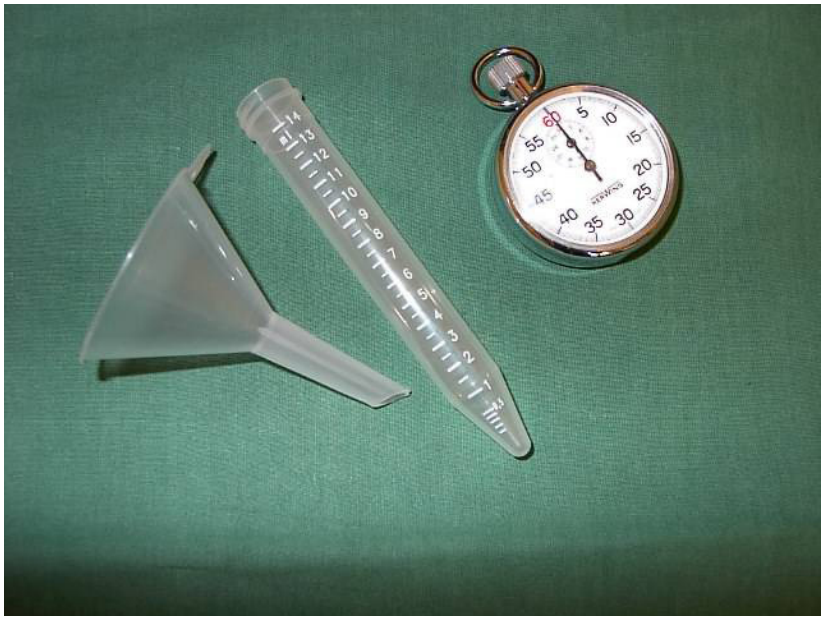


Figure 4.
The ophthalmological and oral exocrine function tests were performed at the Department of Rheumatology by the author (Schirmer I test and determination of the van Bijsterveld score) or a trained nurse (unstimulated whole sialometry). Reproduced with permission from Dr Elke Theander.

Standardization of the autonomic nervous function tests

Since autonomic nervous system function usually deteriorates with advancing age, the autonomic nervous function variables were age-corrected and expressed as z-scores by comparison with three previously examined control groups (80, 82, 212). The z-scores of the pSS patients were then compared with the z-scores of the controls to detect differences between the groups. Since gender does not appear to significantly affect the autonomic variables measured in the tests used in the studies in this thesis, matching for sex was not done (80, 82, 85).

Exocrine tests

The function of the lacrimal glands in pSS patients in **Study I** was evaluated by Schirmer I test (S1t) and determination of the van Bijsterveld score (vBs) as previously described (213). The ocular tests were all performed by the author at the Department of Rheumatology, Malmö University Hospital, using standard Schirmer paper strips and a slit lamp. To avoid unnecessary discomfort to the patients when determining the vBs, the rose bengal stain was replaced by lissamine green, since these stains are interchangeable and give virtually the same information—the latter, however, with substantially less eye discomfort (214). Ocular parameters were expressed in terms of sum of both eyes. The unstimulated whole sialometry (UWS) was measured for 15 minutes (215) and was performed by a trained nurse in our department. In addition, the UWS was performed under standardized conditions, i.e. the subject was not allowed to eat, drink, smoke, or use chewing gum or lozenges within the last hour prior to testing (Figure 4). All exocrine and autonomic nervous function tests in each individual patient in **Study I** were performed close in time (median (IQR) 1 (0–2) months apart).

The Autonomic Symptom Profile

The autonomic nervous function tests describe objective signs of AD. Although these objective parameters predict mortality to some extent (133–135), they do not detect symptoms of AD. Since AD symptoms can be very debilitating with manifestations such as orthostatic intolerance, erectile dysfunction, and secretomotor dysfunction, it is also important to assess the impact of the presence of AD symptoms on the well-being of such patients. Thus, the Autonomic Symptom Profile (ASP) was constructed at the Mayo Clinic and validated in patients with AD of different etiologies (216), and used in a study of AD symptoms in patients with diabetes (217). In **Study II**, the questionnaire was translated into Swedish and was validated in patients with type I diabetes for subsequent assessment of AD symptoms in patients with pSS (**Study III**).

In **Study II**, the ASP was first translated from English to Swedish by one translator and then back-translated to English by another translator, followed by comparison of the translations by the main author. No changes to the Swedish version were made. Reliability of the ASP was studied by test-retest where 25 of the patients completed the questionnaire on two separate occasions two weeks apart and intraclass correlation coefficients (ICC) were determined for the ASP domain and total scores. In addition, correlations between the ASP total score and the ASP domain scores were calculated for the 31 patients in the study. Validity was evaluated by studying content validity, construct validity and discriminant validity of the ASP. Content validity of the Swedish version of the ASP was evaluated by two Swedish AD experts. Construct validity was evaluated by studying correlations between the five different autonomic nervous function parameters and the ASP total score as well as by studying differences in the ASP autonomic domain scores in patients with normal and abnormal autonomic nervous function test results. Finally, discriminant validity was evaluated by hypothesizing that the patients would score higher in the ASP total score than the controls.

The questionnaire took approximately 30 minutes to fill out and consisted of 151 items, as well as some additional questions regarding age, gender, height, and weight. Among these items were 73 that were considered by the original constructors as being the most important clinically, and frequently asked questions when evaluating autonomic symptoms. These questions evaluated nine domains of autonomic symptoms, i.e. orthostatic intolerance (n = 9), secretomotor dysfunction (n = 8), male sexual dysfunction (n = 8), urinary dysfunction (n = 3), gastrointestinal dysfunction divided into 3 sub-domains—namely gastroparesis, diarrhoea, and constipation (n = 14), pupillomotor dysfunction (n = 7), vasomotor dysfunction (n = 11), sleep disorder (n = 8) and reflex syncope (n = 5). In addition, 12 interspersed questions were added addressing psychosomatic (n = 6) and understatement tendencies (n = 6). The autonomic symptom domains consisted of questions evaluating presence, severity, distribution, frequency, and progression of various autonomic symptoms. The separate answers in each domain were scored according to their predictability of disease.

Due to the different degrees of clinical importance of the various domains, scores were also weighted according to their clinical relevance. The weighted maximum domain scores were as follows: orthostatic intolerance, 40; secretomotor dysfunction, 20; male sexual dysfunction, 30; urinary dysfunction, 20; gastroparesis, 10; diarrhoea, 20; constipation, 10; pupillomotor dysfunction, 5; vasomotor dysfunction, 10; sleep disorder, 15; and reflex syncope, 20. By adding the autonomic domain scores an ASP total score could be calculated with a maximum of 200 for males

and 170 for females. The score was lower for females due to the lack of questions addressing female sexual dysfunction. In addition, the psychosomatic and understatement domains were allocated a maximum score of 10 each. The results of these domains were not included in the ASP total score but were presented separately.

Before data analysis, several ASP domain scores and the ASP total score were age-, gender-, height- and weight-standardized, based on the ASP scores of the 200 controls, using a linear regression model into which age, gender, height, and weight were added as covariates to each respective ASP score. Due to a preponderance of zero values—although with gender differences—among controls in some ASP domains, the gastroparesis and reflex syncope domains were expressed as gender stratified raw scores. Similarly, the psychosomatic and underestimation domains were expressed as gender-stratified raw scores (see Appendix A). Since two questions on psychosomatic symptoms from the original questionnaire addressed the existence of swallowing difficulties and experiencing that all food tastes the same (symptoms that cannot necessarily be regarded as psychosomatic symptoms in pSS patients with dry mouth), these questions were omitted from the psychosomatic domain and an adjusted psychosomatic index was calculated and re-weighted with a maximum score of 10 in **Study III**. The pSS patients who filled out the ASP in **Study III** had been studied previously with objective autonomic nervous function tests (in **Study I**). The difference in time between the completion of the autonomic nervous function tests and the ASP for the pSS patients was median 17 months (interquartile range limits: 10, 24 months) whereas the diabetic patients in **Study II** completed the ASP and the autonomic nervous function tests closely in time (at a maximum of 4 weeks apart).

The questionnaire on pharyngeal and esophageal symptoms

To evaluate the presence of dysphagia and also pharyngeal, esophageal and gastroesophageal reflux disease (GERD) symptoms in pSS patients, an as yet un-validated questionnaire that had been developed at the Department of Radiology, Malmö University Hospital, was used.

The subjects were interviewed using this questionnaire, which consisted of 15 questions screening for different clinically important pharyngeal and esophageal symptoms, the presence of which may result in seeking medical attention. The first question was related to the presence of dysphagia (defined as a positive answer to the question “Do you experience weekly occurrence of swallowing difficulties when eating solids and/or drinking liquids?”). Furthermore, the subjects who apparently had dysphagia were asked about the severity of the dysphagia, i.e. whether the dys-

phagia involved solids and/or liquids, and also the location of the dysphagia, i.e. pharyngeal, upper-esophageal, mid-esophageal, or distal-esophageal location.

Subjects were then asked questions related to GERD symptoms (weekly occurrence of: globus feeling, regurgitation, pyrosis, nocturnal asthma, and subjective feeling of an increased amount of fluid in the oral cavity (5 questions)), pharyngeal symptoms (weekly occurrence of: fluid/food in the nasal cavity after swallowing, misdirected swallowing, i.e. a sensation of passage of food or liquid into the airways when swallowing, coughing after swallowing, and hawking when eating (4 questions)), and also esophageal symptoms (weekly occurrence of: a feeling of obstruction when swallowing, avoidance of certain foods due to dysphagia, increased intake of liquids when eating, presence of odynophagia, and any previous episodes of acute obstruction that resulted in the need to vomit or in endoscopy (5 questions)). By adding the positive answers, i.e. presence of symptoms, the GERD (0–5), pharyngeal (0–4) and esophageal symptom scores (0–5) were calculated (Appendix B).

Pharyngeal and esophageal video-radiography

To objectively evaluate the presence of functional and morphological pharyngeal and esophageal abnormalities, pSS patients in **Study IV** were also studied by pharyngeal and esophageal video-radiography. This radiological technique was performed according to a protocol used at our hospital (218, 219), and is considered to be a minimally invasive method with little or no discomfort for the subject under study. However, the examination results in a dose of radiation equivalent to 15 chest X-rays (antero–posterior and lateral projections).

All radiography results were read by one of the co-authors (OE), who was not blinded with regard to what group the subject belonged to, as a consequence of the radiation protection committee's request for continuous monitoring of the prevalence of dysmotility in the control group. During the radiological procedure, pharyngeal and esophageal motility and morphology were monitored fluoroscopically and registered on a video tape for later evaluation (Figure 5 and 6). First, the subject had to swallow a solid bolus, i.e. a radiolucent tablet of antacid with a diameter of 13 mm, together with a thin liquid barium suspension (40% w/v). If the tablet was arrested in combination with symptoms of obstruction, the patient was considered to have bolus-specific esophageal dysfunction (BSED). The methodology did not permit assessment of esophageal transit time.

Then, the subject performed 5 swallows of high-density (240 % w/v) barium suspension in the standing and the supine positions. Esophageal motility was evaluated for signs of aperistalsis/peristaltic escape and non-propulsive peristalsis/esophageal

spasm in both the erect and supine positions. In addition, the presence of aperistalsis/peristaltic escape and non-propulsive peristalsis/esophageal spasm was semi-quantified as being normal (no signs), mild (present in 1 of 5 swallows), moderate (present in 2 of 5 swallows), or severe (present in ≥ 3 of 5 swallows) in both the erect and the supine positions. The subject was considered to have esophageal dysmotility if he/she had BSED or aperistalsis/peristaltic escape or non-propulsive peristalsis/esophageal spasm in at least 1 of 5 swallows in the erect position and/or the supine position. Finally, pharyngeal motility was evaluated by performing 5 swallows while being recorded video-radiographically both in the antero–posterior and in the lateral projections. The video-radiographies were evaluated afterwards for signs of radiological misdirected swallowing, defined as radiological signs that part of the swallowed bolus reaches the laryngeal vestibule or trachea, i.e. penetration or aspiration, pharyngeal retention, and pharyngoesophageal segment dysfunction (PESD). Presence of radiological misdirected swallowing, pharyngeal retention, and PESD was also semiquantified as above. The subject was considered to have pharyngeal dysmotility if he/she had radiological evidence of misdirected swallowing, pharyngeal retention, or PESD in at least 1 of 5 swallows. Due to the use of a single-contrast examination technique, the esophageal mucosa could not be evaluated for the presence of reflux-related mucosal changes. However, presence of more severe morphological changes, i.e. strictures and esophageal webs, was evaluated (Figures 5 and 6).

Statistics

Power calculations were performed in **Studies II** and **IV**. In **Study II**, the power calculation was based on the raw ASP total scores from the original publication of the ASP (216). Accordingly, the diabetic patients and controls in this study were assumed to have a raw ASP total score as found in patients with peripheral neuropathies and controls, respectively, in the original publication. Based on these values, the power calculation showed that inclusion of 30 patients with type I diabetes would require at least 12 age- and sex-matched controls to enable detection of a difference in the raw ASP total score with a power of 80 % at a significance level of $p < 0.05$. However, to ensure a balanced sex and age distribution for future studies with other patient groups (with various sex and age distributions), equal numbers of male and female controls were selected in each 10-year stratum. Thus, 20 controls were included per sex and age stratum, resulting in a control group of 200 subjects. This also enabled standardization of the ASP scores with regard to age, gender, height, and weight.

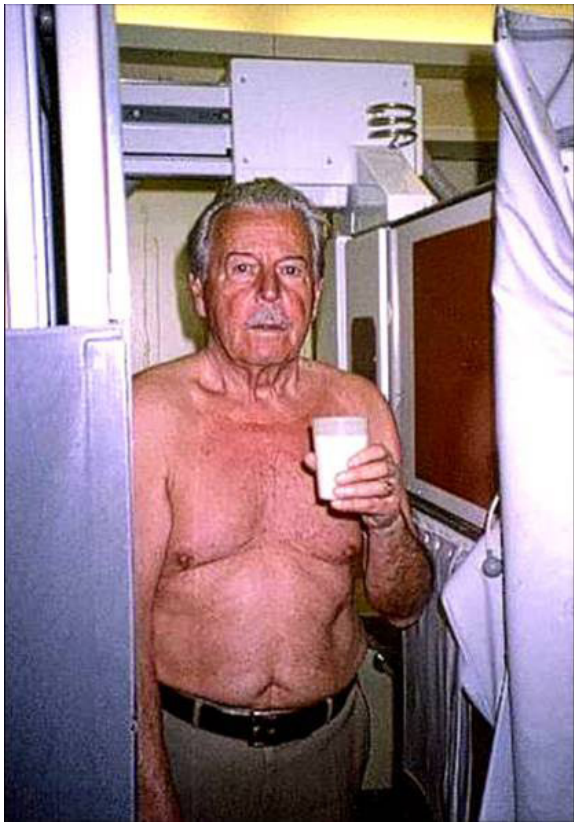


Figure 5.
Pharyngeal and esophageal video-radiography, in the erect and supine position, reproduced with permission from Professor Olle Ekberg.

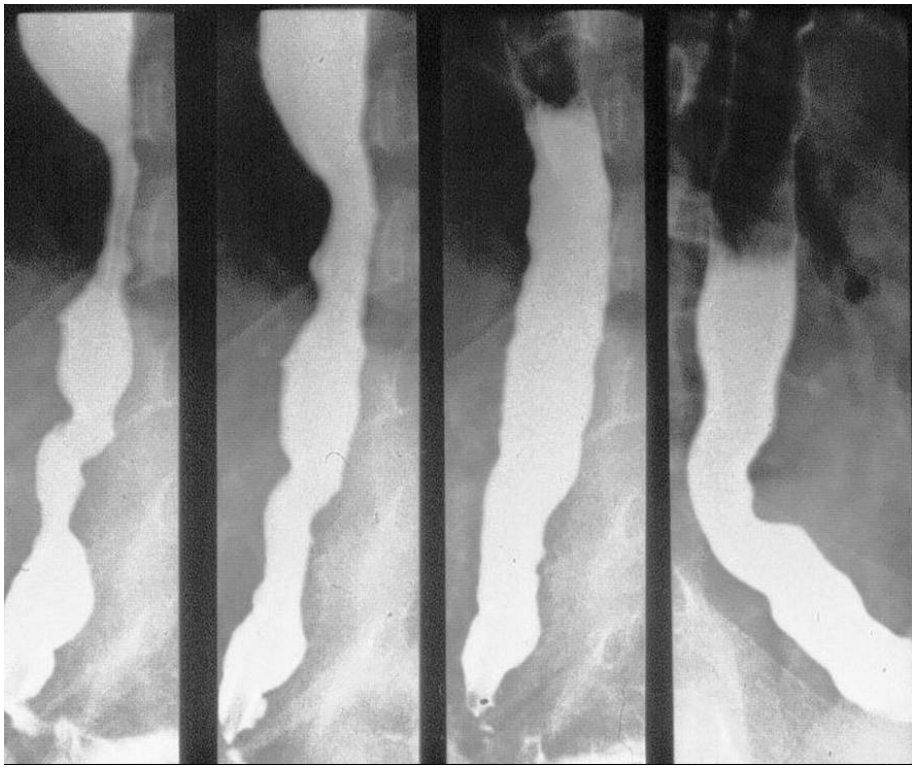


Figure 6.
Esophageal video-radiographies, reproduced with permission from Professor Olle Ekberg.

In **Study IV**, we first assessed the prevalence of esophageal dysmotility in the 20 pSS patients to be 40 %. Due to the lack of radiology data in subjects from the normal population, the prevalence of esophageal dysmotility had to be based on the assumption by our radiologist that the prevalence of esophageal dysmotility would be 5 % at most in the control group. Based on the above, power calculation indicated an 80% power to detect a difference (at the $p < 0.05$ significance level) in esophageal dysmotility if at least 30 controls were included.

Due to the often skewed distribution of the objective and subjective autonomic nervous function parameters, the Mann-Whitney U test was used for group comparisons and the Spearman rank correlation test for correlations. To study associations between discrete variables, the Chi-square test and Fisher's exact test were used. In **Study II**, several ASP domain scores and the ASP total score were age-, gender-, height- and weight-standardized, based on the ASP scores of the 200 controls. This was done using a linear regression model into which age, gender, height, and weight

were added as covariates to each respective ASP score. Values are presented as median with interquartile range limits in parenthesis (if not stated otherwise), and p-values of < 0.05 were considered significant.

Ethics

Studies I–IV were all approved by the Medical Ethics Committee of Lund University. Moreover, **Study IV** was also approved by the Radiation Protection Committee at Malmö University Hospital. All participating subjects gave written informed consent.

Table 4 – Characteristics of patients and controls in Study I–IV

Study	Group	Study target	Number (n)	Females (n)	Age in years Median (range)	Disease duration in years median (range)	Selection
I	pSS patients	Objective AD in pSS	46	43	54 (24–60)	12 (1–49)	Cohort of pSS outpatients followed at the Dept. of Rheumatology
	Controls		56 80 238	22 37 106	40 (16–59) 43 (19–81) 60 (16–96)	-	Healthy individuals who had passed a health examination
II	Type I diabetics	Validation of ASP	31	12	52 (39–69)	33 (21–50)	Cohort of type I diabetes outpatients followed at the Dept. of Endocrinology
	Controls		200	100	45 (20–69)	-	Randomly selected from the Swedish general population registry
III	pSS patients	Subjective AD in pSS	38	35	56 (25–61)	14 (1–50)	Patients participating in Study I were asked to participate
	Controls		200	100	45 (20–69)	-	Randomly selected from the Swedish general population registry
IV	pSS patients	Dysphagia and pharyngo-esophageal dysmotility in pSS	20	18	47 (19–60)	11 (2–44)	Consecutive pSS outpatients followed at the Dept. of Rheumatology
	Controls		30	27	48 (18–60)	-	Randomly selected from the Swedish general population registry

AD: autonomic dysfunction; ASP: autonomic symptom profile; pSS: primary Sjögren's syndrome

Results and discussion

Study I – Objective signs of autonomic dysfunction in pSS

Results

In this study, objective signs of AD in pSS patients were studied by 3 autonomic reflex tests and autonomic nervous function was related to exocrine function. The E/I ratio was significantly reduced in pSS patients as compared to the controls, indicating a parasympathetic dysfunction. Furthermore, pSS patients had a significantly increased VAC index and significantly reduced lSBP ratio and lDBP ratio compared to controls, indicating a sympathetic dysfunction. Thus, 9 % (4/44) and 2 % (1/44) of patients showed an lSBP ratio of ≤ – 2SD and an lDBP ratio of ≤ – 2SD, respectively and 11 % (5/44) and 7 % (3/44) of pSS patients had orthostatic systolic and diastolic hypotension, respectively, defined as a drop in orthostatic systolic blood pressure of ≥ 30 mm Hg and a drop in orthostatic diastolic blood pressure of ≥ 10 mm Hg, respectively (Table 5).

Eighty-four per cent (38/45), 74 % (34/46), and 59 % (27/46) had an abnormal UWS (abnormal being ≤ 1.5 mL/15 min), abnormal S1t (abnormal being ≤ 10 mm/5 min (sum of both eyes)), and abnormal vBs (abnormal being ≥ 8 (sum of both eyes)), respectively, when tested. When comparing autonomic nervous function variables between patients with normal and abnormal UWS, S1t, and vBs, respectively, these showed poor associations (Table 6). Moreover, when comparing the autonomic nervous function indices in patients with and without anti-SS-A antibodies and anti-SS-B antibodies, and also non-exocrine clinical signs and symptoms (arthralgia/arthritis in the joints of the hand, Raynaud's phenomenon, peripheral neuropathy symptoms, vasculitis, renal disease, liver disease, interstitial lung disease, and myositis), no significant differences were found. In addition, there was no significant difference in autonomic nervous function parameters between current smokers and non-smokers.

Discussion

In this study, objective signs of both parasympathetic and sympathetic dysfunction were found in pSS patients but there was no clear association between cardiovascular autonomic nervous function and exocrine function.

As AD is a common feature of many chronic diseases (124–132), and pSS patients may present different symptoms of AD (29, 49, 136–139) and other neurological deficits (47–54, 220), it is not surprising that AD may also be detected in pSS. In-

Table 5 – Results of the autonomic nerve function tests in Study I
Results of the deep breathing, orthostatic heart rate, finger-skin blood flow, and orthostatic blood pressure tests in 46 patients with primary Sjögren's syndrome (pSS) and 3 control groups (expiration/inspiration (E/I) ratio and acceleration index (AI), n = 56, vasoconstrictory (VAC) index, n = 80, lSBP and lDBP ratio and orthostatic change in SBP & DBP, n = 238). The E/I ratio, AI, VAC index, lSBP and lDBP ratio were age-corrected and expressed as z-scores (SD). The orthostatic systolic and diastolic blood pressure (SBP and DBP) changes were expressed as the relative blood pressure change to tilt (%). Results are presented as median (interquartile range). SD: standard deviation; NS: not significant.

	pSS patients (n = 46)	Controls (n = 56/80/238)	p-value
E/I ratio (SD)	–0.50 (–1.29 – 0.32)	–0.25 (–0.62 – 0.60)	0.03
AI (SD)	–0.08 (–1.11 – 0.37)	0.03 (–0.67 – 0.65)	0.22
VAC index (SD)	0.62 (-0.36 – 1.40)	0.09 (–0.67 – 0.62)	0.02
Orthostatic SBP change (%)	–10.3 (–14.7 – –6.0)	–5.3 (–9.1 – 0.0)	0.00
lSBP ratio (SD)	–0.75 (–1.33 – –0.08)	–0.02 (–0.62 – 0.70)	0.00
Orthostatic DBP change (%)	0.0 (–5.9 – 5.26)	0.0 (0.0 – 7.1)	0.02
lDBP ratio (SD)	–0.38 (–1.04 – 0.14)	0.00 (–0.47 – 0.54)	0.00

deed, most previous studies on autonomic nervous function in pSS using autonomic reflex tests (ARTs) have shown objective signs of AD, while studies on HRV and BRS have yielded divergent results (Table 3). The use of different classification criteria for pSS, however, and sometimes inclusion of patients on vasoactive medications affecting autonomic nervous function make comparisons between these studies difficult.

The strengths of this study were the use of the AECC for pSS, the exclusion of patients on vasoactive medications, and the use of large control groups for the autonomic nervous function tests, which allowed for age-standardization of the different indices. Possible concerns were the fact that the controls were collected several years earlier and that they were recruited mainly from laboratory staff, their friends and relatives, and not from the general population. Another concern was the gender difference between pSS patients and controls, since it has been shown previously that certain autonomic nervous function indices, e.g. BRS and HRV (83, 84), show gender differences. However, no significant gender-related differences in the autonomic nervous function indices used in this study have been reported (80, 82).

Primary SS-associated AD has previously been ascribed to various immunological mechanisms including anti-M3-receptor antibodies, cytokines interfering with

Table 6 – Associations between autonomic and exocrine function

Comparisons of age-corrected autonomic nerve function parameters (expiration/inspiration (E/I) ratio, acceleration index (AI), vasoconstrictory (VAC) index, and lowest systolic and diastolic blood pressure (lSBP and lDBP) ratio) between patients with normal and abnormal unstimulated whole sialometry (abnormal being ≤ 1.5 mL/15min), Schirmer I test (abnormal being ≤ 10 mm/5 min) and van Bijsterveld score (abnormal being ≥ 8). Ocular tests are presented as the sum of both eyes. Results are presented as median (interquartile range)

	Unstimulated whole sialometry (mL / 15min)			Schirmer I test (mm / 5 min)			Van Bijsterveld score		
	Abnormal ≤ 1.5	Normal > 1.5	p-value	Abnormal ≤ 10	Normal > 10	p-value	Abnormal ≥ 8	Normal < 8	p-value
E/I ratio	–0.48 (–1.30 – 0.40)	–0.49 (–0.69 – 0.07)	0.57	–0.33 (–0.90 – 0.51)	–1.25 (–1.87 – –0.55)	0.01	–0.30 (–1.21 – 0.61)	–0.62 (–1.42 – –0.36)	0.18
AI	–0.50 (–1.34 – 0.30)	0.24 (–0.06 – 1.35)	0.07	–0.07 (–0.82 – 0.35)	–0.77 (–1.68 – 0.53)	0.38	–0.06 (–1.02 – 0.39)	–0.56 (–1.21 – 0.45)	0.76
VAC index	0.62 (–0.39 – 1.56)	0.96 (0.37 – 1.25)	0.83	0.71 (–0.24 – 1.53)	0.46 (–1.17 – 1.01)	0.21	0.58 (–0.28 – 1.11)	0.69 (–0.71 – 1.74)	0.65
LSBP ratio	–0.75 (–1.46 – –0.19)	–0.84 (–1.01 – –0.02)	0.75	–0.77 (–1.33 – –0.15)	–0.63 (–1.68 – –0.08)	0.93	–0.77 (–1.86 – –0.07)	–0.63 (–0.99 – –0.11)	0.55
LDBP ratio	–0.70 (–1.20 – –0.13)	–0,01 (–0.27 – 0.51)	0.03	–0.58 (–1.20 – 0.14)	–0.33 (–0.80 – 0.17)	0.44	–0.38 (–1.34 – 0.22)	–0.51 (–0.98 – –0.09)	0.65

transmission of nervous signals, and inflammation affecting nerves and ganglia (49, 52, 151–156). Considering that exocrine gland destruction due to inflammation in pSS is often much less pronounced than the reduced exocrine function implies (19, 20), mechanisms other than or in addition to exocrine gland destruction would have to explain the exocrine insufficiency in pSS. Since autonomic nervous function is a prerequisite for exocrine secretion and since disturbance of these signaling pathways (160, 221) has been suggested as a possible explananation for the discrepancies between exocrine gland morphology and function, we wanted to study associations between autonomic and exocrine function. No clear association between autonomic and exocrine function was detected, however. This lack of association may have several explanations. Firstly, the autonomic nervous function tests used in this study mainly evaluate autonomic nervous function in the cardiovascular system, and do not necessarily reflect exocrine autonomic nervous function. Secondly, the presence of end-organ damage, i.e. exocrine gland destruction, also contributes to exocrine dysfunction, especially in patients with long disease duration. This also makes studies of associations between autonomic and exocrine function difficult and may obscure a possible association that might have existed before end-organ damage occurred. Thirdly, if anti-M3-receptor antibodies, as has been suggested, play an important role in pSS-related AD, the autonomic nervous function tests used in this study are probably not ideal for the detection of the physiological effects of such antibodies, due to differences in the presence of muscarine receptor subtypes in the heart (mainly M2 receptors), which are involved in the cardiovagal reflexes, and in the exocrine glands (mainly M3 receptors), which are involved in exocrine secretion. Finally, the small variation in exocrine function parameters in the pSS patients combined with the limited number of the patients in this study also make association studies difficult, and may conceal a true association.

Future studies on this topic should therefore include patients with short disease duration, where exocrine destruction is not yet apparent, autonomic nervous function tests assessing exocrine autonomic function, and also assessment of the anti-M3-receptor antibodies.

Study II – The Swedish version of the Autonomic Symptom Profile

Results

In this study, a questionnaire in English addressing autonomic nervous symptoms, the Autonomic Symptom Profile (ASP), was translated into Swedish and its reli-

ability and validity was evaluated in patients with type I diabetes. The patients who participated were found to have a significantly reduced E/I ratio, AI, and lDBP ratio and a significantly increased VAC index, and therefore had objective signs of both parasympathetic and sympathetic dysfunction. The lSBP ratio was, however, not significantly different between patients and controls, which contrasts with our findings in the pSS patients in **Study I**. Even when patients with co-morbidities and medications possibly affecting autonomic function or when patients ≥ 60 years of age were excluded from the analyses, the differences remained statistically significant.

The agreement of the various ASP scores between two separate completions of the ASP, performed 2 weeks apart, was generally judged as good, with a median ICC of 0.83. In addition, there was a significant correlation between orthostatic intolerance, sexual dysfunction, urinary dysfunction and secretomotor dysfunction domain scores and the ASP total score (Table 7).

Table 7 – Reliability of the Autonomic Symptom Profile (ASP)
Results of the test-retest performed by 25 type I diabetes mellitus patients two weeks apart and the Spearman correlations of the various domain scores of the Autonomic Symptom Profile (ASP) with the ASP total score in the 31 patients with type I diabetes.
ICC: intraclass correlation coefficient.

Domains (score range)	ICC	Correlation with ASP total score: r_S (p-value)
Orthostatic intolerance (0–40)	0.92	0.51 (0.00)
Sexual dysfunction (males 0–30)	0.85	0.69 (0.00)
Urinary dysfunction (0–20)	0.83	0.49 (0.01)
Diarrhoea (0–20)	0.59	0.23 (0.23)
Gastroparesis (0–10)	0.83	0.28 (0.13)
Constipation (0–10)	0.98	0.17 (0.36)
Secretomotor dysfunction (0–20)	0.67	0.59 (0.00)
Sleep disorder (0–15)	0.82	0.13 (0.48)
Vasomotor dysfunction (0–10)	0.87	0.21 (0.28)
Pupillomotor dysfunction (0–5)	0.73	0.29 (0.12)
Reflex syncope (0–20)	0.66	0.12 (0.52)
Total (males 0–200 & females 0–170)	0.87	–

Content validity of the Swedish translation of the ASP was judged as good by two Swedish experts on AD. Construct validity was evaluated by studying associations between the ASP scores and objective autonomic nerve test parameters. There was a significant correlation between the ASP total score and the VAC index and lSBP ratio but not with the other ART variables (Table 8). When comparing ASP scores in patients with abnormal and normal parasympathetic test parameters, i.e. the E/I ratio and AI, the former were found to have higher scores in the ASP secretomotor dysfunction domain. Comparing ASP scores in patients with abnormal and normal sympathetic test parameters, i.e. VAC index, and lSBP and lDBP ratios, patients with an abnormal VAC index scored higher in the sexual dysfunction and diarrhoea domains than patients with normal VAC indices. Furthermore, patients with an abnormal lSBP ratio scored lower in the vasomotor dysfunction domain than patients with normal lSBP ratios, and patients with abnormal lDBP ratios scored higher in the secretomotor dysfunction and constipation domains as well as in the ASP total score than patients with normal lDBP ratios. Based on these results, construct validity was judged to be acceptable.

Finally, discriminant validity was evaluated by studying differences in ASP scores between patients and controls. The sexual dysfunction, sleep disorder, and vasomotor dysfunction domain scores were significantly higher in patients than in controls, and there was a tendency, although not statistically significant, for there to be a higher score for the orthostatic intolerance domain in the patients than in the controls. Consequently the ASP total score was significantly elevated in patients with type I diabetes compared with controls, and 13 % (4/31) of the patients had a standardized ASP total score of ≥ 2SD indicating a pathological autonomic symptomatology (Table 9). When patients with co-morbidities and medications possibly affecting

Table 8 – Construct validity of the Autonomic Symptom profile (ASP)
Correlations of the autonomic nervous function parameters and the Autonomic Symptom Profile (ASP) total score in 31 patients with type I diabetes. Results are presented as Spearman rank correlation coefficient (p-value).

Autonomic parameters	ASP total score: r_S (p-value)
Expiration inspiration index	–0.12 (0.54)
Acceleration index	–0.09 (0.64)
Vasoconstrictory index	0.39 (0.04)
Lowest systolic blood pressure ratio	–0.36 (0.05)
Lowest diastolic blood pressure ratio	–0.29 (0.12)

Table 9 – Discriminant validity of the Autonomic Symptom Profile (ASP)
Comparison of ASP scores in patients with type I diabetes and controls. Scores were age-, gender-, height-, and weight-standardized and expressed as z-scores. The standardized scores were used for comparisons between groups the standardized scores were used, except for the gastroparesis, reflex syncope, psychosomatic, and underestimation domains where gender-stratified raw scores were used. Results are presented as median (interquartile range limits). NA: Not Assessed.

Domains (rawscore range)	**Rawscores Type I diabetics (n=31, 12 females)**	**Standardized scores Type I diabetics (n=31, 12 females)**	**Raw scores Controls (n=200, 100 females)**	**Standardized scores Controls (n=200, 100 females)**	**p-value**
Orthostatic intolerance (0–40)	2.5 (0.0 , 12.5)	–0.24 (–0.51 , 1.17)	1.3 (0.0 , 12.5)	–0.39 (–0.78 , 0.79)	0.07
Sexual dysfunction (males 0–30)	10.5 (1.5 , 15.4)	2.04 (–0.03 , 3.34)	0.0 (0.0 , 1.5)	–0.22 (–0.51 , 0.11)	0.00
Urinary dysfunction (0–20)	0.0 (0.0 , 2.0)	–0.54 (–0.71 , 0.16)	0.0 (0.0, 2.0)	–0.51 (–0.71 , 0.32)	0.53
Diarrhoea (0–20)	0.0 (0.0 , 0.0)	–0.40 (–0.56 , –0.14)	0.0 (0.0 , 4.0)	–0.42 (–0.60 , 0.68)	0.82
Gastroparesis – females (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.82
Gastroparesis – males (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.89
Constipation (0–10)	0.0 (0.0 , 0.0)	–0.30 (–0.50 , –0.21)	0.0 (0.0 , 0.0)	–0.30 (–0.52 , –0.18)	0.93
Secretomotor dysfunction (0–20)	1.5 (0.0 , 4.5)	–0.07 (–0.70 , 1.46)	0.0 (0.0 , 3.0)	–0.45 (–0.72 , 0.52)	0.15
Sleep disorder (0–15)	1.5 (1.5 , 4.0)	0.18 (0.01 , 1.51)	1.5 (0.0 , 1.5)	–0.05 (–0.79 , 0.35)	0.00
Vasomotor dysfunction (0–10)	0.0 (0.0 , 0.0)	–0.26 (–0.42 , –0.10)	0.0 (0.0 , 0.0)	–0.33 (–0.49 , –0.20)	0.05
Pupillomotor dysfunction (0–5)	1.0 (0.0 , 2.0)	0.13 (–0.74 , 1.15)	0.5 (0.0 , 1.5)	–0.42 (–0.71 , 0.55)	0.25
Reflex syncope – females (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.87
Reflex syncope – males (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.96
Total score (males 0–200 & females 0–170)	24.8 (13.9 , 31.8)	0.89 (0.03 , 1.29)	13.0 (4.5 , 23.4)	–0.21 (–0.82 , 0.72)	0.00
Psychosomatic index – females (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.21
Psychosomatic index – males (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.36
Understatement index – females (0–10)	0.0 (0.0 , 1.5)	NA	0.0 (0.0 , 3.5)	NA	0.26
Understatement index – males (0–10)	3.5 (0.0 , 6.5)	NA	1.5 (0.0 , 5.0)	NA	0.11

autonomic function were excluded from the comparison, the remaining 18 patients still had increased sexual dysfunction, increased sleep disorder, and elevated ASP total scores compared to the controls (data not shown). Thus, discriminant validity was also considered to be acceptable.

Discussion

The English-language version of the ASP was translated into Swedish and its reliability and validity were evaluated in patients with type I diabetes. Reliability and content validity of the Swedish version of the ASP were considered good and construct and discriminant validity acceptable.

The ASP in English has been validated previously in patients with AD of various etiologies, including patients with pathology localized both in the peripheral and central nervous system (216). The English version of the ASP was considered valid both regarding content validity (based on experts' opinions), construct validity (based on associations between ASP scores and objective autonomic nervous function tests), and discriminant validity (based on differences between patients with AD, patients with non-autonomic peripheral neuropathies, and controls) (216). In contrast, when using the English-language ASP in patients with type I and II diabetes, AD symptoms were mild in this patient group and associations between objectively assessed AD and AD symptoms were weak (217).

The strength of this study was the use of a homogenous group, i.e. diabetics with objective signs of AD, a long disease duration, and also a large population-based control group enabling standardization of the ASP scores according to gender, age, height, and weight. Possible concerns are the generalizability of these results to other diabetics with less pronounced objective signs of AD and to other patient groups. Another concern is the fact that some of the significant differences found when comparing ASP scores of patients with and without abnormal autonomic nervous function indices may be related to multiple comparisons rather than true differences.

In this study, reliability of the ASP was studied by test-retest and the ICC varied from moderate to very good (0.59–0.98). According to the literature, it is reasonable to demand stability measures, i.e. ICC greater than 0.5 (222), and the ICCs for all autonomic domains were above this limit. Due to the multidimensional nature of this questionnaire, evaluation of internal consistency was considered inappropriate, as was factor analysis due to the limited number of patients. Instead correlations between the ASP total score and the ASP domain scores were studied and the orthostatic intolerance, sexual dysfunction, urinary dysfunction, and secretomotor dysfunction domain scores were found to correlate most closely to the ASP total score.

Content validity of the Swedish translation of the ASP was considered good and appropriate for use in Swedish patients by two Swedish AD experts. When studying construct validity, the ASP total score was found to be most closely correlated to the VAC index and lSBP ratio, two of the sympathetic nervous function tests. Thus, the ASP total score in our diabetic patients appears to reflect mainly sympathetic deficits. However, as patients with abnormal objective parasympathetic nervous function tests had significantly elevated secretomotor domain scores, parasympathetic deficits may also be associated with certain symptoms in diabetics. Although sicca symptoms are recognized in patients with diabetes, it is debatable whether such symptoms are caused by disturbed glycemic control (223, 224) or AD (225). In addition, patients with an abnormal sympathetic function, as evaluated with the VAC index, scored significantly higher in the sexual dysfunction domain, which was an unexpected finding as erection is usually considered to be a parasympathetically modulated function (226). The orthostatic blood pressure ratios were found to be associated with some ASP domains, although not with the orthostatic domain, a finding possibly related to the lack of both objective and subjective signs of orthostatic hypotension in the patients. The overall lack of more solid associations between the ASP domains and the autonomic nervous function parameters may have several explanations. Firstly, the relative lack of AD symptoms in diabetics in combination with the few stepped scales in some ASP domains make association studies difficult. Still, this is in accordance with what was described in diabetic patients studied with the English ASP (217). Secondly, insufficient reliability in the test procedures for some ASP domains and for the autonomic nervous function tests may complicate studies of associations. Due to the often discordant findings of objective and subjective signs of AD, the importance of evaluating these entities separately must be emphasized.

When studying discriminant validity of the ASP, diabetes patients scored significantly higher in the sexual dysfunction, vasomotor dysfunction, and sleep disorder domains and showed a tendency of having higher scores in the orthostatic intolerance domain. Thus, the ASP total score was significantly elevated in patients relative to controls, and discriminated between those. In accordance with this study, erectile dysfunction (ED) is reported to be a common complication of diabetes, with a reported prevalence that varies from 20 % to 75 % (227). ED may be related to various factors namely arterial insufficiency, drugs, endocrine abnormalities, and psychogenic factors, but also to AD (227). Although it may be argued that the ED symptoms in the diabetics were related to either drug use or atherosclerotic disease, the differences in the sexual dysfunction domain remained after exclusion of patients on psychoactive drugs, on vasoactive medication, or with concomitant hypertension or cardiovascular disease. Thus, a direct relationship between AD and ED appears

to exist in these patients. Another feature of AD is sleep-disordered breathing with obstructive sleep apnoeas since AD may cause an increased collapsibility of the upper airways due to impairment of the autonomic reflex arches activating the upper airway dilator muscles (228). Thus, our findings of an increased occurrence of symptoms of sleep disorder are compatible with a relationship between AD and sleep-disordered breathing in diabetics also. Moreover, patients were found to have a significantly increased vasomotor dysfunction score and a tendency to have an increased orthostatic intolerance score. Although more pronounced symptoms of AD in these diabetics with long disease duration were to be expected, this relative lack of more severe symptoms is in agreement with a previous report (217).

Future studies should therefore involve other and larger patient groups with AD of variable severity, in order to better assess construct and discriminant validity, the applicability of the ASP in various patient groups as well as its sensitivity to change. In addition, this would also make it possible to shorten the questionnaire, as certain domains might not be as applicable in all AD patients, thus giving a form that is filled out in a shorter time.

Study III – Autonomic symptoms in pSS

Results

In this study the presence of symptoms of AD was evaluated using the ASP in pSS patients, as were possible associations between AD symptoms and clinical features of pSS. As previously reported (**Study I**), the pSS patients were found to have significantly depressed E/I ratios, lowest systolic and diastolic blood pressure (lSBP and lDBP) ratios, and significantly increased VAC indices, reflecting both parasympathetic and sympathetic dysfunction.

As expected, patients with pSS scored higher than controls in the secretomotor and pupillomotor dysfunction domains, but also in other parasympathetic domains, i.e. the urinary disorder and gastroparesis (females only) domains. Moreover, pSS patients also scored higher in the sympathetic domains, i.e. the orthostatic intolerance and vasomotor dysfunction domains. Consequently, the ASP total score was significantly elevated in pSS patients compared to controls (Table 10), and 45% (17/38) of the pSS patients had a standardized ASP total score ≥ 2 SD, indicating a pathological autonomic symptomatology.

Female pSS patients also scored significantly higher in the psychosomatic domain, however, reflecting psychosomatic tendencies. If two questions on psychosomatic symptoms from the original questionnaire, addressing the existence of swallowing

Table 10 – Comparisons of the Autonomic Symptom Profile (ASP) domain scores in patients with primary Sjögren's syndrome (pSS) and controls

Standardized scores were age-, gender-, height- and weight-standardized and expressed as z-scores. For comparisons between groups the standardized scores were used, except for the gastroparesis, reflex syncope, psychosomatic, adjusted psychosomatic, and underestimation domains where gender-stratified raw scores were used. Results are presented as median (interquartile range limits).

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$. Adj: adjusted; NA: Not Assessed.

Domains (raw score range)	Raw scores pSS patients (n=38, 35 females)	Standardized scores pSS patients (n=38, 35 females)	Raw scores Controls (n=200, 100 females)	Standardized scores Controls (n=200, 100 females)	p-value
Orthostatic intolerance (0–40)	15.0 (0.0 , 22.5)	1.21 (–0.56 , 2.38)	1.3 (0.0 , 12.5)	–0.39 (–0.78 , 0.79)	0.00***
Sexual dysfunction (males 0–30)	0.0 (0.0 , 6.0)	–0.18 (–0.67 , 0.70)	0.0 (0.0 , 1.5)	–0.22 (–0.51 , 0.11)	0.92
Urinary dysfunction (0–20)	2.0 (0.0 , 6.0)	0.13 (–0.67 , 1.98)	0.0 (0.0, 2.0)	–0.51 (–0.71 , 0.32)	0.04*
Diarrhoea (0–20)	2.0 (0.0 , 8.0)	0.08 (–0.67 , 1.41)	0.0 (0.0 , 4.0)	–0.42 (–0.60 , 0.68)	0.42
Gastroparesis – females (0–10)	0.0 (0.0 , 1.5)	NA	0.0 (0.0 , 0.0)	NA	0.04*
Gastroparesis – males (0–10)	0.0 (0.0 , 3.5)	NA	0.0 (0.0 , 0.0)	NA	0.41
Constipation (0–10)	0.0 (0.0 , 3.0)	–0.46 (–0.56 , 2.57)	0.0 (0.0 , 0.0)	–0.30 (–0.52 , –0.18)	0.82
Secretomotor dysfunction (0–20)	7.5 (6.0 , 10.5)	2.86 (2.26 , 4.02)	0.0 (0.0 , 3.0)	–0.45 (–0.72 , 0.52)	0.00***
Sleep disorder (0–15)	1.5 (0.0 , 4.0)	–0.09 (–0.81 , 1.46)	1.5 (0.0 , 1.5)	–0.05 (–0.79 , 0.35)	0.37
Vasomotor dysfunction (0–10)	0.0 (0.0 , 5.5)	–0.19 (–0.44 , 2.94)	0.0 (0.0 , 0.0)	–0.33 (–0.49 , –0.20)	0.01**
Pupillomotor dysfunction (0–5)	2.5 (0.9 , 4.1)	1.50 (0.00 , 3.07)	0.5 (0.0 , 1.5)	–0.42 (–0.71 , 0.55)	0.00***
Reflex syncope – females (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.41
Reflex syncope – males (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.89
Total score (males 0–200 & females 0–170)	39.3 (25.1 , 55.0)	1.77 (0.57 , 3.15)	13.0 (4.5 , 23.4)	–0.21 (–0.82 , 0.72)	0.00***
Psychosomatic index – females (0–10)	0.0 (0.0 , 2.0)	NA	0.0 (0.0 , 0.0)	NA	0.02*
Adj. psychosomatic index – females (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.09
Psychosomatic index – males (0–10)	0.0 (0.0 , 5.5)	NA	0.0 (0.0 , 0.0)	NA	0.40
Adj. psychosomatic index – males (0–10)	0.0 (0.0 , 3.0)	NA	0.0 (0.0 , 0.0)	NA	0.41
Understatement index –females (0–10)	1.5 (0.0 , 1.5)	NA	0.0 (0.0 , 3.5)	NA	0.51
Understatement index –males (0–10)	5.0 (0.0 , 10.0)	NA	1.5 (0.0 , 5.0)	NA	0.36

difficulties and experience that all food tastes the same—symptoms that cannot necessarily be regarded as psychosomatic symptoms in hyposalivating pSS patients—were omitted from the psychosomatic domain and an adjusted psychosomatic index was calculated and re-weighted with a maximum score of ten, the significant difference between female pSS patients and female controls became less pronounced and not statistically significant. Moreover, if pSS patients with adjusted psychosomatic indices of greater than zero were excluded from the analysis, the remaining 31 pSS patients still scored significantly higher in the above-mentioned domains, except for the urinary disorder domain where the difference became statistically non-significant. Several ASP domain scores correlated with each other, and with the ASP total score (Table 11).

When studying the relationship between the objective autonomic nervous function test parameters and the ASP scores, significant correlations were only found between the VAC index and the sleep disorder domain score ($r_S = 0.42$, $p = 0.01$), and also between the lowest systolic blood pressure ratio and the constipation domain score ($r_S = –0.43$, $p = 0.01$). Even when ASP domains possibly reflecting both end-organ damage/exocrine destruction and autonomic function (i.e. the secretomotor and pupillomotor dysfunction domains), were omitted and a new standardized ASP total score was calculated, there was no correlation between this adjusted ASP total score and the objective autonomic nervous function test parameters. In addition, when comparing pSS patients with abnormal scores (≥ 2 SD) and normal scores (< 2 SD) in the orthostatic intolerance, urinary dysfunction, vasomotor dysfunction, secretomotor dysfunction, pupillomotor dysfunction, and total score domains and also the gastroparesis domain in female patients (abnormal being > 0), respectively, no significant differences in the objective autonomic indices were found. However, when comparing pSS patients with abnormal and normal lSBP ratios (≤ –2 SD, n=3, and > –2 SD, n=33, respectively), the former had significantly increased scores in the orthostatic intolerance domain (median 2.86 (IQR limits 2.29, 3.43) vs. 1.00 (–0.63, 1.84), p = 0.01), the constipation domain (2.72 (2.56, 4.23) vs. –0.47 (–0.56, 1.05), p = 0.03), the vasomotor dysfunction domain (3.98 (2.37, 4.04) vs. –0.26 (–0.50, 2.92), p = 0.02), the pupillomotor dysfunction domain (3.25 (3.06, 3.69) vs. 1.44 (–0.18, 2.65), p = 0.02), and the ASP total score (4.26 (3.52, 6.55) vs. 1.65 (0.39 , 2.47), p = 0.00) plus non-significant tendencies of increased scores in the urinary dysfunction domain (2.13 (1.89, 8.32) vs. 0.08 (–0.70, 1.93), p = 0.07) and the gastroparesis domain (females only) (1.50 (1.50, 5.00) vs. 0.00 (0.00, 1.50), p = 0.06).

ASP scores were not affected by disease duration, smoking habits, or presence of anti-SS-A or anti-SS-B-antibodies, or non-exocrine symptoms (as defined in **Study I**). However, when comparing patients with and without Raynaud's phenomenon, a

Table 11 – Correlations between the standardized Autonomic Symptom Profile domain scores in patients with primary Sjögren's syndrome (pSS)
The gastroparesis and reflex syncope domains were omitted since these domain scores were not standardized. In addition, the sexual dysfunction domain was omitted, since only 3 pSS patients were male. Results are presented as Spearman's rank correlation test coefficients (p-values). * $p < 0.05$; ** $p < 0.01$.

DOMAINS	OI	UD	DIA	CON	SMD	SLD	VMD	PMD	TS
Orthostatic intolerance (OI)	---	0.15 (0.36)	0.05 (0.76)	-0.06 (0.71)	0.30 (0.07)	0.36* (0.03)	0.41* (0.01)	0.58** (0.00)	0.82** (0.00)
Urinary dysfunction (UD)	0.15 (0.36)	---	0.30 (0.07)	0.34* (0.04)	0.18 (0.28)	–0.02 (0.90)	0.09 (0.59)	0.13 (0.44)	0.43** (0.01)
Diarrhoea (DIA)	0.05 (0.76)	0.30 (0.07)	---	0.20 (0.24)	0.26 (0.11)	0.10 (0.56)	0.20 (0.24)	0.25 (0.13)	0.44** (0.01)
Constipation (CON)	–0.06 (0.71)	0.34* (0.04)	0.20 (0.24)	---	0.01 (0.97)	–0.09 (0.61)	0.22 (0.19)	0.30 (0.07)	0.19 (0.26)
Secretomotor dysfunction (SMD)	0.30 (0.07)	0.18 (0.28)	0.26 (0.11)	0.01 (0.97)	---	0.45** (0.01)	0.29 (0.08)	0.17 (0.30)	0.53** (0.01)
Sleep disorder (SLD)	0.36* (0.03)	–0.02 (0.90)	0.10 (0.56)	–0.09 (0.61)	0.45** (0.01)	---	0.24 (0.15)	0.26 (0.12)	0.46** (0.00)
Vasomotor dysfunction (VMD)	0.41* (0.01)	0.09 (0.59)	0.20 (0.24)	0.22 (0.19)	0.29 (0.08)	0.24 (0.15)	---	0.51** (0.00)	0.58** (0.00)
Pupillomotor dysfunction (PMD)	0.58** (0.00)	0.13 (0.44)	0.25 (0.13)	0.30 (0.07)	0.17 (0.30)	0.26 (0.12)	0.51** (0.00)	---	0.68** (0.00)
Total score (TS)	0.82** (0.00)	0.43** (0.01)	0.44** (0.01)	0.19 (0.26)	0.53** (0.01)	0.46** (0.00)	0.58** (0.00)	0.68** (0.00)	---

significantly higher score in the vasomotor dysfunction domain (2.92 (1.70, 3.22) vs. –0.32 (–0.50, 2.42), $p = 0.04$) and the constipation domain (1.05 (–0.50 , 5.80) vs. –0.53 (–0.57, 0.95), $p = 0.03$) and a non-significant tendency for a lower score in the orthostatic intolerance domain (0.31 (–0.91, 1.46) vs. 1.55 (–0.10, 2.80), $p = 0.09$) were found in the former. When comparing patients with and without symptoms of peripheral neuropathy, i.e. reported paresthesia and numbness in the feet and/or hands, the former scored significantly higher in the sleep disorder domain (1.26 (0.10, 2.15) vs. –0.42 (–0.83, 0.80), $p = 0.05$), while no significant differences were found in the remaining ASP domains.

Discussion

In this study, pSS patients were found to report various parasympathetic and sympathetic AD symptoms which, however, showed limited associations with objective autonomic nervous function tests. Objective signs of AD in pSS have been examined previously in several studies using various physiological tests (Table 3), but although several case reports and case series have reported on pSS patients experiencing various AD symptoms e.g. orthostatic intolerance (49, 136–138), urinary symptoms (29, 138), Adie's syndrome (139), or constipation (49), symptoms of AD have not previously been systematically studied in pSS patients. The strengths of this study were the use of the AECC for pSS, the exclusion of patients on medication affecting autonomic nervous function, and the use of a large control group for the autonomic nervous function tests, which permitted standardization of the different scores with regard to gender, age, height, and weight. One possible concern was the fact that the Swedish version of the ASP was not specifically validated in pSS patients. Especially since some of the symptoms evaluated in the secretomotor and pupillomotor dysfunction domains are influenced both by end-organ damage and by autonomic nervous function, it is probable that these domain scores not only reflect AD but exocrine gland destruction also. However, since other parasympathetic domain scores measuring symptoms that are less affected by end-organ damage, e.g. the urinary dysfunction and gastroparesis scores (the latter in females), were also significantly elevated and the E/I ratio was significantly reduced, this suggests a parasympathetic dysfunction in pSS. In addition, the increased scores in the orthostatic intolerance and vasomotor disorder domains in combination with the significantly increased VAC index and attenuated blood pressure response in pSS patients are suggestive of a sympathetic dysfunction as well. A possible concern was that several correlation analyses were performed when evaluating possible associations between the ASP domains and the results of objective autonomic nervous function tests. Thus, it is possible that some significant correlations could have been due to multiple comparisons rather than being true correlations.

Although pSS patients had an increased occurrence of both symptoms and objective signs of AD, these showed limited associations. This lack of association could well be due to end organ damage, obscuring a possible association between objective and subjective AD. However, omission of the secretomotor and pupillomotor domains from the ASP total score did not improve the association between this adjusted ASP total score and the objective autonomic nervous function tests. Other possible explanations for the lack of association could be the fact that certain ASP domain scores have a limited range of values (leading to apparently limited variability), insufficient power in the present study to address this issue, and also the time

lapse between performance of the subjective and objective tests. In addition, if the anti-M3-receptor antibodies (as suggested) have a central role in AD pathogenesis in pSS, the objective cardiovascular autonomic nervous function tests are probably not ideal for measurement of the physiological effects of these—although the presence of such might still result in various symptoms. The exocrine autonomic nervous function tests such as the QSART (76), at least hypothetically, seem to be a more appropriate method for detection of the physiological effects of these antibodies. Moreover, variable concentrations of the anti-M3-receptor antibodies in various tissues, if present, may also obscure possible associations between objective and subjective AD. The discrepancy between the large differences in subjective signs of AD and the small, although statistically significant, differences in objective AD signs in pSS patients compared to controls would also fit with the presence of such antibodies. Since female pSS patients scored significantly higher in the psychosomatic domain, it may be argued the increased autonomic domain scores observed reflect an overall increased tendency to report various symptoms. However, when (for pSS patients) inappropriate psychosomatic questions were omitted, the difference was no longer statistically significant. Furthermore, omitting subjects with adjusted psychosomatic scores above zero did not change most statistically significant differences in ASP scores between patients and controls, arguing against the possibility that the increased prevalence of AD symptoms merely reflects a general tendency in pSS patients to report psychosomatic symptoms. Finally, the presence of disease associated antibodies and non-exocrine symptoms were poorly associated with AD symptoms, probably reflecting a different etiopathogenesis behind AD and these various features of pSS.

The results of this study would be strengthened if these results could be reproduced in a larger cohort of pSS patients. In addition it would be of great interest to relate the presence of anti-M3-receptor antibodies to AD symptoms as these antibodies have been suggested to be related not only to exocrine insufficiency (91) but also to urinary symptoms (29, 66) and impaired gastric emptying (66).

Study IV – Dysphagia and pharyngo-esophageal dysmotility in pSS

Results

In this work the presence of pharyngeal and esophageal symptoms and dysmotility was studied, and also their association with signs of autonomic dysfunction. Dysphagia, GERD, and pharyngeal and esophageal symptoms were more prevalent

and severe in pSS patients than in controls, as illustrated by significantly increased GERD, and pharyngeal and esophageal symptom scores (Table 12). The presence of pharyngeal and esophageal dysmotility, non-exocrine symptoms, and the presence of anti-SS-A and anti-SS-B antibodies, was not more common in patients with dysphagia than in patients without dysphagia. Comparing patients with and without dysphagia for liquids, no significant differences were found for the prevalence of pharyngeal and esophageal dysmotility either. In addition, there was no significant difference in disease duration between patients with and without dysphagia.

Pharyngeal and esophageal dysmotility were not statistically significantly more common in pSS patients (15 % and 40 %, respectively) than in controls (17 % and 30%, respectively). The most common finding regarding pharyngeal dysmotility was radiological misdirected swallowing, which had a similar prevalence in both groups. The most common esophageal dysmotility finding was aperistalsis/peristaltic escape in the supine position which was also a common finding in both pSS patients and controls. When signs of esophageal dysmotility—i.e. BSED, aperistalsis/peristaltic escape and esophageal spasm/non-propulsive peristalsis in the erect and supine positions—were found in pSS patients and controls, these were mainly detected in the distal esophagus (Table 13). When comparing the presence of moderate and severe signs of dysmotility in pSS patients and controls, a statistically non-significant tendency of a higher prevalence of severe esophageal peristaltic escape/aperistalsis in the supine position in the latter was seen, but overall differences between patients and controls with regard to dysmotility in the pharynx and the esophagus were small. No morphological changes such as esophageal webs or strictures, were observed in pSS patients or in controls. There was no significant difference between patients with and without signs of pharyngeal and esophageal dysmotility with regard to disease duration or presence of non-exocrine symptoms, including Raynaud's phenomenon or anti-SS-A and anti-SS-B antibodies.

However, pSS patients had a significantly reduced age-corrected E/I ratio (–0.46 (–1.35 – –0.23) vs. –0.25 (–0.62 – 0.60), $p = 0.05$) compared to ART controls as a sign of impaired parasympathetic function, and there tended to be increased age-corrected VAC indices in pSS patients (0.51 (–0.58 – 2.10) vs. 0.09 (–0.67 – 0.62), $p = 0.08$) compared to ART controls. Moreover, comparing patients with and without dysphagia, the former had a significantly reduced E/I ratio (–1.05 (–1.51 – –0.40] vs. –0.21 (–0.39 – 0.65), $p < 0.01$) (Figure 7) whereas there was no statistically significant difference with regard to the VAC index (0.89 (–0.35 – 2.07) vs. –0.05 (–0.85 – 2.15), p = ns). When comparing patients with and without pharyngeal and esophageal dysmotility, respectively, no significant differences in the E/I ratio and VAC index were found.

Table 12 - Results of the questionnaire on pharyngeal and esophageal symptoms

Results are presented as median (IQR) or percentage of abnormal results in each group. GERD: gastroesophageal reflux disease; NS: not significant.

	pSS patients (n = 20)	Controls (n = 30)	p-value
QUESTIONNAIRE			
Dysphagia	65%	3%	< 0.001
-Dysphagia for solids	65%	3%	< 0.001
-Dysphagia for liquids	25%	0%	< 0.01
-Pharyngeal location	50%	0%	< 0.001
-Esophagel location	30%	3%	< 0.05
--Upper esophageal location	15%	3%	NS
--Mid-esophageal location	10%	0%	NS
--Distal esophageal location	5%	0%	NS
GERD symptom score (0–5)	1.50 (0.00-3.00)	0.00 (0.00-0.25)	< 0.01
Any GERD symptom (of the below)	60%	23%	< 0.01
-Globus feeling	45%	10%	< 0.01
-Regurgitation	45%	10%	< 0.01
-Pyrosis	45%	10%	< 0.01
-Nocturnal asthma	15%	0%	NS
-Feeling of increased amount of fluid in oral cavity	5%	0%	NS
Pharyngeal symptom score (0–4)	0.00 (0.00-1.75)	0.00 (0.00-0.00)	< 0.01
Any pharyngeal symptom (of the below)	45%	7%	< 0.01
-Food/fluid in nasal cavity after swallowing	5%	0%	NS
-Misdirected swallowing	25%	3%	< 0.05
-Coughing after swallowing	25%	0%	< 0.01
-Hawking when eating	25%	3%	< 0.05
Esophageal symptom score (0–5)	1.00 (1.00-2.00)	0.00 (0.00-0.00)	< 0.001
Any esophageal symptom (of the below)	80%	7%	< 0.001
-Feeling of obstruction when swallowing	45%	7%	< 0.01
-Previous episodes of acute obstruction	30%	3%	< 0.05
-Avoidance of certain foods due to dysphagia	60%	3%	< 0.001
-Increased liquid intake when eating	15%	3%	NS
-Odynophagia	10%	7%	NS

Table 13 – Results of the pharyngeal and esophageal video-radiographies
Results are presented as percentage of abnormal (mild/moderate/severe) results in each group. NS: not significant.

	pSS patients (n = 20)	**Controls (n = 30)**	**p-value**
VIDEO-RADIOGRAPHY			
Pharyngeal dysmotility	15%	17%	NS
– Radiological misdirected swallowing	15% (67/33/0%)	13% (50/50/0%)	NS
– Retention	0%	0%	NS
– Pharyngoesophageal segment dysfunction	0%	3% (0/100/0%)	NS
Esophageal dysmotility	40%	30%	NS
– Aperistalsis/peristaltic escape – erect position	5% (0/0/100%)	3% (0/0/100%)	NS
– Non-propulsive peristalsis – erect position	0%	0%	NS
– Aperistalsis/peristaltic escape – supine position	35% (14/43/43%)	30% (44/33/22%)	NS
--Mild (= 1 of 5 swallows)	5%	13%	NS
--At least moderate (≥ 2 of 5 swallows)	20%	23%	NS
--Severe (≥ 3 of 5 swallows)	15%	7%	NS
– Non-propulsive peristalsis – supine position	5% (0/100/0%)	0%	NS
– Bolus-specific esophageal dysfunction	5%	3%	NS
Morphological changes	0%	0%	NS
– Esophagal webs	0%	0%	NS
– Strictures	0%	0%	NS

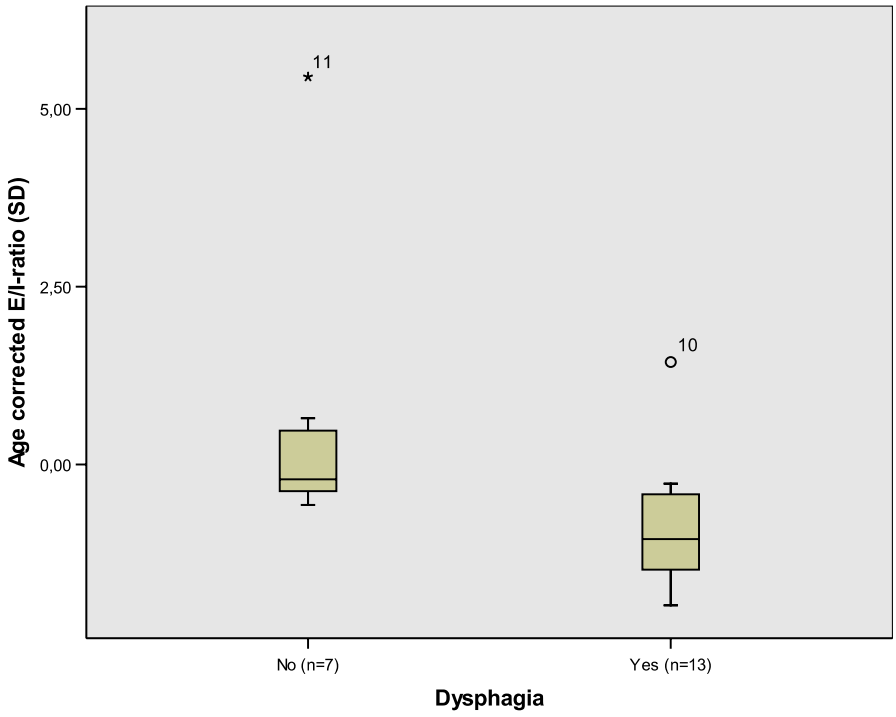


Figure 7.
Distribution of expiration/inspiration (E/I) ratios in patients with and without dysphagia.The E/I ratio was significantly depressed in pSS patients with dysphagia compared to those without ($p < 0.01$).

Discussion

Swallowing difficulties are a very common complaint in pSS patients, although the mechanisms are unclear. Previously proposed mechanisms for pSS-related dysphagia have been xerostomia, dry mucosal surfaces, esophageal webs, esophageal dysmotility, or combinations of these factors. However, most previous studies have failed to show any correlation between salivary flow and dysphagia (59, 60). Esophageal webs only seem to be found in a small group of patients (58, 64), and according to most previous studies dysphagia and signs of esophageal dysmotility show poor correlation (56, 58, 60, 61). The strengths of this study were the use of the AECC, and a population-based age- and gender-matched control group. Some concerns are the limited size of the study, and that examinations could always be more extensive—with, for example, an increased number of swallows during the radiological procedure, thereby increasing the possibility of stratifying patients with regard to different degrees of severity of dysmotility. However, due to concerns

about excessive radiation exposure, this was not possible. Furthermore, a combination with another technique, e.g. esophageal manometry, might have yielded more information on different aspects of dysmotility. However, esophageal manometry is not practical, especially not when studying population based controls, and for this reason the technique was not used in this study. Finally, since the radiographs were not evaluated by a radiologist who was blinded with regard to whether the subject was a pSS patient or a control, this could have affected his evaluation. Since no significant differences were found between pSS patients and controls, however, the need for a re-evaluation of the radiographs by another radiologist was not considered necessary.

In our study, dysphagia and other pharyngeal and esophageal symptoms, as well as GERD symptoms, were all more common in pSS patients than in the population-based controls, which is in agreement with previous studies reporting a prevalence of 33–92% of dysphagia in pSS patients (although diagnosed according to different classification criteria) (56–62). In addition, radiological signs of dysmotility were a common finding in pSS patients—though, however, not more frequently than in controls. Especially, radiological misdirected swallowing and aperistalsis/peristaltic escape in the supine position were frequent findings in both pSS patients and controls. Even if the limits for what was perceived as being pathological were put at ≥ 2 or ≥ 3 of 5 swallows for these findings, respectively, no significant differences were found between pSS patients and controls. Thus, radiological misdirected swallowing and aperistalsis/peristaltic escape in the supine position appear to be a rather unspecific finding without any obvious pathological or symptomatic correlate. Due to the inability of pharyngoesophageal video-radiography to detect any clear differences between pSS patients and controls, this method is not suitable for the objective study of the common swallowing difficulties that were experienced by the majority of pSS patients. The method probably excludes other more severe reasons for dysphagia, however, e.g. morphological changes, although such findings were not found in any of the pSS patients in this study.

In accordance with several previous studies, no associations between dysphagia and radiological signs of dysmotility were found. Thus, in most cases dysphagia does not seem to be due to dysmotility as detected by this radiological technique. Still, the possibility that a minor dysmotility, not detectable by video-radiography but possibly by manometry, could be associated with dysphagia has to be acknowledged. Morphological abnormalities were not found in any pSS patient, which is why this seems to be a less common reason for dysphagia in pSS. Since sialometries were not measured in this study, the relationship between salivary flow and dysphagia could not be established. However, most previous studies have not been able to show any

correlation between salivary flow and dysphagia (59, 60). On the other hand, this may be due to the floor effect of salivary flow measurements in pSS patients, with many patients having unstimulated sialometry values close to zero. Thus, future studies evaluating the possible association between salivary flow and the degree of dysphagia should include pSS patients with various degrees of salivary flow and possibly also non-AECC sicca patients with less diminished salivary flow than pSS patients, since swallowing difficulties possibly occur already at salivary flows above those considered abnormal and diagnostic of pSS.

Since gastrointestinal motility and secretion are influenced by the ANS, disturbed autonomic nervous signaling may have implications for functioning of the gastrointestinal system. In fact, it has been reported that pSS patients have an abnormally slow gastric emptying (66), which could be due to disturbed parasympathetic signaling to the gastrointestinal nervous system. When comparing our pSS patients with and without dysphagia, we found a significantly lower E/I ratio in the former and thus an association between a parasympathetic dysfunction and dysphagia.

Besides controlling esophageal motility, the parasympathetic nervous system also influences salivary and esophageal exocrine secretion. Parasympathetic dysfunction could thus cause gastrointestinal dysmotility as well as reduced exocrine secretion from the salivary glands and in the esophagus, all of which are factors that could cause dysphagia. Since radiological signs of dysmotility were as common in pSS patients as in controls, and were not associated with the two autonomic indices, the possibility of an autonomic nervous dysfunction causing the observed dysmotility findings seems less plausible. Since sialometries were not performed in this study, salivary flow could thus not be related to dysphagia, dysmotility, or parasympathetic function. Finally, since esophageal exocrine function is difficult to measure, its possible relationship to dysphagia is difficult to assess. To sum up, parasympathetic dysfunction may be related to dysphagia by impairing gastrointestinal motility, possibly with an increased esophageal transit time and reduced contraction amplitudes, which may not, however, be detectable by video-radiography but perhaps by esophageal manometry and/or scintigraphy. Another explanation may be that impairment in parasympathetic function would lead to reduced secretion from the salivary glands and esophageal exocrine glands resulting in dry mucosal surfaces and interference with bolus passage.

General discussion

Neurological involvement in pSS has been described by several others and entails both CNS and PNS involvement (35, 43–55, 220) as well as neuropsychiatric disease (32, 42, 220). It is thus not surprising that the ANS may also be involved in the disease. However, since the ANS governs various functions that may be impaired in pSS, e.g. exocrine and gastrointestinal function, and inflammation and related destruction cannot fully explain the impairment of these, the importance of ANS involvement and disturbed neural transmission in pSS has gained increasing interest in recent years. ANS function in pSS has therefore been studied using different methodologies, and most studies (140–146, 149, 171), although not all (147, 148), have reported signs of disturbed ANS function. However, due to the use of different classification criteria for pSS, varying control groups, and not always exclusion of patients on medications affecting ANS function, the results are difficult to compare. In addition, reports of anti-M3-receptor antibodies in pSS and sSS patients interfering with parasympathetic nervous signaling to the exocrine glands and other organs has further strengthened the hypothesis that a disturbed nervous signaling may partly explain the diminished exocrine function (152, 153, 160), bladder irritability (29, 66, 170), and reduced gastric emptying (66) encountered in SS patients.

In our studies, patients with pSS were found to have both objective and subjective signs of AD. Fourty-five per cent of pSS patients had a pathological ASP total score (i.e. of ≥2 SD), indicating a pathological autonomic symptomatology. However, substantially fewer pSS patients had pathological (≤ –2 SD for the E/I ratio, AI, lSBP ratio, and lDBP ratio, and ≥ 2 SD for the VAC index) objective autonomic variables (5 %, 6 %, 8 %, 8 % and 0 % for the E/I ratio, AI, VAC index, lSBP ratio, and lDBP ratio respectively), although they differed to a statistically significant degree from controls. This discrepancy might have several explanations. Firstly, all features of autonomic dysfunction in pSS may not be detected by the use of cardiovascular ARTs, especially not those related to disturbances in nervous signaling in the exocrine glands. Secondly, if the alleged anti-M3-receptor antibodies are important in pSS-related AD, the cardiovascular ARTs are probably not the ideal methods for the detection of the physiological effects of these. Instead, exocrine autonomic nervous function tests, such as the QSART (76), would probably be more appropriate. Thirdly, end-organ damage may also obscure a possible relationship between objective and subjective AD as well as between objective AD and exocrine function. Thus, pSS patients with shorter disease duration should be studied, before end-organ damage has occurred. Moreover, methodological reasons such as low reliability sometimes and few stepped scales for various variables, and limited study sizes also, may obscure possible associations.

In patients with type I diabetes, AD is a well-recognized complication resulting in various symptoms such as orthostatic intolerance, erectile dysfunction and gastroparesis (133), and also increased mortality (133–134). The prevalence of abnormal cardiovascular autonomic nervous function test variables in diabetic patients ranged from 13 % to 27 % and was thus higher in the diabetics than in the pSS patients (16 % vs. 5 %, 16 % vs. 6 %, 27 % vs. 8 %, 13 % vs. 8 %, and 16 % vs. 0 % for the E/I ratio, AI, VAC index, lSBP ratio, and lDBP ratio, respectively). This implies a more severe cardiovascular AD in diabetes compared with pSS, also reflected by the increased mortality in the former (133–134) which is not seen in the latter (157, 179). In contrast to what was expected, the patients with type I diabetes in our study reported relatively few symptoms of AD when filling out the ASP. Consequently, merely 13 % (4/31) of diabetics had a pathological ASP total score in comparison to 45 % in pSS patients. The prevalence of AD symptoms in patients with type I diabetes was thus fairly much in line with the prevalence of objective signs of AD. Although the surplus of reported AD symptoms in patients with pSS compared with diabetic patients might reflect a general tendency of the former to report various symptoms, this is contradicted by the fact that both patient groups had similar psychosomatic indices. However, presence of the alleged anti-M3-receptor antibodies in pSS patients could well explain these differences, since such antibodies would be expected to give rise to various AD symptoms possibly without affecting cardiovascular autonomic nervous function test variables to the same degree.

Since some ASP domains, such as the reflex syncope domain, were not significantly different between patients and controls, and several questions in the ASP did not contribute with points to any domain score, it should be possible to shorten the questionnaire. Such an abbreviated version of the ASP could be filled out in a shorter time than the 30 minutes that it normally took for most patients to complete the original questionnaire, and it would make subjects more likely to take the time to fill it out correctly. However, an adaptation of the ASP to various patient groups—where certain questions and possibly whole domains could be omitted—would require participation of a larger number of patients, preferably with varying degrees of AD. However, an abbreviated version of the ASP would have to be re-validated in each patient group in which it was to be used, and comparison of AD symptoms between AD patients of various etiologies would no longer be possible.

Dysphagia is a common symptom in pSS, but its etiology remains obscure. Although diminished salivary flow and dry mucosal surfaces have been suggested as possible etiological factors behind the swallowing difficulties in pSS, several studies have not found unequivocal evidence for this hypothesis. This might, however, be due to the low variability in salivary flow, with many patients having maximally decreased

sialometric values. Esophageal dysmotility has also been put forward as a possible cause, but although signs of dysmotility appear to be common in pSS patients, radiographical signs of dysmotility were as common in population-based controls as in the pSS patients in our study. Finally, esophageal webs have been suggested as another possible cause of dysphagia in some pSS patients. However, none of the pSS patients in our study were found to have any esophageal webs or strictures. Thus, morphological changes do not appear to be a common etiological factor behind dysphagia in pSS. Dysphagia in pSS is thus probably due to exocrine insufficiency and dry mucosal surfaces, or possibly to dysmotility of a kind that the radiographic technique used in our study was not able to detect, or both.

As exocrine secretion and esophageal motility are both influenced by autonomic function, AD might cause dysphagia by interfering with any or both of these. Indeed, in our study, patients with dysphagia were found to have signs of parasympathetic dysfunction. Signs of cardiovascular parasympathetic AD were thus associated with dysphagia. This is in contrast to the lack of association found between cardiovascular parasympathetic AD and exocrine insufficiency measured by the ocular and oral tests performed when diagnosing pSS. The explanations for these differences remain to be answered, but there could be differences in the mechanisms behind dysphagia and ocular and oral exocrine insufficiency, including different types of AD.

Strengths and limitations

The strengths of these studies were the use of the widely accepted AECC for pSS in all studies, the exclusion of pSS patients on medications that interfere with ANS function, and the use of population based controls in Studies II–IV.

There are, however, several limitations—not least due to the limited size of these studies—affecting the power to address several issues. Although the MSSR included most patients diagnosed with pSS in the city of Malmö during the previous two decades, exclusion of older patients and also patients with co-morbidities and those on medications affecting ANS function significantly reduced the number of patients that could be included. Analyses on various associations between different parameters, where patients were stratified in subgroups, were especially uncertain due to limited sample sizes and multiple comparisons. Furthermore, the small samples of patients with pSS and diabetes also limited the use of certain statistical techniques, e.g. regression analyses, when studying associations. In addition, limited variation in various variables with considerable floor and ceiling effects, e.g. exocrine function variables and some ASP domains, also make studies of associations difficult and uncertain.

Another limitation was the use of historical controls instead of population-based controls for the objective autonomic nervous function tests. Most controls had been recruited from laboratory staff, and their friends and relatives, years earlier, but they had been studied by the same protocol using equipment identical to that used for the patients.

Moreover, the ASP should also be properly validated in a large cohort of pSS patients, as the usefulness of the ASP has not been assessed in pSS patients before and since certain domains probably measure end-organ damage in addition to symptoms of AD in pSS patients.

Finally, studies on associations between subjective and objective signs of AD and objective signs of neuropathy (assessed by electroneurography), and presence of anti-M3-receptor antibodies, would also have made it possible to further describe the contributions of various mechanisms to pSS-related AD.

Future research directions

Validation of the ASP in pSS patients

The results of these studies would be strengthened if the findings on subjective and objective AD could be reproduced, and if the ASP was validated in a larger cohort of pSS patients. Since the ARTs used in these studies mostly showed small, although significant, differences compared to controls, such a validation study should probably also include some exocrine autonomic nervous function test, e.g. the QSART (76), as well as assessment of the anti-M3-receptor antibodies when appropriate tests are available. Apart from better assessment of the efficaciousness of the ASP in pSS, such a validation would also make it possible to shorten the ASP, as certain domains may not be as applicable in pSS patients as in AD patients with other etiologies. Moreover, the sensitivity to change over time of various ASP domains in pSS patients should be assessed. Due to the difficulties in finding eligible patients for inclusion in these studies, such a study with a larger sample size of pSS patients would probably require recruitment of patients from an area larger than that served by our rheumatological unit alone.

Anti-M3-receptor antibodies

Since anti-M3-receptor antibodies have been reported to interfere with the function in exocrine glands (160, 169), and also in the bladder (29, 66, 170) and the gastroin-

testinal system (66, 173), analysis of such antibodies in our pSS patients would be of great interest in order to determine whether the presence of such antibodies shows associations with various objective signs of AD and symptoms of AD. Furthermore, the relationship between these antibodies and gastrointestinal signs and symptoms should also be a topic for further study. Due to the current lack of clinically feasible methods for the detection of these antibodies, this could not be evaluated in these studies but it should be done in the future.

Non-AECC sicca

As many patients experience sicca symptoms without fulfilling the AECC for pSS or sSS, the pathogenesis behind the dryness in such non-AECC sicca patients merits further studies. As these patients lack autoimmune features typical of SS, other mechanisms apart from inflammation and destruction may explain the exocrine insufficiency in this patient group. One possible mechanism could be disturbed autonomic nervous transmission to the exocrine glands. Thus, it would be of interest to study these patients with regard to objective and subjective ANS function, and possibly also with regard to presence of anti-M3-receptor antibodies.

Gastrointestinal symptoms in pSS

Since dysphagia is a common complaint in pSS patients (56–62), and other gastrointestinal signs and symptoms—e.g. delayed gastric emptying (66) and constipation (49)—are reported in pSS patients, the prevalence and pathogenesis of these should be investigated further. Since dry esophageal mucosal surfaces may be expected to prolong esophageal bolus transit, the esophageal transit time should be studied in various sicca patients, not only in those with maximally depressed salivary flow, to establish an association between dryness and dysphagia. Moreover, the relationship between swallowing difficulties and anti-M3-receptor antibodies merits further studies.

Irritable bowel syndrome (IBS) is another condition in which patients present with various gastrointestinal complaints (229). Both IBS and pSS have been shown to be associated with fibromyalgia (33, 230–231). Both syndromes predominantly affect women (2, 232) and both may show signs of disturbed gastrointestinal motility (66, 233). In addition, sicca symptoms have been reported to be common in IBS patients (234). Thus it would be of interest evaluating pSS patients with regard to the prevalence of IBS and try to find possible common denominators between IBS and pSS.

Conclusions

- Patients with primary Sjögren's syndrome show increased frequency of objective signs of parasympathetic and sympathetic nervous dysfunction, and an abnormal orthostatic blood pressure response using cardiovascular autonomic reflex tests.
- There appears to be a poor association between objective signs of cardiovascular autonomic dysfunction and exocrine in patients with primary Sjögren's syndrome.
- The Swedish translation of the Autonomic Symptom Profile, a questionnaire for evaluation of autonomic symptoms, showed good reliability and content validity, and also acceptable construct and discriminant validity in patients with type I diabetes of long duration.
- Patients with primary Sjögren's syndrome were found to have subjective signs suggestive of parasympathetic and sympathetic dysfunction.
- There was generally a poor association between autonomic dysfunction symptoms, objective signs of autonomic dysfunction, and other clinical features of primary Sjögren's syndrome.
- Dysphagia and pharyngeal, esophageal and GERD symptoms were all more common in patients with primary Sjögren's syndrome than in controls.
- Video-radiographically demonstrated esophageal and pharyngeal dysmotility was a common and unspecific finding both in patients with primary Sjögren's syndrome and controls, which is why this method seems less suited for studying and describing the common swallowing difficulties seen in patients with primary Sjögren's syndrome.
- Dysphagia was not associated with dysmotility, but with signs of an impaired parasympathetic function.

Summary in Swedish / Sammanfattning på svenska

Underfunktion i autonoma nervsystemet vid primärt Sjögrens syndrom

Thomas Mandl

Sjögrens syndrom är en autoimmun sjukdom som drabbar kroppens så kallade exokrina körtlar såsom spottkörtlar och tårkörtlar och som ger upphov till en nedsatt utsöndringsfunktion i dessa, med därav följande torrhet i bland annat mun och ögon.

Ett flertal andra organ kan också drabbas i sjukdomen, såsom leder, njurar och nerver. Exempelvis, har man sedan längre tid känt till att de perifera nerverna kan vara drabbade i sjukdomen och därigenom, hos vissa patienter, ge upphov till symtom i form av rubbad känsel med domningar & stickningar i fötter och händer. Även symtom relaterade till störning i det autonoma (icke viljestyrda) nervsystemet såsom exempelvis yrsel vid uppresning från liggande och störd urinblåsefunktion har tidigare rapporterats förekomma hos patienter med Sjögrens syndrom.

Det autonoma nervsystemet (ANS) är indelat i två delar, det parasympatiska och det sympatiska nervsystemet. Dessa delar av autonoma nervsystemet påverkar utöver exempelvis puls, blodtryck, mag-tarm kanalens och urinblåsans funktion även funktionen i de exokrina körtlarna. Det parasympatiska nervsystemet styr över vätskeutsöndringen från tår- och spottkörtlar genom att frisätta bland annat signalsubstansen acetylkolin som i sin tur binder till en mottagare (M3-receptorn) som finns på körtelcellerna. Efter att acetylkolinet bundits till denna receptor börjar körteln utsöndra vätska. Det sympatiska nervsystemet, å andra sidan, påverkar också de exokrina körtlarna bland annat genom att stimulera utsöndring av äggviteämnen, vilka fyller en viktig funktion i att skydda mun och ögon mot exempelvis bakterier och andra mikroorganismer.

Då man sett att körtelvävnadsförstörelsen vid Sjögrens syndrom oftast är mindre uttalad än den kraftigt nedsatta utsöndringsfunktionen antyder, har man börjat intressera sig för de faktorer som påverkar utsöndringen från de exokrina körtlarna, inklusive nervsignaleringen via ANS till körtlarna.

Första studien studerade hururvida det förelåg objektiva tecken på störd funktion i ANS vid primärt Sjögrens syndrom. I studien undersöktes funktionen i ANS genom att studera hur bland annat puls, blodtryck och blodflöde varierar vid olika typer av stimuli, som aktiverar olika delar av ANS. I studien kunde vi påvisa objektiva tecken på en störd funktion i både parasympatiska och sympatiska nervsystemen vid primärt Sjögrens syndrom. Dock hittades inget samband mellan graden av nedsatt

funktion i ANS och graden av nedsatt utsöndringsfunktion från saliv och tårkörtlar, vilket skulle kunna bero på att våra tester, avseende ANS funktion, huvudsakligen mätte ANS funktion i hjärta-kärl området och således inte nödvändigtvis avspeglar ANS funktionen i de exokrina körtlarna.

Andra studien, utvärderade ett från engelska översatt frågeformulär (Autonoma symptom profilen – ASP), utvärderande symptom tydande på störningar i ANS. I studien testades det översatta frågeformuläret på diabetiker, en patientgrupp som ofta uppvisar störningar i ANS, avseende sin förmåga att sanningsenligt (giltigt) och med precision (pålitligt) kunna bedöma förekomst och allvarlighetsgrad av symptom tydande på störd ANS funktion. Frågeformuläret bedömdes ha god pålitlighet och acceptabel till god giltighet avseende bedömning av symptom på störd ANS funktion hos diabetiker.

I tredje studien undersöktes patienter med primärt Sjögrens syndrom med frågeformuläret ASP för att utröna huruvida symtom tydande på störd funktion i ANS förelåg. Patienterna med primärt Sjögrens syndrom företedde symtom tydande på störd funktion i såväl parasympatiska nervystemet (störd urinblåsefunktion och magsäckstömning) som sympatiska nervsystemet (yrsel vid uppresning och påverkat blodflöde till bland annat händer och fötter vid kyla och stress). Som förväntat företedde patienterna även symptom i form av torra ögon, torr mun och ljuskänslighet i ögonen, vilka kan bero på störd funktion i ANS men även på skada orsakad av inflammation och förstörelse i de exokrina körtlarna. Vidare noterades ett dåligt samband mellan förekomst av symtom och objektiva tecken tydande på störd funktion i ANS vid primärt Sjögrens syndrom, vilket skulle kunna bero på skillnader i uppkomstmekanismer till dessa.

I fjärde studien, undersöktes förekomst av sväljningsbesvär och svalg/matstrups symptom hos patienter med primärt Sjögrens syndrom. Med ett frågeformulär konstaterades att 65 % av patienter med primärt Sjögrens syndrom upplever sväljningssvårigheter men även att de har ökad förekomst av bland annat sura uppstötningar och felsväljning. Vid röntgenundersökning av sväljningsfunktionen, där sväljningen undersöks med röntgenfilmning medan patienterna får dricka kontrastmedel, sågs inga skillnader gentemot kontroller, varför denna typ av röntgenundersökning tycks sämre lämpad att beskriva och undersöka de sväljningsbesvär flertalet primära Sjögren patienter upplever, emedan allvarligare orsaker till sväljningsbesvären dock kan uteslutas. Slutligen noterades också att de patienter som upplevede sväljningsbesvär i högre grad uppvisade en störd funktion i det parasympatiska nervsystemet än de som saknade sväljningsbesvär. Detta skulle kunna tyda på att en störd funktion i ANS kan ha en roll i uppkomsten av de sväljningsbesvär patienter med primärt Sjögrens syndrom upplever.

Sammanfattningsvis föreligger således såväl objektiva som subjektiva tecken på en störd funktion i ANS hos patienter med primärt Sjögrens syndrom, något som skulle kunna förklara en del av de symptom som patienter med primärt Sjögrens syndrom upplever.

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References

1. Sjögren H. Zur Kenntnis der Keratokonjunktivitis sicca (Keratitis filiformis bei Hypofunktion der Tränendrüse). Acta Ophthalmol 1933; 11: 1–151.
2. Moutsopoulos HM, Tzioufas AG. Sjögren's syndrome. In Rheumatology. Klippel JH, Dieppe PA, eds. London: Mosby-Year Book Europe Ltd, 1994; part 6, chap.27: 1–12.
3. Vitali C, Bombardieri S, Moutsopoulos HM, Balestrieri G, Bencivelli W, Bernstein RM et al. Preliminary criteria for the classification of Sjögren's Syndrome. Results of a prospective connected action supported by the European community. Arthritis Rheum 1993; 3: 340–7.
4. Vitali C, Bombardieri S, Moutsopoulos HM, Coll J, Gerli R, Hatron PY et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. AnnRheum Dis 1996; 55: 116–21.
5. Manthorpe R, Oxholm P, Prause JU, Schioedt MT. The Copenhagen Criteria for Sjögren's Syndrome. Scand J Rheumatol 1986; 15 Suppl 61: 19–21.
6. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002; 61: 554–8.
7. Bowman SJ, Ibrahim GH, Holmes G, Hamburger J, Ainsworth JR. Estimating the prevalence among Caucasian women of primary Sjogren's syndrome in two general practices in Birmingham, UK. Scand J Rheumatol, 2004; 33: 39–43.
8. Trontzas PI, Andrianakos AA. Sjögren's syndrome. A population based study of prevalence in Greece. The ESORDIG study. Ann Rheum Dis 2005; 64: 1240–1.
9. Ramos-Casals M, Brito-Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum 2007; 36: 246–55.
10. Mannousakis MN, Georgopoulou C, Zintzaras E, Spyropoulou M, Stavropoulou A, Skopouli FN, Moutsopoulos HM. Sjögren's syndrome associated with systemic lupus erythematosus. Clinical and laboratory profiles and comparison with primary Sjögren's syndrome. Arthritis Rheum 2004; 50: 882–91.
11. Gilboe IM, Kvien TK, Uhlig T, Husby G. Sicca symptoms and secondary Sjögren's syndrome in systemic lupus erythematosus: comparison with rheumatoid arthritis and correlation with disease variables. Ann Rheum Dis 2001; 60: 1103–9.
12. Avouac J, Sordet C, Depinay C, Ardizonne M, Vacher-Lavenu MC, Sibilia J et al. Systemic sclerosis-associated Sjögren's syndrome and relationship to the limited cutaneous subtype. Arthritis Rheum 2006; 54: 2243–9

13. Pedersen AM, Bardow A, Nauntofte B. Salivary changes and dental caries as potential oral markers of autoimmune salivary gland dysfunction in primary Sjögren's syndrome. BMC Clin Pathol 2005; 5: 4.
14. Kalk WW, Vissink B, Stegenga B, Bootsma H, Nieuw Amerongen AV, Kallenberg CG. Sialometry and sialochemsistry: a non-invasive approach for diagnosing Sjögren's syndrome. Ann Rheum Dis 2002; 61: 137–44.
15. Fox PC. Salivary enhancement therapies. Caries Res 2004; 38: 241–6.
16. Asmussen K, Andersen V, Bendixen G, Schiodt M, Oxholm P. A new model for classification of disease manifestations in primary Sjögren's syndrome: evaluation in a retrospective long-term study. J Intern Med 1996; 239: 475–82.
17. Chisholm DM, Mason DK. Labial salivary gland biopsy in Sjögren's disease. J Clin Pathol 1968; 21: 656–60.
18. Greenspan JS, Daniels TE, Talal N, Sylvester RA. The histopathology of SS in labial salivary gland biopsies. Oral Surg Oral Med Oral Pathol. 1974 Feb; 37: 217–29.
19. Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. Scand J Immunol 1999; 49: 7–10.
20. Jonsson R, Kroneld U, Tarkowski A. Histological and functional features of salivary glands in rheumatic patients with oral sicca symptoms. Scand J Rheumatol 1988; 17: 387–91.
21. Pennec YL, Leroy JP, Jouquan J, Lelong A, Katsikis P, Youinou P. Comparison of labial gland biopsies in the diagnosis of Sjögren's syndrome. Ann Rheum Dis 1990; 49: 37–9.
22. Chisholm DM, Waterhouse JP, Mason DK. Lymphocytic sialadenitis in the major and minor glands: a correlation in postmortem subjects. J Clin pathol 1970; 23: 690–4.
23. Ghezzi EM, Wagner-Lange LA, Schorck MA, Metter EJ, Baum BJ, Streckfus CF et al. Longitudinal influence of age, menopause, hormone replacement therapy, and other medications on parotid flow rates in healthy women. J Gerontol A biol Sci Med Sci 2000; 55: M34–42.
24. Barendregt PJ, Visser MR, Smets EM, Tulen JH, van den Meiracker AH, Boomsma F, et al. Fatigue in primary Sjogren's syndrome. Ann Rheum Dis 1998; 57: 291–5.
25. Strömbeck B, Ekdahl C, Manthorpe R, Jacobsson LT. Physical capacity in women with primary Sjogren's syndrome: a controlled study. Arthritis Rheum 2003; 49: 681–8.

26. Strömbeck B, Theander E, Jacobsson LTH. Assessment of fatigue in primary Sjögren's syndrome: the Swedish version of the Profile of Fatigue. Scand J Rheumatol 2005; 34: 455–9.
27. Johnsson EO, Vlachoyiannopoulos PG, Skopouli FN, Tzioufas AO, Moutsopoulos HM. Hypofunction of the stress axis in Sjögren's syndrome. J Rheumatol 1998; 25: 1508–14.
28. Gudbjörnsson B, Broman EB, Hetta J, Hällgren R. Sleep disturbances in patients with primary Sjögren's syndrome. Br J Rheumatol 1993; 32: 1072–6.
29. Walker J, Gordon T, Lester S, Downie-Doyle S, McEvoy D, Pile K, et al. Increased severity of lower urinary tract symptoms and daytime somnolence in primary Sjogren's syndrome. J Rheumatol 2003; 30: 2406–12.
30. Bax HI, Vriesendorp TM, Kallenberg CGM, Kalk WWI. Fatigue and immune activity in Sjögre n's syndrome. Ann Rheum Dis 2002; 61: 284.
31. D'Arbonneau F, Ansart S, Le Berre R, Dueymes M, Youinou P, Pennec YL. Thyroid dysfunction in Primary Sjögren's Syndrome: A Long-Term Followup Study. Arthritis Rheum (Arthritis Care Research) 2003; 6: 804–9.
32. Valtysdóttir ST, Gudbjörnsson B, Lindquist U, Hällgren R, Hetta J. Anxiety and depression in patients with primary Sjögren's syndrome. J Rheumatol 2000; 27: 165–9.
33. Eriksson P, Andersson C, Ekerfelt C, Ernrudh J, Skogh T. Sjögren's Syndrome with myalgia is associated with subnormal secretion of cytokines by peripheral blood mononuclear cells. J Rheumatol 2004; 31: 729–35.
34. Sheikh SH, Shaw-Stiffel TA. The gastrointestinal manifestations of Sjogren's syndrome. Am J Gastroenterol 1995; 90: 9–14.
35. Neurological manifestations in primary Sjögren syndrome: a study of 82 patients. Medicine (Baltimore) 2004; 83: 280–91.
36. Soy M, Piskin S. Cutaneous findings in patients with primary Sjögren's syndrome. Clin Rheumatol 2007; 26: 1350–2.
37. Theander E, Henriksson G, Ljungberg O, Mandl T, Manthorpe R, Jacobsson LT. Lymphoma and other malignancies in primary Sjogren's syndrome: a cohort study on cancer incidence and lymphoma predictors. Ann Rheum Dis 2006; 65: 796–803.
38. Pertovaara M, Pukkala E, Laippala P, Miettinen A, Pasternack A. A longitudinal cohort study of Finnish patients with primary Sjogren's syndrome: clinical, immunological, and epidemiological aspects. Ann Rheum Dis 2001; 60: 467–72.
39. Voulgarelis M, Dafni UG, Isenberg DA, Moutsopoulos HM. Malignant lymphoma in primary Sjogren's syndrome: a multicenter, retrospective, clinical study by the European Concerted Action on Sjogren's Syndrome. Arthritis Rheum 1999; 42: 1765–72.

40. Mandl T, Bredberg A, Jacobsson LTH, Manthorpe R, Henriksson G. CD4+ T-lymphocytopenia—A frequent finding in Anti-SSA Antibody Seropositive Patients with Primary Sjögren's Syndrome. J Rheumatol 2004; 31: 726–8.
41. Manganelli P, Fietta P, Quaini P. Hematologic manifestations of primary Sjögren's syndrome. Clin Exp Rheumatol 2006; 24: 438–48.
42. Drosos AA, Andonopoulos AP, Lagos G, Angelopoulos NV, Moutsopoulos HM. Neuropsychiatric abnormalities in primary Sjogren's syndrome. Clin Exp Rheumatol 1989; 7: 207–9.
43. Alexander EL. Central nervous system (CNS) manifestations of primary Sjogren's syndrome: an overview. Scand J Rheumatol Suppl 1986; 61: 161–5.
44. Alexander EL, Provost TT, Stevens MB, Alexander GE. Neurologic complications of primary Sjogren's syndrome. Medicine (Baltimore) 1982; 61: 247–57.
45. Lafitte C. Neurological manifestations in Sjogren syndrome. Arch Neurol 2000; 57: 411–3.
46. Coates T, Slavotinek JP, Rischmueller M, Schultz D, Anderson C, Dellamelva M, et al. Cerebral white matter lesions in primary Sjogren's syndrome: a controlled study. J Rheumatol 1999; 26: 1301–5.
47. Barendregt PJ, van den Bent MJ, van Raaij-van den Aarssen VJ, van den Meiracker AH, Vecht CJ, van der Heijde GL, et al. Involvement of the peripheral nervous system in primary Sjogren's syndrome. Ann Rheum Dis 2001; 60: 876–81.
48. Göransson LG, Herigstad A, Tjensvoll AB, Harboe E, Mellgren SI, Omdahl R. Peripheral neuropathy in primary Sjögren's syndrome. A population-based study. Arch Neurol 2006; 63: 1612–5.
49. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, et al. The wide spectrum of clinical manifestations in Sjogren's syndrome-associated neuropathy. Brain 2005; 128: 2518–34.
50. Gemignani F, Marbini A, Pavesi G, Di Vittorio S, Manganelli P, Cenacchi G, et al. Peripheral neuropathy associated with primary Sjogren's syndrome. J Neurol Neurosurg Psychiatry 1994; 57: 983–6.
51. Grant IA, Hunder GG, Homburger HA, Dyck PJ. Peripheral neuropathy associated with sicca complex. Neurology 1997; 48: 855–62.
52. Griffin JW, Cornblath DR, Alexander E, Campbell J, Low PA, Bird S, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann Neurol 1990; 27: 304–15.
53. Mellgren SI, Conn DL, Stevens JC, Dyck PJ. Peripheral neuropathy in primary Sjogren's syndrome. Neurology 1989; 39: 390–4.
54. Mellgren SI, Göransson LG, Omdahl R. Primary Sjögren's syndrome associated neuropathy. Can J Neurol Sci 2007; 34: 280–7.

55. Satake M, Yoshimura T, Iwaki T, Yamada T, Kobayashi T. Anti-dorsal root ganglion neuron antibody in a case of dorsal root ganglionitis associated with Sjogren's syndrome. J Neurol Sci 1995; 132: 122–5.
56. Volter F, Fain O, Mathieu E and Thomas M. Esophageal function and Sjögren's syndrome. Dig Dis Sci 2004; 49: 248–53.
57. Türk T, Pirildar T, Tunc E, Bor S and Doganavsargil E. Manometric assessment of esophageal motility in patients with primary Sjögren's syndrome. Rheumatol Int 2005; 25: 246–9.
58. Kjellen G, Fransson SG, Lindström F, Sokjer H, Tibbling L. Esophageal function, radiography and dysphagia in Sjögren's syndrome. Dig Dis Sci 1986; 31: 225–9.
59. Anselmino M, Zaninotto G, Constantini M, Ostuni P, Ianiello A, Boccu C et al. Esophageal Motor Function in Primary Sjögren's Syndrome. Dig Dis Sci 1997; 42: 113–8.
60. Grande L, Lacima G, Ros E, Font J, Pera C. Esophageal Motor Function in Primary Sjögren's Syndrome. Am J Gastroenterol 1993; 88: 378–81.
61. Palma R, Freire J, Freitas J, Morbey A, Costa T, Saraiva F et al. Esophageal Motility Disorders in Patients with Sjögren's Syndrome. Dig Dis Sci 1994; 38: 758–61.
62. RosztóczyA, Kovács L, Wittmann T, Lonovics J and Pokorny G. Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome. Clin Exp Rheumatol 2001; 19: 147–52.
63. Tsianos EB, Vasakos S, Drosos AA, Malamou-Mitsi VD and Moutsopoulos HM. The gastrointestinal involvement in primary Sjögren's syndrome. Scand J Rheumatol 1986; Suppl.61: 151–5.
64. Hradsky M, Hybasek J, Cernoch V, Sazmova V and Juran J. Oesophageal Abnormalities in Sjögren's syndrome. Scand J Gastroenterol 1967; 2: 200–3.
65. TsianosEB, Chiras CD, Drosos AA, Moutsopoulos HM. Oesophageal dysfunction in patients with primary Sjögren's syndrome. Ann Rheum Dis 1985; 44: 610–3.
66. Kovacs L, Papos M, Takacs R, Roka R, Csenke Z, Kovacs A, et al. Autonomic nervous system dysfunction involving the gastrointestinal and the urinary tracts in primary Sjogren's syndrome. Clin Exp Rheumatol 2003; 21: 697–703.
67. Ostuni PA, Gazzetto G, Chieco-Bianchi F, Riga B, Plebani M, Betterle C, Gambari PF. Pancreatic exocrine involvement in primary Sjögren's syndrome. Scand J Rheumatol 1996; 25: 47–51.
68. Szodoray P, Barta Z, Lakos G, Szakáll S, Zeher M. Coeliac disease in Sjögren's syndrome—a study of 111 Hungarian patients. Rheumatol Int 2004; 24: 278–82.

69. Abraham S, Begum S, Isenberg D. Hepatic manifestations of autoimmune rheumatic diseases. Ann Rheum Dis 2004; 63: 123–9.

70. Robertson D, Biaggioni I, Burnstock G, Low PA. (eds) (2004). Primer on the autonomic nervous system, 2nd edition. Elsevier Academic press, San Diego.

71. Keene LC, Davies PH Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 1999; 18: 5–24.

72. Baum BJ, Dai Y, Hiramatsu Y, Horn VJ, Ambudkar IS. Signaling mechanisms that regulate saliva formation. Crit Rev Oral Biol Med 1993; 4: 379–84.

73. Ekström J. Salivationens reglering. Tandläkartidningen 2000; 92: 36–43.

74. Freeman R. Assessment of cardiovascular autonomic function. Clin Neurophysiol 2006; 117: 716–30.

75. Hilz MJ, Dütsch M. Quantitative studies of autonomic function. Muscle Nerve 2006; 33: 6–20.

76. Riedel A, Braune S, Kerum G, Schulte-Monting J, Lucking CH. Quantitative sudomotor axon reflex test (QSART): a new approach for testing distal sites. Muscle Nerve 1999; 22: 1257–64.

77. Shimada H, Kihara M, Kosaka S, Ikeda H, Kawabata K, Tsutada T, et al. Comparison of SSR and QSART in early diabetic neuropathy-the value of length-dependent pattern in QSART. Auton Neurosci 2001; 92: 72–5.

78. Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J 1984; 52: 396–402.

79. Huikuri HV, Kessler KM, Terracall E, Castellanos A, Linnaluoto MK, Myerburg RJ. Reproducibility and circadian rhythm of heart rate variability in healthy subjects. Am J Cardiol 1990; 65: 391–3.

80. Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol 1998; 18: 103–7.

81. Tank J, Neuke A, Mölle A, Jordan J, Weck M. Spontaneous baroreflex sensitivity and heart rate variability are not superior to classic autonomic testing in older patients with type 2 diabetes. Am J Med Sci 2001; 322: 24–30.

82. Bergström B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. Clin Physiol 1986; 6: 523–8.

83. Liao D, Barnes RW, Chambless LE, Simpson RJ, Sorlie P, Heiss G. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability – The ARIC study. Am J Cardiol 1995; 76: 906–12.

84. Huikuri HV, Pikkujamsa SM, Airaksinen KEJ, Ikaheimo MJ, Rantala AO, Kauma H et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 1996; 94: 122–5.

85. Low PA, Denq J-C, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. Muscle Nerve 1997; 20: 1561–8.
86. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993; 68: 748–52.
87. Dartt DA. Control of mucin production by ocular surface epithelial cells. Exp Eye Res 2004; 78: 173–85.
88. Bron AJ, Tiffany JM, Gouveia SM, Yokoi N, Voon LW. Functional aspects of the lipid layer. Exp Eye Res 2004; 78: 347–60.
89. Sullivan, DA, Wickham LA, Rocha EM, Krenzer KL, Sullivan BD, Steagall R et al. Androgens and dry eye in Sjögren's syndorme. Ann NY Acad Sci 1999; 876: 312–24.
90. Bromberg BB. Autonomic control of lacrimal protein secretion. Invest Ophthalmol Vis Sci 1981; 20: 110–6.
91. Dawson L, Tobin A, Smith P, Gordon T. Antimuscarinic antibodies in Sjogren's syndrome: where are we, and where are we going? Arthritis Rheum 2005; 52: 2984–95
92. Steinfeld S, Cogan E, King LS, Agre P, Kiss R, Delporte C. Abnormal distribution of aquaporin-5 water channel protein in salivary glands from Sjogren's syndrome patients. Lab Invest 2001; 81: 143–8.
93. Williams PH, Cobb BL, Namjou B, Scofield RH, Sawalha AH, Harley JB. Horizons in Sjögren's syndrome genetics. Clinic Rev Allergy Immunol 2007; 32: 201–9.
94. Sawalha AH, Potts R, Schmid WR, Scofield RH, Harley JB. The genetics of primary Sjögren's syndrome. Curr Rheumatol Rep 2003; 5: 324–32.
95. Bolstad AI, Jonsson R. Genetic aspects of Sjogren's syndrome. Arthritis Res 2002; 4: 353–9.
96. Pernis AB. Estrogen and CD4+ T cells. Curr Opin Rheumatol 2007; 19: 414–20.
97. Valtýsdottir ST, Wide L, Hällgren R. Low serum dehydroepiandrosterone sulfate in women with primary Sjögren's syndrome as an isolated sign of impaired HPA axis function. J Rheumatol 2001; 28: 1259–65.
98. Brennan MT, Sankar V, Leakan RA, Grisius MM, Collins MT, Fox PC et al. Sex steroid hormones in primary Sjögren's syndrome. J Rheumatol 2003; 30: 1267–71.
99. Konttinen YT, Kasna-Ronkainen L. Sjogren's syndrome: viewpoint on pathogenesis. One of the reasons I was never asked to write a textbook chapter on it. Scand J Rheumatol 2002; Suppl 116: 15–22.
100. Haga HJ, Rygh T. The prevalence of hyperprolactinemia in patients with primary Sjögren's syndrome. J Rheumatol 1999; 26: 1291–5.

101. Mostafavi B, Akyuz S, Jacobsson ME, Nilsen LV, Theander E, Jacobsson LH. Perinatal characteristics and risk of developing primary Sjogren's syndrome: a case-control study. J Rheumatol 2005; 32: 665–8.

102. Youinou P, Pers JO, Saraux A, Pennec YL. Viruses contribute to the development of Sjögren's syndrome. Clin Exp Immunol 2005; 141: 19–20.

103. Ramos-Casals M, Garcia-Carrasco M, Brito Zeron MP, Cervera R, Font J. Viral etiopathogenesis of Sjogren's syndrome: role of the hepatitis C virus. Autoimmun Rev 2002; 1: 238–43.

104. Wen S, Shimizu N, Yoshiyama H, Mizugaki Y, Shinozaki F, Takada K. Association of Epstein-Barr virus (EBV) with Sjögren's syndrome: differential EBV expression between epithelial cells and lymphocytes in salivary glands. Am J Pathol 1996; 149: 1511–7.

105. Triantafyllopoulou A, Tapinos N, Moutsopoulos HM. Evidence for coxsackievirus infection in primary Sjogren's syndrome. Arthritis Rheum 2004; 50: 2897–902.

106. Bredberg A, Henriksson G, Larsson Å, Mathorpe R, Sallmyr A. Sjögren's syndrome and the danger model. Rheumatology 2005; 44: 965–70.

107. Karp DR. Complement and systemic lupus eythematosus. Curr Opin Rheumatol 2005; 17: 538–42.

108. Alexander EL, Arnett FC, Provost TT, Stevens MB. Sjögren's syndrome: association of anti-Ro (SS-A) antibodies with vasculitis, hematologic abnormalities, and serologic hyperreactivity. Ann Intern Med 1983; 98: 155–9.

109. Kawakami A, Nakashima K, Tamai M, Nakamura H, Iwnaga N, Fujikawa K et al. Toll-like receptor in salivary glands from patients with Sjögren's syndrome: functional analysis by human salivary gland cell line. J Rheumatol 2007; 34: 1019–25.

110. Speight PM, Cruchley A, Williams DM. Epithelial HLA-DR expression in labial salivary glands in Sjögren's syndrome and non-specific sialadenitis. J Oral Pathol Med 1989; 18: 178–83.

111. Kapsogeorgou EK, Moutsopoulos HM, Manoussakis MN. Functional expression of a costimulatory B7.2 (CD86) protein on human salivary gland epithelial cells that interacts with the CD28 receptor, but has reduced binding to CTLA4. J Immunol 2001; 166: 3107–13.

112. Ohlsson M, Jonsson R, Brokstad KA. Subcellular redistribution and surface exposure of the Ro52, Ro60 and La48 autoantigens during apoptosis in human ductal epithelial cells: a possible mechanism in the pathogenesis of Sjogren's syndrome. Scand J Immunol 2002; 56: 456–69.

113. Båve U, Nordmark G, Lövgren T, Rönnelid J, Cajander S, Eloranta ML et al. Activation of the type I interferon system in primary Sjögren's syndrome. Arthritis Rheum 2005; 52: 1185–95.

114. Ittah M, Miceli-Richard C, Gottenberg JE, Lavie F, Lazure T, Ba N et al. B-cell activating factor of the tumor necrosis family (BAFF) is expressed under stimulation by interferon in salivary gland epithelial cells in primary Sjögren's syndrome. Arthritis Res Ther 2006; 8: R51.

115. Groom J, Kalled SL, Cutler AH, Olson C, Woodcock SA, Schneider P, et al. Association of BAFF/BLyS overexpression and altered B cell differentiation with Sjogren's syndrome. J Clin Invest 2002; 109: 59–68.

116. Hansen A, Lipsky PE, Dorner T. Immunopathogenesis of primary Sjogren's syndrome: implications for disease management and therapy. Curr Opin Rheumatol 2005; 17: 558–65.

117. Mariette X, Ravaud P, Steinfeld S, Baron G, Goetz J, Hachulla E, et al. Inefficacy of infliximab in primary Sjogren's syndrome: results of the randomized, controlled Trial of Remicade in Primary Sjogren's Syndrome (TRIPSS). Arthritis Rheum 2004; 50: 1270–6.

118. Jonsson R, Gordon TP, Konttinen YT. Recent advances in understanding molecular mechanisms in the pathogenesis and antibody profile of Sjogren's syndrome. Curr Rheumatol Rep 2003; 5: 311–6.

119. Manganelli P, Fietta P. Apoptosis and Sjogren syndrome. Semin Arthritis Rheum 2003; 33: 49–65.

120. Reina S, Orman B, Anaya JM, Sterin-Borda L, Borda E. Cholinoreceptor autoantibodies in Sjögren's syndrome. J Dent Res 2007; 86: 832–6.

121. Beroukas D, Hiscock J, Gannon BJ, Jonsson R, Gordon TP, Waterman SA. Selective down-regulation of aquaporin-1 in salivary glands in primary Sjogren's syndrome. Lab Invest 2002; 82: 1547–52.

122. Beroukas D, Hiscock J, Jonsson R, Waterman SA, Gordon TP. Subcellular distribution of aquaporin 5 in salivary glands in primary Sjogren's syndrome. Lancet 2001; 358: 1875–6.

123. Ramos-Casals M, Font J. Primary Sjögren's syndrome: current and emergent aetiopathogenic concepts. Rheumatology 2005; 44: 1354–67.

124. Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in type I diabetes: Influence of duration and other diabetic complications. Acta Med Scand 1987; 222: 147–54.

125. Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in non insulin dependent (type II) diabetes mellitus. Possible influence of obesity. J Intern Med 1990; 227: 57–63.

126. Leden I, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol 1983; 12: 166–70.

127. Toussirot E, Serratrice G, Valentin P. Autonomic nervous system involvement in rheumatoid arthritis. 50 cases. J Rheumatol 1993; 20: 1508–14.

128. Laversuch CJ, Seo H, Modarres H, Collins DA, McKenna W, Bourke BE. Reduction in heart rate variability in patients with systemic lupus erythematosus. J Rheumatol 1997; 24: 1540–4.

129. Stojanovich L, Milovanovich B, de Luka SR, Popovich-Kuzmanovich D, Bisenich V, Djukanovich et al. Cardiovascular autonomic dysfunction in systemic lupus, rheumatoid arthritis, primary Sjögren's syndrome and other autoimmune diseases. Lupus 2007; 16: 181–5.

130. Bertinotti L, Bracci S, Nacci F et al. The autonomic nervous system in systemic sclerosis. A review. Clin Rheumatol 2004; 23: 1–5.

131. Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients eith Crohn's disease. Scand J Gastroenterol 1991; 4: 361–6.

132. Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol 1993; 7: 638–49.

133. Vinik AI, Maser RE, Mitchell BD, Freeman BD. Diabetic Autonomic Neuropathy. Diabetes Care 2003; 26: 1553–79.

134. Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes. Diabetes Care 2003; 26: 1895–1901.

135. Huikuri HV, Makikallio TH, Airaksinen KE, Seppanen T, Puukka P, Raiha IJ, Sourander LB. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. Circulation 1998; 97: 2031–6.

136. Andonopoulos AP and Ballas C. Autonomic cardiovascular neuropathy in primary Sjögren's syndrome. Rheumatol Int 1995; 15: 127–9.

137. Sakakibara R, Hirano S, Asahina M, Sawai S, Nemoto Y, Hiraga A et al. Primary Sjögren's syndrome presenting with generalized autonomic failure. Eur J Neurol 2004; 11: 635–8.

138. Sorajja P, Poirier MK, Bundrick JB, Matteson EL. Autonomic failure and proximal skeletal myopathy in a patient with primary Sjögren syndrome. Mayo Clin Proc 1999; 74: 695–7.

139. Waterschoot MP, Guerit JM, Lambert M, de Barsy T. Bilateral tonic pupils and polyneuropathy in Sjögren's syndrome: a common pathophysiological mechanism? Eur Neurol 1991; 31: 114–6.

140. Mandl T, Wollmer P, Manthorpe R, Jacobsson L. Autonomic and orthostatic dysfunction in primary Sjögren's syndrome. J Rheumatol, 2007; 34: 1869–74.

141. Mandl T, Jacobsson L, Lilja B, Sundkvist G, Manthorpe R. Disturbances of autonomic nervous function in primary Sjögren's syndrome. Scand J Rheumatol 1997; 26: 401–6.

142. Mandl T, Bornmyr SV, Castenfors J, Jacobsson LT, Manthorpe R, Wollmer P. Sympathetic dysfunction in patients with primary Sjögren's syndrome. J Rheumatol 2001,28: 296–301.

143. Andonopoulos AP, Christodoulou J, Ballas C, Bounas A, Alexopoulos D. Autonomic cardiovascular neuropathy in Sjogren's syndrome. A controlled study. J Rheumatol 1998; 25: 2385–8.

144. Barendregt PJ, van den Meiracker AH, Markusse HM, Tulen JH, Boosma F, van der Heijde GL et al. Parasympathetic failure does not contribute to ocular dryness in primary Sjogren's syndrome. Ann Rheum Dis 1999; 58: 746–50.

145. Kovacs L, Paprika D,Takacs R, Kardos A, Varkonyi TT, Lengyel C et al. Cardiovascular autonomic dysfunction in primary Sjogren's syndrome. Rheumatology 2004; 43: 95–9.

146. Barendregt PJ, Tulen JH, van den Meiracker AH, Markusse HM. Spectral analysis of heart rate and blood pressure variability in primary Sjogren's syndrome. Ann Rheum Dis 2002; 61: 232–6.

147. Niemela RK, Pikkujamsa SM, Hakala M, Huikuri HV, Airaksinen KE. No signs of autonomic nervous system dysfunction in primary Sjorgen's syndrome evaluated by 24 hour heart rate variability. J Rheumatol 2000; 27: 2605–10.

148. Niemela RK, Hakala M, Huikuri HV. Airaksinen KE. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J Rheumatol 2003; 30: 74–9.

149. Tumiati B, Perazzoli F, Negro A, Pantaleoni M, Regolisti G. Heart rate variability in patients with Sjogren's syndrome. Clin Rheumatol 2000; 19: 477–80.

150. Wright RA, Grant IA, Low PA. Autonomic neuropathy associated with sicca complex. J Auton Nerv Syst 1999; 75: 70–6.

151. Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjogren's syndrome. Arthritis Rheum 2000; 43: 1647–54.

152. Gordon TP, Bolstad AI, Rischmueller M, Jonsson R, Waterman SA. Autoantibodies in primary Sjogren's syndrome: new insights into mechanisms of autoantibody diversification and disease pathogenesis. Autoimmunity 2001; 34: 123–32.

153. Dawson LJ, Allison HE, Stanbury J, Fitzgerald D, Smith PM. Putative antimuscarinic antibodies cannot be detected in patients with primary Sjogren's syndrome using conventional immunological approaches. Rheumatology 2004; 43: 1488–95.

154. Fox RI, Stern M. Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. Scand J Rheumatol 2002; Suppl.116: 3–13.

155. Haddad EB, Rousell J, Lindsay MA, Barnes PJ. Synergy between tumor necrosis factor alpha and interleukin 1 beta in inducing transcriptional down-regulation of muscarinic M2 receptor gene expression. Involvement of protein kinase A and ceramide pathways. J Biol Chem 1996; 271: 32586–92.

156. Zoukhri D, Hodges RR, Byon D, Larkin Kublin C. Role of proinflammatory cytokines in the impaired lacrimation associated with autoimmune xerophthalmia. Invest Ophthalmol Vis Sci 2002; 43: 1429–36.

157. Theander E, Manthorpe R, Jacobsson LT. Mortality and causes of death in primary Sjogren's syndrome: a prospective cohort study. Arthritis Rheum 2004; 50: 1262–9.

158. Borovikova LV, Ivanova S, Zhang M, Yang H, Botchkina GI, Watkins LR, et al. Vagus nerve stimulation attenuates the systemic inflammatory response to endotoxin. Nature 2000; 405: 458–62.

159. Manthorpe R, Benoni C, Jacobsson L, Kirtava Z, Larsson A, Liedholm R, et al. Lower frequency of focal lip sialadenitis (focus score) in smoking patients. Can tobacco diminish the salivary gland involvement as judged by histological examination and anti-SSA/Ro and anti-SSB/La antibodies in Sjogren's syndrome? Ann Rheum Dis 2000; 59: 54–60.

160. Dawson LJ, Fox PC, Smith PM. Sjögren's syndrome – the non-apoptotic model of glandular hypofunction. Rheumatology 2006; 45: 792–8.

161. Konttinen YT, Sorsa T, Hukkanen M, Segerberg M, Kuhlefelt-Sundstrom M, Malmstrom M, et al. Topology of innervation of labial salivary glands by protein gene product 9.5 and synaptophysin immunoreactive nerves in patients with Sjogren's syndrome. J Rheumatol 1992; 19: 30–7.

162. Zoukhri D, Kublin CL. Impaired neurotransmitter release from lacrimal and salivary gland nerves of a murine model of Sjögren's syndrome. Invest Ophthalmol Vis Sci 2001; 42: 925–32.

163. Dawson LJ, Caulfield VL, Stanbury JB, Field AE, Christmas SE, Smith PM. Hydroxychloroquine therapy in patients with primary Sjögren's syndrome may improve salivary gland hypofunction by inhibition of glandular cholinesterase. Rheumatology 2005; 44: 449–55.

164. Bacman S, Sterin-Borda L, Camusso JJ, Arana R, Hubscher O, Borda E. Circulating antibodies against rat parotid gland M3 muscarinic receptors in primary Sjogren's syndrome. Clin Exp Immunol 1996; 104: 454–9.

165. Bacman S, Perez Leiros C, Sterin-Borda L, Hubscher O, Arana R, Borda E. Autoantibodies against lacrimal gland M3 muscarinic acetylcholine receptors in patients with primary Sjogren's syndrome. Invest Ophthalmol Vis Sci 1998; 39: 151–6.

166. Gao J, Cha S, Jonsson R, Opalko J, Peck AB. Detection of anti-type 3 muscarinic acetylcholine receptor autoantibodies in the sera of Sjogren's syndrome patients by use of a transfected cell line assay. Arthritis Rheum 2004; 50: 2615–21.

167. Kovacs L, Marczinovits I, Gyorgy A, Toth GK, Dorgai L, Pal J, et al. Clinical associations of autoantibodies to human muscarinic acetylcholine receptor 3(213–228) in primary Sjogren's syndrome. Rheumatology 2005; 44: 1021–5.

168. Cavill D, Waterman SA, Gordon TP. Antiidiotypic antibodies neutralize autoantibodies that inhibit cholinergic neurotransmission. Arthritis Rheum 2003; 48: 3597–602.

169. Dawson LJ, Stanbury J, Venn N, Hasdimir B, Rogers SN, Smith PM. Antimuscarinic antibodies in primary Sjogren's syndrome reversibly inhibit the mechanism of fluid secretion by human submandibular salivary acinar cells. Arthritis Rheum 2006; 54: 1165–1173.

170. Wang F, Jackson MW, Maughan V, Cavill D, Smith AJ, Waterman SA, et al. Passive transfer of Sjogren's syndrome IgG produces the pathophysiology of overactive bladder. Arthritis Rheum 2004; 50: 3637–45.

171. Kovacs L, Torok T, Bari F, Keri Z, Kovacs A, Makula E, et al. Impaired microvascular response to cholinergic stimuli in primary Sjogren's syndrome. Ann Rheum Dis 2000; 59: 48–53.

172. Tornwall J, Konttinen YT, Tuominen RK, Tornwall M. Protein kinase C expression in salivary gland acinar epithelial cells in Sjogren's syndrome. Lancet 1997; 349: 1814–5.

173. Smith AJ, Jackson MW, Wang F, Cavill D, Rischmueller M, Gordon TP. Neutralization of muscarinic receptor autoantibodies by intravenous immunoglobulin in Sjogren syndrome. Hum Immunol 2005; 66: 411–6.

174. Cavill D, Waterman SA, Gordon TP. Antibodies raised against the second extracellular loop of the human muscarinic M3 receptor mimic functional autoantibodies in Sjogren's syndrome. Scand J Immunol 2004; 59: 261–6.

175. Kruize AA, van Bijsterveld OP, Hené RJ, de Wilde PCM, Feltkamp TEW, Kater L 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.

176. Gannot G, Lancaster HE, Fox PC. Clinical course of primary Sjögren's syndrome: salivary, oral, and serological aspects. J Rheumatol 2000; 27: 1905–9.

177. Theander E, Andersson SI, Manthorpe R, Jacobsson LT. Proposed core set of outcome measures in patients with primary Sjogren's syndrome: 5 year follow up. J Rheumatol 2005; 32: 1495–502.

178. Kassan SS, Thomas TL, Moutsopoulos HM, Hoover R, Kimberley RP, Budman DR et al. Increased risk of lymphoma in sicca syndrome. Ann Intern Med 1978; 89: 888–92.

179. Ioannidis JP, Vassiliou VA, Moutsopoulos HM. Long-term risk of mortality and lymphoproliferative disease and predictive classification of primary Sjogren's syndrome. Arthritis Rheum 2002; 46: 741–7.

180. Brito-Zerón P, Ramos-Casals M, Bove A, Sentis J, Font J. Predicting adverse outcomes in primary Sjögren's syndrome: identification of prognostic factors. Rheumatology 2007; 46: 1359–62.

181. Ramos-Casals M, Brito-Zerón P, Yagüe J, Akasbi M, Bautista R, Ruano M et al. Hypocomplementemia as an immunological marker of morbidity and mortality in patients with primary Sjögren's syndrome. Rheumatology 2005; 44: 89–94.

182. Tzioufas AG, Boumba DS, Skopouli FN, Moutsopoulos HM. Mixed monoclonal cryoglobulinemia and monoclonal rheumatoid factor cross-reactive idiotypes as predicitive factors for the development of lymphoma in primary Sjögren's syndrome. Arthritis Rheum 1996; 39: 767–72.

183. Font J, Ramos-Casals M, de la Red G, Pou A, Casanova A, Garcia-Carrasco M et al. Pure sensory neuropathy in primary Sjögren's syndrome. Longterm prospective followup and review of the literature. J Rheumatol 2003; 30: 1552–7.

184. Thanou-Stavraki A, James JA. Primary Sjögren's syndrome: Current and prospective therapies. Semin Arthritis Rheum 2007 Aug 20; (Epub ahead of print).

185. Sall K, Stevenson OD, Mundorf TK, Reis BL. Two multicenter, randomized studies of the efficacy and safety of cyclosporine ophthalmic emulsion in moderate to severe dry eye disease. CsA Phase 3 Study Group. Ophthalmology 2000; 107: 631–9.

186. Cummins MJ, Papas A, Kammer GM, Fox PC. Treatment of primary Sjogren's syndrome with low-dose human interferon alfa administered by the oromucosal route: combined phase III results. Arthritis Rheum 2003; 49: 585–93.

187. Blom M, Kopp S, Lundeberg T. Prognostic value of the pilocarpine test to identify patients who may obtain long-term relief from xerostomia by acupuncture treatment. Arch Otolaryngol Head Neck Surg 1999; 125: 561–6.

188. Blom M, Lundeberg T. Long-term follow-up of patients treated with acupuncture for xerostomia and the influence of additional treatment. Oral Dis 2000; 6: 15–24.

189. Vivino FB, Al-Hashimi I, Khan Z, Le Veuwe FG, Salisbury PL. Tran-Johnson TK et al. Pilocarpine tablets for the teatment of dry mouth and dry eye symptoms in patients with Sjögren's syndrome. Arch Intern Med 1999; 159: 174–81.

190. Petrone D, Condemi JJ, Fife R, Gluck O, Cohen S, Dalgin P. A double-blind, randomized, placebo-controlled study of cevimeline in Sjögren's syndrome patients with xerostomia and keratoconjunctivitis sicca. Arthritis Rheum 2002; 46: 748–54.

191. Prause JU, Frost-Larsen K, Hoj L, Isager H, Manthorpe R. Lacrimal and salivary secretion in Sjogren's syndrome: the effect of systemic treatment with bromhexine. Acta Ophthalmol 1984; 62: 489–97.

192. Fox RI, Chan E, Benton L, Fong S, Friedlaender M, Howell FV. Treatment of primary Sjogren's syndrome with hydroxychloroquine. Am J Med 1988; 85: 62–7.

193. Ferraccioli GF, Salaffi F, De Vita S, Casatta L, Avellini C, Carotti M et al. Interferon alpha-2 increases lacrimal and salivary function in Sjögren's syndrome patients. Preliminary results of an open pilot trial versus hydroxychloroquine. Clin Exp Rheumatol 1996; 14: 367–71.

194. Shiozawa S, Tanaka Y, Shiozawa K. Single-blinded controlled trial of low-dose oral IFN-alpha for the treatment of xerostomia in patients with Sjögren's syndrome. J Interferon Cytokine Res 1998; 18: 255–62.

195. Yamada S, Mori K, Matsuo K, Inukai A, Kawagashira Y, Sobue G. Interferon-alpha treatment for Sjögren's syndrome associated neuropathy. J Neurol Neurosurg Psychiatry 2005; 76: 576–8.

196. Pillemer SR, Brennan MT, Sankar V, Leakan RA, Smith JA, Grisius M, et al. Pilot clinical trial of dehydroepiandrosterone (DHEA) versus placebo for Sjogren's syndrome. Arthritis Rheum 2004; 51: 601–4.

197. Ramos-Casals M, Brito-Zerón P. Emerging biological therapies in primary Sjögren's syndrome. Rheumatology 2007; 46: 1389–96.

198. Steinfeld SD, Demols P, Salmon I, Kiss R, Appelboom T. Infliximab in patients with primary Sjögren's syndrome: a pilot study. Arthritis Rheum 2001; 44: 2371–5.

199. Sankar V, Brennan MT, Kok MR, Leakan RA, Smith JA, Manny J, et al. Etanercept in Sjogren's syndrome: a twelve-week randomized, double-blind, placebo-controlled pilot clinical trial. Arthritis Rheum 2004; 50: 2240–5.

200. Pijpe J, van Imhoff GW, Spijkervet FK, Roodenburg JL, Wolbink GJ, Mansour K, et al. Rituximab treatment in patients with primary Sjogren's syndrome: an open-label phase II study. Arthritis Rheum 2005; 52: 2740–50.

201. Devauchelle-Pensec V, Pennec Y, Morvan J, Pers JO, Daridon C, Jousse-Joulin S, et al. Improvement of Sjogren's syndrome after two infusions of rituximab (anti-CD20). Arthritis Rheum 2007; 57: 310–7.

202. Seror R, Sordet C, Guillevin L, Hachulla E, Masson C, Ittah M, et al. Tolerance and efficacy of rituximab and changes in serum B cell biomarkers in patients with systemic complications of primary Sjogren's syndrome. Ann Rheum Dis 2007; 66: 351–7.

203. Yamout B, El-Hajj T, Barada W, Uthman I. Successful treatment of refractory neuroSjogren with Rituximab. Lupus 2007; 16: 521–3.

204. Kizawa M, Mori K, Iijima M, Koike H, Hattori N, Sobue G. Intravenous immunoglobulin treatment in painful sensory neuropathy without sensory ataxia associated with Sjögren's syndrome. J Neurol Neurosurg Psychiatry 2006; 77: 967–9.

205. Dupond JL, Gil H, de Wazieres B. Five-year efficacy of intravenous gamma-globulin to treat dysautonomia in Sjogren's syndrome. Am J Med 1999; 106: 125.

206. Caroyer JM, Manto MU, Steinfeld SD. Severe sensory neuronopathy responsive to infliximab in primary Sjogren's syndrome. Neurology 2002; 59: 1113–4.

207. Sève P, Gachon E, Petiot P, Stankovic K, Chahon A, Broussolle C. Successful treatment with rituximab in a patient with mental nerve neuropathy in primary Sjögren's syndrome. Rheumatol Int 2007; 28: 175–7.

208. Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart rate in diabetes mellitus. Br Med J 1979; 1: 924–5.

209. Bergström B, Mattiasson I, Rosen I, Lilja B, Sundkvist G. Platelet sodium and potassium ATPase activity and noradrenaline efflux rate in relation to autonomic and peripheral nerve function in insulin dependent diabetic patients. J Intern Med 1989; 225: 185–90.

210. Bergström B, Manhem P, Bramnert M, Lilja B, Sundkvist G. Impaired responses of plasma cathecolamines to exercise in diabetic patients with abnormal heart reactions to tilt. Clin Physiol 1989; 9: 259–67.

211. Sundkvist G, Lilja B, Almer L-O. Abnormal diastolic blood pressure and heart rate reactions to tilting in diabetes mellitus. Diabetologia 1980; 19: 433–8.

212. de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G. A prospective study of orthostatic blood pressure in diabetic patients. Clin Auton Res 1998 8: 189–93.

213. van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol 1969; 82: 10–4.

214. Manning FJ, Wehrly SR, Foulks GN. Patient tolerance and ocular surface staining characteristics of lissamine green versus rose Bengal. Ophthalmology 1995; 102: 1953–7.

215. Manthorpe R, Axell T. Xerostomia. Clin Exp Rheumatol 1990; 8 Suppl 5: 7–12.

216. Suarez GA, Opfer-Gehrkring TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile. A new instrument to assess autonomic symptoms. Neurology 52: 523–528, 1999.

217. Low PA, Benrud-Larson LM, Sletten DM et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004; 27: 2942–7.

218. Ekberg O, Olsson R. Dynamic Radiology of Swallowing Disorders. Endoscopy 1997; 29: 439–46.

219. Lundquist A, Olsson R, Ekberg O. Clinical and radiologic evaluation reveals high prevalence of abnormalities in young adults with dysphagia. Dysphagia 1998; 13: 202–7.

220. Hietaharju A, Yli-Kerttula, Häkkinen V, Frey H. Nervous system manifestations in Sjögren's syndrome. Acta Neurol Scand 1990; 81: 144–52.
221. Konttinen YT, Hukkanen M, Kemppinen P, Segerberg M, Sorsa T, Malmström M et al. Peptide-containing nerves in labial salivary glands in Sjögren's syndrome. Arthritis Rheum 1992; 35: 815–20.
222. Streiner DL, Norman GR, editors. Health measurement scales: a practical guide to their development and use. Oxford: Oxford University Press, 1995.
223. Sreebny LM, Yu A, Green A, Valdini AM. Xerostomia in diabetes mellitus. Diabetes Care, 1992; 15: 900–4.
224. Kaiserman I, Kaiserman N, Nakar S, Vinker S. Dry eye in diabetic patients. Am J Ophthalmol 2005; 139: 498–503.
225. Ramos-Remus C, Suarez-Almazor M, Russell AS. Low tear production in patients with diabetes mellitus is not due to Sjogren's syndrome. Clin Exp Rheumatol 1994; 12: 375–80.
226. Keene LC, Davies PH. Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev 1999; 18: 5–24.
227. Morano S. Pathophysiology of diabetic sexual dysfunction. J Endocrinol Invest, 2003; 26 Suppl 3: 65–9.
228. Bottini P, Dottorini ML, Cristina Cordoni M, Casucci G, Tantucci C. Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. Eur Respir J 2003; 22: 654–60.
229. Talley NJ. Irritable bowel syndrome. Intern Med J 2006; 36: 724–8.
230. Lindvall B, Bengtsson A, Ernerudh J, Eriksson P. Subclinical myositis is common in primary Sjögren's syndrome and is not related to muscle pain. J Rheumatol 2002; 29: 717–25.
231. Sperber AD, Atzmon Y, Neumann L, Weisberg I, Shalit Y, Abu-Shakrah M et al. Fibromyalgia in the irritable bowel syndrome: Studies of prevalence and clinical implications. Am J Gastroenterol 1999; 94: 3541–6.
232. Akkus S, Senol A, Bayram Ayavacioglu N, Tunc E, Eren I, Isler M. Is female predominance in irritable bowel syndrome related to fibromyalgia? Rheumatol Int 2004; 24: 106–9.
233. Foxx-Orenstein. IBS – Review and What's new. MedGenMed 2006; 8: 20.
234. Barton A, Whorwell PJ, Marshall D. Increased prevalence of sicca complex and fibromyalgia in patients with irritable bowel syndrome. Am J Gastroenterol 1999; 94: 1898–1901.
235. Mandl T, Ekberg O, Wollmer P, Manthorpe R, Jacobsson L. Dysphagia and dysmotility of the pharynx and esophagus in patients with primary Sjögren's syndrome. Scandinavian Journal of Rheumatology 2007; 36: 394–401.

Appendix A – The Swedish version of the ASP

Autonom Symptomprofil
(ASP)

Publikation:
Suarez GA, Opfer-Gehrkring TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA.
The autonomic symptom profile. A new instrument to assess autonomic symptoms.
Neurology 52:523-528, 1999.
Svensk översättning / validering:
Mandl T, Granberg V, Apelqvist J, Wollmer P, Manthorpe R, Jacobsson L.
Assessment of autonomic symptoms in diabetics. The Swedish version of the ASP.
Manuscript.

Namn: _____

Personnummer: _____

Dagens datum: _____

Din längd (cm): _____ Din vikt (kg): _____

Instruktioner: Besvara frågorna genom att sätta kryss i lämplig ruta / lämpliga rutor eller med egna ord.

Q18 **Har Du under senaste året <u>vid något tillfälle</u> känt Dig svimfärdig, yr eller "dum" eller haft svårt att tänka snart efter Du har rest Dig upp från sittande eller liggande?**

1 □ Ja → Om Du svarat "JA" fortsätt här!
2 □ Nej
↓
Om du svarat "NEJ" gå vidare till sidan 4!

Q19 **Hur ofta får Du dessa symtom eller känslor när Du reser Dig upp?**
1 □ Sällan 2 □ Ibland 3 □ Ofta 4 □ Nästan alltid

Q20 **Hur bedömer Du svårighetsgraden på dessa symtom / känslor?**
1 □ Lindrig 2 □ Måttlig 3 □ Svår

Q21 **Under hur lång tid har Du upplevt dessa symtom / känslor?**
1 □ Mindre än 3 månader
2 □ 3 – 6 månader
3 □ 7 – 12 månader
4 □ 13 månader – 5 år
5 □ Mer än 5 år
6 □ Så länge jag minns

Q22 **Hur ofta under senaste året har Du svimmat strax efter Du har rest Dig upp från sittande eller liggande?**
0 □ Aldrig 1 □ En gång 2 □ Två gånger 3 □ Tre gånger
4 □ Fyra gånger 5 □ Fem eller flera gånger

Q23 **Hur försiktig är Du när du reser Dig upp från sittande eller liggande?**
1 □ Inte alls försiktig 2 □ Något försiktig 3 □ Mycket försiktig

Q24 **När under dygnet är dessa symtom / känslor svårast?**
(Sätt endast ett kryss!)
1 □ Tidigt på morgonen
2 □ Under resten av morgonen / förmiddagen
3 □ På eftermiddagen
4 □ På kvällen
5 □ Under natten, när jag kliver upp efter att jag har sovit
6 □ Ingen speciell tid är svårast
7 □ Annan tid. När? _____

Q25 **Under senaste året har dessa symtom / känslor Du upplevt:**

1 □ Blivit mycket sämre
2 □ Blivit något sämre
3 □ Är ungefär oförändrade
4 □ Blivit något bättre
5 □ Blivit mycket bättre
6 □ Försvunnit helt och hållet

Gradera genomsnittliga svårighetsgraden som Du har upplevt under senaste året för vart och ett av följande symtom:

		Har inte haft	Lätt	Måttlig	Svår
Q26	Snabb eller ökad puls (hjärtklappning)?	1□	2□	3 □	4□
Q27	Illamående eller kräkning?	1□	2□	3 □	4□
Q28	Snurrande eller gungande känsla?	1□	2□	3 □	4□
Q29	Yrsel?	1□	2□	3 □	4□
Q30	Suddigt seende?	1□	2□	3 □	4□
Q31	Svaghetskänsla?	1□	2□	3 □	4□
Q32	Skakighet eller darrighet?	1□	2□	3 □	4□
Q33	Känsla av oro eller nervositet?	1□	2□	3 □	4□
Q34	Känsla av att Du bleknat?	1□	2□	3 □	4□
Q35	Känsla av kladdig och kall hud?	1□	2□	3 □	4□

Q36 **Har Du några anhöriga bland Dina föräldrar, mor/farföräldrar, syskon eller barn som upplever ofta förekommande yrsel när de reser sig upp från sittande eller liggande?**

1 □ Ja → Anteckna deras släktskap till dig
Släktskap:

_____
_____
_____
_____

2 □ Nej

Under senaste året har Du <u>någonsin</u> känt dig svimfärdig, yr eller "dum" eller haft svårt att tänka:

Q37	strax efter Du har ätit mat?	1 □ Ja	2 □ Nej
Q38	när Du stått upp en längre tid?	1 □ Ja	2 □ Nej
Q39	under eller strax efter fysisk aktivitet eller träning?	1 □ Ja	2 □ Nej
Q40	under eller strax efter ett hett bad, het dusch, eller vistelse i bastu?	1 □ Ja	2 □ Nej

Q41 **Har Du <u>någonsin</u> känt Dig yr, svimfärdig eller faktiskt svimmat av när Du sett blod eller lämnat blodprov?**
1 □ Ja 2 □ Nej

Har Du svimmat under senaste året när Du gjort följande:

Q42	Kissat?	1 □ Ja	2 □ Nej
Q43	Hostat?	1 □ Ja	2 □ Nej
Q44	Tryckt på sidan av halsen (till exempel vid rakning)?	1 □ Ja	2 □ Nej
Q45	Innan Du skulle tala för publik?	1 □ Ja	2 □ Nej
Q46	Vid andra tillfällen?	1 □ Ja	2 □ Nej

Om Du har svarat "JA" på några av dessa frågor beskriv omständigheterna.

_____

_____

Q47 **Har Du vid något tillfälle under senaste året tappat medvetandet efter en yrselattack?**
1 □ Ja 2 □ Nej

Q48 **Har Du haft några anfall eller kramper under senaste året?**
1 □ Ja – beskriv omständigheterna.

_____

_____

2 □ Nej

Hur skulle Du beskriva besvären, om Du har haft några, under senaste 5 åren, av:

		Inga	Vissa	Stora	Konstanta
Q49	Förlamning i delar av ansiktet?	1 □	2 □	3 □	4 □
Q50	Känsla av total svaghet i hela kroppen?	1 □	2 □	3 □	4 □
Q51	Attacker av okontrollerbara rörelser i armar eller ben?	1 □	2 □	3 □	4 □
Q52	Anfall när Du inte kunde kontrollera Ditt tal, t.ex. sluddrigt tal?	1 □	2 □	3 □	4 □

Q53 **Har Du <u>någonsin under Ditt vuxna liv</u> upplevt en yrselattack?** 1 □ Ja 2 □ Nej

Q54 **Har Du under det senaste året lagt märke till att huden ändrar färg – Har huden exempelvis blivit röd, vit eller blåröd?**

1 □ Ja →

2 □ Nej
↓

Om Du svarat "JA" här fyll i denna ruta!

Vilka färgändringar har skett? (Kryssa för alla som stämmer)

Q55 □ Huden blir röd
Q56 □ Huden blir vit
Q57 □ Huden blir blåröd
Q58 □ Huden får annan färg – vilken?_____

Vilka kroppsdelar påverkas av dessa färgändringar?
(Kryssa för alla som stämmer)

Q59 □ Mina händer
Q60 □ Mina fötter
Q61 □ Andra delar – beskriv vilka _____
Q62 □ Hela kroppen

Hur länge har Du upplevt dessa färgändringar i huden?

Q63
1 □ Mindre än 3 månader.
2 □ 3 – 6 månader.
3 □ 7 – 12 månader.
4 □ 13 månader – 5 år
5 □ Längre än 5 år
6 □ Så länge som jag minns.

Hur förändras dessa färgändringar i huden:

Q64
1 □ Håller på att bli mycket sämre
2 □ Håller på att bli något sämre
3 □ Är ungefär desamma
4 □ Håller på att bli något bättre
5 □ Håller på att bli mycket bättre
6 □ Har försvunnit helt

Q65 **Under senaste året har Du efter ett långt hett bad eller dusch märkt att fingertopparna blir "skrynkliga"?**

1 □ Ja 2 □ Nej

Q66 **Har Du upplevt några förändringar i din kroppsliga svettning under de senaste 5 åren – i så fall vilka?**

1 □ Jag svettas mycket mer än tidigare
2 □ Jag svettas något mer än tidigare
3 □ Jag har inte lagt märke till några förändringar
4 □ Jag svettas något mindre än tidigare
5 □ Jag svettas mycket mindre än tidigare

Q67 **Har Du lagt märke till några förändringar i din fotsvett under de senaste 5 åren – i så fall vilka?**

1 □ Jag har mycket mer fotsvett än tidigare
2 □ Jag har något mer fotsvett än tidigare
3 □ Jag har inte lagt märke till några förändringar
4 □ Jag har något mindre fotsvett än tidigare
5 □ Jag har mycket mindre fotsvett än tidigare

Q68 **Har Du lagt märke till några förändringar i svettningen från ansiktet efter att du ätit kryddad mat under de senaste 5 åren – i så fall vilka?**

1 □ Jag svettas mycket mer än tidigare
2 □ Jag svettas något mer än tidigare
3 □ Jag har inte lagt märke till några förändringar
4 □ Jag svettas något mindre än tidigare
5 □ Jag svettas mycket mindre än tidigare
6 □ Jag undviker att äta kryddad mat p g a att jag svettas så mycket
7 □ Jag undviker att äta kryddad mat p g a andra orsaker

Har Du lagt märke till några förändringar under de senaste 5 åren i Din förmåga att tåla värme en het dag eller vid ansträngande arbete eller motion, hett bad, het dusch eller bastu?

(Kryssa för alla svar som stämmer)

Q69 □ Numera känner jag mig mer överhettad
Q70 □ Numera blir jag yr
Q71 □ Numera blir jag andfådd
Q72 □ Andra förändringar – Vilka?_____
Q73 □ Ingen förändring

Q74 **Känns ögonen onormalt torra?**

1 ☐ Ja 2 ☐ Nej

Q75 **Känns munnen onormalt torr?**

1 ☐ Ja 2 ☐ Nej

Q76 **Känns det som om Du bildar överdrivet mycket saliv?**

1 ☐ Ja 2 ☐ Nej

Q77 **Vilken är den längsta tidsperioden Du har upplevt någon eller några av följande symtom: Torra ögon, torr mun eller ökad salivbildning?**

0 ☐ Jag har inte upplevt något av dessa symtom
1 ☐ Mindre än 3 månader
2 ☐ 3 – 6 månader
3 ☐ 7 – 12 månader
4 ☐ 13 månader – 5 år
5 ☐ Mer än 5 år
6 ☐ Så länge jag minns

Q78 **Hur förändras symtomet som Du har haft längst tid**:

0 ☐ Jag har inte upplevt några av dessa symtom
1 ☐ Håller på att bli mycket sämre
2 ☐ Håller på att bli något sämre
3 ☐ Är ungefär detsamma
4 ☐ Håller på att bli något bättre
5 ☐ Håller på att bli mycket bättre
6 ☐ Har helt försvunnit

Q79 **Har Du lagt märke till några viktförändringar under senaste året – i så fall vilka?**

1 □ Jag har tappat cirka _____ kg.
2 □ Vikten är oförändrad.
3 □ Jag har ökat cirka _____ kg.

Q80 **Har Du lagt märke under senaste året till några förändringar i hur fort mätt Du blir när Du äter – i så fall vilka?**

1 □ Numera blir jag mätt mycket snabbare än tidigare
2 □ Numera blir jag mätt snabbare än tidigare
3 □ Jag har inte lagt märke till några förändringar
4 □ Numera blir jag inte lika fort mätt som tidigare
5 □ Numera blir jag inte *alls* lika fort mätt som tidigare

Q81 **Har Du känt Dig överdrivet mätt eller ständigt mätt (uppsvälld känsla) efter en måltid under senaste året?**

1 □ Aldrig 2 □ Ibland 3□ Ofta

Q82 **Har Du under senaste året känt dig illamående stora delar av dagen?**

1 □ Aldrig 2 □ Ibland 3 □ Ofta

Q83 **Har Du under senaste året kräkts efter en måltid?**

1 □ Aldrig 2 □ Ibland 3 □ Ofta

Q84 **Har Du under senaste året känt krampartade eller kolikliknande magsmärtor?**

1 □ Aldrig 2 □ Ibland 3 □ Ofta
↓ ↓

Q85 **Kommer dessa smärtor oftast efter att Du har ätit en måltid?**

1 □ Ja 2 □ Nej

Q86 **Hur länge har Du haft dessa krampartade eller kolikliknande magsmärtor?**

1 □ Mindre än 3 månader
2 □ 3 – 6 månader
3 □ 7 – 12 månader
4 □ 13 månader – 5 år
5 □ Mer än 5 år
6 □ Så länge jag minns

Q87 **Har Du haft någon episod med diarré (lös avföring) under senaste året?**

1 □ Ja →
2 □ Nej
↓

Om du har svarat "JA", besvara frågorna i denna ruta!

Q88 **Hur ofta har detta inträffat?**
1 □ Sällan
2 □ Emellanåt
3 □ Ofta, _____ gånger per månad
4 □ Alltid

Q89 **Hur allvarliga är dessa episoder med diarré?**
1 □ Milda 2 □ Måttliga 3 □ Svåra

Q90 **Under vilken del av dagen förefaller de vara svårast?**
1 □ Genast efter att jag stigit upp
2 □ Under resterande delen av morgonen / förmiddagen
3 □ Under eftermiddagen
4 □ På kvällen
5 □ Under natten
6 □ Ingen särskild tid

Q91 **Inträffar dessa episoder med diarré vanligtvis efter måltid?**
1 □ Ja 2 □ Nej

Q92 **Är dessa episoder med diarré åtföljda av mycket väderspänningar / gaser i magen?**
1 □ Aldrig 2 □ Ibland 3 □ Ofta 4 □ Alltid

Q93 **Hur håller Dina episoder med diarré på att bli:**
1 □ Håller på att bli mycket sämre
2 □ Håller på att bli något sämre
3 □ Är oförändrade
4 □ Håller på att bli något bättre
5 □ Håller på att bli mycket bättre
6 □ De har helt försvunnit

Q94 **Har Du under senaste året varit förstoppad?**

1 □ Ja →
2 □ Nej
↓

Om du har svarat "JA", besvara frågorna i denna ruta!

Q95 **Hur ofta är du förstoppad?**
1 □ Sällan
2 □ Emellanåt
3 □ Ofta, _____ gånger per månad
4 □ Alltid

Q96 **Hur allvarliga är dessa förstoppningsepisoder?**
1□ Milda 2□ Måttliga 3□ Svåra

Q97 **Hur håller Din förstoppning på att bli:**
1 □ Håller på att bli mycket sämre
2 □ Håller på att bli något sämre
3 □ Är ungefär densamma
4 □ Håller på att bli något bättre
5 □ Håller på att bli mycket bättre
6 □ Har helt försvunnit

Q98 **Hur känner Du att Dina magsymtom överlag i form av kräkning, diarré, förstoppning eller viktnedgång håller på att bli:**

0 ☐ Jag har inte haft några av dessa symtom.
1 ☐ Håller på att bli mycket sämre
2 ☐ Håller på att bli något sämre
3 ☐ Är oförändrade
4 ☐ Håller på att bli något bättre
5 ☐ Håller på att bli mycket bättre
6 ☐ Har helt försvunnit

Q99 **Vilket symtom har varit mest besvärligt? (Kryssa bara för ett!)**

0 ☐ Inget 1 ☐ Kräkning 2 ☐ Diarré 3 ☐ Förstoppning 4 ☐ Viktnedgång

Q100 **Hur länge har Du haft det mest besvärliga symtomet?**

0 ☐ Jag har inga av dessa symtom
1 ☐ Mindre än 3 månader
2 ☐ 3 – 6 månader
3 ☐ 7 – 12 månader
4 ☐ 13 månader – 5 år
5 ☐ Mer än 5 år
6 ☐ Så länge jag minns

Q101 **Hur känner Du att det mest besvärliga symtomet håller på att bli:**

0 ☐ Jag har inga av dessa symtom
1 ☐ Håller på att bli mycket sämre
2 ☐ Håller på att bli något sämre
3 ☐ Är oförändrat
4 ☐ Håller på att bli något bättre
5 ☐ Håller på att bli mycket bättre
6 ☐ Har helt försvunnit

Hur bedömer Du hur mycket besvär Du har haft – om Du har haft besvär - under de senaste 5 åren med:

		Inget besvär	Visst besvär	Mycket besvär	Konstanta besvär
Q102	**svårigheter att svälja**	1 ☐	2 ☐	3 ☐	4 ☐
Q103	**att allt Du äter smakar likadant**	1 ☐	2 ☐	3 ☐	4 ☐

Har Du någonsin under Ditt vuxna liv:

Q104	Känt Dig illamående eller kräkts?	1 ☐ Ja	2 ☐ Nej
Q105	Fått en släng av diarré?	1 ☐ Ja	2 ☐ Nej
Q106	Tappat aptiten under åtminstone en del av dagen?	1 ☐ Ja	2 ☐ Nej
Q107	Känt obehag eller smärta i maggropen?	1 ☐ Ja	2 ☐ Nej

Q108 **Har Du under senaste året upplevt urinläckage eller tappat kontrollen över urinblåsan?**

1 ☐ Aldrig
2 ☐ Emellanåt
3 ☐ Ofta, _____ gånger per månad
4 ☐ Alltid

Q109 **Har Du under senaste året haft svårigheter att kissa?**

1 ☐ Aldrig
2 ☐ Emellanåt
3 ☐ Ofta, _____ gånger per månad
4 ☐ Alltid

Q110 **Har Du under senaste året haft besvär med att helt tömma urinblåsan?**

1 ☐ Aldrig
2 ☐ Emellanåt
3 ☐ Ofta, _____ gånger per månad
4 ☐ Alltid

Q111 **Hur skulle Du beskriva Din sexlust för närvarande?**

1 ☐ Den finns inte alls
2 ☐ Den är mycket nedsatt
3 ☐ Den är något nedsatt
4 ☐ Den är mer eller mindre samma som tidigare

Manliga patienter fyll i denna sida.
Kvinnliga patienter fortsätt till nästa sida. →

Q112 **Kan Du få full erektion (kraftigt stånd)?**
1 ☐ Aldrig – under inga som helst omständigheter
2 ☐ Inte alls lika ofta som tidigare
3 ☐ Något mer sällan än tidigare
4 ☐ Lika ofta som tidigare eller oftare

Vilka av följande påståenden gäller för Dig? (Kryssa för alla som stämmer)

Q113 ☐ Min förmåga att genomföra ett samlag är oförändrad
Q114 ☐ Jag kan få erektion (stånd) men kan inte genomföra eller fullfölja ett samlag
Q115 ☐ Jag klarar endast ibland av att genomföra ett samlag
Q116 ☐ Mina erektioner (mina stånd) är definitivt försämrade
Q117 ☐ Jag klarar att genomföra ett samlag men kan inte ejakulera (få utlösning)
Q118 ☐ Jag har "torra" orgasmer och efteråt är urinen "mjölkig" eller grumlig.
Q119 ☐ Jag har inte kunnat få eller haft försämrad erektion (stånd) sedan jag började ta en medicin som heter_____
Q120 ☐ Övrigt – beskriv_____
Q121 ☐ Inget av ovan stämmer in på mig

Q122 **Hur länge har Du haft besvär med erektionsfunktionen (förmågan att få stånd)?**

0 ☐ Jag har inga besvär.
1 ☐ Mindre än 3 månader.
2 ☐ 3 – 6 månader
3 ☐ 7 – 12 månader
4 ☐ 13 månader – 5 år
5 ☐ Mer än 5 år
6 ☐ Så länge jag minns

Q123 **Hur håller svårigheterna på att bli:**
0 ☐ Jag har inte haft besvär.
1 ☐ Håller på att bli mycket sämre
2 ☐ Håller på att bli något sämre
3 ☐ Är oförändrade
4 ☐ Håller på att bli något bättre
5 ☐ Håller på att bli mycket bättre
6 ☐ Har helt försvunnit

Q124 **Om Du inte använt solglasögon eller tonade glasögon under senaste året har Du upplevt ögonbesvär i skarpt ljus?**

1 □ Aldrig 2 □ Emellanåt 3 □ Ofta 4 □ Alltid

↓ ↓ ↓

Q125 **Hur pass allvarlig är denna känslighet för skarpt ljus?**
1 □ Lindrig 2 □ Måttlig 3 □ Svår

Q126 **Har Du haft svårigheter under senaste året att fokusera (ställa in skärpan) med ögonen?**

1 □ Aldrig 2 □ Emellanåt 3 □ Ofta 4 □ Alltid

↓ ↓ ↓

Q127 **Hur pass besvärligt har det varit att fokusera med ögonen?**
1 □ Lindrigt 2 □ Måttligt 3 □ Svårt

Q128 **Har Du haft suddigt seende under senaste året?**

1 □ Aldrig 2 □ Emellanåt 3 □ Ofta 4 □ Alltid

↓ ↓ ↓

Q129 **Hur pass allvarligt har det suddiga seendet varit?**
1 □ Lindrigt 2 □ Måttligt 3 □ Svårt

Q130 **Har Du haft svårt med mörkerseende under senaste året?**

1 □ Aldrig 2 □ Emellanåt 3 □ Ofta 4 □ Alltid

↓ ↓ ↓

Q131 **Hur pass allvarliga har svårigheterna med mörkerseende varit?**
1 □ Lindriga 2 □ Måttliga 3 □ Svåra

Q132 **Har Du under senaste året upplevt samma grad av ljus, jämfört med tidigare, som:**

1 □ Påtagligt mycket dunklare 2 □ Mycket dunklare 3 □ Ungefär detsamma 4 □ Mycket klarare 5 □ Påtagligt mycket klarare

Q133 **Vilket av dessa ögonsymtom tycker Du är mest besvärligt?** (Kryssa endast för ett!)

0 □ Inget 1 □ Fokuseringsproblem 2 □ Suddigt seende 3 □ Dåligt mörkerseende

Q134 **Hur länge har Du haft symtomet som Du bedömer som det mest besvärliga?**

0 □ Jag har inga symtom
1 □ Mindre än 3 månader.
2 □ 3 – 6 månader
3 □ 7 – 12 månader
4 □ 13 månader – 5 år
5 □ Mer än 5 år
6 □ Så länge jag minns

Q135 **Hur håller det mest besvärliga symtomet på att bli:**

0 □ Jag har inga av dessa symtom
1 □ Håller på att bli mycket sämre
2 □ Håller på att bli något sämre
3 □ Är oförändrat
4 □ Håller på att bli något bättre
5 □ Håller på att bli mycket bättre
6 □ Har helt försvunnit

Q136 **Har Du under det senaste året lagt märke till, eller blivit upplyst om, att Du slutar andas under några sekunder när du sover?**

1 ☐ Ja 2 ☐ Nej

Q137 **Har Du under det senaste året lagt märke till, eller blivit upplyst om, att Du snarkar högt när Du sover?**

1 ☐ Ja 2 ☐ Nej

Har Du någonsin fått reda på att Du har diagnosen:

		Ja	Nej	Vet ej
Q138	**Narkolepsi**	☐	☐	☐
Q139	**Obstruktivt sömnapné syndrom**	☐	☐	☐
Q140	**Onormala eller oroliga sömnmönster**	☐	☐	☐

Q141 **Hur uppiggande och stärkande känns sömnen för närvarande?**

1 ☐ Inte alls stärkande – upplever ingen nytta från tiden i sängen
2 ☐ Något litet stärkande
3 ☐ Stärkande men inte tillräckligt
4 ☐ Relativt tillfredsställande
5 ☐ Mycket tillfredsställande – känner mig helt återställd och redo för dagen

Q142 **Hur skulle Du bedöma sömnen under senaste månaden jämfört med sömnen för ett år sedan?**

1 ☐ Senaste månaden var sömnen mycket sämre än för ett år sen
2 ☐ Senaste månaden var sömnen något sämre än för ett år sen
3 ☐ Senaste månaden var sömnen ungefär densamma som för ett år sen
4 ☐ Senaste månaden var sömnen något bättre än för ett år sen
5 ☐ Senaste månaden var sömnen mycket bättre än för ett år sen

Q143 **Har Du någonsin under Ditt vuxna liv upplevt att det varit svårt att somna eller fortsätta att sova när Du väl sov?**

1 ☐ Ja 2 ☐ Nej

Q144 **Har Du under senaste året lagt märke till eller blivit tillsagd att Du ibland under dagen andas mycket högt (till exempel kruppaktigt)?**

1 ☐ Ja 2 ☐ Nej

Hur skulle Du beskriva Dina alkoholvanor under senaste året?
(Kryssa för alla som stämmer)

Q145 ☐ Jag har inte druckit alkohol under senaste året
Q146 ☐ Jag dricker enbart vid sociala tillfällen
Q147 ☐ Jag har druckit påtagligt mycket under senaste året
Q148 ☐ Jag har varit berusad vid ett eller flera tillfällen under senaste året
Q149 ☐ Jag har tuppat av p g a att jag har druckit för mycket alkohol vid ett eller flera tillfällen under det senaste året

Hur skulle Du beskriva Dina drog (narkotika) vanor under det senaste året?

Q150 ☐ Jag har inte brukat droger under senaste året
Q151 ☐ Jag har brukat droger påtagligt mycket under senaste året
Q152 ☐ Jag har varit påverkad vid ett eller flera tillfällen under senaste året
Q153 ☐ Jag har tuppat av p g a att jag har brukat droger vid ett eller flera tillfällen under det senaste året

Q154 **Har Du <u>någonsin</u> känt att Du har brukat droger eller druckit alkohol överdrivet mycket?**

1 ☐ Ja 2 ☐ Nej

Q155 **Har Du någonsin fått reda på att Du är eller fått diagnosen alkohol- eller drogberoende?**

1 ☐ Ja 2 ☐ Nej

Q156 **Har Du någonsin fått behandling för alkohol- eller drogberoende?**

1 ☐ Ja – skriv upp på grund av vilka droger (inkl. alkohol) 1._____
2 ☐ Nej 2._____
3._____

Vilka av följande påståenden beskriver bäst dina rökvanor?
(Kryssa för alla som stämmer)

Q157 ☐ Jag har aldrig rökt
Q158-162 ☐ Jag har tidigare rökt men röker ej längre
Jag slutade _____/____
Månad År
Q163:164-165 ☐ För närvarande röker jag c:a ____ cigaretter per dag

Q166 **Hur skulle Du beskriva besvären under de senaste 5 åren som Du haft – om Du har haft några - med överkänslig hörsel?**

1 ☐ Inga besvär 2 ☐ Vissa besvär 3 ☐ Stora besvär 4 ☐ Konstanta besvär

Q167 **Har Du <u>någonsin under Ditt</u> <u>vuxna liv</u> upplevt svårigheter att koncentrera Dig på Ditt arbete eller en uppgift?**

1 ☐ Ja 2 ☐ Nej

Vilka mediciner har Du tagit under senaste månaden?

Medicinens namn	Hur ofta tar du den?	Hur många tabletter och vilken styrka (dos) per gång?

Vi är tacksamma för kommentarer angående vad Du tycker kan ha orsakat eller varit förknippat med Din nuvarande sjukdom – vad som helst Du kan komma på som kanske kan hjälpa oss att förstå Ditt nuvarande tillstånd.

ASP - NYCKEL

Domäner:

1. Ortostatism	40
2. Sexuell dysfunktion*	30
3. Urinblåsebesvär	20
4. Autonom diarré	20
5. Gastropares	10
6. Sekretomotorisk störning	20
7. Sömnbesvär	15
8. Förstoppning	10
9. Vasomotorisk störning	10
10. Pupillomotorisk störning	5
11. Reflexsyncope	20

Symtomens svårighetsgrad:	Maximum	200 för män
(exkluderar sexuella dysfunktionsskalan)	Maximum	170 för kvinnor
12. Underskattningsindex:	Maximum	10
13. Överskattnings (Psykosomatiskt) index:	Maximum	10

*Enbart manliga patienter

Svaret följes av ett poäng till ex 2=0p.
Före viktning sätt negativa domänpoäng till 0p.

Totalscore:.....

Underskattningsindex:.....

Överskattningsindex:.....

DOMÄNER:

1. Ortostatism (Generaliserat adrenergt)

Närvaro	(2=0p; 1=2p)	Q18	.....
Frekvens	(1=0p; 2=1p; 3,4=3p)	Q19	.....
Svårighetsgrad	(1=1p; 2=2p; 3=3p)	Q20	.....
Syncope	(0=0p; 1=2p; 2-5=3p)	Q22	.....
Förändring	(1-4=1p; 5,6=0p)	Q25	.....
Försvårande faktorer	(37-40 1=1p för varje)	Q37-40	.....

Obs: Reflex syncope inte inkluderad

Max poäng = 40p
Vikt = 40/16 =2.5 **Total:.....**

2. Sexuell dysfunktion:
***Manlig erektil dysfunktion**

Närvaro	(1=3p; 2=2p; 3=1p)	Q112	.....
Svårighetsgrad			
Q114=2p; Q115=3p; Q116=3p		Q114-116	.....
Duration	(1-4=2p; 5=1p)	Q122	.....
Förändring	(1-3=1p; 4=-2p 5=-4p; 6=-8p)	Q123	.....

Max poäng =20p
Vikt = 20/14 = 1.5 **Subtotal:.....**

***Ejakulationsproblem**

Oförmåga att ejakulera	(117=5p)	Q117	.....
Torra orgasmer	(118=5p)	Q118	.....

Max poäng =10p
Vikt = 10/10 = 1 **Subtotal:.....**

***Sexuell dysfunktion = Summa av subtotalerna** **Max poäng =30p** **Total:.....**

3. Urinblåsebesvär

Tappad kontroll	(2=1p; 3=3p; 4=4p)	Q108	.....
Retention	(2=1p; 3=2p; 4=3p)	Q109	.....
Residualurin	(2=1p; 3=2p; 4=3p)	Q110	.....

Max poäng =20p
Vikt = 20/10 = 2 **Total:.....**

4. Autonom diarré

Q87 : 1=1p	Q87	.....
Q88 : 3=1p; 4=2p	Q88	.....
Q89 : 2, 3=1p	Q89	.....
Q93 : 1, 2=1p; 4=-1p; 5=-2p; 6=-3p	Q93	.....

Max poäng =20p
Vikt = 20/5 = 4 **Total:.....**

5. Gastropares

Tidig mättnad	(1=1p; 2-5=0p)	Q80	……
Uppsvälldhet	(3=1p; 1,2=0p)	Q81	……
Illamående	(3=1p)	Q82	……
Kräkning	(3=2p; 2=1p)	Q83	……
Magsmärtor	(3=1p)	Q84	……
		Max poäng =10p	
		Vikt = 10/6 = 1.67	**Total:…….**

6. Sekretomotorisk störning (Kolinergt)

Förändring	(1,4=1p; 2,3=0p; 5=2p)	Q66	……
Fotsvett	(1,4=1p; 2,3=0p, 5=2p)	Q67	……
Gustatorisk svettning	(1=2p; 2-7=0p)	Q68	……
Värmeintolerans	(69-71, varje =1p)	Q69-73	……
Torra ögon	(1=2p; 2=0p)	Q74	……
Torr mun	(1=2p; 2=0p)	Q75	……
		Max poäng =20p	
		Vikt = 20/13 = 1.5	**Total:…….**

7. Sömnbesvär

Andningsuppehåll	(1=3p; 2=0p)		Q136
……			
Snarkning	(1=2p; 2=0p)		Q137
……			
Dx narkolepsi	(1=3p)	Q138	……
Dx obstruktiv sömnapné	(1=3p)	Q139	……
Dx abnorma sömnmönster	(1=3p)	Q140	……
Stärkande sömn	(1=2p; 2=1p)	Q141	……
Sömnkvalitet	(1=1p; 5=-3p)	Q142	……
Kruppartad andning	(1=3p)	Q144	……
		Max poäng = 15p	
		Vikt 15/20=0.75	**Total:…….**

8. Förstoppning

Närvaro	(1=1p)	Q94	……
Frekvens	(4=2p)	Q95	……
Svårighetsgrad	(3=2p; 2=1p)	Q96	……
Förändring	(1=2p; 2=1p; 4=-1p; 5=-3p; 6=-4p)	Q97	……
		Max poäng =10p	
		Vikt = 10/7 =1.5	**Total:…….**

9. Vasomotorisk störning (Perifert adrenergt)

närvaro	(1=4p)	Q54	.....
typ	(55-58, varje=1p)	Q55-58	.....
distribution	(59-62, varje=1p)	Q59-62	.....
duration	(1-4=2p; 5=1p; 6=0p)	Q63	.....
förändring	(1-2=2p; 4=-1p; 5,6=-2p)	Q64	.....
		Max poäng = 10p	
		Vikt = 10/16 = 0.63	**Total:.....**

10. Pupillomotorisk störning

Skarpt sken

Närvaro	(3,4=2p)	Q124	.....
Svårighetsgrad	(1=0p; 2=1p; 3=2p)	Q125	.....
Svårighetsgrad	(4,5=1p)	Q132	.....

Fokusering

Närvaro	(1,2=0p; 3,4=2p)	Q126	.....
Svårighetsgrad	(1=0p; 2=1p; 3=2p)	Q127	.....
Duration	(1-4=1p)	Q134	.....
Förlopp	(1,2=1p; 4=-1p; 5,6=-2p)	Q135	.....
		Max poäng =5p	
		Vikt = 5/11 = 0.5	**Total:.....**

11. Reflexsyncope

Urin	(1=2p)	Q42	.....
Hosta	(1=2p)	Q43	.....
Tryck på halsen	(1=2p)	Q44	.....
Tal	(1=2p)	Q45	.....
Annan tid	(1=2p)	Q46	.....
		Max poäng = 20p	
		Vikt = 20/10 = 2	Total:.....

12. Underskattning

Någonsin illamående	(2=2p)	Q104	.....
Någonsin diarré	(2=2p)	Q105	.....
Någonsin tappad aptit	(2=2p)	Q106	.....
Någonsin smärta i maggropen	(2=2p)	Q107	.....
Sömn	(2=2p)	Q143	.....
Koncentration	(2=2p)	Q167	.....
		Max poäng = 10p	
		Vikt = 10/12 = 0.83	Total:.....

13. Överskattning (Psykosomatik)

Ansiktsförlamning	(3,4=2p)	Q49	.....
Attack av okontrollerbara rörelser	(3,4=1p)	Q51	.....
Okontrollerbart tal	(3,4=2p)	Q52	.....
Svårighet att svälja	(3,4=2p)	Q102	.....
Smak	(3,4=2p)	Q103	.....
Överkänslig hörsel	(3,4=2p)	Q166	.....
		Max poäng = 10p	
		Vikt = 10/11 = 0.91	Total:.....

STANDARDISERADE VÄRDEN
Autonom Symptom Profil (ASP)

Respektive domäns score (totalpoäng) införs i ekvationen.

Kön: man = 1 & kvinna = 0

Ålder – år

Vikt – kg

Längd - cm

1. Zortostatism = (ortostatism - (-0.679 - 3.236 * kön – 0.110 * ålder – 0.085 * vikt + 0.112 * längd)) / 6.9657
2. Zsexuell dysfunktion = (sexuell dysfunktion - (-7.153 + 0.114 * ålder – 0.028 * vikt + 0.033 * längd)) / 3.9091
3. Zurinblåsebesvär = (urinblåsebesvär - (4.904 + 0.272 * kön + 0.017 * ålder – 0.025 * längd)) / 2.1921
4. Zautonom diarré = (autonom diarré - (10.708 – 0.436 * kön – 0.030 * ålder + 0.038 * vikt – 0.059 * längd)) / 2.9787
5. Gastropares – Könsstratifierade rawscores
6. Zsekretomotorisk störning = (sekretomotorisk störning - (5.917 + 0.046 * kön + 0.015 * ålder + 0.015 * vikt – 0.036 * längd)) / 2.0451
7. Zsömnbesvär = (sömnbesvär - (2.136 + 0.071 * kön – 0.007 * ålder + 0.017 * vikt – 0.010 * längd)) / 1.5850
8. Zförstoppning = (förstoppning - (2.207 – 0.111 * kön + 0.001 * ålder – 0.001 * vikt – 0.010 * längd)) / 0.9367
9. Zvasomotorisk störning = (vasomotorisk störning - (-1.777 – 0.504 * kön – 0.003 * ålder – 0.012 * vikt + 0.021 * längd)) / 1.5817
10. Zpupillomotorisk störning = (pupillomotorisk störning - (4.440 + 0.261 * kön + 0.006 * ålder – 0.007 * vikt – 0.020 * längd)) / 1.0881
11. Reflexsyncope – Könsstratifierade rawscores
12. Ztotal score = (total score - (27.476 – 2.418 * kön – 0.085 * ålder – 0.038 * vikt – 0.025 * längd)) / 12.2728
13. Underskattning – Könsstratifierade rawscores
14. Överskattning - Könsstratifierade rawscores

Appendix B – The questionnaire on pharyngeal and esophageal symptoms

Frågeformulär sväljningsbesvär

		Ja	Nej
1.	Upplever Ni sväljningssvårigheter när Ni äter och/eller dricker varje vecka?	□	□
	- Om Ni svarat Ja – vänligen besvara frågorna nedan!		
	- Upplever Ni sväljningssvårigheter när Ni äter varje vecka?	□	□
	- Upplever Ni sväljningssvårigheter när Ni dricker varje vecka?	□	□
	- Var är dessa sväljningssvårigheter belägna? (Om sväljningssvårigheterna är belägna på flera av nedan nämnda lokaler går det att kryssa för flera) i. I svalget □ ii. Upptill i bröstet □ iii. Mitt i bröstet □ iv. Nedtill i bröstet □		
2.	Upplever Ni varje vecka en känsla av en klump i halsen som Ni har svårt att svälja ned?	□	□
3.	Upplever Ni varje vecka sura uppstötningar?	□	□
4.	Upplever Ni varje vecka halsbränna?	□	□
5.	Upplever Ni varje vecka nattlig astma?	□	□
6.	Upplever Ni varje vecka onaturligt mycket vätska i munnen?	□	□
7.	Upplever Ni varje vecka att Ni får upp vätska eller annan föda i näsan när Ni sväljer?	□	□
8.	Upplever Ni varje vecka felsväljning?	□	□
9.	Upplever Ni varje vecka att Ni hostar när Ni sväljer?	□	□
10.	Upplever Ni varje vecka att Ni harklar er mycket när Ni äter?	□	□
11.	Upplever Ni varje vecka upphakning när Ni sväljer?	□	□
12.	Upplever Ni varje vecka att Ni undviker viss föda pga. sväljningssvårigheter?	□	□
13.	Upplever Ni varje vecka att Ni dricker mycket till maten för att få ned densamma?	□	□
14.	Upplever Ni varje vecka att Ni har ont när Ni sväljer?	□	□
15.	Har Ni någonsin upplevt en akut episod av upphakning av föda när Ni ätit som resulterat i att Ni behövt kräkas upp maten eller skoperas?	□	□

Gatroesophageal reflux disease (GERD) symptom score (Ja=1, Nej=0; q2-q6) .....

Faryngealt symptom score (Ja=1, Nej=0; q7-10) .....

Esofagealt symptom score(Ja=1, Nej=0; q11-q15) .....

I

Autonomic and Orthostatic Dysfunction in Primary Sjögren's Syndrome

THOMAS MANDL, PER WOLLMER, ROLF MANTHORPE, and LENNART T.H. JACOBSSON

ABSTRACT. ***Objective.*** Exocrine function always is and autonomic nervous function may be impaired in primary Sjögren's syndrome (pSS). Since autonomic nervous signaling is a prerequisite for exocrine secretion we wanted to assess autonomic nervous function in pSS and relate it to diagnostic measures of exocrine function.

Methods. Autonomic nervous function was determined in 46 patients with pSS using the deep breathing test [expiration/inspiration (E/I) ratio], orthostatic test [acceleration index (AI), orthostatic systolic and diastolic blood pressure response (lSBP ratio and lDBP ratio)], and finger skin blood flow test [vasoconstrictory (VAC) score]. The results were corrected for age and expressed as z-scores by comparison with 3 control groups (E/I ratio and AI, n = 56; lSBP ratio and lDBP ratio, n = 238; and VAC score, n = 80). Exocrine gland function was determined in patients with pSS using the objective functional Schirmer-I test and rose-bengal staining (van Bijsterveld score) for the lacrimal glands and unstimulated whole sialometry for the salivary glands.

Results. The E/I ratio and orthostatic systolic and diastolic blood pressures were significantly decreased and the VAC score was significantly increased in patients with pSS compared to controls, indicating both parasympathetic and sympathetic dysfunction. Autonomic and exocrine function measures were found to associate poorly.

Conclusion. Patients with pSS showed signs of both parasympathetic and sympathetic dysfunction. However, an association between cardiovascular autonomic and exocrine function in pSS was not detected. (First Release July 15 2007; J Rheumatol 2007;34:1869–74)

Key Indexing Terms:
AUTONOMIC NERVOUS DYSFUNCTION PRIMARY SJÖGREN'S SYNDROME

Primary Sjögren's syndrome (pSS) is an autoimmune disease affecting the exocrine glands, giving rise to hypofunction, especially of the lacrimal and salivary glands. Many non-exocrine organs may also be involved in the disease, including the nervous system. Signs of peripheral neuropathy have been found in about 20% of patients with pSS[1,2] and several case reports suggest autonomic nervous system (ANS) involvement in pSS as well, manifested by orthostatic hypotension[3-5], urinary retention[5], and Adie's syndrome[6]. Exocrine secretion is controlled by the ANS, where liquid secretion mainly is parasympathetically and protein secretion mainly sympathetically modulated[7]. Since the degree of exocrine gland destruction and exocrine function in pSS correlate poorly[8], other possible mechanisms behind the diminished exocrine secretion, including disturbed nervous signaling to the exocrine glands, have been proposed[8]. Using autonomic reflex tests, it has been shown that patients with pSS show signs of impaired parasympathetic and sympathetic nervous function[9-13]. Studies of autonomic function in pSS using current methods measuring heart rate variability (HRV) and baroreflex sensitivity have yielded contradictory results, with 2 studies on short-term HRV showing divergent results[13,14] and one study reporting no abnormalities in 24 h HRV and baroreflex sensitivity[15]. Different immunological mechanisms have been suggested for the observed autonomic dysfunction in pSS: anti-muscarine-3-receptor antibodies[16,17], cytokines interfering with nervous signaling[18,19], and inflammation of autonomic nerves or ganglia[20,21].

Due to use of different criteria sets for pSS in the different studies on ANS involvement in pSS, it is difficult to compare results. The American-European Consensus Criteria (AECC)[22] were applied in only 2 of the studies[13,15]. According to the AECC, some evidence of autoimmunity, i.e., anti-SSA/anti-SSB seropositivity and/or a positive lip biopsy (focus score ≥ 1) is mandatory for diagnosis of pSS. If immunological mechanisms affect ANS functioning[16-21], increased ANS involvement would be expected in patients with pSS diagnosed according to the AECC compared to older criteria sets[23,24] where signs of autoimmunity were not a prerequisite for diagnosis.

From the Departments of Rheumatology and Clinical Physiology, Malmö University Hospital, and the Sjögren's Syndrome Research Centre, Malmö, Sweden.

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T. Mandl, MD; L.T.H. Jacobsson, MD, PhD, Department of Rheumatology; P. Wollmer, MD, PhD, Department of Clinical Physiology, Malmö University Hospital; R. Manthorpe, MD, PhD, Sjögren's Syndrome Research Centre.

Address reprint requests to Dr. T. Mandl, Department of Rheumatology, Ing 25 plan 2, Malmö University Hospital, S-205 02 Malmö, Sweden. E-mail: thomas.mandl@med.lu.se

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Our aims were (1) to assess the prevalence and degree of ANS involvement in a cohort of patients with pSS according to the AECC; and (2) to relate autonomic nervous function to exocrine measures performed when diagnosing pSS.

MATERIALS AND METHODS

Forty-six patients fulfilling the AECC for pSS (median age 54 yrs, range 24–60 yrs, 43 women) were recruited from the outpatient clinic at the Department of Rheumatology, Malmö University Hospital. No patient had any other disease known to affect autonomic nervous function or was currently treated with any drugs affecting autonomic nervous function (anticholinergic drugs, beta-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, and angiotensin-2-receptor blockers) or with disease modifying antirheumatic drugs. Two patients were treated with pilocarpine 5 mg qid and one with prednisolone 5 mg daily, in whom treatment was discontinued 1 week prior to testing. Two patients could not be investigated by the tilt-table test due to feeling of panic when being strapped on the tilt table, one patient could not perform the finger skin blood flow test due to pain in the hand when exposed to cold, and one patient did not perform the unstimulated whole sialometry. Further patient characteristics are shown in Table 1.

The control group for the deep breathing test and orthostatic heart rate test consisted of 56 healthy individuals (median age 40 yrs, range 16–59 yrs, 22 women), all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders, or diabetes mellitus[25]. The orthostatic blood pressure reaction test controls consisted of 238 healthy nondiabetic individuals (median age 60 yrs, range 16–96 yrs, 106 women)[26]. Finally, the finger skin blood flow test consisted of 80 healthy subjects (median age 43 yrs, range 19–81 yrs, 37 women), all of whom were nonsmokers, had no history of vascular disease, and were not taking any medication[27].

Table 1. Characteristics of the patients with primary Sjögren's syndrome (pSS). Results are presented as median (interquartile range) or % abnormal results. Ocular measures are presented as sum of both eyes.

Characteristic	Patients with pSS, n = 46
Age, yrs	55 (38-58)
Male/female	3/43
Disease duration, yrs	11 (6–15)
Schirmer-I test, mm/5 min	5 (1–10)
Van Bijsterveld score (0–18)	10 (6–14)
Unstimulated whole sialometry, ml/15 min	0.4 (0.0–1.0)
Anti-SSA antibody seropositives, %	80
Anti-SSB antibody seropositives, %	41
ANA seropositives, %	74
RF seropositives, %	83
IgG, g/l	18.7 (15.5–22.6)
C3, g/l	1.20 (1.13–1.38)
C4, g/l	0.21 (0.20–0.29)
Lip biopsy focus score ≥ 1, %	87
Non-exocrine symptoms, %	76
Arthralgia in joints of hands	63
Raynaud's phenomenon	28
Arthritis in joints of hands	20
Peripheral neuropathy	20
Vasculitis-purpura	4
Renal disease	2
Liver disease	0
Interstitial lung disease	0
Myositis	0
Current smokers/nonsmokers	7/39

ANA: antinuclear antibodies; RF: rheumatoid factor.

The patients were investigated by 3 different autonomic nervous function tests, the deep breathing test, the orthostatic heart rate and blood pressure test, and the finger skin blood flow test.

Our study was approved by the ethics committee at Lund University (LU 576-01). All participants gave written informed consent.

Deep breathing test. After supine rest for 15 min, the subject's heart rate was monitored by electrocardiogram (ECG) for 4 min and, once constant, 6 maximal expirations and inspirations were performed during a 1-min period. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R-R intervals during the expirations divided by the mean of the shortest R-R intervals during the inspirations[28]. The E/I ratio mainly reflects parasympathetic nervous function[28,29].

Orthostatic heart rate and blood pressure test. The subject was strapped on a tilt table in the supine position for 10 min, and then, within 2 s, tilted to an erect position in which he/she remained for 8 min. The heart rate was monitored by ECG during the entire procedure beginning 1 min before tilt. Systolic and diastolic blood pressures were measured before and every minute after tilt. A mean of the R-R intervals before tilt (A) was calculated and the shortest R-R interval during the first minute after tilting (B) was determined. From the values above, an acceleration index, defined as $[(A - B)/A \times 100]$, was calculated[30,31]. The acceleration index seems to be influenced by both the parasympathetic and sympathetic nervous system[32,33]. The systolic and diastolic blood pressures before tilt (SBPrest and DBPrest) as well as the lowest systolic and diastolic blood pressures during the first 8 min after tilt (lSBP and lDBP) were determined. From these, orthostatic SBP and DBP ratios were calculated (lSBP ratio = lSBP/SBPrest and lDBP ratio = lDBP/DBPrest). In addition, the relative orthostatic SBP and DBP changes (%) in response to tilt were determined.

Finger skin blood flow test. The subject was seated in a semirecumbent position with the left hand on an aluminum holder situated at heart level, with the middle finger placed in a groove of the holder. The temperature of the aluminium holder was kept stable at 40°C by a Peltier element. The finger skin blood flow was monitored by a laser Doppler imaging (LDI) instrument, scanning an area of 2 × 2 cm of the distal phalanx of the middle finger. The finger skin blood flow was then monitored every minute for 6 min, during rest at the 40°C heating (h) procedure. The subject then immersed the contralateral hand and forearm into a water bath, kept at a stable temperature of 15°C, and kept the forearm there for 3 min. A scan of the left middle finger was made every 30 s during immersion and afterwards for a further 3 min. Hence, the finger skin blood flow of the left hand was being monitored during this contralateral cooling (c) procedure. By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDI_c) by the mean of the 2 last measurements of finger skin blood flow at rest, before the cooling procedure (LDI_h), a vasoconstriction (VAC) score could be calculated (VAC score = LDI_c/LDI_h). This has been shown to be a sensitive test for sympathetic nervous function in the skin[34].

Since ANS function usually deteriorates with advancing age, the autonomic nervous function variables were age-corrected and expressed as z-scores by comparison with 3 control groups. The z-scores of patients with pSS were then compared with z-scores of controls to detect differences between the groups. Since sex does not seem to significantly affect the autonomic variables measured in the tests used in our study[25,27], data were not matched for sex. All autonomic nervous function tests were performed in the morning under standard conditions, i.e., the temperature conditions were kept stable and patients were not allowed to eat, drink coffee, or smoke later than 2 h prior to testing.

Exocrine tests and questions. The function of lacrimal and salivary glands in patients with pSS was evaluated by Schirmer-I test, rose bengal staining/van Bijsterveld score, and unstimulated whole sialometry (UWS). Ocular measures were expressed as sum of both eyes. All autonomic nervous function and exocrine tests, on each patient, were performed closely in time [median 1 month apart (interquartile range 0–2)]. Moreover, patients were asked for smoking habits and for presence of Raynaud's phenomenon, i.e., an intermittent 2–3 color change [white – (blue) – red] of the fingers and/or toes. The

patients' journals were reviewed for other signs of non-exocrine symptoms (arthralgia/arthritis in the joints of the hands, symptoms of peripheral neuropathy, i.e., paresthesias in the extremities, vasculitis, renal disease, liver disease, interstitial lung disease, and myositis).

Statistics. Due to a skewed distribution of the autonomic nervous function test measures, nonparametric tests were used. For comparison between groups the Mann-Whitney U-test was used. P values < 0.05 were considered statistically significant. If not stated otherwise, values are presented as median (IQR) or percentage with abnormal results.

RESULTS

The E/I ratio was significantly decreased and the VAC score significantly increased in patients with pSS compared with controls, indicating parasympathetic and sympathetic dysfunction (Table 2). Four percent (2/46) and 9% (4/45) of patients had an E/I ratio ≤ –2 standard deviation (SD) and a VAC score ≥ 2 SD, as a sign of significant parasympathetic and sympathetic neuropathy, respectively. Although the acceleration index did not significantly differ between patients with pSS and controls, 7% (3/44) had an acceleration index ≤ –2 SD.

Further, patients with pSS had significantly reduced lSBP ratio and lDBP ratio compared with controls, representative of an attenuated blood pressure response to tilt (Table 2).

Nine percent (4/44) and 2% (1/44) of patients displayed an lSBP ratio ≤ –2 SD and lDBP ratio ≤ –2 SD, respectively, and 11% (5/44) and 7% (3/44) of patients with pSS had orthostatic systolic and diastolic hypotension, defined as orthostatic systolic blood pressure drop of ≥ 30 mm Hg and orthostatic diastolic blood pressure drop ≥ 10 mm Hg.

When correlating the autonomic nervous function indices only, the acceleration index and lDBP ratio were found to be significantly correlated (r_s = 0.54; p < 0.001). Comparing patients with normal (> –2 SD) and abnormal (≤ –2 SD) lSBP ratio, the latter had higher VAC scores than the former, although the difference was not statistically significant [1.20 (0.64 to 1.67) vs 0.48 (–0.40 to 1.35); p = NS], still implying that the lSBP ratio is also a sympathetic index.

Eighty-four percent (38/45), 74% (34/46), and 59% (27/46) had an abnormal UWS (abnormal ≤ 1.5 ml/15 min), Schirmer-I test (abnormal ≤ 10 mm/5 min), and van Bijsterveld score (abnormal ≥ 8), respectively, when tested. Comparing autonomic nervous function variables between patients with normal and abnormal UWS, a significantly lower lDBP ratio and a tendency toward a lower acceleration index were found in the latter. However, when comparing patients with a normal and abnormal Schirmer-I test, a significantly lower E/I ratio was found in the former (Table 3). Moreover, when comparing the autonomic nervous function indices in patients with and those without anti-SSA and anti-SSB antibodies as well as non-exocrine symptoms (arthralgia/arthritis in the joints of the hand, Raynaud's phenomenon, peripheral neuropathy, vasculitis, renal disease, liver disease, interstitial lung disease, and myositis), no significant differences were found. Finally, current smokers and nonsmokers were not found to differ significantly in autonomic nervous function indices.

DISCUSSION

In our study we found signs of a parasympathetic and a sympathetic dysfunction as well as an impaired orthostatic blood pressure response in patients with pSS. However, autonomic nervous function, as assessed by cardiovascular reflex tests, was poorly associated with exocrine function.

Autonomic nervous dysfunction is a feature in many different chronic diseases such as type I and II diabetes mellitus[30,35], rheumatoid arthritis[36], systemic lupus erythematosus[37], scleroderma[38], and inflammatory bowel disease[39,40]. Patients with primary Sjögren's syndrome may also show symptoms due to impaired autonomic nervous function, especially orthostatic hypotension[3-5]. Most previous studies on autonomic nervous function in pSS have shown signs of ANS disturbances[9-13], and different immunological mechanisms for these findings have been suggested[16-21]. Considering that exocrine gland destruction due to inflammation in pSS often is much less pronounced than the extremely decreased

Table 2. Results of the deep breathing, orthostatic heart rate, finger skin blood flow, and orthostatic blood pressure tests in 46 patients with primary Sjögren's syndrome (pSS) and 3 control groups (E/I ratio and acceleration index, n = 56; vasoconstrictory [VAC] score, n = 80; lSBP and lDBP ratio, orthostatic SBP and DBP change, n = 238). E/I ratio, acceleration index, VAC score, lSBP and lDBP ratio are age-corrected and expressed as z-scores (SD). Orthostatic systolic and diastolic blood pressure (SBP, DBP) changes are expressed as relative blood pressure change to tilt (%). Results are median (interquartile range).

	pSS Patients, n = 46	Controls, n = 56/80/238	p
E/I ratio (SD)	–0.50 (–1.29 to 0.32)	–0.25 (–0.62 to 0.60)	0.03
Acceleration index (SD)	–0.08 (–1.11 to 0.37)	0.03 (–0.67 to 0.65)	0.22
VAC score (SD)	0.62 (–0.36 to 1.40)	0.09 (–0.67 to 0.62)	0.02
Orthostatic SBP change (%)	–10.3 (–14.7 to –6.0)	–5.3 (–9.1 to 0.0)	0.00
lSBP ratio (SD)	–0.75 (–1.33 to –0.08)	–0.02 (–0.62 to 0.70)	0.00
Orthostatic DBP change (%)	0.0 (–5.9 to 5.3)	0.0 (0.0 to 7.1)	0.02
lDBP ratio (SD)	–0.38 (–1.04 to 0.14)	0.00 (–0.47 to 0.54)	0.00

NS: not significant.

Table 3. Age-corrected autonomic nerve function measure comparisons between patients with normal and abnormal unstimulated whole sialometry (abnormal ≤ 1.5 ml/15 min), Schirmer-I test (abnormal ≤ 10 mm/5 min), and van Bijsterveld score (abnormal ≥ 8). Ocular tests are presented as sum of both eyes. Results are median (interquartile range).

	Unstimulated Whole Sialometry, ml/15 min			Schirmer-I test, mm/5 min			Van Bijsterveld Score		
	Abnormal ≤ 1.5	Normal > 1.5	p	Abnormal ≤ 10	Normal > 10	p	Abnormal ≥ 8	Normal < 8	p
E/I ratio	–0.48 (–1.30 to 0.40)	–0.49 (–0.69 to 0.07)	0.57	–0.33 (–0.90 to 0.51)	–1.25 (–1.87 to –0.55)	0.01	–0.30 (–1.21 to 0.61)	–0.62 (–1.42 to –0.36)	0.18
AI	–0.50 (–1.34 to 0.30)	0.24 (–0.06 to 1.35)	0.07	–0.07 (–0.82 to 0.35)	–0.77 (–1.68 to 0.53)	0.38	–0.06 (–1.02 to 0.39)	–0.56 (–1.21 to 0.45)	0.76
VAC score	0.62 (–0.39 to 1.56)	0.96 (0.37 to 1.25)	0.83	0.71 (–0.24 to 1.53)	0.46 (–1.17 to 1.01)	0.21	0.58 (–0.28 to 1.11)	0.69 (–0.71 to 1.74)	0.65
lSBP ratio	–0.75 (–1.46 to –0.19)	–0.84 (–1.01 to –0.02)	0.75	–0.77 (–1.33 to –0.15)	–0.63 (–1.68 to –0.08)	0.93	–0.77 (–1.86 to –0.07)	–0.63 (–0.99 to –0.11)	0.55
lDBP ratio	–0.70 (–1.20 to –0.13)	–0.01 (–0.27 to 0.51)	0.03	–0.58 (–1.20 to 0.14)	–0.33 (–0.80 to 0.17)	0.44	–0.38 (–1.34 to 0.22)	–0.51 (–0.98 to –0.09)	0.65

exocrine function implies, another mechanism besides exocrine gland destruction has to explain the exocrine insufficiency in pSS. Lately, much interest has been directed to the anti-M3-receptor antibodies, found in a subgroup of pSS patients[16,17]. These antibodies seem to block parasympathetic nervous signaling to the exocrine glands, which is mainly transmitted via the parasympathetic M3-receptor, thereby depriving the glands of the necessary nervous signal to start liquid secretion. Since the M3-receptor is also found in other tissues, e.g., the bladder and the gastrointestinal system, these antibodies may be involved in other symptoms such as irritable bladder and constipation[41]. Since orthostatic hypotension may be found in patients with pSS, which is usually considered a sign of sympathetic dysfunction[42], the possible presence of anti-M3 antibodies cannot explain all demonstrated disturbances in ANS function. Inflammation of sympathetic ganglia in patients with pSS[21] and cytokines interfering with neural transmission[19] have for example been reported as other mechanisms behind ANS dysfunction in pSS.

Several studies have described autonomic nervous function in pSS, but due to the use of different criteria sets for pSS and sometimes concomitant use of vasoactive medication among study subjects, results become difficult to compare. The widely used AECC for pSS comprise a more homogenous immunological active population of sicca patients as compared with the older European and Copenhagen criteria[23,24].

The strength of our study was the use of the widely accepted AECC for pSS and exclusion of patients taking vasoactive medication as well as the use of large control groups for the autonomic nervous function tests, allowing for age correction of the different indices. Possible concerns with this and all other case-control studies is the choice of controls, which in this study were collected several years ago to serve as reference materials in previous studies on autonomic dysfunction. Although population based controls would be preferable, the controls were mainly recruited among laboratory staff and their friends and relatives. However, the protocol and equipment used when studying patients and controls were identical. Another concern might be the sex difference between patients and controls, with a female preponderance among the former. Since it has been shown that women have a decreased baroreflex sensitivity and HRV[43,44] in comparison to men, it may be argued that the abnormal autonomic nervous function indices in patients with pSS could be explained by sex differences. However, we found no significant sex related differences in the autonomic nervous function indices we used in this study[25,27], a finding supported by another study, which similarly found no sex related differences regarding the heart rate reaction to deep breathing or heart rate and blood pressure reactions to tilt[45]. Repeated measures of the autonomic nervous function indices and calculation of means from several measurements would probably improve reproducibility, which would facilitate assessment of associations between autonomic and exocrine measures. However, this was not done for practical purposes. Finally, the clinical implications of the detected autonomic dysfunction with regard to symptoms and prognosis needs to be further clarified.

We found that the E/I ratio was significantly decreased and the VAC score significantly increased in patients with pSS compared to controls, reminiscent of what we previously have reported[9,10]. The E/I ratio is considered a parasympathetic index, measuring a reflex inhibited by atropine but not by propranolol[29]. The VAC score, on the other hand, has been demonstrated to be a sensitive test of sympathetic function, since the reflex it measures is abolished in patients sympathectomized due to excessive hand sweating[27]. In addition, patients with pSS were not able to maintain orthostatic blood pressures as were healthy controls, which probably explains the orthostatic symptoms experienced by some pSS patients. Patients with pSS thus show signs of both parasympathetic and sympathetic dysfunction.

Autonomic and exocrine function was found to be poorly associated. While patients with an abnormal UWS test had a

significantly lower lDBP ratio and a tendency toward a lower acceleration index, patients with an abnormal Schirmer-I test showed a paradoxically increased E/I ratio, a finding for which we have no explanation. Possible reasons for this lack of association are low reliability in the test procedures for autonomic and exocrine function (although all were performed in a standardized manner) and too little exocrine variability in patients with pSS, with a high proportion having maximal exocrine dysfunction. A relation between autonomic and exocrine function could perhaps be found early in the disease before structural damage to the exocrine glands has occurred. Due to the limited number of patients with pSS in our study, a subanalysis of patients with short disease duration was not possible. Moreover, the autonomic nervous function measures we used mainly measure cardiovascular autonomic nervous function, not necessarily reflecting autonomic nervous function in the exocrine glands. In the context of the anti-M3-receptor antibodies in pSS, these findings may also reflect differences in the presence of muscarine receptor subtypes in the heart (mainly M2-receptors), involved in the cardiovagal reflexes, and in the exocrine glands (mainly anti-muscarine-3-receptors), involved in exocrine secretion. For that reason future studies on patients with pSS using tests measuring exocrine autonomic nervous function, such as the quantitative sudomotor axon reflex test[46], would be of great interest. Development of more widespread and feasible methods for the detection of M3-receptor antibodies than the biological assays used today would also enable correlations of these, with different signs of ANS involvement and clinical measures, including exocrine function.

We found that patients with pSS according to the AECC show signs of both parasympathetic and sympathetic dysfunction as well as an attenuated orthostatic blood pressure response. However, an association between cardiovascular autonomic and exocrine function in pSS was not detected.

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REFERENCES

1. Gemignani F, Marbini A, Pavesi G, et al. Peripheral neuropathy associated with primary Sjögren's syndrome. J Neurol Neurosurg Psychiatry 1994;57:983-6.
2. Barendregt PJ, van den Bent MJ, van Raaij-van den Aarssen VJ, et al. Involvement of the peripheral nervous system in primary Sjögren's syndrome. Ann Rheum Dis 2001:60:876-81.
3. Andonopoulos AP, Ballas C. Autonomic cardiovascular neuropathy in primary Sjögren's syndrome. Rheumatol Int 1995;15:127-9.
4. Sakakibara R, Hirano S, Asahina M, et al. Primary Sjögren's syndrome presenting with generalized autonomic failure. Eur J Neurol 2004;11:635-8.
5. Sorajja P, Poirier MK, Bundrick JB, Matteson EL. Autonomic failure and proximal skeletal myopathy in a patient with primary Sjögren syndrome. Mayo Clin Proc 1999;74:695-7.
6. Waterschoot MP, Guerit JM, Lambert M, de Barsy T. Bilateral tonic pupils and polyneuropathy in Sjögren's syndrome: a common pathophysiological mechanism? Eur Neurol 1991;31:114-6.
7. Konttinen YT, Sorsa T, Hukkanen M, et al. Topology of innervation of labial salivary glands by protein gene product 9.5 and synaptophysin immunoreactive nerves in patients with Sjogren's syndrome. J Rheumatol 1992;19:30-7.
8. Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. Scand J Immunol 1999;49:7-10.
9. Mandl T, Jacobsson L, Lilja B, Sundkvist G, Manthorpe R. Disturbances of autonomic nervous function in primary Sjögren's syndrome. Scand J Rheumatol 1997;26:401-6.
10. Mandl T, Bornmyr SV, Castenfors J, Jacobsson LT, Manthorpe R, Wollmer P. Sympathetic dysfunction in patients with primary Sjögren's syndrome. J Rheumatol 2001,28:296-301.
11. Andonopoulos AP, Christodoulou J, Ballas C, Bounas A, Alexopoulos D. Autonomic cardiovascular neuropathy in Sjogren's syndrome. A controlled study. J Rheumatol 1998;25:2385-8.
12. Barendregt PJ, van den Meiracker AH, Markusse HM, et al. Parasympathetic failure does not contribute to ocular dryness in primary Sjogren's syndrome. Ann Rheum Dis 1999;58:746-50.
13. Kovacs L, Paprika D, Takacs R, et al. Cardiovascular autonomic dysfunction in primary Sjogren's syndrome. Rheumatology Oxford 2004;43:95-9.
14. Barendregt PJ, Tulen JH, van den Meiracker AH, Markusse HM. Spectral analysis of heart rate and blood pressure variability in primary Sjogren's syndrome. Ann Rheum Dis 2002;61:232-6.
15. Niemela RK, Hakala M, Huikuri HV, Airaksinen KE. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J Rheumatol 2003;30:74-9.
16. Gordon TP, Bolstad AI, Rischmueller M, Jonsson R, Waterman SA. Autoantibodies in primary Sjogren's syndrome: new insights into mechanisms of autoantibody diversification and disease pathogenesis. Autoimmunity 2001;34:123-32.
17. Dawson L, Tobin A, Smith P, Gordon T. Antimuscarinic antibodies in Sjogren's syndrome: where are we, and where are we going? Arthritis Rheum 2005;52:2984-95.
18. Fox RI, Stern M. Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. Scand J Rheumatol 2002;Suppl 116:3-13.
19. Haddad EB, Rousell J, Lindsay MA, Barnes PJ. Synergy between tumor necrosis factor alpha and interleukin 1-beta in inducing transcriptional down-regulation of muscarinic M2 receptor gene expression. Involvement of protein kinase A and ceramide pathways. J Biol Chem 1996;271:32586-92.
20. Griffin JW, Cornblath DR, Alexander E, et al. Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann Neurol 1990;27:304-15.
21. Mori K, Iijima M, Koike H, et al. The wide spectrum of clinical manifestations in SS associated neuropathy. Brain 2005; 128:2518-34.
22. Vitali C, Bombardieri S, Jonsson R, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554-8.
23. Manthorpe R, Oxholm P, Prause JU, Schioedt MT. The Copenhagen Criteria for Sjögren's Syndrome. Scand J Rheumatol 1986;15 Suppl 61:19-21.
24. Vitali C, Bombardieri S, Moutsopoulos HM, et al. Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. Ann Rheum Dis 1996;55:116-21.

25. Bergstrom B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. Clin Physiol 1986;6:523-8.
26. de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G. A prospective study of orthostatic blood pressure in diabetic patients. Clin Auton Res 1998;8:189-93.
27. Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol 1998;18;2:103-7.
28. Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart rate in diabetes mellitus. BMJ 1979;1:924-5.
29. Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J 1984;52:396-402.
30. Bergstrom B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in type I diabetes: Influence of duration and other diabetic complications. Acta Med Scand 1987;222:147-54.
31. Sundkvist G, Lilja B, Almer L-O. Abnormal diastolic blood pressure and heart rate reactions to tilting in diabetes mellitus. Diabetologia 1980;19:433-8.
32. Bergstrom B, Mattiasson I, Rosen I, Lilja B, Sundkvist G. Platelet sodium and potassium ATPase activity and noradrenaline efflux rate in relation to autonomic and peripheral nerve function in insulin dependent diabetic patients. J Intern Med 1989;225:185-90.
33. Bergstrom B, Manhem P, Bramnert M, Lilja B, Sundkvist G. Impaired responses of plasma cathecolamines to exercise in diabetic patients with abnormal heart reactions to tilt. Clin Physiol 1989;9:259-67.
34. Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol 1998;18;2:103-7.
35. Bergstrom B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in non insulin dependent (type II) diabetes mellitus. Possible influence of obesity. J Intern Med 1990;227:57-63.
36. Leden I, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol 1983;12:166-70.
37. Bertinotti L, Bracci S, Nacci F, et al. The autonomic nervous system in systemic sclerosis. A review. Clin Rheumatol 2004;23:1-5.
38. Laversuch CJ, Seo H, Modarres H, Collins DA, McKenna W, Bourke BE. Reduction in heart rate variability in patients with systemic lupus erythematosus. J Rheumatol 1997;24:1540-4.
39. Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. Scand J Gastroenterol 1991;4:361-6.
40. Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol 1993;7:638-49.
41. Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor antibodies on parasympathetic neurotransmission in Sjögren's syndrome. Arthritis Rheum 2000;43:1647-54.
42. Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993;68:748-52.
43. Huikuri HV, Pikkujamsa SM, Airaksinen KEJ, et al. Sex-related differences in autonomic modulation of heart rate in middle-aged subjects. Circulation 1996;94:122-5.
44. Liao D, Barnes RW, Chambless LE, Simpson RJ, Sorlie P, Heiss G. Age, race, and sex differences in autonomic cardiac function measured by spectral analysis of heart rate variability — The ARIC study. Am J Cardiol 1995;76:906-12.
45. Low PA, Denq J-C, Opfer-Gehrking TL, Dyck PJ, O'Brien PC, Slezak JM. Effect of age and gender on sudomotor and cardiovagal function and blood pressure response to tilt in normal subjects. Muscle Nerve 1997;20:1561-8.
46. Riedel A, Braune S, Kerum G, Schulte-Monting J, Lucking CH. Quantitative sudomotor axon reflex test (QSART): a new approach for testing distal sites. Muscle Nerve 1999;22:1257-64.

II

Assessment of Autonomic Symptoms in Diabetics

The Swedish version of the Autonomic Symptom Profile (ASP)

Thomas Mandl MD[1], Viktoria Granberg MD[2], Jan Apelqvist MD PhD[2],
Per Wollmer MD PhD[3], Rolf Manthorpe MD PhD[4],
and Lennart TH Jacobsson MD PhD[1]

[1]Dept of Rheumatology, [2]Dept of Endocrinology, [3]Dept of Clinical Physiology,
Malmö University Hospital, SE-205 02 Malmö, Sweden,
[4]Sjögren's Syndrome Research Centre, Jägersrov.80, SE-212 37 Malmö, Sweden

Short title: Assessment of Autonomic Symptoms in Diabetics

Corresponding author:
Thomas Mandl
Department of Rheumatology, Ing 25 plan 2
Malmö University Hospital
SE-205 02 Malmö, Sweden
Phone +46/40/331000
Fax +46/40/455004

E-mail: thomas.mandl@med.lu.se

Summary

Objectives: Autonomic dysfunction (AD) is a complication of diabetes and may be associated with troubling symptoms and increased mortality. Commonly, AD is detected by objective physiological tests and only recently, a validated self-completed English questionnaire assessing AD symptoms, the Autonomic Symptom Profile (ASP) was developed. The aims of this study were to translate the ASP into Swedish and evaluate its reliability and validity.

Methods: Forward and back translations were performed. 31 patients with type I diabetes, 200 population based controls and 2 AD experts participated in the study. Test-retest reliability was evaluated by letting 25 patients fill in the ASP twice. Content validity was evaluated by two Swedish AD experts and construct validity by studying associations between the ASP domains and 5 objective autonomic nervous function test parameters. Finally, discriminant validity was evaluated by studying differences in the ASP total and domain scores between patients and controls.

Results: The translation was accepted without changes. Test-retest reliability and the content validity of the Swedish ASP were considered good. The construct validity was considered acceptable with several associations between ASP domains and autonomic nervous function test parameters. In addition, discriminant validity was considered acceptable with regard to the ASP total score as well as the sexual dysfunction, sleep disorder and vasomotor dysfunction domain scores significantly differing between patients and controls.

Conclusion: The Swedish version of the ASP was considered a reliable and valid instrument for the study of AD symptoms in patients with type I diabetes.

Keywords: Autonomic dysfunction, diabetes, questionnaire

Introduction

Autonomic dysfunction (AD) is a complication of many chronic diseases i.e. type I and II diabetes (Bergström et al., 1987; Bergström et al., 1990), rheumatoid arthritis (Leden et al., 1983), primary Sjögren's syndrome (Mandl et al., 2001; Mandl et al., 2007), systemic lupus erythematosus (Laversuch et al., 1997), scleroderma (Bertinotti et al., 2004) and inflammatory bowel disease (Lindgren S et al., 1991; Lindgren et al., 1993) and may result not only in debilitating symptoms (Vinik et al., 2003) but also in increased mortality (Huikuri et al., 1998; Maser et al., 2003; Vinik et al., 2003). Commonly, AD is detected using various objective physiological tests e.g. autonomic reflex tests. However, physiological tests only measure objective signs of AD and do not evaluate the impact of associated subjective symptoms. Recently, a validated English questionnaire addressing AD symptoms, the Autonomic Symptom Profile (ASP), was constructed (Suarez et al., 1999). The aims of this study were 1) to translate the English ASP into Swedish and 2) to investigate the reliability and validity of the Swedish version of the ASP.

Methods

Patients

31 patients (median age 52 (range 39–69) years, 12 females), with type I diabetes were included in the study. 6 patients were ≥60 years of age (range 61–69 years). The patients belonged to a cohort of type I diabetics followed since 1984–1985 at the Dept of Endocrinology, Malmö University Hospital, with regard to autonomic nervous function. The patients had been diagnosed with type I diabetes at 15–25 years of age and had a median disease duration of 33 years. Thirteen patients had co-morbidities or medications possibly affecting autonomic function (Table 1). Due to co-morbidities, the medications were not possible to be stopped prior to the study. All patients completed the ASP once and 25 of these also a second time two weeks later. Furthermore, the patients were studied by 3 different autonomic nervous function tests i.e. the deep-breathing test, the orthostatic test and the finger skin blood flow test. One patient could not be assessed by the latter due to a skewed finger. Patient characteristics are presented in Table 1.

Controls

The controls were randomly selected from the Swedish general population registry and were living in the City of Malmö or its surroundings. Controls were asked via mail if they would like to participate in the study, if they had any disease (diabetes mellitus, rheumatoid arthritis or Sjögren's syndrome) or were on any medication (anti-hypertensives, cardiovascular medication or antidepressants) possibly affecting autonomic function. If the subject was willing to participate and had no disease or

medication affecting autonomic function the questionnaire was filled in once and sent back by post. A ticket to the cinema was sent back to each subject returning a completed questionnaire. If not having answered for 4 weeks, a reminding letter was sent and if no answer was received to that, a new control of the same age and gender was selected. Of 467 letters sent, 339 were returned, resulting in a 73% response rate. Among the returned letters, 43 were from subjects who did not want to participate and 96 from subjects excluded due to fulfilling of one or more exclusion criteria (diabetes n=14, rheumatoid arthritis n=6, anti-hypertensive treatment n=59, cardiovascular medication n=8, and use of anti-depressants n=25). Two-hundred controls (median age 45 (range 20–69) years, 100 females) were thus included in the study. Further characteristics are presented in Table 1.

Table 1. **Clinical characteristics of the patients with type I diabetes and controls**.
Results are presented as median (interquartile range limits) and n/% with abnormal findings.
ACE=Angiotensin Converting Enzyme, AT2=Angiotensin-2 receptor. NA=Not assessed.

	Patients (n=31)	**Controls (n=200)**
Age (years)	52 (48 , 59)	45 (32 , 57)
Gender (males/females)	19/12	100/100
Weight (kg)	74 (66 , 81)	73 (63 , 83)
Height (m)	1.76 (1.68 , 1.85)	1.73 (1.68 , 1.81)
Disease duration (years)	33 (28 , 35)	–
Clinical peripheral neuropathy (N / %)	22 / 71 %	NA
Clinical nephropathy (N / %)	6 / 19 %	NA
Clinical retinopathy (N / %)	30 / 97 %	NA
Hypertension (N / %)	8 / 26 %	0
Cardiovascular disease (N / %)	5 / 16 %	0
Treatment with		
beta blockers (N / %)	5 / 16 %	0
calcium channel blockers (N / %)	4 / 13 %	0
diuretics (N / %)	2 / 6 %	0
nitrates (N / %)	1 / 3 %	0
ACE-inhibitors (N / %)	5 / 16 %	0
AT2-blockers (N / %)	5 / 16 %	0

Experts

Two Swedish experts on AD were asked to judge the content validity of the Swedish translation of the ASP.

The Autonomic Symptom Profile (ASP)

The questionnaire consisted of 151 items as well as some additional questions regarding age, gender, height and weight. Among the items were 73 which by the original constructors were considered the clinically most important and frequently asked questions when evaluating autonomic symptoms. These questions evaluated nine domains of autonomic symptoms i.e. orthostatic intolerance (n=9), secretomotor dysfunction (n=8), male sexual dysfunction (n=8), urinary dysfunction (n=3), gastrointestinal dysfunction, divided in 3 sub-domains namely gastroparesis, diarrhoea and constipation, (n=14), pupillomotor dysfunction (n=7), vasomotor dysfunction (n=11), sleep disorder (n=8) and reflex syncope (n=5). In addition, 12 interspersed questions were added addressing psychosomatic (n=6) and understatement tendencies (n=6). The autonomic symptom domains consisted of questions evaluating presence, severity, distribution, frequency and progression of various autonomic symptoms. The separate answers in each domain were scored according to their predictability for disease. Due to the different clinical importance of various domains, scores were also weighted according to their clinical relevance. The weighted maximum domain scores were as follows: orthostatic intolerance, 40; secretomotor dysfunction, 20; male sexual dysfunction, 30; urinary dysfunction, 20; gastroparesis, 10; diarrhoea, 20; constipation, 10; pupillomotor dysfunction, 5; vasomotor dysfunction, 10; sleep disorder, 15; and reflex syncope, 20. By adding the autonomic domain scores an ASP total score could be calculated with a maximum of 200 for males and 170 for females, lower for females due to the lack of questions addressing female sexual dysfunction. In addition, the psychosomatic and understatement domains were allocated a maximum score of 10 each. The results of these domains were not included in the ASP total score but were presented separately. This has previously been described in detail (Suarez et al., 1999).

Autonomic nervous function tests

Deep breathing test

After supine rest, the subject's heart rate was monitored by ECG during 4 minutes and, once constant, six maximal expirations and inspirations were performed during one minute. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R-R intervals during expiration divided by the mean of the shortest R-R intervals during inspiration (Sundkvist et al., 1979). The E/I-ratio mainly reflects parasympathetic nervous function (Sundkvist et al., 1979; Ewing et al., 1984).

Orthostatic test

After supine rest, the subject was tilted within 2 seconds to an erect position in which he/she remained for 8 minutes. The heart rate was monitored by ECG and blood pressures were measured before as well as every minute after tilt. A mean of the R-R

intervals before tilt (A) was calculated and the shortest R–R interval during the first minute after tilt (B) was determined. From these values, an acceleration index (AI), defined as [(A–B)/A×100] was calculated (Bergström et al., 1987; Sundkvist et al., 1980). The AI seems to be influenced mainly by the parasympathetic (Vinik et al., 2003) but also to some degree by the sympathetic nervous system (Bergström et al., 1989a; Bergström et al., 1989b). The systolic and diastolic blood pressures before tilt (SBPrest and DBPrest) as well as the lowest systolic and diastolic blood pressures during the first 8 minutes after tilt (lSBP and lDBP) were determined. From these orthostatic systolic and diastolic blood pressure-ratios were calculated [lSBP-ratio = lSBP/SBPrest] and [lDBP-ratio = lDBP/DBPrest]. The orthostatic blood pressure response is considered a test of sympathetic nervous function (Low, 1993).

Finger skin blood flow test

The subject was sitting with the left hand on an aluminum holder, the temperature of which was kept stable at 40° C, while the finger skin blood flow was monitored by a laser doppler imaging (LDI) instrument. The subject then immersed the contralateral hand and forearm into cold water (15° C), for 3 minutes. By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDI_c) by the mean of the two last measurements of finger skin blood flow at rest, before the cooling procedure, (LDI_h) a vasoconstriction (VAC) index could be calculated (VAC-index=LDI_c/LDI_h). This has been shown to be a sensitive test for sympathetic nervous function in the skin (Bornmyr et al., 1998).

Since autonomic function tends to deteriorate with advancing age, the autonomic nervous function variables were age corrected and expressed as z-scores by comparison with 3 control groups, namely 56 controls for the E/I-ratio and AI consisting of healthy subjects (median age 40 years [range 16–59 years], 22 females) all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders or diabetes (Bergström et al., 1986), 80 controls for the VAC-index consisting of healthy subjects (median age 43 years [range 19–81 years], 37 females) all of whom were non-smokers, had no history of vascular disease and were not on any medication (Bornmyr et al., 1998) and 238 controls for the lSBP & lDBP-ratios consisting of healthy non-diabetic individuals (median age 60 years [range 16–96 years], 106 women) (de Kanter et al., 1998). Since gender does not seem to significantly affect the autonomic variables measured in this study (Bornmyr et al., 1998; Bergström et al., 1986), sex was not matched for. All autonomic nervous function tests were performed in the morning under standard conditions, i.e. the temperature conditions were kept stable and the patients were not allowed to eat, drink coffee or smoke later than 2 hours prior to testing.

The translational process

The ASP was first translated from English to Swedish by one translator and then back-translated to English by another translator. The Swedish and English versions were afterwards compared by one of the authors (TM). No changes of the Swedish version were made.

Reliability

Test-retest was performed by letting 25 patients complete the questionnaire on two separate occasions two weeks apart. The intraclass correlation coefficient (ICC) was determined for the ASP domain and total scores. Correlations between the ASP total score and the ASP domain scores were calculated for the 31 patients in the study.

Validity

Content validity was evaluated by two Swedish AD experts.

Construct validity was evaluated by studying correlations between the five different autonomic nervous function parameters and the ASP total score as well as by studying differences in the ASP autonomic domain scores in patients with normal and abnormal autonomic nervous function test results.

Discriminant validity was evaluated by hypothesizing that the patients would score higher in the ASP total score than the controls.

Statistics

Before data analysis, several ASP domain scores as well as the ASP total score were age, gender, height and weight standardized based on the ASP scores of the 200 controls. This was done using a linear regression model into which age, gender, height and weight were added as covariates to each ASP score respectively. Due to a preponderance of zero values, although with gender differences, among controls in some ASP domains, the gastroparesis and reflex syncope domains were expressed as gender stratified raw scores. Similarly the psychosomatic and underestimation domains were expressed as gender stratified raw scores. Mann Whitney U test was used for group comparisons and Spearman rank correlation test for correlations. Test-retest reliability was studied by calculating the ICC. E/I-ratio, AI, lSBP- & lDBP-ratios $\leq$–2SD and VAC-index $\geq$2SD were considered abnormal. P-values <0.05 were considered significant.

Ethics

The study was approved by the ethics committee at Lund University (LU814-04). All participants gave written informed consent.

Results

Autonomic nervous function tests

The E/I-ratio, AI and lDBP-ratio were lower and the VAC-index higher in diabetic patients compared with controls, indicating a parasympathetic and sympathetic dysfunction. In contrast the lSBP-ratio did not differ between patients and controls (Table 2). The differences still remained if patients with co-morbidities and medications affecting autonomic function as well as if patients ≥60 years of age were excluded.

Table 2. Autonomic nervous function test results in patients with type I diabetes and autonomic nervous function control materials as well as correlations of the autonomic nervous function parameters and the Autonomic Symptom Profile (ASP) total score in patients with type I diabetes. All values were age corrected and expressed as z-scores. Results are presented as median (interquartile range limits) and r_S (p-value).

Autonomic parameters	**Patients (n=31)**	**Controls (n=56/80/238)**	p-value	**ASP total score r_S** (p-value)
Expiration inspiration index	–1.55 (–1.92 , –0.64)	–0.25 (–0.62 , 0.60)	0.00	–0.12 (0.54)
Acceleration index	–0.88 (–1.59 , –0.30)	0.03 (–0.67 , 0.65)	0.00	–0.09 (0.64)
Vasoconstriction index	1.50 (0.34 , 2.55)	0.09 (–0.67 , 0.62)	0.00	0.39 (0.04)
Lowest systolic blood pressure ratio	–0.11 (–1.03 , 0.63)	0.00 (–0.61 , 0.70)	0.17	–0.36 (0.05)
Lowest diastolic blood pressure ratio	–0.54 (–1.46 , –0.24)	0.00 (–0.47 , 0.54)	0.00	–0.29 (0.12)

Reliability

When performing test-retest, the agreement of the different ASP scores between two separate completions of the ASP, performed 2 weeks apart, was generally judged as good, with a median ICC of 0.83. Furthermore, the orthostatic intolerance, sexual dysfunction, urinary dysfunction and secretomotor dysfunction domain scores correlated with the ASP total score (Table 3).

Validity

Content validity of the Swedish ASP was judged as good by two Swedish experts on AD.

The ASP total score correlated with the VAC-index and lSBP-ratio (Table 2). When comparing ASP domain scores in patients with abnormal vs. normal E/I-ratio and AI, the former were found to have higher scores in the ASP secretomotor dysfunction

Table 3. Reliability of the Autonomic Symptom Profile (ASP). Results of the test-retest performed by 25 patients with type I diabetes mellitus two weeks apart as well as Spearman's correlations of the various Autonomic Symptom Profile (ASP) autonomic domain scores with the ASP total score in the 31 patients with type I diabetes.
ICC = Intraclass Correlation Coefficient.

Domains (score range)	ICC	ASP Total score r_S (p-value)
Orthostatic intolerance (0–40)	0.92	0.51 (0.00)
Sexual dysfunction (males 0–30)	0.85	0.69 (0.00)
Urinary dysfunction (0–20)	0.83	0.49 (0.01)
Diarrhoea (0–20)	0.59	0.23 (0.23)
Gastroparesis (0–10)	0.83	0.28 (0.13)
Constipation (0–10)	0.98	0.17 (0.36)
Secretomotor dysfunction (0–20)	0.67	0.59 (0.00)
Sleep disorder (0–15)	0.82	0.13 (0.48)
Vasomotor dysfunction (0–10)	0.87	0.21 (0.28)
Pupillomotor dysfunction (0–5)	0.73	0.29 (0.12)
Reflex syncope (0–20)	0.66	0.12 (0.52)
Total (males 0–200 & females 0–170)	0.87	–

domain respectively (Table 4). These associations still remained if patients ≥60 years of age were excluded. Patients with an abnormal VAC-index scored higher in the sexual dysfunction and diarrhoea domains compared with patients with normal VAC-indices. Patients with an abnormal lSBP-ratio scored lower in the vasomotor dysfunction domain compared with patients with normal lSBP-ratios and patients with abnormal lDBP-ratios scored higher in the secretomotor dysfunction and constipation domains as well as in the ASP total score compared with patients with normal lDBP-ratios (Table 5). Construct validity was thus considered acceptable.

The ASP total score as well as the sexual dysfunction, sleep disorder and vasomotor dysfunction domain scores were higher in patients compared with controls and there was a tendency towards a higher score in the orthostatic domain in patients compared with controls (Table 6). If patients with co-morbidities and medications possibly affecting autonomic function were excluded from the comparison, the remaining 18 patients still had increased sexual dysfunction, sleep disorder and ASP total scores compared to controls. Discriminant validity was thus considered acceptable.

Table 4. Comparisons of the Autonomic Symptom Profile (ASP) domain scores in diabetic patients with and without abnormal results in the two main parasympathetic test parameters i.e. the expiration inspiration (EI) ratio (abnormal if ≤–2SD) and acceleration (AI) index (abnormal if ≤–2SD). The ASP domain scores were age, gender, weight and height standardized except the gastroparesis and reflex syncope domains where raw scores were used. Results are presented as median (interquartile range limits).

	Abnormal EI (n=5)	**Normal EI (n=26)**	p-value	**Abnormal AI (n=5)**	**Normal AI (n=26)**	p-value
Orthostatic	–0.42 (–0.89 , 1.13)	0.18 (–0.48 , 1.23)	0.45	0.61 (–0.61 , 1.13)	–0.28 (–0.51 , 1.23)	0.98
Sexual	2.18 (0.05 , 4.17)	2.04 (–0.11 , 2.90)	0.57	2.18 (0.05 , 4.17)	2.04 (–0.11 , 2.90)	0.57
Urinary	–0.54 (–0.74 , 2.50)	–0.27 (–0.71 , 0.17)	0.94	–0.54 (–0.69 , 2.50)	–0.27 (–0.74 , 0.17)	0.62
Diarrhoea	–0.14 (–0.40 , 1.50)	–0.45 (–0.59 , –0.23)	0.08	–0.14 (–0.40 , 1.54)	–0.45 (–0.59 , –0.23)	0.07
Gastro-paresis	0.00 (0.00 , 0.75)	0.00 (0.00 , 0.00)	0.70	0.00 (0.00 , 0.75)	0.00 (0.00 , 0.00)	0.70
Constipation	–0.30 (–0.45 , –0.20)	–0.31 (–0.50 , –0.21)	0.94	–0.30 (–0.42 , –0.20)	–0.31 (–0.50 , –0.21)	0.78
Secretomotor	2.42 (1.08 , 2.99)	–0.52 (–0.77 , 0.95)	0.01	2.42 (0.79 , 2.99)	–0.52 (–0.77 , 1.38)	0.01
Sleep disorder	0.21 (–0.01 , 0.63)	0.16 (0.01 , 1.60)	0.86	0.21 (–0.01 , 1.44)	0.16 (0.01 , 1.53)	0.82
Vasomotor	–0.30 (–0.45 , –0.23)	–0.23 (–0.43 , 2.13)	0.36	–0.28 (–0.36 , 1.19)	–0.25 (–0.45 , 0.42)	0.86
Pupillomotor	0.57 (–0.16 , 2.09)	–0.13 (–0.79 , 0.98)	0.31	0.41 (–0.79 , 1.71)	0.07 (–0.75 , 1.19)	0.98
Syncope	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.82	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.82
Total	0.85 (0.23 , 2.27)	0.93 (–0.15 , 1.28)	0.55	1.25 (0.66 , 2.27)	0.77 (–0.18 , 1.28)	0.17

Table 5. Comparisons of the Autonomic Symptom Profile domain scores in diabetic patients with and without abnormal results in the three main sympathetic test parameters i.e. the vasoconstriction (VAC) index (abnormal if ≥2SD) and the lowest systolic and diastolic blood pressure (LSBP & LDBP) ratios (abnormal if ≤–2SD). The ASP domain scores were age, gender, weight and height standardized excep t the gastroparesis and reflex syncope domains where raw scores were used. Results are presented as median (interquartile range limits).

	Abnormal VAC (n=8)	**Normal VAC (n=22)**	**p-value**	**Abnormal LSBP (n=4)**	**Normal LSBP (n=27)**	**p-value**	**Abnormal LDBP (n=5)**	**Normal LDBP (n=26)**	p-value
Orthostatic	0.09 (-0.71 , 0.89)	0.36 (-0.51 , 1.33)	0.30	1.16 (-0.31 , 1.20)	-0.31 (-0.51 , 1.11)	0.51	1.09 (-0.63 , 1.40)	-0.28 (-0.51 , 1.18)	0.74
Sexual	3.46 (3.03 , 3.96)	0.69 (-0.16 , 2.23)	0.01	2.09 (-0.23 , 4.41)	2.04 (0.09 , 3.16)	0.84	3.46 (0.49 , 4.41)	1.87 (-0.23 , 2.76)	0.25
Urinary	-0.24 (-0.66 , 0.32)	-0.25 (-0.71 , 0.17)	0.60	1.10 (-0.50 , 4.16)	-0.60 (-0.73 , 0.16)	0.17	0.12 (-0.65 , 3.47)	-0.63 (-0.71 , 0.16)	0.26
Diarrhoea	-0.20 (-0.37 , 1.79)	-0.49 (-0.59 , -0.26)	0.01	-0.47 (-0.60 , -0.19)	-0.40 (-0.56 , -0.14)	0.59	-0.14 (-0.53 , 0.92)	-0.41 (-0.57 , -0.23)	0.31
Gastroparesis	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.91	0.75 (0.00 , 3.00)	0.00 (0.00 , 0.00)	0.14	0.00 (0.00 , 2.50)	0.00 (0.00 , 0.00)	0.21
Constipation	-0.29 (-0.50 , -0.21)	-0.31 (-0.50 , -0.20)	0.95	-0.27 (-0.54 , 7.59)	-0.31 (-0.50 , -0.21)	0.76	-0.17 (-0.28 , 5.62)	-0.31 (-0.53 , -0.23)	0.02
Secretomotor	1.08 (-0.40 , 2.17)	-0.36 (-0.78 , 1.60)	0.14	1.13 (0.65 , 2.18)	-0.50 (-0.76 , 1.43)	0.16	2.42 (0.34 , 3.69)	-0.34 (-0.71 , 0.94)	0.05
Sleep disorder	0.21 (0.07 , 1.42)	0.11 (-0.08 , 1.53)	0.45	-0.26 (-0.80 , 0.84)	0.18 (0.04 , 1.58)	0.35	0.05 (-0.43 , 1.01)	0.18 (0.03 , 1.53)	0.51
Vasomotor	-0.30 (-0.39 , 1.87)	-0.23 (-0.45 , 0.42)	0.95	-0.44 (-0.52 , -0.31)	-0.23 (-0.38 , 1.98)	0.05	-0.41 (-0.52 , -0.25)	-0.23 (-0.39 , 2.13)	0.07
Pupillomotor	-0.08 (-0.76 , 2.13)	0.29 (-0.73 , 0.98)	0.98	1.22 (-0.38 , 2.57)	0.02 (-0.77 , 0.92)	0.21	0.41 (-0.79 , 2,19)	0.07 (-0.75 , 1.19)	0.90
Syncope	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.73	0.00 (0.00 , 0.00)	0.00 (0.00 , 0.00)	0.84	0.00 (0.00 , 2.00)	0.00 (0.00 , 0.00)	0.58
Total	1.25 (1.03 , 2.24)	0.77 (-0.06 , 1.28)	0.08	1.42 (0.60 , 2.18)	0.85 (-0.10 , 1.28)	0.30	2.02 (1.04 , 2.27)	0.77 (-0.18 , 1.20)	0.02

Table 6. Comparisons of the Autonomic Symptom Profile domain scores in patients with type I diabetes and controls. Scores were age, gender, height and weight standardized and expressed as z-scores. For comparisons between groups the standardized scores were used, except for the gastroparesis, reflex syncope, psychosomatic and underestimation domains where gender stratified raw scores were used.
Results are presented as median (interquartile range limits). NA = Not Assessed.

Domains (rawscore range)	**Rawscores Type I diabetics (n=31, 12 females)**	**Standardized scores Type I diabetics (n=31, 12 females)**	**Raw scores Controls (n=200, 100 females)**	**Standardized scores Controls (n=200, 100 females)**	p-value
Orthostatic intolerance (0-40)	2.5 (0.0 , 12.5)	-0.24 (-0.51 , 1.17)	1.3 (0.0 , 12.5)	-0.39 (-0.78 , 0.79)	0.07
Sexual dysfunction (males 0-30)	10.5 (1.5 , 15.4)	2.04 (-0.03 , 3.34)	0.0 (0.0 , 1.5)	-0.22 (-0.51 , 0.11)	0.00
Urinary dysfunction (0-20)	0.0 (0.0 , 2.0)	-0.54 (-0.71 , 0.16)	0.0 (0.0, 2.0)	-0.51 (-0.71 , 0.32)	0.53
Diarrhoea (0-20)	0.0 (0.0 , 0.0)	-0.40 (-0.56 , -0.14)	0.0 (0.0 , 4.0)	-0.42 (-0.60 , 0.68)	0.82
Gastroparesis – females (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.82
Gastroparesis – males (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.89
Constipation (0–10)	0.0 (0.0 , 0.0)	–0.30 (–0.50 , –0.21)	0.0 (0.0 , 0.0)	-0.30 (-0.52 , -0.18)	0.93
Secretomotor dysfunction (0–20)	1.5 (0.0 , 4.5)	-0.07 (-0.70 , 1.46)	0.0 (0.0 , 3.0)	-0.45 (-0.72 , 0.52)	0.15
Sleep disorder (0–15)	1.5 (1.5 , 4.0)	0.18 (0.01 , 1.51)	1.5 (0.0 , 1.5)	-0.05 (-0.79 , 0.35)	0.00
Vasomotor dysfunction (0–10)	0.0 (0.0 , 0.0)	-0.26 (-0.42 , -0.10)	0.0 (0.0 , 0.0)	-0.33 (-0.49 , -0.20)	0.05
Pupillomotor dysfunction (0–5)	1.0 (0.0 , 2.0)	0.13 (-0.74 , 1.15)	0.5 (0.0 , 1.5)	-0.42 (-0.71 , 0.55)	0.25
Reflex syncope – females (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.87
Reflex syncope – males (0–20)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.96
Total score (males 0–200 & females 0–170)	24.8 (13.9 , 31.8)	0.89 (0.03 , 1.29)	13.0 (4.5 , 23.4)	-0.21 (-0.82 , 0.72)	0.00
Psychosomatic index – females (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.21
Psychosomatic index – males (0–10)	0.0 (0.0 , 0.0)	NA	0.0 (0.0 , 0.0)	NA	0.36
Understatement index –females (0–10)	0.0 (0.0 , 1.5)	NA	0.0 (0.0 , 3.5)	NA	0.26
Understatement index –males (0–10)	3.5 (0.0 , 6.5)	NA	1.5 (0.0 , 5.0)	NA	0.11

Discussion

In this study we translated the ASP, an English questionnaire assessing autonomic symptoms, to Swedish and evaluated its reliability and validity. The Swedish version of the ASP provided good test-retest reliability, good content validity and acceptable construct and discriminant validity.

AD is a recognised complication of many chronic diseases, including diabetes (Leden et al., 1983; Bergström et al., 1987; Bergström et al., 1990; Lindgren S et al., 1991; Lindgren et al., 1993; Laversuch et al., 1997; Mandl et al., 2001; Bertinotti et al., 2004; Mandl et al., 2007) and may result in debilitating symptoms and increased mortality (Huikuri et al., 1998; Maser et al., 2003; Vinik et al., 2003). Commonly, autonomic function has been evaluated by different objective physiological tests and only seldom the subjective correlates of AD have been studied. Recently, the ASP, a questionnaire evaluating autonomic symptoms was constructed and validated in patients with symptomatic autonomic neuropathy of different etiologies. The ASP was reported to show good content, construct and discriminant validity (Suarez et al., 1999). In contrast, another study showed that population based diabetic patients only reported mild autonomic symptoms as well as weak associations between autonomic symptoms and autonomic nervous function tests (Low et al., 2004). However, such discrepancies may reflect differences in frequency and severity of autonomic symptoms in population based diabetic patients in comparison to patients with more severe autonomic involvement. Since diabetic patients with autonomic deficits are more frequent than patients with more severe autonomic neuropathy e.g. patients with pure autonomic failure and multiple system atrophy, we chose to validate the Swedish version of the ASP in the former.

The strengths of this study were the use of a homogenous group, i.e. diabetics with objective signs of AD and a large population based control group enabling standardisation of the ASP scores according to gender, age, height and weight. Possible concerns are the generalizability of these results to other diabetics with less pronounced objective AD signs and to other patient groups. In addition, the sensitivity to change of the ASP still has to be evaluated.

The reliability of the ASP was evaluated by calculating the ICC for the different ASP autonomic domains and the ICC were found to vary between moderate and very good (0.59–0.98). It is reasonable to demand stability measures i.e. ICC greater than 0.5 (Streiner et al., 1995), and the ICC for all autonomic domains exceeded that limit.

The ASP total score correlated significantly with both the VAC-index and the lSBP-ratio implying that an increased ASP total score in type I diabetic patients mainly reflects a disturbed sympathetic function. However, patients with an abnormal parasympathetic function, as evaluated by the E/I-ratio and AI, had significantly

increased secretomotor domain scores. This is in accord with a previous study showing that exocrine dysfunction in diabetes may be associated not only with a disturbed glycemic control (Sreebny et al., 1992; Kaiserman et al., 2005) but also with AD (Ramos-Remus et al., 1994). Patients with an abnormal sympathetic function, as evaluated by the VAC-index, scored significantly higher in the sexual dysfunction domain. Although erection is usually considered a parasympathetic modulated function, it is known that the penile nerves act via adrenergic, nitrergic and cholinergic pathways to produce erection (Keene et al., 1999). Since adrenergic pathways are involved both in reflectory vasoconstriction to cooling and in erectile function, a dysfunction in these may be accountable for both. The orthostatic blood pressure ratios were found to be associated with some ASP domains, although not with the orthostatic domain, a fact possibly related to the lack of both objective and subjective signs of orthostatic hypotension in the patients. The overall lack of more solid associations between the ASP domains and the autonomic nervous function indices may have several explanations. A low reliability in the test procedures for some ASP domains as well as for the autonomic nervous function tests may complicate studies of associations. The relative lack of symptoms in patients, e.g. orthostatic symptoms, with a preponderance of zero-values as well as the sometimes few stepped scales in some ASP domains, e.g. urinary dysfunction, also makes association studies difficult. Due to the not always concordant findings of objective and subjective AD signs, this underlines the importance of evaluating these entities separately.

When comparing ASP domain scores in patients and controls, the former scored higher in the sexual, vasomotor dysfunction and sleep disorder domains and showed a tendency towards higher scores in the orthostatic domain. Accordingly, the ASP total score was significantly higher in patients compared with controls and discriminated between those. Erectile dysfunction (ED) is common in diabetes with a reported prevalence varying between 20 and 75% (Morano, 2003) and may be due to AD, arterial insufficiency on atherosclerotic basis, drugs, endocrine abnormalities and psychogenic factors (Morano, 2003). It may be argued that the ED symptoms in our patients were related to either drug use or atherosclerotic disease. However, no patients were on any psychotherapeutic drugs and after exclusion of patients on vasoactive medication, with prior hypertension or cardiovascular disease, the differences remained, implying an etiological relationship between AD and ED. Sleep-disordered breathing with obstructive sleep apnoeas may be related to obesity, causing an anatomical narrowing of the upper airways but also to AD, causing an increased collapsibility of the upper airways due to impairment of the autonomic reflex arches activating the upper airway dilator muscles (Bottini et al., 2003). Our findings of an increased standardized sleep disorder score in patients, implies a relationship between AD and sleep disordered breathing as well. Moreover, patients were found to have a significantly increased vasomotor dysfunction score and a

tendency towards an increased orthostatic intolerance score. However, the relative lack of more severe symptoms in the diabetics is in agreement with previous reports (Low et al., 2004).

In conclusion, the Swedish version of the ASP is to the best of our knowledge the first validated instrument for assessment of AD symptoms in Swedish. It was considered a reliable and valid instrument for the study of AD symptoms in patients with type I diabetes. Further studies are required to evaluate its use in different patient groups with AD as well as its sensitivity to change.

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References

Bergström B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. Clin Physiol (1986); **6:** 523–8.

Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in type I diabetes: Influence of duration and other diabetic complications. Acta Med Scand (1987); **222**: 147–54.

Bergström B, Manhem P, Bramnert M, Lilja B, Sundkvist G. Impaired responses of plasma cathecolamines to exercise in diabetic patients with abnormal heart reactions to tilt. Clin Physiol (1989a); **9**: 259–67.

Bergström B, Mattiasson I, Rosen I, Lilja B, Sundkvist G. Platelet sodium and potassium ATPase activity and noradrenaline efflux rate in relation to autonomic and peripheral nerve function in insulin dependent diabetic patients. J Intern Med (1989b); **225**: 185–90.

Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in non insulin dependent (type II) diabetes mellitus. Possible influence of obesity. J Intern Med (1990); **227**: 57–63.

Bertinotti L, Bracci S, Nacci F, Colangelo N, Del Rosso A, Casale R, Pignone A, Matucci-Cerinic M. The autonomic nervous system in systemic sclerosis. A review. Clin Rheumatol (2004); **23**: 1–5.

Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol (1998); **18**:103–7.

Bottini P, Dottorini ML, Cristina Cordoni M, Casucci G, Tantucci C. Sleep-disordered breathing in nonobese diabetic subjects with autonomic neuropathy. Eur Respir J (2003); **22**: 654–60.

de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G. A prospective study of orthostatic blood pressure in diabetic patients. Clin Auton Res (1998); **8**: 189–93.

Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J (1984); **52**: 396–402.

Huikuri HV, Makikallio TH, Airaksinen KE, Seppanen T, Puukka P, Raiha IJ, Sourander LB. Power-law relationship of heart rate variability as a predictor of mortality in the elderly. Circulation (1998); **97**: 2031–6.

Kaiserman I, Kaiserman N, Nakar S, Vinker S. Dry eye in diabetic patients. Am J Ophthalmol (2005); **139**: 498–503.

Keene LC, Davies PH. Drug-related erectile dysfunction. Adverse Drug React Toxicol Rev (1999); **18**: 5–24.

Laversuch CJ, Seo H, Modarres H, Collins DA, McKenna W, Bourke BE. Reduction in heart rate variability in patients with systemic lupus erythematosus. J Rheumatol (1997); **24**: 1540–4.

Leden I, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol (1983); **12**: 166–70.

Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients eith Crohn's disease. Scand J Gastroenterol (1991); **4**: 361–6.

Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol (1993); **7**: 638–49.

Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc (1993); **68**: 748–52.

Low PA, Benrud-Larson LM, Sletten DM et al. Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care (2004); **27**: 2942–7.

Mandl T, Bornmyr SV, Castenfors J, Jacobsson LT, Manthorpe R, Wollmer P. Sympathetic dysfunction in patients with primary Sjögren's syndrome. J Rheumatol (2001); **28**: 296–301.

Mandl T, Wollmer P, Manthorpe R, Jacobsson L. Autonomic and orthostatic dysfunction in primary Sjögren's syndrome. J Rheumatol, (2007); **34**: 1869–74.

Maser RE, Mitchell BD, Vinik AI, Freeman R. The association between cardiovascular autonomic neuropathy and mortality in individuals with diabetes. Diabetes Care (2003); **26**: 1895–1901.

Morano S. Pathophysiology of diabetic sexual dysfunction. J Endocrinol Invest (2003); **26(3 Suppl)**: 65–9.

Ramos-Remus C, Suarez-Almazor M, Russell AS. Low tear production in patients with diabetes mellitus is not due to Sjogren's syndrome. Clin Exp Rheumatol (1994); **12**: 375–80.

Sreebny LM, Yu A, Green A, Valdini AM. Xerostomia in diabetes mellitus. Diabetes Care (1992); **15**: 900–4.

Streiner DL, Norman GR, editors. Health measurement scales: a practical guide to their development and use. (1995) Oxford University Press, Oxford.

Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The Autonomic Symptom Profile: a new instrument to assess autonomic symptoms. Neurology (1999); **52**: 523–8.

Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart rate in diabetes mellitus. Br Med J (1979); **1**: 924–5.

Sundkvist G, Lilja B, Almer L-O. Abnormal diastolic blood pressure and heart rate reactions to tilting in diabetes mellitus. Diabetologia (1980); **19**: 433–8.

Vinik AI, Maser RE, Mitchell BD, Freeman BD. Diabetic Autonomic Neuropathy. Diabetes Care (2003); **26**: 1553–79.

III

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Autonomic nervous symptoms in primary Sjögren's syndrome

T. Mandl[1], V. Granberg[2], J. Apelqvist[2], P. Wollmer[3], R. Manthorpe[4] and L. T. H. Jacobsson[1]

Objectives. Objective signs of autonomic dysfunction (AD) have been reported in patients with primary SS (pSS) while the presence of associated symptoms has not been systematically studied. Therefore, the aims of this study were (i) to assess the presence and severity of various AD symptoms in pSS patients and (ii) to relate AD symptoms to other clinical features of pSS.

Methods. Thirty-eight pSS patients and 200 population-based controls were studied for presence and severity of AD symptoms using the Autonomic Symptom Profile (ASP), a validated self-completed questionnaire evaluating various AD symptoms. In addition, patients were investigated by three different objective autonomic nervous function tests.

Results. pSS patients scored significantly higher in the parasympathetic [secretomotor disorder, urinary disorder, gastroparesis (females only) and pupillomotor disorder] as well as sympathetic (orthostatic intolerance and vasomotor disorder) ASP domains compared with controls. Consequently, the standardized ASP total score was significantly increased in pSS patients [1.77 (0.57, 3.15) *vs* −0.21 (−0.82, 0.72); $P = 0.00$] and 45% of pSS patients had an ASP total score ≥ 2 S.D. Furthermore, the autonomic nervous function tests showed signs of objective parasympathetic and sympathetic dysfunction as well. However, the ASP domain and total scores showed limited associations with the objective autonomic nervous function test parameters as well as clinical and serological factors of pSS.

Conclusions. pSS patients showed subjective and objective signs of both a parasympathetic and a sympathetic dysfunction. However, AD symptoms showed limited associations with objective autonomic nervous function as well as other clinical features of the disease.

Key words: Autonomic symptoms, Primary Sjögren's syndrome, Cardiovascular, Nervous, Physiology.

Introduction

Primary Sjögren's syndrome (pSS) is an autoimmune disease not only affecting the exocrine glands always but also affecting various non-exocrine organs, including the nervous system, frequently. Several studies report signs of peripheral neuropathy in pSS [1–6] and the autonomic nervous system (ANS), according to case reports and case series, may also be involved in the disease manifested by various autonomic dysfunction (AD) symptoms [6–11]. In pSS, the degree of exocrine gland destruction and function often correlate poorly [12, 13]. Since exocrine secretion is modulated by the ANS, impaired secretion could partly be due to interference with nervous signals to the exocrine glands [12, 14]. In previous studies, using autonomic reflex tests, parasympathetic and sympathetic dysfunction in pSS has been demonstrated [15–18] while studies measuring heart rate variability and baroreflex sensitivity have yielded contradictory results [18–21]. The observed AD in pSS has been ascribed to various immunological factors [6, 22–27]. Since immunological mechanisms have been proposed to affect autonomic function and the recent American–European Consensus Criteria (AECC) [28] in comparison with older criteria [29, 30] include pSS patients with at least some evidence of autoimmunity, an increased prevalence of ANS involvement would be expected in pSS patients diagnosed according to the AECC. Whilst objective signs of AD in pSS have been studied in several previous studies [15–21] and although only three of these applied the AECC [15, 18, 20], its subjective correlates have not been systematically studied.

The aims of this study were to evaluate AD symptoms in pSS patients using the Autonomic Symptom Profile (ASP), a validated and self-completed questionnaire assessing AD symptoms [31, 32], and to study associations between AD symptoms and clinical and serological features of pSS.

Materials and methods

Patients

Thirty-eight patients [median age 56 (range 25–61) yrs, 35 females], with pSS according to the AECC were recruited from the outpatient clinic at the Department of Rheumatology, Malmö University Hospital.

Eight patients were ≥ 60 yrs of age (60 yrs, $n = 3$, 61 yrs, $n = 5$). None of the patients had any comorbidity or was currently on any medication (anti-cholinergic drugs, β-blockers, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin-2 receptor blockers or pilocarpine) known to affect autonomic nervous function. All patients completed the ASP. In addition, the patients had previously been studied by three different objective autonomic nervous function tests i.e. the deep-breathing test, the orthostatic test and the finger skin blood flow test, the results of which have been previously reported [15]. One patient could not perform the finger skin blood flow test due to pain during cold provocation and two patients could not be investigated by the tilt table test due to feeling of panic, when being strapped to the tilt table. Further characteristics of the patients are presented in Table 1.

Controls

Two hundred controls [median age 45 (range 20–69) yrs, 100 females] were randomly selected from the Swedish general population registry and were required to be living in the City of Malmö or its surroundings. To ensure a balanced sex- and age-distribution, equal numbers of male and female controls were selected in each 10-yr stratum. The controls were asked via mail if they would like to participate in the study. If the subject was willing to participate and had no disease (diabetes mellitus, RA orSS) or medication (anti-hypertensives, cardiovascular medication or anti-depressants) affecting autonomic nervous function, then the questionnaire was filled out and sent back by post. A ticket to the cinema was sent back to each subject returning

[1]Department of Rheumatology, [2]Department of Endocrinology, [3]Department of Clinical Physiology, Malmö University Hospital and [4]Sjögren's Syndrome Research Centre, Malmö, Sweden.

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Correspondence to: T. Mandl, Department of Rheumatology, Ing 25 plan 2, Malmö University Hospital, S-205 02 Malmö, Sweden.
E-mail: thomas.mandl@med.lu.se

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a fully completed questionnaire. If no answer was received within 4 weeks, then a reminding letter was sent and if that was not answered either, a new control of the same age and gender was selected, until 200 controls were included. Further characteristics of the controls are presented in Table 1.

Autonomic nervous function tests

The pSS patients had, as previously reported [15], been studied regarding autonomic nervous function by three autonomic nervous function tests—the deep-breathing test, the orthostatic test and the finger skin blood flow test. The time difference between the completion of the autonomic nervous function tests and the ASP was median 17 [interquartile range (IQR) 10, 24] months.

Deep-breathing test

This test measured the heart rate variation, monitored by ECG, during deep-breathing. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R–R intervals, i.e. inter beat intervals, during expirations divided by the mean of the shortest R–R intervals during inspirations [33]. According to previous studies, the E/I-ratio mainly reflects parasympathetic nervous function [33, 34].

Orthostatic test

This test measured the heart rate, monitored by ECG and blood pressure reaction to tilt, the latter manually measured by a trained nurse before as well as every minute after tilt. A mean of the R–R intervals before tilt (A) was calculated and the shortest R–R interval during the first minute after tilting (B) was determined. From these values, an acceleration index (AI), defined as $[(A-B)/A \times 100]$, was calculated [35, 36]. The AI seems to be influenced mainly by the parasympathetic [37] but also to some degree by the sympathetic nervous system [38, 39]. The systolic and diastolic blood pressures before tilt (SBPrest and DBPrest) as well as the lowest systolic and diastolic blood pressures during the first 8 min after tilt (lSBP and lDBP) were determined. From these, orthostatic systolic and diastolic blood pressure-ratios were calculated [lSBP-ratio = lSBP/SBPrest] and [lDBP-ratio = lDBP/DBPrest]. According to previous studies, the orthostatic blood pressure response is considered reflecting sympathetic nervous function [40].

Table 1. Characteristics of the patients with pSS and ASP controls

	Patients ($n=38$)	Controls ($n=200$)
Age (yrs)	56 (39, 59)	45 (32, 57)
Gender (Males/Females)	3/35	100/100
Weight (kg)	70 (59, 85)	73 (63, 83)
Height (m)	1.65 (1.63, 1.70)	1.73 (1.68, 1.81)
Disease duration (yrs)	14 (8, 21)	–
Schirmer-I test (mm/5 min)	4 (1, 12)	NA
van Bijsterveld's score (0–18)	8 (6, 13)	NA
Unstimulated whole sialometry (ml/15 min)	0.4 (0.0, 1.0)	NA
Anti-SS-A antibody seropositives (%)	79	NA
Anti-SS-B antibody seropositives (%)	42	NA
ANA seropositives (%)	79	NA
RF seropositives (%)	68	NA
IgG (g/l)	18.4 (13.7, 22.0)	NA
C3 (g/l)	1.22 (1.12, 1.39)	NA
C4 (g/l)	0.22 (0.20, 0.29)	NA
Lip biopsy—focus score ≥ 1 (%)	88	NA
Non-exocrine symptoms/signs (of those given below) (%)	76	NA
Raynaud's phenomena (%)	26	NA
Arthralgia in the joints of the hands (%)	63	NA
Arthritis in the joints of the hands (%)	24	NA
Peripheral neuropathy (%)	21	NA
Vasculitis-purpura (%)	5	NA
Renal disease (%)	3	NA
Liver disease (%)	0	NA
Interstitial lung disease (%)	0	NA
Myositis (%)	0	NA
Current smokers (%)	13	24

Results are presented as median (IQR) as well as *n* or % with abnormal findings. Ocular parameters are presented as sum of both eyes. NA: not assessed.

Finger skin blood flow test

This test measured the reflex vasoconstriction to contralateral cold provocation. The subject's finger skin blood flow was monitored by a laser doppler imaging (LDI) instrument, at first during a 40°C heating procedure, and subsequently during immersion of the contralateral hand and forearm into a 15°C water bath. By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDI_c) by the mean of the two last measurements of finger skin blood flow at rest, before the cooling procedure, (LDI_h) a vasoconstriction (VAC) index could be calculated (VAC-index = LDI_c/LDI_h). According to previous studies, this reflects the sympathetic nervous function in the skin [41].

Since autonomic function tends to deteriorate with increasing age, the autonomic nervous function variables were age corrected and expressed as *z*-scores by comparison with three control groups, namely 56 controls for the E/I-ratio and AI consisting of healthy subjects [median age 40 yrs (range 16–59 yrs), 22 females] all of whom had passed a health examination without signs of cardiovascular disease, respiratory disorders or diabetes mellitus [42], 80 controls for the VAC-index consisting of healthy subjects [median age 43 yrs (range 19–81 yrs), 37 females] all of whom were non-smokers, had no history of vascular disease and were not on any medication [41] and 238 controls for the lSBP and lDBP-ratios consisting of healthy non-diabetic individuals [median age 60 yrs (range 16–96 yrs), 106 women] previously described in detail [43]. Since gender does not seem to affect significantly the autonomic variables measured in this study [41, 42], sex was not matched for. All autonomic nervous function tests were performed in the morning under standard conditions, i.e. the temperature conditions were kept stable and the patients were not allowed to eat, drink coffee or smoke later than 2 h prior to testing.

ASP

The ASP is a self-completed questionnaire assessing autonomic nervous symptoms which in its original English version has been validated in patients with autonomic neuropathies of different aetiologies [31] and used in patients with diabetes [32]. Recently, the questionnaire was also translated into Swedish and validated in patients with type I diabetes (Mandl *et al.*, unpublished data). Both the English and Swedish versions of the ASP were considered valid.

The ASP consists of questions evaluating nine domains of autonomic symptoms i.e. orthostatic intolerance, secretomotor dysfunction, male sexual dysfunction, urinary dysfunction, gastrointestinal dysfunction (divided into three subdomains namely gastroparesis, diarrhoea and constipation), pupillomotor dysfunction, vasomotor dysfunction, sleep disorder and reflex syncope. In addition, 12 interspersed questions addressing psychosomatic and understatement tendencies are included. The autonomic symptom domains consists of questions evaluating presence, severity, distribution, frequency and progression of various autonomic symptoms and the separate answers are scored according to their predictability for disease. In addition, domain scores are weighted according to their clinical relevance.

Consequently, the weighted maximum domain scores are as follows: orthostatic intolerance, 40; secretomotor dysfunction, 20; male sexual dysfunction, 30; urinary dysfunction, 20; gastroparesis, 10; diarrhoea, 20; constipation, 10; pupillomotor dysfunction, 5; vasomotor dysfunction, 10; sleep disorder, 15 and reflex syncope, 20. By adding the autonomic domain scores, an ASP total score is calculated with a maximum score of 200 for males

and 170 for females, lower for females due to the lack of questions addressing female sexual dysfunction. Furthermore, the psychosomatic and understatement domains are given a maximum score of 10 each and are presented separately. Since some of the ASP domain scores are affected by age, gender, height and weight, several of the ASP scores were age, gender, height and weight standardized in comparison with the 200 controls and expressed as *z*-scores. Due to a preponderance of zero values in the gastroparesis and reflex syncope domains among controls, although with some gender differences, these domains were expressed as gender stratified raw scores. Similarly, the psychosomatic and underestimation domains were also expressed as gender-stratified raw scores.

Statistics

Due to a skewed distribution of the ASP scores as well as for the autonomic nervous function parameters, the Mann–Whitney U-test was used for group comparisons and the Spearman rank correlation test for correlations. Fisher's exact test was used for discrete variables. Values were presented as median (IQR) or percentages with pathological results. *P*-values <0.05 were considered statistically significant.

Ethics

The study was approved by the ethics committee at Lund University (LU814-04). All participants gave written informed consent.

Results

The pSS patients, as previously reported [15], were found to have a decreased E/I-ratio and an increased VAC-index compared with controls reflecting a parasympathetic and a sympathetic dysfunction, respectively. Furthermore, the lSBP- and lDBP-ratios were decreased in pSS patients compared with controls, also indicating a sympathetic dysfunction (Table 2).

As expected, pSS patients scored higher compared with controls in the secretomotor and pupillomotor domains, but also in other parasympathetic domains, i.e. urinary disorder, and gastroparesis (females only) domains. In addition, pSS patients scored higher in the sympathetic domains, i.e. orthostatic intolerance and vasomotor disorder domains. Consequently, the ASP total score was significantly increased in pSS patients compared with controls (Table 3) and 45% (17/38) of the pSS patients had a standardized ASP total score ≥ 2 S.D. indicating a pathological autonomic symptomatology.

The female pSS patients also scored significantly higher in the psychosomatic domain, reflecting psychosomatic tendencies. However, two questions on psychosomatic symptoms from the original questionnaire addressed presence of swallowing difficulties and experience that all food tastes the same, symptoms which cannot necessarily be regarded as psychosomatic symptoms in hyposalivating pSS patients. If these two questions were omitted from the psychosomatic domain and an adjusted psychosomatic index was calculated and re-weighted with a maximum score of ten, then the difference between female pSS patients and female controls was no longer significant (Table 3). Even if patients and controls with an adjusted psychosomatic score >0 were omitted, pSS patients still scored significantly higher in the orthostatic intolerance, gastroparesis (females only), secretomotor, pupillomotor and vasomotor disorder domains as well as in the ASP total score. Moreover, several ASP domain scores correlated with each other as well as with the ASP total score (Table 4).

When correlating the objective autonomic nervous function test parameters with the ASP scores, significant correlations were only found between the VAC-score and the sleep disorder domain score (r's $= 0.42$; $P = 0.01$) as well as between the lSBP-ratio and the constipation domain score (r's $= -0.43$; $P = 0.01$). Even when ASP domains possibly reflecting end-organ damage/exocrine destruction as well as autonomic function, i.e. the secretomotor

TABLE 2. Autonomic nervous function test results in the 38 patients with pSS and autonomic nervous function controls, representing a subgroup of pSS patients previously evaluated for objective AD as formerly reported [15]

Autonomic parameters	Patients ($n=38$)	Controls ($n=56/80/238$)	*P*-value
Expiration inspiration index	−0.57 (−1.33, 0.32)	−0.25 (−0.62, 0.60)	0.02
Acceleration index	−0.11 (−1.11, 0.31)	0.03 (−0.67, 0.65)	0.13
Vasoconstriction index	0.62 (−0.31, 1.30)	0.09 (−0.67, 0.62)	0.03
lSBP-ratio	−0.71 (−1.45, −0.06)	−0.02 (−0.62, 0.70)	0.00
lSBP-ratio	−0.70 (−1.05, −0.03)	0.00 (−0.47, 0.54)	0.00

All values were age corrected and expressed as *z*-scores. Results are presented as median (IQR).

TABLE 3. Comparisons of the ASP domain scores in 38 patients with pSS and 200 controls

Domains (raw score range)	Raw scores: pSS patients ($n=38$, 35 females)	Standardized scores: pSS patients ($n=38$, 35 females)	Raw scores: controls ($n=200$, 100 females)	Standardized scores: controls ($n=200$, 100 females)	*P*-value
Orthostatic intolerance (0–40)	15.0 (0.0, 22.5)	1.21 (−0.56, 2.38)	1.3 (0.0, 12.5)	−0.39 (−0.78, 0.79)	0.00***
Sexual dysfunction (males, 0–30)	0.0 (0.0, 6.0)	−0.18 (−0.67, 0.70)	0.0 (0.0, 1.5)	−0.22 (−0.51, 0.11)	0.92
Urinary disorder (0–20)	2.0 (0.0, 6.0)	0.13 (−0.67, 1.98)	0.0 (0.0, 2.0)	−0.51 (−0.71, 0.32)	0.04*
Diarrhoea (0–20)	2.0 (0.0, 8.0)	0.08 (−0.67, 1.41)	0.0 (0.0, 4.0)	−0.42 (−0.60, 0.68)	0.42
Gastroparesis—females (0–10)	0.0 (0.0, 1.5)	NA	0.0 (0.0, 0.0)	NA	0.04*
Gastroparesis—males (0–10)	0.0 (0.0, 3.5)	NA	0.0 (0.0, 0.0)	NA	0.41
Constipation (0–10)	0.0 (0.0, 3.0)	−0.46 (−0.56, 2.57)	0.0 (0.0, 0.0)	−0.30 (−0.52, −0.18)	0.82
Secretomotor disorder (0–20)	7.5 (6.0, 10.5)	2.86 (2.26, 4.02)	0.0 (0.0, 3.0)	−0.45 (−0.72, 0.52)	0.00***
Sleep disorder (0–15)	1.5 (0.0, 4.0)	−0.09 (−0.81, 1.46)	1.5 (0.0, 1.5)	−0.05 (−0.79, 0.35)	0.37
Vasomotor disorder (0–10)	0.0 (0.0, 5.5)	−0.19 (−0.44, 2.94)	0.0 (0.0, 0.0)	−0.33 (−0.49, −0.20)	0.01**
Pupillomotor disorder (0–5)	2.5 (0.9, 4.1)	1.50 (0.00, 3.07)	0.5 (0.0, 1.5)	−0.42 (−0.71, 0.55)	0.00***
Reflex syncope—females (0–20)	0.0 (0.0, 0.0)	NA	0.0 (0.0, 0.0)	NA	0.41
Reflex syncope—males (0–20)	0.0 (0.0, 0.0)	NA	0.0 (0.0, 0.0)	NA	0.89
Total score (males, 0–200 and females, 0–170)	39.3 (25.1, 55.0)	1.77 (0.57, 3.15)	13.0 (4.5, 23.4)	−0.21 (−0.82, 0.72)	0.00***
Psychosomatic index—females (0–10)	0.0 (0.0, 2.0)	NA	0.0 (0.0, 0.0)	NA	0.02*
Adj. psychosomatic index—females (0–10)	0.0 (0.0, 0.0)	NA	0.0 (0.0, 0.0)	NA	0.09
Psychosomatic index—males (0–10)	0.0 (0.0, 5.5)	NA	0.0 (0.0, 0.0)	NA	0.40
Adj. psychosomatic index—males (0–10)	0.0 (0.0, 3.0)	NA	0.0 (0.0, 0.0)	NA	0.41
Understatement index—females (0–10)	1.5 (0.0, 1.5)	NA	0.0 (0.0, 3.5)	NA	0.51
Understatement index—males (0–10)	5.0 (0.0, 10.0)	NA	1.5 (0.0, 5.0)	NA	0.36

Standardized scores were age, gender, height and weight standardized and expressed as *z*-scores. For comparisons between groups the standardized scores were used, except for the gastroparesis, vasomotor dysfunction, psychosomatic, adjusted psychosomatic and underestimation domains where gender-stratified raw scores were used. The adjusted psychosomatic score means that for pSS patients inappropriate psychosomatic questions were omitted from the psychosomatic index. Results are presented as median (IQR). $^{*}P<0.05$, $^{**}P<0.01$, $^{***}P<0.001$. Adj: adjusted; NA: not assessed.

TABLE 4. Correlations between the age-, gender-, height- and weight-standardized ASP domain scores in the 38 patients with pSS

Domains	OI	UD	DIA	CON	SMD	SLD	VMD	PMD	TS
Orthostatic intolerance (OI)	–	0.15 (0.36)	0.05 (0.76)	−0.06 (0.71)	0.30 (0.07)	0.36* (0.03)	0.41* (0.01)	0.58** (0.00)	0.82** (0.00)
Urinary disorder (UD)	0.15 (0.36)	–	0.30 (0.07)	0.34* (0.04)	0.18 (0.28)	−0.02 (0.90)	0.09 (0.59)	0.13 (0.44)	0.43** (0.01)
Diarrhoea (DIA)	0.05 (0.76)	0.30 (0.07)	–	0.20 (0.24)	0.26 (0.11)	0.10 (0.56)	0.20 (0.24)	0.25 (0.13)	0.44** (0.01)
Constipation (CON)	−0.06 (0.71)	0.34* (0.04)	0.20 (0.24)	–	0.01 (0.97)	−0.09 (0.61)	0.22 (0.19)	0.30 (0.07)	0.19 (0.26)
Secretomotor disorder (SMD)	0.30 (0.07)	0.18 (0.28)	0.26 (0.11)	0.01 (0.97)	–	0.45** (0.01)	0.29 (0.08)	0.17 (0.30)	0.53** (0.01)
Sleep disorder (SLD)	0.36* (0.03)	−0.02 (0.90)	0.10 (0.56)	−0.09 (0.61)	0.45** (0.01)	–	0.24 (0.15)	0.26 (0.12)	0.46** (0.00)
Vasomotor disorder (VMD)	0.41* (0.01)	0.09 (0.59)	0.20 (0.24)	0.22 (0.19)	0.29 (0.08)	0.24 (0.15)	–	0.51** (0.00)	0.58** (0.00)
Pupillomotor disorder (PMD)	0.58** (0.00)	0.13 (0.44)	0.25 (0.13)	0.30 (0.07)	0.17 (0.30)	0.26 (0.12)	0.51** (0.00)	–	0.68** (0.00)
Total score (TS)	0.82** (0.00)	0.43** (0.01)	0.44** (0.01)	0.19 (0.26)	0.53** (0.01)	0.46** (0.00)	0.58** (0.00)	0.68** (0.00)	–

The gastroparesis and reflex syncope domains were omitted since these domain scores were not standardized. In addition, the sexual dysfunction domain was omitted, since only three pSS patients were male. Results are presented as Spearman's rank correlation test coefficients. (*P*-values). $^{*}P<0.05$, $^{**}P<0.01$.

and pupillomotor disorder domains, were omitted and a new standardized ASP total score was calculated, this adjusted ASP total score did not correlate with the objective autonomic nervous function test parameters. Furthermore, when comparing pSS patients with abnormal (≥2 S.D.) and normal (<2 S.D.) scores in the orthostatic intolerance, urinary disorder, vasomotor disorder, secretomotor disorder, pupillomotor disorder and total score domains as well as the gastroparesis domain in female patients (abnormal >0), respectively, no significant differences in the objective autonomic indices were found. However, when comparing pSS patients with abnormal (≤2 S.D.; $n=3$) and normal (>2 S.D.; $n=33$) lSBP-ratios, the former had significantly increased scores in the orthostatic intolerance [median 2.86 (IQR 2.29, 3.43) *vs* 1.00 (−0.63, 1.84); $P=0.01$], constipation [2.72 (2.56, 4.23) *vs* −0.47 (−0.56, 1.05); $P=0.03$], vasomotor disorder [3.98 (2.37, 4.04) *vs* −0.26 (−0.50, 2.92); $P=0.02$], pupillomotor disorder [3.25 (3.06, 3.69) *vs* 1.44 (−0.18, 2.65); $P=0.02$] domains, the ASP total score [4.26 (3.52, 6.55) *vs* 1.65 (0.39, 2.47); $P=0.00$] as well as a non-significant tendencies towards increased scores in the urinary disorder [2.13 (1.89, 8.32) *vs* 0.08 (−0.70, 1.93); $P=0.07$] and gastroparesis (females only) [1.50 (1.50, 5.00) *vs* 0.00 (0.00, 1.50); $P=0.06$] domains.

ASP scores were not affected by disease duration, or presence of anti-SS-A and B-antibodies or non-exocrine symptoms (as defined in Table 1), respectively. However, when comparing patients with and without RP, there was, as expected, a significantly higher score in the vasomotor [2.92 (1.70, 3.22) *vs* −0.32 (−0.50, 2.42); $P=0.04$] but also in the constipation [1.05 (−0.50, 5.80) *vs* −0.53 (−0.57, 0.95); $P=0.03$] domains and a non-significant tendency towards a lower score in the orthostatic intolerance domain [0.31 (−0.91, 1.46) *vs* 1.55 (−0.10, 2.80); $P=0.09$] among the former. When comparing patients with and without symptoms of peripheral neuropathy the former scored significantly higher in the sleep disorder domain [1.26 (0.10, 2.15) *vs* −0.42 (−0.83, 0.80); $P=0.05$], while no significant differences were found in the remaining ASP domains. Finally, the prevalence of current smokers did not significantly differ between pSS patients and controls (13 *vs* 24%; $P=$NS) and the ASP domain scores were not found to significantly differ between smoking and non-smoking pSS patients.

Discussion

In this first larger cohort study systematically studying subjective AD symptoms in pSS, patients were found to have various subjective and objective signs equivalent of parasympathetic and sympathetic dysfunction. However, AD symptoms showed limited associations with objective AD signs and other clinical features of pSS.

AD is a complication of many chronic diseases [35, 44–49] and may result in several debilitating symptoms [50]. Objective signs of AD have previously been demonstrated in pSS patients [15–19, 21] including the present group of patients [15] and various immunological mechanisms behind AD in pSS, namely anti-muscarine-3 (M3)-receptor antibodies [22–24], cytokines interfering with nervous signalling [25, 26, 51] and inflammation of autonomic nerves or ganglia [6, 27], have been proposed. Considering that exocrine gland destruction in pSS is often much less pronounced than the decreased exocrine function, other mechanisms beside exocrine gland destruction have to be accountable for exocrine impairment in pSS. Since autonomic nervous signalling to the exocrine glands is a prerequisite for secretion, a disturbance in these signalling pathways in pSS, as suggested already in the early 1990s, by Konttinen and co-workers [52], could explain the discrepancy between exocrine gland morphology and function in pSS. Although, several case reports and case series report on AD signs and symptoms, e.g. orthostatic hypotension [6–9], urinary symptoms [9, 10], Adie's syndrome [6, 11] and constipation [6] in association with pSS, the subjective correlates of AD in pSS have not previously been systematically studied.

The strengths of this study were the use of the nowadays widespread AECC [28] for pSS, the exclusion of patients on medications interfering with autonomic function as well as a large population-based control group for the ASP, allowing for standardization with regards to age, gender, height and weight. One of the possible concerns, is the fact that the ASP has not been validated specifically in pSS patients, although the original English version of the ASP has been validated in patients with symptomatic AD due to different aetiologies [31] and the Swedish version in patients with type I diabetes (Mandl *et al.*, unpublished data). However, if the anti-M3-receptor antibodies, as suggested, play a central role in pSS-related AD, a validation of the ASP in pSS patients should include analysis of these antibodies. Another possible concern with this study is the risk that some of the ASP domains, e.g. the secretomotor and pupillomotor disorder domains, could evaluate end-organ damage rather than AD in pSS patients. Finally, since several correlation analyses were performed when performing correlations between the ASP domains and the objective autonomic nervous function tests, there is a risk that some significant correlations could be due to multiple comparisons.

In this study, we found an increased frequency of both symptoms and objective signs related to a parasympathetic and sympathetic dysfunction, although they showed limited associations. This lack of association, however, could well be due to end-organ damage, obscuring a possible association between objective and subjective AD. Other possible explanations could be variable concentrations of the putative anti-M3-receptor antibodies in various tissues; the inability of the objective autonomic nervous function tests to measure the physiological effects of anti-M3 receptor antibodies, which might still result in various symptoms; the sometimes few stepped ASP domain score scales; insufficient power in the present study to address this issue, as well as the time lap between subjective and objective tests.

Although the increased secretomotor and pupillomotor disorder domain scores in pSS were expected and could be due to exocrine gland destruction, i.e. end-organ damage, the increased

scores in the urinary disorder and gastroparesis (females only) as well as the decreased E/I-ratio imply a parasympathetic dysfunction in pSS. Moreover, the increased scores in the orthostatic intolerance and vasomotor disorder domains in pSS patients, the increased VAC-index and decreased orthostatic blood pressure response imply a sympathetic dysfunction as well. Due to the excess of AD symptoms in pSS patients, 45% of these had an ASP total score $\geq$2 S.D., indicating a pathological AD symptomatology. We also found a tendency that female pSS patients scored higher in the psychosomatic domain, which however, became statistically non-significant when for pSS patients inappropriate psychosomatic questions were omitted. Furthermore, omitting subjects with adjusted psychosomatic scores above zero did not change most statistical differences in ASP scores between patients and controls. It is thus unlikely that the increased ASP scores in pSS patients reflect an overall increased tendency to report symptoms. Presence of orthostatic symptoms correlated with sleep disorder, pupillary and vasomotor symptoms implying a common cause for such symptoms. Although secretomotor symptoms, as expected, are common in pSS patients such symptoms only correlated with sleep disorder symptoms and not with the majority of the other AD symptoms, implying that other mechanisms beside AD, e.g. end-organ damage in patients with long disease duration, may be accountable for the secretomotor dysfunction in pSS. For that reason, future studies should investigate the presence of objective and subjective AD signs as well as anti-M3-receptor antibodies in pSS patients with shorter disease duration, to establish if an association between these entities is more apparent in the disease before exocrine destruction has occurred. Finally, AD symptoms were also found to associate poorly with the presence of different diagnostic autoantibodies as well as with other non-exocrine symptoms.

In conclusion, pSS patients were found to have various subjective and objective signs of parasympathetic and sympathetic dysfunction. Generally, however, AD symptoms showed limited associations with objective AD signs as well as other clinical features of pSS.

Rheumatology key messages

- Autonomic nervous dysfunction symptoms are common in pSS patients.
- AD symptoms show limited associations with objective AD signs as well as other clinical features of the disease.
- Objective signs and subjective symptoms of AD suggest both parasympathetic and sympathetic dysfunction in primary Sjögren's syndrome.

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References

1 Hietaharju A, Yli-Kerttula U, Häkkinen V, Frey H. Nervous system manifestations in Sjögren's syndrome. Acta Neurol Scand 1990;81:144–52.
2 Barendregt PJ, van den Bent MJ, van Raaij-van den Aarssen VJ *et al.* Involvement of the peripheral nervous system in primary Sjögren's syndrome. Ann Rheum Dis 2001;60:876–81.
3 Gemignani F, Marbini A, Pavesi G *et al.* Peripheral neuropathy associated with primary Sjögren's syndrome. J Neurol Neurosurg Psychiatry 1994;57:983–6.
4 Grant IA, Hunder GG, Homburger HA, Dyck PJ. Peripheral neuropathy associated with sicca complex. Neurology 1997;48:855–62.
5 Griffin JW, Cornblath DR, Alexander E *et al.* Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann Neurol 1990;27:304–15.
6 Mori K, Iijima M, Koike H *et al.* The wide spectrum of clinical manifestations in SS associated neuropathy. Brain 2005;128:2518–34.
7 Andonopoulos AP, Ballas C. Autonomic cardiovascular neuropathy in primary Sjögren's syndrome. Rheumatol Int 1995;15:127–9.
8 Sakakibara R, Hirano S, Asahina M *et al.* Primary Sjögren's syndrome presenting with generalized autonomic failure. Eur J Neurol 2004;11:635–8.
9 Sorajja P, Poirier MK, Bundrick JB, Matteson EL. Autonomic failure and proximal skeletal myopathy in a patient with primary Sjögren syndrome. Mayo Clin Proc 1999;74:695–7.
10 Walker J, Gordon T, Lester S *et al.* Increased severity of lower urinary tract symptoms and daytime somnolence in primary Sjogren's syndrome. J Rheumatol 2003;30:2406–12.
11 Waterschoot MP, Guerit JM, Lambert M, de Barsy T. Bilateral tonic pupils and polyneuropathy in Sjögren's syndrome: a common pathophysiological mechanism? Eur Neurol 1991;31:114–6.
12 Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. Scand J Immunol 1999;49:7–10.
13 Jonsson R, Kroneld U, Tarkowski A. Histological and functional features of salivary glands in rheumatic patients with oral sicca symptoms. Scand J Rheumatol 1988;17:387–91.
14 Dawson LJ, Fox PC, Smith PM. Sjögren's syndrome – the non-apoptotic model of glandular hypofunction. Rheumatology 2006;45:792–8.
15 Mandl T, Wollmer P, Manthorpe R, Jacobsson L. Autonomic and orthostatic dysfunction in primary Sjögren's syndrome. J Rheumatol 2007;34:1869–74.
16 Andonopoulos AP, Christodoulou J, Ballas C, Bounas A, Alexopoulos D. Autonomic cardiovascular neuropathy in Sjogren's syndrome. A controlled study. J Rheumatol 1998;25:2385–8.
17 Barendregt PJ, van den Meiracker AH, Markusse HM *et al.* Parasympathetic failure does not contribute to ocular dryness in primary Sjogren's syndrome. Ann Rheum Dis 1999;58:746–50.
18 Kovacs L, Paprika D, Takacs R *et al.* Cardiovascular autonomic dysfunction in primary Sjogren's syndrome. Rheumatology 2004;43:95–9.
19 Barendregt PJ, Tulen JH, van den Meiracker AH, Markusse HM. Spectral analysis of heart rate and blood pressure variability in primary Sjogren's syndrome. Ann Rheum Dis 2002;61:232–6.
20 Niemela RK, Hakala M, Huikuri HV, Airaksinen KE. Comprehensive study of autonomic function in a population with primary Sjogren's syndrome. No evidence of autonomic involvement. J Rheumatol 2003;30:74–9.
21 Tumiati B, Perazzoli F, Negro A, Pantaleoni M, Regolisti G. Heart rate variability in patients with Sjogren's syndrome. Clin Rheumatol 2000;19:477–80.
22 Waterman SA, Gordon TP, Rischmueller M. Inhibitory effects of muscarinic receptor autoantibodies on parasympathetic neurotransmission in Sjogren's syndrome. Arthritis Rheum 2000;43:1647–54.
23 Gordon TP, Bolstad AI, Rischmueller M, Jonsson R, Waterman SA. Autoantibodies in primary Sjogren's syndrome: new insights into mechanisms of autoantibody diversification and disease pathogenesis. Autoimmunity 2001;34:123–32.
24 Dawson L, Tobin A, Smith P, Gordon T. Antimuscarinic antibodies in Sjogren's syndrome: where are we, and where are we going? Arthritis Rheum 2005;52: 2984–95.
25 Fox RI, Stern M. Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. Scand J Rheumatol 2002;(Suppl 116):3–13.
26 Haddad EB, Rousell J, Lindsay MA, Barnes PJ. Synergy between tumor necrosis factor alpha and interleukin 1beta in inducing transcriptional down-regulation of muscarinic M2 receptor gene expression. Involvement of protein kinase A and ceramide pathways. J Biol Chem 1996;271:32586–92.
27 Griffin JW, Cornblath DR, Alexander E *et al.* Ataxic sensory neuropathy and dorsal root ganglionitis associated with Sjogren's syndrome. Ann Neurol 1990;27:304–15.
28 Vitali C, Bombardieri S, Jonsson R *et al.* Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American-European Consensus Group. Ann Rheum Dis 2002;61:554–8.
29 Manthorpe R, Oxholm P, Prause JU, Schioedt MT. The Copenhagen criteria for Sjögren's syndrome. Scand J Rheumatol 1986;15(Suppl 61):19–21.
30 Vitali C, Bombardieri S, Moutsopoulos HM *et al.* Assessment of the European classification criteria for Sjögren's syndrome in a series of clinically defined cases: results of a prospective multicentre study. Ann Rheum Dis 1996;55:116–21.
31 Suarez GA, Opfer-Gehrking TL, Offord KP, Atkinson EJ, O'Brien PC, Low PA. The autonomic symptom profile: a new instrument to assess autonomic symptoms. Neurology 1999;52:523–8.
32 Low PA, Benrud-Larson LM, Sletten DM *et al.* Autonomic symptoms and diabetic neuropathy: a population-based study. Diabetes Care 2004;27:2942–7.
33 Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart rate in diabetes mellitus. Br Med J 1979;1:924–5.
34 Ewing DJ, Neilson JM, Travis P. New method for assessing cardiac parasympathetic activity using 24 hour electrocardiograms. Br Heart J 1984;52:396–402.
35 Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in type I diabetes: influence of duration and other diabetic complications. Acta Med Scand 1987;222:147–54.
36 Sundkvist G, Lilja B, Almer L-O. Abnormal diastolic blood pressure and heart rate reactions to tilting in diabetes mellitus. Diabetologia 1980;19:433–8.
37 Vinik AI, Maser RE, Mitchell BD, Freeman BD. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553–79.
38 Bergström B, Mattiasson I, Rosen I, Lilja B, Sundkvist G. Platelet sodium and potassium ATPase activity and noradrenaline efflux rate in relation to autonomic

and peripheral nerve function in insulin dependent diabetic patients. J Intern Med 1989;225:185–90.
39 Bergström B, Manhem P, Bramnert M, Lilja B, Sundkvist G. Impaired responses of plasma cathecolamines to exercise in diabetic patients with abnormal heart reactions to tilt. Clin Physiol 1989;9:259–67.
40 Low PA. Composite autonomic scoring scale for laboratory quantification of generalized autonomic failure. Mayo Clin Proc 1993;68:748–52.
41 Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol 1998;18;2:103–7.
42 Bergström B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. Clin Physiol 1986;6:523–8.
43 de Kanter M, Lilja B, Elmstahl S, Eriksson KF, Sundkvist G. A prospective study of orthostatic blood pressure in diabetic patients. Clin Auton Res 1998;8: 189–93.
44 Bergström B, Lilja B, Österlin S, Sundkvist G. Autonomic neuropathy in non insulin dependent (type II) diabetes mellitus. Possible influence of obesity. J Intern Med 1990;227:57–63.
45 Leden I, Lilja B, Sturfelt G, Sundkvist G. Autonomic nerve function in rheumatoid arthritis of varying severity. Scand J Rheumatol 1983;12:166–70.
46 Laversuch CJ, Seo H, Modarres H, Collins DA, McKenna W, Bourke BE. Reduction in heart rate variability in patients with systemic lupus erythematosus. J Rheumatol 1997;24:1540–4.
47 Bertinotti L, Bracci S, Nacci F *et al.* The autonomic nervous system in systemic sclerosis. A review. Clin Rheumatol 2004;23:1–5.
48 Lindgren S, Lilja B, Rosen I, Sundkvist G. Disturbed autonomic nerve function in patients with Crohn's disease. Scand J Gastroenterol 1991;4:361–6.
49 Lindgren S, Stewenius J, Sjölund K, Lilja B, Sundkvist G. Autonomic vagal nerve dysfunction in patients with ulcerative colitis. Scand J Gastroenterol 1993;7:638–49.
50 Vinik AI, Maser RE, Mitchell BD, Freeman BD. Diabetic autonomic neuropathy. Diabetes Care 2003;26:1553–79.
51 Zoukhri D, Hodges RR, Byon D, Larkin Kublin C. Role of proinflammatory cytokines in the impaired lacrimation associated with autoimmune xerophthalmia. Invest Ophthalmol Vis Sci 2002;43:1429–36.
52 Konttinen YT, Hukkanen M, Kemppinen P *et al.* Peptide-containing nerves in labial salivary glands in Sjögren's syndrome. Arthritis Rheum 1992;35:815–20.

IV

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Dysphagia and dysmotility of the pharynx and oesophagus in patients with primary Sjögren's syndrome

T Mandl[1], O Ekberg[2], P Wollmer[3], R Manthorpe[4], LTH Jacobsson[1]

Departments of [1]Rheumatology, [2]Radiology and [3]Clinical Physiology, Malmö University Hospital, and [4]Sjögren's Syndrome Research Centre, Malmö, Sweden

Objectives: To assess the prevalence of pharyngeal and oesophageal symptoms and dysmotility in patients with primary Sjögren's syndrome (pSS) and relate these to autonomic nervous function.
Methods: Twenty consecutive pSS patients, according to the American–European Consensus Criteria (AECC), and 30 age- and sex-matched controls from the Swedish general population registry were studied. All subjects completed a pharyngeal and oesophageal symptoms questionnaire and were examined by pharyngeal and oesophageal video radiography. In addition, the pSS patients were examined by two different autonomic nervous function tests, the deep breathing test [calculating the expiration/inspiration (E/I) ratio] and the finger skin blood flow test [the vasoconstriction (VAC) index].
Results: pSS patients experienced significantly more dysphagia compared with controls (65% vs. 3%; $p<0.001$). Pharyngeal (45% vs. 7%; $p<0.01$), oesophageal (80% vs. 7%; $p<0.001$) and gastro-oesophageal reflux symptoms (60% vs. 23%; $p<0.01$) were also more prevalent in pSS patients compared with controls while pharyngeal (15% vs. 17%; p=NS) and oesophageal dysmotility (40% vs. 30%; p=NS) were not. Dysphagia was not associated with dysmotility but was found to be associated with a decreased E/I ratio [−1.05 (−1.51 to −0.40) in patients with dysphagia vs. −0.21 (−0.39 to 0.65) in patients without dysphagia; $p<0.01$].
Conclusion: Subjective swallowing difficulties were more common in pSS patients than in controls while objective signs of pharyngeal and oesophageal dysmotility were not. Dysphagia in pSS patients does not seem to be related to video radiographical signs of dysmotility but may be related to an impaired parasympathetic function.

Primary Sjögren's syndrome (pSS) is an autoimmune disease affecting the exocrine glands, resulting in diminished or absent glandular secretion and mucosal dryness. In addition, various non-exocrine organs may be involved in the disease, including the gastrointestinal and nervous systems. Dysphagia is a common gastrointestinal complaint in pSS (1) and has been reported to affect 33–92% of pSS patients (2–8). In previous studies these symptoms have been attributed to either lack of saliva (3, 4, 8), oesophageal dysmotility (5, 8, 9) or oesophageal webs (4). The lack of saliva makes swallowing difficult by interfering with pharyngeal contraction (3) and passage of the bolus over the dry mucosal surfaces of the oesophagus in pSS (10). However, only one study has found correlations between lack of saliva, dysphagia and oesophageal dysmotility (8). Oesophageal manometry in pSS patients has shown that about one-third of patients display varying degrees of oesophageal dysmotility (2, 5, 7, 9, 11). Although some previous studies reported a correlation between dysphagia and oesophageal dysmotility (5, 8), most others did not (2, 4, 6, 7). Oesophageal webs have also been suggested as a reason for dysphagia and have been found in about 10% (4, 10) of pSS patients.

One problem regarding dysphagia and oesophageal dysmotility studies in pSS is the use of different classification criteria for pSS. In only one previous study (3) was the American–European Consensus Criteria (AECC) for Sjögren's syndrome (12) applied.

Oesophageal peristalsis and exocrine secretion are both influenced by the autonomic nervous system and autonomic nervous system signalling is affected in pSS (13–18). Therefore, dysphagia and oesophageal dysmotility may be due to impaired autonomic nervous function, as reported in other diseases with gastrointestinal symptoms such as systemic sclerosis (19), diabetes mellitus (20), gastro-oesophageal reflux disease (GERD) (21, 22) and non-specific oesophageal motility disorder (23).

Thomas Mandl, Department of Rheumatology, Ing 25 plan 2, Malmö University Hospital, S-205 02 Malmö, Sweden.
E-mail: thomas.mandl@med.lu.se

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The aims of this study were to (i) assess the prevalence of pharyngeal and oesophageal symptoms and dysmotility in patients with pSS as compared with age- and sex-matched controls and (ii) relate dysphagia and video radiographically assessed dysmotility to autonomic nervous function in pSS patients.

Materials and methods

Study population

Twenty consecutive patients with pSS according to the AECC (12) [median age (interquartile range, IQR) 47 years (31.0–55.5), 18 females] were recruited and followed up at the outpatient clinic at the Department of Rheumatology, Malmö University Hospital. Thirty age- and sex-matched controls [48 years (31.0–54.5), 27 females], randomly selected from the Swedish general population registry, emerging from the city of Malmö and surroundings, were also studied. None of the subjects was found to have any other chronic disease that could affect autonomic nervous function. Moreover, subjects were not currently (i.e. in the past year) being treated with any drugs affecting autonomic nervous function [anti-cholinergic drugs, beta blockers, calcium channel blockers, angiotensin-converting enzyme (ACE) inhibitors or angiotensin-2 receptor blockers] or with glucocorticosteroids or disease-modifying antirheumatic drugs (DMARDs). None of the subjects had undergone gastro-oesophageal surgery prior to the study. Finally, for radiation safety purposes, pregnancy and prior (≥5) chest X-ray examinations were also exclusion criteria.

Eighty-nine per cent of pSS patients (17/19) had a pathological lower lip biopsy (focus score≥1) and 75% (15/20) were anti-SS-A-antibody seropositives, of whom 33% (5/15) were also anti-SS-B antibody seropositives. Lower lip biopsy had not been performed in one patient who was anti-SS-A antibody seropositive. Seventy per cent of pSS patients had non-exocrine symptoms, of which the most prevalent were Raynaud's phenomena and arthralgia/arthritis in the joints of the hands. Further characteristics are presented in Table 1.

The study was approved by the ethics committee at Lund University and the radiation protection committee at Malmö University Hospital. All participating subjects gave written informed consent.

Questionnaire

Subjects were interviewed using a questionnaire consisting of 15 questions screening for different clinically important pharyngeal and oesophageal symptoms, the presence of which may have resulted in them seeking medical attention. The first question was related to the presence of dysphagia (defined as a positive answer to the question 'Do you experience weekly occurrence of swallowing difficulties when eating solids and/or drinking liquids?'). Subjects were then asked questions related to GERD symptoms (weekly occurrence of: globus feeling, regurgitation, pyrosis, nocturnal asthma, and subjective feeling of an increased amount of fluid in the oral cavity – five questions), pharyngeal symptoms [weekly occurrence of: fluid/food in the nasal cavity after swallowing, misdirected swallowing (i.e. a sensation of food or liquid passage into the airways when swallowing), coughing after swallowing, and hawking when eating – four questions] as well as oesophageal symptoms (weekly occurrence of: feeling of obstruction when swallowing, avoidance of certain food due to dysphagia, increased intake of liquids when eating, the presence of odynophagia as well as previous episodes ever of acute obstruction that resulted in need of vomiting or endoscopy – five questions). By adding the positive answers (i.e. the presence of symptoms), GERD (0–5), pharyngeal (0–4) and oesophageal symptom scores (0–5) were calculated. Subjects with dysphagia complained of a sensation of obstruction or misdirected swallowing when eating solids and/or drinking liquids, of different severity and location. Therefore, the subjects with dysphagia were also asked about the severity of dysphagia (i.e. dysphagia for solids and/or liquids), as well as the location of dysphagia (i.e. pharyngeal, upper-oesophageal, mid-oesophageal and distal-oesophageal location).

Table 1. Characteristics of the pSS patients and controls.

	pSS patients (n=20)	Controls (n=30)
Age (years)	47 (31–55.5)	48 (31–54.5)
Males/females	2/18	3/27
Disease duration (years)	11 (5–16)	NA
Schirmer-I test (mm/5 min)	3 (0–5)	NA
Van Bijsterveld's score (0–18)	9 (7–16)	NA
Unstimulated whole sialometry (mL/15 min)	0.3 (0.0–1.1)	NA
Anti-SS-A antibody seropositives	75	NA
Anti-SS-B antibody seropositives	25	NA
Lip biopsy – focus score≥1	89	NA
Non-exocrine symptoms	70	NA
Raynaud's phenomena	25	NA
Arthralgia/arthritis in the joints of the hands	55/25	NA
Vasculitis purpura	10	NA
Interstitial lung disease	5	NA
Liver disease (primary biliary cirrhosis)	5	NA
Renal disease	0	NA
Myositis	0	NA
Polyneuropathy	0	NA

NA, not assessed. Results are presented as median (IQR) or percentage of abnormal results in each group. Ocular parameters are presented as the sum of both eyes.

Pharyngeal and oesophageal video radiography

This radiological technique was performed according to a protocol used at our hospital and has previously been described in detail (24, 25). It is considered to be a minimally invasive method with little or no discomfort for the subject studied. However, the examination results in a radiation dose equivalent to 15 chest X-rays (antero-posterior and lateral projections).

All radiographies were read by one of the co-authors (OE), who was not blinded with regard to which group the subject belonged to, as a consequence of the radiation protection committee's request for continuous monitoring of the prevalence of dysmotility in the control group.

During the radiological procedure, pharyngeal and oesophageal motility and morphology were monitored fluoroscopically and registered on a video tape for later evaluation. First, the subject had to swallow a solid bolus (a radiolucent tablet of antacid), with a diameter of 13 mm, together with a thin liquid barium suspension (40% w/v). If the tablet was arrested in combination with symptoms of obstruction, the patient was considered to have bolus-specific oesophageal dysfunction (BSED). BSED has been shown to be related to obstruction due to dysmotility, as a combination of oesophageal video radiography and manometry in patients with this finding has demonstrated a decreased contraction amplitude in the oesophageal segment where the tablet was arrested, without signs of morphological changes (24, 26). It was not possible to assess the oesophageal transit time from the solid bolus test video radiographies.

Then, the subject performed five high-density (240% w/v) barium suspension swallows in the erect and also in the supine position. Oesophageal motility was evaluated for signs of aperistalsis/peristaltic escape and non-propulsive peristalsis/oesophageal spasm in the erect and in the supine position. In addition, the presence of aperistalsis/peristaltic escape and non-propulsive peristalsis/oesophageal spasm was semiquantified as being normal (no signs), mild (present in 1/5 swallows), moderate (present in 2/5 swallows) or severe (present in $\geq$3/5 swallows) in the erect and supine positions, respectively. Subjects were considered to have oesophageal dysmotility if they had BSED or aperistalsis/peristaltic escape or non-propulsive peristalsis/oesophageal spasm in at least 1/5 swallows in the erect and/or supine position. Finally, pharyngeal motility was evaluated by performing five swallows while recording video radiographically in both the antero-posterior and lateral projections. The video radiographies were later evaluated for signs of radiological misdirected swallowing, defined as radiological signs that part of the swallowed bolus reaches the laryngeal vestibule or trachea, which is penetration or aspiration, pharyngeal retention and pharyngo-oesophageal segment dysfunction (PESD). The presence of radiologically misdirected swallowing, pharyngeal retention and PESD was also semiquantified as described earlier. Subjects were considered to have pharyngeal dysmotility if they had radiological evidence of misdirected swallowing, pharyngeal retention or PESD in at least one out of five swallows. Because of the use of a single contrast examination technique, the oesophageal mucosa could not be evaluated for the presence of reflux-related mucosal changes. However, the presence of more severe reflux-related structural changes (i.e. strictures) could be evaluated.

Autonomic nervous function tests

Deep breathing test. After being in the supine position for 15 min, the subject's heart rate was monitored by electrocardiography for 4 min and, once constant, six maximal expirations and inspirations were performed during a 1-min period. An expiration/inspiration (E/I) ratio was calculated as the mean of the longest R–R interval during the expirations, divided by the mean of the shortest R–R intervals during the inspirations (27). According to previous studies, the E/I ratio reflects parasympathetic nervous function (27).

Finger skin blood flow test. During this test the subject was in a semi-recumbent position with the left hand on an aluminium holder that was situated at heart level and with the middle (third) finger placed in a groove of the holder. The temperature of the aluminium holder was kept stable at 40°C by a Peltier element. The finger skin blood flow was monitored by a laser Doppler imaging (LDI) instrument, scanning an area of 2 × 2 cm of the distal phalanx of the middle finger. The finger skin blood flow was monitored every minute for 6 min during the 40°C heating (h) procedure. The subject then immersed the contralateral hand and forearm in a water bath that was kept at a temperature of 15°C, and the forearm was kept there for 3 min. A scan of the left middle finger was made every 30 s, both during immersion and afterwards for a further 3 min. In this way, the finger skin blood flow of the left hand was monitored during this contralateral cooling (c) procedure. By dividing the lowest finger skin blood flow value during the first minute of contralateral cooling (LDI_c) by the mean of the two last measurements of finger skin blood flow at rest, before the contralateral cooling procedure (LDI_h), a vasoconstriction (VAC) index could be calculated (VAC index$=LDI_c/LDI_h$). This test measures the reflex vasoconstrictor response to cooling of the contralateral hand and forearm and is a sensitive test for sympathetic nervous function in the skin (28).

As autonomic nervous system function tends to deteriorate with advancing age, the autonomic nervous function variables were age corrected and expressed as z-scores by comparison with two control groups. These comprised 56 deep breathing test controls consisting of healthy subjects [median age 40 years (range 16–59 years), 22 females], all of whom had passed a health examination and were without signs of cardiovascular disease, respiratory disorders or diabetes mellitus (29), and 80 finger skin blood flow test controls consisting of healthy subjects [median age 43 years (range 19–81 years), 37 females], all of whom were non-smokers, had no history of vascular disease and were not on any medication (28). As gender does not seem to significantly affect the autonomic variables measured (28, 29), sex was not matched for. All autonomic nervous function tests were performed in the morning under standard conditions, that is the temperature conditions were kept stable and the patients were not allowed to eat, drink coffee or smoke later than 2 hours prior to the testing procedure.

Statistics

We assessed the prevalence of oesophageal dysmotility in pSS patients to 40% and expected a prevalence of a maximum of 5% in the control group, based on assumptions by our radiologist, because oesophageal motility, to the best of our knowledge, has not been studied previously in population-based controls with this technique. Based on the above, the power calculation gave us an 80% power to detect a significant ($p<0.05$) difference in oesophageal dysmotility if at least 30 controls were included. We thus decided on the inclusion of 40 controls, that is two age- and sex-matched controls per pSS patient. To avoid unnecessary radiation exposure, the radiation protection committee requested continuous monitoring of dysmotility prevalence in the controls and cessation of further inclusion of controls if the power was breached. For that reason the inclusion of controls was stopped after having studied 30, as the prevalence of oesophageal dysmotility was higher among the controls than the expected 5%. When comparing groups, the Mann–Whitney U-test, the χ^2-test and Fisher's exact test were used.

p-values <0.05 were considered statistically significant. Values are, if not stated otherwise, presented as median (IQR) or percentage with abnormal results.

Results

Questionnaire

Dysphagia, defined as a positive answer to the question 'Do you experience swallowing difficulties when eating solids and/or drinking liquids on a weekly basis?', was significantly more common in pSS patients than in controls (65% vs. 3%; $p<0.001$). Moreover, GERD, pharyngeal and oesophageal symptoms were more prevalent and severe in pSS patients than in controls, as illustrated by the significantly increased GERD, pharyngeal and oesophageal symptom scores (Table 2). The presence of pharyngeal and oesophageal dysmotility, non-exocrine symptoms (Raynaud's phenomena, arthralgia, arthritis, interstitial lung disease, renal disease, liver disease, and vasculitis) and also the presence of anti-SS-A and anti-SS-B antibodies were not more common in patients with dysphagia vs. patients without dysphagia. Comparing patients with and without dysphagia for liquids, no significant differences were found for the prevalence of pharyngeal and oesophageal dysmotility, respectively. When studying patients with and without dysphagia in any location as well as stratified with regard to pharyngeal or oesophageal location, the prevalence of pharyngeal and oesophageal dysmotility did not differ significantly between groups. In addition, disease duration did not differ significantly between patients with and without dysphagia.

Video radiographies

Pharyngeal and oesophageal dysmotility were not significantly more common in pSS patients (15% and 40%) than in controls (17% and 30%; p=NS for both). The most common pharyngeal dysmotility finding was radiological misdirected swallowing, which had a similar prevalence in both groups (Table 3). The most common oesophageal dysmotility finding was aperistalsis/peristaltic escape in the supine position, which again was a common finding in both pSS patients and controls (Table 3). When signs of oesophageal dysmotility (BSED, aperistalsis/peristaltic escape and oesophageal spasm/non-propulsive peristalsis in the erect and supine positions) were found in pSS patients and controls, these were always detected in the distal oesophagus, except in a few cases when the proximal oesophagus was also engaged. When comparing the presence of moderate and severe pharyngeal and oesophageal dysmotility in pSS patients and controls, no significant differences were found. No oesophageal webs or strictures were observed in pSS patients or controls. The presence of non-exocrine symptoms, anti-SS-A and anti-SS-B antibodies were not more common in patients with vs. without pharyngeal and oesophageal dysmotility, respectively. Disease duration did not differ significantly between patients with and without signs of pharyngeal and oesophageal dysmotility, respectively.

Table 2. Results of the questionnaire.

	pSS patients (n=20)	Controls (n=30)	p-value
Dysphagia	65	3	<0.001
Dysphagia for solids	65	3	<0.001
Dysphagia for liquids	25	0	<0.01
Pharyngeal location	50	0	<0.001
Oesophageal location	30	3	<0.05
Upper oesophageal location	15	3	NS
Mid-oesophageal location	10	0	NS
Distal oesophageal location	5	0	NS
GERD symptom score (0–5)	1.50 (0.00–3.00)	0.00 (0.00–0.25)	<0.01
Any GERD symptom	60	23	<0.01
Globus feeling	45	10	<0.01
Regurgitation	45	10	<0.01
Pyrosis	45	10	<0.01
Nocturnal asthma	15	0	NS
Feeling of increased amount of fluid in oral cavity	5	0	NS
Pharyngeal symptom score (0–4)	0.00 (0.00–1.75)	0.00 (0.00–0.00)	<0.01
Any pharyngeal symptom	45	7	<0.01
Food/fluid in nasal cavity after swallowing	5	0	NS
Misdirected swallowing	25	3	<0.05
Coughing after swallowing	25	0	<0.01
Hawking when eating	25	3	<0.05
Oesophageal symptom score (0–5)	1.00 (1.00–2.00)	0.00 (0.00–0.00)	<0.001
Any oesophageal symptom	80	7	<0.001
Feeling of obstruction when swallowing	45	7	<0.01
Previous episodes of acute obstruction	30	3	<0.05
Avoidance of certain food due to dysphagia	60	3	<0.001
Increased liquid intake when eating	15	3	NS
Odynophagia	10	7	NS

Table 3. Results of the video radiographies.

	pSS patients (n=20)	Controls (n=30)	p-value
Pharyngeal dysmotility	15	17	NS
Radiological misdirected swallowing	15 (67/33/0)	13 (50/50/0)	NS
Retention	0	0	NS
Pharyngo-oesophageal segment dysfunction	0	3 (0/100/0)	NS
Oesophageal dysmotility	40	30	NS
Aperistalsis/peristaltic escape – erect position	5 (0/0/100)	3 (0/0/100)	NS
Non-propulsive peristalsis – erect position	0	0	NS
Aperistalsis/peristaltic escape – supine position	35 (14/43/43)	30 (44/33/22)	NS
Non-propulsive peristalsis – supine position	5 (0/100/0)	0	NS
Bolus specific oesophageal dysfunction	5	3	NS
Morphological changes	0	0	NS
Oesophageal webs	0	0	NS
Strictures	0	0	NS

Results are presented as percentage of abnormal (mild/moderate/severe) results in each group.

Autonomic nervous function tests

The patients had a significantly decreased age-corrected E/I ratio compared with controls [−0.46 (−1.35 to −0.23) vs. −0.25 (−0.62 to 0.60); p=0.05], indicating impaired parasympathetic function. There was also a tendency towards an increased age-corrected VAC index in pSS patients compared with controls [0.51 (−0.58 to 2.10) vs. 0.09 (−0.67 to 0.62); p=0.08]. Moreover, patients with dysphagia had a significantly decreased E/I ratio [−1.05 (−1.51 to −0.40) vs. −0.21 (−0.39 to 0.65); p<0.01] (Figure 1) compared with those without, whereas the VAC index did not differ significantly between the groups [0.89 (−0.35 to 2.07) vs. −0.05 (−0.85 to 2.15); p=NS]. When comparing patients with and without pharyngeal and oesophageal dysmotility, respectively, no significant differences in the E/I ratio and VAC index were found.

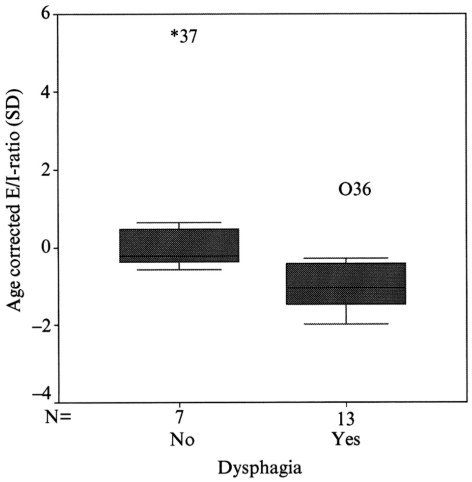

Figure 1. The expiration/inspiration (E/I) ratio was significantly lower in pSS patients with dysphagia compared to those without ($p<0.01$).

Discussion

In this study we found dysphagia and video radiographical signs of dysmotility to be common in pSS patients, although only the former was more common compared to population-based controls. Dysphagia did not seem to be related to pharyngeal or oesophageal dysmotility. However, dysphagia was related to a parasympathetic dysfunction, while pharyngeal and oesophageal dysmotility were not.

Dysphagia is a common symptom in pSS but the pathogenesis behind it is obscure. Dysphagia in pSS patients has previously been suggested to be caused by xerostomia, dry mucosal surfaces, oesophageal webs, oesophageal dysmotility or combinations of these factors. Most previous studies have failed to show any correlation between salivary flow and dysphagia (5, 6). Oesophageal webs have not been found to be related to dysphagia (4), and according to most prior studies dysphagia and oesophageal dysmotility correlate poorly (2, 4, 6, 7). However, a correlation between GERD symptoms, increased reflux time and tertiary contractions in pSS has been reported (2). Although these findings have to be confirmed by others, the diminished saliva formation in pSS patients could result in a decreased oesophageal acid clearance capability, oesophageal morphological changes and oesophageal dysmotility (2), possibly causing dysphagia. These problems appear, however, to be less severe compared to scleroderma patients (30).

Some strengths of the present study are the thorough examination protocol as well as the use of pSS patients according to the AECC (12) and a population-based control group.

Some limitations are the size of the study and the possibility that examinations can always be more extensive. For example, an increased number of swallows during the radiological procedure would increase the possibility of stratifying patients with regard to different severity of dysmotility, but this was not practical because of concerns about excessive radiation exposure. Furthermore, a combination of this technique with oesophageal manometry might have yielded more information about different aspects of dysmotility. However, oesophageal manometry is not practical, especially not when studying population-based controls, and therefore that technique was not used in this study. Finally, as treatment with anti-hypertensive drugs was an exclusion criterion, older patients were often excluded, resulting in a fairly young patient group (median age 47 years), possibly underestimating the prevalence of dysphagia and dysmotility in the whole pSS patient group.

Dysphagia and also pharyngeal and oesophageal symptoms were all more common in the pSS patients than in the controls, in accordance with other reports (2–8). Pharyngeal and oesophageal dysmotility were found in 15% and 40% of pSS patients, respectively, also in accord with previous studies reporting dysmotility in about one-third of pSS patients (2, 5, 7, 9, 11). A similar high prevalence of dysmotility was seen in age- and gender-matched controls, which implies that such findings of dysmotility are non-specific, particularly because all controls with signs of dysmotility reported no dysphagia. As in several other studies (2, 4, 6, 7), we could not find any association between dysphagia and signs of dysmotility, not even when stratifying patients with regard to severity or location of dysphagia. Hence, in most cases dysphagia does not seem to be due to dysmotility. However, the possibility that a minor dysmotility, not detectable by videoradiography, could correlate with dysphagia has to be considered. As no oesophageal webs were found in our subjects, it seems less likely that this is a major cause of dysphagia in pSS.

In this study we also wanted to investigate whether autonomic nervous dysfunction could be related to dysphagia and signs of dysmotility. It is well known that the degree of destruction of the exocrine glands correlates poorly with exocrine function (31). This raises the possibility of impairment of the neural signalling controlling exocrine secretion. Previously it has been shown that pSS patients show signs of both impaired parasympathetic and sympathetic nervous function (13–15) and different mechanisms have been reported, for example anti-M3-receptor antibodies (16), cytokines interfering with neural signalling (17, 32) or inflammation affecting autonomic nerves or

ganglia (18). As gastrointestinal motility and secretion are influenced by the autonomic nervous system, disturbed autonomic neural signalling may have implications for gastrointestinal system functioning. Indeed, pSS patients have been reported to have an abnormally slow gastric emptying and anti-M3-receptor antibodies were suggested as a possible pathogenetic factor (33). However, the presence of such antibodies has not yet been demonstrated in our patients. When comparing our pSS patients with and without dysphagia, we found a significantly lower E/I ratio, a parasympathetic index, among the former. This suggests that a parasympathetic dysfunction could contribute to dysphagia. Besides controlling oesophageal motility, the parasympathetic nervous system also influences oesophageal and salivary exocrine secretion. Parasympathetic dysfunction could thus cause dysmotility as well as diminished exocrine secretion in the oesophagus and salivary glands, all possible factors causing dysphagia. In our study, pharyngeal and oesophageal dysmotility was as common in pSS patients as in controls and did not associate with the two autonomic indices, arguing against the hypothesis that an autonomic nervous dysfunction caused the observed dysmotility findings. As oesophageal exocrine function is difficult to measure, its possible relationship to dysphagia is difficult to assess. Sialometries were not performed in this study and salivary flow could thus not be related to dysphagia, dysmotility or parasympathetic function. However, previous studies have failed to show any correlation between salivary flow and dysphagia (5, 6), although this lack of correlation could be explained by a lack of variation in salivary flow among the patients included in those studies. It would be interesting to see, in future studies, if pSS patients with anti-M3-receptor antibodies are more prone to developing dysphagia and disturbed oesophageal manometry variables, especially because these antibodies have also been demonstrated in scleroderma patients (34), a group with a disturbed oesophageal motility and dysphagia, where a neuropathic factor has been suggested as a cause of oesophageal dysmotility early in the disease (30). Several factors may thus contribute to the swallowing difficulties experienced by pSS patients. Increased knowledge of these in the future could facilitate the search for new drugs (35) in the treatment of dysphagia as well as of other symptoms of the disease.

In conclusion, we found that dysphagia, pharyngeal, oesophageal and GERD symptoms were more common in pSS patients compared to controls while dysmotility was not. Dysphagia was not associated with dysmotility but was associated with an impaired parasympathetic function.

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References

1. Sheikh SH, Shaw-Stiffel TA. The gastrointestinal manifestations of Sjögren's syndrome. Am J Gastroenterol 1995;90:9–14.
2. Volter F, Fain O, Mathieu E, Thomas M. Esophageal function and Sjögren's syndrome. Dig Dis Sci 2004;49:248–53.
3. Türk T, Pirildar T, Tunc E, Bor S, Doganavsargil E. Manometric assessment of esophageal motility in patients with primary Sjögren's syndrome. Rheumatol Int 2005;25: 246–9.
4. Kjellen G, Fransson SG, Lindström F, Sokjer H, Tibbling L. Esophageal function, radiography and dysphagia in Sjögren's syndrome. Dig Dis Sci 1986;31:225–9.
5. Anselmino M, Zaninotto G, Constantini M, Ostuni P, Ianiello A, Boccu C, et al. Esophageal motor function in primary Sjögren's syndrome. Dig Dis Sci 1997;42: 113–18.
6. Grande L, Lacima G, Ros E, Font J, Pera C. Esophageal motor function in primary Sjögren's syndrome. Am J Gastroenterol 1993;88:378–81.
7. Palma R, Freire J, Freitas J, Morbey A, Costa T, Saraiva F, et al. Esophageal motility disorders in patients with Sjögren's syndrome. Dig Dis Sci 1994;38:758–61.
8. Rosztóczy A, Kovács L, Wittmann T, Lonovics J, Pokorny G. Manometric assessment of impaired esophageal motor function in primary Sjögren's syndrome. Clin Exp Rheumatol 2001;19:147–52.
9. Tsianos EB, Vasakos S, Drosos AA, Malamou-Mitsi VD, Moutsopoulos HM. The gastrointestinal involvement in primary Sjögren's syndrome. Scand J Rheumatol 1986;61: 151–5.
10. Hradsky M, Hybasek J, Cernoch V, Sazmova V, Juran J. Oesophageal abnormalities in Sjögren's syndrome. Scand J Gastroenterol 1967;2:200–3.
11. Tsianos EB, Chiras CD, Drosos AA, Moutsopoulos HM. Oesophageal dysfunction in patients with primary Sjögren's syndrome. Ann Rheum Dis 1985;44:610–13.
12. Vitali C, Bombardieri S, Jonsson R, Moutsopoulos HM, Alexander EL, Carsons SE, et al. Classification criteria for Sjögren's syndrome: a revised version of the European criteria proposed by the American–European Consensus Group. Ann Rheum Dis 2002;61:554–8.
13. Mandl T, Jacobsson L, Lilja B, Sundkvist G, Manthorpe R. Disturbances of autonomic nervous function in primary Sjögren's syndrome. Scand J Rheumatol 1997;26:401–6.
14. Mandl T, Bornmyr SV, Castenfors J, Jacobsson LTH, Manthorpe R, Wollmer P. Sympathetic dysfunction in patients with primary Sjögren's syndrome. J Rheumatol 2001;28: 296–301.
15. Kovacs L, Paprika D, Takacs R, Kardos A, Varkonyi TT, Lengyel C, et al. Cardiovascular autonomic dysfunction in primary Sjogren's syndrome. Rheumatology 2004;43: 95–9.
16. Dawson L, Tobin A, Smith P, Gordon T. Antimuscarinic antibodies in Sjogren's syndrome: where are we, and where are we going? Arthritis Rheum 2005;52:984–95.
17. Fox RI, Stern M. Sjogren's syndrome: mechanisms of pathogenesis involve interaction of immune and neurosecretory systems. Scand J Rheumatol 2002;116:3–13.

18. Mori K, Iijima M, Koike H, Hattori N, Tanaka F, Watanabe H, et al. The wide spectrum of clinical manifestations in SS associated neuropathy. Brain 2005;128:2518–34.
19. Lock G, Straub R, Zeuner M, Antoniou E, Holstege A, Scholmerich J, et al. Association of autonomic nervous dysfunction and esophageal dysmotility in systemic sclerosis. J Rheumatol 1998;25:1330–5.
20. Channer KS, Jackson PC, O'Brien I, Corrall RJ, Coles DR, Davies ER, et al. Oesophageal function in diabetes mellitus and its association with autonomic neuropathy. Diabet Med 1985;2:278–82.
21. Heatley RV, Collins RJ, James PD, Atkinson M. Vagal function in relation to gastroesophageal reflux and associated motility changes. Br Med J 1980;280:755–7.
22. Campo SMA, Capria A, Antonucci F, Martino G, Ciamel A, Rossini PM, et al. Decreased sympathetic inhibition in gastroesophageal reflux disease. Clin Autonom Res 2001;11:45–51.
23. Pirtniecks A, Smith L, Thorpe J. Autonomic dysfunction in non-specific disorders of oesophageal motility. Eur J Cardiothorac Surg 2000;17:101–5.
24. Ekberg O, Olsson R. Dynamic radiology of swallowing disorders. Endoscopy 1997;29:439–46.
25. Lundquist A, Olsson R, Ekberg O. Clinical and radiologic evaluation reveals high prevalence of abnormalities in young adults with dysphagia. Dysphagia 1998;13:202–7.
26. van Westen D, Ekberg O. Solid bolus swallowing in the radiologic evaluation of dysphagia. Acta Radiol 1993;34:372–5.
27. Sundkvist G, Almer L-O, Lilja B. Respiratory influence on heart rate in diabetes mellitus. Br Med J 1979;1:924–5.
28. Bornmyr S, Svensson H, Söderström T, Sundkvist G, Wollmer P. Finger skin blood flow in response to indirect cooling in normal subjects and in patients before and after sympathectomy. Clin Physiol 1998;18;2:103–7.
29. Bergström B, Lilja B, Rosberg K, Sundkvist G. Autonomic nerve function tests. Reference values in healthy subjects. Clin Physiol 1986;6:523–8.
30. Sjögren RW. Gastrointestinal motility disorders in scleroderma. Arthritis Rheum 1994;37:1265–82.
31. Humphreys-Beher MG, Brayer J, Yamachika S, Peck AB, Jonsson R. An alternative perspective to the immune response in autoimmune exocrinopathy: induction of functional quiescence rather than destructive autoaggression. Scand J Immunol 1999;49:7–10.
32. Haddad EB, Rousell J, Lindsay MA, Barnes PJ. Synergy between tumor necrosis factor alpha and interleukin 1beta in inducing transcriptional down-regulation of muscarinic M2 receptor gene expression. Involvement of protein kinase A and ceramide pathways. J Biol Chem 1996;271:32586–92.
33. Kovacs L, Papos M, Takacs R, Roka R, Csenke Z, Kovacs A, et al. Autonomic nervous system dysfunction involving the gastrointestinal and the urinary tracts in primary Sjogren's syndrome. Clin Exp Rheumatol 2003;216:697–703.
34. Goldblatt F, Gordon TP, Waterman SA. Antibody-mediated gastrointestinal dysmotility in scleroderma. Gastroenterology 2002;123:1144–50.
35. Manthorpe R, Bredberg A, Henriksson G, Larsson Å. Progress and regression within primary Sjögren's syndrome. Scand J Rheumatol 2006;35:1–6.